7-2003

Rethinking Nutritional Support for Persons with Cancer Cachexia

Donna O. McCarthy
Marquette University, donnalee.mccarthy@marquette.edu

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Cancer cachexia is a poorly understood syndrome of anorexia, weight loss, and muscle wasting that negatively impacts quality of life and survival in cancer patients. Research has clearly implicated proinflammatory cytokines in the biology of cancer cachexia. More recent research implicates products of arachidonic acid and suggests that cachexia may be a chronic inflammatory condition rather than a nutritional aberration. To date, nutritional support to slow weight loss has focused primarily on increasing calorie intake. Alternatively, many foods contain factors that can modulate the synthesis or activity of proinflammatory mediators, especially the synthesis of prostaglandin E2 from arachidonic acid. These factors and foods are sometimes called nutraceuticals, and research is needed to evaluate their efficacy in combating cancer cachexia.

Key words: *cancer cachexia, nutrition, cytokines, cyclooxygenase, prostaglandin E2, fish oil, polyphenols, flavonoids, catechins*

Cancer cachexia is a poorly understood syndrome involving altered metabolism of proteins, carbohydrates, and lipids that results in anorexia, weight loss, and skeletal muscle wasting (Tisdale 2001). It occurs primarily with advanced disease and negatively affects the patient's functional status and quality of life (O'Gorman and others 1998; Chang and others 2000). Poor nutritional status is associated with the experience of fatigue in persons with cancer (Wang and others 2002). Nutritional decline (Gogos and others 1998; Okusaka and others 1998; Martin and others 1999) and weight loss (O'Gorman and others 2000; Langer and others 2001) are negatively associated with patient survival.

Interventions to maintain or improve the nutritional status of patients during cancer treatment are an important part of cancer nursing; increasing the food intake of patients with cancer cachexia is intuitively attractive (Stepp and Pakis 2001; Whitman 2000; Dell 2002). However, reduced food intake alone does not explain the extent of weight loss seen in patients with advanced cancer (Boseaus and others 2001; Baracos 2002). Except in the case of gastrointestinal tumors, cancer patients often fail to gain weight with increased calorie or protein intake (Espat and others 1995; Brown 2002). Clinical trials using drugs to increase food appetite have shown some improvements in calorie intake and body weight of cancer patients (Simons and others 1996; Maltoni and others 2001) but minimal effects on laboratory measures of nutritional status or lean body mass (Strang 1997; Simons and others 1998). Others have suggested that the alterations in lipid, protein, and carbohydrate metabolism that characterize cancer cachexia (Simons and others 1999; Baracos 2002; Langhans 2002) may prevent anabolic responses to nutritional repletion (Espat and others 1995; Kern and Norton 1988; Moldawer and Copeland 1998). Finally, there is little evidence that increased caloric intake per se improves functional status, morbidity, or quality of life in cancer patients (Simons and others 1996; Tisdale 2001; Brown 2002).

Donna O. McCarthy, PhD, RN, is an adjunct investigator at the National Institute of Nursing Research, Bethesda, MD. Address for correspondence: Donna O. McCarthy, National Institute of Nursing Research, 31 Center Drive, Room 5B-13, Bethesda, MD 20892-2178; e-mail: mccarthd@mail.nih.gov.

BIOLOGICAL RESEARCH FOR NURSING
Vol. 5, No. 1, July 2003, 3-17
DOI: 10.1177/1099800403253858

The literature regarding the biology of cancer cachexia suggests that it is a chronic inflammatory disorder rather than a nutritional aberration. If this is the case, the concept of nutritional support will have to be expanded to include interventions that alter the expression or activity of proinflammatory factors that play a role in the biology of cancer cachexia. The purpose of this article is to review current research on the role of proinflammatory mediators in cancer cachexia. The effects of selected anti-inflammatory drugs and nutraceuticals on the synthesis or activity of these mediators and on the symptoms of cancer cachexia will also be reviewed. Nutraceuticals are foods or food-derived products that have pharmacological effects; hence, the melding of the terms *nutritional* and *pharmaceutical*.

Nutraceuticals with known anti-inflammatory effects include omega-3 polyunsaturated fatty acids, polyphenols from fruits and tea, and vitamin antioxidants. Each has been shown to alter the activity or synthesis of proinflammatory mediators. This article summarizes laboratory studies, animal models of tumor growth and cancer cachexia, descriptive studies of cancer patients, and clinical trials of these agents in patients with cancer cachexia. Gaps in the literature and areas for future research are identified. Because of the overlap in factors affecting tumor or host-cell synthesis of cytokines, prostanoids, and other proinflammatory mediators, the schema of the article is represented in 3 figures that are more global than specific in their representation of the content of the article.

The Biology of Cancer Cachexia

Cytokines as Mediators of Cancer Cachexia

Symptoms of cachexia occur in 50% to 80% of cancer patients, which led early investigators to examine the effects of tumor growth on the host. In 1974, Theologides proposed that cancer cachexia, and especially cancer anorexia, was mediated by circulating factors released by the tumor. In 1985, Norton and others demonstrated that plasma from a tumor-bearing rat caused weight loss in a healthy rat. Many of the symptoms of cachexia are similar to those seen with chronic infection or inflammation, which are mediated by small-molecular-weight proteins secreted by white blood cells, called interleukins (between white cells) or cytokines (cell proteins). In 1988, Kern and Norton proposed that cancer cachexia was mediated by proinflammatory cytokines produced by the host in response to tumor growth. These cytokines—interleukin-1 alpha (IL-1α), IL-1 beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNFα), and interferon-gamma (IFNγ)—suppress food intake, alter protein lipid and carbohydrate metabolism, and cause proteolysis in skeletal muscle when injected into healthy animals (Argiles and Lopez-Soriano 1999). Early experiments in which tumor-bearing animals were injected with antibodies to IL-1α, IL-1β, IL-6, TNFα, or IFNγ clearly implicated these cytokines in the biology of cachexia (Argiles and Lopez-Soriano 1999; Tisdale 2001).

The notion that proinflammatory cytokines were produced by the host in response to tumor growth was subsequently revised with evidence that tumor cells also produce proinflammatory cytokines. More recent experiments conducted in gene knockout mice suggest that tumor-derived cytokines may be more important in the development of cancer cachexia than host-derived cytokines (Cahlin, Korner, and others 2000). The contribution of tumor-derived cytokines to the development of cancer cachexia would explain why cachexia more often occurs with advanced disease. Cytokines are rarely detected in the serum of persons with stage 1 or stage 2 disease, but IL-1, TNF, IL-6, or their receptors have been detected in the serum of patients with advanced disease (Maccio and others 1998; Shibata and others 1998; Martin and others 1999), metastatic disease (Bansal and others 1997; Karayiannakis and others 2001), and cachexia (Kiyama and others 1994; Nakashima and others 1998). These observations support the idea that progressive tumor growth results in progressive synthesis of cytokines.

One school of thought for the treatment of cancer cachexia has involved the use of drugs that block the synthesis or activity of selected cytokines. For example, drugs that block the synthesis of TNFα, such as thalidomide or pentoxyfylline, or interfere with the binding of IL-6 or IL-1 to their receptors, such as suramin, were shown to retard weight loss and muscle wasting in tumor-bearing rodents (Strassmann and Kambayashi 1995; Combaret and others 1999; Costelli and others 2002). However, these drugs have

not had a significant clinical impact on the symptoms of cachexia in cancer patients (Argiles and others 2001). Thus, the targeting of specific cytokines for the treatment of cancer cachexia may not be a fruitful area of research, although this approach has shown promise in the treatment of AIDS-related wasting (Klausner and others 1996).

Other Mediators of Cancer Cachexia

Tumors secrete other small proteins that are not proinflammatory cytokines but induce the signs and symptoms of cancer cachexia (Argiles and Lopez-Soriano 1999; Tisdale 2001). Two such factors, proteolysis-inducing factor (PIF) and lipid mobilizing factor, were isolated from a murine tumor cell line that induced weight loss and muscle wasting in tumor-bearing mice (Beck and Tisdale 1987). Injection of PIF into healthy mice caused weight loss and muscle wasting, and injection of antibodies to PIF prevented weight loss and muscle wasting in tumor-bearing animals. PIF has been isolated from a human melanoma cell line (Todorov and others 1999) and human gastrointestinal tumors (Cabal-Manzano and others 2001) and detected in the urine of weight-losing cancer patients (Wigmore, Todorov, and others 2000; Cabal-Manzano and others 2001). These data remind researchers and clinicians of the complexity of cancer cachexia and of the likelihood that multiple circulating factors from both the tumor and the host contribute to the signs and symptoms of cachexia.

Prostanoid Mediators of Cancer Cachexia

Research has also implicated the products of arachidonate metabolism in the biology of cancer cachexia (Ross and Fearon 2002). Arachidonic acid (AA) is a 20-carbon polyunsaturated fatty acid (PUFA) and is one of many fatty acids in the phospholipids of cell membranes. It is liberated from the cell membrane by phospholipase enzymes and converted by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes to prostaglandins and leukotrienes (see Fig. 1). There are 2 isoforms of the COX enzyme: COX1 is constitutively produced by most cells, and the synthesis of COX2 is upregulated with cell hypoxia, injury, or infection.

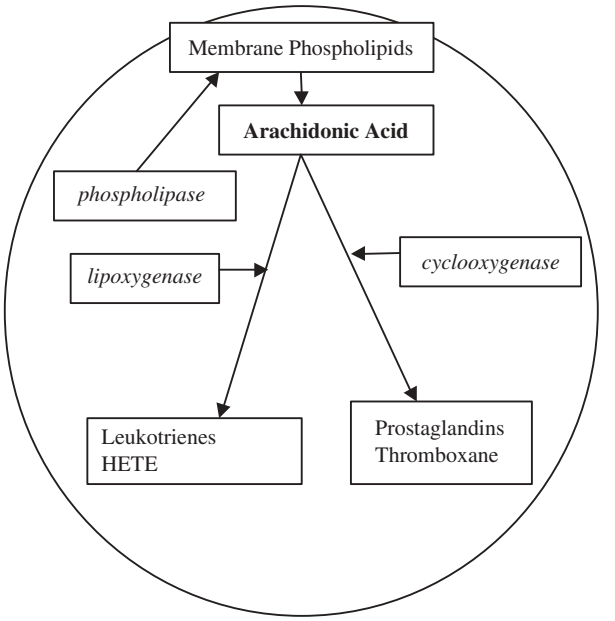

Figure 1. Phospholipases release arachidonic acid (AA) from membrane phospholipids. Cyclooxygenases act on AA to produce prostaglandins and thromboxanes. Lipoxygenase acts on AA to produce leukotrienes and hydroxyeicosatetraenoic acid (HETE).

COX is the rate-limiting enzyme in the synthesis of prostaglandins (PG), most notably PGE2. Outside the cell, PG act through subtypes of PG receptors that are differentially distributed on various cell types (Tilley and others 2001). For example, PGE2 can induce the synthesis of IL-1, IL-6, and TNF in macrophages; these cytokines in turn increase the expression of COX2 and synthesis of PGE2 in macrophages and other cell types (Williams and Shacter 1997; Eisengart and others 2000; Walch and Morris 2002). Hence, PGE2 is a potent paracrine mediator of the local inflammatory response. Inhibition of COX2 activity explains the anti-inflammatory effects of most nonsteroidal anti-inflammatory drugs (NSAIDs), whereas inhibition of COX1 activity explains the gastrointestinal side effects of these drugs. Steroids, on the other hand, are very potent anti-inflammatory agents as they block the expression of genes controlling cell synthesis of phospholipases, COX, and LOX as well as cytokines, with far more negative side effects on protein synthesis and gastrointestinal function.

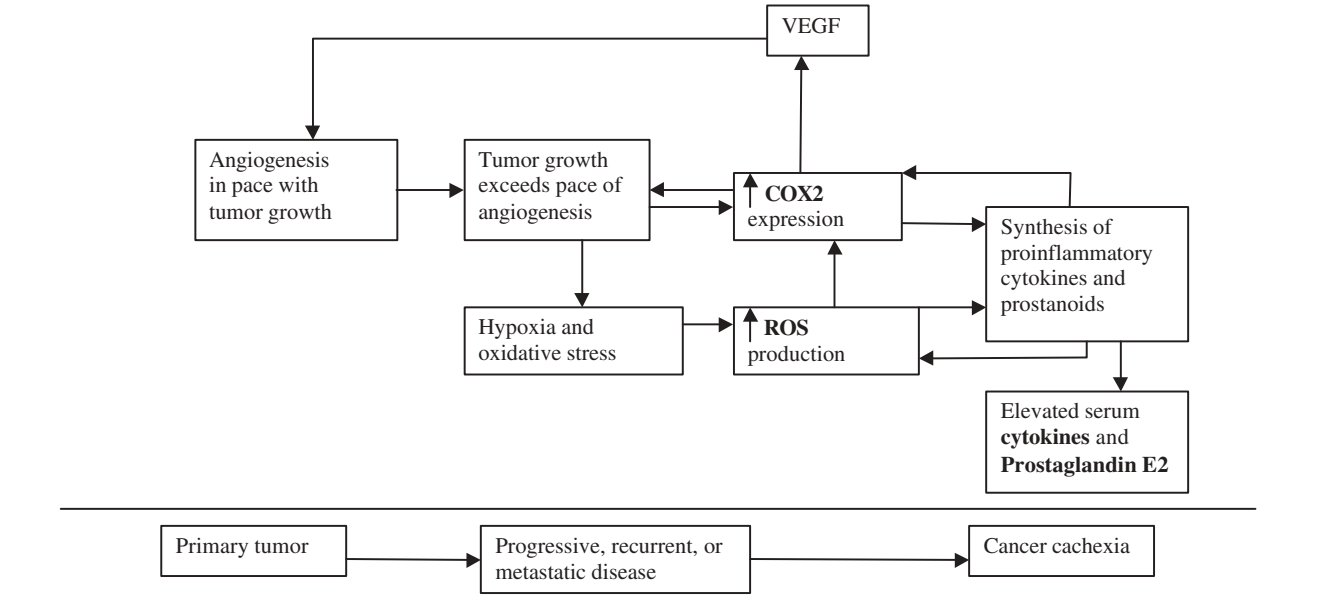

Figure 2. Schematic of factors associated with cancer cachexia. VEGF = vascular endothelial growth factor; COX2 = cyclooxygenase2; ROS = reactive oxygen species.

Elevated plasma levels of PGE2 have been reported in both animal models and clinical studies of cancer cachexia (Kundu and others 2001; Ross and Fearon 2002). One group noted that treatment with indomethacin, a nonspecific inhibitor of COX activity, reduced serum PGE2 levels and improved body weight and food intake in tumor-bearing mice without reducing serum IL-6 levels. Indomethacin also reduced serum PGE2 levels and improved body weight and food intake in tumor-bearing IL-6 and TNF-receptor knockout mice (Cahlin, Korner, and others 2000). These investigators concluded that PGE2 might play a larger role in tumor-induced weight loss and anorexia than the proinflammatory cytokines.

NSAIDS, Tumor Growth, and Cancer Cachexia

Many tumor cell lines constitutively express high levels of COX2 (Cao and Prescott 2002), and this is especially true in metastatic cell lines (Kundu and others 2001; Ohike and Morohoshi 2001). There is extensive evidence that inhibition of COX activity with NSAIDs reduces tumor growth in vitro by inducing cell cycle arrest and increasing the number of cells undergoing apoptosis, programmed cell death (Eli and others 2001; Cao and Prescott 2002; Cheng and others 2002; Raz 2002). There is one preliminary report that treatment of tumor-bearing mice with NSAIDs reduced the expression of genes involved in cell cycle progression and increased markers of apoptosis in lung tumors taken from the treated mice (Yao and others 2000).

It has also been reported that expression of COX2 by tumor cells is associated with increased expression of vascular endothelial growth factor (VEGF), a factor important in stimulating the growth of new blood vessels (Gately 2000; Williams and others 2000). It is tempting to speculate that growing tumor cells can outpace the growth of supporting blood vessels, creating a hypoxic tumor environment (see Fig. 2). This environment would "select" for tumor cells with increased COX2 and/or VEGF expression that are able to survive because they stimulate the growth of blood vessels needed to sustain continued tumor growth and metabolism (Masferrer and others 2000).

There is some evidence that production of COX2 and VEGF by host fibroblasts surrounding the tumor also contribute to tumor angiogenesis. Hence, tumor cells grow more slowly in COX2 knockout mice where host fibroblasts cannot contribute to the local level of vascular endothelial growth factors produced by the tumor (Williams and others 2000). Inhibition of COX activity with NSAIDs reduces in vitro synthesis of

VEGF by tumor cells and host fibroblasts (Gately 2000; Williams and others 2000). Tumor-bearing mice treated with NSAIDs show reduced tumor growth, reduced growth of blood vessels in the tumor bed, and reduced incidence of metastasis (Liu and others 2000; Masferrer and others 2000; Kundu and others 2001; Kundu and Fulton 2002). NSAIDs are currently being examined as adjuvant agents in the chemotherapy of cancer.

Decreased tumor growth in mice treated with NSAIDs is often associated with increased survival time and preservation of muscle mass and body weight compared with untreated controls (Hussey and Tisdale 2000; Ross and Fearon 2002). Although the improved health of the animal may be the result of the reduced tumor growth, others have shown that indomethacin can abrogate weight loss and muscle wasting in tumor-bearing mice without affecting tumor size (Al-Majid and McCarthy 2000; Cahlin, Korner, and others 2000). Alternatively, treatment with indomethacin can reduce tumor growth without affecting the body weight of tumor-bearing rats (McCarthy 1999). Others reported that indomethacin had no effect on tumor growth, body weight, or food intake in mice implanted with a tumor cell line that did not express high levels of COX2; nor did these animals demonstrate weight loss or reduced food intake with progressive growth of the tumor (Cahlin, Gelin, and others 2000). In a related study, these investigators showed that indomethacin reduced tumor growth and improved body weight and food intake in the tumor-bearing mice, whereas an inhibitor of nitric oxide synthesis reduced tumor growth without affecting food intake or body weight of the tumor-bearing animals (Cahlin, Gelin, and others 2000). Thus, cancer cachexia cannot be explained by tumor burden alone and may involve PG-dependent as well as PG-independent mechanisms.

Clinical trials of NSAIDs in persons with cancer cachexia are limited. In one study, 135 weight-losing cancer patients with various solid tumors were randomly assigned to 1 of 3 treatment groups: 50 mg of indomethacin twice a day, 10 mg of prednisolone twice a day, or a placebo. Survival time was doubled in the indomethacin and the prednisolone groups compared to placebo-treated controls (510 versus 274 days), and there was no difference between indomethacin- and prednisolone-treated subjects. Both the indomethacin and prednisolone groups maintained a higher Karnofsky rating of functional status than did the placebo control group, and the indomethacin group reported using less pain medication. There were no group differences in other clinical or nutritional variables that could explain the group differences in survival (Lundholm and others 1994). A thorough search of the literature shows that this study has not been replicated.

In a 2nd study, 73 weight-losing cancer patients with advanced or metastatic disease were randomly assigned to take megestrol acetate (MA), an appetite stimulant, or MA plus ibuprofen for 12 weeks. At the end of the 12 weeks, patients in the group taking MA alone had maintained or lost weight (median change = –2.8 kg), and patients taking MA plus ibuprofen had maintained or gained weight (median change = +2.3 kg). Upper-arm circumference had declined over 12 weeks in the MA group but had not changed in the group taking MA plus ibuprofen. Quality of life declined in the MA group but was stable in the ibuprofen group. Of greater note was the observation that 12 of the 38 patients (75%) taking MA alone were not able to complete the 12 weeks of study due to disease progression, whereas only 11 of 35 patients (30%) taking MA plus ibuprofen were lost to follow-up at 12 weeks (McMillan and others 1999).

There is good experimental evidence that even short-term ingestion of ibuprofen may be beneficial in reducing signs or symptoms of cancer cachexia. Resting energy expenditure was reduced in weight-losing patients with pancreatic cancer after 7 days of treatment with ibuprofen (Wigmore and others 1995), and serum levels of IL-6 were reduced after 11 days in patients with colon cancer (McMillan and others 1995). A significant decrease in serum levels of C-reactive protein, a protein synthesized in the liver as part of the acute phase response to inflammation, was noted in both studies. A reduction in whole body protein turnover in cancer patients treated with ibuprofen was noted in a 3rd study (Preston and others 1995). These authors proposed that ibuprofen might abrogate catabolic processes contributing to weight loss and muscle wasting in cancer patients.

As a collective, this literature supports the idea that cachexia may be a chronic inflammatory condition driven by increased expression of COX2 and subsequent synthesis of PGE2 by tumor and host cells. It also suggests that interruption of the metabolism of

AA to PGE2 may directly or indirectly alter synthesis or activity of proinflammatory mediators that contribute to progression of cancer cachexia. One potential target is phospholipase A2, an enzyme that catalyzes the release of AA from membrane phospholipids (Gijon and others 2000). Indomethacin inhibits LOX activity as well as COX activity (see Fig. 1). There is one report that a LOX-specific inhibitor was superior to indomethacin in suppressing tumor growth in vitro (Hussey and Tisdale 1994). To date, the effects of LOX inhibitors on tumor growth or cancer cachexia have not been examined in vivo.

Nutraceuticals and the Treatment of Cancer Cachexia

Fatty Acids

One nutritional approach to moderating PGE2 production is to moderate the availability of AA as a substrate for COX activity. This has been done by reducing the relative amount of AA versus other PUFA in the membrane phospholipids (Babcock and others 2000; Calder and Grimble 2002; Ross and Fearon 2002). AA is synthesized from linoleic acid, an 18-carbon PUFA present in most vegetable oils. It is one of several omega-6 PUFA, so named for the location of double bonds in the fatty acid chains. Eicosapentaenoic acid (EPA) is a 20-carbon PUFA, and one of several omega-3 PUFA present in fish oil. It is also incorporated into membrane phospholipids and released into the cytoplasm by the action of phospholipases.

In the cytoplasm, EPA competes with AA as a substrate for COX and LOX activity (see Fig. 3). Although AA is metabolized via COX to prostaglandins of the 2 series, EPA is metabolized to prostaglandins of the 3 series (PGE3), which is less biologically active than PGE2 (Ross and Fearon 2002). AA is also metabolized by LOX to leukotrienes of the 4 series. As a competitor of AA, EPA is metabolized by LOX to leukotrienes of the 5 series, which are less active as proinflammatory mediators than leukotrienes of the 4 series (Ross and Fearon 2002). Last, AA is also metabolized by LOX to 5 and 15-hydroxyeicosatetraenoic acid (HETE). EPA cannot be metabolized to 15-HETE, which may explain in part why increased intake of EPA reduces the cellular response to inflammatory stimuli (Tisdale 2002).

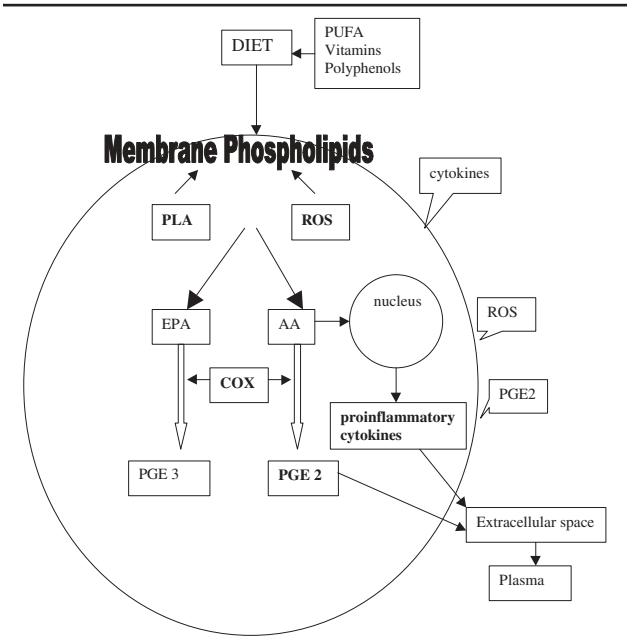

Figure 3. Metabolism of arachidonic acid (AA) to prostaglandin E2 (PGE2). ROS = reactive oxygen species; COX = cyclooxygenase; EPA = eicosapentaenoic acid; PLA = phospholipase; PUFA = polyunsaturated fatty acids. The nucleus is responsible for subsequent expression of genes controlling cell synthesis of PLA, COX, and proinflammatory cytokines. Cytokines, ROS, and PGE2 can each activate a cell to produce COX2, PGE2, ROS, and cytokines in a paracrine, autocrine, and endocrine fashion. Dietary intake can alter the level of AA in the cell membrane and/or the activity of COX for production of PGE2 or other proinflammatory mediators.

Altering the fatty acid composition of the cell membrane may alter signaling pathways that affect cell synthesis of proinflammatory cytokines. Macrophages from mice fed a diet in which fish oil was substituted for corn oil secreted less PGE2 and TNF than macrophages from animals given the standard diet containing corn oil. The reduced synthesis of PGE2 and TNF did not impair the ability of the macrophages to kill tumor cells in vitro (Wallace and others 2000). Others reported that serum levels of IL-1, IL-6, and TNF following injection of endotoxin were lower in mice fed chow with proportionally more omega-3 than omega-6 PUFA (Sadeghi and others 1999). Similarly, mRNA for IL-1 and TNF following injection with an

intracellular bacterial pathogen were lower in spleen cells of mice given omega-3 as compared to mice given omega-6 PUFA in their diet (Fritsche and others 2000). In this study, plasma levels of IL-12 and interferon-γ were also suppressed, which could have negative effects on T cell activation and clearance of the infection. Thus, further study to determine the effects of increased EPA intake on immune cell function are needed. Alternatively, studies of the clinical effects of EPA intake in persons with cancer cachexia should include measurements of T cell activation or function ex vivo.

When healthy humans were fed a diet containing more omega-3 than omega-6 PUFA, their peripheral blood mononuclear leukocytes secreted less TNF, IL-1, and IL-6 when stimulated ex vivo with a bacterial toxin (Calder 2001). The levels of TNF secreted by the participants' cells varied with the occurrence of 2 polymorphisms in TNF genotypes, as did the suppressive effect of fish oil capsules on TNF secretion (Grimble and others 2002). Persons with an inherently high level of TNF production were more sensitive to the suppressive effects of fish oil on TNF secretion than were persons with an inherently low level of TNF secretion. These data suggest that the ability of omega-3 fatty acids to suppress cytokine secretion may vary with TNF genotypes. Thus, clinical trials of omega-3 PUFA, EPA or fish oil supplements, or any agent that could potentially affect TNF secretion should address this possibility before concluding there was or was not a beneficial effect of the intervention in persons with cancer cachexia.

Data from animal models of tumor growth and cancer cachexia indicate that increased intake of fish oil or omega-3 PUFA produces effects similar to those seen when the animals are treated with NSAIDs. There is reduced tumor growth, reduced metastasis, and reduced angiogenesis in the tumor bed (Mukutmoni-Norris and others 2000; Jho and others 2002; Tevar and others 2002). Some reports also noted preservation of body weight and muscle mass and increased survival in the tumor-bearing animals (Babcock and others 2000; Argiles and others 2001; Tisdale 2001; Hardman and others 2002; Jho and others 2002).

The clinical effects of fish oil supplements or omega-3 PUFA on the signs and symptoms of cancer cachexia have been extensively studied in patients with pancreatic cancer (Wigmore, Barber, and others 2000). Findings include stable or improved body weight and performance status, reduced serum levels of PGE2 and IL-6, and reduced numbers of patients with PIF in the urine (Barber and others 2001). In one study of 60 patients with advanced solid tumor disease, half were categorized as well nourished and half as malnourished. One half of each group was randomly assigned to take an omega-3 supplement, whereas the other half was assigned a placebo. Patients taking the omega-3 supplement had significantly improved performance scores. The well-nourished patients survived significantly longer than the malnourished patients did (418 versus 213 days), and patients taking the omega-3 supplement survived significantly longer than did patients taking placebo (Gogos and others 1998).

Based on the premise that metabolism of AA may be important in the biology of cancer cachexia, conjugated linoleic acids (CLA) are another potential anti-inflammatory nutraceutical. Linoleic acid is a precursor of AA, and CLA refers to naturally occurring isomers of linoleic acid, many of which are found in red meat and dairy products (MacDonald 2000). These isomers, once converted to AA, may be differentially susceptible to enzymatic processing by COX2, which would reduce the synthesis of PGE2. CLA has been shown to suppress the growth of mammary tumor cells in vitro (Cunningham and others 1997; Durgam and Fernandes 1997). The addition of 1% CLA to the diet reduced tumor growth and metastasis in immune-deficient mice inoculated with human breast (Visonneau and others 1997) or prostate tumor cells (Cesano and others 1998). However, others have reported that CLA did not alter tumor growth or signs of cachexia in tumor-bearing rats (McCarthy-Beckett 2002) and mice (Wong and others 1997), although it did reduce the incidence of metastasis in tumor-bearing mice (Hubbard and others 2000). These disparate findings may reflect some variation in the expression of COX2 in the tumor cell lines used in the experiments or in the isomeric mixture of CLA given the tumor-bearing animals. One cautionary report noted that some isomers may have a proinflammatory effect (Riserus and others 2002). Thus, more research is

needed before this over-the-counter nutraceutical is recommended for patients with cancer cachexia.

Plant-Derived Polyphenols

The health benefits of fruits and vegetables are many. Recent research suggests that the polyphenols found in fruits and vegetables may modulate the AA-PGE2 pathway via inhibitory effects on COX2 activity (Cao and others 2002). Polyphenols include the flavonoids found in purple grapes and green tea. A recent study reported that 43% of cancer patients use herbal products, including green tea and grape seed extract (Bernstein and Grasso 2001). There have been no large clinical studies of the effects of these nutraceuticals on the signs or symptoms of cancer cachexia. However, there are several in vitro studies that suggest that polyphenols may slow tumor growth or reduce the synthesis of proinflammatory mediators associated with cancer cachexia (Middleton and others 2000).

Polyphenolic compounds in purple grapes include catechin, resveratrol, and quercetin. Resveratrol was shown to inhibit both COX and LOX activity in cultured epithelial cells (Kim and others 1998), and quercetin inhibited PGE2 synthesis in a tumor cell line (Banerjee and others 2002). Quercetin inhibited expression of IL-1β and TNFα mRNA in murine macrophages exposed to heat-killed bacteria (Svensson and others 1995), and other flavonoid compounds blocked the synthesis of IL-6 and PGE2 in endothelial cells stimulated with IL-1 or TNF (Gerritsen 1998). Resveratrol and quercetin reduced the growth of tumor cell lines in vitro (Guthrie and Carroll 1998; Joe and others 2002), and the combination of the 2 compounds had an additive suppressive effect on cell growth (El-Attar and Virji 1999). Similarly, resveratrol and quercetin inhibited capillary-like tube formation in cultures of bovine aorta endothelial cells (Igura and others 2001). Like NSAIDs, the antiproliferative effects of resveratrol are associated with cell cycle arrest and apoptosis (Carbo and others 1999; Wolter and others 2001; Joe and others 2002).

There are several studies showing that oral administration of resveratrol or extracts of purple grapes reduces tumor growth, tumor angiogenesis, and metastases in tumor-bearing mice (Menon and others 1995; Carbo and others 1999; Caltagirone and others 2000; Brakenhielm and others 2001; Kimura and Okuda 2001). Red wine polyphenols added to the diet of rats treated with a chemical carcinogen resulted in reduced numbers of colon tumors formed and reduced expression of COX2 in the tumors as compared to rats whose diets were not supplemented with the polyphenols (Luceri and others 2002). When given intravenously, resveratrol reduced tumor growth but had "toxic" effects on body weight and food intake of the tumor-bearing animals (Carbo and others 1999). No toxicity has been reported when resveratrol or grape extracts are ingested orally (Freemont 2000). Further studies are needed to determine if the administration of purple grape juice, grape extracts, or purified polyphenolic compounds will reduce the signs and symptoms of cancer cachexia in tumor-bearing animals and clinical patients.

Catechins, which are the predominant anti-inflammatory and anticancer compounds in green tea, are also found in purple grapes and red wine. Several of the catechins have been shown to inhibit COX and LOX activity when added to cultures of human colon tumor cells (Hong and others 2001). Added to cultures of murine macrophages, green tea extract suppressed TNFα gene expression in cells and reduced the synthesis of TNF and IL-1 by alveolar macrophages of mice genetically modified to overexpress TNF (Suganuma and others 2000). Thus, green tea extracts or catechin compounds could potentially alter the course of cachexia by altering the synthesis of proinflammatory cytokines or PGE2.

Other studies suggest that purified catechins, green tea extract, or brewed green tea are all capable of retarding tumor cell growth in vitro and in tumor-bearing rodents. Epigallocatechin-3, the most abundant catechin in green tea, caused cell cycle arrest and apoptosis when added in physiological concentrations to cultures of human squamous carcinoma cells (Masuda and others 2001), human prostate carcinoma cells (Gupta and others 2000), and human colon adenocarcinoma cells (Salucci and others 2002). Similarly, epigallocatechin has been shown to reduce cell growth and secretion of angiogenic factors when added to cultures of breast cancer cells (Sartippour and others 2002). These authors had previously reported that mice implanted with this tumor cell line and given green tea extract had smaller tumors with less vessel density (Sartippour and others 2001). Similar findings

were reported when mice implanted with a human colon cancer cell line were given epigallocatechin (Jung and others 2001). Green tea in the drinking water of mice was also shown to suppress tumor growth (Zhu and others 1999).

In a series of experiments, one group showed that green tea extract suppressed in vitro growth of 2 tumor cell lines to levels seen when purified catechin compounds were added to the cell cultures (Zhang and others 2000). Of greater note was the observation that serum taken from rats given green tea extract by gastric gavage also suppressed growth when added to cultures of the tumor cell lines. Thus, biologically active levels of the antiproliferative factors in the extract were absorbed from the gastrointestinal tract in sufficient amount and form to be biologically active in the serum of mice given the green tea extract by gastric gavage. To date, no one has examined the effects of green tea, green tea extracts, or catechins on the signs and symptoms of cancer cachexia or serum levels of proinflammatory mediators in tumor-bearing animals or cancer patients. However, a phase 1 clinical trial found that a green tea extract containing the equivalent of 8 cups of tea induced caffeine-related toxicities that required discontinuation of the extract (Pisters and others 2001). Thus, further studies of the dosing of green tea versus green tea extracts are needed before clinical trials of these agents can be undertaken in cancer patients.

Antioxidants

Flavonoids in fruits and vegetables and catechins in green tea are best known for their antioxidant activity (Cai and others 1997; Salucci and others 2002). Antioxidants act as scavengers that inactivate the reactive oxygen species (ROS), which all cells produce as a byproduct of metabolism and oxidative phosphorylation in the mitochondria. As free radicals, ROS have the potential to damage proteins, DNA, and lipids in the cell. In fact, phagocytes release ROS in the process of destroying invading pathogens, and inappropriate release of ROS by these cells contributes to the pathology of many chronic inflammatory disorders. Inside the cell, ROS induce the release of AA from cell membranes (McIntyre and others 1999) and act as intracellular messengers to increase the synthesis of COX2, TNFα, IL-1, and IL-6 (Conner and Grisham 1996; Schulze-Osthoff and others 1997; Pearlstein and others 2002). TNF and PGE2 in turn increase the production of ROS, making ROS very effective mediators of the acute inflammatory response (see Fig. 3).

Production of ROS parallels the metabolic rate and is increased with hypoxia (Pearlstein and others 2002; Warnholtz and others 2002). Resting energy expenditure is increased with tumor growth (Boseaus and others 2001), and oxidative stress occurs when the oxygen demands of the growing tumor outpace the growth of blood vessels to the tumor (see Fig. 2). Progressive tumor disease is associated with increased cell and plasma markers of oxidative stress (Mantovani and others 2002) and depletion of tissue and plasma antioxidants in patients with non-small-cell lung cancer (Talwar and others 1997) and other solid tumors (Abiaka and others 2001; McMillan and others 2002). Some of this may be due to reduced dietary intake of fruits and vegetables rich in vitamin antioxidants or to the method used to measure antioxidant levels in tissue or plasma (Lunetta and others 2002). However, treatment with 1200 mg ibuprofen daily for 14 days improved serum levels of antioxidants in patients with gastrointestinal tumors, suggesting that COX activity may influence circulating levels of antioxidants as much as reduced dietary intake (McMillan and others 2000).

The best-known diet-derived antioxidants are vitamin E (α-tocopherol), vitamin A (retinoic acid), vitamin C (ascorbic acid), and the carotenoids lutein, lycopene, and betacarotine. Retinoic acid was shown to reduce the synthesis of TNF in cultures of murine macrophages (Mehta and others 1994) and to reduce the synthesis of COX2 in cultures of human epithelial cells (Subbaramaiah and others 2002) and esophageal cancer cells (Li and others 2002). Macrophages from mice given supplemental amounts of vitamin E produced significantly less PGE2 when stimulated ex vivo (Wu and others 1998). Others observed that pretreatment with vitamin E prevented weight loss and muscle wasting in mice injected with TNF (Buck and Chojkier 1996). Similarly, pretreatment with vitamin E reduced serum levels of TNF and IL-6, blunted anorexia and weight loss, and enhanced survival in mice infected with influenza (Han and others 2000). Finally, there is in vitro evidence that antioxidant treat-

ment of hypoxic endothelial cells reduces release of IL-6 from the cells (Pearlstein and others 2002). It is exciting to hypothesize that administration of antioxidants to cancer patients could alter the synthesis or activity of these proinflammatory cytokines and thus reduce the signs and symptoms of cachexia (Connor and Grisham 1996; Meydani 2001).

In a series of experiments using pharmacological antioxidants, Chinery and others (1998) demonstrated that antioxidants decreased in vitro growth and COX2 expression in a human tumor cell line. Combination of an antioxidant with an NSAID produced an additive suppressive effect on cell growth and PGE2 synthesis. Treatment of tumor-bearing mice with the same antioxidants reduced growth of this tumor cell line in vivo, and treatment with an antioxidant and an NSAID resulted in tumor regression. To date, no one has examined whether antioxidant treatment will alter serum PGE2 or IL-6 levels or improve body weight or food intake in tumor-bearing mice or cancer patients.

Although it is only speculative, the combination of antioxidants and omega-3 PUFA might have greater effects on the signs of cancer cachexia than either nutraceutical alone. One group reported that administration of fish oil in the diet improved body weight and food intake in tumor-bearing mice; food intake and body weight in animals given the fish oil and supplemental amounts of vitamin E and C were no different from animals given the fish oil alone (Yam and others 2001). However, tumor mass was larger in the animals given the vitamins and fish oil as compared to animals given the fish oil alone. These data suggest that oxidation of the omega-3 PUFA was important in the growth-inhibitory effects of the fish oil (Cognault and others 2000; Yam and others 2001). Conversely, the effectiveness of chemotherapy, in terms of reduced tumor growth and increased life span in tumor-bearing mice, was enhanced by the combination of dietary fish oil and vitamin E (Yam and others 2001; Liu and Tan 2002). Further studies exploring potential interactions between omega-3 PUFA/fish oil and vitamin antioxidants in the context of tumor growth and cancer cachexia are clearly needed. Others are currently examining whether antioxidants will reduce the symptoms experienced by cancer patients during chemotherapy (Mantovani and others 2001).

Summary

Obviously, the best treatment for cancer cachexia is eradication of the malignancy. However, patients with progressive, recurrent, or metastatic disease often have tumors that are resistant to treatment, and these are the patients that most often develop cancer cachexia. Some tumors express high levels of COX2, which may give the cells a survival advantage for growth, metastasis, and angiogenesis. The development of cancer cachexia appears to be related to COX activity because drugs that block COX activity reduce tumor growth in animals and reduce in vitro synthesis of cytokines and prostanoids implicated in the signs and symptoms of cachexia. This body of literature also suggests that cancer cachexia is a chronic inflammatory condition rather than a nutritional aberration. Hence, we may need to expand the concept of nutritional support of cancer patients to include nutritional strategies to alter the synthesis or activity of proinflammatory mediators.

Several diet-derived factors have come to be regarded as nutraceuticals because they mimic the biological effects of pharmacological agents. Several of these are relevant to the treatment of cancer cachexia because they can reduce the synthesis or activity of proinflammatory mediators. EPA and other omega-3 PUFA in fish oil substitute for AA in the cell membrane, reducing cell synthesis of PGE2. Both EPA and fish oil supplements have shown promising effects in animal models of cancer cachexia and in clinical trials with cancer patients.

A large percentage of cancer patients take over-the-counter plant extracts and vitamin supplements containing polyphenols and antioxidants. Many of the compounds in these dietary supplements have anti-inflammatory activity. Clinical trials examining the effects of these compounds on the signs and symptoms of cancer cachexia are sorely needed. Animal models are an excellent way to develop preclinical data for subsequent clinical trials of these agents in the management of cancer cachexia. Nurses in clinical practice or clinical research settings are in an excellent position to pursue this area of research. Data regarding patient use of such compounds may be already available in ongoing clinical trials or could be incorporated

into the nutritional assessment of patients for later analysis of clinical responses to cancer treatment protocols. Finally, because so many cancer patients do take these compounds, it is important that nurses be aware of scientific studies to evaluate the efficacy of these compounds in the management of cancer cachexia.

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