Supplements & Cancer Treatments: What Should We Tell Our Patients

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Disclosure

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• Nothing to Disclose
Learning Outcomes:

• Describe the use of dietary supplements by cancer survivors.

• Provide recommendations for dietary supplements using evidence-based practice.

• List the supplement ingredients to avoid.

• Discuss resources available to obtain evidence related to supplement use.

• Discuss the gaps in evidence.
1994 Dietary Supplement Health and Education Act (DSHEA)

• Authorized Office of Supplements at NIH
• Definition of a dietary supplement:
  • “A product (other than tobacco) that is intended to supplement the diet; contains one or more dietary ingredients (vits, min, botanicals), is intended to be taken by mouth as a pill, capsule, tablet of liquids, is labeled on the front panel as being a dietary supplement”
Background:

• Sales: Over $96 billion in 2012
  • 81% ↑ in past decade
• Use by oncology patients: 67% to 97%
• ~55% receive no recommendations

• U.S. Preventative Task Force:
  • Current evidence insufficient to assess the benefits/harms from MV or single/paired nutrient supplements
  • Little evidence, except for B-carotene & vitamin E, to discourage people from taking vitamin supplements
Background:

• Easier to obtain than prescriptions
• Labels promise solutions for health issues that are difficult to manage
• ? Risk
• 2008-2011 ➔ ~6,300 reports of health problems filed with FDA
• Lax regulation ➔ contaminated with:
  • Microbes
  • Heavy metals
• Spiked w/illegal or prescription drugs
10 Most Common Complementary Health Approaches Among Adults—2007

Percentage of U.S. Adults Who Used Complementary Health Approaches in 2007

- Natural Products: 17.7%
- Deep Breathing: 12.7%
- Meditation: 9.4%
- Chiropractic & Osteopathic: 8.6%
- Massage: 8.3%
- Yoga: 6.1%
- Diet-based Therapies: 3.6%
- Progressive Relaxation: 2.9%
- Guided Imagery: 2.2%
- Homeopathic Treatment: 1.8%

Challenges: Dietary Supplement Use

• Emergency Room visits:
  • 23,000 visits per year

• Supplements recommended by M.D. or self-prescribed

• ~7% of M.D.s selling supplements

• Type & dosage of supplements varies widely between MVM and botanicals
Common Dietary Supplements Used

**Micronutrients:**
- Vitamins D & C
- Calcium
- Antioxidants
- Multivitamin/minerals
- Glutamine

**Botanicals:**
- Tumeric
- Resveratrol
- Ginseng
- Mushroom extracts
- Garlic
- Astragalus
- other
54 y.o. female just finish 1 round of chemo for stage 3 ER+ breast cancer. Her primary reported nutrition-impact sxs include: diarrhea, fatigue and some abdominal cramping. No exercise since treatment started. Has been avoiding caffeine, dairy products, meat, soda and all junk food.

**Meds:** chemo (herceptin, taxel, carboplatin, perjeta, neulasta), Imodium

**Ht:** 5’6  
**Wt:** 126#  
**UBW:** 130# (1 month ago)

**B:** 9 grain toast (1) w tiny amt butter & sugar-free jam + green tea w/splash of almond milk

**10 am:** protein shake (1 tbsp muscle milk powder + water)

**L:** nothing much

**D:** toast, HB egg w/small amount of mayo
Supplements:

- 25,000 u B carotene
- Mg x 3 (750 mg)
- Bioflavonoid complex w/quercetin
- Propolis extract x 2
- NAC x 3 (500 mg)
- Selenium x 2 (200 mg)
- Hawthorne extract x 3
- Alpha lipoid acid x 2
- Milk thistle
- Gingko biloba
- Mg (300 mg) x 3
- Niacinamide x 2 (500 mg)
- Mg x 3 (500 mg)
- Gamma oryzanol
- Biotin x 2
- Prenatal MVM
- Vitamin E x 3 (400 mg)
- Quercein x 3
- Hesperidin x 3
- Curcumin x 3
- Licorice root & slippery elm
- Marshmallow root
- CoQ10 x 3
- Vitamin C (3 g/d)
- Folate (800 mcg)
- Pyridoxal (50 mg)
- Vitamin x 3 (500 mg)
- Ginger extract
Audience Response Question: *what would you recommend to the patient?*

A. Discontinue all supplements  
B. Discontinue magnesium & vitamin C  
C. Discontinue magnesium, slippery elm & licorice  
D. Make no changes – it’s the chemo
Antioxidants

- Vitamins C & E; selenium
- Controversial

- **Chemotherapy:**
- Alkylating agents (anthracyclines, platinum, etc.) produce free radicals → apoptosis in cancer cells
- 2007 systemic review concluded no evidence
- Unclear

- **Radiation:** unclear
### Antioxidants & Radiation

<table>
<thead>
<tr>
<th>Study:</th>
<th>Sample:</th>
<th>Intervention:</th>
<th>Outcome:</th>
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<tbody>
<tr>
<td>Bairati et al.</td>
<td>N=540 HNC w/ XRT</td>
<td>α-tocopherol (400 IU/d) or α-tocopherol + 30 mg/d β-carotene or placebo x 37 months</td>
<td>38% ↓ in severity of acute side effects; smoking + antioxidants = ↑ disease recurrence (HR=2.41, 95% CI=1.25-4.64)</td>
</tr>
<tr>
<td>Meyer et al. 2008</td>
<td>Follow-up to Bairati et al.</td>
<td></td>
<td>Smoking during XRT + supplementation = the HR were 2.41 (95% CI: 1.25-4.64) for recurrence (P=0.03), 2.26 (95% CI: 1.29-3.97) for all-cause mortality and 3.38 (95% CI: 1.11-10.34) for HNC mortality.</td>
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## Antioxidants & Radiation

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<tr>
<td>Ferreira et al.</td>
<td>N=54 HNC + XRT</td>
<td>Oral rinse w/400 IU/d vitamin E or placebo before/after XRT</td>
<td>36% ↓ in mucositis sx; ↓ 2 yr. overall survival (32% vs. 63% placebo)</td>
</tr>
<tr>
<td>Lesperance et al.</td>
<td>N=90 x/ recurrent breast CA w/convt txmt or convt txmt + supplements</td>
<td>β-carotene, vit. C, niaicn, Se, CoQ 10 +/or zinc</td>
<td>Breast cancer-specific survival &amp; dz-free survival in supplement group (HR=1.75; 95% CI=0.83-2.69)</td>
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</table>
Which of the following may provide high doses of antioxidants that may be concerning during treatment?

- A. prenatal vitamin/mineral supplement
- B. Emergenc-C
- C. tube feedings
- D. none of the above
Antioxidants & Tube Feedings

- Antioxidant content varies
- Vitamin C: 240 mg to 520 mg/L
- Vitamin E: 37 IU to 51 IU
- Selenium: 64 mcg to 100 mcg/L
- B-carotene: none to 2080 mg/L
Vitamin D

- **Vitamin and pro-hormone**
  - Involved in cell proliferation/differentiation/apoptosis, neuromuscular & immune function, & anti-inflammatory benefits

- Chemotherapy agents (cyclophosphamide, paclitaxel) \( \uparrow \) breakdown of calcidiol & calcitriol to inactive metabolites by 24-hydroxylase

- Serum concentrations 25(OH)D best indicator
  - Good for reflecting exposure
  - ? About reflecting outcomes
Vitamin D

- **RDA:**
  - 18-70 y.o.: 600 IU/d
  - > 70 y.o.: 800 IU

- ? Optimal serum concentrations
- Declines in serum concentrations reported in men
  - ↑ body wt., < milk consumed, & > sun protection

- **Supplements:**
  - D3 (cholecalciferol) or D2 (ergocalciferol)
Vitamin D & Cancer Risk

- 60% ↓ in cancer of any type w/1400-1500 mg Ca++ + 1100 IU/d vit. D in PM women
  - ? Take vitamin D w/wo calcium

- 17% ↓ in overall cancer incidence (>25 nmol/L) in men

- 29% ↓ in cancer-related mortality in men

- ? > serum levels of 25 (OH) D (>40 ng/mL) associated with > risk of pancreatic cancer

- Conflicting results in cohort studies
Vitamin D & Survival:

- N = 143 patients undergoing underwent radiofrequency ablation (1999 and 2011) of liver mets w/colon cancer

- **Study Outcome:** 25-hydroxyvitamin D levels on overall survival and time to recurrence

- **RESULTS:**
  - Median survival was 44 months (36-62) & survival rate was 91.4%, 46.5%, and 42.2% at 1, 4, and 5 years in the whole cohort.
  - Median survival = 65 months (52-74) if 25-hydroxyvitamin D >20 ng/mL
  - Median survival 34 months (24-41) if ≤20 ng/mL (P < 0.001).
  - Median time to recurrence = 34 months (26-47), 50 months (36-62) in the case of 25-hydroxyvitamin D >20 ng/mL
  - 24 months (20-32) if ≤20 ng/mL (P < 0.001).
  - Nodule size and 25-hydroxyvitamin D resulted as significant predictors of both overall survival and time to recurrence in multivariate analysis.

Facciorusso et al. 2016;;31(8):1483
Future Directions

• **Phase I trials:** ? Vitamin D chemopreventive for prostate, colorectal & lung cancers

• **Vitamin D/Calcium Polyp Prevention trial:** Vit. D vs. Vit. D & Ca++ to prevent adenoma recurrence in colon/rectum

• **VITAL trial:** ? Vitamin D & Omega-3 for chemoprevention for various cancers
Multi-vitamin/mineral supplements:

- 20%-80% malnourished
- Intake <60% x 7-10 days inadequate micronutrients
- Poor tolerance to txment/delays
- Target nutrition-impact sxls
- ↑ morbidity & mortality

FNCE 2016
Guidelines:

• Promote dietary intake of micronutrients & botanicals
• Select a MVM supplements not exceeding 100% of the DV
• Avoid supplements w/therapeutic doses
• Supplements (folate & B12) recommended for some chemo regimens ➔ reduced treatment-related toxicities
• Intake < 50% of estimated needs
Other:

- **Glutamine:**
  - 30 g/d glutamine swishes ➔ severity of mucositis in XRT for HNC

- **Omega-3 fatty acids:**
  - May ➔ fatigue & may stabilize loss of LBM (2 g/d EPA)

- **Probiotics:**
  - Chemotherapy & XRT-induced diarrhea
  - VSL#3 and Lactobacillus casei DN-114 001
Botanical Supplements
Botanical Supplements

- **Usage:** 7% to 77% during treatment

- **Most common:** turmeric, resveratrol, ginger, astragalus, milk thistle

- **Concerns:** metabolism by CYP3A4 isoform of hepatic cytochrome p450 enzymatic system
Tumeric:

- **Purported uses:** antioxidant benefits, diarrhea, cancer, loss of appetite, etc.
- **Active ingredient:** curcuminoids & tumerone oil
- **Likely Safe**
- **Mechanism of action:**
  - Modulate cell proliferation, signaling pathways, transcription factors, & tumor angiogenesis
Tumeric

- **Potential drug-nutrient interactions** – moderate:
  - May have anti-platelet activities - ↓ platelet aggregation
  - Caution with diabetic drugs ➔ may reduce glucose & A1C levels

- **Cavets:**
  - Bioavailability very low
  - Goal: tissue-targeted delivery
  - piperine
  - Rapidly metabolized
  - Human data lacking – preclinical & phase I trials
Evidence:

• Insufficient Reliable Evidence to Rate:
• CR cancer (preliminary evidence it may stabilize disease)

• Prostate Cancer: formulation w/broccoli powder, tumeric pomegranate & green tea extract (3 x/d) may maintain PSA levels in prostate cancer patients

• Radiation mucositis: HNC swishing w/10 mL of tumeric solution (400 mg in 80 mL of H2O) 6 x/d delays & intolerable mucositis ↓ 49% vs. Povidone-iodine solution
Curcumin/Tumeric

- Prostate Cancer:
  - Phase II trial: 3 cycles of docetaxel/prednisone & curcumin (6 g/d x 7 consecutive days w/chemo)
  - N=29 castration-resistant prostate cancer
  - 26 patients completed treatment
  - PSA ↓ in 17; normalized in 4; progressed in 4
  - No toxicity > docetaxel associated side effects
Summary:

• Evidence limited
• Poor absorption & rapid metabolism
• Curcumin is known to interfere with cytochrome P450 enzymes → ? Interfere with cyclophosphamide & doxorubicin

• Dosage:
  • Powdered capsules: 1-3 g/d
  • Fluid extract or tincture: follow recommendations
Resveratrol

• **Source:** polyphenolic compound in peanuts, grapes, red wine & some berries

• **Purported Uses:** antioxidant, anticarcinogenic, cardiovascular, etc. benefits

• **Active ingredient:** polyphenol compounds called stilbenes

• **Mechanism of Action:** \( \downarrow \) pro-inflammatory pathways (eicosanoids/COX/NFkB or AP-1)

• **Evidence:**
  - Phase I studies in progress

• **Drug-nutrient interactions:**

  • \( \bigcirc \) for hormonal-sensitive cancers

  • **Moderate** interactions with: anticoagulants/antiplatelet/chemo agents/H2 blockers & PPIs/statins, etc.
Ginger:

- **Purported Uses:** CINV, diarrhea & loss of appetite
- **Active Ingredients:** gingerol components
- **Mechanism of action:** stimulation of oral & gastric secretions, regulate gastrointestinal motility & interact with the 5HT$_3$ and NK1 receptors involved in the CINV reflex; act as a scavenger for free radicals

- **Safety:** Likely safe except w/lactation
- **Potential Drug-Nutrient Interactions:**
  - Moderate: anticoagulants/antiplatelet drugs; major: nifedipine; minor: DM/Ca$^{++}$ channel blockers/cyclosporine
- **Evidence:** contradictory
- **Dosage:** .5 g/d – 1 g/d
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<td>Manusirivithaya et al. 2004</td>
<td>N=48 gynecological cancers</td>
<td>1 g/d x 5 d w/chemo or placebo + metoclopramide for 1st cycle ➔ crossover</td>
<td>No ↓ in acute nausea w/anti-emetics but helped with delayed (= to metoclopramide)</td>
</tr>
<tr>
<td>Zick et al. 2009</td>
<td>N=162</td>
<td>1 g (250 mg x 4/d) or 2 g/d + 5-HT3 or aprepitant for delayed CINV</td>
<td>No benefits; delayed CINV worse w/2g + aprepiant</td>
</tr>
<tr>
<td>Fahimi et al. 2010</td>
<td>N=36</td>
<td>1 g (250 mg 4x/d) or placebo + std. anti-emetics ➔ crossover</td>
<td>No benefit; only 2 cycles</td>
</tr>
<tr>
<td>Panahi et al. 2012</td>
<td>N=100 adv. breast cancer</td>
<td>1.5 g/d (500 mg 3x/d) + std. anti-emetic or anti-emetic regimen (granisetron + DM)</td>
<td>➔ CINV 6-24 hrs past chemo (P=0.04); not blinded</td>
</tr>
<tr>
<td>Ryan et al. 2012</td>
<td>N=576</td>
<td>Placebo, 0.5 g, 1 g or 1.5 g/d</td>
<td>All doses ➔ acute (P=0.03) but not delayed; &gt; 1.5 g/d not effective</td>
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</table>
Study Limitations:

- No placebo or not blinded
- Small studies
- Compared to older anti-emetics
- Various doses used
- ? amount of active components in supplements
- ? if bind to receptor sites for anti-emetics (5-HT\textsubscript{3} & substance P)
Future Directions:

• **Italian study:**
• PCRT recruiting with highly emetogenic treatments
• Standard prophylaxis cisplatin-induced acute and delayed N/V
• Aprepitant, dexamethasone & 5 HT₃ antagonist
Mushrooms (Maitake/Grifola frondosa)

- **Purported Uses:** promote tumor regression & stimulate immune system
- **Active Ingredients:** β-1,6 glucan
- **Mechanism of action:** ↑ NK cells, lymphocytes, macrophages, & IL-1 possibly
- **Safety:** Likely safe
- **Potential Drug-Nutrient Interactions:**
  - may have hypoglycemic effect & ↑ INR w/warfarin
- **Dosage:** 5-7 mg/kg/d
- **Evidence:** limited
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<tr>
<td>Kodama N et al. 2002</td>
<td>Non-RCT N=36 Breast/liver/lung cancers</td>
<td>MD-Fraction &amp; whole maitake powder past chemotherapy</td>
<td>Cancer regression or significant improvements in symptoms: 11/16 breast; 7/12 liver; 5/8 lung</td>
</tr>
<tr>
<td>Deng G et al. 2009</td>
<td>Phase I/II trial N=34 PM breast cancer (stages I-III)</td>
<td>↑ Doses of extract taken orally (0.1, 0.5, 1.5, 3 &amp; 5 mg/kg BID x 3 wks)</td>
<td>Granulocytes &amp; IL 1; suppressed other immunologic parameters; IL-2 &amp; IFN-Y</td>
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Ginseng:

• **Purported Uses:** ↑energy, stimulate immune system

• **Active Ingredients:** ginsenosides

• **Mechanism of action:** anti-inflammatory & cortisol modulating effects; activation of monocytes, induce tumor necrosis factor (TNF)-alpha, interferon-gamma, natural killer cell activity, IL-2 & B-lymphocyte proliferation

• **Safety:** Likely safe

• **Potential Drug-Nutrient Interactions:**
  - Warfarin, DM agents & immunosuppressants

• **Dosage:** 2000 mg/d

• **Evidence:** limited
### Evidence:

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<tr>
<td>Barton et al., 2010 (pilot)</td>
<td>N=290 Cancer survivors w/breast, colon &amp; lung</td>
<td>Placebo vs. various doses (750 mg, 1000 mg or 2000 mg/d)</td>
<td>Fatigue by 40% w/ginseng vs. 17% placebo</td>
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<td>QOL &gt; w/ginseng (3.6 (P) vs. 3.0, 6.1 &amp; 9.4 (2000 mg)</td>
</tr>
<tr>
<td>Barton et al., 2013 (phase III)</td>
<td>N=364 multi-centers Stage I-III cancers w/49% on treatment</td>
<td>Placebo vs. 2000 mg/d MFSI scale to assess fatigue</td>
<td>Significant difference: 20 ginseng (SD=27) vs. 10.3 placebo (SD=26.1) (P=.003)</td>
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<td>Best results: on txmt &amp; 8 weeks use</td>
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Supplement Ingredients to Avoid:

- Red Yeast Rice
- Comfrey
- Greater Celandine
- Kava
- Green Tea Extract Powder
- Yohimbe
- Lobelia
- Pennyroyal Oil
When is a Supplement Needed?

- Deficiency present
- Medical condition present
- Recommended with treatment
- Certain medications prescribed
- Poor intake

**Providing recommendations:**

- Review PMH & current clinical status
- ? Why take them
- Assess benefits vs. harm
- Non-judgmental approach
Audience Response: If you were going to recommend 1 dietary supplement during treatment, which of the following might you recommend?

• A. Vitamin C
• B. Vitamin D
• C. Tumeric
• D. Resveratrol
Resources:

• Natural Medicines Comprehensive Database
• Consumer Lab: consumerlab.com
• Memorial Sloan Kettering Cancer Center: https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs
• U.S.D.A. National Agricultural Library: https://fnic.nal.usda.gov/dietary-supplements/herbal-information
• National Center for Complementary & Integrative Health: https://nccih.nih.gov/
• Linus Pauling Institute @ Oregon State University: http://lpi.oregonstate.edu/mic
Practice Applications:

• Comprehensive nutrition assessment critical.

• Multivitamin-mineral supplementation use → consuming < 50% of estimated nutrient needs.

• Provide recommendations for the use of botanical supplements during treatment by cancer survivors based on evidence & treatment.
References


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