Nutritional Supplements and Cancer: Potential Benefits and Proven Harms

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OVERVIEW

Nutritional supplements are widely used among patients with cancer who perceive them to be anticancer and antitoxicity agents. Large-scale, randomized cancer prevention trials have mainly been negative, with some notable adverse and beneficial effects. For example, these trials showed that beta-carotene increases the risk of lung and stomach cancer, vitamin E increases prostate cancer and colorectal adenoma, and selenium reduces gastric and lung cancer in populations with low selenium levels but increase rates in those with higher levels. Both beta-carotene and vitamin E supplementation increase overall mortality. This article reviews phase II and III trials that examine the effects of multivitamins, antioxidants, vitamin D, and n-3 supplements on outcome and toxicity from cancer treatments. Although vitamin E and beta-carotene reduce toxicity from radiotherapy among patients with head and neck cancer, it has been found to increase recurrence, especially among smokers. Antioxidants have mixed effects on chemotherapy toxicity, but there are no data on outcome. Vitamin D deficiency is relatively common among patients with cancer, and ongoing phase III trials are studying the effect of vitamin D on outcome as well as optimum vitamin D and calcium intakes for bone health. Docosahexanoic and eicosopentanoic acid supplements have mixed effects on cachexia and are currently being tested as potential adjuncts to maximize response to chemotherapy. Nutritional supplementation tailored to an individual's background diet, genetics, tumor histology, and treatments may yield benefits in subsets of patients. Clinicians should have an open dialogue with patients about nutritional supplements. Supplement advice needs to be individualized and come from a credible source, and it is best communicated by the physician.

Expert guidelines from the American Cancer Society, the World Cancer Research Fund, and the American Institute for Cancer Research advise patients with cancer against the use of supplements and advocate obtaining nutrients from foods wherever possible.[1,2] Despite this, self-prescribed nutritional supplements use is widespread among patients with cancer. The lack of high-quality evidence of benefits or harms leads to inconsistent or lack of supplement advice from clinicians. Data collected between 2003 and 2010 within the Intergroup phase III Breast Cancer Chemotherapy trial (S0221) found 48% of patients were taking multivitamins; 20% were taking Vitamin C, D, and n-3 oils; 15% vitamin E, B6, and folic acid; and 34% calcium. Clinicians advised one-third to start taking a supplement during treatment, 10% to stop taking one, and 7% to stop all except a multivitamin; 51% received no advice.[3]

MULTIVITAMIN AND MINERAL SUPPLEMENTS

These include a range of multivitamin and mineral supplements often found in amounts comparable to the recommended daily allowance, and are the most popular supplements taken by approximately one-third of the U.S. population and half of patients with cancer.[4]

No randomized trials have assessed the effect of multivitamins on toxicity or survival after diagnosis. Observational data from colorectal and breast cancer cohorts in which 50% to 72% of patients were self-prescribing multivitamins showed neither beneficial nor harmful effects of these supplements on toxicity or survival.[5,6] A recent meta-analysis of 21 randomized trials in the general population based on 91,074 people and 8,794 deaths found no overall beneficial or detrimental effects of multivitamin supplements on either all-cause mortality (relative risk [RR] 0.98 [0.94 to 1.02]), cancer mortality (RR 0.96 [0.88 to 1.04]), or vascular mortality (RR 1.01 [0.93 to 1.09]).[7] However, two large-scale, randomized controlled trials have reported reduced cancer incidence among men taking a daily multivitamin versus a placebo. In the Physicians' Health Study (PHS) II trial (14,641 male U.S. physicians), multivitamins reduced incidence of cancer (hazard ratio [HR] 0.92 [0.86 to 0.998]).[8] Likewise in the French SU.VI.MAX Study, men had a modestly reduced risk of cancer (HR 0.69 [0.53 to 0.91]). Supplementation may be effective in men in these trials as it may be

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restoring adequate intakes of nutrients that were low in baseline diets.[9] There is insufficient evidence to make recommendations for the use of multivitamins and minerals in patients with cancer.

ANTIOXIDANT VITAMINS AND MINERALS

Antioxidants have been studied in patients with cancer first as potential anticancer agents to improve outcome and second to reduce oxidative damage from chemotherapy and radiotherapy and hence the dose-limiting toxicities of therapies.

Antioxidants have well-defined potential anticancer effects, including reduced oxidative damage to DNA lipids and proteins; reduced proliferation and angiogenesis; and increased apoptosis and therefore possible reduced initiation, promotion, progression, and metastases of cancer.[10] Laboratory findings and observations of lower antioxidant status among those who develop cancers led to a number of large-scale, randomized antioxidant cancer prevention trials. These trials recently summarized by Dolara et al have mainly been negative, with some notable harmful effects.[11] Supplementation with beta-carotene increases risk of lung cancer (RR 1.16 [1.06 to 1.27]) and stomach cancer (RR 1.34 [1.06 to 1.7]), while vitamin E increases prostate cancer (RR 1.17 [1.00 to 1.36]) and colorectal adenoma (RR 1.74 [1.09 to 1.79]). Selenium reduced lung cancer in populations with low selenium status (serum $<$ 106 ng/mL), increased rates in those with higher serum levels (serum $>$ 126 ng/mL), and reduced gastric cancer occurrence (RR 0.59 [0.46 to 0.75]). Antioxidant supplements can increase cardiovascular disease (CVD), diabetes, and mortality in the general population. A recent meta-analysis of randomized trials reported increased overall mortality with beta-carotene (RR 1.05 [1.01 to 1.09]) and vitamin E (RR 1.03 [1.00 to 1.05]) and higher doses of vitamin A. Neither vitamin C (RR 1.02 [0.98 to 1.07]) nor selenium (RR 0.97 [0.91 to 1.03]) were beneficial, (RR 1.0006 [1.0002 to 1.001] P = 0.002).[12]

KEY POINTS

- Nutritional supplements are widely used among patients with cancer who perceive them to be anticancer and antitoxicity agents.
- Beta-carotene and vitamin E supplementation increase risk of lung, stomach, prostate cancer, and colorectal adenoma and overall mortality in the general population.
- Vitamin E and beta-carotene may reduce toxicity from radiotherapy, but there is an associated increase in recurrence especially among smokers.
- Antioxidants have variable effects on chemotherapy toxicity, but there are no data on outcome.
- Vitamin D and n-3 fats are currently being tested as potential adjuncts to maximize response to cancer therapies.

These trials highlight the potential cancer-promoting and adverse effects of antioxidants on overall mortality for patients with cancer. An additional concern for patients with cancer is that although antioxidants may reduce the toxicity of chemotherapy and radiotherapy, this reduced toxicity may be at the cost of reduced treatment efficacy since radiotherapy and many chemotherapy agents (e.g., alkylating agents, anthracyclines, podophyllin derivatives, platinum complexes, and camptothecins), exert their anticancer effects by production of reactive oxygen species (ROS) and increased apoptosis.[10] Accumulating evidence from phase II and III trials summarized in Table 1 does not support the widespread use of antioxidants in patients with cancer.

Antioxidant Supplementation during Radiotherapy

Although antioxidants reduce radiotherapy toxicity among patients with head and neck cancer, it comes at the cost of increased overall recurrence and mortality, particularly among those who smoked during radiotherapy treatment.[13-16] Both smoking and antioxidants may reduce radiation effects. Smoking increases blood carboxyhemoglobin and tissue hypoxia, which may reduce the oxygen-dependent effects of radiation therapy. In contrast beta-carotene supplements did not reduce outcome among patients with prostate cancer in the PHS.[17] Other trials of antioxidants have produced mixed effects on radiotherapy toxicity (Table 1A).

Antioxidant Supplementation during Chemotherapy

Short-term studies have reported beneficial effects of antioxidants for some but not all cisplatin toxicities. Vitamin E reduced neuropathy, and selenium reduced hemotologic toxicity but did not affect nephrotoxicity or ototoxicity.[18-21] No benefits have been reported for vitamin E versus taxane neuropathy, oxaliplatin-induced peripheral neuropathy, anthracycline cardiotoxicity, or general carboplatin toxicity.[22-24] None of these trials have assessed the long-term effects of antioxidant supplementation during chemotherapy on recurrence and survival (Table 1B).

Antioxidant Supplementation in Patients with Cancer Not Receiving or after Chemotherapy or Radiotherapy

Three trials reported no effect of supplementation on outcome (Table 1C). These were trials of selenium among patients with stage I, post-op non-small cell lung cancer (NSCLC), beta-carotene among patients with head and neck cancer after radiotherapy, and vitamin E, selenium, vitamin C, and coenzyme Q10 for patients with untreated progressing prostate cancer.[25-27] Supplementation with antioxidants decreased the recurrence of colon adenomas among nonsmokers and drinkers (RR 0.56 [0.35 to 0.89]), but it doubled risk among participants who smoked and also drank more than one alcoholic drink per day (RR 2.07 [1.39 to 3.08]; $p <$ 0.001 for difference from nonsmoker/nondrinker).[28] A recent randomized controlled trial reported reduced recur-

Table 1A. The Effect of Antioxidants on Outcome and Toxicity for Patients Receiving Radiotherapy

Study	Cancer Population	Study Type and Length	Dose of Antioxidant				Recurrence/Survival Supplement versus Placebo	Toxicity Supplement versus Placebo
			Beta-carotene mg	Vitamin E mg	Selenium μg	Vitamin C mg		
Mueche 2010[56]	81 cervical and endometrial selenium-deficient patients; < 84 mg/L; 81 patients	Phase III SB 6 wk			500		5 yr DFS 80 versus 83.2% p = 0.74	Reduced diarrhoea CTC grade ≥ 2; 20.5 versus 44.5% p = 0.04
Buntzel 2010[57]	Head and neck; 39 patients	Phase II SB 9-11 wk			500 on radiotherapy days 300 on other days		ND	No significant effects: dysphagia 22.7 versus 35.3% Loss of taste 22.7 versus 47.1% Dry mouth 22.7 versus 23.5% Stomatitis 36.4 versus 23.5%
Bairata 2005 a 2005 b 2006 Mayer 2008[13,15,16,58]	Head and neck stage I and II; 540 patients	Phase III DB 3 yr	30 discontinued early in trial; only in 77/273 patients for median 320 (21—609 d)	267	-	-	All-cause mortality HR: 1.38 (1.03-1.85) among smokers Recurrence HR 2.41(1.25-4.64) HNC mortality 3.38 (1.11-10.34) All-cause mortality 2.26 (1.29-3.97) Second primary cancers HR = 2.88 (1.56 to 5.31)	Less severe acute adverse effects during radiation therapy OR 0.72 (0.52 to 1.02)
Ferraira 2004[14]	Head and neck; 28 patients	Phase II DB 7 wk		400			Overall and median survival 32.2% and 8.5 mo (range, 2-24 mo) versus 62.9% and 12.5 mo (range, 2-23 mo) p = 0.126	Reduced mucositis 21.6 versus 32.5% p = 0.038
Margalit 2012[17]	Prostate; 383 patients	Nested in a RCT Pre, during, and average 7 yr post treatment	25 mg				Prostate cancer death HR 1.54 (0.86-2.78) p = 0.15	ND

Abbreviations: DFS, disease-free survival; SB, single blind; ND, no data; HR, hazard ratio; HNC, head and neck cancer; OR, overall response; RCT, randomized controlled trial; yr, year; wk, week; mo, months.

rence of noninvasive bladder cancer with vitamin E supplementation.[29] Two large-scale, phase III trials in Belgium (SELEBLAST trial; 200 μg selenium, 700 patients, NCT00729287) and the United Kingdom (SELENIB Trial; 200 μg selenium and 15 mg α tocophorol vitamin E NCT00553345) are studying the benefits of antioxidants for this population but have not yet reported.

Summary and Future Directions for Antioxidant Research

Antioxidants can have antineoplastic or neoplastic effects among patients with cancer that are a function of (1) the antioxidant (i.e., the specific choice of antioxidants, dose, and format used); (2) the phenotype of the patient (i.e., poor nutrition, smoking, or high alcohol intakes may lead to pro-oxidant and other carcinogenic effects of antioxidants); and (3) tumor site and therapy (i.e., antioxidants can act as pro-oxidants in tissues with elevated partial pressures of oxygen).[30] This could partly explain the apparent adverse effects in more oxygenated head and neck cancer cells that were not seen in the prostate.[17] Antioxidants appear to reduce the efficacy of radiotherapy, but there are no trial data on outcomes with chemotherapy.

Table 1B. The Effect of Antioxidants on Outcome and Toxicity for Patients Receiving Chemotherapy

Study	Cancer Population	Chemotherapy	Study Type and Length	Dose of Antioxidant: Beta-carotene mg	Vitamin E mg	Selenium μg	Vitamin C mg	Recurrence/Survival Supplement versus Placebo	Toxicity Supplement versus Placebo
Wiejl 2004[21]	Mixed solid tumors; 48 patients	Cisplatin	Phase II DB 4 mo		400	100 sodium selenite	1000	9 patients CR, 2 patients PR; overall response 44%. versus 6 patients CR 5 PR; overall response 48%	No difference nephrotoxicity or ototoxicity
Kottschade 2011[22]	Mixed solid tumors; 207 patients	Neurotoxic chemotherapy (i.e., taxanes)	Phase III DB Chemo + 1 mo	-	400 mg	-	-	ND	Neuropathy ≥ CTC Grade 2 34 versus 28% p = 0.43
Arigynou 2006[18]	Mixed solid tumors; 35 patients	Cisplatin	Phase II SB Chemo + 3 mo		600 mg				Neuropathy PNS 31.5 versus 68.4% p = 0.03
Sieja 2004[20]	Ovarian; 62 patients	Cisplatin Cyclophos-phamide	Phase II DB 3 mo	-	-	200	-	No difference in treatment response marker CA-125	Increased WBC, Decreased toxicity: Hair loss Abdominal pain Weakness Loss of appetite p < 0.001
Whittaker 1984[24]	Leukemia; 61 patients	Anthracycline	Phase II DB 1 yr	-	600	-	-	ND	No effect on cardiac toxicity
Fuchs-Tarlovsky 2012[19]	Cervical; 103 patients	Cisplatin and radiotherapy	Phase II SB 16 wk	4.8	133	15	100	ND	Serum haemoglobin 12.50 ± 1.22 g/dL, versus 11.62 ± 1.36 g/dL p < 0.05
Pathak 2005[31]	Stage IV NSCLC; 136 patients	Paclitaxel Carboplatin	Phase II SB Chemo + 1 mo	60	1050	-	6100	OS: 1 yr 39.1 versus 32.9% 2 yr 15.6 versus 11.1% p = 0.20	Toxicity profiles reported as similar in both arms.
Alifonseco, 2013[23]	Colon (adjuvant and metastatic; advanced gastric; rectum; 38 patients	Oxaliplatin	Phase II DB Chemotherapy		400			ND	Peripheral neuropathy CTC grade 1/2 83 versus 61% p = 0.41 Diarrhea 56 versus 18% p = 0.06

Abbreviations: CR, complete response; PR, partial response; DB, double blind, CTC, Common Terminology Criteria; SB, single blind; PNS, paraneoplastic neurological syndromes; WBC, white blood cells; ND, no data; OS, overall survival; mo, months; wk, week; yr, year.

Further studies should investigate adjusting dosing schedules of antioxidants at the time of radio- and chemotherapy.[31] Targeting individuals on the basis of polymorphisms that influence antioxidant enzymes may be important. Increased exogenous antioxidants could worsen the already poorer prognosis (three-fold) among patients with polymorphisms, which activate endogenous antioxidant enzymes (i.e., glutathione, manganese superoxide dismutase, and catalase) with already lower levels of ROS.[32]

Consideration should be given to patients with cancer who are prescribed high-dose antioxidants for conditions such as age-related macular degeneration (ARMD). These formulations typically contain vitamin C (500 mg), vitamin E (10 μg), beta-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide). Although these are being reformulated to include lutein and xanthin, which do not appear to have cancer promoting effects of beta-carotene among patients with ARMD.[33]

Adverse effects have been reported with antioxidant supplements but not high antioxidant intakes derived from food. The Women's Healthy Eating & Living Study (WHELS) tested a very high fruit and vegetable diet among patients with early breast cancer, which included 12 portions of fruit and vegetables and approximately 80 mg of beta-carotene and 1,000 mg of vitamin C per day. These high intakes had neither a beneficial nor detrimental effect on outcome. Because this diet was initiated after chemotherapy or radiotherapy treatments, this trial does not inform any potential interactions between high dietary intakes and efficacy of chemotherapy and radiotherapy.[34] Vitamin E and beta-carotene

Table 1C. The Effect of Antioxidants on Outcome in the Absence of Chemo/Radiotherapy

Study	Cancer Population	Study Type	Dose of Antioxidant				Recurrence/Survival Supplement versus Placebo
			Beta-carotene mg	Vitamin E mg	Selenium μg	Vitamin C mg	
Karp 2013[25,59]	Stage 1A or 1B NSCLC Post-surgery or chemo/radiotherapy 1,772 patients	Phase III DB 4 yr	-	-	200		Second cancers 3.54 versus 3.39/100 person years p = 0.294 5 yr survival 74 versus 79%
Mayne 2001[26]	Head and neck Post-surgery/ radiotherapy 264 patients	Phase III DB 51 mo	50				Second head and neck cancer RR, 0.69 (0.39-1.25) Total mortality RR, 0.86; 95% CI, 0.52-1.42
Baron 2003[28,59]	Post-surgery for colorectal adenoid 864 patients	Phase III DB 4 yr	25	400	-	1000	Adenoma recurrence No effect overall; RR 1.01 (0.85-1.20) Smoker/drinker + supplement versus no supplement RR = 2.07 (1.39 to 3.08) p < 0.001
Mazdak 2012[29]	Noninvasive bladder cancer Post-surgery 46 patients	Phase II SB 2 yr		266			Recurrence 19 versus 36% p = 0.04 Median time to recurrence: 9.0 (8.1) versus 8.3 (6.2) months p = 0.9
Hoenjel 2005[27]	Untreated prostate cancer and increasing PSA levels 70 patients	Phase II DB 21 wk	350	200	750	200	PSA 11.3 g/L versus 12.2 g/L p = 0.2

Abbreviations: NSCLC, non-small cell lung cancer; DB, double blind; RR, relative risk; SB, single blind; PSA, prostate-specific antigen; yr, year; wk, week; mo, months.

may reduce toxicity from radiotherapy, but there is an associated increase in recurrence especially among smokers.

VITAMIN D

Vitamin D and Outcome after Diagnosis

Vitamin D is a fat soluble vitamin mainly acquired through endogenous synthesis via ultraviolet exposure of the skin, with minor contributions from dietary sources such as oily fish, fish liver oils, beef, liver, cheese, egg yolks, and fortified foods. Endogenously synthesized and ingested vitamin D undergoes first and second step hydroxylations in the liver and kidney to produce the active metabolite 1,25(OH)D3 (calcitriol). Calcitriol regulates the expression of genes important in development and progression of cancer and can induce cell differentiation and apoptosis and also inhibit proliferation, angiogenesis, invasivion, inflammation, and metastatic potential. Calcitriol also suppresses aromatase activity leading to reduced estrogen levels and reduced breast cancer risk.[35]

Vitamin D deficiency is relatively common among patients with cancer. Typically 30% of patients have greatly reduced serum 1,25(OH)D (< 25 nmol/L), and 70% have somewhat reduced serum 1,25(OH)D (25–50 nmol/L).[36] Observational studies reviewed by Teleni and Buttigliero have linked low serum 25(OH)D with poorer outcome in some trials, with more consistent links reported for prostate and hematologic cancers and melanoma, inconsistent links with breast and colorectal cancer, and no relationship with lung cancer.[36-37] Observational data can only infer association and not causality and are likely to be confounded by factors such as age, race, body mass index, and physical activity. Some trials have suggested a U-shaped relationship with greater mortality at lower and higher serum levels.[38]

There are limited randomized data to assess the effects of vitamin D supplementation on outcome after diagnosis. A phase II trial of the active vitamin D metabolite calcitriol showed encouraging results among patients with advanced prostate cancer receiving docetaxel chemotherapy. However, the follow-up, open-labeled, phase III Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT) trial (953 patients) was prematurely stopped after an interim analysis showed a greater mortality in the supplemented versus placebo arm (36% vs. 29%).[37] This may have been linked to different docetaxel dosing schedules between the supplemented (weekly) and unsupplemented (three weekly) arms.

Ongoing phase III randomized trials registered on the National Institutes of Health (NIH) clinical trials database (www.clinicaltrials.gov) are assessing whether vitamin D3 improves survival in patients with Chronic Lymphoid Leukemia (NCT01518959) and resected stage II Melanoma

(NCT01264874).[39] A partially randomized phase II trial is testing whether vitamin D3 improves survival in patients who are vitamin D–deficient with newly diagnosed large B-cell lymphoma, early-stage chronic lymphocytic leukemia, and colorectal or breast cancer (NCT01787409; NCT01516216). There is unlikely to be a universal benefit from vitamin D supplementation on survival among patients with cancer. Effects will be influenced by baseline vitamin D status, vitamin D receptor polymorphisms—which determine the biologic activity of vitamin D—and variable target effects dependent on the vitamin D receptor status of the tumor.

Effects of Vitamin D on Bone Health Among Cancer Survivors

Clinical practice guidelines recommend vitamin D and calcium supplements for subsets of patients with breast and prostate cancer whose bone density can be compromised by chemotherapy-induced menopause, aromatase inhibitors, and androgen deprivation therapy. Recommended doses range between 10 and 25 μg vitamin D and 1,000 to 1,500 mg for calcium.[40,41] The assumption that supplements would benefit bone health and would not cause harm in patients with cancer was based on practice in the noncancer setting. However, recent meta-analyses have questioned the benefits and harms of vitamin D and calcium in the general population and have reported no benefits for vitamin D supplementation alone for bone density or fracture risk. Benefits are limited to higher doses of vitamin D ($>$ 10 μg/day) when combined with calcium ($>$ 1,000 mg) in free living (noninstitutionalized) individuals.[42,43] Other reviews have linked calcium supplementation to increased risk of CVD, although there is a lack of consensus on these findings.[44,45]

The efficacy, safety, and optimum dosage of vitamin D and calcium supplementation for patients with cancer has not been rigorously tested in randomized trials comparing supplements to a no supplement group. A recent review of 16 trials among patients with breast cancer reported declines in lumbar bone mineral density (BMD; 1.5–7.5% during 12 months of breast cancer treatments) in both pre- and postmenopausal women despite daily supplementation with 5 to 25 μg vitamin D and 500 to 1,500 mg calcium. Likewise, a review of 12 trials among patients with prostate cancer concluded that daily supplementation with 5 to 10 μg vitamin D and 500 to 1,000 mg calcium was ineffective in preventing androgen deprivation therapy–related BMD loss.[40] The need for vitamin D and calcium supplementation alongside bisphosphonate therapy for patients with osteoporosis is currently being debated in the noncancer setting. However, supplementation is indicated in patients with low vitamin D status in whom bisphosphonates can provoke hypocalcaemia.[46] Daily supplements of vitamin D (20–25 μg) improve lower limb strength and balance and reduce falls in older adults in the noncancer setting who are vitamin D deficient, but the benefits of vitamin D on musculoskeletal health of patients with cancer is not proven.[47] Given the potential lack of benefit and potential adverse effects of vitamin D and calcium supplements, randomized trials are needed to evaluate the safety and efficacy of calcium and vitamin D on bone and musculoskeletal health and CVD risk and among patients with cancer.

DOCOSAHEXANOIC ACID AND EICOSO PENTANOIC ACID N-3 OIL SUPPLEMENTS

Effects on the Efficacy of Chemotherapy and Outcome

Docosahexanoic Acid (DHA) and eicoso pentanoic acid (EPA) polyunsaturated fats can increase the production of ROS in cancer cells since they are unsaturated and highly peroxidizable. They are currently being tested as potential adjuncts to chemotherapy to maximize the chemosensitivity of tumor cells while either decreasing or not altering drug sensitivity within non-tumor cells. Preliminary data from two recent phase II trials has demonstrated the safety and potential benefits of n-3 fats alongside chemotherapy. DHA supplementation (1.8 g/day) among 25 patients with metastatic breast cancer receiving anthrycycline-based chemotherapy reported increased disease-free survival and longer time to progression in the sub-population of patients with high versus low DHA incorporation into plasma phospholipid. Median time to progression was 8.7 versus 3.5 months ($p = 0.02$), and median overall survival was 34 versus 18 months ($p = 0.007$), associated with reduced anemia and thrombocytopenia (both $p < 0.05$).[48] Likewise, a two-arm nonrandomized phase II study among 46 patients with advanced NSCLC (2.2 g EPA and 0.24–0.5 g DHA/day) reported a greater response: 60% versus 35% ($p = 0.08$).[49] The NIH's clinical trials database includes three ongoing phase III trials assessing the effects of n-3 fats on chemotherapy efficacy and toxicity in patients with metastatic breast cancer (DHALYA NCT01548534), patients with lung cancer (NCT01048970,), and children receiving chemotherapy for acute lymphoblastic leukemia (NCT01051154).

Effects on Cachexia and Performance Status

The potential for EPA and DHA as anticachexia agents was originally demonstrated 20 years ago among patients with cachexic pancreatic cancer by Wilmore et al.[50] N-3 oils downregulate pro-inflammatory cytokine production and the acute-phase protein response in patients with cancer, which plays a central role in cancer cachexia. Furthermore, EPA may inhibit the ubiquitin proteasome pathway, which induces atrophy of skeletal muscle. A recent review by the European Palliative Care Research Collaboration identified only six randomized controlled trials that had directly compared the effects of n-3 fatty acids to standard care without n-3 fatty acids among patients with cancer cachexia.[51] Four out of six high-quality studies found no significant benefits of n-3 oil on appetite, weight, performance status, and quality of life, whereas one reported statistically significant improved survival, median survival 150 days versus 400 days ($p = 0.025$), and one increased physically activity, change in TEE (kcal day 340 [92] versus 68 [134] $p < 0.05$). Eight random-

ized trials reported perioperative n-3 fats reduced postoperative complications. The maximum tolerated dose is 12 g of n-3 oil/day providing 2 g of EPA and 1.5 g DHA. The most common side effects of n-3 oil supplements in these trials are mild abdominal discomfort, flatulence, nausea, steatorrhea, and a fish aftertaste.

A further large randomized controlled trial of EPA (2.18 g/day) versus megestrol acetate (412 patients) reported reduced weight gain with n-3 oil compared with the megestrol acetate arms: 6% versus 18% gained 10% or more of baseline weight ($p = 0.004$). Neither survival nor quality of life was significantly different between the groups ($p = 0.82$). Two recent small trials have reported benefits of n-3 among patients with advanced NSCLC receiving chemotherapy. A randomized controlled trial of 33 patients receiving daily 510 mg EPA and 340 mg DHA reported weight gains of 3.4 kg versus those receiving the placebo.[52] Although a two-arm, nonrandomized phase II trial of 40 patients found 2.2 g/day EPA had better weight maintenance than placebo (−2.3 (0.9) vs. −0.5 (1.0) kg).[52,53] Three ongoing trials are currently assessing the effects of DHA and EPA on chemotherapy-related toxicity or nutritional status (NCT01048463, NCT01025167, NCT01049295).[39]

CONCLUSIONS AND FUTURE PERSPECTIVES

Predictably, administering supplements to unselected patients—often with adequate vitamin status—has not been successful. Identifying and repleting individuals with poor vitamin status may be appropriate and beneficial (e.g., patients undergoing gastric surgery may require B12, iron, or calcium supplementation, while heavy smokers with high alcohol intakes may have low folate status).[1] Although difficult, future research should develop targeted nutritional therapies tailored to background diet, the patients' genetic makeup, tumor histology, and treatments. A targeted approach may yield benefits in subsets of patients in the same way that the pharmaceutical industry has developed more effective cancer therapies targeted to variations in the individual and tumor type. This is not a trivial challenge and will require standardized nutritional data collection within ongoing observational and randomized clinical cancer treatment trials, large-scale collaborations, and pooling of results.[54]

Patients remain highly interested in supplements. This desire to take supplements often diverts patients' attention from pursuing more holistic diet- and exercise-based approaches for maintaining general health and improving outcome after diagnosis. For example, 50% of a breast cancer cohort was taking multivitamins, but 70% of these patients were overweight or obese and 13% were current smokers.[3]

Clinicians should provide appropriate advice for the patient on living a healthy lifestyle, including weight control, a low saturated fat, high fiber, low-refined carbohydrate, moderate alcohol diet, and nutrition support.[1] Clinicians should openly discuss with patients their interest to self-prescribe nutritional supplements and any potential contraindications. Most patients believe that nutritional supplements can do no harm as they are natural, and they are skeptical of adverse reports from clinical trials, which are perceived to be biased toward a medical model.[55] Clinicians should stay up to date with this fast-moving field of research to advise any potential benefits and contraindications that may apply to their patients. Supplements advice needs to be individualized to the patient, come from a credible source, and be communicated by the patient's cancer physician.

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The author(s) indicated no potential conflicts of interest.

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