



CLL SOCIETY

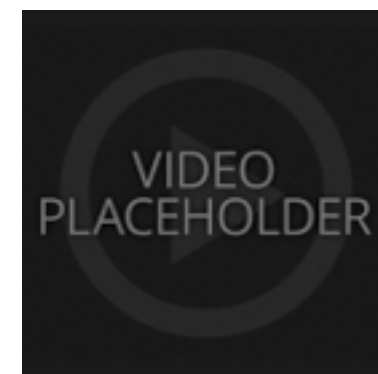
Smart Patients Get Smart Care™

NAVIGATING CLL WITH A COMPREHENSIVE WELLNESS APPROACH

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Deborah Stephens, DO

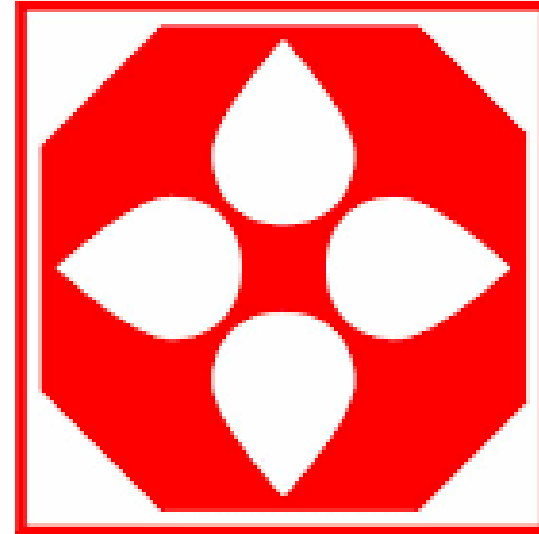
Director of the CLL and
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*University of North Carolina
at Chapel Hill*



OVERVIEW

- What is Integrative Medicine?
- Cancer-Related Fatigue
- Exercise
- Impact of Stress
- Diet
- Supplementation



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WHAT IS INTEGRATIVE MEDICINE?

Approach to healthcare that combines traditional medicine with complementary and/or alternative approaches (CAM). A few examples of CAM approaches are:

- **Mind-body therapies:** Yoga, meditation, acupuncture
- **Biologically-based therapies:** Herbal supplements, nutritional counseling
- **Manipulative and body-based therapies:** Massage, chiropractic care
- **Energy therapies:** Reiki, qigong

Integrative Oncology – Practice of Using Integrative Medicine in the Healthcare of Patients with Cancer



CANCER-RELATED FATIGUE

- Fatigue is a common symptom in people with CLL, and at times is the only physical symptom
- Fatigue in CLL is not usually alleviated simply by resting; it is thought to be related to chronic activation of the immune system that occurs with CLL
- Recommendations: good diet, hydration, and physical activity to help alleviate fatigue



CANCER-RELATED FATIGUE

- A meta-analysis of 113 studies revealed that pharmacological treatments (medicines) do not improve cancer-related fatigue significantly, while exercise and psychological interventions have a positive effect
- There is no magic pill!



EXERCISE AND IMMUNE SYSTEM

- A small study of patients with previously untreated CLL classified the patients as fit vs unfit based on physical fitness testing
- Studies of the plasma (liquid part of blood without cells) showed lower levels of inflammation and higher levels of mature (functional) immune cells (NK-cells)
- Additionally, when the plasma of fit patients was mixed with CLL cells (OSU-CLL), the cancer cells grew more slowly
- Data suggest that exercise may boost immune function, which could slow CLL growth
- More data needed



STRESS & CLL



- Study of 96 patients with CLL who were receiving ibrutinib for relapse of CLL
- Patients with higher stress levels had evidence of immune system overactivation with increased markers of inflammation, which was also associated with higher number of CLL cancer cells
- Suggests that higher levels of stress may impact the course of CLL



STRESS REDUCTION

- Hobbies and Activities:
 - Do things you like to do!
- Exercise:
 - Improve mood, reduce anxiety, and enhance overall well-being
- Relaxation Techniques:
 - Yoga, meditation, and deep breathing
 - Check out app library
- Mindfulness, Meditation, Journaling:
 - Become more aware of your thoughts and feelings
 - Check out app library
- Social Support:
 - Connect with friends, family, or support groups
 - Check the CLL Society Website for a Support Group



ACUPUNTURE

- Traditional Chinese medicine technique that involves inserting needles into specific points on the body with a goal of stimulating nerves and promoting healing
- No drug interactions!
- Evidence is the strongest for reducing pain and nausea/vomiting
- Some evidence to support relief of peripheral neuropathy, fatigue, constipation, insomnia, night sweats, and pruritus in cancer patients



DIET

- **“Was this caused by bad diet?”**
- **“Is there something I can eat to fight this?”**
- **“Should I cut out sugar?”**
- **“Do I need to eat organic foods only?”**
- **“Are there supplements that I should take?”**



DIET

- **Example: One study found that dietary factors are among the leading cause of death in 195 countries, including the United States.**
 - High intake of sodium (>3g/day)
 - Low intake of whole grains (<125g/day)
 - Low intake of fruits (<250g/day)

Additional Dietary Risk Factors Studied	
↓ Vegetables	↓ Fiber
↓ Legumes	↓ Calcium
↓ Nuts & Seeds	↓ Omega 3 Fatty Acids
↑ Red Meat	↓ Poly-unsaturated Fatty Acids
↑ Processed Meat	↑ Trans-fatty Acids
↑ Sugar-sweetened beverages	



DIET

- Another study completed in Spain found that a “Western-style dietary pattern” was associated with risk of CLL
 - High intake of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, convenience food and sauces
- It is unlikely that diet is the sole factor leading to CLL. Multiple factors play in.



SUGAR

- Higher fasting insulin levels are associated with increased risk of recurrence and death in breast cancer, but the data is unclear in hematologic malignancies
- Sugar present in foods naturally does not appear to be problematic, but there are mixed data that suggests that consumption of added sugars and sugary beverages, artificial sweeteners, as well as high dietary glycemic loads can affect treatment response and risk of relapse in certain types of cancers



SWEETENER

- Do artificial sweeteners cause cancer?
- This is especially important because many people with cancer try to decrease their sugar intake and end up increasing intake of artificial sugars



ARTIFICIAL SWEETENERS

- **Aspartame (Equal® and NutraSweet®; max recommended 40-50mg/kg/day)**
 - Study in rats found that high doses of aspartame associated with leukemia and lymphoma
 - Some issues with study design and study mostly dismissed
 - In humans:
 - 2006 study found no link in 500,000 individuals
 - 2013 review found no link
 - 2022 study of ~102,000 people followed in France over 8 year period found an association with developing cancer (higher association with breast cancer and other obesity-associated cancers)
- **Sucralose (Splenda®; 5mg/kg/day):**
 - Study in mice suggested consumption of high doses resulted in greater risk of blood cancers (note done by same lab as aspartame study)
 - Same 2022 French study did not find an association with cancer (but less intake compared with aspartame)
- **Saccharin (Sweet'N Low®, Sugar Twin®, Necta Sweet®; 5mg/kg/day):**
 - Study in rats found relationship between bladder cancer and consumption of saccharin (might be specifically related to rat biology)
 - Same 2022 French study did not find an association with cancer (but less intake compared with aspartame)



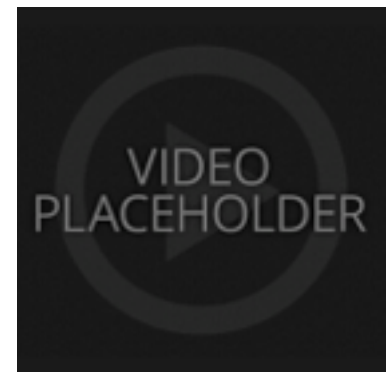
ARTIFICIAL SWEETENERS

Most of the risks were flagged in animal studies that gave very high doses of the sweetener to animals, which would be above the maximum daily limits suggested by the FDA

- Aspartame (Equal® and NutraSweet®; max recommended 40-50mg/kg/day)
- Sucralose (Splenda®; max recommended 5mg/kg/day):
- Saccharin (Sweet'N Low®, Sugar Twin®, Necta Sweet®; max recommended 5mg/kg/day):

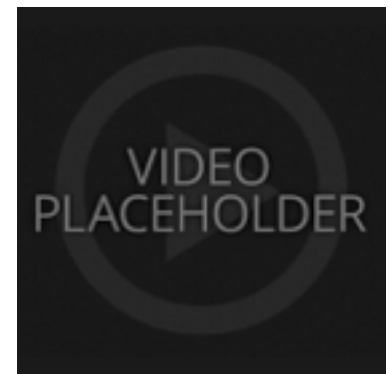
Example Calculation:

- For a 70 kg person (154 pounds), the acceptable daily intake is $40 \text{ mg/kg} * 70 \text{ kg} = 2800 \text{ mg}$ (WHO/EFSA) or $50 \text{ mg/kg} * 70 \text{ kg} = 3500 \text{ mg}$ (FDA).
- One 12 oz can of Diet Coke = 200 mg aspartame.
- If use more conservative estimate 2800mg allowed daily / 200mg per can = 14 (12 oz) cans per day.



ORGANIC FOOD

- Organic foods are foods produced without synthetic chemicals or fertilizers, pesticides, genetic engineering, or radiation
- Research has shown that several pesticides are carcinogenic, in fact, research on occupational pesticide exposure has shown that there is an association with pesticide residue and increased risk of non-Hodgkin lymphoma
- High organic food intake has been associated with a decreased risk of developing non-Hodgkin lymphoma



ORGANIC FOOD

- **BUT organic food is expensive, therefore the American Cancer Society notes that for individuals with limited resources, it is more important to prioritize a diet rich in vegetables and fruits**
- **The Clean 15 vs the Dirty Dozen**
 - Foods on the “clean 15” list do not need to be purchased organic
 - Foods on the “Dirty Dozen” list should be purchased organic when possible





EWG'S 2024

DIRTY DOZEN™

- | | |
|-----------------------------------|-------------------------|
| 1. Strawberries | 7. Nectarines |
| 2. Spinach | 8. Apples |
| 3. Kale, Collard & Mustard Greens | 9. Bell and hot peppers |
| 4. Grapes | 10. Cherries |
| 5. Peaches | 11. Blueberries |
| 6. Pears | 12. Green beans |



EWG'S 2024

CLEAN FIFTEEN™

- | | |
|-------------------|--------------------|
| 1. Sweet corn | 9. Kiwi |
| 2. Avocados | 10. Cabbage |
| 3. Pineapple | 11. Watermelon |
| 4. Onions | 12. Mushrooms |
| 5. Papaya | 13. Mango |
| 6. Sweet peas | 14. Sweet potatoes |
| 7. Asparagus | 15. Carrots |
| 8. Honeydew melon | |



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<https://www.ewg.org/foodnews/dirty-dozen.php>

WHAT TO EAT

- **Mediterranean diet may be a reasonable aim**
 - Lots of plant based, minimally processed foods such as fruits, vegetables, whole grains, nuts and legumes
 - Principal source of fat is olive oil
 - Cheese and yogurt, consumed daily in low to moderate amounts
 - Fish and poultry, consumed in low to moderate amounts a few times a week
 - Red meat, consumed infrequently and in small amounts
 - Fresh fruit for dessert, limiting sweets containing added sugars



SUPPLEMENTS

- “Are there any supplements that I should be taking?”



GREEN TEA EXTRACT

EGCG: MAYO Phase 2 study of Polyphenon E capsules containing ~200 mg of EGCG (this proprietary product is not available currently) at a dose of 2000 mg twice daily for 6 months in 42 patients

- The most common side effects were nausea, diarrhea, liver inflammation, mostly mild
- Twelve patients discontinued therapy early (9 from adverse events, 3 due to disease progression)
- One patient had a partial remission (overall response rate, 2.4%)
- 30% of patients had a decline in their ALC of $> 20\%$ for ≥ 2 months, and ~70% of those with enlarged nodes experienced a $> 50\%$ reduction in node size as determined by physical examination
- Generally considered safe with liver inflammation a concern but it's rare: need to monitor liver tests
- Conservatively estimated to be like drinking 22 8oz cups of green tea per day



TUMERIC (CURCUMIN)

Curcumin is the likely active agent in the common yellow spice turmeric, used in many curries

- 1 CLL trial: 21 patients with high ALC, stage 0 to 1 CLL received 2000 mg of curcumin daily for 6 mos
- Generally, well tolerated and safe, but some nausea and diarrhea
- No objective responses, but 4 patients showed a > 20% reduction in ALC, but it increased after stopping

SUMMARY: Both green tea and curcumin are likely safe with some activity but efficacy is unproven and may be minimal



VITAMIN D



- Study of 390 patients with newly diagnosed CLL seen at Mayo Clinic/U of Iowa
- 30-40% were Vitamin D deficient ($25\text{-D} < 25 \text{ ng/mL}$)
- Those with lower Vitamin D had shorter time to first treatment and trended towards shorter survival
- This study did not test whether supplementation could improve these findings

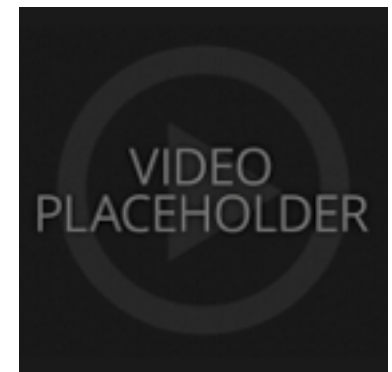


VITAMIN D



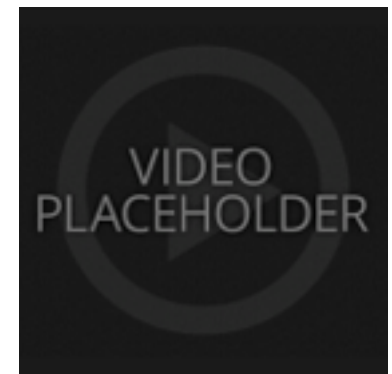
- Study of 3474 patients with newly diagnosed CLL included in a population database in Israel
- During the observation period 27% received a Vitamin D (6 months +)
- Those who received Vitamin D had a longer treatment-free survival
- In patients < 65 years, those who received Vitamin D had a longer time to first CLL treatment
- This study did not sequentially test Vitamin D levels and may not account for people taking over the counter Vitamin D supplements
- This was not a prospective (pre-planned study)
- Note of caution – follicular lymphoma story – prospective study did not show benefit of longer event free survival when given with rituximab

Summary: Vitamin D supplementation may be associated with better outcomes but prospective study is needed



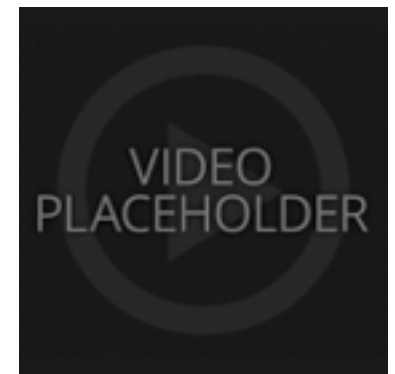
MUSHROOMS

- Active Hexose-Correlated Compound (AHCC): mushroom extract from several species of mushrooms, including Shiitake and Shimeji
- Extract was tested against CLL patient samples in the lab and found:
 - Toxic to the CLL cells
 - Reduced the number of cells in the environment that were helping to support the CLL cells
- Tested on a mouse model of CLL and found:
 - Reduced tumor load
 - Increased survival
 - Made immune therapy (antibodies) work better against CLL
- Has not been tested in a clinical trial, but shows some promise



OTHER MUSHROOMS

- Y3 Protein from Shaggy Mane Mushroom – Lab studies show killing of T-cell acute lymphoblastic leukemia
- Scarlet Caterpillarclub (*Cordyceps militaris*) – Various lab studies with leukemia cells, not CLL. Clinical trial noted on CLL Society website suggested decrease in lymphocyte count with drinking tea from the extract.
- Turkey tail (*Coriolus versicolor*) extract has demonstrated immune system stimulation, cancer cell growth inhibition, and antioxidant effects
- Maitake (*Grifola frondosa*) used in traditional Asian medicine
- Reishi (*Ganoderma lucidum*) referred to as the “mushroom of immortality”
- Have not been tested in a clinical trial, but shows some promise
- Please consult with your doctor before taking any supplements. Make sure to check for drug interactions.



SUPPLEMENTS

- Likely *eating a balanced diet* is the best option
- *Keep in mind* that supplements aren't as closely regulated as drugs that are approved for marketing
- *Be critical* of very expensive supplements
- Ask your medical team about any *potential drug interactions*



Dietary Supplement Verification Program Process

Good Manufacturing Practice (GMP) Facility Audit



Quality Control & Manufacturing (QCM) Process Evaluation



Ingredient Testing



Key: USP Company Both



Continued surveillance



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<https://www.quality-supplements.org/>

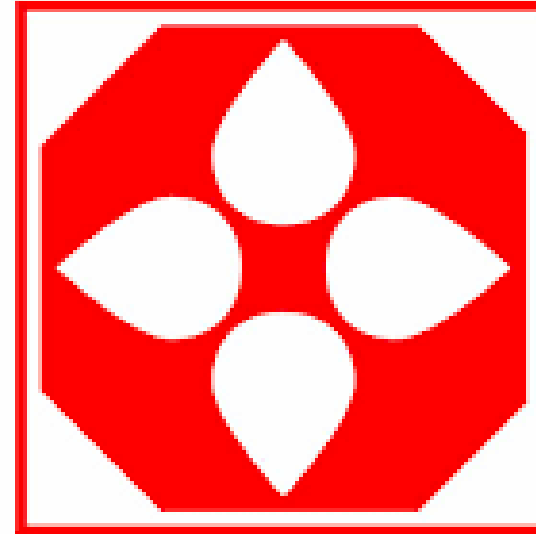
“DR. GOOGLE”

- Question the source of the information
- Consider the website’s editorial policies
- Check the level of evidence behind the claims
- Be aware of polarized and over-simplistic theories on cancer. For example: “Natural chemicals are good, synthetic chemicals are bad”
- Watch for logical errors. “Correlation but not causation”
- Don’t forget your medical team is there to answer your questions

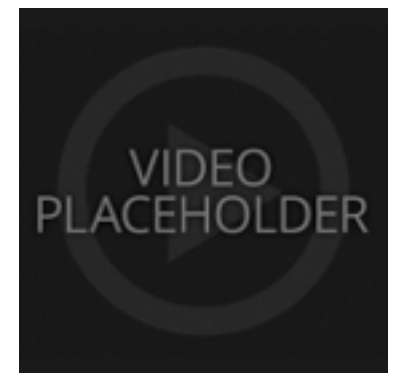


REVIEW

- What is Integrative Medicine?
- Cancer-Related Fatigue
- Exercise
- Impact of Stress
- Diet
- Supplementation



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AUDIENCE Q&A



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If your question was not answered,
please feel free to email: asktheexpert@cllsociety.org

Join us for our next virtual event,
ASK ME ANYTHING – FEATURING DR. LINDSEY ROEKER AND JEFF FOLLODER
May 23rd

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