Dietary Supplements During Cancer Therapy and Survivorship

What we know and what we don’t

Johanna Dwyer, D.Sc, RD
Office of Dietary Supplements
National Institutes of Health
Agenda

What we know

What we don’t

Knowing and doing
What We Know
Rx: Foods,
Not Supplements
Supplements are different from foods

- Ingredient composition varies and adulterants sometimes present
- Dose (often much higher)
- Matrices
- Conditions of use (often without food)

* Major determinants of safety
They are more like drugs

- Shorter history of safe use than foods
- Regulated more like foods, less strictly than drugs

Some supplements sold in USA are regulated as drugs or herbal medicines in other countries.
Dietary supplement use is high in cancer survivors

• Take many different doses and kinds
  • (nutrients, non-nutrients like botanicals, herbals, others)

• Are receiving many other medications & therapies simultaneously
  • potential for interactions
Supplement use high before and even higher after cancer diagnosis (63% used DS after Dx, esp women and higher education levels)
(Prevalence in 10 most common cancers)

Ferrucci et al
Supplement safety and efficacy cannot be assumed and must be tested

Adverse events and lack of efficacy in;

- ATBC, CARET trials in high risk patients
- NPC and SELECT trials in average risk patients

Very few trials in cancer survivors
Supplements need scrutiny—esp those with ingredients other than vitamins and minerals

- Possible interactions with cancer treatments
- Adverse events unrelated to cancer
  - Effects on other meds

*Web based tools* available to help
Supplements differ greatly in their benefits and risks
Some common supplements have adverse effects

- Beta carotene, Se

- Vit C attenuates cytotoxicity experimentally in mice

_Little evidence supplements prevent cancer recurrence_
Vitamin C attenuates the cytotoxicity of antineoplastic agents in vivo (mice).

Some supplements may be harmful and cause cancer
Pyrrolizidine alkaloids (PAs) are hepatotoxins.
FDA banned comfrey for internal use in 2001.
But still being sold on the web.

Comfrey may cause cancer.
Aristolochic acid harmful and may cause cancer

Common in Traditional Chinese Medicine

Cause of Chinese Herbs nephropathy and kidney cancer in Belgian weight loss clinic in ‘90s
Some supplements help
Sometimes nutrient supplements help

- Anorectic, poor appetite or frail patients during or after treatment:
  - Multivitamin mineral supplement at RDA (DV) levels
  - Oral nutritional supplements for calories and protein

- Other uses
  - Women likely to conceive:
    - folic acid pre conception to end of first trimester
  - Pregnant women and nursing mothers:
    - vitamin D supplement, possibly iron (if levels low)
  - Children 6 months to 5 yr if ill or frail:
    - multivitamins with vitamins A, C and D
  - Frail older people with low calorie needs:
    - low-dose, balanced multi-vitamin.
  - Older people, homebound and shut-ins, vegans, sun avoiders: Vitamin D
Methotrexate

• Methotrexate and related drugs operate by blocking cell reproduction

• Large doses of folic acid are not helpful in methotrexate treatment since the drug is an analogue of folic acid
Small doses of folic acid may prevent some of the toxic effects of antifolates without diminishing chemotherapeutic effects

- Small doses of folic acid (350-1000mcgm/d) and vitamin B-12 don’t interfere with efficacy of antifolate treatment and decrease toxicity (neutropenia) increase tolerance to treatment, and survival
  - Scaglotti et al J Clin Oncol 2003I 21(8) : 1556-61
  - Janne et al Jclin Oncol 2016
What We Don’t Know
If use of supplements delays initiation of active therapy, it may affect disease-free survival
Delays initiating adjuvant chemotherapy in breast cancer affect disease free survival

Figure 4

<table>
<thead>
<tr>
<th>Disease-free Survival</th>
<th>Hazard Ratio per 4-wk of Delay (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colleoni et al. 2000</td>
<td>1.14 (0.98, 1.32)</td>
<td>81.56</td>
</tr>
<tr>
<td>Kerbrat, et al. 2005</td>
<td>1.24 (0.90, 1.71)</td>
<td>18.44</td>
</tr>
<tr>
<td>Overall</td>
<td>1.16 (1.01, 1.33)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2=0.0\%$, $P=0.623$

Individual study and overall hazard ratios of relationships between every 4-week delay in initiation of adjuvant chemotherapy and disease-free survival. Individual and overall hazard ratios (HR) per 4-week of delay with 95% confidence interval (CI) for DFS is shown. The size of each square is proportional to the weight of the study. For the combined result, the length of the diamond represents the 95% CI of the summary.
Supplements and complementary or alternative medicine use in place of conventional care may be harmful to health and quality of life.
685 women with nonmetastatic invasive breast cancer
  Half Chemo indicated, half not
  87% used CAM at baseline

Among women for whom chemo was indicated, DS users and those with high CAM scores were less likely to start chemo

VM users strongest correlates of non-initiation
  71% vs 28%
### Table 1. Use of Complementary and Alternative Medicine by BQUAL Participants at Study Enrollment, by Chemotherapy Clinical Indication, and Chemotherapy Initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Sample (n = 685)</th>
<th>Chemotherapy Indicated (n = 306)</th>
<th>Chemotherapy Discretionary (n = 379)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Initiated (n = 272)</td>
<td>Did Not Initiate (n = 34)</td>
</tr>
<tr>
<td>Current use of any CAM(^b)</td>
<td>598 (87)</td>
<td>234 (86)</td>
<td>32 (34)</td>
</tr>
<tr>
<td>Dietary supplements</td>
<td>482 (70)</td>
<td>169 (62)</td>
<td>30 (88)</td>
</tr>
<tr>
<td>Vitamins and/or minerals</td>
<td>246 (36)</td>
<td>75 (28)</td>
<td>24 (71)</td>
</tr>
<tr>
<td>Herbs and/or botanicals</td>
<td>287 (42)</td>
<td>98 (36)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Other natural products</td>
<td>284 (41)</td>
<td>107 (39)</td>
<td>18 (53)</td>
</tr>
<tr>
<td>Mind-body practices</td>
<td>483 (71)</td>
<td>197 (72)</td>
<td>22 (65)</td>
</tr>
<tr>
<td>Self-practice(^c)</td>
<td>458 (67)</td>
<td>184 (68)</td>
<td>21 (62)</td>
</tr>
<tr>
<td>Practitioner-based(^d)</td>
<td>164 (24)</td>
<td>70 (26)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>CAM Index(^e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>87 (13)</td>
<td>38 (14)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>1</td>
<td>164 (24)</td>
<td>75 (28)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>2</td>
<td>173 (25)</td>
<td>69 (25)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>3</td>
<td>144 (21)</td>
<td>48 (18)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>4</td>
<td>88 (13)</td>
<td>33 (12)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>5</td>
<td>29 (4)</td>
<td>9 (3)</td>
<td>7 (21)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BQUAL, Breast Cancer Quality of Care Study; CAM, complementary and alternative medicine.

\(^a\) P values were calculated utilizing χ² tests and Fisher exact test.

\(^b\) CAM use is defined as the current use of any of the following five modalities: vitamins and/or minerals, herbs and/or botanical, other natural products, self-practice mind-body therapies, and practitioner-based mind-body therapies.

\(^c\) For example, yoga and meditation.

\(^d\) The CAM index is based on the sum of the score of using each of the following five modalities: vitamins/minerals, herbs/botanical, other natural products, self-practice mind-body therapies, and practitioner-based mind-body therapies.
Percent of women recommended for chemotherapy of nometastatic Invasive breast cancer by use of DS Grenleee et al Bqual
### Table 2. Multivariable Logistic Regression Models Examining Associations Between Current CAM Use and Chemotherapy Initiation in BQUAL, by Chemotherapy Indication or Discretionary

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chemotherapy, Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Discretionary (n = 379)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indicated (n = 306)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary Supplement Use (Yes vs No)</td>
<td>Model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>0.22 (0.06-0.58)</td>
<td>.006</td>
<td>0.76 (0.47-1.24)</td>
</tr>
<tr>
<td></td>
<td>Adjusteda</td>
<td>0.16 (0.03-0.51)</td>
<td>.006</td>
<td>0.66 (0.36-1.21)</td>
</tr>
<tr>
<td>Mind-Body Practice Use (Yes vs No)</td>
<td>Model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>1.43 (0.66-3.00)</td>
<td>.35</td>
<td>0.73 (0.46-1.15)</td>
</tr>
<tr>
<td></td>
<td>Adjusteda</td>
<td>1.45 (0.57-3.59)</td>
<td>.43</td>
<td>0.89 (0.50-1.58)</td>
</tr>
<tr>
<td>CAM Index (Every 1-Unit Increase)</td>
<td>Model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>0.71 (0.55-0.91)</td>
<td>.008</td>
<td>0.85 (0.72-0.99)</td>
</tr>
<tr>
<td></td>
<td>Adjustedb</td>
<td>0.64 (0.46-0.87)</td>
<td>.005</td>
<td>0.83 (0.67-1.01)</td>
</tr>
</tbody>
</table>

Abbreviations: BQUAL, Breast Cancer Quality of Care Study; CAM, complementary and alternative medicine; OR, odds ratio.

*a* Dietary supplements include vitamin and/or minerals, herbs and/or botanicals, and other natural products.

*b* Adjusted models controlled for age, race/ethnicity, education, grade, tumor size, estrogen receptor and/or progesterone receptor status, ERBB2 (formerly HER2 or HER2/neu) status, and Charlson comorbidity score.

*c* Mind-body practices include self-practice and practitioner-based therapies.

*d* The CAM index is based on the sum of the score of using each of the following five modalities: vitamins and/or minerals, herbs and/or botanical, other natural products, self-practice mind-body therapies, and practitioner-based mind-body therapies.
Dietary supplements with adverse effects during active treatment

• Very large doses folic acid and chemotherapy with antifolates like methotrexate

• Very large doses antioxidants and radiation therapy

• Large doses of iron and radiation and possibly also with chemotherapy

• Herbs causing skin sensitivity during radiation
Chemotherapy with antifolates can be compromised by use of large doses of folic acid supplements
What We Don’t Know

Motivations
- Why do survivors take dietary supplements and how do they decide to do so?

Exposures
- Prevalence of use in various cancers

Harms
- Do iron supplements given with erythropoietin treatment to prevent anemia promote angiogenesis?
- Is depression seen with use of some supplements due to them or simply to the disease itself?
Benefits

• Are there any supplements that increase disease free survival and lessen recurrence rates?

• What are later effects of use of supplements for prevention?

• Are there subgroups who may benefit?
Physician’s Health Study II: Multivitamins and Cancer Prevention

Randomized, double-blind study of 14,641 male U.S. Physicians given a multivitamin

In PHS only participants who had cancer already had benefit from MV supplements

Gaziano JM et al. JAMA 308(18):71-80, 2012
Knowing and Doing
Clinicians
"I won’t tell if you don’t ask"

20-70% of cancer patients Using CAM don’t tell doctor Usually because doctor does Not ask
Pay more attention to what we know helps patients

- Ask about dietary supplement use
- Find out what patients are taking
  - Brown bag checks
  - Check ingredients on web DSLD (Dietary supplement label database)
Take time to talk about their supplement decisions all thru treatment and survivorship process

• *Timing not a “one-off” event*
Patients make supplement decisions many times over cancer continuum
Help those who choose to use supplements

- High quality products don’t have to be high cost
- Discourage use of expensive heavily hyped tailored or personalized cancer site specific supplements that imply they cure or treat disease
- Report adverse effects to FDA
Evidence of efficacy of botique products is lacking.
Issues

- Benefits and risks of specific supplement being considered

- Dose

- Watch for and report adverse events (esp with known bad actors)

- Efficacy-- not assured
  - Marketing claims-- aren’t reality
Keep up with and communicate AICR, NCI, ACS and FDA recommendations
Don’t promote or sell supplements out of your office or health center
Dispensing physicians
Flexner Report 1910

MEDICAL EDUCATION IN THE UNITED STATES AND CANADA
A REPORT TO THE CARNEGIE FOUNDATION FOR THE ADVANCEMENT OF TEACHING
BY ABRAHAM FLEXNER
Researchers

- Obtain better data on exposures
  - During treatment
  - Key events in survivorship
  - Population based studies

- Do more research on supplement use during active therapy and survivorship

- Larger studies powered to evaluate decreased symptoms, also tumor response, magnitude of effects and survival
Don't use supplements to protect against cancer.

To reduce your risk of cancer, choose a balanced diet with a variety of foods rather than taking supplements.
After treatment, cancer survivors should follow the recommendations for cancer prevention.

Anyone who has received a diagnosis of cancer should receive specialized nutritional advice from an appropriately trained professional.
We know a lot and let’s be sure to let our patients know too.
Thank you!

Johanna Dwyer DSc RD
Office of Dietary Supplements
NIH
dwyerj1@od.nih.gov