World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

# EFFICACY AND SAFETY OF SUPPLEMENTS IN CANCER PATIENTS: A 10-YEAR REVIEW AND UPDATES

***Silvia Ussai M.D., PharmD**

Irhythmia Research Organization, Bolzano, Italy.
Bocconi School of Management, Milan, Italy.

***Corresponding Author: Silvia Ussai M.D., PharmD**
Irhythmia Research Organization, Bolzano, Italy.

**Article Received on 08/05/2017** **Article Revised on 28/05/2017** **Article Accepted on 19/06/2017**

## ABSTRACT

Cancer treatment has been always challenging not only because of immediate results but also due to long term outcomes such as survival rates, disease-free intervals and quality of life. Classical treatments (surgery, chemotherapy and radiotherapy) were focused on the tumor itself, leading aside general patient health conditions. Later nutrition began to play a role on cancer treatments, because of its potential implications on long term evolution, especially when abdominal surgery was performed; nevertheless these first findings were related to macronutrients such as proteins. Considering the big number of cancer types and so many potentially beneficial macro and micronutrients, there were still a long way to go and even when many physicians and nutritionists were using a dietary approach as cancer adjuvant therapy, most of knowledge was empirical and no evidence based. On XXI Century experimental research was conducted to identify what's real and what's fake about cancer and nutrition. On this systematic review it's summarized the state of the art and what we know so far regarding nutrition role on cancer patients outcome, i.e. nowadays we are aware that a polyunsaturated fatty acids rich diet may reduce inflammatory status on cervical cancer patients, trace elements such as selenium showed no impact on cancer outcomes when compared to placebo, but its is still recommended due to its effect diminishing chemotherapy side effects. Lycopene and soy isoflavones rich diet may be beneficial on relapsed prostate cancer leading to a slower diseases progression while folic acid is associated to a reduction of colorectal adenoma. On the other hand some nutrients could have deleterious effects such as 25-hydroxyvitamin D which seems to be associated with a slightly risk increase of breast as well on prostatic cancer, however further, larger researches are mandatory to continue the evolution of this novel therapeutic field.

**KEYWORDS:** Cancer, nutrition, cancer prevention, micronutrients cancer, nutritional cancer therapy.

## INTRODUCTION

This review is concerned with supplementations and its effect on cancer patients. We will discuss related papers published on Pubmed up to 10 years ago (95 studies included, Table 1).

First calcium and vitamin D3, a study conducted in 2015 proved that daily supplementation with vitamin D3 (1000 IU), calcium (1200 mg), or both after removal of colorectal adenomas did not significantly reduce the risk of recurrent colorectal adenomas over a period of 3 to 5 years.[1] Another study in 2015 suggested that supplemental calcium and vitamin D3 may increase TGFβ1 expression and shift TGFα expression downward from the differentiation to the proliferation zone in the crypts in the normal-appearing colorectal mucosa of sporadic colorectal adenoma patients, and support further investigation in a larger clinical trial.[2]

Adding fatty acids to diet also affected cancer, in 2015 a study proved that dietary supplementation enriched with polyunsaturated fatty acids (PUFA) can reduce inflammatory status in patients with advanced cervical cancer.[3] Reduced Prostaglandin E2 (PGE2) level will lower the survival of cancer cells; therefore dietary supplementation enriched with PUFA with a ratio of -6: -3 fatty acid = 1.27 : 1 along with radiation therapy may improve tumor response to radiation. Another study was conducted in 2015 in which participants were advised to increase intake of n-3 PUFAs, including fish/shell fish, fish oil supplement and perilla oils, and to decrease consumption of n-6 PUFAs and fats/oils as a whole for 24 months.[4] Results were that plasma concentrations, and compositions of the Red Blood Cells (RBC) and sigmoid colon membranes of n-3 PUFAs, LC n-3 PUFAs, Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) increased, and the ratios of n-6 PUFAs/n-3 PUFAs and AA/LC n-3 PUFAs

decreased without any adverse response. Twenty-four months after the intervention, the multivariate-adjusted hazard ratio (95% confidence intervals) was estimated to be 0.805 (0.536-1.209) with a signal towards the reduced colorectal tumors (CRT) incidence. In 2014, a study made it clear that EPA is incorporated rapidly into colonic mucosa and colonic muscular layer in patients given 3 g of ω-3 FA daily for 7 days before surgery for colorectal cancer. This may lead to potential beneficial effects on (local) immune function, which might benefit these patients.

A study in 2013 alleged that Selenium was safe but conferred no benefit over placebo in the prevention of second primary tumors (SPTs) in patients with resected non-small-cell lung cancer (NSCLC).[5] While another study in 2015 showed that supplementation with Selenium promotes the reduction of chemotherapy side effects in cancer patients, especially by improving the conditions of patients with fatigue, nausea, and impaired physical function and improving renal and hepatic functions.[6] On the other hand, a study conducted in 2015 warned against administration of high doses of lycopene, GTCs, and selenium in men with precancerous prostatic lesions as it was associated with a higher incidence of prostatic cancer (PCa) at re-biopsy and expression of microRNAs implicated in PCa progression at molecular analysis.[7]

In 2015 a study came to a conclusion that zinc sulfate supplementation during head and neck radiation therapy showed no increase in absolute numbers of circulating T lymphocytes, T lymphocyte subpopulations, or survival with acceptable side effects.[8] Although, another study in 2013 proved that zinc supplementation can prevent some of the chemotherapy adverse effects in children with leukemia, improving their quality of life.[9]

Considering probiotics and prebiotics, a study in 2015 proved that perioperative administration of symbiotics reduces postoperative mortality and complication rates in patients undergoing surgery for periampullary neoplasms.[10] While in 2014, a study suggested that Bifidobacterium tetragenous viable bacteria tablets are effective and safe in treating cancer patients with functional constipation during chemotherapy.[11] The results of another study in 2014 open up the possibility that consumption of First Leaf (FL; composed of blackcurrant extract powder, lactoferrin and lutein) and Cassis Anthomix 30 (CAM30; blackcurrant extract powder) can offer various benefits to human health through acting as novel prebiotic agents via increasing the numbers of beneficial bacteria (lactobacilli and bifidobacteria) in the gut.[12] On the other hand, a study in 2013 showed that Dietary supplementation with A. sylvaticus improved nutritional status and reduced abnormal bowel functions, nausea, vomiting, and anorexia in patients with breast cancer receiving chemotherapy.[13]

In the case of omega 3 fatty acids, a study in 2008 concluded that a dose of two omega 3 fatty acid enhanced formulas with different omega3/omega6 ratios improved serum protein concentrations in ambulatory postoperative head and neck cancer patients with good tolerance.[14] Another study conducted in 2012 showed that despite a significant increase in plasma concentrations of Omega-3 fatty acids (O-3FA), immunonutrition with O-3FA did not affect overall HLA-DR expression on leucocytes or clinical outcome following oesophagogastric cancer surgery.[15] Then a study in 2013 proved that Omega 3 and arginine enhanced formulas improved blood protein concentrations and lymphocyte levels in ambulatory postoperative head and neck cancer patients. Also, a high dose of arginine and omega 3 fatty acids formula improved weight, too.[16] Besides, a study in 2014 alleged that a short intervention with EPA was insufficient to reduce inflammation, which may be caused by the frequent abandoning of treatment.[17] Thus, the beginning of chemotherapy may not be the optimal time point to initiate EPA supplementation because uncomfortable effects of both treatments may lead to poor adherence. Additionally, another study in 2014 concluded that oral n-3 FA (n-3 fatty acids) exerts anti-inflammatory effects in surgical patients, without reducing the risk of postoperative complications.[18]
A study in 2014 came to a conclusion that after 4 weeks of daily consumption of flavonoid-rich purple grape juice, no measurable change in vascular function was observed in these childhood cancer survivors.[19]

Regarding Beta-carotene, a decreased prostate cancer risk was observed with increasing intakes of vitamin C-rich vegetables, including bell peppers and broccoli in a study conducted in 2008.[20] While fruits, other vegetables and vitamin A intakes did not appear to be strong factors in the development of prostate cancer in this study. Also in a study in 2011, antioxidant supplementation including β-carotene showed to be effective in reducing oxidative stress in proteins, but it did not on food ingestion. Patients did not meet their antioxidants requirement in their diets in spite of an excess in energy consumption.[21] Antioxidant plasma levels in most of the patients were lower than normal and Quality of Life (QoL) score was better in the supplemented group. According to another study in 2015, no unfavorable side-effects were noted and beta-carotene (10 mg day(-1) ) and vitamin C were neither effective for clinical remission, nor for protection against the development of cancer. Data from this Randomized Controlled Trial (RCT) does not support the hypothesis that chemoprevention with this treatment is effective for oral leukoplakia.[22]

The results of a study in 2007 showed that lycopene and soy isoflavones have activity in prostate cancer patients with Prostatic Specific Antigen (PSA) relapses disease and may delay progression of both hormone-refractory and hormone-sensitive prostate cancer.[23] However,

there may not be an additive effect between the 2 compounds when taken together. Future studies are warranted to further investigate the efficacy of lycopene and soy isoflavones in prostate cancer as well as the mechanism of potential negative interaction between them. Another study in 2010 came to a conclusion that although high amounts of aglycone isoflavones (aglycone-rich soy extract) may result in significantly elevated serum concentrations of genistein and daidzein, these dietary supplements alone did not lower PSA levels in men with low-volume prostate cancer.[24] Meanwhile, the trial of a study in 2011 does not support the hypothesis that combination vitamin E, selenium, and soy prevents progression from High-grade prostatic intraepithelial neoplasia (HGPIN) to invasive prostate cancer (InPCa).[25] In 2012, a study proved that a 6-month intervention of mixed soy isoflavones in healthy, high-risk adult western women did not reduce breast epithelial proliferation, suggesting a lack of efficacy for breast cancer prevention and a possible adverse effect in premenopausal women.[26] Moreover, a study in 2013 proved that daily consumption of a beverage powder supplement containing soy protein isolate for 2 years following radical prostatectomy did not reduce biochemical recurrence of prostate cancer in men at high risk of PSA failure.[27] Another study in 2013 concluded that three-year ISP (isoflavone soy protein) supplementation has no effect on endometrial thickness or on the rates of endometrial hyperplasia and cancer in postmenopausal women.[28] On the other hand, a study in 2014 found that gene expression associated with soy intake and high plasma genistein defines a signature characterized by overexpression of FGFR2 (Fibroblast growth factor receptor 2) and genes that drive cell cycle and proliferation pathways.[29] These findings raise the concerns that in a subset of women soy could adversely affect gene expression in breast cancer. According to the results of another study conducted in 2014, patients in the MB-6 group (MB-6 is a promising botanical supplement that may increase the effectiveness of chemotherapy in patients with metastatic colorectal cancer) had a significantly lower disease progression rate than patients in the placebo group, during the study period (0.0% vs 15.8%, P = .026). The placebo group had a significantly higher incidence of adverse events at least grade 4 compared with the MB-6 group (28.9% vs 2.9%, respectively, P = .004) and a significantly higher occurrence of increased serum creatinine compared with the MB-6 group (29%vs5.9%, P=.014).[30]

A study in 2014 proved that *Echium* oil effectively increased erythrocyte EPA and γ-linolenic acid (GLA) fatty acids in head and neck cancer patients. It failed however to protect against weight loss, or improve nutritional parameters.[31]

In a study conducted in 2014 on combination herbal supplement, Prostate Health Cocktail (PHC), it was concluded that although the primary end point was not met, PHC was well tolerated and was associated with PSA declines and stabilization in a significant number of patients. We believe this is the first report of detecting Circulating tumor cells (CTCs) in men with biochemical recurrence (BCR) prostate cancer. Randomized studies are needed to better define the effect of PHC in men with BCR.[32]

Another study was done in 2014 on oral capsule containing a blend of pomegranate, green tea, broccoli and turmeric. This study found a significant short-term, favourable effect on the percentage rise in PSA in men managed with active surveillance and watchful waiting following ingestion of this well-tolerated, specific blend of concentrated foods.[33] Its influence on decision-making suggests that this intervention is clinically meaningful, but further trials will evaluate longer term clinical effects, and other markers of disease progression.

In 2011 a study on fish oil (FO)-derived eicosapentaenoic acid (EPA) came to a conclusion that nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with non small cell lung cancer (NSCLC) receiving chemotherapy.[34] Whereas nutritional intervention with 2.2 g of FO per day appears to provide a benefit over standard of care (SOC), resulting in the maintenance of weight and muscle mass during chemotherapy. In 2014, another study on oral nutritional supplement containing eicosapentaenoic acid showed that patients with NSCLC receiving ONS-EPA significantly improves energy and protein intake, body composition and decreased fatigue, loss of appetite and neuropathy.[35]

The findings of a study in 2014 suggest that beta glucan can be useful as a complementary or adjuvant therapy and immunomodulatory agent in breast cancer patients in combination with cancer therapies, but further studies are needed for confirmation.[36]

A study in 2014 researched the effect of perioperative omega-3 fatty acid supplements in elective colorectal cancer surgery. EPA, DHA and DPA (Docosapentaenoic acid) were incorporated into granulocytes in patients receiving ω-3 FAs, but this was not associated with improved postoperative outcomes.[37]

In a study in 2013 chemotherapy has been supplemented with ascorbic acid (vitamin C dose of 600 mg per day). In conclusion, the supplementation of the chemotherapy of NSCLC patients with C vitamin leads to rise of the low concentrations of A, C and E vitamins in the plasma. This suggests strengthening of the antioxidative barrier in patients.[38]

An exploratory pilot study conducted in 2013 suggests that the probiotic studied promotes the clearance of Human Papillomavirus (HPV) related cytological abnormalities.[39] If confirmed, this would represent an

entirely new option to manage cervical cancer precursors.

Regarding fish oil, a study in 2011 that researched the effect of lycopene and fish oil supplementation in prostate cancer patients did not detect significant individual genes associated with dietary intake and supplementation of lycopene and fish oil.[40] However, exploratory analyses revealed candidate in vivo pathways that may be modulated by these micronutrients. Another study in 2011 researched the effect of low-fat diet with fish oil supplementation in prostate cancer patient and found that four to six weeks of a low-fat diet and fish oil capsules to achieve an omega-6:omega-3 fatty acid ratio of 2:1 had no effect on serum IGF-1 (Insulin-like growth factor 1) levels,[41] though in secondary analyses, the intervention resulted in decreased prostate cancer proliferation and decreased prostate tissue omega-6:omega-3 ratios. These results support further studies evaluating reduction of dietary fat with fish oil supplementation on modulating prostate cancer biology. A third study also conducted in 2011 researched the effect of fish oil in patients with advanced non-small cell lung cancer.[42] The results have shown that supplementation with fish oil (FO) can increase chemotherapy efficacy without negatively affecting non target tissue. This study evaluated whether the combination of FO and chemotherapy (carboplatin with vinorelbine or gemcitabine) provided a benefit over SOC (standard of care) on response rate and clinical benefit from chemotherapy in patients with advanced NSCLC. Compared with SOC, supplementation with FO results in increased chemotherapy efficacy without affecting the toxicity profile and may contribute to increased survival. On the other hand, a study in 2012 proved that colorectal cancer patients supplemented with fish oil (SG) showed a clinically relevant decrease in the C-reactive protein/albumin relation (P = 0.005). Low doses of fish oil supplement can positively modulate the nutritional status and the C-reactive protein/albumin ratio.[43] Another study in 2012 alleged that Fish oil may be useful in preventing chemotherapy-induced decline in neutrophil number and function.[44] Meanwhile, a third study in 2012 came to a conclusion that supplementation of fish oil has a positive effect on appetite level, caloric intake and MUAMC (mid upper arm muscle circumference) among children with leukaemia.[45] In 2013, a study demonstrated that 2 g/day of fish oil for 9 weeks of chemotherapy improves C Reactive Protein (CRP) values, CRP/albumin status, plasma fatty acid profile and potentially prevents weight loss during treatment.[46] Whereas another study in 2013 showed that ω-3 PUFAs supplemented parenteral nutrition can reduce inflammation and improve immune function in patients following esophageal cancer surgery.[47] A larger trial is required to see whether ω-3 PUFAs supplementation of PN improves the clinical outcomes of patients following esophageal cancer surgery.

A study in 2013 concluded that Deuterium depleted water (DDW) counteracts the 7,12-dimethylbenzanthracene (DMBA)-induced overexpression of Bcl2, Kras and Myc genes in mouse lung and it may extend survival of lung cancer patients as a nontoxic anticancer dietary supplement, especially for women with tumors overexpressing cancer-related genes as MST of DDW-consuming group was 2-4 times longer than it is generally observed in lung cancer patients.[48]

Considering flaxseed supplementation, a study in 2008 suggested that flaxseed is safe and associated with biological alterations that may be protective for prostate cancer.[49] Also another study in 2013 came to a conclusion that flaxseed-derived enterolignans may hinder cancer cell proliferation via Vascular Endothelial Growth Factor (VEGF)-associated pathways.[50]

According to the results of a study in 2013 conjugated linoleic acid (CLA) supplementation improved inflammatory factors, MMP-2, and MMP-9 as biomarkers of angiogenesis and tumor invasion. It seems that CLA may provide new complementary treatment by reducing tumor invasion and resistance to cancer treatment in patients with rectal cancer.[51]

Another study in 2013 concluded that primary prevention with 1 mg/day folic acid supplementation could reduce the incidence of CRA (colorectal adenoma), especially left-sided and advanced disease in those with no previous adenomas.[52] People with differing baseline plasma folate levels should be given individualized treatment. Those with low plasma folate should be encouraged to take adequate supplements; plasma folate should be elevated to an effective therapeutic level, which may reduce the incidence of CRA.

A study in 2012 alleged that four weeks of 2 g of L-carnitine supplementation did not improve fatigue in patients with invasive malignancies and good performance status.[53] Another study in 2012 announced that although these data are preliminary and need confirmation they indicate that patients with pancreatic cancer may have a clinically relevant benefit from the inexpensive and well tolerated oral supplementation of L-Carnitine.[54] As for the effect of Acetyl-L-carnitine in women undergoing adjuvant breast cancer therapy, a study in 2013 showed that there was no evidence that ALC (Acetyl-L-carnitine) affected CIPN (Chemotherapy-induced peripheral neuropathy) at 12 weeks; however, ALC significantly increased CIPN by 24 weeks. This is the first study to our knowledge showing that a nutritional supplement increased CIPN. Patients should be discouraged from using supplements without proven efficacy.[55]

A study in 2013 investigated two types of enteral supplements, an antioxidant-enriched enteral nutrition (AeEN) and an immune-enhancing enteral nutrition

(IeEN) after esophagectomy for cancer. The results of this pilot study suggest that AeEN and IeEN have a similar effect on nutrition, the immunoinflammatory response, antioxidant capacity and clinical outcomes after esophagectomy for cancer. These findings, therefore, warrant further studies on a larger scale.[56] Additionally, another study in 2013 showed that antioxidant supplementation in patients treated with chemotherapy and radiotherapy apparently decreased oxidative stress, maintained hemoglobin levels, and improved QoL; however, more studies are needed to study the long-term effect of this intervention.[57]

The result of a pilot study conducted in 2013 suggest ginger may reduce proliferation in the normal-appearing colorectal epithelium and increase apoptosis and differentiation relative to proliferation-especially in the differentiation zone of the crypts and support a larger study to further investigate these results.[58]

On the other hand, a study in 2012 oral supplements of selenium (Se) and zinc (Zn) produce metabolic effects in patients with liver cirrhosis/cancer. It was observed that the status of essential trace elements, Se and Zn, was improved in biological samples of all patients after 60 days of treatment with mineral supplementation.[59]

Synsepalum dulcificum-known as "miracle fruit" was proven to improve food palatability for patients receiving chemotherapy by a study in 2012.[60]

A study in 2012 came to a conclusion that daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.[61]

A study in 2013 proved that oral supplementation of branched-chain amino acids (BCAA) reduces early recurrence after hepatic resection in patients with Hepatocellular Carcinoma (HCC). This treatment regimen offers potential benefits for clinical use in such patients, even in cases with a well-preserved preoperative liver function.[62]

In a study in 2011, Dietary supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men.[63] Another study in 2011 confirmed that in all other subsets defined by baseline blood selenium levels, selenium supplementation had no effect on prostate cancer risk.[64] The 36% prostate cancer rate in men with High-Grade Prostatic Intraepithelial Neoplasia (HGPIN) indicates the association of this lesion with an elevated prostate cancer risk. Future study in this setting should focus on selenium-deficient populations and selenium pharmacogenetics**.** Furthermore, the analysis of a study in 2012 showed no preventive effect of selenium or vitamin E alone or combined on bladder cancer in this population of men and that further studies are needed to assess the effect in women, and at different doses and formulations.[65] On the other hand, in a study in 2013, Selenium supplementation appeared to have no effect on the incidence of prostate cancer in men at high risk.[66] In conjunction with results of other studies, these data indicate that selenium supplementation may not have a role in prostate cancer chemoprevention.

Back again on Vitamin D, but this time specifically on 25-hydroxyvitamin D [25(OH)D]; several studies have examined its associations with cancer risk with inconclusive results; however by 2016 a metanalysis from the two biggest cohorts studies in Europe, ESTHER (Germany) and TROMSØ (Norway), showed that decreased 25(OH)D circulating level are not associated with an increased risk of cancer while elevated levels may show different behaviors depending of the onset, on this regard evidence suggest a slightly breast cancer risk increase associated with high levels of 25-hydroxyvitamin D while lymphoma risk seems to be decreased.[67] On the other hand, same as in breast cancer, data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial suggest a moderate increase of prostatic cancer among black men with higher 25-hydroxyvitamin D circulating levels.[68] Still related to Vitamin D but this time D2 and D3 Vitamins, a case control trials conducted by Haznadar et al. on 2016 showed a potential protective effect against lung cancer.[69] Regarding colorectal cancer, despite of inconclusive data associated with Vitamin D3 protective role against colon adenomas proliferation,[1] 25-hydroxyvitamin D showed an inverse association with colorectal cancer on a report from Warren et al. on 2016, opening a new research window on research about the protective role of Vitamin D on colorectal cancer.[70]

## REFERENCES


1. Baron, J. A., Barry, E. L., Mott, L. A., Rees, J. R., Sandler, R. S., Snover, D. C., ... & Beck, G. J. (2015). A trial of calcium and vitamin D for the prevention of colorectal adenomas. *N Engl J Med*, 2015; 373: 1519-1530.
2. Tu, H., Flanders, W. D., Ahearn, T. et al. Effects of calcium and vitamin D3 on transforming growth factors in rectal mucosa of sporadic colorectal adenoma patients: a randomized controlled trial. *Molecular carcinogenesis*, 2015; 54(4): 270-280.
3. Wuryanti, S., Andrijono, A., Susworo, S. and Witjaksono, F., The Effect of High Poly Unsaturated Fatty Acid (PUFA) Dietary Supplementation on Inflammatory Status of Patients with Advanced Cervical Cancer on Radiation Treatment. *Acta Medica Indonesiana*, 2015; 47(1).
4. Tokudome, S., Kuriki, K., et al., Dietary n-3/long-chain n-3 polyunsaturated fatty acids for prevention of sporadic colorectal tumors: a randomized controlled trial in polypectomized participants. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA)*, 2015; 94: 1-11.
5. Karp, D. D., Lee, S. J.et al., Randomized, double-blind, placebo-controlled, phase III

chemoprevention trial of selenium supplementation in patients with resected stage I non–small-cell lung cancer: ECOG 5597. *Journal of Clinical Oncology*, 2013; 31(33): 4179-4187.
6. Vieira, M. L. D. S., Fonseca, F. L. A. et al., Supplementation with selenium can influence nausea, fatigue, physical, renal, and liver function of children and adolescents with cancer. *Journal of medicinal food*, 2015; 18(1): 109-117.
7. Gontero, P., Marra, G. et al., A randomized double-blind placebo controlled phase I–II study on clinical and molecular effects of dietary supplements in men with precancerous prostatic lesions. Chemoprevention or "chemopromotion"?. *The Prostate*, 2015; 75(11): 1177-1186.
8. Sangthawan, D., Phungrassami, T., Sinkitjarurnchai, W., Effects of zinc sulfate supplementation on cell-mediated immune response in head and neck cancer patients treated with radiation therapy. *Nutrition and cancer*, 2015; 67(3): 449-456.
9. Consolo, L. Z. Z., Melnikov, P. et al., Zinc supplementation in children and adolescents with acute leukemia. *European journal of clinical nutrition*, 2013; 67(10): 1056-1059.
10. Sommacal, H. M., Bersch, V. P. et al., Perioperative synbiotics decrease postoperative complications in periampullary neoplasms: a randomized, double-blind clinical trial. *Nutrition and cancer*, 2015; 67(3): 457-462.
11. Liu, J., & Huang, X. E. Efficacy of bifidobacterium tetragenous viable bacteria tablets for cancer patients with functional constipation. *Asian Pac J Cancer Prev*, 2014; 15: 10241-4.
12. Molan, A. L., Liu, Z., Plimmer, G., Evaluation of the effect of blackcurrant products on gut microbiota and on markers of risk for colon cancer in humans. *Phytotherapy Research*, 2014; 28(3): 416-422.
13. Valadares, F., Novaes, M. R. C. G., Cañete, R., Effect of Agaricus sylvaticus supplementation on nutritional status and adverse events of chemotherapy of breast cancer: A randomized, placebo-controlled, double-blind clinical trial. *Indian journal of pharmacology*, 2013; 45(3); 217.
14. De Luis, D. A., Izaola, O., Aller, R., Cuellar, L., Terroba, M. C., Martin, T. A randomized clinical trial with two omega 3 fatty acid enhanced oral suplements in head and neck cancer ambulatory patients. *European review for medical and pharmacological sciences*, 2008; 12(3): 177.
15. Sultan, J., Griffin, S. M. et al., Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. *British Journal of Surgery*, 2012; 99(3): 346-355.
16. Sultan, J., Griffin, S. M. et al., Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. *British Journal of Surgery*, 2012; 99(3): 346-355.
17. Pastore, C. A., Orlandi, S. P., Gonzalez, M. C., Introduction of an omega-3 enriched oral supplementation for cancer patients close to the first chemotherapy: may it be a factor for poor compliance?. *Nutrition and cancer*, 2014; 66(8): 1285-1292.
18. Sorensen, L. S., Thorlacius-Ussing, O., Schmidt, E. B., Rasmussen, H. H., Lundbye-Christensen, S., Calder, P. C., Lindorff-Larsen, K. Randomized clinical trial of perioperative omega-3 fatty acid supplements in elective colorectal cancer surgery. *British Journal of Surgery*, 2014; 101(2): 33-42.
19. Blair, C. K., Kelly, A. S., Steinberger, J., Eberly, L. E., Napurski, C., Robien, K., Ross, J. A., Feasibility and preliminary efficacy of the effects of flavanoid-rich purple grape juice on the vascular health of childhood cancer survivors: A randomized, controlled crossover trial. *Pediatric blood & cancer*, 2014; 61(12): 2290-2296.
20. Ambrosini, G. L., de Klerk, N. H., Fritschi, L., Mackerras, D., Musk, B., Fruit, vegetable, vitamin A intakes, and prostate cancer risk. *Prostate cancer and prostatic diseases*, 2008; 11(1): 61-66.
21. Fuchs-Tarlovsky, V., Bejarano-Rosales, M., Gutierrez-Salmeán, G., Casillas, M. A., López-Alvarenga, J. C., Ceballos-Reyes, G. M., Effect of antioxidant supplementation over oxidative stress and quality of life in cervical cancer. *Nutricion hospitalaria*, 2010; 26(4): 819-826.
22. Nagao, T., Warnakulasuriya, S., Nakamura, T. et al., Treatment of oral leukoplakia with a low-dose of beta-carotene and vitamin C supplements: A randomized controlled trial. *International Journal of Cancer*, 2015; 136(7): 1708-1717.
23. Vaishampayan, U., Hussain, M. et al., Lycopene and soy isoflavones in the treatment of prostate cancer. *Nutrition and cancer*, 2007; 59(1): 1-7.
24. deVere White, R. W., Tsodikov, A., Stapp, E. C., Soares, S. E., Fujii, H., Hackman, R. M., Effects of a high dose, aglycone-rich soy extract on prostate-specific antigen and serum isoflavone concentrations in men with localized prostate cancer. *Nutrition and cancer*, 2010; 62(8): 1036-1043.
25. Fleshner, N. E., Kapusta, L., Donnelly, B., Tanguay, S., Chin, J., Hersey, K., Lacombe, L. Progression from high-grade prostatic intraepithelial neoplasia to cancer: a randomized trial of combination vitamin-E, soy, and selenium. *Journal of Clinical Oncology*, 2011; 29(17): 2386-2390.
26. Khan, S. A., Chatterton, R. T., Michel, N., Bryk, M., Lee, O., Ivancic, D., Franke, A. A., Soy isoflavone supplementation for breast cancer risk reduction: a randomized phase II trial. *Cancer Prevention Research*, 2012; 5(2): 309-319.
27. Bosland, M. C., Kato, I. et al., Effect of soy protein isolate supplementation on biochemical recurrence

of prostate cancer after radical prostatectomy: a randomized trial. *Jama*, 2013; 310(2): 170-178.
28. Quaas, A. M., Kono, N., Mack, W. J., Hodis, H. N., Felix, J. C., Paulson, R. J., Shoupe, D. The effect of isoflavone soy protein supplementation on endometrial thickness, hyperplasia and endometrial cancer risk in postmenopausal women: a randomized controlled trial. *Menopause (New York, NY)*, 2013; 20(8): 840.
29. Shike, M., Doane, A. S. et al., The effects of soy supplementation on gene expression in breast cancer: a randomized placebo-controlled study. *Journal of the National Cancer Institute*, 2014; 106(9): 189.
30. Chen, W. T. L., Yang, T. S. et al., Effectiveness of a novel herbal agent MB-6 as a potential adjunct to 5-fluoracil–based chemotherapy in colorectal cancer. *Nutrition Research*, 2014; 34(7): 585-594.
31. Pottel, L., Lycke, M. et al., Echium oil is not protective against weight loss in head and neck cancer patients undergoing curative radio (chemo) therapy: a randomised-controlled trial. *BMC complementary and alternative medicine*, 2014; 14(1): 382.
32. Dorff, T. B., Groshen, S. et al., A Phase II trial of a combination herbal supplement for men with biochemically recurrent prostate cancer. *Prostate cancer and prostatic diseases*, 2014; 17(4): 359-365.
33. Thomas, R., Williams, M., Sharma, H., Chaudry, A., Bellamy, P., A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer—the UK NCRN Pomi-T study. *Prostate cancer and prostatic diseases*, 2014; 17(2): 180-186.
34. Murphy, R. A., Mourtzakis, M., Chu, Q. S., Baracos, V. E., Reiman, T., Mazurak, V. C., Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. *Cancer*, 2011; 117(8): 1775-1782.
35. Sánchez-Lara, K., Turcott, J. G., Juárez-Hernández, E., Nuñez-Valencia, C., Villanueva, G., Guevara, P., Arrieta, O. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: Randomised trial. *Clinical Nutrition*, 2014; 33(6): 1017-1023.
36. Ostadrahimi, A., Ziaei, J. E., Esfahani, A., Jafarabadi, M. A., Movassaghpourakbari, A., Farrin, N. Effect of beta glucan on white blood cell counts and serum levels of IL-4 and IL-12 in women with breast cancer undergoing chemotherapy: a randomized double-blind placebo-controlled clinical trial. *Asian Pac J Cancer Prev*, 2014; 15(14): 5733-9.
37. Sorensen, L. S., Rasmussen, H. H., Aardestrup, I. V., Thorlacius-Ussing, O., Lindorff-Larsen, K., Schmidt, E. B., Calder, P. C., Rapid incorporation of ω-3 fatty acids into Colonic tissue after oral supplementation in patients with colorectal cancer: a randomized, placebo-controlled intervention trial. *Journal of Parenteral and Enteral Nutrition*, 2014; 38(5): 617-624.
38. Tokarski, S., Rutkowski, M., Godala, M., Mejer, A., Kowalski, J., The impact of ascorbic acid on the concentrations of antioxidative vitamins in the plasma of patients with non-small cell lung cancer undergoing first-line chemotherapy. *Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego*, 2013; 35(207): 136-140.
39. Verhoeven, V., Renard, N., Makar, A., Van Royen, P., Bogers, J. P., Lardon, F., Baay, M., Probiotics enhance the clearance of human papillomavirus-related cervical lesions: a prospective controlled pilot study. *European Journal of Cancer Prevention*, 2013; 22(1): 46-51.
40. Aronson, W. J., Kobayashi, N. et al., Phase II prospective randomized trial of a low-fat diet with fish oil supplementation in men undergoing radical prostatectomy. *Cancer prevention research*, 2011; 4(12): 2062-2071.
41. Magbanua, M. J. M., Roy, R. et al., Gene expression and biological pathways in tissue of men with prostate cancer in a randomized clinical trial of lycopene and fish oil supplementation. *PLoS One*, 2011; 6(9): e24004.
42. Murphy, R. A., Mourtzakis, M., Chu, Q. S., Baracos, V. E., Reiman, T., Mazurak, V. C., Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. *Cancer*, 2011; 117(16): 3774-3780.
43. Silva, J. D. A. P., Trindade, E. B. S. D. M., Fabre, M. E. D. S., Menegotto, V. M., Gevaerd, S., Buss, Z. D. S., Frode, T. S., Fish oil supplement alters markers of inflammatory and nutritional status in colorectal cancer patients. *Nutrition and cancer*, 2012; 64(2): 267-273.
44. Bonatto, S. J., Oliveira, H. H. et al., Fish oil supplementation improves neutrophil function during cancer chemotherapy. *Lipids*, 2012; 47(4): 383-389.
45. Zaid, Z. A., Shahar, S., Jamal, A. R. A., Yusof, N. A. M. Fish oil supplementation is beneficial on caloric intake, appetite and mid upper arm muscle circumference in children with leukaemia. *Asia Pacific journal of clinical nutrition*, 2012; 21(4): 502-510.
46. Mocellin, M. C. et al., Fish oil decreases C-reactive protein/albumin ratio improving nutritional prognosis and plasma fatty acid profile in colorectal cancer patients. *Lipids*, 2013; 48(9): 879-888.
47. Long, H., Yang, H., Lin, Y., Situ, D., Liu, W., Fish oil-supplemented parenteral nutrition in patients following esophageal cancer surgery: effect on inflammation and immune function. *Nutrition and cancer*, 2013; 65(1): 71-75.
48. Gyöngyi, Z., Budán, F., Szabó, I., Ember, I., Kiss, I., Krempels, K., Somlyai, G., Deuterium depleted water effects on survival of lung cancer patients and

expression of Kras, Bcl2, and Myc genes in mouse lung. *Nutrition and cancer*, 2013; 65(2): 240-246.
49. Demark-Wahnefried, W., Polascik, T. J. et al., Flaxseed supplementation (not dietary fat restriction) reduces prostate cancer proliferation rates in men presurgery. *Cancer Epidemiology and Prevention Biomarkers*, 2008; 17(12): 3577-3587.
50. Azrad, M., Vollmer, R. T. et al., Flaxseed-derived enterolactone is inversely associated with tumor cell proliferation in men with localized prostate cancer. *Journal of medicinal food*, 2013; 16(4): 357-360.
51. Mohammadzadeh, M., Faramarzi, E., Mahdavi, R., Nasirimotlagh, B., Asghari Jafarabadi, M., Effect of conjugated linoleic acid supplementation on inflammatory factors and matrix metalloproteinase enzymes in rectal cancer patients undergoing chemoradiotherapy. *Integrative cancer therapies*, 2013; 12(6): 496-502.
52. Gao, Q. Y., Chen, H. M. et al., Folic acid prevents the initial occurrence of sporadic colorectal adenoma in Chinese older than 50 years of age: a randomized clinical trial. *Cancer Prevention Research*, 2013; 6(7): 744-752.
53. Cruciani, R. A., Zhang, J. J., Manola, J., Cella, D., Ansari, B., Fisch, M. J., L-carnitine supplementation for the management of fatigue in patients with cancer: an eastern cooperative oncology group phase III, randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology*, 2012; 30(31): 3864-3869.
54. Kraft, M., Kraft, K., Gärtner, S., Mayerle, J., Simon, P., Weber, E., Gröber, U., L-Carnitine-supplementation in advanced pancreatic cancer (CARPAN)-a randomized multicentre trial. *Nutrition journal*, 2012; 11(1): 52.
55. Hershman, D. L., Unger, J. M. et al., Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. *Journal of Clinical Oncology*, 2013; 31(20): 2627-2633.
56. Nagano, T., Fujita, H., Tanaka, T., Matono, S., Murata, K., Ishibashi, N, Yanagawa, T., A randomized controlled trial comparing antioxidant-enriched enteral nutrition with immune-enhancing enteral nutrition after esophagectomy for cancer: a pilot study. *Surgery today*, 2013; 43(11): 1240-1249.
57. Fuchs-Tarlovsky, V., Rivera, M. A. C., Altamirano, K. A., Lopez-Alvarenga, J. C., Ceballos-Reyes, G. M. Antioxidant supplementation has a positive effect on oxidative stress and hematological toxicity during oncology treatment in cervical cancer patients. *Supportive Care in Cancer*, 2013; 21(5): 1359-1363.
58. Citronberg, J., Bostick, R., Ahearn, T. et al., Effects of ginger supplementation on cell-cycle biomarkers in the normal-appearing colonic mucosa of patients at increased risk for colorectal cancer: results from a pilot, randomized, and controlled trial. *Cancer Prevention Research*, 2013.
59. Kazi, T. G., Kolachi, N. F., Afridi, H. I., Kazi, N. G., Arain, S. S. Effects of mineral supplementation on liver cirrhotic/cancer male patients. *Biological trace element research*, 2012; 150(1-3): 81-90.
60. Wilken, M. K., Satiroff, B. A., CHTP, R. Pilot study of" miracle fruit" to improve food palatability for patients receiving chemotherapy. *Clinical journal of oncology nursing*, 2012; 16(5): E173.
61. Gaziano, J. M., Sesso, H. D. et al., Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *Jama*, 2012; 308(18): 1871-1880.
62. Ichikawa, K., Okabayashi, T. et al. Oral supplementation of branched-chain amino acids reduces early recurrence after hepatic resection in patients with hepatocellular carcinoma: a prospective study. *Surgery today*, 2013; 43(7): 720-726.
63. Klein, E. A., Thompson, I. et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Jama*, 2011; 306(14): 1549-1556.
64. Marshall, J. R., Tangen, C. M. et al., Phase III trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia: SWOG S9917. *Cancer Prevention Research*, 2011; 4(11): 1761-1769.
65. Lotan, Y., Goodman, P. J. et al., Evaluation of vitamin E and selenium supplementation for the prevention of bladder cancer in SWOG coordinated SELECT. *The Journal of urology*, 2012; 187(6): 2005-2010.
66. Algotar, A. M., Stratton, M. et. al., Phase 3 clinical trial investigating the effect of selenium supplementation in men at high-risk for prostate cancer. *The Prostate*, 2013; 73(3): 328-335.
67. Ordóñez-Mena, J. M., et al., Pre-diagnostic vitamin D concentrations and cancer risks in older individuals: an analysis of cohorts participating in the CHANCES consortium. *European Journal of Epidemiology*, 2016; 31(3): 311-323.
68. Peters, U., Leitzmann, M. F. et al., Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiology and Prevention Biomarkers*, 2007; 16(5): 962-968.
69. Haznadar, M., Krausz, K. W. et al., Circulating vitamin D2 and D3 levels and single nucleotide polymorphism associations with lung cancer status: A case-control study. AACR 107th Annual Meeting 2016; April 16-20, 2016; New Orleans, LA, 2016.
70. Warren et al., Total and free vitamin D, vitamin D binding protein, and colorectal cancer risk in the Southern Community Cohort Study. *Cancer Research*, 2017; 17(77): (3 Supplement) B34.