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The anticancer effects of Vitamin D and omega-3 PUFAs in combination via cod-liver oil: One plus one may equal more than two

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ABSTRACT

In the past number of years, the anticancer activities of omega-3 polyunsaturated fatty acids (ω3-PUFAs) as well as Vitamin D have been intensively studied, but separately. Supplementation of Vitamin D and omega-3 PUFA via cod-liver oil, one of few natural sources of both of these molecules, may have additive and possibly synergistic anticancer effects. Cod-liver oil has been used effectively to treat diseases such as Rheumatism but has not been studied as an anticancer agent. This review examines the prominent, striking and possibly important similarities between the anticancer effects of ω3-PUFAs and Vitamin D metabolites as well as the possible overlapping signaling pathways by which they may operate. The mechanisms that will be examined in this review fall broadly under the categories of being anti-inflammatory, pro-apoptotic, anti-angiogenic and anti-proliferative. Finally, we compare the potential for use of ω3-PUFAs, Vitamin D combinatorial supplementation both in prevention and treatment of disease. Some data also suggests that the timing of supplementation modifies the effects of Vitamin D and ω3 fatty acids.

Introduction

The World Health Organization estimated that 30–40% of cancers worldwide could be prevented by diet [1]. It was estimated by Giovannucci and Willett [2] that 70% of colon cancer could be prevented by small alterations in lifestyle and diet.

In recent years, there has been considerable interest in the anticancer properties of both omega-3 poly-unsaturated fatty acids (ω3-PUFAs) and Vitamin D. The mounting evidence is generally supportive of anticancer activity for both groups of chemicals. *In vitro* studies on the effects of ω3-PUFAs on tumor cells has been promising in breast [3–5], prostate [4,6] and colorectal [6–12] cancers. The epidemiological evidence in human populations has been less convincing, but does seem to suggest an inverse correlation between increasing ω3-PUFAs consumption and decreased cancer risk [4,13–23]. *In vitro* studies on the effects of Vitamin D on breast [24], prostate [25,26], colorectal [27,28] and lung [29] cancer have likewise been consistently supportive but unlike omega-3 epidemiological studies, Vitamin D studies seem to show a consistent inverse correlation between intake and risk of breast [30–32], prostate [33], colorectal [34] and other cancers [35].

That chemically dissimilar molecules have some very similar effects on cancer, begs the question: Would the combination of these two be more than the sum of their parts? The anticancer functions of these two molecules have been the focus of much recent research; however no studies have examined their combined effect. One recent study by Istfan et al. [36] demonstrated that the combination of 1α,25-dihydroxyvitamin D_3 (1,25$[OH]_2$ D_3) and fish oil (high in ω3-PUFAs [3,37]) produced significantly more inhibition of G_1/S phase transition in prostate cancer cells than either treatment alone ($p < 0.005$). This novel study may be an indication of the benefit of combining these two in the battle against cancer.

Cod liver oil, first used in 1789 to treat Rheumatism [38,39], is an unusually good source of Vitamin D [40], and like other fish, a good source of ω3-PUFAs. It is a possible vehicle for the combined supplementation of these molecules. Historically, cod-liver oil had been used primarily as a source of Vitamins A and D and more recently as a source of ω3-PUFAs. The combined effect of these molecules has been virtually ignored. Between 1908 and 1912, Schabad, a Russian pediatrician showed that cod liver oil supplementation could treat and cure rickets, caused by Vitamin D deficiency [41]. By the 1920's cod-liver oil was a common prophylactic against rickets, which ravaged the European urban populations [42,43]. It was also used to reduce bacterial fever in woman after childbirth around 1930. Vitamin A in cod-liver oil continued being used to reduce infection severity until the late 1930's, with the advent of sulfa antibiotics [44].

Cod-liver oil is still thought to have benefits in treating some of these ailments, including Rheumatoid arthritis. Research has established independent links between Vitamin D [45,46] ω3-PUFAs [47,48] and their combination benefits in Rheumatism [49]. Cod liver oil has been successfully used as an Non-steroidal anti-inflammatory drug (NSAID) sparing agent in this condition, aiding

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the decrease in inflammation [49]. Attenuation of this inflammatory disease is thought to operate mainly by decreasing levels and inhibiting the production of omega-6 PUFA (ω6-PUFA) inflammatory eicosanoids from arachidonic acid (AA) [50]. The mechanism for Vitamin D in Rheumatism is less clear.

Inflammation also plays a role in other chronic diseases including cancer. While both Vitamin D metabolites and ω3-PUFAs have been examined independently as cancer therapeutic agents, the anticancer benefits of cod-liver oil as a vehicle for the delivery of these compounds has not been investigated.

In this article we pose the following hypothesis:

The combination of ω3-PUFAs and Vitamin D is more efficacious in cancer prevention and treatment than either supplement alone.

1α,25-Dihydroxy Vitamin D_3 (1,25$[OH]_2$ D_3)

The major sources of Vitamin D_3 are from the UV conversion of 7-dehydrocholesterol in the skin or from the diet primarily as cholecalciferol [57]. Vitamin D_3 is readily converted to 25-hydroxy Vitamin D_3 (25-OHD_3) in the liver through action of 25-hydroxylase. Circulating 25-OH D_3 is often used as a biomarker of Vitamin D status in humans and is typically present at 1000-fold higher concentrations than other metabolites such as 1α,25-Dihydroxy Vitamin D_3, (1,25$[OH]_2$ D_3) and 24, 25-Dihydroxy Vitamin D_3. 1,25$[OH]_2$ D_3, one of the most active forms of Vitamin D_3, is synthesized mainly in the proximal tubule of the kidney by hydroxylating the 1α position of 25 Hydroxy Vitamin D_3 [51]. 1,25$[OH]_2$ D_3 can also be synthesized in small amounts in keratinocytes [52], prostate [53], mammary and colonic epithelial cells [54] due to local expression of 1-α hydroxylase. 1,25$[OH]_2$ D_3 is a few-hundred fold more potent than 25[OH] D_3 [55], and its concentration is tightly regulated systemically by parathyroid hormone (PTH) and [Ca^{2+}] via renal 1-α Hydroxylase. Non-renal 1-α hydroxylase activity seems to function independently of systemic regulation, allowing for local control of 1α,25$[OH]_2$ D_3 concentrations [56].

Many of the actions of 1,25$[OH]_2$ D_3 are transduced by a nuclear Vitamin D Receptor (nVDR), a ligand dependant transcription factor. Ligand bound nVDR forms a heterodimer with the Retinoid X receptor (RXR) that binds to Vitamin D response elements (VDRE) and controls the transcription of at least 200 target genes [57,58]. Other activities, including rapid responses to 1,25$[OH]_2$ D_3, have been attributed to a novel membrane receptor designated 1,25-D_3 MARRS (Membrane Activated Rapid Response Steroid) that is currently being studied in cell differentiation and cellular transformation models [59]. Some rapid effects have also been attributed to a membrane-bound version of the nVDR (mVDR).

Omega-3 and omega-6 polyunsaturated fatty acids

Fatty acids are hydrocarbon chains with a methyl group at one end and a carboxylic acid on the other. Polyunsaturated fatty acids have two or more double bonds. The first double bond found in ω3-PUFAs is three carbons from the methyl end [60]. Similarly, the first double bond in ω6-PUFAs is six carbons from the methyl end. Both ω3 and ω6 fatty acids are essential in the human diet because humans do not express the necessary enzymes to desaturate the ω3 and ω6 positions. Therefore, γ-linoleic acid (LA, 18:2ω6) and alpha-linolenic acid (ALA, 18:3ω3) are defined as essential fatty acids. Because of the poor endogenous conversion of ALA to its longer and more highly desaturated fatty acids, there is considerable debate as to whether the longer versions such as eicosapentaenoic acid (EPA, 20:5ω3) and docosahexaenoic acid (DHA, 22:6ω3) may be considered conditionally essential. In the omega-6 series, arachidonic acid (AA, 20:4ω6) is an important metabolite [61] required for the synthesis of eicosanoids. These PUFAs are incorporated into membrane phospholipids creating a variety of phospholipids with different compositions and biophysical characteristics depending on which fatty acids compose the acyl chains on the glycerol backbone. Also of relevance to this review is that ω3- and ω6-PUFAs compete for the enzymes both in the elongation and desaturation pathways as well as those used to synthesize eicosanoids. Eicosanoids are hormone-like lipids that are important in various physiological functions including cell growth, cell proliferation, immune responses and regulation of inflammation. In some cases the ω3 series derived eicosanoids have the opposite biological effects of their ω6 counterparts or have lower potency. The enzymes that are of particular interest are the cyclooxygenases (COX) and lipoxygenases (LOX).

Effect of combinationing ω3-PUFAs and Vitamin D metabolites

Calcium absorption

Following dietary consumption, Ca^{2+} is primarily absorbed in the duodenum. Ca^{2+} initially enters via calcium channels in the brush border membrane of mucosal cells, is transported to the apical membrane via calcium binding proteins (CaBP) and then transported into the circulation via membrane bound transporters on the basolateral surface [62]. Both calcium and Vitamin D metabolites have been shown to play important roles in cell proliferation and differentiation, not only in the gastrointestinal mucosa, but also in mammary and other epithelial tissues [63]. In the small intestine, 1,25 $[OH]_2$ D_3 stimulates the production of CaBP [64] and induces rapid calcium uptake via a process described as transcaltachia [65]. This process involves translocation of Ca^{2+} from the luminal side of the brush border through the cytoplasm and into the vasculature through stimulation of membrane bound Vitamin D receptors and signaling through protein kinases that activate voltage gated channels in the basolateral membrane. It is much less well known that PUFA's play a role in the third and rate limiting step – transport through the basolateral membrane [66]. There are three mechanisms for calcium extrusion. First, a Vitamin D promoted Ca^{2+}, Mg^{2+} dependant ATPase pumps calcium out of the cell. Next, a Na^+Ca^{2+}Exchanger using a gradient erected by a Na^+/K^+ ATPase facilitates about 20% of the calcium movement. There is evidence that PUFAs can activate this enzyme [67]. Lastly, there is a Ca^{2+}-ATPase, which is localized in the caveolae whose effects are potentiated by the presence of ω3-PUFAs through interaction of the phospholipids with the regulatory chains of the enzyme [68].

Apoptosis

Apoptosis is an important aspect of the body's defense against tumorigenesis, and it is essential to tumor survival that it be down-regulated. This is especially important because in general tumor cells are thought to be under increased oxidative stress that normally would lead to apoptosis.

The tumor suppressor gene p53, a transcription factor involved in apoptosis, is triggered in response to cellular stresses like cell proliferation, DNA damage and hypoxia [69]. In addition, p53 blocks cell survival pathways by inhibiting PI3-K/Akt activation, which normally inhibits apoptosis promoters Caspase 9, Bax, Bad and FAS/CD95 [70]. Omega-3 PUFA's seem to play a role in p53 phosphorylation and activity [71]. It also appears that the VDR is a direct target of p53 [72]. Further, there is some evidence that VDR activation indirectly up-regulates p53 via activation of Prostate Derived Factor (PDF) synthesis [73].

1,25-D_3 represses anti-apoptotic/pro-survival proteins like Bcl-2 and Bcl-X and also induces promoters of apoptosis [74,75]. DHA has also been shown to inactivate Bcl-2 genes [76].

1,25-D_3 treatment of prostate cells inhibited p38 mitogen-activated protein kinase(MAPK) phosphorylation, leading to a decrease in IL-6; typically IL-6 is pro-inflammatory, and therefore associated with stimulation of carcinogenesis [25]. MAPKs form a network of signal transduction pathways conveying information between the extracellular environment and the nucleus [77]. p38 is activated in response to oxidative stress, hypoxia and inflammatory cytokines [78] and is linked to increased COX-2 transcription, which has been positively associated with cancer [79]. The mechanism for p38 inhibition by 1,25-D_3 was suggested to be due to increased transcription of the MKP5 protein [25], however DHA in some models has been shown to be a p38 activator – not an inhibitor [5,71].

Omega-3s could also indirectly induce apoptosis by inhibiting the LOX conversion of AA into 12-HETE, which suppresses apoptosis [80]. This is closely associated with ω3-PUFAs ability to inhibit COX and LOX activity and compete with ω6-PUFAs for use as substrate by these enzymes. As a result, ω3-PUFAs play a role in restoring apoptosis in cancerous cells [60]. 1,25-D_3 could also complement this role through its role in suppressing COX-2 expression [81].

Immune function

Both 1,25-D_3 and ω3-PUFAs are capable of attenuating inflammation. Inflammatory environments, such as elevated levels of pro-inflammatory cytokines (i.e. interleukins and TNF-α) have been shown to be procarcinogenic [69], and in some cases, linked to aggressive disease and decreased survival [82]. There is evidence that inflammation is a causal factor in various cancers, including liver, bladder and gastric [25].

1,25-D_3 down-regulates inflammatory markers such as IL-2 and IL-12 [83], IL-6 [25], and has an anti-proliferative effect. EPA and DHA may inhibit TNF-α and IL-1 [84].

The transcription factor NF-κB is one of the main regulators of inflammation, inducing expression of inflammatory cytokines, including TNF-α [85] and up-regulating COX-2 transcription [77]. DHA appears to down-regulate NF-κB [76] as does 1,25-D_3 in various immune cells [86]. Indirectly, Vitamin D and ω3-PUFAs also achieve a similar effect by down-regulating AKT (via p53 activation), which normally up-regulates NF-κB [70]. While NFκB activation, is classically associated with inflammation and immune stimulation, and therefore down-regulation of its activity might be seen as a cancer inhibitory activity, in some cell types, 1,25-D_3 action is associated with NFκB activation and translocation to the nucleus which promotes cell differentiation and reduction in the tumor cell proliferative pool [87]. This activity is probably mediated by MARRS rather than membrane associated VDR. Thus, the model system of study is critical to the role that activation/inhibition of specific signaling molecules plays.

Omega-3 treatment of immune cells has been shown to displace signaling proteins from lipid rafts [88,89], altering their cell signaling. Omega-3 poly-unsaturated fatty acid incorporation into lipid rafts of T-cells inhibits receptor assembly, thereby attenuating inflammation [90]. Type I Diabetes research has demonstrated that 1,25-D_3 is also capable of down-regulating immune cell activity, Th1 cells specifically, by suppressing the antigen-presentation capacity of macrophages and dendritic cells while stimulating macrophage phagocytic activity [91]. Cod-liver oil has also been shown to reduce neutrophil and monocyte chemotaxis in healthy subjects [92]. Interestingly, the recently identified MARRS protein is not only a Vitamin D binding protein, but also possesses protein disulfide isomerase and chaperone-like activities, which is why it has been previously named pdia3 and also Erp57 since it resides in some cells primarily in the endoplasmic reticulum. Erp57, through its interaction with calcium-binding proteins including calreticulin, is critical for normal processing and presentation of MHC class I molecules, pivotal to antigen presentation [93]. Knockout of erp57 in the B cell lineage results in impaired MHC class I recruitment [94] and possibly impairs B-cell maturation and interaction with other cells involved in immune activation. This could be important in both diabetes and cancer development.

Angiogenesis

Angiogenesis, the formation of new blood vessels, is critical for cancer progression. Omega-3 dietary intake plays an indirect role in reducing angiogenesis; ω3-PUFAs compete with ω6-PUFAs thereby decreasing the production of pro-angiogenic COX and LOX products [95,96]. 1,25-D_3 has also been shown to inhibit angiogenesis in prostate cancer cells by impeding endothelial cell migration and tube formation via IL-8 inhibition [97].

Omega-3 PUFAs and the Retinoid X receptor

Following nuclear translocation of 1,25-D_3-bound, VDR, the most common partner with which it complexes is RXR to activate transcription of target genes [29] (Table 1). Among the responsive target genes are several associated with G0/G1 cell cycle arrest, apoptosis [98,99] and cellular differentiation [40]. DHA preferentially activates RXR in rat colonocytes [100], and though it has not been specifically studied, this could further potentiate 1,25-D_3 action by enhancing the pool of RXR partners.

Membrane bound VDR – caveolae

1,25-D_3 has been shown to exert its effect by way of both nuclear initiated (historically referred to as the genomic pathway) and a rapid (within minutes [101]) membrane/cytoplasmic initiated response (historically referred to as the non-genomic response) [102]. Both a membrane form of the nVDR (mVDR) and the novel Vitamin D receptor, MARRS, have been implicated in the rapid responses to 1,25-D_3. Turano and colleagues have localized erp57 to multiple locations outside the ER including lipid rafts. Huhtakangas et al. [103] recently demonstrated both *in vivo* and *in vitro,* that mVDR is present in caveolae – highly specialized, flask shaped invaginations in the plasma membrane which are rich in many signaling proteins, especially caveolin [104].

The mechanisms of action of the mVDR and/or MARRS could involve such signaling molecules as Phospholipase C [105] (PLC) phospholipase A2 [106] (PLA_2) and various isoforms of Protein Kinase C (PKC) [65,102,107–109] Various isoforms of PKC have been implicated in cell differentiation, angiogenesis, apoptosis, cell-adhesion, metastases and oncogene expression regulation [110]. Increasing PKC abundance can increase proliferative capacity in breast [111] and lung cancer [112] but it is decreased in colon cancer [113]. In non-tumor tissue, such as is the case in germline VDR knockout mice, 1,25-D_3 treatment causes a dose–response increase in proliferation [105]. Since all cells in these mice lack VDR (both nuclear and membrane) these responses must be mediated by MARRS or another Vitamin D binding protein. We recently showed that knockdown of MARRS in breast cancer cells actually increased the anti-proliferative effect of 1,25-D_3 in breast cancer cells (MCF-7) and suggested that action through the nVDR may have accounted for this anti-proliferative response [114]. Because many of these studies have used different tissues, at various stages of maturation or stages of carcinogenesis, it is difficult to make

Table 1
Mechanisms of action of vitamin D and omega-3 fatty acids.

Effect	Mediator of effect	Omega-3 PUFA mechanism	Vitamin D mechanism
Apoptosis			
	BAX (Pro-apoptotic)		
		Stimulation via P53 stimulation, (P53 stimulates BAX and inhibits Akt/PI3-k mediates BAX inhibition)	Stimulation via P53 stimulation (P53 stimulates BAX and inhibits Akt/PI3-k mediates BAX inhibition) Direct stimulation
	Cytochrome C (Pro-apoptotic)		
		Stimulation via inhibiting BCL2 (BCL2 inhibits Cytochrome C) Stimulation via P53 stimulation (P53 inhibits Akt/PI3-k mediated Cytochrome C inhibition)	Stimulation via inhibiting BCL2 (BCL2 inhibits Cytochrome C) Stimulation via P53 stimulation (P53 inhibits Akt mediated Cytochrome C inhibition)
	BAD (Pro-apoptotic)		
		Stimulation via P53 stimulation (P53 inhibits Akt/PI3-k mediated BAD inhibition)	Stimulation via P53 stimulation (P53 inhibits Akt/PI3-k mediated BAD inhibition)
	FAS/CD95 (Pro-apoptotic)		
		Stimulation via P53 phosphorylation (P53 inhibits Akt/PI3-k mediated FAS/CD95 inhibition)	Stimulation via P53 stimulation (P53 inhibits Akt/PI3-k mediated FAS/CD95 inhibition)
	Caspase 9 (Pro-apoptotic)		
		Stimulation via P53 stimulation (P53 stimulates VDR activation)	Stimulation via P53 stimulation (P53 stimulates VDR activation)
	VDR (Pro-apoptotic)		
		Stimulation via P53 stimulation (P53 stimulates VDR activation)	Stimulation via P53 stimulation (P53 stimulates VDR activation) Stimulation via PDF synthesis (PDF up-regulates P53)
		Stimulation via RXR activation (RXR binds VDR to activate the VDRE)	
	LOX and COX (Anti-apoptotic)		
		Inhibition of AA based products (ω3-PUFA competes with ω6-PUFA as LOX substrate)	
			Direct inhibition of COX-2
	MARRS (Anti-apoptotic)		
			Direct stimulation
Inflammation			
	NFκB (Pro-inflammatory)		
		Direct inhibition Inhibition via P53 activation (P53 causes AKT down-regulation, which normally causes NFκB up-regulation)	Direct inhibition Inhibition via P53 activation (P53 causes AKT down-regulation, which normally causes NFκB up-regulation)
	TNF-α (Pro-inflammatory)		
		Inhibition via NFκB down-regulation (NFκB stimulates TNFα) Direct inhibition	Inhibition via NFκB down-regulation (NFκB stimulates TNFα)
	IL1 (Pro-inflammatory)		
		Direct inhibition	
	IL2 (Pro-inflammatory)		
		Direct inhibition	
	IL6 (Pro-inflammatory)		
		Stimulation via P38 MAPK activation (P38 up-regulates IL6)	
			Inhibition via MKP5 stimulation (MKP5 inhibits P38 MAPK, causing IL6 activation)
	IL12 (Pro-inflammatory)		
			Direct inhibition
	Immune Activation (Pro-inflammatory)		
		Inhibition via ω3-PUFA incorporation into lipid rafts (this impairs T-cell receptor assembly)	
			Inhibition via MARRS activation (MARRS interacts with Pdia3 to decrease MHC1 processing)
Angiogenesis			
	COX2 (Pro-angiogenic)		
		Inhibition via NFκB inhibition (NFκB up-regulates COX2 transcription) Inhibition via down-regulation of ω6-PUFA utilization	Inhibition via NFκB inhibition (NFκB up-regulates COX2 transcription)
		Stimulation via P38 potentiation (P38 increases COX2 expression)	Inhibition via P38 down-regulation (P38 increases COX2 expression) Inhibition via MKP5 stimulation (MKP5 inhibits P38, decreasing COX2 expression activation)
	LOX (Pro-angiogenic)		
		Inhibition of AA based products (ω3-PUFA competes with ω6PUFA as LOX substrate)	
	HIF-1α (Pro-angiogenic)		
		Direct HIF-1α inhibition	
	IL8 (Pro-angiogenic)		
		Direct IL8 inhibition	

(*continued on next page*)

Table 1 (*continued*)

Effect	Mediator of effect	Omega-3 PUFA mechanism	Vitamin D mechanism
Proliferation			
	VDR (Anti-proliferative)		
		Inhibition via P53 inhibition (P53 stimulates VDR activation)	Stimulation via P53 stimulation (P53 stimulates VDR activation)
			Direct stimulation
		Stimulation via RXR stimulation (RXR binds VDR to activate the VDRE)	
	mVDR/MARRS (proliferative) – Caveolae bound		
			Direct stimulation
		Stimulation via up-regulation of PKC signaling	
	EGFR (Proliferative) – Caveolae bound		
		Direct stimulation	

universal conclusions about the activities of 1,25-D3 in cancer progression or response as being mediated by one specific Vitamin D receptor or one specific signaling pathway. Significantly, altering the fatty acid composition of lipid rafts (including caveolae) has been shown to alter cell signaling [115]. In some cases ω3-PUFA enrichment is associated with decreased receptor signaling. Such is the case in MDA-MB-231 cells which express fewer epidermal growth factor receptors and this phenotype is associated with decreased proliferative capacity [116]. In contrast, ω3-PUFA enrichment is associated with increased insulin sensitivity in a variety of tissues, suggesting that receptor signaling changes depend on the cell type and nature of the receptor. Since both mVDR and MARRS have been found in lipid rafts, the effect of ω3-PUFA membrane enrichment on 1,25-D_3 signaling will undoubtedly depend on the cellular and molecular context of the system under study. As far as we are aware, no one has examined the cellular response via either mVDR or MARRS when cells are enriched with specific fatty acids. Cod-liver oil provides an excellent matrix on which to study the combinatorial effects of Vitamin D metabolites and long chain omega-3 fatty acids in cancer biology.

Prevention or treatment?

Most of the literature examined in this review has focused on the early stages of carcinogenesis. The practical utility of using cod-liver oil, or any other nutritional strategy in cancer treatment, requires that we consider additional issues. Vitamin D and its metabolites, and long chain ω3-PUFAs must be compatible with other standard treatments. Foremost among these is chemotherapy. Not only must one consider whether either supplement alone will affect drug toxicity to tumor or normal tissues, but must also determine the effects on immune function since chemotherapy on its own can result in profound immune suppression. Our studies in cells in culture, animal models of fibrosarcoma and lymphocytic leukemia suggest that ω3 supplementation assists targeting of nucleoside drugs toward tumor cells and protects normal bone marrow and the gastrointestinal tract from drug toxicity [84]. Clinical studies in breast cancer patients undergoing anthracycline chemotherapy have suggested that higher DHA incorporator's respond better to chemotherapy and have increased overall survival compared to low incorporators [117,118]. The Vitamin D status, as typically measured by circulating 25-OH levels is not described in this patient population.

In one study by Porojnicu et al. [35] it was proposed that calcidiol acts synergistically with conventional cancer treatment, and found that higher 25[OH] D_3 status was associated with increased patient survival. Cancer cells can experience increased oxidative stress from reactive oxygen species (ROS) because of their dramatically increased metabolic rate [119], and decreased ability to produce protective intermediates such as glutathione and antioxidant enzymes such as Glutathione S-transferase, Glutathione peroxidase and catalase [120]. Weitsman et al. showed that1,25-D_3 increased tumor cell sensitivity to H_2O_2, a very common ROS precursor. The field is clearly ripe for clinical studies using combinations of ω3 and Vitamin D metabolites.

Conclusions

From the available evidence it seems there is good reason to consider Vitamin D (or metabolites) and ω3-PUFAs for combinatorial supplementation in both cancer treatment and prevention. Studies using individual agents are supportive but there are virtually no studies of their interactions in any stage of carcinogenesis, but the verity of this can only be found with further study. Research looking at the singular and combined effects of omega-3 PUFAs and Vitamin D are lacking in nearly every area of their anti-cancer function. The most obvious place to start these studies is in cancer treatment, where the potential benefit would appear to far exceed the expected risks and the timeline for outcomes may be quite short. This is in contrast to prevention studies that require very long follow-up periods and the potential risk may be much higher. At the same time as these clinical trials are proceeding it will be important to continue the mechanistic studies in cell culture and animal models to both understand the ways in which these nutrients operate to affect cancer development and treatment and to provide the evidence base on which to develop future advancements in chemoprevention and chemotherapy.

Conflict of interest

None declared.

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