Most Common Supplements Used by Oncology Patients: *If, When and Why*

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MAY 25, 2016

Disclosure

I have nothing to disclose

Menu for Today

- Introduction
- Identify resources to get current information regarding dietary supplements
- Identify dietary supplements most commonly used by cancer patients
- Recognize dietary supplements with potential benefits and adverse treatment interaction
- Review some of the newer research
- Conclusions
- Questions

Not on the Menu for Today (will not discuss…)

- Pediatrics
- IV supplements
- Chinese/Ayurvedic medicines
- Supplements with multiple ingredients
- Oral liquid supplements (Ensure, Enu…)
- Tube feeding formulas (Impact…)
- Supplements related to cancer prevention
- Food…

Why Focus on Dietary Supplements?

J Cancer Surviv. 2016 Feb 26. [Epub ahead of print]

Complementary and alternative medicine use among US cancer survivors.

John GM[1], Hershman DL[1,2,3], Falci L[1], Shi Z[1], Tsai WY[3,4], Greenlee H[5,6].

⊕ **Author information**

Abstract

PURPOSE: US cancer survivors commonly use vitamins/minerals and complementary and alternative medicine (CAM). We compare use of vitamins/minerals and CAM between adult cancer survivors and cancer-free adults and estimate annual out-of-pocket expenses.

METHODS: Data on self-reported vitamin/mineral and CAM use in the past 12 months from the cross-sectional 2012 US National Health Interview Survey were used to estimate prevalence of use and out-of-pocket expenditures. The cohort included adults with (n = 2977) and without (n = 30,551) a self-reported cancer diagnosis.

RESULTS: Approximately 79 % of cancer survivors and 68 % of cancer-free adults reported using ≥1 vitamins/minerals and/or CAM modality in the past year. Compared to cancer-free adults, cancer survivors were more likely to report use of vitamin/minerals (75 vs. 61 %, P < 0.001), non-vitamin/mineral natural products (24 vs. 19 %, P < 0.001), manipulative and body-based therapies (19 vs. 17 %, P = 0.03), and alternative medical systems (5 vs. 4 %, P = 0.04). Adult cancer survivors and cancer-free adults spent an annual estimated $6.7 billion and $52 billion out-of-pocket, respectively, on vitamins/minerals and CAM. Survivors spent 60 % of the total on vitamins/minerals ($4 billion), 18 % ($1.2 billion) on non-vitamin/mineral natural products, and 7 % ($0.5 billion) on massage.

CONCLUSIONS: Compared with cancer-free adults, a higher proportion of cancer survivors report vitamin/mineral and CAM use. Cancer survivors, who accounted for 6.9 % of the total population, accrued more than 11.4 % of the annual out-of-pocket costs on vitamins/minerals and CAM spent by US adults.

IMPLICATIONS FOR CANCER SURVIVORS: Given the high use of vitamins/minerals and CAM in cancer survivors, studies are needed to analyze health outcomes and the cost/benefit ratio of such use.

Some Common Side Effects During Cancer Treatment (Acute)

- Nausea
- Vomiting
- Diarrhea
- Constipation
- Fatigue
- Chemotherapy-induced peripheral neuropathy
- Dysgeusia
- Xerostomia
- Weight loss /Weight gain
- Hair loss
- Low white blood cell count
- Anemia

Some Potential Side Effects After Cancer Treatment (Chronic) - Survivorship

- Fatigue
- Osteoporosis/Osteopenia
- High lipid levels (cholesterol/triglycerides)
- Joint/muscle pain
- Chemotherapy-induced peripheral neuropathy
- Weight gain / Weight loss
- GI issues

Reasons for Dietary Supplement Use by Cancer Patients

- Manage cancer-related side effects
- Manage treatment-related side effects
- Enhance efficacy of cancer treatment
- Support or strengthen immune system
- Reduce risk of cancer recurrence and prevent other cancers
- Manage other chronic conditions
- Improve quality of life (QOL)

“Dietary Supplement” (DS)

- Contains one or more of the following dietary ingredients:
  - Vitamins
  - Minerals
  - Herbs or other botanicals
  - Amino acids
  - A dietary substance for use by people to supplement the diet by increasing the total dietary intake (enzymes…)
  - A concentrate, metabolite, constituent, extract
  - A combination of any ingredient mentioned above

Legislation

"Dietary supplements" were defined in a law passed by Congress in 1994 called the Dietary Supplement Health and Education Act (DSHEA)

DS regulated as a class of food, not drug

Under jurisdiction of Food and Drug Administration (FDA)

DSHEA

A “dietary supplement” is:

- Intended to be taken by mouth
- In the form of tablet, capsule, powder, softgel, gelcap or liquid (not IV)
- Not intended to diagnose, treat, cure, alleviate or prevent any disease
- Can be used to enhance, optimize, promote, aid, manage, support or maximize a response

DSHEA - FDA Allows Certain Health Claims

- 3 types of claims are allowed to be used for the advertising of dietary supplements:
  1. Structure/Function claim
     - " Magnesium builds strong bones"
       - CANNOT SAY "Magnesium prevents osteoporosis"
  2. Health claim
     - "Fiber may reduce the risk of heart disease"
     - CANNOT SAY " Fiber decreases risk of heart disease"
  3. Nutrient Content claim
     - "Contains 300 mg of curcumin"

DSHEA - FDA Allows Certain Claims

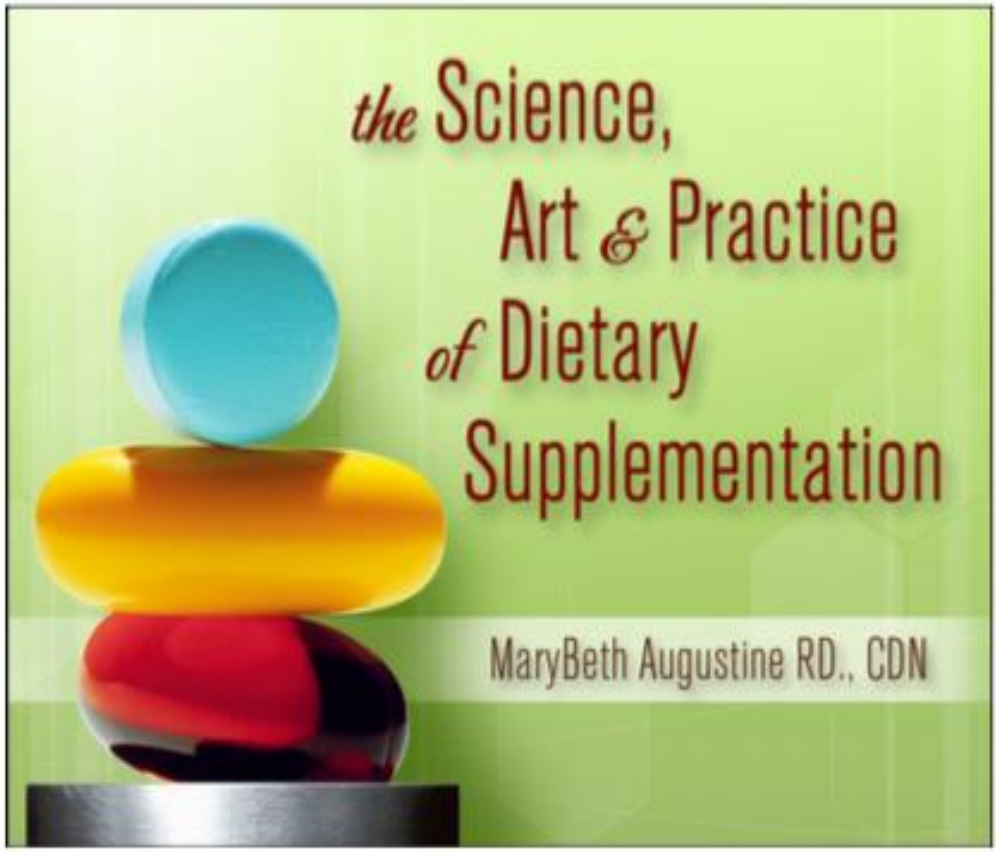
- However, a couple of DS have been proven to reduce risk of certain diseases/conditions and are authorized to make these label claims:
  - Folic acid reduces the risk of birth defects of the brain and spinal cord
  - Calcium can reduce risk of osteoporosis.

Excellent Webinar 2014

Dietitians in Integrative and Functional Medicine

a dietetic practice group of the Academy of Nutrition and Dietetics

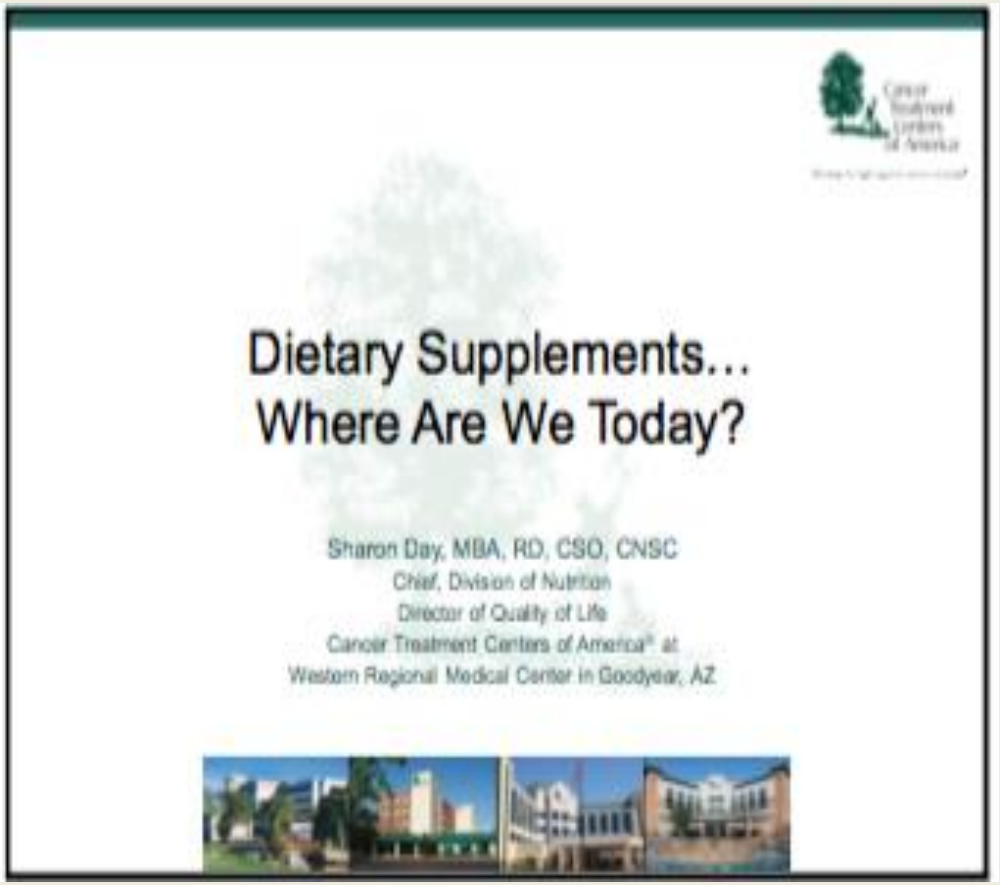
Webinar archives



Recent Presentation

Oncology Nutrition
Symposium
April 2016

Oncology Nutrition
a dietetic practice group of the
Academy of Nutrition and Dietetics



Commonly Use Resources for DS Information

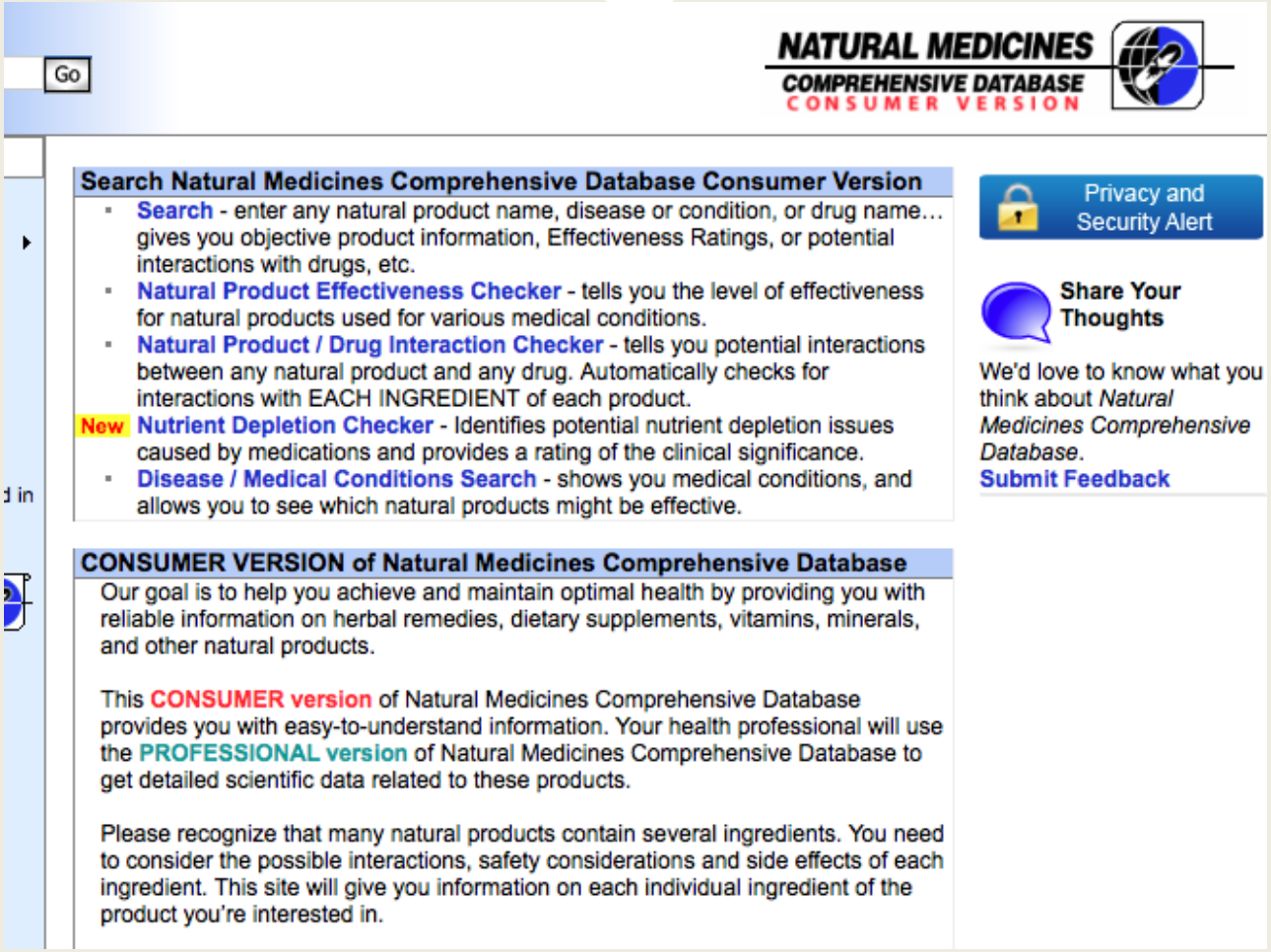
- Memorial Sloan-Kettering Cancer Center database (free)
  1. Good summary of studies
  2. References available

  https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs/search

- Natural Medicine Comprehensive Database (professional or consumer subscription)
  1. Good summary of studies
  2. Ranks safety and efficacy
  3. Reference not available in “consumer version”

  http://naturaldatabaseconsumer

Comprehensive Resource



Natural Medicine Comprehensive Database

- Search for DS:
  - What is It?
  - Is it effective?
  - How does it work?
  - Are there safety concerns?
  - Are there any interactions with medications?
  - Are there any interactions with herbs and supplements?
  - Are there interactions with foods?
  - What dose is used?
  - What other names in the product known by?

Profession version (not available to consumers) has references, consumer version does not

Educate and Document About Safety of DS

Rank safety based on science:

- **Likely safe:** Undergone rigorous scientific evaluation equivalent to an FDA review, ≥ 2 RCTs with several hundred or more pts
- **Possibly** safe: Reputable references agree that safe, and no human studies with serious adverse effects
- **Possibly unsafe**: There is some evidence that might be unsafe
- **Likely unsafe:** Reputable references agree that harmful, based on human studies or reliable reports of significant adverse effects
- **Unsafe**: Undergone rigorous scientific evaluation or a review by a reliable by a regulatory agency and found to often cause clinically significant harm to humans…
- **Insufficient evidence**: There is not enough reliable evidence to provide safety rating

http://naturaldatabaseconsumer.therapeuticresearch.com

1. Remember, different doses or route of administration affect safety
2. A product can be effective but unsafe
3. No product is safe for all people all of the time

Educate and Document About Effectiveness or Efficacy of DS

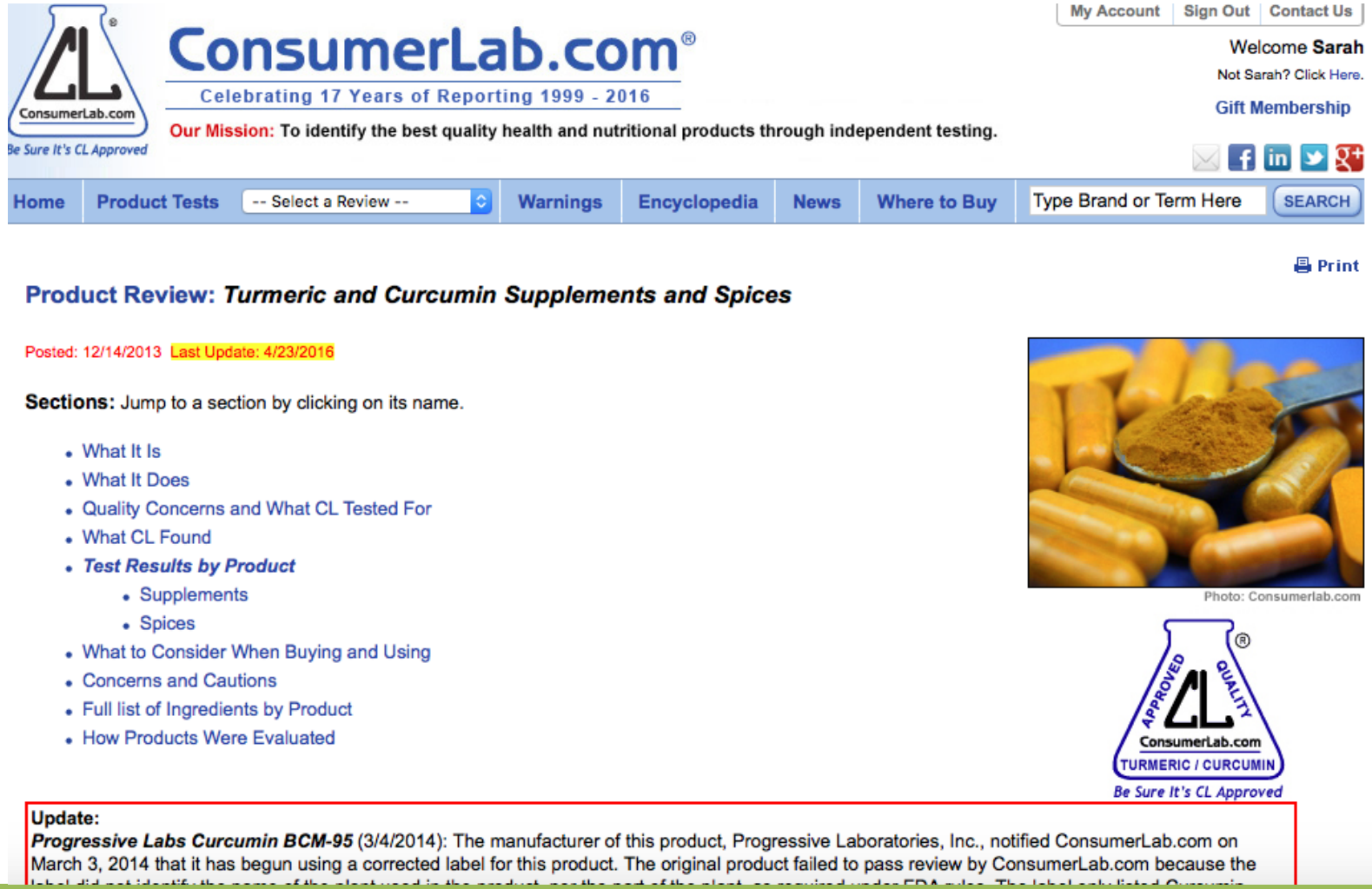
- **Effective**: Rigorous scientific review and found to be effective for a specific use
- **Likely effective**: Reputable scientific references generally agree that it is effective for a specific use – at least 2 scientifically rigorous studies (several hundred or more pts) found to be effective…
- **Possibly effective**: Reputable scientific references suggest that might work for a specific use – ≥ 1 human study found it might to be effective
- **Possibly ineffective**: Reputable scientific references suggest that the product might not work for a specific use - ≥ 1 human study found that it might not be effective
- **Likely ineffective**: Reputable scientific references generally agree that the product is not effective for a specific use – at least 2 scientifically rigorous studies found it likely to be ineffective…
- **Ineffective**: Most reputable references agree that it is not effective for a specific use and no reliable human studies show it to be effective
- **Insufficient evidence**: If claims are being made about it but there is no scientific info available about the effectiveness or ineffectiveness

http://naturaldatabaseconsumer.therapeuticresearch.com

Commonly Use Resources for DS Information

- Consumer Labs – (subscription)
  1. Good summary of studies
  2. References available
  3. Result of third party testing of products – easy to read charts

Selecting DS



Selecting DS

RESULTS OF CONSUMERLAB.COM TESTING OF MELATONIN SUPPLEMENTS
Click on $ Price Check beneath a product name to find a vendor that sells it.
To find retailers that sell some of the listed products click here.

Product Name, Amount Listed of Melatonin per Unit, Serving Size, and Servings Per Day Suggested on Label Click on "Ingredients" for Full Listing	Claimed Amount of Melatonin Per Labeled Daily Serving	--TEST RESULTS--				Cost for Daily Suggested Serving on Label [Cost 3 per mg of Melatonin] Other Notable Ingredients/Features1 Price Paid
		OVERALL RESULTS: APPROVED or *NOT* APPROVED	Contained Labeled Amount of Melatonin	Did Not Exceed Contamination Limit for Lead	Disintegrated Properly (NA=Not Applicable)	
CVS/pharmacy® Melatonin (5 mg per tablet; 1 tablet, once daily) ⚠™ Dist. by CVS Pharmacy, Inc. Ingredients 	5 mg	APPROVED	✓	✓	✓	$0.09 [$0.05] *Contains no wheat, gluten free, yeast free* $10.49/120 tablets
Finest Nutrition [Walgreens] Melatonin (3 mg per tablet; 1 tablet, once daily) ⚠™ Dist. by Walgreen Co. Ingredients $ Price Check 	3 mg	APPROVED	✓	✓	✓	$0.05 [$0.05] *Contains no wheat, gluten free, yeast free* $11.99/240 tablets
Finest Nutrition [Walgreens] Melatonin Cherry Flavor (5 mg per dissolvable 	5 mg	APPROVED	✓	✓	✓	$0.09

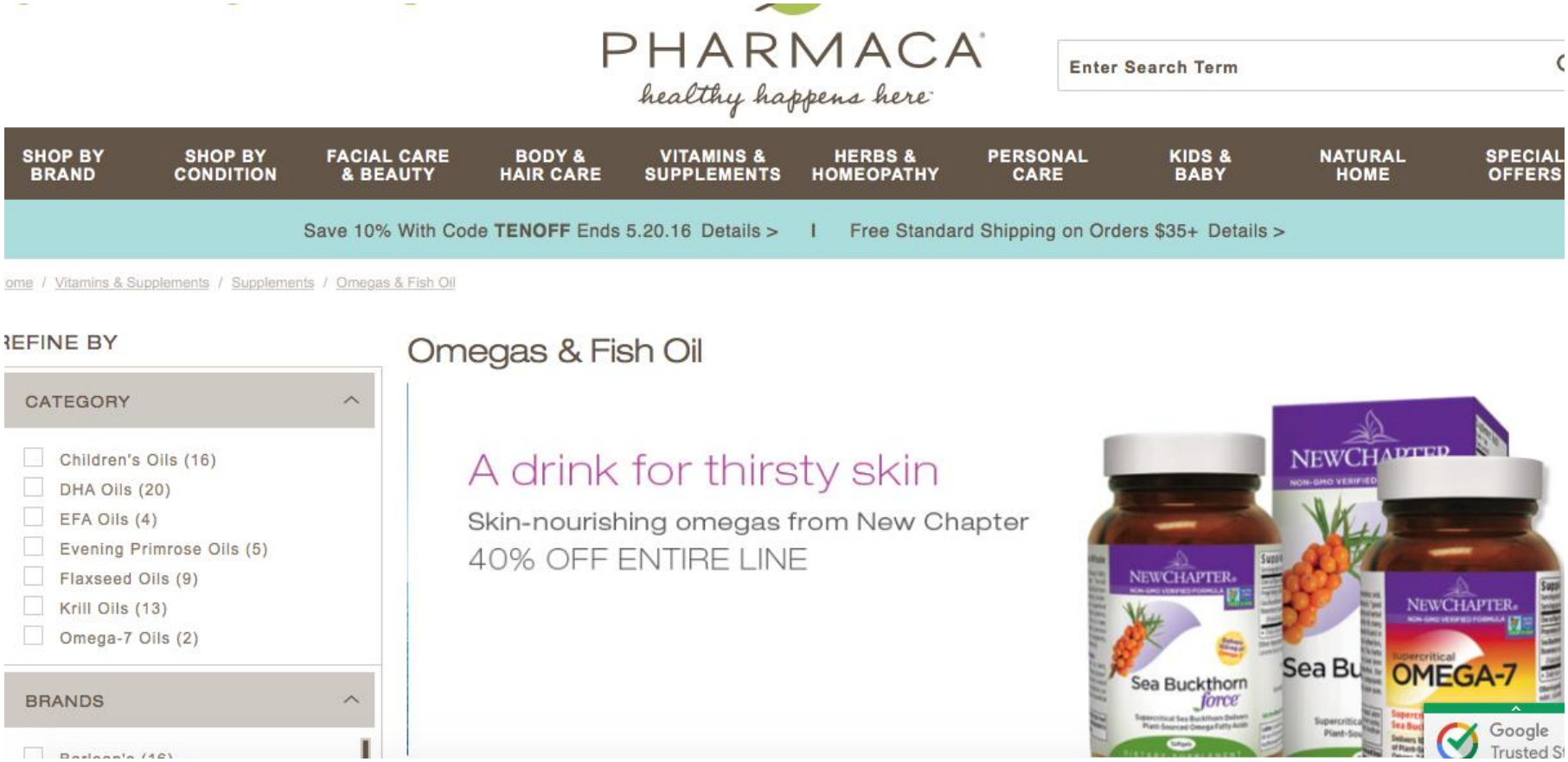
Purchasing DS: Seal of Approval

Seals of approval from Consumerlab.com, the National Sanitation Foundation (NSF) and United States Pharmacopeia (USP) are indicators that a product has been tested by a third party. This assures that the product has been properly manufactured, contains the ingredients listed on the label and does not contain harmful levels of contaminants. However, the absence of such a seal is no reflection on quality, either good or bad.

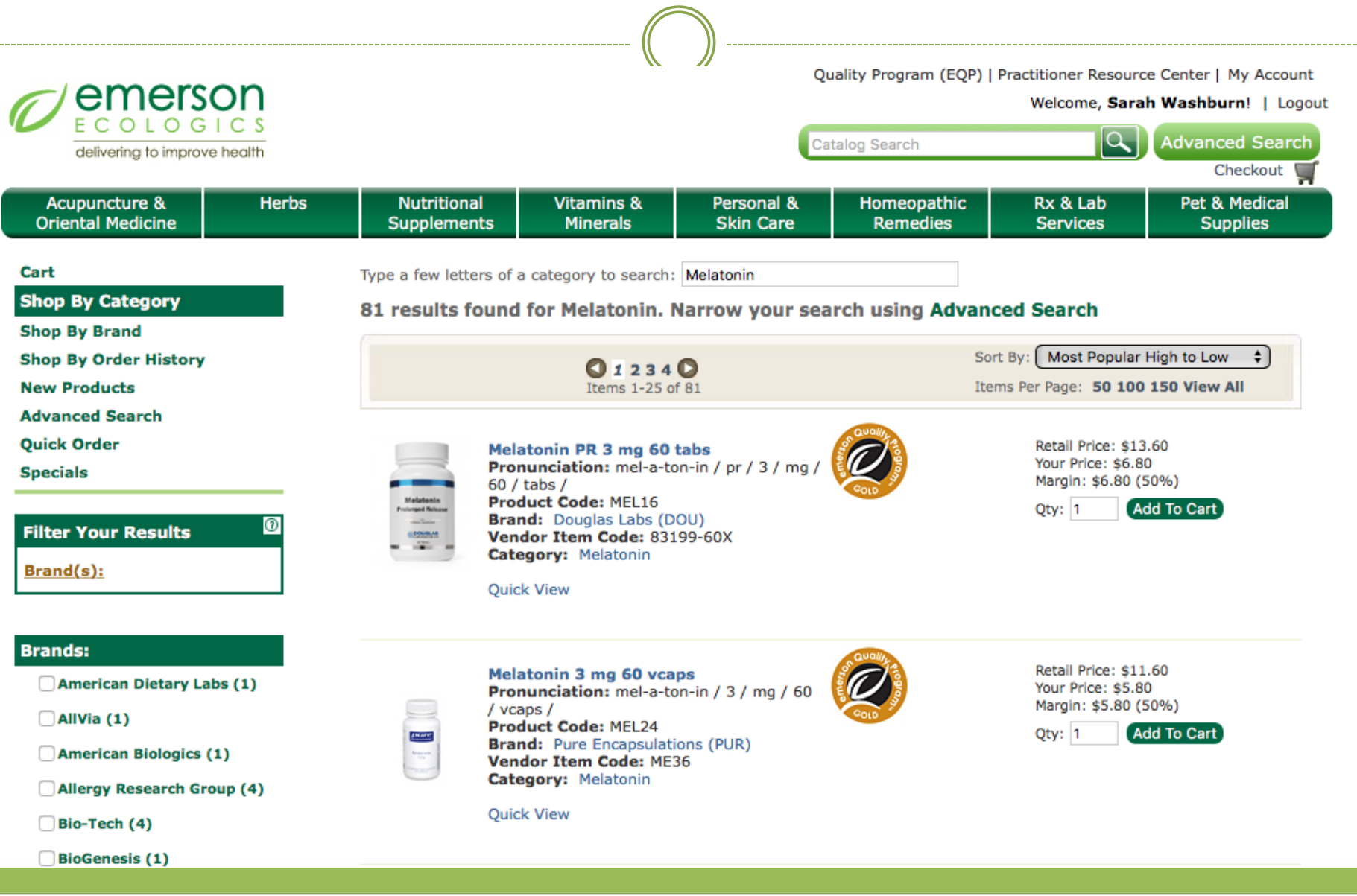
Coaching Patients on *Where* to Purchase DS

- Visit local retail stores that have DS in your area – make list of most commonly recommended DS that can be purchase at each store
  - Pros: Patient satisfaction, supports local economy
  - Cons: Time consuming, products change in stores, list needs to be updated frequently
- On-line resources (*examples*)
  - Patients can order:
    - Pharmaca (free access)
  - Professionals can order "professional-grade nutritional supplements":
    - Emerson Ecologics (free access)
      - Have their own "third party" testing label
- In-house resources

Where to Purchase Supplements?



Where to Purchase Supplements?



“In-House” – Pharmacy in Your Institution?

- Does your pharmacy sell supplements? If so, find out how those supplements were chosen
- Become involved in the process of choosing supplements; work with or create a multi-disciplinary team including a dietitian nutritionist, oncologist, pharmacist, naturopath, other qualified professionals
- Minimize financial gain of selling supplements to reduce bias
- Represents convenience for patient

Advising Patients: Use and Purchase of DS

- Provide the patient with details and document in EMR:
  - Evidence of efficacy and safety – site a study!
  - Full name of supplement (ex. Alpha Lipoic Acid, not just "ALA")
  - Compound of focus (ex. 400 mg of EPA and 300 mg DHA
  - Form – Pill, capsule, powder, liquid…
  - Dose in units (milligrams, not just "mg"…)
  - Brand name
  - When to take the DS in relation to other medications and supplements
  - Start and stop date

Cancer Drugs

- Over 200 cancer drugs (cancer.gov)
  - 6 new in 2016, 21 new in 2015 (Centerwatch.com)
    - May be reluctant to use DS as unfamiliarity with side effects of new drugs
  - Many clinical trial
    - Protocols may restrict DS use. Check with research team
- Much more tumor genetic testing
- Many more targeted therapies

http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet#q1

Targeted Therapies

- Several types
  - Monoclonal antibodies that deliver toxic molecules
  - Immunotherapies trigger immune system to destroy cells
  - Angiogenesis inhibitor block growth of new blood vessels
  - Apoptosis inducers cause controlled death of cancer cell
  - Gene expression modulators that modify proteins involved in controlling gene expression
  - Signal transduction inhibitors that block activity of molecules involved in signal transduction
  - Vaccines interfere with growth of specific cancer cells

Bacillus Calmette-Guerin (BCG) – bacteria that boost immune

http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet#q1

Interactions Between Cancer Drugs and DS

- Work with a pharmacist if available, otherwise use available resources
- Find out as much as possible about absorption, distribution, metabolism and elimination of the cancer drug and the DS to help anticipate drug – DS interactions. However, this information may be limited which can contribute to unwanted interactions/adverse events
- Many DS influence the activity of the cytochrome P450 (CYP) enzyme system, which metabolizes many prescription medication, including cancer drugs. DS can be inducers or inhibitors of this system.
- Also, interactions can take place via P-glycoprotein, which mediates transmembrane transport of drugs
- Cancer drug – DS interactions may be positive, neutral or negative, may depend on dose or timing DS taken, may be altered by single versus multiple DS use and often are unknown

Minimize Cancer Drug – DS Interactions

- IV Cancer drugs/ Cytochrome P450 system
  - Talk with a pharmacist
  - Avoid taking DS 1 to 2 days before and 2 days after cancer drug given (1/2 life of many cancer drugs is ~48 hours) unless there is a definitive clinical advantage to take the DS at time that cancer drug is given
- Oral oncolytics (which represent >25% of all cancer drugs - estimate in 2010)
  - At the very least, avoid taking DS at the same time as oral oncolytics

//www.communityoncology.org

Review Articles

- Review of 10 leading supplements that may have some benefit and likely carry minimal risk
  - Background, mechanism of action in cancer care and clinical trials, safety and side effects, dosage and interactions discussed for:
    - Curcumin, vitamin D, maitake mushrooms, fish oil, green tea, milk thistle, astragalus, melatonin, probiotics
  - Few RCTs, author points out difficulty in finding conclusive recommendations based on poor quality studies

Frenkel, M. Integrating Dietary Supplements into cancer care. Integrative Can Ther. 2013;12(5).

Review Articles

- Systematic review of 203 RCTs, articles published 1990-2013
- Provide recommendations for safe and effective integrative therapies relating to relaxation, mood, fatigue, nausea, depression, pain, neuropathy, hot flashes.
  - Glutamine not recommended for use by breast cancer pts receiving chemotherapy for the treatment of chemotherapy-induced nausea and vomiting due to lack of effect
  - Acetyl-L-carnitine not recommended for prevention of chemotherapy-induced peripheral neuropathy due to harm

Greenlee H. Clinical practice guidelines on the use of integrative therapies as supportive care in patients treated for breast cancer. J Natl Cancer Inst Monogr 2014; 50.

Review Articles

- Review of supplements that have biological activities that may help manage common chronic side effects of cancer treatment
  - Mood and sleep disorders
  - Products for GI health
  - Products for pain
  - Products for fatigue
- Few RTCs reviewed
- Concrete recommendations lacking
- Advocates “shared decision making” between health practitioner and pt regarding use of supplements
- Concluded that more research needed

Fouladbakhsh, JM. Understanding CAM Natural Health Products: Implications of use among cancer patients and survivors. J Adv Prac Oncol. 2013; Sep-Oct;4(5).

Turmeric/Curcumin

- Several different formulations have been developed to enhance bioavailability
  - As a result, lower doses may be required
  - Impact on drug – DS interactions is unclear
  - Difficult to compare studies in the future unless same brand is used in each study
    - If positive result in a study, use the exact supplement used in the study
- Phase I and II studies looking at potential synergistic effect with cancer drugs in advanced cancer
- Likely to be used more in nanomedicine to deliver targeted therapies to cancer cells

Vitamin D

- Current recommendations during and after cancer treatment:
  - Replete deficiencies and insufficiencies
- Future role:
  - May work synergistically with certain chemotherapies or other medications to reduce cancer cell viability and increase apoptosis
  - May reduce pain

Bjorkhem-Bergman L. Vitamin D and patients with palliative cancer. BMJ Support Palliat Care. 2016; Apr 15.

Vitamin D

- Other considerations:
  - Bisphosphonates/RANKLs – low vitamin D repleted may result in additional risk for hypocalcemia
    - Ex. Zoledronic Acid – Zometa®, Denosumab - Prolia® and Xgeva® - read Full Prescription Information for recommended calcium and vitamin D supplementations which is independent of dietary intake
  - Aromatase inhibitors (ex. Anastrozole - Arimidex®) – replete vitamin D as may helps improve arthralgias and myalgias
  - Chemotherapies containing anthracyclines, taxanes or monoclonal antibodies may accelerate vitamin D catabolism
  - May improve fatigue, pain and cachexia by reducing inflammation

Gröber U. Micronutrients in oncology intervention. Nutrients 2016;Mar 8(3).

Fish Oil As Treatment Enhancer

Nutr Res Rev. 2016 May 13:1-24. [Epub ahead of print]

How plausible is the use of dietary n-3 PUFA in the adjuvant therapy of cancer?

Serini S[1], Ottes Vasconcelos R[2], Fasano E[1], Calviello G[1].

Author information

Abstract

Considerable debate exists regarding the potential antineoplastic effect of dietary long-chain n-3 PUFA contained in fatty fishes. Since the majority of published data has proven that their intake does not induce toxic or carcinogenic effects in humans, their possible preventive use against cancer has been suggested. On the other hand, it is unlikely that they could be effective in cancer patients as a single therapy. Nevertheless, a considerable effort has been put forth in recent years to evaluate the hypothesis that n-3 PUFA might improve the antineoplastic efficiency of currently used anticancer agents. The rationale for this therapeutic combinatory strategy is trying to increase cancer sensitivity to conventional therapies. This could allow the use of lower drug/radiation doses and, thereby, a reduction in the detrimental health effects associated with these treatments. We will here critically examine the studies that have investigated this possibility, by focusing particularly on the biological and molecular mechanisms underlying the antineoplastic effect of these combined treatments. A possible use of n-3 PUFA in combination with the innovative single-targeted anti-cancer therapies, that often are not completely devoid of dangerous side-effects, is also suggested.

KEYWORDS: n-3 PUFA; 5-FU 5-fluorouracil; AA arachidonic acid; ALA α-linolenic acid; COX cyclo-oxygenase; FA fatty acid; FO fish oil; LC-n-3-PUFA long-chain n-3 PUFA; MDR multidrug resistance; NSCLC non-small cell lung cancer; PARP poly(ADP-ribose) polymerase; ROS reactive oxygen species; TRAIL TNF-related apoptosis-inducing ligand; i.v. intravenous; Antineoplastic drugs; Combinations; Human trials; Preclinical studies

Avoid Fish and Fish Oils Around Chemo Days?

Increased Plasma Levels of Chemoresistance-Inducing Fatty Acid 16:4(n-3) After Consumption of Fish and Fish Oil.

Daenen LG[1], Cirkel GA[1], Houthuijzen JM[2], Gerrits J[3], Oosterom I[1], Roodhart JM[1], van Tinteren H[4], Ishihara K[5], Huitema AD[6], Verhoeven-Duif NM[3], Voest EE[7].

⊕ **Author information**

Abstract

IMPORTANCE: Our research group previously identified specific endogenous platinum-induced fatty acids (PIFAs) that, in picomolar quantities, activate splenic macrophages leading to resistance to chemotherapy in mouse models. Fish oil was shown to contain the PIFA 16:4(n-3) (hexadeca-4,7,10,13-tetraenoic acid) and when administered to mice neutralized chemotherapy activity.

OBJECTIVE: Because patients with cancer frequently use fish oil supplements, we set out to determine exposure to 16:4(n-3) after intake of fish or fish oil.

DESIGN, SETTING, AND PARTICIPANTS: (1) In November 2011, 400 patients with cancer undergoing treatment at the University Medical Center Utrecht were surveyed to determine their use of fish oil supplements; 118 patients responded to the questionnaire (30%); (2) pharmacokinetic analysis of the 16:4(n-3) content of 6 fish oils and 4 fishes was carried out; (3) from April through November 2012, a healthy volunteer study was performed to determine 16:4(n-3) plasma levels after intake of 3 different brands of fish oil or 4 different fish species. Thirty healthy volunteers were randomly selected for the fish oil study; 20 were randomly selected for the fish study. These studies were supported by preclinical tumor experiments in mice to determine chemoresistance conducted between September 2011 and December 2012.

MAIN OUTCOMES AND MEASURES: (1) Rate of use of fish oil supplements among patients undergoing cancer treatment at our institution; (2) levels of 16:4(n-3) present in 3 brands of fish oil and 4 species of fish; and (3) plasma levels of 16:4(n-3) present in healthy volunteers after consuming fish oil or fish.

RESULTS: Eleven percent of respondents reported using omega-3 supplements. All fish oils tested contained relevant amounts of 16:4(n-3), from 0.2 to 5.7 μM. Mouse experiments showed that addition of 1 μL of fish oil to cisplatin was sufficient to induce chemoresistance, treatment having no impact on the growth rate of tumors compared with vehicle-treated controls (estimated tumor volume difference, 44.1 mm3; $P > .99$). When the recommended daily amount of 10 mL of fish oil was administered to healthy volunteers, rises in plasma 16:4(n-3) levels were observed, reaching up to 20 times the baseline levels. Herring and mackerel contained high levels of 16:4(n-3) in contrast to salmon and tuna. Consumption of fish with high levels of 16:4(n-3) also resulted in elevated plasma levels of 16:4(n-3).

CONCLUSIONS AND RELEVANCE: All tested fish oils and herring and mackerel fishes contained relevant levels of fatty acid 16:4(n-3), a fatty acid with chemotherapy-negating effects in preclinical models. After ingestion of these fish oils or fishes, 16:4(n-3) was rapidly taken up in the plasma of human volunteers. Until further data become available, fish oil and fish containing high levels of 16:4(n-3) may best be avoided on the days surrounding chemotherapy.

Chemotherapy/RT and Fish Oil

- Review article of 10 RCTs: Use of EPA and/or DHA during chemo and/or radiation to assess treatment outcomes
  - Daily dose range from 600 mg to 3.6 gm
  - Most effective in preservation of body composition
  - No difference in tumor size or patient survival

Silva, J. Omega-3 supplements for patients in chemotherapy and/or radiotherapy: a systemic review. Clin Nutr. 2015;34.

Advanced Cancer Cachexia/Fish Oil

- Systemic review investigating role of omega-3-fatty acids in advanced cancer cachexia
- 38 articles included
- Larger RCTs did not find significant effect
- However, adverse effects were infrequent, with no serious adverse effects

Ries, A. Palliat Med. 2012; Jun;26(4).

Colorectal Cancer and Fish Oil: Details of Studies

- 17 pts given 2 gm fish oil/day (360 mg EPA and 240 mg DHA) vs control group given during the first 9 weeks of treatment for colorectal cancer
- Excluded pts who had taken fish oil prior to study
- Greater median time to disease progression in fish oil group (p=0.04) and a trend towards a reduction in CEA levels (NS) in advanced stages of disease
- Conclusion: Larger clinical trial needed

Camargo, C. Nutr and Can. 2016; 68(1).

Non-Small Cell Lung Cancer (NSCLC) and Fish Oil – Brand of DS

- Pts with stage III or IV NSCLC chemo-naïve, given carboplatin with vinorebine or carboplatin with gemcitabine
  - 15 pts received fish oil daily (gelatin capsules containing 2.2 g EPA and 240 mg DHA (Ocean Nutrition Canada®) or liquid containing 2.2 g EPA and 500 mg DHA (NutraSea®))
  - 31 pts received standard therapy
- Increased response rate (60 vs 25.6%, p=.008) and clinical benefit of chemotherapy (80 vs 41.9%, p=.02) in pts receiving fish oil
- No difference in toxicity profile
- RCT warranted to confirm results

Murphy, RA. Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. Cancer 2011;117.

Finding A Specific Fish Oil Supplement…

- Goal: Find the same product that was used in a study
- Searched for NutraSea Brand containing 2.2 gm EPA and 500 mg DHA
  - Could not find one with same amount of EPA and DHA composition
  - Closest match is same brand that contains 1.5 gm EPA and 500 mg DHA
- Dose changes may impact study results!!

Oral Mucositis and L-Glutamine

- Oral Mucositis (OM) during chemo/RT
- Review of 15 studies
  - 11 of 15 studies showed significant reduction in:
    - Grade II, III and IV OM
    - Time of onset of OM
    - Duration of OM
    - Maximum grade of OM
    - Weight loss
  - Most common dose used: 30 gms/day, divided into 3 doses
  - Rates of nausea, vomiting, xerostomia and anorexia similar in glutamine and control groups

Sayles, C. Oral glutamine in preventing treatment-related mucositis in adults with cancer: A systemic review. Nutr Clin Prac. 2016;Apr 31(2).

Oral Mucositis (OM) and L-Glutamine

- Head and neck cancer, meta-analysis (5 RCTs, 234 pts)
  - Oral glutamine reduced risk and severity of OM (grade IV) (RR 0.17, 95% CI 0.06, 0.47) and shortened the duration of OM by 2 to 3 days
    - Oral doses – 10 to 30 gm L-glutamine per day, 1 IV study
  - Further prospective and larger trials required to support findings

Leung HW Glutamine in alleviation of radiation-induced severe oral mucositis: A meta-analysis. Nutr Cancer. 2016;Apr 4.

Radiation-Induced Dermatitis and L-Glutamine

- RCT with breast cancer pts undergoing RT in which 20 pts given 15 gm L-glutamine vs 20 pts given placebo
  - 9% of pts with dermatitis, grade I toxicity, in glutamine group
  - 80% of pts with dermatitis, grade II toxicity, in placebo group

Eda, K. The effects of enteral glutamine on radiotherapy induced dermatitis in breast cancer. Clin Nutr. Apr 2016;35(2).

Chemotherapy-Induced Peripheral Neuropathy

- Most often seen with:
  - Platinum-derived drugs
  - Vinca alkaloids
  - Taxanes
  - Proteasome inhibitor, Bortezomib (Velcade®)
- Prevalence
  - 68% within 1st month post chemotherapy
  - 60% at 3 months
  - 30% at 6 months

Seretny, M. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systemic review and meta-analysis. Pain 2104;Dec 155(12).

Chemotherapy-Induced Peripheral Neuropathy

- Review of natural products and complementary therapies for chemotherapy-induced peripheral neuropathy (CIPN)
  - Of 1465 publications screened, 13 prospective RCTs reviewed
  - Vitamin E, L-glutamine, and fish oil are promising
  - Acetyl-L-carnitine may worsen CIPN
  - Alpha-lipoic acid activity is unclear

Brami, C:Natural products and complementary therapies for chemotherapy-induced peripheral neuropathy: A systemic review. Crit Rev Onc/Hem. 2016;98.

Acetyl-L-Carnitine and Chemotherapy-Induced Peripheral Neuropathy

- 208 pt received 3,000 mg acetyl-L-carnitine (ALC) vs 201 received placebo for 24 weeks during adjuvant taxane-based chemotherapy
- Various neuropathy scores statistically worse in ALC group vs placebo group

Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. Hershman DL. Clin Oncol. 2013 Jul 10;31(20).

Alpha Lipoic Acid (ALA) and Chemotherapy-Induced Peripheral Neuropathy: High Attrition Rate

- 1,800 mg ALA for 24 weeks during and after chemotherapy, except for 2 days before and 4 days after chemotherapy
- High attrition: 34/122 (28%) pts given ALA vs 36/121 (30%) pts given placebo did not completed study
- No significant difference (SD) in patient-reported scores (FACT/GOG-Nx) between groups
- No SD in 2 secondary outcomes including pain, function and tumor outcome
- Attrition and low power impacted results

Guo, Y. Supp Care Can. 2014;22.

Colon Cancer and L-Glutamine: Intermittent Dosing

- Metastatic colon cancer receiving FOLFOX
  - 42 pts received glutamine, 15 gm twice a day for 7 consecutive days every 2 weeks starting on day of oxaliplatin, vs 44 control pts
  - Lower grade I-II peripheral neuropathy (PN) in glutamine group (17% vs 39%) after 2 cycles
  - Lower grade III-IV PN in glutamine group after 4th cycle (5% vs 18%) and 6th cycle (12% vs 32%)
  - Glutamine group had lower interference with activities of daily living (17% vs 41%) and need for dose reduction of oxaliplatin (7% vs 27%)

Wang, WS, Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. Oncologist Mar;12(3), 2007

L-Glutamine – Concerns

- "…recent findings show that glutamine transporters are upregulated in tumor cells and that glutamine acts as a mitochondrial substrate and promotes protein translation. This indicates tumor cell dependence on glutamine for its growth and maintenance. And a recent study demonstrated that glutamine helps cancer cells survive acidic stress, rather than provide nutrition….

  https://www.mskcc.org/cancer-care/integrative-medicine/herbs/glutamine

- "Glutamine Addiction"/ Metabolism

  Ratnikov, B. Oncoscience. 2015; Aug 20;2(8)

L-Glutamine – Timing of Supplementation?

- Glutamine supplementation can affect cancer metabolism depending on:
  - pyruvate dehydrogenase complex (PDHC) activity, individual tricarboxylic acid cycle (TCA) enzymes activity profile, malonate concentration, function of oxidative phosphorylation, oxidative stress and hypoxia inducible factor (HIF-1apha)
  - Main aim of glutamine supplementation: support immunity, intestinal tract and glutathione synthesis and inhibit the cancer cachexia.
  - Individual type of cancer metabolism
    - Dependent on activities in the TCA cycle
      - In normal versus reduced activity of pyruvate dehydrogenase complex (PDHC)
  - Components of the diet
    - In the case of lower ATP level in the cancer cell, the supplemental glutamine may be beneficial, rather than disadvantageous. However, this is best accomplished if the ATP reduction is supported by accompanying glucose withdrawal in the diet or glysolysis inhibiting therapy that decreases ATP

Michalak, KP Key role of glutamine pathways in regprogramming the cancer metabolism. Oxidative Med and Cell Longevity. 2015; April.

Probiotics and Radiation, Surgery and/or Chemotherapy-Induced Diarrhea

- Should probiotics be used?
- Systemic review
  - 11 RCTs assessing efficacy
    - Decrease in ≥ grade 2 diarrhea in 4 studies (OR=0.32, CI 0.13-0.79, p=.01)
  - 17 RCTs assessing safety (756/1530 consuming probiotics)
    - 105 adverse events (AE) in those consuming probiotic
      - 5 bacteremia/fungaemia
      - Included GI issues, dysphagia, urinary symptoms, blood pressure issues
    - 145 AE in those not consuming probiotics

Redman, MG. The efficacy and safety of probiotics in people with cancer: A systemic review. Ann of Oncology. 2014; 25.

Probiotics and Radiation After +/- Surgery: Dosing

- If decide to use probiotics, what dose?
- 3 groups: Prostate, GYN without chemo and GYN or rectal CA with chemo
- RCT: 1.3 billion CFU BID Bifilact® (n=91), 10 billion CFU TID Bifilact® (n=64) or placebo (n=91) started on first day of RT, ending last day of RT
- RDN instructed pts to record GI symptoms daily – translated to WHO or NCI grading systems
- No difference in diarrhea, QOL, although trended towards diarrhea reduction at the end of treatment. No clear evidence to use high dose probiotic

Demers, M. A randomized double-blinded controlled trial: Impact of probiotics on diarrhea in patients treated with pelvic radiation. Clin Nutr. 2014; 33.

Effectiveness of Ginger For Chemotherapy-Induced Nausea and Vomiting Is Still Unclear

- Bossi, P. Searching for Evidence to Support the Use of Ginger in the Prevention of Chemotherapy-Induced Nausea and Vomiting. J Altern Complement Med. 2016;Apr 26.
- Marx, WM. Ginger (Zingiber officinale) and chemotherapy-induced nausea and vomiting: a systematic literature. Nutr Rev. 2013;Apr 71(4).
- Lee, J. Ginger as an antiemetic modality for chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis. Oncol Nurs Forum. 2013;Mar40(2).

Chemotherapy-Induced Nausea and Vomiting (CINV) and Ginger

- Ginger should not be coadministered with the antiemetic aprepitant (Emend®) because of a possible negative interaction between the two agents on delayed CINV – more severe nausea and vomiting

Zick, SM. Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting. Support Care Cancer May. 2009;17(5).

Melatonin – Recent Studies
Different Outcomes – Same Dose

- Phase II trial, 32 metastatic breast cancer pts receiving hormonal or trastuzumab given 20 mg melatonin for 2 months. Significant improvement in sleep and fatigue comparing pre/post treatment. No control group. Need RCT for more conclusive evidence

  Innominato, PF. Supportive Care Can. 2016;Mar 24(3).

- Dose of 20 mg was not found to improve fatigue or other symptoms in patients with advanced cancer (RTC, double blinded, cross over study)

  Lund Rasmussen, C. Cancer. 2015:121(20).

- RCT, double blinded, placebo-controlled, 10 or 20 mg melatonin given to advanced non-small cell lung cancer pt undergoing chemotherapy. No difference in survival or adverse events, trend towards better quality of life

  Sookprasert, A. Anticancer Res. 2014;34(12).

Melatonin and Cancer Survivors
Validated Tools

- 48 women with prior history of stage 0-III breast cancer who had completed treatment (including hormonal therapy) randomized to received 3 mg melatonin vs 47 pts given placebo for 4 months, double-blinded
- 8% (4 pts) in melatonin group withdrew due to side effects, grade 1-2 headaches, fatigue, bad dreams
- Pittsburgh Sleep Quality Index (PSQI) - subjective rating of sleep quality, latency, duration, efficiency, disturbances, medication use, daytime dysfunction – improved for melatonin group vs placebo (p=.001)

Chen, WY. Breast Can Res Treat. 2014;145(2).

Surgery and DS Use

Several studies report that ~25% of surgical patients use DS.

DS can have an effect on blood coagulation and platelet function. Therefore, preoperative assessment should include a question about DS use.

Wang, CZ. Commonly used dietary supplements on coagulation function during surgery. Medicines (Basel). 2016;Mar 3.

Stop 2 Weeks Before Surgery

- Chondroitin
- CoQ10
- Echinacea
- Ephedra
- Fish oil
- Garlic
- Ginger
- Ginko
- Ginseng
- Glucosamine
- Green tea
- Kava
- Saw Palmetto
- St John's Wort
- Valerian
- Soy isoflavones
- Grape seed extract
- Milk thistle
- Boldo
- Danshen
- Dong quai
- Papaya
- Vitamin C
- Vitamin E

Wang, CZ. Medicines (Basel). 2016;Mar 3.

Surgery and DS Use

- Review to assess the benefits and risks of widely used herbal supplements. From that analysis, they compiled this list of herbs to avoid in the 2 weeks prior to surgery:
  - For bleeding effects: gingko biloba, garlic, ginseng, dong quai, feverfew, fish oilsFor drug interactions: echinacea, goldenseal, licorice, St. John's wort, kava, valerian root
  - For cardiovascular effects: ephedra, garlic
  - For anesthetic effects: valerian root, St. John's wort, kava
  - For photosensitivity effects: St. John's wort, dong quai
  - For hypoglycemia effects: ginseng

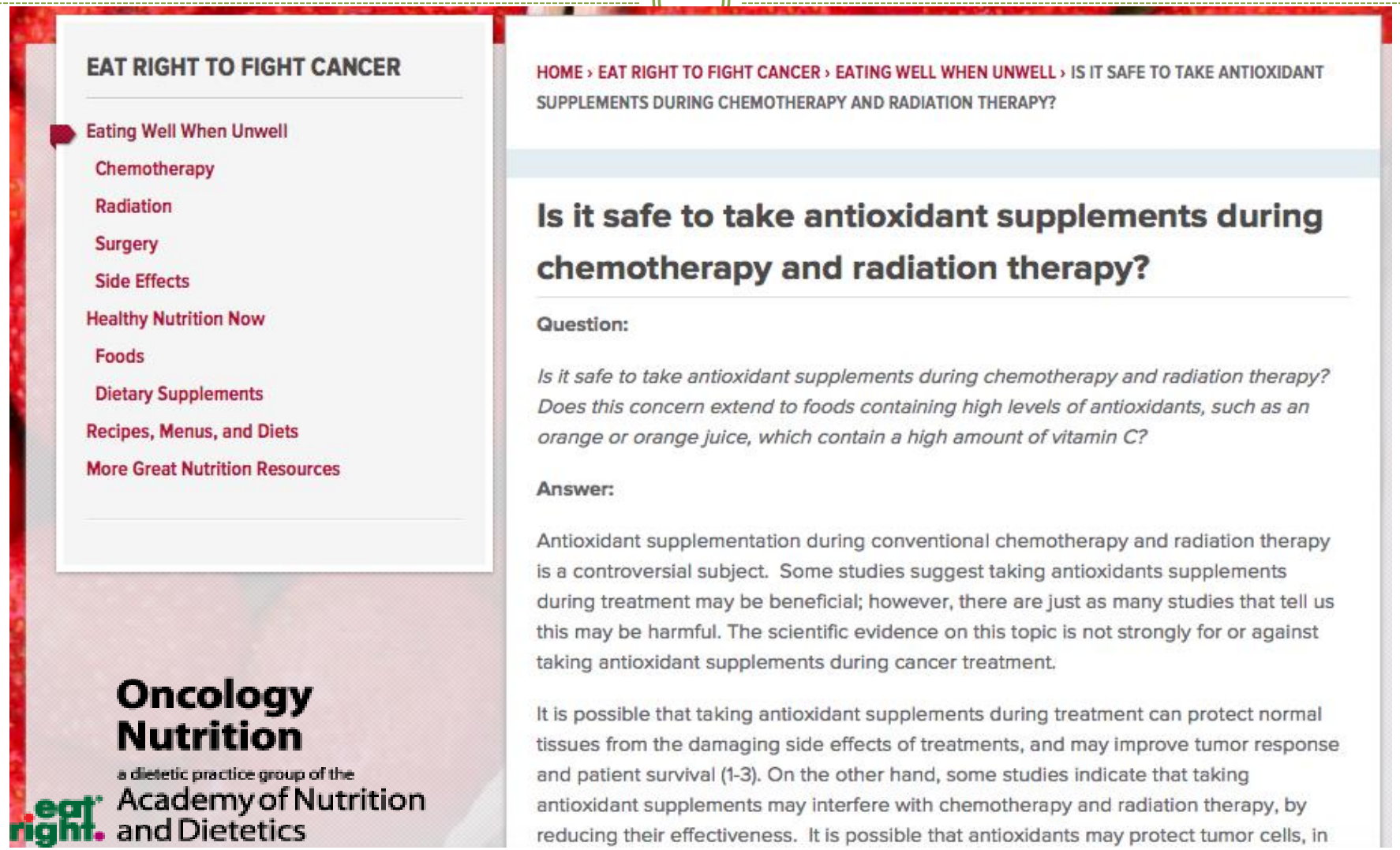
Rowe, DJ. Perioperative Risks and Benefits of Herbal Supplements in Aesthetic Surgery. Aesthetic Surg J. 2009;29(2).

Radiation Therapy (RT) and DS Use

- Long-standing controversy regarding use of antioxidants during RT based on mechanism of action:
  - Pros – Antioxidants help protect healthy cells resulting in improved tumor response and survival
  - Cons – RT creates free radicals and produces oxidative damage. Supplemental antioxidants destroy these free radicals making RT potentially less effective

RT and Antioxidant Supplement Use

http://www.oncologynutrition.org/erfc/eating-well-when-unwell/is-it-safe-to-take-antioxidant-supplements-during-chemotherapy-and-radiation-therapy/



EAT RIGHT TO FIGHT CANCER

- Eating Well When Unwell
  - Chemotherapy
  - Radiation
  - Surgery
  - Side Effects
- Healthy Nutrition Now
  - Foods
  - Dietary Supplements
- Recipes, Menus, and Diets
- More Great Nutrition Resources

Oncology Nutrition

a dietetic practice group of the Academy of Nutrition and Dietetics

eat right.

HOME › EAT RIGHT TO FIGHT CANCER › EATING WELL WHEN UNWELL › IS IT SAFE TO TAKE ANTIOXIDANT SUPPLEMENTS DURING CHEMOTHERAPY AND RADIATION THERAPY?

Is it safe to take antioxidant supplements during chemotherapy and radiation therapy?

Question:

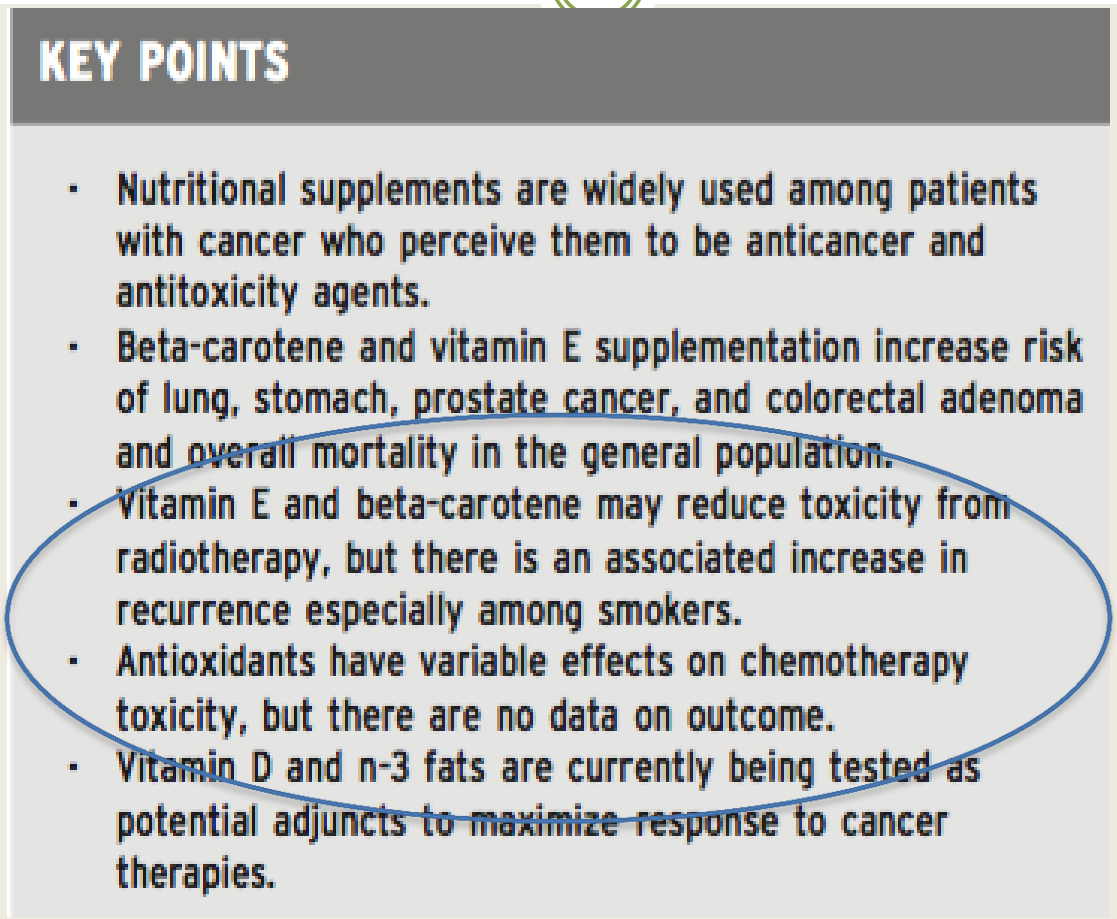
Is it safe to take antioxidant supplements during chemotherapy and radiation therapy? Does this concern extend to foods containing high levels of antioxidants, such as an orange or orange juice, which contain a high amount of vitamin C?

Answer:

Antioxidant supplementation during conventional chemotherapy and radiation therapy is a controversial subject. Some studies suggest taking antioxidants supplements during treatment may be beneficial; however, there are just as many studies that tell us this may be harmful. The scientific evidence on this topic is not strongly for or against taking antioxidant supplements during cancer treatment.

It is possible that taking antioxidant supplements during treatment can protect normal tissues from the damaging side effects of treatments, and may improve tumor response and patient survival (1-3). On the other hand, some studies indicate that taking antioxidant supplements may interfere with chemotherapy and radiation therapy, by reducing their effectiveness. It is possible that antioxidants may protect tumor cells, in

American Society of Clinical Oncology (ASCO)



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.

Harvie, M. Nutritional supplements and cancer: potential benefits and proven harms. 2014 ASCO Education Book

RT and Antioxidant Supplement Use

- Recent study demonstrates that antioxidant supplements may not impact RT outcomes
  - 39 Se-deficient pts supplemented with Se vs 42pts in control group
    - Significantly less diarrhea in the Se-supplemented group vs control group, published in 2010
    - Follow-up study found
      - 10-year overall survival rates of Se-supplemented pts higher compared with control group (p=.09)
      - No difference in 5-year or 10-year disease-free survival or 5-year overall survival

Muecke, R. Multicenter, phase III trial comparing selenium supplementation with observation in gynecologic radiation oncology: Follow-up analysis of the survival data 6 years after cessation of randomization. Integrative Can Ther. 2014;13(6).

Chemotherapy/RT and Antioxidant Use

- 49 RCTs reviewed in which antioxidants given to patients during chemotherapy (alkylating agents, platinum and anti-tumor antibiotics) and radiation
- Conclusion: Difficult to determine whether antioxidant impacted outcomes or decreased adverse treatment effects, except for smokers undergoing radiation therapy

Yasueda A. Efficacy and interaction of antioxidant supplements as adjuvant therapy in cancer: a systemic review. Integr Cancer Ther 2016; Mar;15(1).

RT, Antioxidants and Smoking…

Int J Cancer. 2008 Apr 1;122(7):1679-83.

Interaction between antioxidant vitamin supplementation and cigarette smoking during radiation therapy in relation to long-term effects on recurrence and mortality: a randomized trial among head and neck cancer patients.

Meyer F[1], Bairati I, Fortin A, Gélinas M, Nabid A, Brochet F, Têtu B.

Author information

Abstract

There has been concern that the efficacy of radiation therapy may be reduced when patients smoke or take antioxidant vitamins during treatment. Cancer prevention trials with beta carotene supplements documented adverse effects only among smokers. We conducted a randomized trial with alpha tocopherol (400 IU/day) and beta carotene (30 mg/day) supplements among 540 head and neck cancer (HNC) patients treated by radiation therapy. We examined whether smoking during radiation therapy modified the effects of the supplementation on HNC recurrence and on mortality. During the follow-up, 119 patients had a HNC recurrence and 179 died. Cox models were used to test the interaction between smoking and supplementation and to estimate the hazard ratios (HR) for HNC recurrence and death associated with the supplementation. Cigarette smoking either before or after radiation therapy did not modify the effects of the supplementation. In contrast, the interactions between supplementation and cigarette smoking during radiation therapy were statistically significant for HNC recurrence ($p = 0.03$), all-cause mortality ($p = 0.02$) and mortality from the initial HNC ($p = 0.04$). Among cigarette smokers, the HR were 2.41 (95% CI: 1.25-4.64) for recurrence, 2.26 (95% CI: 1.29-3.97) for all-cause mortality and 3.38 (95% CI: 1.11-10.34) for HNC mortality. All corresponding HR among nonsmokers were close to 1. These results could best be explained by the hypothesis that the combined exposures reduced the efficacy of radiation therapy. Particular attention should be devoted to prevent patients from both smoking and taking antioxidant supplements during radiation therapy.

Radiation Therapy (RT) and DS Use

- Recommend:
  - Continue DS replacement for nutritional deficiencies during RT unless there is a clear negative impact demonstrated or short RT course
  - Usual amounts of food and fluid containing natural sources of antioxidants need not be restricted
  - Find out about smoking history
- Additional thought:
  - Might low hemoglobin levels have more of a negative impact on outcomes of RT than antioxidants?

Multivitamin/Minerals Supplements

- So many varieties…
- Use during cancer treatment mostly unclear
- Drug – supplement interaction:
  - Bortezomib (Velcade®) – supplements with vitamin C may decrease anti-tumor effect

    Perrone G. Ascorbic acid inhibits antitumor activity of bortezomid in vivo. Leukemia. 2009;23(9).
  - Fluorouricil (IV - 5FU) and Capecetibine (Oral - Xeloda®) – supplements containing folic acid may increase cytotoxicity of drugs (case reports)
    - BUT, could be related to dihydropyrimidine dehydrogenase (DPD), an enzyme encoded by the DPYD gene, is the rate-limiting step in pyrimidine catabolism and deactivates more than 80% of standard doses of 5FU and the oral 5FU prodrug capecitabine. True deficiency of DPD affects approximately 5% of the overall population, 3 – 5% of population has a partial DPD deficiency due to variations in DPYD gene. In these patients, the lack of enzymatic activity increases the half-life of the drug, resulting in excess drug accumulation and toxicity.

Multivitamin/Mineral Supplements

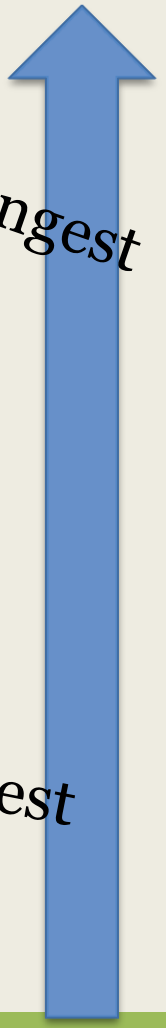
- Avoid 1 to 2 days before and 2 days after chemotherapy to prevent potential adverse drug - DS interactions
- Avoid taking at same time as oncolytic
- Malnourished pts, cachectic pts and pts with weight loss may benefit most as a poor diet is detrimental to the immune system, organ and metabolic function
- Conservative approach for well-nourished pts is to avoid during RT/chemotherapy/targeted/immune therapies
- Dose – do not exceed 100 to 200% DRI for
- micronutrients
- More research needed, likely to be valuable for a subset of patients

Conclusions

- Many inconclusive results of DS intervention trials due to:
  - Small studies
  - Different:
    - Scales/tools used to measure side effects
    - Forms of DS
    - Doses of DS
    - Timing and duration of use
    - Cancer drugs and other medications
    - Outcomes measured
  - Compliance of DS use is variable
  - Attrition rates high
  - Food intake and other lifestyle choices may impact results
  - Unique biology/genetics of pt

Evaluating Evidence in Medicine

1. Large, randomized, placebo-controlled, double-blinded, human trials
2. Large-scale, human trials
3. Large-scale, placebo-controlled, animal studies
4. "Test tube" studies
5. "Traditional use" or "Historical use"
6. "Anecdotal reports" or "Testimonials"



Evaluating Evidence For DS Use

- Does this biomedical model work for DS?
- Do we need more of a whole systems research approach?
- What about best available evidence?
  - Small placebo controlled, double-blinded RCTs
    - Meta-analysis
  - Clinical experience
- What about individual biochemistry/genetics?
  - Tailored approach will likely to be most robust method for recommending use of DS

Finally…

- Don’t recommended DS to cancer patients casually
- Learn more about DS every day; If not you, then who??
- No one person knows everything about DS
- DS recommendations need to be tailored to an individual’s background (medical, social…), diet, genetics, tumor histology, and treatments to potentially yield benefit in a subset of patients
- Monitor your patients on DS with validated measuring tools
  - At the very least, use the NCI Common Terminology Criteria for Adverse Effects (CTCAE) grading system – in EMR

Finally

- Document in EMR the rationale for supplement recommendations and site studies to support these recommendations (*smart phrases*)
- Let's work together to establish protocols for subsets of patients, collect data, assess our findings and publish…
  - We need results of many small double-blinded, placebo controlled, RCTs to write a meta-analysis
  - We need people to help facilitate this collaboration
- Exciting nanotechnology and nutrigenomic/nutrigenetics is changing/will change our practice dramatically in cancer care

HOLD ON TO YOUR HAT.. THIS WILL BE WILD RIDE

Questions