THE ROLE OF LONG-CHAIN POLYUNSATURATED FATTY ACIDS IN THE TREATMENT OF CANCER CACHEXIA AND TUMOUR GROWTH IN PATIENTS WITH MALIGNANT DISEASES: A REVIEW

Elizabeth A Symington
BSc Dietetics
Junior Lecturer, Department of Life and Consumer Sciences, University of South Africa
Corresponding author: syminea@unisa.ac.za

Gerda J Gericke
M Dietetics
Head: Division of Human Nutrition, University of Pretoria

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ABSTRACT

Recent studies show that ω-3 polyunsaturated fatty acids (PUFAs) have the capacity to modulate cancer outcomes. The body responds to cancer in the same way that it responds to inflammation and wound healing. Nutrients with anti-inflammatory effects could therefore be expected to play a role in cancer treatment.

This review focuses on the role of ω-3 PUFAs in tumourigenesis and cancer cachexia. Studies indicate that eicosapentaenoic acid (EPA) supplementation may promote arrest of tumour growth and reduce cell proliferation. Patients need to consume at least 2 g of EPA per day for it to have a therapeutic effect. Positive outcomes related to cachexia include diminished weight loss, increased appetite, improved quality of life and prolonged survival, although there is controversy regarding these clinical outcomes.

The effects of ω-3 PUFAs on tumourigenesis and cachexia are viewed in the context of altered lipid and protein metabolism. This altered metabolism usually experienced by cancer patients results in increased formation of pro-inflammatory eicosanoids and cytokines. Cytokines play an indirect role by stimulating the production of arachidonic acid-derived eicosanoids, which support inflammation, cell proliferation and angiogenesis, and inhibit apoptosis. It can be concluded that ω-3 PUFA supplementation offers a means of augmenting cancer therapy, inhibiting tumourigenesis and possibly contributing to cachexia alleviation.

OPSOMMING

Onlangse studies toon dat ω-3-poli-onversadigde vetsure (POVSe) oor die vermoë beskik om kankeruitkomste te moduleer. Die liggaam reageer op kanker op dieselfde wyse as wat dit op inflammasie en wondgenesing reageer. Daar kan dus verwag word dat voedingstowwe met 'n anti-inflammatoriese uitwerking 'n rol in die behandeling van kanker kan speel.

In hierdie oorsig word daar op die rol van ω-3-POVSe in tumorigenese en kankerkageksie gefokus. Studies dui daarop dat eikosapentanoënsuur- (EPS-)aanvulling tumorgroei moontlik kan stuit en selproliferasie verlaag. Pasiënte moet minstens 2 g EPS per dag inneem om 'n terapeutiese uitwerking te verseker. Positiewe uitkomste verbonde aan kageksie sluit minder gewigsverlies, beter eetlus, beter lewensgehalte en langer oorlewing in, hoewel daar 'n geskil bestaan oor hierdie kliniese uitkomste.

Die uitwerking van ω-3-POVSe op tumorigenese en kageksie word in die konteks van gewysigde lipied- en proteïenmetabolisme beskou. Die metabolisme wat dikwels in kankerpasiënte voorkom, lei tot 'n verhoogde vorming

van pro-inflammatoriese eikosanoïede en sitokiene. Sitokiene speel ook 'n indirekte rol deur die produksie van aragidoonsuurafkomstige eikosanoïede te stimuleer. Laasgenoemde ondersteun inflammasie, selproliferasie en angiogenese, en inhibeer apoptose. Die gevolgtrekking kan gemaak word dat ω-3-POVS-aanvulling 'n manier is om kankerterapie uit te brei, tumorigenese te inhibeer en moontlik tot die verligting van kageksie by te dra.

INTRODUCTION

Nutrition intervention and research have evolved from preventive and supportive practices towards therapeutic practices, especially in cancer treatment. Studies from the past two decades have shown that ω-3 polyunsaturated fatty acids (PUFAs) have the capacity to modulate the outcomes of cancer, as opposed to the prevalent hypothesis that all PUFAs, and ω-6 PUFA in particular, promote the development and enhance the growth of tumours (Rose & Connolly, 1990:7139-7143; Abou-El-Ela, Prasse, Farrell, Carroll, Wade & Bunce, 1989:1434-1439; Reddy & Sugie, 1988:6642; Begin, Ells, Das & Horrobin, 1986:1053; Carroll, 1975 *in* Karmali, 1996:S2). The response of the body to cancer shows similarities to the inflammatory response and wound healing (Balkwill & Mantovani, 2001:539). Thus, it could be reasoned that nutrients that have anti-inflammatory effects could play a role in cancer treatment.

This review will focus on two effects of ω-3 PUFAs in cancer, namely suppressing tumourigenesis and alleviating cancer cachexia. Dietary supplementation with the ω-3 long-chain PUFAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), shows various beneficial effects in cancer patients. Outcomes regarding tumourigenesis indicate that EPA supplementation results in arrest of tumour growth and reduces cell proliferation (Kelavkar, Hutzley, Dhir, Kim, Allen & McHugh, 2006:121; Stehr & Heller, 2006:4; Vang & Ziboh, 2005:363; Hardman, 2004:3427S; Karmali, 1996:S2). Reported positive outcomes related to cachexia include diminished weight loss, increased appetite, improved quality of life and prolonged survival in weight-losing cancer patients (Fearon, Von Meyenfeldt, Moses, Van Geenen, Roy, Gouma, Giacosa, Van Gossum, Bauer, Barber, Aaronson, Voss & Tisdale, 2005:1479; Barber, Ross & Fearon, 1998:118; Wigmore, Ross, Falconer, Plester, Tisdale, Carter & Fearon, 1996:S27). Recently, in vitro and animal studies have elucidated some of these antiproliferative and anticachectic mechanisms, which are part of the wide range of biological effects produced by ω-3 PUFAs (Hardman, 2004:3427S; Barber *et al*. 1998:571-572).

The effects of EPA and DHA on tumourigenesis and cachexia will be discussed from two perspectives, namely altered lipid metabolism and altered protein metabolism. An altered lipid metabolism in cancer includes the increased formation of pro-inflammatory metabolites in fatty acid metabolism. It results in increased lipid mobilisation, lypolysis and oxidation of free fatty acids; hypertriglyceridaemia; decreased lipogenesis; reduced plasma levels of nutrient-carrying phospholipids; and reduction in total body fat (Pratt, Watanabe, Bruera, Mackey, Clandinin, Baracos & Field, 2002:1375; Zuijdgeest-Van Leeuwen, Dagnelie, Wattimena, Van den Berg, Van der Gaast, Swart & Wilson, 2000:417; Barber *et al*. 1998:571). Two causal factors in cancer patients, other than the increased formation of pro-inflammatory metabolites, include the weakened activity of lipoprotein lipase and a lipid-mobilising factor that induces lipolytic activity and therefore induces lipolysis (Zuijdgeest-Van Leeuwen *et al*. 2000:417).

The second perspective is an altered protein metabolism. The balance between proteolysis and proteosynthesis is altered in malignant diseases (Uomo, Gallucci & Rabitti, 2006:158). This change is driven by the activation of the typical response to trauma (metabolic response) which is a systemic inflammatory reaction (Arends, Bodky, Bozzetti, Fearon, Muscaritoli, Selga, Van Bokhorst, Van der Schuren, Van Meyenfeldt, Zurcher, Fietkau, Aulbert, Frick, Holm, Kneba, Mestrom & Zander, 2006:248). This response involves, inter alia, synthesis of acute-phase proteins, hormonal responses, immune responses, increased energy expenditure and protein catabolism (Uomo *et al*. 2006:158; Barber *et al*.1998:571). Typical effects are increased insulin secretion, resulting in increased gluconeogenesis and suppression of ketogenesis from fat stores. These outcomes mediate muscle catabolism, resulting in the typical wasting associated with cachexia (Frankmann, 2000:874-5; Barber *et al*.1998:571). Furthermore, the

increased acute-phase protein synthesis is sustained by amino acids retrieved from skeletal muscle breakdown. This also contributes to the typical cachexia characteristic, namely the loss of lean body mass (Uomo *et al*. 2006:158).

This continuous metabolic response also results in increased numbers of immunological factors such as the cytokines interleukin-1, (IL-1), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-á) (Babcock, Helton & Espat, 2000:1116; Wigmore, Fearon, Maingay & Ross, 1997:218). These cytokines are associated with the stimulation of hepatic amino acid uptake and protein synthesis (usually of positive acute-phase proteins), accelerated muscle breakdown and the induction of gluconeogenesis (Balkwill & Mantovani, 2001:540; Winkler & Manchester, 2000:725). For these reasons the cytokines are regarded as the driving force behind cancer cachexia. The direct source of the cytokines during cancer cachexia is not clearly defined. It is postulated that tumour cells may synthesise them or that the immune system reacts to the tumour by producing these cytokines from mononuclear cells. Thus, the acute-phase response to the cancerous invasion could also be considered to be a contributor to the formation of cytokines (Barber *et al*. 1998:572).

The aim of this review is to accentuate the interrelation between factors mediating tumourigenesis and cancer cachexia (lipid and peptide inflammatory mediators), and the anti-inflammatory properties of ω-3 PUFAs. The essential mechanisms responsible will also be discussed briefly.

In order to understand some of the mechanisms through which ω-3 PUFAs exert their protective and anti-inflammatory effects, it is necessary to understand the metabolism of PUFAs.

FATTY ACID METABOLISM

Fatty acids consist of hydrocarbon chains with a carboxyl and methyl group at each end. The degree of saturation of the carbon atoms with hydrogen atoms is responsible for the type of fatty acid. Fully saturated carbon atoms in a carbon chain present a saturated fatty acid, whereas single or several unsaturated carbons with double bonds between carbon atoms present monosaturated and polyunsaturated fatty acids, respectively (Ettinger, 2000:47). There are two distinctly different groups of PUFAs: (i) the ω-6 PUFAs, in which the first double bond is between the sixth and seventh carbon atoms of the carbon atom chain - always counted from the methyl end of the carbon chain molecule; and (ii) the ω-3 PUFAs, in which the first double bond is located between the third and fourth carbon atoms (Hardman, 2004:3427S).

When considering the metabolism of fatty acids in mammalian cells, it is important to note that these cells contain enzymes for the biosynthesis of fatty acids. These enzymes include desaturases, which, during fatty acid synthesis, desaturate the structure of the fatty acid by inserting double bonds between two carbon atoms, alternating with elongase enzymes, which lengthen the fatty acid structure by adding carbon atoms (Larsson, Kumlin, Ingelman-Sundberg & Wolk, 2004:936; James, Gibson & Cleland, 2000:343S). The 18 carbon chain PUFAs α-linolenic acid and linoleic acid, ω-3 and ω-6, respectively, are essential to humans and cannot be synthesised by mammalian cells (James *et al.*, 2000:343S). Even so, these fatty acids can be desaturated and elongated by enzymes to form longer chain PUFAs (Larsson *et al*. 2004:936) (see Figure 1). The same desaturase and elongase enzymes are used for the synthesis, desaturation and elongation of various fatty acids, causing competition for these enzymes between the metabolic pathways (see Figure 1) (Stehr & Heller, 2006:2).

As is evident from Figure 1, the long-chain ω-3 fatty acids, EPA and DHA, can be formed by elongation and desaturation from α-linolenic acid. Currently it is not clear how important this pathway is in humans (Hardman, 2004:3427S). Thus the consumption of EPA and DHA remains essential. The richest dietary sources of EPA and DHA are fatty fish such as mackerel, herring, salmon, sardines, pilchards and kippers. DHA is also included in animal feeds to develop ω-3-enriched egg, milk and meat products (Ettinger, 2000:47).

Owing to the competition between α-linolenic acid and linoleic acid for the desaturation and chain elongation enzymes, the incorporation of α-linolenic acid into plasma and tissue lipids and its conversion to long-chain ω-3 PUFAs are influenced by linoleic acid levels and vice versa. The typical Western diet contains 20 to 25 times more ω-6 than ω-3 fatty acids, leading to a

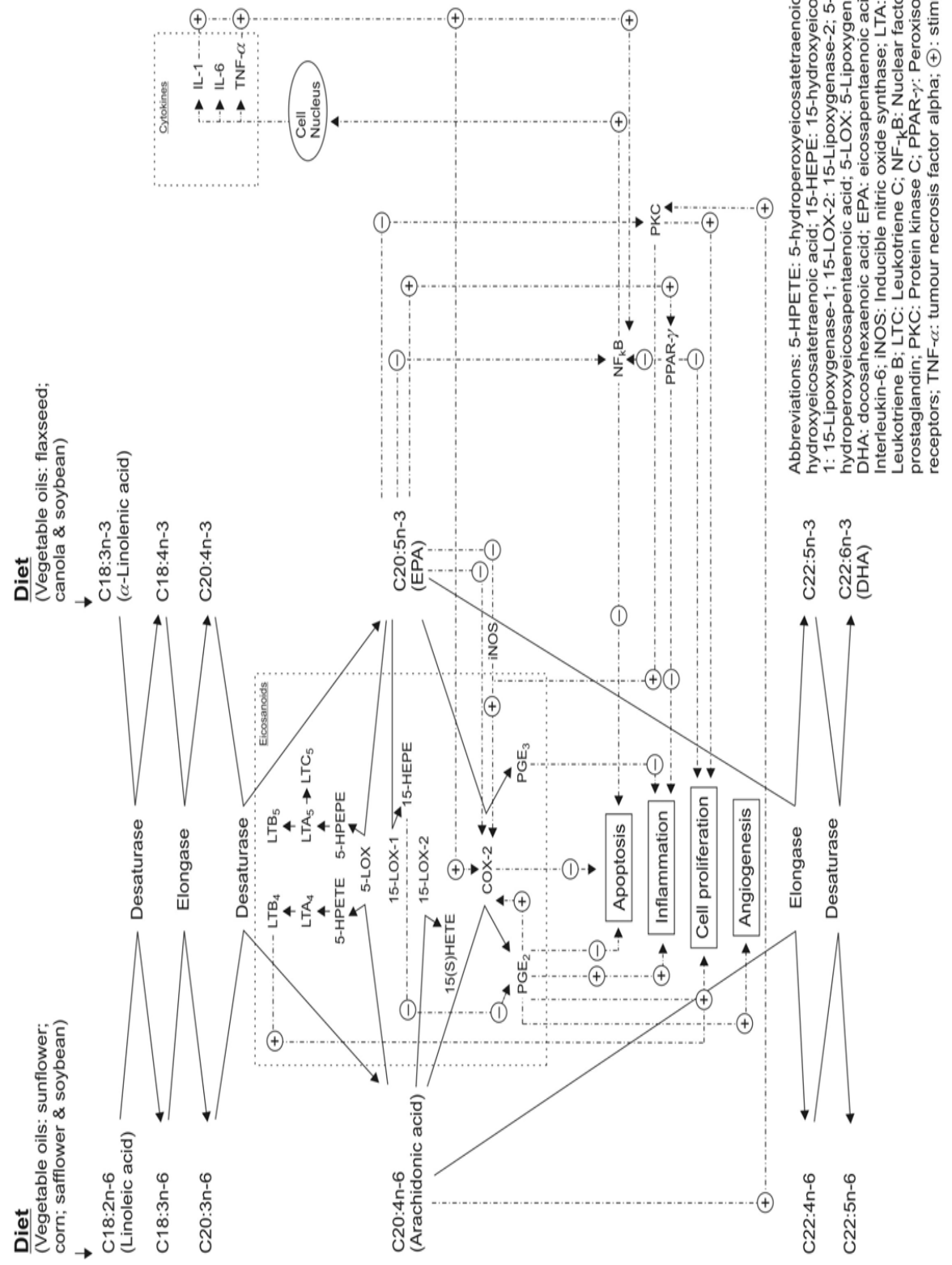

Figure 1: Metabolic pathway of ω-6 linoleic acid and ω-3 α-linolenic acid and the effects of the eicosanoids on other factors related to cancer (Larsson *et al.* 2004; Trifan & Hla, 2003; Hardman, 2002; Wallace, 2002; Ziboh *et al.* 2000)

skewed balance between these types of PUFAs (Ettinger, 2000:47; James *et al*. 2000:346S).

As mentioned in the introduction, the metabolites created in this chain desaturation and elongation pathway also play a role in the human body. The metabolism of the 20 carbon chain PUFAs (EPA and arachidonic acid) leads to the creation of the metabolites named eicosanoids, that is cell-signalling hormone-like compounds (Hardman, 2002:3508S; Wallace, 2002:7). The eicosanoids produced consist mainly of three general groups, namely prostanoids (due to the enzyme cyclooxygenase (COX) activity), leukotrienes (due to enzymes of the lipoxygenase family (LOX)) and thromboxanes (also due to COX activity) (see Figure 1) (Stehr & Heller, 2006:3; Ziboh, Miller & Cho, 2000:362S). Two distinct isoforms of COX have been discovered, namely COX-1 and COX-2. COX-1 is constitutively expressed and is cytoprotective. COX-2 is inducible and expressed primarily following inflammatory insult (Wallace, 2002:7; Williams, Mann & Dubois, 1999:7914).

The eicosanoids produced from arachidonic acid in the ω-6 fatty acid pathway are the 2-series prostanoids (thromboxane A_2, prostaglandin E_2 and prostacyclin$_2$) and the 4-series leukotrienes (leukotriene B_4 and leukotriene C_4) (Stehr & Heller, 2006:3). In the ω-3 fatty acid pathway EPA is metabolised into 3-series prostanoids and 5-series leukotrienes. The 5-series leukotrienes derived from EPA cause less of an inflammatory response than the 4-series from arachidonic acid (Ali & Roberts, 2006:136). Therefore, with a ratio of leukotrienes in favour of the 5-series, the result is a suppressed immune response, or in other words an anti-inflammatory effect. Prostanoids have pro-inflammatory and pro-proliferative effects in some tissues and are responsible for vasodilation, platelet aggregation and pain. The 2-series prostanoids synthesised from arachidonic acid are more active than the 3-series from EPA (Ali & Roberts, 2006:136; Hardman, 2004:3428S; James *et al*. 2000:344S). Again, a ratio favouring the eicosanoids from EPA results in anti-inflammatory outcomes.

It is postulated that the lipid inflammatory mediators, namely eicosanoids, play a role in tumourigenesis and cachexia, with either positive or negative outcomes, depending on which 20 carbon fatty acid is the source. The following sections discuss the role of PUFAs and their metabolites (lipid inflammatory mediators) in tumourigenesis and cachexia, as well as where peptide inflammatory mediators fit in.

MECHANISMS AND EFFECTS OF PUFAs IN CANCER

The main nutritional goals in diagnosed cancer are to suppress tumourigenesis and improve quality of life (Argilés, 2005:S45). Supplementing the diet of the cancer patient with ω-3 PUFAs has shown promising effects (Kelavkar *et al*. 2006:121; Vang & Ziboh, 2005:363; Hardman, 2004:3427S; Karmali, 1996:S2).

Tumourigenesis

Pharmacological agents can inhibit arachidonic acid metabolism, resulting in inhibition of the growth of carcinogen-induced and transplanted tumours. Animal studies have identified the tumour growth-suppressing effect of ω-3 PUFA-enriched diets in mouse model systems (Rose & Connolly, 1993:1743). Human studies have shown similar effects from the administration of ω-3 compared with ω-6 PUFAs. Supplementation led to a consistent significant inhibition of proliferation in each of the in vitro and animal tumour models studied and to impeded tumour growth (Kelavkar *et al*. 2006:121; Vang & Ziboh, 2005:363; Hardman, 2004:3427S; Karmali, 1996:S2). Kelavkar *et al.* (2006:121) made it clear that a mixture of DHA and EPA was a more effective non-toxic in vitro growth inhibitor than EPA alone.

The first approach in elucidating the inhibiting role of ω-3 PUFAs involves considering mitosis in tumour growth. Protein kinase C (PKC), activated by, inter alia, linoleic acid and arachidonic acid (both ω-6 fatty acids) and increased during the acute-phase response, induces mitosis, and therefore also growth of the tumour (Blobe, Obeid & Hannun, 1994:411), and is possibly responsible for the direct regulation of COX enzymes (Trifan & Hla, 2003:209). EPA and DHA appear to reverse the PKC activity. Also, although much more research is necessary in this area, the oncogenes, such as Ras, c-myc and AP-1, have been shown to stimulate mitosis and play a role in proliferation regulation in animal models (Hardman, 2002:3510S; Collett, Davidson, Fan,

Lupton & Chapkin, 2001:C1066; Liu, Bibus, Bode, Ma, Holman & Dong, 2001:7510-7515; Schwartz, Hernandez & Evers, 1999:145). Omega-3 fatty acids have been shown to decrease the activity of these oncogenes (Stehr & Heller, 2006:4; Larsson *et al*. 2004:939; Hardman, 2002:3510S). DHA appears to have a greater effect than EPA when considering AP-1 (Liu *et al*. 2001:7510). Wang, Liu, Ni, Aygun, Goldberg and Shi (2000:6486) also demonstrated tumour growth inhibition in DHA-treated human breast cancer cells proportional to the expression of the mammary-derived growth inhibitor-related gene. They postulate that the growth-suppressing activity of DHA in breast cancer cells may be mediated in part by this gene and that it may predict tumour-suppressive response to ω-3 PUFAs, which warrants further investigation.

Secondly, the competition between ω-3 PUFAs and linoleic acid and arachidonic acid for the enzymes 15-LOX-1 and COX-2 has been shown to influence tumour growth. 15-LOX-1 metabolises EPA to form 15-hydroxyeicosapentaenoic acid (15-HEPE), a metabolite shown to have antitumourigenic properties as it inhibits prostaglandin E_2 generation (Vang & Ziboh, 2005:364). On the other hand, it has been indicated that COX-2 is overexpressed in cancer patients (Stehr & Heller, 2006:4; Bing, Miyataka, Rich, Hanson, Wang, Slosser & Shi, 2001:3385; Williams *et al*. 1999:7908), leading to the production of pro-inflammatory prostaglandins (for example, prostaglandin E_2) which support cell proliferation (Kelavkar *et al*. 2006:113; Vang & Ziboh, 2005:364; Wallace, 2002:14; James *et al*. 2000:343S). Further, increased LOX products generated from arachidonic acid, such as leukotriene B_4, augment metastatic potential and tumour promotion (Larsson *et al*. 2004:937; Abou-El-Ela *et al*. 1989:1493), but if the ω-6:ω-3 ratio tends towards ω-3, COX-2 and LOX metabolise EPA to the anti-inflammatory and antitumourigenic prostaglandin E_3 and leukotriene B_5. Thus, the competition for these enzymes results in two positive outcomes when the ratio tends towards ω-3: it not only decreases the production of protumourigenic metabolites from the ω-6 fatty acid pathway, but may also result in increased production of antitumourigenic metabolites (Kelavkar *et al*. 2006:113; Larsson *et al*. 2004:938).

The third approach concerns the apoptotic pathways (for example, the programmed cell death). With optimally functioning apoptotic pathways, cells with irreparable genetic damage are destroyed. However, in cancers these pathways are frequently disrupted, promoting proliferation of dysfunctional cells. The overexpressed COX-2 (Bing *et al*. 2001:3388) and nuclear factor kappa B (NF-κB) (acute-phase protein) have been shown to block or suppress apoptosis (Trifan & Hla, 2003:208; Wallace, 2002:14; Narayanan, Narayanan & Reddy, 2001:1255), and NF-κB, specifically, plays a role in tumour growth (Larsson *et al*. 2004:937). Thus, reduced activation and down-regulation of COX-2 and NF-κB by ω-3 PUFAs would be expected to restore apoptosis (Stehr & Heller, 2006:4; Larsson *et al*. 2004:940; Hardman, 2002:3511S). One pathway of down-regulation can be described by the fact that EPA increases the activity of peroxisome proliferator activated receptors (PPAR-γ). PPAR-γ is involved in cell proliferation, cell differentiation and inflammatory responses through gene transcription (Vang & Ziboh, 2005:367). EPA is one of the natural agonists of PPAR-γ and has been found to have antiproliferative effects (Larsson *et al*. 2004:937). Upon activation, PPAR-γ has been shown to inhibit specific DNA synthesis, including that for NF-κB, and thus to suppress cancer growth in several tissues (Stehr & Heller, 2006:4; Vang & Ziboh, 2005:371; Schwartz *et al*. 1999:147). On the other hand, Narayanan *et al.* (2001:1255) have indicated that DHA itself alters the expression of PPAR-γ in human colon cancer cells and seems to show a lipid peroxidation-induced apoptosis. Although Schwartz *et al.* (1999:143-151) identified NF-κB as a potential molecular target for novel anticancer therapies, they did not list ω-3 PUFAs under inhibitors of NF-κB, but rather proteasome inhibitors, antioxidants, anti-inflammatory drugs, synthetic peptides etc.

Another pathway for down-regulating one of these apoptotic inhibitors is the competition between ω-3 PUFAs and linoleic acid and arachidonic acid pathways for the enzymes used, including COX-2 (Kelavkar *et al*. 2006:121). Kelavkar *et al.* demonstrated that increased apoptosis occurred in tumours of mice fed a diet of ω-3 PUFAs versus tumours of mice fed a diet of ω-6 PUFAs for 15 weeks.

Fourthly, angiogenesis supports tumour growth. New vessel formation is stimulated and regulated by a variety of peptides produced by tumour cells as well as by host inflammatory cells (Vang & Ziboh, 2005:363; Bing *et al*. 2001:3385-6). Firstly, PKC is a peptide inflam-

matory mediator supporting angiogenesis. Fish oil supplementation indicates that hormone-mediated activation of PKC can be inhibited (McCarty, 1996:110). It is predicted that PKC suppression will lead to a reduction in (i) the ability of mononuclear cells to infiltrate tumours and elaborate angiogenic factors; (ii) the responsiveness of endothelial cells to angiogenic stimuli; and (iii) the ability of cancer cells to secrete collagenase, thus limiting their metastatic potential (Vang & Ziboh, 2005:370; McCarty, 1996:110-111). Other peptide inflammatory mediators, namely TNF-á, IL-1 and IL-6, are able to stimulate production of angiogenic factors (Balkwill & Mantovani, 2001:542), thereby supporting tumour growth. It is well documented that inclusion of ω-3 PUFAs in the diet can suppress the production of both TNF-á and IL-1 (James *et al*. 2000:345S). Apart from the peptide inflammatory mediators mentioned previously, COX-2 also plays an important role in promoting angiogenesis in cancer as it supports prostaglandin E_2, which is the promoting factor (Wallace, 2002:14; Bing *et al*. 2001:3385). Again, with increased ω-3 PUFAs, COX-2 would support the formation of prostaglandin E_3 and therefore suppress the production of prostaglandin E_2.

Another factor that plays a role in the formation of new vessels is nitric oxide (activated by inducible nitric oxide synthase). Nitric oxide also activates COX-2, thus producing more eicosanoids (Larsson *et al*. 2004:938; Bing *et al*. 2001:3385). It has been confirmed that nitric oxide plays a role in tumour angiogenesis (Bing *et al*. 2001:3385). The suppression of nitric oxide production would therefore suppress this supportive action of tumour growth. Inducible nitric oxide synthase can be down-regulated by ω-3 PUFAs (Stehr & Heller, 2006:4; Larsson *et al*. 2004:983).

It should be noted that the above areas of action for ω-3 PUFAs have been described in a simplified form in order to reach a conclusion on the overall effect of supplementation in cancer patients. Although some of the mechanisms could be elucidated to some extent, the clinical implications for tumourigenesis need further research.

Cachexia

Although the outcomes of ω-3 PUFA supplementation appear promising in relation to tumourigenesis, the outcomes are controversial regarding cachexia. Cachexia can be characterised by anorexia, early satiety, changes in taste perception, weight loss, weakness, anaemia and oedema - all affecting appetite and diet (Uomo *et al*. 2006:157). There is an association between advanced cachexia and a shorter survival time as well as poor quality of life (Barber *et al*. 1998:571). Generally, administration of nutritional support does not attenuate the problem (Fearon *et al*. 2005:1479; Zuijdgeest-Van Leeuwen *et al*. 2000:417). In one specific study, however, pancreatic cancer patients with cachexia receiving an energy and protein supplement in conjunction with 2.2 g of EPA plus 0.96 g of DHA per day gained weight and showed improved quality of life after eight weeks, whereas the control group receiving the same supplement without the EPA and DHA had significantly lower weight gains (Moses, Slater, Pretson, Barber & Fearon, 2004:999). On the other hand, Fearon *et al.* (2005:1483) also supplemented human subjects in a double-blind controlled trial for eight weeks with an energy and protein supplement that included EPA but at a level of 1.5 g of EPA per day. This resulted in the arrest of further loss of both weight and lean tissue in both the control and the experimental groups, but no net gain of lean body mass was observed. The team nevertheless wanted to determine whether there was a dose-effect relationship within the present study and conducted a post hoc series of correlation analyses. In the experimental group the analyses demonstrated a significant positive correlation between intake of the supplement and gain in either body weight or lean body mass and improved quality of life. Furthermore, this correlation between supplement intake and increase in lean body mass was significantly different between the experimental and control group. It is worth mentioning that although lean body mass was influenced, the median survival of all patients (experimental and control) from the time of enrolment was 130 days. Thus, the effect of ω-3 supplementation and survival time needs further investigation. Bruera, Strasser, Palmer, Willey, Calder, Amyotte and Baracos (2003:129) did not obtain promising outcomes when supplementing advanced cancer patients with 1.8 g of EPA and 1.2 g of DHA per day for two weeks. They found no significant influence on appetite, tiredness, nausea, wellbeing or nutritional status.

The loss of lean body mass is one of the factors in cachexia that causes the most concern, and amelioration of weight loss in cancer patients is crucial. The effects of ω-3 PUFA supplementation on cancer patients suggest a potential role for EPA in the clinical management of these patients (Barber *et al*. 2001:118; Babcock *et al*. 2000:1116). Although Bruera and colleagues (2003:133) did not find an improvement in body mass, they stated that a treatment period of two weeks might not be sufficient. Thus, the possible role of ω-3 PUFAs in lean body mass is acknowledged. The mechanisms that could explain this effect will be discussed in the following sections.

Pro-inflammatory cytokines (peptide inflammatory mediators) have been identified as one of the main driving forces behind cancer cachexia, and are considered to be both tumour and host derived (Uomo *et al*. 2006:157; Argilés, 2005:S39; Fearon *et al*. 2005:1479). Pro-inflammatory cytokines, including TNF-α, IL-1 and IL-6, are secondary pathway mediators of the multistep cascade that controls the response to an inflammatory stimulus such as malignancy. For example, cytokines activate NF-κB (Schwartz *et al*. 1999:143), which in turns inhibits apoptosis. Elevated serum levels of TNF-α and IL-6 in cancer patients (Barber *et al*. 1998:572) have been found to lead to a hypermetabolic state and increased hepatic acute-phase response (Espat, Auffenberg, Rosenberg, Rogy, Martin, Fang, Hasselgren, Copeland & Moldawer, 1996:R185). Long-lasting production and release of pro-inflammatory cytokines result in metabolic abnormalities, all of which contribute to the syndrome of cachexia (Babcock *et al*. 2000:1116; Hardman, 2002:3509S). Barber, Fearon, Tisdale, McMillan and Ross (2001:118) demonstrated a significant fall in IL-6 production after three weeks of 2 g of EPA per day in weight-losing pancreatic cancer patients in association with weight gain.

Cytokines can also stimulate the production of arachidonic metabolites (lipid-derived mediators), such as prostaglandins, prostacyclins and thromboxanes, which are important in the inflammatory and tissue-damaging actions of these cytokines (Figure 1) (Karmali, 1996:S2). Therefore, the effects of the lipid (fatty acid metabolites) and peptide (cytokines) inflammatory mediators cannot be considered individually. The ω-6-derived mediator prostaglandin E_2 generally has pro-inflammatory properties. Even so, it also moderately suppresses production of the pro-inflammatory cytokines TNF-α and IL-1 (Caughey, Mantzioris, Gibson, Cleland & James, 1996:120). Considering these facts, ω-3 fatty acid metabolites, especially prostaglandin E_3 with less marked pro-inflammatory actions than prostaglandin E_2, would still have further beneficial anti-inflammatory effects owing to the suppression of prostaglandin E_2 (Vang & Ziboh, 2005:367). Evidence for this is that diets containing ω-3 fatty acids and dietary supplementation with encapsulated fish oil have shown suppressed production of both TNF-α and IL-1β after eight weeks in healthy volunteers (Caughey *et al*. 1996:120).

This may be supported by the fact that leukotriene B_4 and thromboxane A_2 (both arachidonic acid-derived) are considered to be stimulators of TNF-α and IL-1β production (Caughey *et al*. 1996:120). Leukotriene B_4 synthesis is inhibited by ω-3 fatty acids (James *et al*. 2000:345S; Abou-El-Ela *et al*. 1989:1434). Although Caughey *et al.* (1996:120) did not identify this, they acknowledged the inhibition of thromboxane A_2. Thus, ω-3 PUFAs inhibit the arachidonic acid-derived leukotriene B_4, thromboxane A_2 and prostaglandin E_2 synthesis, which will decrease cytokine activity.

Increased lipolysis has been identified as one of the underlying factors contributing to the weight-losing characteristics of cachexia (Arends *et al*. 2006:248; Zuijdgeest-Van Leeuwen *et al*. 2000:417). Zuijdgeest-Van Leeuwen *et al.* (2000:420) were unable to detect a significant change in whole-body lipolysis after one week of supplementation with 6 g of EPA/day in cancer patients or in healthy subjects.

RECOMMENDED DIETARY INTAKE FOR CANCER PATIENTS

According to the European Society of Parenteral and Enteral Nutrition (ESPEN) (Arends *et al*. 2006:250), the nutritional goals in cancer patients are preventing and treating undernutrition, enhancing anti-tumour treatment effects, reducing adverse effects of anti-tumour therapies and improving quality of life. As is evident from the previous discussions, ω-3 PUFAs cannot convincingly be recommended when considering the above goals. The anti-tumour effects of ω-3 PUFAs as discussed above could be considered when making recommendations with possible positive outcomes on im-

proving quality of life (Tisdale, 2007:161).

It is important that recommendations focus on both total fat and specific types of fatty acids in cancer patients. When considering total fat, it is generally recommended that intake be less than 30% of total energy intake even though the patient is cachectic. Justification for this statement firstly includes the fact that high total fat intakes seem to promote cancer development (Whitney, Cataldo & Rolfes, 1998:937). Secondly, the activity of human natural killer cells is significantly increased by a reduction in fat intake to less than 30% of total energy (Calder & Field, 2002:64). Natural killer cells are capable of killing a tumour or microbial cell without prior exposure to the target cell and without having it presented with or marked by a histocompatibility antigen (Venes, 1997:355). Thirdly, low-fat diets (<30% of total energy) result in an increased conversion of α-linolenic acid to EPA (Larsson *et al*. 2004:941), compared with a diet containing more than 30% of energy from fat. Fourthly, a reduction in total fat intake from 35% to 25% of total energy has been shown to slightly elevate TNF-α and IL-1β synthesis unless the intake of PUFAs is increased (Caughey *et al*. 1996:120).

Intensive discussion would be necessary when considering recommendations regarding the type of fat; thus the focus will be on the PUFAs only. When the diet is enriched with EPA, ALA or both, interaction between ω-3 and ω-6 fatty acids for the enzymes is still highly competitive. It has been reported that when the intake of the ω-6 fatty acid linoleic acid is held constant at 15 g per day, the total percentage of conversion of α-linolenic acid to EPA and DHA is 11-18%. However, when the intake of linoleic acid is increased from 15 to 30 g per day, this conversion is reduced to 5-11% (Larsson *et al*. 2004:940). Also, higher EPA tissue concentrations are observed when diets are low in linoleic acid. The linoleic acid content of the diet needs to be modified in order to prevent the negative effect on tissue concentrations of ω-3 fatty acids (James *et al*. 2000:346S). The optimal ratio between ω-3 and ω-6 fatty acids as indicated by experimental data is 1:1 or 1:2, whereas the current Western diet ratio is approximately between 1:10 and 1:20 (Larsson *et al*. 2004:940).

In practice oral supplementation is dependent on the patient's tolerance, state of anorexia and early satiety (Arends *et al*. 2006:252; Burns, Halabi, Clamon, Hars, Wagner, Hohl, Lester, Kirshner, Vinciguerra & Paskett, 1999:3944). Human tolerance of fish oil supplementation is estimated at a maximum of 0.3 g/kg/day or up to 21 g/day for a 70 kg patient. This can be made up of 13.1 g of EPA plus DHA per day (Burns *et al*. 1999:3942). Initial aggressive supplementation is less tolerated and supplementation by inclination is therefore recommended, generally 0.1 g of fish oil/kg of actual body weight per day (Burns *et al*. 1999:3943). Patients need to consume at least 2 g of EPA per day for it to have a therapeutic effect (Tisdale, 2007:161).

Although low dosages of fish oil supplementation (3.24 g of EPA and 2.16 g of DHA per day) for short periods (14 days) do not raise neutrophil phospholipid ω-3 PUFA levels, they do significantly reduce arachidonic acid levels (Pratt *et al*. 2002:1375-1377). Elevation in ω-3 fatty acid levels, accompanied by reduction in arachidonic acid levels in neutrophils, has been reported after three weeks of fish oil supplementation in healthy volunteers consuming doses of 9.4 g of EPA and 5 g of DHA daily. Although it seems to be a high dose, this combination of fatty acids shows the most promising effects when supplementing sufficiently (Pratt *et al*. 2002:1377).

Increasing the amount of α-linolenic acid in the diet may also elevate cellular EPA. With flaxseed oil (rich in α-linolenic acid), compared with sunflower oil (rich in linoleic acid), healthy male volunteers showed increased leukocyte EPA concentrations and both TNF-α and IL-1β were significantly suppressed after four weeks (Caughey *et al*. 1996:119). However, with altered lipid metabolism in the cancer patient, the effect of -linolenic acid is not assured, although cytokine production decreases as cellular EPA increases to approximately 1% of total fatty acids (James *et al*. 2000:345S).

CONCLUSION

Although there is some controversy, a vast number of studies indicate that ω-3 PUFAs seem to be beneficial in cancer treatment in both tumour growth and cachexia. Inflammatory mediators seem to play a major role in both tumour growth and cachexia. Metabolism of the 20 carbon PUFAs results in the formation of inflammatory mediators, namely eicosanoids.

Eicosanoids produced from ω-6 PUFAs have pro-inflammatory effects and have been shown to be increased in patients with cancer cachexia. Furthermore, these eicosanoids stimulate the production of pro-inflammatory cytokines (peptide inflammatory mediators). It has been found that eicosanoids from the ω-3 PUFA pathway suppress the production of the pro-inflammatory eicosanoids as well as pro-inflammatory cytokines. Several mechanisms relating to the effects of ω-3 PUFAs on carcinogenesis have been identified and therefore ω-3 PUFAs could be considered to play an important role. Even so, more human studies are needed to evaluate and verify these mechanisms and investigate them in terms of nutritional status in order to arrive at conclusions on the overall effect.

It can be concluded that nutritional support that includes ω-3 PUFAs at a minimum of 2 g of EPA per day offers a non-toxic means of augmenting cancer therapy, inhibiting tumourigenesis and possibly contributing to cancer cachexia alleviation.

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