American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
May 9, 2018
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Alcohol and Cancer Risk

Alcohol and Cancer Risk Fact Sheet
https://www.cancer.gov/about-cancer/causes-prevention/risk/alcohol/alcohol-fact-sheet

Alcohol is a Human Carcinogen (US Dept of HHS)
Evidence indicates that the more alcohol a person drinks and the more alcohol a person drinks regularly over time—the higher the risk of developing an alcohol-associated cancer.

- Whether alcohol impacts cancer initiation or progression is not well understood
- Immunosuppressive effects have been linked to progression and metastasis
- Alcohol consumption may lead to damage of every organ of the body
  (Testino, 2011), (Meadows, 2015)

Alcohol links to increased risk of:

- Breast, Prostate, Colon, Esophagus, Health and Neck, Liver and Pancreas cancers
  (Printz, 2018) (LoConte et al, 2018)

Gut Microbiome

- Alcohol is a risk factor of colorectal cancer
- Many microbial metabolites formed from consumption of alcohol and red meat may mediate the microbial diversity and the composition and abundance of the gut microbiota, which eventually affects the balance between health and disease (Rossi, 2018) (Tuan et al, 2016)

Oral Microbiome

- Lactobacillus species decreased with higher alcohol consumption in heavy and moderate drinkers
- Certain oral bacterial genera were enriched in subjects with higher alcohol consumption, including Actinomyces, Leptotrichia, Cardiobacterium, and Neisseria;
- Oral Neisseria can synthesize the human carcinogen acetaldehyde from ethanol (Fan et al, 2018)

Alcohol & Cancer: Mechanisms

- Genotoxic Effect of Acetaldehyde, DNA damage
- P450 CYP2E1 SNP Ethanol->Acetaldehyde
- Increased Estrogen Concentrations
- Cellular & Mitochondrial Stress (Increased ROS, VEGF)
- Altered Folate Metabolism (MTHFR SNP)
- Inflammation (Increased NFkB, MMP, IL1, IL6, IL8)
- Hindered Retinoic Acid (Vit A) Metabolism
- Immune Modulation (Decreased NK & T Cell function, Abnormal Dendritic Cells)

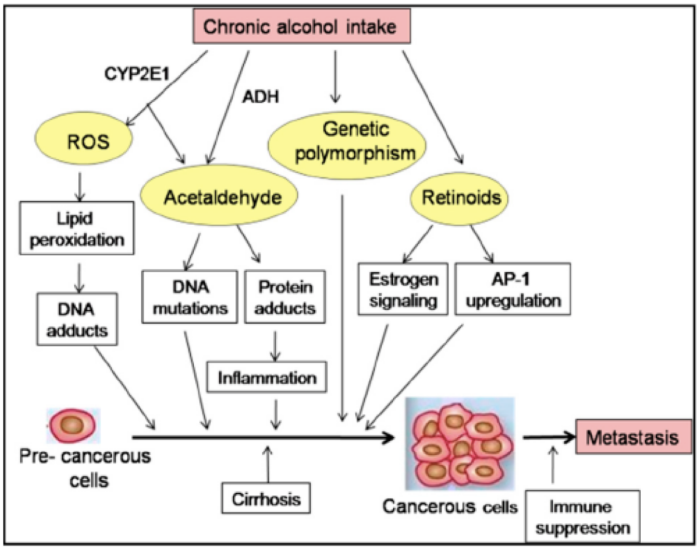
Mechanisms: Breast and Colorectal Cancers (Oyesamni et al, 2010)

Conversion of ethanol to acetaldehyde in mammary tissue has a significant effect on the progression of tumor development.

- increased hormonal receptor levels
- increased cell proliferation
- a direct stimulatory effect on DNA adduct formation
- increase cyclic adenosine monophosphate (cAMP)
- change in potassium channels
- modulation of gene expression

Exposure of human colonic biopsies to acetaldehyde suggests that acetaldehyde:

- disrupts epithelial tight junctions
- mucosal damage after ethanol consumption
- increased degradation of folate
- stimulation of rectal carcinogenesis
- increased cell proliferation
- increased effect of carcinogens
- folate uptake modulation
- tumor necrosis factor modulation
- inflammation and cell death
- DNA adduct formation
- cell differentiation
- modulation of gene expression



Total alcohol dehydrogenase activity is significantly higher in cancer tissues than in healthy organs. Cancer cells have a greater capability for ethanol oxidation but less ability to remove acetaldehyde than normal tissue intensifying carcinogenesis (Jelski, 2008).

Alcohol & Breast Cancer Risk

- Combined results of 98 studies found **women who drank alcohol were 11% more likely** than non-drinkers to get breast cancer (National Cancer Institute, 2011)
- A pooled analysis of data from 53 studies found for each alcoholic drink consumed per day, the relative risk of breast cancer **increased by about 7%**. Women who had **2-3 alcoholic drinks per day had a 20% higher risk** of breast cancer compared to women who didn't drink alcohol (Collaborative Group on Hormonal Factors in Breast Cancer, 2002)
- Estrogen levels are higher in women who drink alcohol than in non-drinkers. These higher estrogen levels may in turn, increase the risk of estrogen receptor positive breast cancer (Endogenous Hormones and Breast Cancer Collaborative Group, 2011)

Timing of Alcohol Exposure & Breast Cancer Risk (Liu et al, 2015)

- Exposures between menarche and first pregnancy, a stage when breast tissue is most susceptible to neoplastic transformation, can affect a woman's lifetime risk of breast cancer.
- A prolonged alcohol consumption before first pregnancy confers excess risk of breast cancer

Informing Clinical Practice:

- Based on the best available evidence it appears that modest alcohol consumption after breast cancer diagnosis, up to approximately one drink per day on average, may be associated with optimal overall survival, without compromising breast cancer–specific survival.
- Women who choose to consume modest amounts of alcohol after their breast cancer diagnosis may not be adversely affected; in fact, they may benefit from such a decision. (Newcomb et al, 2013)

Chemoprevention - P450 Enzyme Inhibition
Garlic diallyl sulfide and CYP2E1

- Organosulfur compounds including diallyl sulfide from garlic are potent inhibitors of CYP2E1
- Many mutagens including alcohol require activation by CYP2E1 (Zhou et al, 2003)

Soy and Quercetin Flavones and Flavonoids inhibit CYP1B1 activity (Yasuda et al, 2017)

Natural Inhibition of Cytochrome P450 CYP1: (Wilsher, 2017)

- APIGENIN celery, parsley, chamomile
- LUTEOLIN Mexican oregano, parsley, artichoke, celery, peppers, olive oil, rosemary, lemons, peppermint, sage, thyme
- KAEMPFEROL apples, onions, leeks, citrus fruits, grapes, red wines, ginkgo biloba, St. John's wort.
- QUERCETIN red apple, Rooibos tea, red onion, nuts, berries, cauliflower, red cabbage.
- RESVERATROL red and purple grapes and berries, Polygonum cuspidatum
- SCUTELLAREIN+BAICAILEIN Scutellaria baicalensis, Huang Qin
- MELATONIN (Chang et al, 2010)

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Case Study: Metastatic Cholangiocarcinoma

Submitted by: Corey Deacon, DNM, MSc

Overview: 41 yo Caucasian male, athletic
Family Hx: Older brother had lymphoma at age 14 and again at age 21

Values QOL, Longevity (healthspan +lifespan)
High Level of Stress Resilience

Metastatic cholangiocarcinoma - lungs and liver + pancreatic tumor (?)

- Liver enlargement, bile duct obstruction
- Immunohistology: CK7+, CK19+, focally+CK20, negative for: CDX2, HEP,PAR-1, TTF-1
- Pancreatobiliary tumor

Tumours were stable Nov 2017 until Jan 2018.
Recent CT indicates increased growth in biliary tree + new 1.3 x1 cm lymph node in mediastinum as of March 2018
Chemotherapy: - Cisplatin + Gemcitabine
Adverse Effects of Tx peripheral neuropathy, bilateral, medial-lateral, plantar

>> Dr. Nalini's Comments:

- Functional issues: Inflammation, Oxidative Stress, Mitochondrial poisoning
- RX: Acetyl L Carnitine (2 grams/day) , L-Glutamine (10 grams/day), R Lipoic Acid, Milk Thistle, O3 DHA (2-4 grams/day), Melatonin (10-20 mg/day)
- Acupuncture
- Good shoes: arch support, shock absorbing soles
- Wear ice pack gloves and booties during chemo

Core Questions:

What is a tumor of this origin most responsive to for treatment in regards to conventional and CAM?

- Pathology states adenocarcinoma-cholangiocarcinoma

- Metastatic advanced cancers challenging due to diverse populations of cells..recurrence=resistant cells

What would be other forms of therapy to add or recommend above and beyond what is currently being done?

- GI (epithelial) cancers typically have low frequency of tumor reactive T cells, therefore immunotherapies such as checkpoint inhibitors have not worked (PD1 PDL1 inhibitors)
- CAR T Cell Immunotherapy? (trials) Check for KRAS mutations, FGFR mutations, ID1 and IDH2 mutations (trials)
- Cycles of IV C, IV Artesunate, IV Curcumin +Oral Cytotoxic Herbs+HBOT (Press-Pulse)
- Consider oral Cu Chelation with Tetrathiomolybdate (check Serum Cu and Cp)
- Personalized TX: Tumor cell analysis--chemo sensitivity, proteomics, genomics
- Intermittent Fasting, Ketosis (protect from sarcopenia and cachexia)

Additional Recommendations:

- Dysbiosis Enterobacter cloacae complex in stool test - overgrowth: **Berberine** (500-1000mg 3x/day)
- Elevated SAMe (S adenosyl methionine) & SAH (S adenosyl homocysteine) levels: **Methylation issues (depression? detoxification?): Methylated B vitamins**
- High urinary mycotoxins with elevated ACTH, cortisol, Low AVP: **Mold panel (Olive leaf, Berberine Thyme oil, Oregano oil; Orthomolecular: Intest-Ol capsules)**
- Elevated VEGF: **Mold panel (Salvia milthiorrihiza Dan Shen)**

Elevated LFT (metastatic dx) - Milk Thistle, NAC, Sulforaphanes
Hypomagnesia
Myelosuppression RBC Anemia (Health Concerns Marrow Plus 3 tid or Natura Immucare 3 tid)
NLR 3.7:1.1 = 3.37 ≤2.0=very positive prognosis ≥4.0=poor prognosis
Albumin normal low albumin=poor prognosis

Corey's Integrative Oncology Care Plan
Neurofeedback + Trauma therapy (lost a daughter to SIDS 8 years ago) - still affecting his nervous system based on quantitative EEG evaluation.

IV glutathione, vitamin C, artemisinin, and curcumin
ADD IV C? YES (test G6PD first)
If possible, consider combining with HBOT Hyperbaric Oxygen Therapy ("Press-Pulse" per Seyfried)
Consider Mistletoe therapy - IV or SubQ
Consider Low Dose Naltrexone (RX) 4.5mg hs
Consider cannabinoids THC for cytotoxicity, appetite and CBD for nausea, pain, anxiety

Targeted Botanicals-Phytochemicals
ORAL CYTOTOXIC THERAPY
Scutellaria baicalensis
Polygonatum spp (Solomon's Seal)
Catharanthus roseus (Madagascar periwinkle)
Taxus brevifolia tips
Very toxic - be careful
I add some digestive herbs such as Citrus Reticulata-Chen Pi (Tangerine peel-and Rz Zingiber off Ginger rhizome and also recommend diluting in ginger tea)
Administer every other week
(Natura Health Products = PhytoCyto Formula)

Alternate with Super Artemisinin 3 tid one week on (with Hyperbaric Oxygen Therapy) one week off (See Seyfried's paper on "Press-Pulse" approach in AIIORE Resource Library)

Consider: Oldenlandia-Heydotis (source of ursolic acid), Tanacetum parthenium (Feverfew source of parthenolide), Tabueia (Pau D Arco), Polygonum cuspidatum (source of Resveratrol), EGCG-Green Tea(caution with methylation issues)

Antifibrotic: Dan Shen Red Sage (Salvia Milthiorrhiza)

Foundation Nutrition Supplements:
Remember OutSmart Cancer FOUNDATION Nutrients

- Multi Cu and Fe Free
- Probiotics-Prebiotics
- Vit D
- Omega 3/6 Fatty Acids
- Magnesium

Zinc picolinate (recommend DFH Zinc Supreme with Molybdenum for Cu chelation)
Vitamin C
Glutathione
High dose probiotic (250 billion CFU per day) (include PROBIOTICS - soluble fibers)
Magnesium bisglycinate
Curcumin
P5P
NAC
L-glutamine (neuropathy, GI repair)
Honokiol (sleep, regulate HPA axis and stress response, tumor inhibition)
Dessicated adrenal (and/or Adaptogenic formula such as DFH Adrenotone (American ginseng, Ashwaganda, Rhodiola, Siberian Ginseng))
Modified Citrus pectin powder (away from meals and supplements-binds to nutrients)
Melatonin (10-20mg hs)
Astragalus
Ox bile + taurine - due to gall bladder involvement (with lipase)
Herbal liver support - milk thistle, rosemary

Dr. Nalini's Comments:

- Give supplements with broad spectrum Digestive enzyme (DFH Paleozyme or Plant Digestive Enzyme PLUS extra Lipase (+ Bile salts -already included in your plan) such as Integrative Therapeutics Lipase--spread out --small frequent doses rather than a lot at once (instead of tid -go to 6x/d)

- Consider adding a Multi to cover micronutrient needs eg. ITI ProThriver Wellness Multi or DFH Twice Daily Multi-both are Cu Free and Iron Free 1 bid (Mitochondria rely upon many micronutrients including methylated b vitamins, Zn, Se, Mg, Mn etc as cofactors)

- Add Vitamin D (measure 25-OH Vit D) eg DFH Vitamin D Supreme (+K) 5000iu/cap

- Oral glutathione does not usually raise serum levels ...use liposomal (great for oral mucositis)or just use precursor N Acetyl Cysteine in your plan already (DFH 900mg/cap) tid

- Recommended Curcumin products: DFH Curcumevail, Thorne Meriva, Euromedica CuraPro

- Consider adding sulforaphanes-glucosinolate, such as glucoraphannin (DFH Broccoprotect or Thorne Crucera)

Targeted Supplements:

- AHCC - Consider Clinical Synergy Mushroom Immune Max powder or caps-broad spectrum high quality medicinal mushrooms formulation 3-5g/day
- Transfer factor - enviro + PlasMyc
- Black cumin oil (with bile and lipase supplements)
- Fibrinolytic enzyme - Lumbrokinase + Nattokinase - With tumors recommend primarily Lumbrokinase..though very expensive
- Zeolite + charcoal (away from food and supplements, acts as a binder..good for mycotoxins)
- Antiviral tincture (Isatis, Andrographis)
- Gamma linoleic acid - due to low omega-6 in testing (Ideal ratio O6:O3 4:1 in literature...prefer 2:1 or even 1:1 in cancer patients)

Lifestyle Guidelines:

- Exercise (moderate-high intensity interval training 2x per week)
- Infrared Sauna
- Meditation
- Neurofeedback
- Other spiritual practices
- **SLEEP!!!!**

>> Dr. Nalini's Comments, Considerations and Additional Recommendations:

- **Intermittent Fasting** (13-16 hours with no calories ..easiest between tonight's dinner and tomorrow's breakfast)
- **Modified Ketogenic (Outsmart Cancer) Diet**...2 days per week strict ketogenic diet if tolerates
- **Probiotics - Prebiotics** crucial (Klaire Therbiotic Complete or Target gbx (New) + Prebiotics saccharomyces boulardii + soluble fibers - see DFH PaleoFiber)
- **Consider Therapeutic Shake to insure nutrient density.**..can then put in powder forms of some supplements to **reduce pill fatigue** and give in a form that can be consumed over a few hours. These patients tend to have **nausea, low appetite and Upper GI pain** due to tumor mass pressure or liver enlargement..a strategy for inuring nutrient density that is easy for patient is needed.
- See OutSmart Cancer Shake in course materials which also includes **Carnitine Tartrate** (mitochondrial support, decrease risk of sarcopenia) and **MCT -immediate energy- (fatigue common i**n metastatic CA)
- Watch for **sarcopenia and cachexia**

Inquire:

- support system?
- digestive function? Adverse effects?
- fatigue, cognitive changes? Most common adverse effects
- issues with sexuality, intimacy, libido, virility? (relatively young man age 41)

Questions & Answers

Corey Deacon: **Update - Patient has metastasis in the peritoneal cavity and development ascites. The fluid has been drained and a sample is being to Consultative Proteomics for analysis. I have ran some VEGF testing. Is avastin a good pharmaceutical option at this point?**

- Assume VEGF is active with metastasis

- Avastin usually has a short duration of action.
- Tumor cells become resistant quickly; cancer cells that survive become very aggressive
- Typically used by oncologists in end-stage disease. It is not curative and not cytotoxic.
- Work with botanicals now and consider Avastin at a later date.

***Corey Deacon*: Can you make a recommendation for a clinic offering other therapies?**

Dr. Akbar Khan in Toronto clinic (naturopathic oncologist)
Medicore Cancer Center
website: www.medicorecancer.com
email: info@medicorecancer.com
phone: 888-622-6644

***Susan Holsapple*: Can you speak into the controversy of l-glutamine?**

- Review August 9, 2017 Clinical Pearl (Glutamine and Cancer Metabolism) and Paul Anderson's paper posted to the AIIORE library
- Certain cancer cells convert to using glutamine for fuel
- Glutamine is the most ubiquitous amino acid in body. Cancer cells can access glutamine through the muscle tissue that is rich in this amino acid.
- Oral glutamine will not accelerate progression and can be given to help repair nerves and repair lining of gastrointestinal tract.

***Susan Holsapple*: My client has a history of chronic low lymphocytes and a high neutrophil:lymphocyte ratio. Is this a concern for someone who doesn't necessarily have cancer?**

- Tumor micro-environment markers are not cancer markers.
- Biomarkers are measurements of physiology that are considered together with, not in isolation from, the history, trends, genetics and context of the patient.
- Pattern recognition is used to evaluate the environment for pro-carcinogenic or pro-tumorigenic factors.
- Immunity, inflammation, bone marrow may be indicated with this patient's lymphocyte markers.

Book Review

Outside the Box Cancer Therapies: Alternative Therapies That Treat and Prevent Cancer
April 24, 2018
by Dr. Mark Stengler (Author), Dr. Paul Anderson

Naturopathic medical doctors **Mark Stengler** and **Paul Anderson** focus on the most critical components of Integrative Oncology Care. Using an accessible, case-history approach, they explore the different types of cancer, the causes of cancer, how proper nutrition can help prevent and treat cancer, the most well-studied supplement to use with cancer treatment, cutting-edge therapies (such as intravenous high dose vitamin C and other studied therapies), and natural solutions to common problems (such as the side effects of chemotherapy and radiation).

Research: PSK decreased FOLFOX4-induced peripheral neuropathy and bone marrow suppression in patients with metastatic colorectal cancer.

Shibata, M., Shimura, T., Nishina, Y., Gonda, K., Matsuo, S., Abe, H., ... & Takenoshita, S. (2011). PSK decreased FOLFOX4-induced peripheral neuropathy and bone marrow suppression in patients with metastatic colorectal cancer. Gan to kagaku ryoho. Cancer & chemotherapy, 38(5), 797-801.[Article in Japanese]

Abstract **FOLFOX4** has been proven to be effective for metastatic colorectal cancer and is now used as a postoperative adjuvant therapy. However, **adverse effects such as cold-sensitive paresthesia and bone marrow suppression are common**, and this may necessitate a change of chemotherapy regimen even though FOLFOX is effective. **PSK, a polysaccharide derived from mushrooms**, has been developed in Japan as an **immune-enhancing agent**, and is widely used in patients with gastric, colorectal and pulmonary cancer. PSK has also been reported to **decrease some adverse effects of chemotherapy**. FOLFOX4 combined with PSK was administered to patients with metastatic colorectal cancer and the results were evaluated. Eight cycles of FOLFOX4 and PSK (3.0 g/day, po) were given to 25 patients with metastatic (19 hepatic, 3 pulmonary and 3 peritoneal) colorectal cancer. There was no CR (0%), while PR, SD and PD were 48, 36 and 16%, respectively. The response rate was 48%, and the disease control rate was 84%. There were **significantly lower frequencies of adverse effects i**n comparison with published data. Grades 1 and 3 **neutropenia** occurred in 48 and 24%, respectively, of the patients; grades 1 and 3 **nausea** in 48 and 4%; and grades 1, 2 and 3 **sensory neurotoxicity i**n 52, 4 and 0%. No patient dropped out due to adverse effect in this study. PSK plus FOLFOX4 seemed to be as effective as FOLFOX4 monotherapy as has been published, and significantly less toxic. **These results suggest that this combination therapy may be more effective than FOLFOX4 monotherapy when given over a longer period, with a lower incidence of adverse effects.** PMID: 21566440

Dr. Nalini's Comments:

- In Japan, PSK is an approved anti-cancer drug supported by 20+ years of research. PSK is widely used in Japan and recommended by medical doctors and oncologists.
- PSK is a concentrated polysaccharide compound derived from Coriolus versicolor Yun Zhi (discussed in Foundations of Integrative Oncology Course).
- Protects bone marrow against myelosuppression, improves levels of WBC, NK Cells, Neutrophils, decreases neuropathy and nausea, promotes immune modulation, tumor control, inflammation control. A traditional Qi and Longevity tonic and adaptogen.
- **Recommended Dose:** 3-5 grams Coriolus (Trametes) versicolor per day during and after chemotherapy treatment cycle

Research: Bladder Cancer and Exposure to Hair Dye

Dr. Nalini's Comments:

- The conflicting studies below reveal that there is clearly a subset of patients for whom hair dye is a risk factor for development of cancer. Most likely this subset of patients has unique SNPs that affect metabolism, detoxification and excretion of chemicals found in hair coloring products.
- This type of genomic risk factor analysis does not seem to have been performed or published to date. Applying anything directly to the skin means that there will be not only local but potentially systemic effects of small amounts absorbed over long periods of time.
- More studies are needed to assess long periods of exposure and identify characteristics of patients at higher risk when exposed to these chemicals and dyes.

Application:

- Educate patients and especially hair dye professionals about risks of exposures especially of black

and dark color dyes.
- Identify patients with compromised detoxification capacities (Genova labs Detoxigenomics panel or analysis of Detoxification SNPs...geneticgenie.org, livewello.com).
- All cancer patients and survivors should also be well informed about risks associated with all personal care products and cosmetics (EWG.org: Skin Deep Cosmetics Database).

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Source: National Cancer Institute

Immunotherapy Research: COX-2 Inhibitors May Improve Cancer Immunotherapy Response

Hennequart, M., Pilotte, L., Cane, S., Hoffmann, D., Stroobant, V., De Plaen, E., & Van den Eynde, B. J. (2017). Constitutive IDO1 expression in human tumors is driven by cyclooxygenase-2 and mediates intrinsic immune resistance. Cancer Immunol Res, 5, 695-709.
https://immuno-oncologynews.com/2017/07/22/cox-2-inhibitors-may-boost-cancer-immunotherapy/

A new study shows that tumors that constantly express the protein IDO1 (indoleamine 2,3-dioxygenase) are sensitive to COX-2 inhibitors, which may provide an increase in T-cell antitumor function.

The study titled, "Constitutive IDO1 Expression in Human Tumors Is Driven by Cyclooxygenase-2 and ***Mediates Intrinsic Immune Resistance,***" was published in the journal Cancer Immunology Research.

Researchers at the Ludwig Institute for Cancer Research wanted to understand the molecular mechanisms that cause some tumors to express the protein IDO1, which can help tumors evade or resist attacks from t-cells, and not others.

In the first part of their study, the research team used various tumor cell lines including human melanoma, lung, ovarian, and head and neck cancer cells, to show that the constant expression of IDO1 is caused by the protein **COX-2 (Cyclooxygenase-2) and its product PGE2 (prostaglandin E2)**, both of which are involved in various pathways of cell signaling that can be utilized to **increase tumor growth.**

"These data provide evidence that ***COX-2 drives tumor-induced immunosuppression*** through constitutive expression of IDO1," said Benoit J. Van den Eynde, MD, PhD, professor at Ludwig Institute for Cancer Research in Brussels, Belgium in a press release.

In the next part of their study, researchers implanted tumors that have constant IDO1 expression as well as human immune cells into mice lacking an immune system to study the response to the COX-2 inhibitor celecoxib and an IDO1 inhibitor epacadostat.

Results from this part of the study showed that both COX-2 inhibitors and IDO1 inhibitors led to an immune rejection of the IDO1 expressing tumors in the mice, which was associated with greater T-cell invasion.

Lastly, by conducting large-scale gene expression analysis from 1041 different human tumors, researchers showed a correlation between expression of IDO1 and activation of the COX-2/PGE2 pathway in many cancer cell types.

Since ***these tumors can be treated by COX-2 inhibitors to improve T-cell invasion*****,** another class of drugs called **anti-PD1 drugs can be used to treat these tumors in combination with COX-2 inhibitors.**

"Our studies provide a clear rationale to test, in the clinics, ***combinations of anti-PD1 immunotherapy and COX-2 inhibitors***," Van den Eynde said. "This should be straightforward given the fact that both anti-PD1 and COX-2 inhibitors are already approved for clinical use in different contexts."

Dr. Nalini's Comments:
Integrative Oncology Application: Recommend use nutraceutical and botanical COX2 inhibitors with patients on immunotherapies especially PD1 and PDL1 inhibitors

Phytochemical and Nutriceutical COX-2 Inhibitors
Omega 3 Fatty Acids (EPA-DHA)
EGCG epigallocatechin gallate (Camelia chinensis-Green Tea catechin flavone)
Curcumin (Curcuma longa-Tumeric rhizome curcuminoid)
Resveratrol stilbene (Polygonum cuspidatum-Japanese Knotweed)
Parthenolide sesquiterpene lactone (Tanacetum parthenium-Feverfew)
Alpha Keto Boswellic Acid (Boswellia serrata-Frankincense)
Gingerols, Zerumbone sesquiterpene (Rhizoma Zingiber spp-Ginger rhizome)
Baicailein polyphenol (Radix Scutellaria baicalensis-Huang Qin)
Berberine isoquinoline alkaloid (Radix Scutellaria baicalensis-Huang Qin, Hydrastis canadensis-Goldenseal)

Research: The effects of high-dose calcitriol and individualized exercise on bone metabolism in breast cancer survivors on hormonal therapy: a phase II feasibility trial

Peppone, L. J., Ling, M., Huston, A. J., Reid, M. E., Janelsins, M. C., Puzas, J. E., ... & Mustian, K. M.

(2018). The effects of high-dose calcitriol and individualized exercise on bone metabolism in breast cancer survivors on hormonal therapy: a phase II feasibility trial. Supportive Care in Cancer, 1-9.

ABSTRACT

Introduction Cancer treatment-induced bone loss (CTIBL) is a long-term side effect of breast cancer therapy. Both calcitriol and weight-bearing exercise improve bone metabolism for osteoporotic patients, but are unproven in a breast cancer population. We used a novel high-dose calcitriol regimen with an individualized exercise intervention to improve bone metabolism in breast cancer survivors.

Methods We accrued 41 subjects to this open label, 2 × 2 factorial, randomized feasibility trial. Breast cancer survivors were randomized to receive the following: (1) calcitriol (45 micrograms/week), (2) individualized exercise with progressive walking and resistance training, (3) both, or (4) a daily multivitamin (control condition) for 12 weeks. Primary outcomes included changes in biomarkers of bone formation, bone resorption, and the bone remodeling index, a composite measure of bone formation and resorption. Safety measures included clinical and biochemical adverse events. A main effect analysis was used for these endpoints.

Results Hypercalcemia was limited to three grade I cases with no grade ≥ 2 cases. Among exercisers, 100% engaged in the prescribed aerobic training and 44.4% engaged in the prescribed resistance training. Calcitriol significantly improved bone formation (Cohen's d = 0.64; $p < 0.01$), resulting in a non-significant increase in the bone remodeling index (Cohen's d = 0.21; $p = 31$). Exercise failed to improve any of the bone biomarkers.

Conclusions: Both calcitriol and exercise were shown to be feasible and well tolerated. Calcitriol significantly improved bone formation, resulting in a net increase of bone metabolism. Compliance with the exercise intervention was suboptimal, which may have led to a lack of effect of exercise on bone metabolism.

Dr. Nalini's Comments:
1,25-(OH)2D3 (Calcitriol), the active form of vitamin D3
Synthetic analog was used in this study

While we learn that increased levels of 1,25 OH Vitamin have a positive impact on bone metabolism **I DO NOT RECOMMEND the use of Calcitriol due to safety concerns** and carcinogens in the material used in this study. This does confirm that safe oral administration of Vitamin D3 (25 OH VIT D) can be used to support healthy bone metabolism.

Synthetic Calcitriol in this study is made with butylated hydroxyanisole (BHA), butylated hydroxytolulene (BHT). Toluene is a known carcinogen.

A safer approach is to give oral Vitamin D3 (cholecalciferol), allow the body to convert to active form, 1-25 OH, which is much safer, and monitor serum levels of 25-OH Vitamin D to optimize to 55-80 mg/dl**.**

High oral doses of Vitamin D should also be given WITH Vitamin K2 (MK4 or MK 7 in supplements) to promote calcium storage in the bone. Vitamin K promotes carboxylation reactions and leads to increase of osteocalcin, a hormone, which promotes bone building via osteoblasts**.** Vitamin K has also been shown to slow tumor growth.

Recommend: Designs for Health Vitamin D Synergy, Vitamin D Supreme both of which contain Vitamin K. Orthomolecular Solutions and Thorne Research also make similar Vitamin D+K products.

Disagree with statement in this paper that exercise has no impact on bone health and density!!

International units (IU) to mcg for VITAMIN D

Vitamin D: 1 IU is the biological equivalent of 0.025 mcg cholecalciferol or ergocalciferol 45mcg=1800iu (dose in this study)

Reference:

From https://www.drugs.com/pro/calcitriol.html

Calcitriol Description (Pharmaceutical)

Calcitriol Oral Solution is **a synthetic vitamin D analog** which is active in the regulation of the absorption of calcium from the gastrointestinal tract and its utilization in the body. Calcitriol Oral Solution is available as an oral solution, for oral administration, containing 1 mcg/mL of Calcitriol. Calcitriol Oral Solution **contains butylated hydroxyanisole (BHA), butylated hydroxytolulene (BHT) and medium chain triglycerides.**

1,25-(OH)2D3 (Calcitriol), the active form of vitamin D3

Human natural supply of vitamin D depends mainly on exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol in the skin to vitamin D3(cholecalciferol). Vitamin D3 must be metabolically activated in the liver and the kidney before it is fully active as a regulator of calcium and phosphorus metabolism at target tissues.

The initial transformation of vitamin D3 is catalyzed by a vitamin D3-25-hydroxylase enzyme (25-OHase) present in the liver, and the product of this reaction is 25-hydroxyvitamin D3 [25-(OH)D3]. Hydroxylation of 25-(OH)D3 occurs in the mitochondria of kidney tissue, activated by the renal 25-hydroxyvitamin D3-1 alpha-hydroxylase (alpha-OHase), to produce 1,25-(OH)2D3 (Calcitriol), the active form of vitamin D3.

Endogenous synthesis and catabolism of Calcitriol, as well as physiological control mechanisms affecting these processes, play a critical role regulating the serum level of Calcitriol. Physiological daily production is normally 0.5 to 1 mcg and is somewhat higher during periods of increased bone synthesis (e.g., growth or pregnancy).

The two known sites of action of Calcitriol are intestine and bone. A Calcitriol receptor-binding protein appears to exist in the mucosa of human intestine. Additional evidence suggests that Calcitriol may also act on the kidney and the parathyroid glands. Calcitriol is the most active known form of vitamin D3 in stimulating intestinal calcium transport. In acutely uremic rats Calcitriol has been shown to stimulate intestinal calcium absorption.

The kidneys of uremic patients cannot adequately synthesize Calcitriol, the active hormone formed from precursor vitamin D. Resultant hypocalcemia and secondary hyperparathyroidism are a major cause of the metabolic bone disease of renal failure. However, other bone-toxic substances which accumulate in uremia (e.g., aluminum) may also contribute.

The beneficial effect of Calcitriol in renal osteodystrophy appears to result from correction of hypocalcemia and secondary hyperparathyroidism. It is uncertain whether Calcitriol produces other independent beneficial effects. Calcitriol treatment is not associated with an accelerated rate of renal function deterioration. No radiographic evidence of extraskeletal calcification has been found in predialysis patients following treatment. The duration of pharmacologic activity of a single dose of Calcitriol is about 3 to 5 days.

Contraindications Calcitriol should not be given to patients with hypercalcemia or evidence of vitamin D toxicity. Use of Calcitriol in patients with known hypersensitivity to Calcitriol (or drugs of the same class) or any of the inactive ingredients is contraindicated.

Warning: Overdosage of any form of vitamin D is dangerous. Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis and other soft-tissue calcification. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

Calcitriol is the most potent metabolite of vitamin D available. **The administration of Calcitriol Oral Solution to patients in excess of their daily requirements can cause hypercalcemia, hypercalciuria and hyperphosphatemia**. Therefore, pharmacologic doses of vitamin D and its derivatives should be withheld during Calcitriol treatment to avoid possible additive effects and hypercalcemia. If treatment is switched from ergocalciferol (vitamin D2) to Calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value.

Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphatemia, **caution is called for in patients with renal failure** because of the danger of ectopic calcification. A non-aluminum phosphate-binding compound and a low-phosphate diet should be used to control serum phosphorus levels in patients undergoing dialysis.

Magnesium-containing preparations (e.g., antacids) and Calcitriol should not be used concomitantly in patients on chronic renal dialysis because such use may lead to the development of hypermagnesemia.

Studies in dogs and rats given Calcitriol for up to 26 weeks have shown that small increases of Calcitriol above endogenous levels can lead to abnormalities of calcium metabolism with the potential for calcification of many tissues in the body.

General Excessive dosage of Calcitriol induces hypercalcemia and in some instances hypercalciuria; therefore, early in treatment during dosage adjustment, serum calcium should be determined twice weekly. In dialysis patients, a fall in serum alkaline phosphatase levels usually antedates the appearance of hypercalcemia and may be an indication of impending hypercalcemia. An abrupt increase in calcium intake as a result of changes in diet (e.g., increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcemia.

Should hypercalcemia develop, treatment with Calcitriol should be stopped immediately. During periods of hypercalcemia, serum calcium and phosphate levels must be determined daily. When normal levels have been attained, treatment with Calcitriol can be continued, at a daily dose of 0.25 mcg lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated. Calcitriol should be given cautiously to patients on digitalis, because hypercalcemia in such patients may precipitate cardiac arrhythmias.

CLINICAL PEARL

OVERVIEW
ALCOHOL and CANCER RISK

Dr. Nalini Chilkov, Founder

CANCER RISK and ALCOHOL

Alcohol is a Human Carcinogen (US Dept of HHS)

Evidence indicates that the more alcohol a person drinks and the more alcohol a person drinks regularly over time—the higher the risk of developing an alcohol-associated cancer.

Alcohol and Cancer Risk Fact Sheet
https://www.cancer.gov/about-cancer/causes-prevention/risk/alcohol/alcohol-fact-sheet.
National Cancer Institute

Both Ethanol and its Major Metabolite Acetylaldehyde are listed as Carcinogens in Humans

- Whether alcohol impacts cancer initiation or progression is not well understood
- Immunosuppressive effects have been linked to progression and metastasis
- Alcohol consumption may lead to damage of every organ of the body

Testino, G. **The burden of cancer attributable to alcohol consumption.** Maedica 2011, 6, 313–320

Meadows, G.G.; Zhang, H. **Effects of alcohol on tumor growth, metastasis, immune response, and host survival**. Alcohol Res. 2015, 37, 311–322

Alcohol consumption is linked to a higher risk of several cancers

Breast Prostate Colon Esophagus
Head and Neck Liver Pancreas

70% of Americans do not recognize drinking alcohol as a risk factor for cancer

Only 38% of Americans limit their alcohol intake to reduce cancer risk.

Cancer. 2018 Apr 15;124(8):1642. doi: 10.1002/cncr.31363.
American Society of Clinical Oncology says 5% to 6% of new cancers and cancer deaths are attributable to alcohol consumption. Printz C.

J Clin Oncol. 2018;36:83-93. DOI: 10.1002/cncr. 31363
Alcohol and cancer: a statement of the American Society of Clinical Oncology. LoConte NK, Brewster AM, Kaur JS, Merrill JK, Alberg AJ.

ALCOHOL IMPACTS the MICROBIOME

Alcohol Intake is One of the Major Risk Factors for Development of Colorectal Cancer

High consumption of fiber, low consumption of red or processed red meat *as well as minimizing alcohol intake* have been associated with a lower risk of CRC.

Many microbial metabolites formed from those three substances may *mediate the microbial diversity and the composition and abundance of the gut microbiota,*
which eventually affects the balance between health and disease, including CRC.

Cancers (Basel). 2018 Feb; 10(2): 38. Published online 2018 Jan 30. doi: 10.3390/cancers10020038
Colorectal Cancer and Alcohol Consumption—Populations to Molecules
Marco Rossi, **Dietary and Lifestyle Factors Associated with Colorectal Cancer Risk and Interactions with Microbiota: Fiber, Red or Processed Meat and Alcoholic Drinks** Juan Tuan Ying-Xuan Chen Gastrointest Tumors 2016;3:17–24

ORAL MICROBIOME Linked to Head and Neck and GI Cancers

- The diversity of oral microbiota and overall bacterial profiles differed between heavy drinkers and non-drinkers
- **Lactobacillis species decreased** with higher alcohol consumption in heavy and moderate drinkers
- **Certain oral bacterial genera were enriched** in subjects with higher alcohol consumption, including Actinomyces, Leptotrichia, Cardiobacterium, and Neisseria;
- **Oral Neisseria can synthesize the human carcinogen acetaldehyde from ethanol**

CONCLUSION: Oral Microbiome impacts alcohol related cancer risk

Microbiome. 2018 Apr 24;6(1):59. doi: 10.1186/s40168-018-0448-x.
Drinking alcohol is associated with variation in the human oral microbiome in a large study of American adults.
Fan X[1 et al]

MECHANISMS

ALCOHOL and CANCER | MECHANISMS

Chronic Use

Dose Dependent

- Genotoxic Effect of Acetylaldehyde, DNA damage
- P450 CYP2E1 SNP Ethanol->Acetylaldehyde
- Increased Estrogen Concentrations
- Cellular & Mitochondrial Stress ⇧ ROS, VEGF
- Altered Folate Metabolism MTHFR SNP
- Inflammation ⇧ NFkB, MMP, IL1, IL6, IL8
- Hindered Retinoic Acid (Vit A) Metabolism
- Immune Modulation ⇩ NK & T Cell function, Abnormal Dendritic Cells

Alcohol Consumption and Cancer Risk Understanding Possible Causal Mechanisms for Breast and Colorectal Cancers

Conversion of Ethanol to Acetaldehyde in Mammary Tissue has a significant effect on the progression of tumor development

- increased hormonal receptor levels
- increased cell proliferation
- a direct stimulatory effect on DNA adduct formation
- increase cyclic adenosine monophosphate (cAMP)
- change in potassium channels
- modulation of gene expression

Evidence Reports/Technology Assessments, No. 197 ECRI Institute Evidence-based Practice Center Rockville (MD): Agency for Healthcare Research and Quality (US); **2010 N**ov. Report No.: 11-E003

Alcohol Consumption and Cancer Risk Understanding Possible Causal Mechanisms for Breast and Colorectal Cancers

Exposure of human colonic biopsies to acetaldehyde suggests that acetaldehyde

- disrupts epithelial tight junctions
- mucosal damage after ethanol consumption
- increased degradation of folate
- stimulation of rectal carcinogenesis
- increased cell proliferation
- increased effect of carcinogens.
- folate uptake modulation
- tumor necrosis factor modulation
- inflammation and cell death
- DNA adduct formation
- cell differentiation
- modulation of gene expression.

Evidence Reports/Technology Assessments, No. 197 ECRI Institute Evidence-based Practice Center Rockville (MD): Agency for Healthcare Research and Quality (US); **2010 N**ov. Report No.: 11-E003

Chronic alcohol consumption is a significant risk factor for cancer in humans

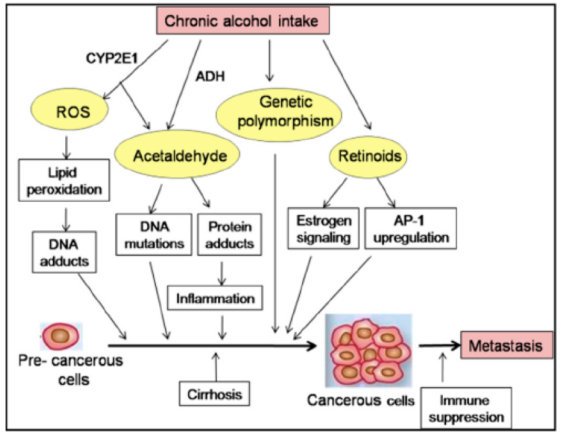
Total alcohol dehydrogenase activity is significantly higher in cancer tissues than in this healthy organs

Cancer cells have a greater capability for ethanol oxidation but less ability to remove acetaldehyde than normal tissue intensifying carcinogenesis

Clin Chim Acta. 2008 Sep;395(1-2):1-5. **Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the cancer diseases.** Jelski W[1], Szmitkowski M.

Various mechanisms by which alcohol may affect carcinogenesis

Review :
Alcohol and Cancer: Mechanisms and Therapies
Anuradha Ratna and Pranoti Mandrekar
Biomolecules 2017, 7, 61; doi:10.3390/biom7030061



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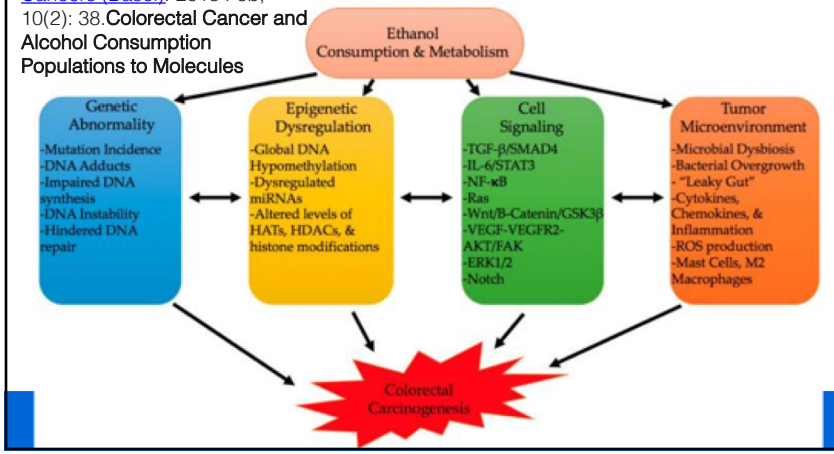
Cancers (Basel). 2018 Feb; 10(2): 38. **Colorectal Cancer and Alcohol Consumption Populations to Molecules**



ALCOHOL AND BREAST CANCER

A pooled analysis of data from 53 studies found for each alcoholic drink consumed per day, the relative risk of breast cancer increased by about 7 percent

Women who had 2-3 alcoholic drinks per day had a 20 percent higher risk of breast cancer compared to women who didn't drink alcohol

Br J Cancer. 87(11):1234-45, 2002.

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ALCOHOL AND BREAST CANCER RISK

Dose Response Relationship between Chronic Consumption and Increased Risk of Breast Cancer

Alcohol is Classified As A Breast Carcinogen

One	Two	Three	Drinks per Day
10%	20%	40%	Increased Risk

4% of all newly diagnosed breast cancer cases (8000 cases per year) are due to alcohol abuse

Longnecker, M.P. **Alcoholic beverage consumption in relation to risk of breast cancer: Meta-analysis and review.** Cancer Causes Control 1994, 5, 73–82.

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www.AIIORE.com

1-2 drinks (or more) of alcohol per day increases the risk of breast cancer.

Combined results of 98 studies found women who drank alcohol were 11 percent more likely than non-drinkers to get breast cancer

National Cancer Institute. Breast Cancer Risk Assessment Tool. http://www.cancer.gov/bcrisktool/Default.aspx, 2011.

Estrogen levels are higher in women who drink alcohol than in non-drinkers. These higher estrogen levels may in turn, increase the risk of estrogen receptor positive breast cancer.

Circulating sex hormones and breast cancer risk factors in postmenopausal women: Reanalysis of 13 studies. Br J Cancer. 105(5):709-22, 2011.

TIMING OF ALCOHOL CONSUMPTION AND BREAST CANCER RISK

- **Exposures between menarche and first pregnancy**, a stage when breast tissue is most susceptible to neoplastic transformation, **can affect a woman's lifetime risk of breast cancer**.
- **Alcohol consumption before first pregnancy is dose dependently associated with a significant increase in risk** of breast cancer
- **A prolonged alcohol consumption before first pregnancy confers excess risk of breast cancer**
- **Alcohol intake in adolescent and early adult years increases risks of breast cancer and proliferative benign breast disease, suggesting that breast cancer prevention efforts should begin early in life.**

Review: Links between alcohol consumption & breast cancer Womens Health (2015) 11(1)

How Does the Latest Research on Alcohol and Breast Cancer Inform Clinical Practice?

Based on the best available evidence, including the report of Newcomb et al. it appears that **modest alcohol consumption after breast cancer diagnosis, up to approximately one drink per day on average, may be associated with optimal overall survival, without compromising breast cancer–specific survival.**
www.jco.org VOLUME 31 NUMBER 16 JUNE 1 2013

Women who choose to consume modest amounts of alcohol after their breast cancer diagnosis may not be adversely affected; in fact, they may benefit from such a decision.
Newcomb PA, Kampman E, Trentham-Dietz A, et al: Alcohol consumption before and after breast cancer diagnosis: Associations with survival from breast cancer, cardiovascular disease, and other causes.
J Clin Oncol 31:1939-1946, 2013

CHEMOPREVENTION

P450 Enzyme Inhibition

Garlic diallyl sulfide and CYP2E1

Garlic's Chemo-preventive Effect

Organosulfur compounds including diallyl sulfide from garlic are potent inhibitors of CYP2E1

Many mutagens including alcohol require activation by CYP2E1

Shufeng Zhou, et al (2003) Interactions of Herbs with Cytochrome P450, Drug Metabolism Reviews, 35:1, 35-98,

Estrogen- and stress-induced DNA damage in breast cancer and chemoprevention with dietary flavonoid

Soy and Quercetin Flavones and Flavonoids inhibit CYP1B1 activity

Michiko T. Yasuda1 , Hiroyuki Sakakibara2 and Kayoko Shimoi1*
Yasuda et al. Genes and Environment (2017) 39:10

NATURAL INHIBITION OF Cytochrome P450 CYP1

APIGENIN celery, parsley, chamomile
LUTEOLIN Mexican oregano, parsley, artichoke, celery, peppers, olive oil, rosemary, lemons, peppermint, sage, thyme
KAEMPFEROL apples, onions, leeks, citrus fruits, grapes, red wines, gingko biloba, St. John's wort.
QUERCETIN red apple, tea, red onion, nuts, berries, cauliflower, red cabbage.
RESVERATROL red and purple grapes and berries, Polygonum cuspidatum
SCUTELLAREIN+BAICAILEIN Scutellaria baicalensis, Huang Qin
MELATONIN Inhibition of procarcinogen-bioactivating human CYP1A1, CYP1A2 and CYP1B1 enzymes by melatonin Journal of Pineal Research 48(1):55-64 · November 2009

Cytochrome P450 CYP1 metabolism of hydroxylated flavones and flavonols: Selective bioactivation of luteolin in breast cancer cells Food and Chemical Toxicology Volume 110, December 2017, Pages 383-394

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Alcohol and Cancer: A Statement of the American Society of Clinical Oncology

Noelle K. LoConte, Abenaa M. Brewster, Judith S. Kaur, Janette K. Merrill, and Anthony J. Alberg

Author affiliations and support information (if applicable) appear at the end of this article.

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0732-183X/17/3599-1/$20.00

ABSTRACT

Alcohol drinking is an established risk factor for several malignancies, and it is a potentially modifiable risk factor for cancer. The Cancer Prevention Committee of the American Society of Clinical Oncology (ASCO) believes that a proactive stance by the Society to minimize excessive exposure to alcohol has important implications for cancer prevention. In addition, the role of alcohol drinking on outcomes in patients with cancer is in its formative stages, and ASCO can play a key role by generating a research agenda. Also, ASCO could provide needed leadership in the cancer community on this issue. In the issuance of this statement, ASCO joins a growing number of international organizations by establishing a platform to support effective public health strategies in this area. The goals of this statement are to:

- Promote public education about the risks between alcohol abuse and certain types of cancer;
- Support policy efforts to reduce the risk of cancer through evidence-based strategies that prevent excessive use of alcohol;
- Provide education to oncology providers about the influence of excessive alcohol use and cancer risks and treatment complications, including clarification of conflicting evidence; and
- Identify areas of needed research regarding the relationship between alcohol use and cancer risk and outcomes.

J Clin Oncol 35. © 2017 by American Society of Clinical Oncology

INTRODUCTION

The importance of alcohol drinking as a contributing factor to the overall cancer burden is often underappreciated. In fact, alcohol drinking is an established risk factor for several malignancies. As a potentially modifiable risk factor for cancer, addressing high-risk alcohol use is one strategy to reduce the burden of cancer. For example, in 2012, 5.5% of all new cancer occurrences and 5.8% of all cancer deaths worldwide were estimated to be attributable to alcohol.[1] In the United States, it has been estimated that 3.5% of all cancer deaths are attributable to drinking alcohol.[2] Alcohol is causally associated with oropharyngeal and larynx cancer, esophageal cancer, hepatocellular carcinoma, breast cancer, and colon cancer.[3] Even modest use of alcohol may increase cancer risk, but the greatest risks are observed with heavy, long-term use.

Despite the evidence of a strong link between alcohol drinking and certain cancers, ASCO has not previously addressed the topic of alcohol and cancer. In addition, alcohol drinking is a potentially modifiable risk factor that can be targeted with preventive interventions at both the policy and the individual levels. Here, we provide an overview of the evidence of the links between alcohol drinking and cancer risk and cancer outcomes. The areas of greatest need for future research are highlighted. On the basis of this evidence and guidelines adopted by other cancer-focused organizations, ASCO-endorsed strategies for the reduction of high-risk alcohol consumption are presented.

EPIDEMIOLOGY OF ALCOHOL USE

Beyond oncology, alcohol use and abuse together pose a significant public health problem. According to the Centers for Disease Control and Prevention, approximately 88,000 deaths were attributed to excessive alcohol use in the United States between 2006 and 2010.[4] Approximately 3.3 million deaths worldwide result from the harmful use of alcohol each year.[5] Population surveys demonstrate that 12% to 14% of adults have a current alcohol use disorder and that 29% have had such a disorder at some point in their lifetime.[6,7] In addition to alcohol use disorder,

DOI: https://doi.org/10.1200/JCO.2017.76.1155

other measures used to assess the impact of alcohol are excessive drinking, binge drinking, and heavy drinking. Excessive drinking includes binge drinking and is defined as consumption of four or more drinks during a single occasion for women, or five or more drinks during a single occasion for men. Binge drinking is the most common form of excessive drinking compared with heavy drinking, which is defined as eight or more drinks per week or three or more drinks per day for women, and as fifteen or more drinks per week or four or more drinks per day for men.[8] Recent work has shown that the prevalence of adults who drink more than four to five drinks per occasion, defined as extreme binge drinking, has been increasing during the past decade.[9] This study estimated that 13% of the US adult population engaged in extreme binge drinking on at least one occasion in the previous year. Moderate drinking is defined at up to one drink per day for women and up to two drinks per day for men.[1,4] Most individuals who drink excessively do not meet the clinical criteria for alcoholism or alcohol dependence.[10]

Alcohol use during childhood and adolescence is a predictor of increased risk of alcohol use disorder as an adult.[11] College-age and younger people who drink are prone to develop an alcohol use disorder later in life.[7] Most adults who engage in high-risk alcohol drinking behavior started drinking before age 21 years. Among US youth age 12 to 20 years, 23% were current drinkers in the past 30 days, 10% were episodic drinkers, 2% were heavy episodic drinkers, and 6% met criteria for alcohol use disorder.[11] Among childhood cancer survivors, the prevalence of alcohol use in the past 30 days in adulthood (7.8 mean years since diagnosis of their cancer) was 25%, which was lower than that observed in the general population.[12] However, alcohol use among teenage patients with cancer is a common occurrence overall and has been observed to be as high among teens without cancer.[13-15]

DRINKING GUIDELINES AND DEFINITIONS

Internationally, more than 40 countries have issued alcohol drinking guidelines; however, these vary substantially.[16] The American Heart Association, American Cancer Society, and US Department of Health and Human Services all recommend that men drink no more than one to two drinks per day and that women drink no more than one drink per day.[17-19] In addition, it is recommended that drinking alcohol should only be done by adults of legal age. People who do not currently drink alcohol should not start for any reason.

Defining risk-drinking can be challenging, because the amount of ethanol contained in an alcoholic beverage will vary considerably depending on the type of alcohol (eg, beer, wine, or spirits) and the size of the drink consumed. In addition, the definition of a standard drink varies among countries and ranges from 8 g to 14 g.[20,21] The National Institute of Alcohol Abuse and Alcoholism (NIAAA) defines a standard drink as one that contains roughly 14 g of pure alcohol, which is the equivalent of 1.5 ounces of distilled spirits (approximately 40% alcohol by volume); 5 ounces of wine (approximately 12% alcohol by volume); or 12 ounces of regular beer (approximately 5% alcohol by volume).[22] However, evidence shows that drinkers are often unaware of how standard drinks are defined and that these standard drink sizes are commonly exceeded.[20]

ALCOHOL AND CANCER

Evidence to Link Alcohol Consumption to Specific Cancers

The relationship between drinking alcohol and cancer risk has been evaluated extensively in epidemiologic case-control and cohort studies. In a thorough systematic review of the world's evidence that adhered to prespecified criteria for drawing inferences, a World Cancer Research Fund/American Institute for Cancer Research (AICR) report judged the evidence to be convincing that drinking alcohol was a cause of cancers of the oral cavity, pharynx, larynx, esophagus, breast, and colorectum (in men).[23] Also, alcohol was judged to be a probable cause of increased risk of liver cancer and colorectal cancer (in women).[23] An updated review of the evidence for liver cancer upgraded the conclusion for an association between alcohol drinking and liver cancer to convincing.[24] The International Agency for Research on Cancer (IARC),[25] a branch of WHO, has assessed the evidence and come to virtually identical conclusions: that alcohol is a cause of cancers of the oral cavity, pharynx, larynx, esophagus, colorectum, liver (ie, hepatocellular carcinoma), and female breast. For esophageal cancer, the association with alcohol drinking is largely specific to squamous cell carcinoma.[25] The more that a person drinks, and the longer the period of time, the greater their risk of development of cancer, especially head and neck cancers.[3]

A valid question is whether these associations are specific to ethanol per se or whether they vary according to the type of alcoholic beverage (ie, beer, wine, or spirits/liquor). The answer is that the associations between alcohol drinking and cancer risk have been observed consistently regardless of the specific type of alcoholic beverage.[25]

The full range of cancers for which alcohol drinking represents a risk factor remains to be clarified. For example, the index of suspicion is high that alcohol drinking leads to excess risk of pancreatic cancer[25] and gastric cancer.[26] For some malignancies, alcohol drinking clearly is statistically associated with increased risk but, because of its strong correlation with other risk factors, it is difficult to discern if alcohol drinking is truly an independent risk factor. For example, alcohol drinking consistently has been statistically strongly associated with increased lung cancer risk.[23] However, cigarette smokers also are more likely to be alcohol drinkers, and cigarette smoking is such an overwhelming lung cancer risk factor that confounding by cigarette smoking—rather than a direct association with alcohol drinking—currently cannot be ruled out as a possible explanation.[27] As evidence continues to accumulate, the list of alcohol-associated cancers is likely to grow.

Magnitude of the Associations

Characterization of the dose-response relationship between alcohol and cancer is important for causal inference, because, if alcohol increases the risk for a specific cancer, one would expect the magnitude of the cancer risk to increase commensurate with increasing levels of alcohol consumption. Furthermore, the nature of the dose-response relationship provides useful information for communicating with patients about this issue. For alcohol-associated cancers, Table 1 summarizes results from a large-scale

meta-analysis[28] that show the relative risks of cancer in a comparison of nondrinkers with categories of people with light, moderate, and heavy alcohol consumption. The results summarized in Table 1 illustrate several key points. First, the magnitude of the association between alcohol drinking and cancer risk varied by type of cancer. Compared with nondrinkers, the summary relative risks (sRRs) for those classified as heavy drinkers ranged from 1.44 for colorectal cancer to 5.13 for cancer of the oral cavity and pharynx. The corresponding sRRs were 1.61, 2.07, 2.65, and 4.95 for cancers of the breast, liver, larynx, and esophagus, respectively. The strongest associations were observed for upper aerodigestive tract cancers (ie, larynx, esophagus, and oral cavity/pharynx), which involve tissues that come into direct contact with ingested alcohol. Second, monotonic dose-response relationships are evident for cancers of the oral cavity and pharynx, squamous cell carcinoma of the esophagus, and breast cancer. For liver, laryngeal, and colorectal cancers, the sRRs for the moderate category were intermediate between nondrinkers and heavy drinkers, but there was no evidence of increased risk in the light-drinker category. In a dose-response meta-analysis, the risk of secondary malignancies in patients with upper aerodigestive tract cancers increased incrementally by 9% for every increase in alcohol intake of 10 g/day.[29]

Clearly, the greatest cancer risks are concentrated in the heavy and moderate drinker categories. Nevertheless, some cancer risk persists even at low levels of consumption. A meta-analysis that focused solely on cancer risks associated with drinking one drink or fewer per day observed that this level of alcohol consumption was still associated with some elevated risk for squamous cell carcinoma of the esophagus (sRR, 1.30; 95% CI, 1.09 to 1.56), oropharyngeal cancer (sRR, 1.17; 95% CI, 1.06 to 1.29), and breast cancer (sRR, 1.05; 95% CI, 1.02 to 1.08), but no discernable associations were seen for cancers of the colorectum, larynx, and liver.[30] On the basis of the lesser overall cancer risk at the lower end of the dose-response continuum, the World Cancer Research Fund/AICR made the following recommendation: "If alcoholic drinks are consumed, limit consumption to two drinks a day for men and one drink a day for women."[23] They also recommend that, "for cancer prevention, it's best not to drink alcohol." Recent updates to the AICR report estimate a 5% increase in premenopausal breast cancer per 10 grams of ethanol consumed per day (pooled relative risk [RR], 1.05; 95% CI, 1.02 to 1.08). The risk was even greater for postmenopausal breast cancer, which had an RR of 1.09 (95% CI, 1.07 to 1.12) for each 10 grams of ethanol per day.[31]

Does Cessation of Alcohol Consumption Lead to Lower Cancer Risk?

A key question relevant both to the assessment of causality and the provision of advice and effective interventions to patients is whether the risk of developing an alcohol-associated cancer is reduced after one stops drinking alcohol. The results of meta-analyses and pooled analyses that have focused directly on this question for upper aerodigestive tract cancers indicate that risk of these cancers declines in those who quit drinking alcohol compared with those who remain alcohol drinkers.[32-35] The evidence from these studies suggests that the risk of cancer may be reduced to that seen in never drinkers after long-term ($\geq$ 20 years) cessation from alcohol drinking. Unfortunately, there are limited existing data on the impact of alcohol cessation on the risk of other alcohol-related cancers. This important topic is in need of more thorough investigation, particularly because those who quit drinking alcohol may differ from current drinkers in important ways that are also associated with cancer risk. For example, similar to smoking cessation, an increased short-term risk of cancer after alcohol cessation may be due to the onset of cancer-related symptoms that contribute to the individual's decision to stop drinking. Studies that carefully assess the time period between alcohol cessation and cancer diagnosis will help disentangle these complex methodological issues. Another potential bias is introduced by the finding that the category of former drinkers can be overrepresented by former heavy drinkers or alcoholics.[36] When present, the risk of cancer after alcohol cessation may be higher than that observed for current drinkers because of the high alcohol exposure doses of those classified as former drinkers. Carefully designed prospective cohort studies will help overcome these bias-based limitations and will lead to a more refined characterization of the impact of cessation of alcohol drinking on cancer risk by longitudinally quantifying the amount of alcohol consumed and the duration of cessation.

Impact of Smoking in Combination With Alcohol Consumption

Some malignancies are causally linked to both alcohol drinking and cigarette smoking; in some cases, an established synergistic interaction between alcohol drinking and cigarette smoking exists. This means that, in cancers for which both alcohol drinking and cigarette smoking are causal factors, the cancer risks in those who are both alcohol drinkers and cigarette smokers are much larger than the risks seen for those who only drink alcohol or

Table 1. Summary of Relative Risks From a Meta-Analysis for the Association Between Amount of Alcohol Drinking and Risk of Cancer

Type of Cancer	Relative Risk (95% CI)			
	Nondrinker	Light Drinker	Moderate Drinker	Heavy Drinker
Oral cavity and pharynx	1.0 (referent)	1.13 (1.0 to 1.26)	1.83 (1.62 to 2.07)	5.13 (4.31 to 6.10)
Esophageal squamous cell carcinoma	1.0 (referent)	1.26 (1.06 to 1.50)	2.23 (1.87 to 2.65)	4.95 (3.86 to 6.34)
Larynx	1.0 (referent)	0.87 (0.68 to 1.11)	1.44 (1.25 to 1.66)	2.65 (2.19 to 3.19)
Liver	1.0 (referent)	1.00 (0.85 to 1.18)	1.08 (0.97 to 1.20)	2.07 (1.66 to 2.58)
Female breast	1.0 (referent)	1.04 (1.01 to 1.07)	1.23 (1.19 to 1.28)	1.61 (1.33 to 1.94)
Colorectum	1.0 (referent)	0.99 (0.95 to 1.04)	1.17 (1.11 to 1.24)	1.44 (1.25 to 1.65)

NOTE. Adapted from results of Bagnardi et al (2015).[28]

only smoke cigarettes. Specific upper aerodigestive tract cancers provide the strongest examples of robust synergistic interactions between alcohol drinking and cigarette smoking. A pooled analysis of 17 case-control studies identified a potent interaction between alcohol drinking and cigarette smoking in cancers of the oral cavity, pharynx, and larynx,[37] and a review identified evidence of robust interaction in 22 of 24 published studies on oral, pharyngeal, laryngeal, and esophageal cancers.[38] Despite the clear presence of synergistic interaction, the biologic underpinnings of the interaction between alcohol drinking and cigarette smoking are not well understood.

The Mechanistic Role of Alcohol in Carcinogenesis

When the evidence of alcohol's role in carcinogenesis is considered, a key point is that, in biochemical reactions that are sequentially catalyzed by alcohol dehydrogenase and aldehyde dehydrogenase, ethanol is eliminated from the body by its oxidation first to acetaldehyde and then to acetate. Ethanol per se is not mutagenic, but acetaldehyde is carcinogenic and mutagenic, by binding to DNA and protein.[39]

The IARC reviewed the potential role of alcohol in carcinogenesis by synthesizing multiple bodies of evidence that included (1) experiments in which ethanol (or aldehyde) is administered to mice and rats in drinking water; (2) the absorption, distribution, metabolism, and excretion of ethanol and its metabolites; and (3) the genotoxicity of alcohol in various experimental systems, including biomarkers in humans.[23] One key conclusion of the review was that, in animal models, administration of ethanol or acetaldehyde in drinking water increased the incidence of various tumors in mice and rats; also administration of other known carcinogens with ethanol in drinking water enhanced tumor development more.[23] Another key conclusion was that "the role of ethanol metabolism in tumor initiation is implied by the associations observed between different forms of cancer and polymorphisms in genes involved in the oxidation of ethanol."[23] This point about polymorphisms is premised on the fact that genetic predisposition may amplify the toxic and mutagenic effects of alcohol consumption. A specific example of this line of reasoning is that most of the acetaldehyde generated during alcohol metabolism in vivo is eliminated promptly by aldehyde dehydrogenase-2 (ALDH2). However, a genetic variant of *ALDH2* exists ([(rs671]*2) that encodes a catalytically inactive protein. Alcohol drinkers with the inactive form of ALDH2 experience excessive accumulation of acetaldehyde, which amplifies its toxic and mutagenic effects, and the amplification would be expected to lead to greater susceptibility to alcohol-induced cancer. Several studies in East Asian populations, who have the highest prevalence of this high-risk genotype, have documented that alcohol drinking is more strongly associated with cancers of the upper aerodigestive tract among those with a high-risk genotype.[40] The IARC review also invoked mechanisms that included oxidative stress, sex hormones, folate metabolism, and DNA methylation as well as cirrhosis for hepatocellular carcinoma. Alcohol-induced oxidative stress, via the CYP2E1 pathway, for example, can result in chronic tissue inflammation.[23] Alcohol drinking affects circulating concentrations of androgens and estrogens, which is a pathway of particular relevance to breast cancer.[23] Consumption of alcohol is associated with lower folate concentrations—a relationship that has been extensively studied in relation to the etiology of colon cancer.[41]

Classification of Alcohol as a Carcinogen by the WHO

On the basis of the sum total of the evidence from research on mechanistic studies of the carcinogenicity of alcohol and the epidemiologic evidence to link alcohol with increased risk of multiple forms of cancer, the IARC classified alcohol as a group 1 carcinogen, because they found that it causes cancer in humans.[41] Specifically, IARC concluded that there is sufficient evidence in humans for the carcinogenicity not only of alcohol consumption but also for the carcinogenicity of acetaldehyde associated with alcoholic beverage consumption.[41]

DISPARITIES IN ALCOHOL USE AND RELATED CANCERS

Blacks, Asian Americans, and Hispanic individuals have lower rates of current alcohol use disorder than whites. However, rates among these groups appear to be increasing overall. The NIAAA has accumulated data during two decades by conducting large general-population surveys among US adults age 18 years and older. Their longitudinal surveys from 1991 to 1992 and 2001 to 2002 showed increases in alcohol abuse among men, women, and young black and Hispanic minorities. Rates of dependence also increased among men, young black women, and Asian men, which underscores the need to continue monitoring of prevalence and trends. It is now known that Hispanics and blacks have a higher risk than whites for developing alcohol-related liver disease.[42] The longitudinal design of the NIAAA surveys enable the collection of data on cultural variables, such as acculturation. In addition to increasing overall rates, blacks and Hispanics are less likely to use alcohol treatment when it is available.[43]

All segments of US social strata are affected by alcohol abuse, but the prevalence of alcohol abuse is particularly high within American Indian and Alaska Native (AIAN) populations. AIAN people drink more alcohol and are more highly affected by alcohol-related illness than other populations.[44] Among people age 12 years and older, the prevalence of binge drinking was 28% for AIAN people compared with 23% for whites, 22% for blacks, and 14% for Asian Americans. Findings from the 2000 to 2006 Behavioral Risk Factor Surveillance System showed that the rate of binge drinking was a major difference between non-Hispanic white and AIAN people, especially men.[45] Similarly, rates of heavy drinking were highest (9%) among AIAN people and lowest (2%) among Asian Americans.[44] The Indian Health Service, which provides a large amount of the health care to the AIAN community, addresses alcohol from a disease-model perspective.[46] The Indian Health Service identifies alcoholism as a chronic disease with genetic, psychosocial, and environmental factors.[47] Individuals with cirrhosis and chronic liver disease are at much higher risk of liver cancer, and the main preventable causes of these conditions are chronic infection with hepatitis B and C, chronic alcohol abuse, and nonalcoholic fatty liver disease. Though viral hepatitis prevention and treatment may be making a significant health difference already, addressing chronic alcohol abuse would be an important cancer prevention strategy.

Differential rates of alcohol use according to socioeconomic status hypothetically could contribute to cancer disparities. In reality, the relationship between alcohol drinking and socioeconomic status is complex, because it depends on how alcohol drinking is measured. When measures of alcohol use are used,

those of a higher socioeconomic status are more likely to drink and to drink more heavily.[48] However, for reasons that are poorly understood, measures of adverse consequences of alcohol tend to concentrate more among those of a lower socioeconomic status.[48] A disproportionate share of the overall burden of cancer occurs in those of a lower socioeconomic status, so alcohol drinking may be a contributing factor to cancer disparities observed across the spectrum of socioeconomic status; however, this remains a relatively unexplored topic.[49]

Patterns of alcohol use and treatment also vary by sex and sexual orientation; higher rates are seen in sexual and gender minority populations (ie, lesbian, gay, bisexual, transgender, and intersex).[50] This population also is known to bear a greater burden of cancer incidence.[50] For example, although men have a higher prevalence of heavy drinking, women are less likely to use alcohol treatment services,[43] even among those with alcohol dependence.[51] Lesbian or bisexual female veterans had higher rates of alcohol misuse than heterosexual female veterans did, which may result at least in part from higher rates of trauma exposure and mental health difficulties experienced by the lesbian/bisexual women.[52] Lesbian, gay, and bisexual young adults (ages 17 to 19 years) consume more alcohol both in high school and in college.[53] A study of the National Longitudinal Study of Adolescent Health also confirmed significantly increased alcohol use and abuse among lesbian, gay, and bisexual youth.[54] A recent ASCO position statement recommended increased cancer prevention education efforts, including reduction in high-risk alcohol use as a target effort.[50]

ALCOHOL AND CANCER: OUTCOMES AND EFFECT ON TREATMENT

Compared with the wealth of evidence about the associations between alcohol drinking and the risk of developing cancer, research on the impact of alcohol drinking on outcomes in patients with cancer is still in its nascent stages. For cancers that have known associations with alcohol drinking, it would be expected that alcohol drinking at the time of diagnosis also would be associated with risk of cancer recurrence and/or secondary primary tumors (SPTs). This association has been observed for patients with upper aerodigestive tract cancer when nondrinkers are compared with occasional drinkers. The risk of cancer-specific mortality is increased significantly in moderate drinkers (RR, 1.79; 95% CI, 1.26 to 2.53) and heavy drinkers (RR, 3.63; 95% CI, 2.63 to 5.0).[55] Among survivors of upper aerodigestive tract cancer, continued alcohol use after diagnosis is associated with a three-fold increased risk of upper aerodigestive tract second primary tumors,[56] and cessation may reduce the increased risk for SPTs in pre-diagnosis drinkers compared with pre-diagnosis nondrinkers.[29] In breast cancer survivors, several studies suggest that alcohol drinking is not associated with decreased overall survival,[57] whereas other studies indicate that breast cancer–specific mortality may be increased in at least some subgroups of the patient population.[58-60] The increase in breast cancer–specific mortality or risk of recurrence has been observed with moderate to heavy levels of alcohol drinking.[60,61] Li et al showed that, among women with estrogen receptor–positive breast cancer, consumers of seven or more drinks per week versus none had a 90% increased risk of asynchronous contralateral breast cancer,[62] which was higher than the 30% increased risk observed in a multicentered case-control study.[63] Other SPTs in patients with breast cancer that have been associated with greater alcohol consumption ($>$ 7 drinks per week versus none) include an increased risk of subsequent colorectal cancer (hazard ratio [HR], 1.92; 95% CI, 1.07 to 3.43) and a decreased risk of ovarian cancer (HR, 0.45; 95% CI, 0.21 to 0.98).[64] Results of studies to evaluate the relationship between alcohol consumption and colorectal cancer have been mixed; one study observed that heavy drinking was associated with poorer survival,[65] whereas the majority of studies have demonstrated either no association between alcohol drinking overall and colorectal cancer outcomes[66] or a suggestion of better overall survival with higher levels of wine consumption.[67] A recent meta-analysis of cohort studies among 209,597 cancer survivors showed a statistically significant 8% increase in overall mortality and a 17% increased risk for recurrence in the highest versus lowest alcohol consumers.[68] More evidence is needed to clarify the impact of both alcohol drinking and cessation on cancer outcomes.

The majority of studies to evaluate the direct effects of alcohol use on cancer treatment have focused on patients with upper aerodigestive tract cancer, because 34% to 57% continue to drink after diagnosis.[69] Smoking and alcohol use during and after radiation therapy have been associated with an increased risk of osteoradionecrosis of the jaw in patients with oral and oropharyngeal cancers.[70-73]

Alcohol abuse also complicates treatment outcomes among patients with cancer by contributing to longer hospitalizations, increased surgical procedures, prolonged recovery, higher health care costs,[74-76] and higher mortality.[77] Heavy alcohol use and abuse are important modifiable risk factors for postoperative morbidity.[78] Heavy alcohol use[79] and alcohol abuse,[80] compared with no alcohol use, are associated with higher risks of anastomotic complications after colorectal surgery. Alcohol abuse, compared with no abuse, also has been shown to contribute to low quality-of-life outcomes in patients with head and neck cancer after treatment.[81,82] Patients with cancer who abuse alcohol have increased comorbidities that can complicate treatment choices and that are affected by alcohol-related subclinical factors, including nutritional deficiencies, immunosuppression, and cardiovascular insufficiencies that increase treatment morbidity.[83-85]

Light alcohol use among cancer survivors has been perceived as potentially beneficial for treatment-related adverse effects, although there is little evidence to support this concept. A cross-sectional study of patients with head and neck cancer showed that patients who reported drinking at least one serving of alcohol in the past month reported better functional scores and lower levels of symptoms, such as fatigue, pain, dysphagia or dry mouth after treatment than those who reported that they had not used alcohol.[86] Given the inability to distinguish the sequence of events in a cross-sectional study design, it is unclear whether light alcohol use promotes treatment recovery and well-being or is the result of improved health-related quality of life among survivors. The consumption of light alcohol for increasing appetite has been regarded as potentially beneficial for patients with cancer,[87] because alcohol can stimulate appetite and snacking in cancer-free individuals.[88] However, a recent study of patients with advanced cancer who had self-reported loss of appetite and who were randomly assigned to white wine with $\leq$ 15% alcohol content

twice a day for 3 to 4 weeks versus a nutritional supplement showed no improvement in appetite or weight.[89]

BARRIERS TO ADDRESSING ALCOHOL AND CANCER IN THE ONCOLOGY SETTING

In addition to the perception that light alcohol use may have a beneficial effect on appetite and tolerance of cancer treatment, conflicting data about the heart health of alcohol, especially red wine, is one additional barrier to addressing alcohol and cancer risk in the oncology setting. However, subsequent work has revealed multiple confounders to this conclusion about heart health, including frequent classification of former and occasional alcohol drinkers as nondrinkers.[90] For example, people who now abstain from alcohol often have underlying health concerns, which explains their reasons to cut down on alcohol and thereby makes the current alcohol drinkers appear healthier than former and occasional drinkers—a so-called abstainer bias.[90] In addition, larger studies and meta-analyses have failed to show an all-cause mortality benefit for low-volume alcohol use compared with abstinence or intermittent use, which suggests the lack of a true benefit to daily alcohol use.[91,92] Differences in alcohol dehydrogenase variants are associated with nondrinking, and nondrinkers have had lower rates of coronary heart disease and stroke than even light drinkers.[93] As such, the benefit of alcohol consumption on cardiovascular health likely has been overstated.[94,95] As reviewed in the Magnitude of the Association section, the risk of cancer is increased even with low levels of alcohol consumption,[30] so the net effect of alcohol is harmful. Thus, alcohol consumption should not be recommended to prevent cardiovascular disease or all-cause mortality.

Low physician knowledge of alcohol use and cancer risk is another barrier to addressing alcohol use with patients. This lack of knowledge has been demonstrated among general practitioners, who were aware of an association of alcohol with cardiovascular health and obesity and who also felt that preventive health was an important aspect of their work; however, the majority of providers did not ask their patients about alcohol consumption, and most were unaware of alcohol as a carcinogen.[96,97] A knowledge deficit was also seen among medical students relative to the role of alcohol as a risk factor in head and neck cancers.[98] Knowledge of the association between cancer and alcohol also has been shown to be low among dentists and allied health professionals, who may be evaluating patients for these cancers. For example, dentists and dental hygienists have lower awareness of the association between alcohol use and head and neck cancers than family physician do (40% for dentists *v* 94% for family physicians), and this lack of knowledge would hamper their ability to counsel patients about alcohol-related cancers.[99]

In addition to a lack of knowledge of alcohol use as a cancer risk factor, physicians use different approaches to counseling patients about alcohol use. Just as overweight or obese physicians are less likely to counsel their patients about obesity,[100] alcohol use among physicians may make them less likely to counsel patients about the risks of alcohol use. In one study of Danish physicians, 18.8% of physicians met criteria for risky alcohol consumption.[101] Estimates indicate that up to 14% of American physicians will have an alcohol use disorder in their lifetime, which is a rate similar to the general population.[102] Burnout, which is very common among oncology providers, also is strongly associated with high-risk alcohol use.[103-107]

RESEARCH NEEDS

Although alcohol is a well-established risk factor for the development of certain cancers, very little is known about how current alcohol use affects cancer treatment delivery. Thus, the most compelling and urgent research need for the oncology community with regard to alcohol is better definition of the effect of concurrent alcohol use on cancer treatments, including chemotherapy, radiation, and surgery, as well as on cancer outcomes. Anecdotal stories from providers about the effect of alcohol on cancer treatment are intriguing, but rigorous scientific studies are needed to accurately quantify the effect. Underexplored research areas include the effects of alcohol exposure on postoperative morbidity; on the efficacy of chemotherapy and radiation; and on novel targeted therapies, such as immunotherapy and radiation.

Increased knowledge about the mechanistic effects of alcohol on cancer-related pathways and treatments may improve understanding of its role in disease progression and therapeutic responsiveness and toxicity. For example, a preclinical study demonstrated overlap between alcohol responsive genes and genes that are involved in responsiveness to endocrine therapy in breast cancer cells.[108] The insufficient knowledge about the detrimental or potentially beneficial effects of alcohol use overall, as well as effects of its dose and frequency, among patients with cancer creates missed opportunities to intervene to improve overall quality of life and to educate patients about the cancer-specific prognostic role of alcohol.

Systems-based research, including research into successful means for the oncology community to identify patients who are currently using alcohol or who may be at high risk for alcohol relapse, will be critical. How to effectively apply evidence-based clinical interventions to assist patients in reduction of abstention from alcohol use also should be explored.

PUBLIC HEALTH STRATEGIES TO REDUCE HIGH-RISK ALCOHOL CONSUMPTION

Policies to reduce excessive alcohol consumption should be evidence based (such as those identified by WHO[109] or the Community Preventive Services Task Force[110]), culturally sensitive, and equitable in their implementation. Recognizing that excessive alcohol use can delay or negatively impact cancer treatment and that reducing high-risk alcohol consumption is cancer prevention, ASCO joins the growing number of cancer care and public health organizations to support strategies designed to prevent high-risk alcohol consumption such as the following and those in Table 2.[111-129]

- Clinical strategies of alcohol screening and brief intervention provided in clinical settings: Health care providers can screen adults, including pregnant women, for excessive alcohol use to identify people whose levels or patterns of alcohol use place them at increased risk of alcohol-related harms. Health care

Table 2. Policy Recommendations of International Cancer Care and Public Health Organizations

Organization	Recommendation
Association of European Cancer Leagues (25 associations)[111,112]	• Supports minimum pricing legislation • Monitoring implementation of the European Union Alcohol Strategy and the impact of the strategy on marketing to young people and reducing alcohol-related harm • Calls for stronger recognition of alcohol causality of cancer and other chronic diseases and European Code Against Cancer
Cancer Research UK[113]	• Supports a comprehensive alcohol strategy to reduce drinking in the United Kingdom to levels where the risks are minimal • Recognizes need for measures to reduce the affordability of alcohol and to restrict young people's exposure to alcohol advertising are needed if alcohol consumption will be reduced to historic levels and reduce the risk of cancer in the United Kingdom
Irish Cancer Society[114]	• In May 2013, called on government to ban alcohol advertising
Cancer Council Australia[115-117]	• Recommends the increased price of alcohol through taxation and an investigation into the need for the introduction of minimum pricing of alcohol[115] • Endorses the need for compulsory warning labels on all alcoholic products[116] • Supports a strategy to limit the exposure of marketing and promotion of alcohol overall and specifically to children[117]
Cancer Council Victoria (Australia)[118,119]	• Member of the Alcohol Policy Coalition • Recognizes the harmful link between advertising and harmful drinking in young people, and actively works to implement alcohol advertising restrictions to reduce exposure among people age 18 years and younger
Cancer Association of South Africa[120]	• Advocates against consumption of any alcohol • Does not support any form of pink washing to market any product that contributes to cancer disease and death (including the alcohol industry)
World Cancer Research Fund International[121]	• Recommends policies that will reduce the availability and affordability of alcohol

European Society for Medical Oncology[123]	• Party to the European Chronic Disease Alliance position statement on the need for European Union action to help Europeans reduce alcohol consumption, and supports the following policy goals[122]:
	  ° ensure the implementation of the WHO Global Strategy to Reduce the Harmful Use of Alcohol
	  ° ensure achievement of WHO Global noncommunicable disease target for a 10% relative reduction in the harmful use of alcohol
	  ° ensure a new comprehensive European Union alcohol strategy
	  ° ensure that countries also have national alcohol strategies
	• Supports both supply- and demand-oriented strategies to reduce alcohol consumption including[123]:
	  ° increasing prices of alcoholic beverages;
	  ° limit the number of alcohol outlets (outlet density);
	  ° limit the hours of sales and establish regulations for minimum age of purchase;
	  ° implement school-based education to influence drinking behavior; and
	  ° restrict advertising, particularly to young people

American Medical Association[124,125]	• Advocates for legislation aimed at minimizing alcohol promotions, advertising, and other marketing strategies by the alcohol industry aimed at adolescents[124] • Supports a ban on the marketing of products, such as alcopops, gelatin-based alcohol products, food-based alcohol products, alcohol mists, and beverages that contain alcohol and caffeine and other additives to produce alcohol energy drinks that have special appeal to youths under the age of 21 years and supports state and federal regulations that would reclassify alcopops as a distilled spirit so that they can be taxed at a higher rate and cannot be advertised or sold in certain locations[125]
American Academy of Family Physicians[126]	• Supports efforts to reduce the amount of alcohol advertising, particularly content appealing to youth, and the development of educational programs and counter-advertising designed to illustrate more realistic images on the effects of alcohol
American Public Health Association[127]	• Supports the development and adoption of an international framework convention on alcohol control[127] • Supports the implementation of the recommendations of the National Research Council and Institute of Medicine's report entitled "Reducing Underage Drinking: A Collective Responsibility," including the monitoring of youth exposure to alcohol advertising and the raising of excise taxes[128]
European Public Health Alliance[129]	• Supports limitations on advertising of alcohol and product placement to minimize youth exposure to the marketing of these products

providers can then recommend or offer treatment services to those at risk. Brief counseling interventions for adults who drink excessively have been found to positively affect several patterns of excessive drinking, including heavy episodic (binge) drinking and high average weekly intake of alcohol.[130]

- Regulate alcohol outlet density: An alcohol outlet is defined as any site where alcohol may be legally sold to an individual to either consume on premises (eg, bars or restaurants) or off premises (eg, liquor stores or other retail settings).[131] Using regulatory authority to reduce the number of alcohol outlets in a given area (ie, density) has proven to be an effective strategy for reducing excessive alcohol consumption.[131-134] This is frequently executed through outlet licensing or zoning processes.
- Increase alcohol taxes and prices: Taxes are placed on all alcohol beverages by both individual states and the federal government, and a portion of the federal excise tax may or may not be used to support treatment programs. Alcohol taxes vary from state to state and also differ in the amount applied based on the type of alcohol (eg, beer, wine, or spirits/hard liquor). Increasing taxes, and therefore the overall price of alcohol, has been shown to inversely effect levels of excessive consumption and related health harms.[135-137] Other regulations that may directly or indirectly affect the price of alcoholic beverages, including regulations on wholesale distribution and bans on price-related promotions, may have some impact on excessive consumption, though more research is needed.[138]

- Maintain limits on days and hours of sale: Limiting the days or hours during which alcoholic beverages can be sold can be applied to both outlets where the alcohol is consumed on premises and retail outlets where the alcohol is consumed off premises. These policies, made at the state and local levels, are intended to prevent excessive consumption by reducing access to the alcohol.[139] Evidence from several studies has demonstrated the positive impact that reducing the number of days or hours that alcoholic beverages are sold generally result in a decrease in related harms.[140,141]
- Enhance enforcement of laws prohibiting sales to minors: The minimum legal drinking age is 21 years in all US states. Enhanced enforcement of the minimum legal drinking age can reduce sales to minors (younger than 21 years) in retail settings (such as, bars, restaurants, liquor stores), thereby helping to reduce youth access to alcohol.[130]
- Restrict youth exposure to advertising of alcoholic beverages: Early onset of drinking has been associated with an increased likelihood of developing dependence on alcohol later in life,[142] and studies have demonstrated that youth exposed to more advertisements also show increases in drinking levels.[143,144] The alcohol industry has only voluntary advertising codes created by the major trade groups, and are not subjected to federal restrictions. Currently, industry codes require that at least 70% of the audience of the advertisements (including print, radio, television, and internet/digital) consists of adults of legal drinking age.[145-147] However, the alcohol industry is frequently noncompliant with its own self-regulation guidelines.[148]
- Resist further privatization of retail alcohol sales in communities with current government control. Following the end of Prohibition in 1933, all states had wholesale of alcoholic beverages under state control. "License" states allowed retail sales by commercial interests, while some "control" states allowed alcohol to be sold, but only through government-run retail stores that restrict off-premises sales outlets (ie, outlets where alcohol is sold for consumption elsewhere). In the United States, all states and counties that permit the sale of alcohol allow privatized retail sales of beer, and most allow privatized retail sale of all alcoholic beverages. Privatization most often affects wine and spirits (eg, vodka and whiskey) in the control states.[149]
- Include alcohol control strategies in comprehensive cancer control plans: State, tribal, and territorial comprehensive alcohol control strategies are not commonly included in comprehensive cancer control plans. Supporting the implementation of evidence-based strategies to prevent the excessive use of alcohol is one tool the cancer control community can use to reduce the risk of cancer.[150]

In addition to these strategies, ASCO supports efforts to eliminate pinkwashing in the marketing of alcoholic beverages. Pinkwashing is a form of cause marketing in which a company uses the color pink and/or pink ribbons to show a commitment to finding a cure for breast cancer. Given the consistent evidence that shows the link between alcohol consumption and an increased risk of breast cancer,[25,151] alcoholic beverage companies should be discouraged from using the symbols of the battle against breast cancer to market their products.

THE ROLE OF THE ONCOLOGIST

Worldwide, alcohol-related cancers are estimated to be 5.5% of all cancers treated annually, which represents a large number of patients. Oncologists frequently are the ones who manage the treatment of these patients, and they have a direct interest in promotion of the health of patients. Such promotion likely will include helping patients reduce high-risk alcohol use. Oncologists also stand in a position to drive the alcohol-related research agenda as it affects patients with cancer. The most pressing questions include how active alcohol use affects cancer treatments, how alcohol use affects risk of recurrence and overall prognosis, and how alcohol interacts with oral chemotherapy and supportive care medications. As front-line providers for these patients, another need to support is identification of the most effective strategies to help patients reduce their alcohol use. Ways to address racial, ethnic, sex, and sexual orientation disparities that will place these populations at increased rates for cancer also are needed. Oncology providers can serve as community advisors and leaders and can help raise the awareness of alcohol as a cancer risk behavior. Finally, because alcohol use is quite common, an initiative to address alcohol use (particularly high-risk alcohol use) is a potential preventive strategy to decrease the burden of cancer. Policy efforts are likely to be the most effective way to address this need.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Alcohol and Cancer: A Statement of the American Society of Clinical Oncology

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American Institute of Integrative Oncology
RESEARCH & EDUCATION

CASE STUDY SUBMISSION

Important: In observance of HIPAA and the sacred trust between care giver and patient, absolutely no patient names or identifying information is to be disclosed. Patient privacy is to be preserved. If you attach any medical records, pathology, surgical or laboratory reports, all names are to be removed.

Date	March 12, 2018
Clinician Name & Credentials	Corey Deacon DNM, MSc
Email	cadeacon@ualberta.ca

Describe Your Patient (Please SUMMARIZE and use economy of words. You will have 15 minutes to present)

Age, Gender & Ethnicity	41 yo Caucasian male
Body Type	athletic
Values *What is most important to this patient? (Quality of Life, Decision Making, Side Effects?)*	Quality & longevity of life
Stress Resilience	High
Other	
Primary Diagnosis & Date *(ex. Breast Cancer L, T3 N1 M0, BRCA1 positive, grade 3, Ki67 > 45%)*	Metastatic cholangiocarcinoma - lungs and liver Immunohistology: CK7+, CK19+, focally+CK20, negative for: CDX2, HEP,PAR-1, TTF-1 Pancreatobiliary tumour
Secondary Diagnosis *(ex. Diabetes Type 2, Obesity)*	

Patient Status

☐ New Diagnosis ☐ Recurrence ☐ In Treatment ☐ In Recovery ☐ In Remission ☐ At Risk

Concomitant and/or Complicating Factors *(ex: poorly controlled diabetes, insomnia, poor support system)*	
Adverse Effects of Cancer or Cancer Treatments *(ex. anxiety-depression, diarrhea, peripheral neuropathy)*	Peripheral neuropathy - bilateral medial/lateral plantar
Relevant Laboratory, Pathology & Medical Reports *(attach a PDF with patient identifying information removed or summarize)*	see attached

Brief Summary of Recent History

Tumours were stable Nov 2017 until Jan 2018.
Recent CT indicates increased growth in biliary tree + new 1.3 x1 cm lymph node in mediastinum as of March 2018 (see pdf of imaging)

Brief Summary of Additional Relevant Health, Medical, Psycho-Social and/or Family History

Older brother had lymphoma at age 14 and again at age 21

Other Relevant Information

Such as Chinese or Ayurvedic diagnosis, Naturopathic/Homeopathic Information, etc. *(ex. Liver Qi Stagnation, Dysbiosis)*

Enterobacter cloacae complex in stool test - overgrowth / Elevated SAMe & SAH levels
High urinary mycotoxins with elevated ACTH, cortisol
Low AVP & Elevated VEGF - mold panel
Low omega 6 (high omega-3:omega-6)

Brief Summary of Relevant Past Oncology or Medical Treatments

(ex. surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)

Chemotherapy - Cisplatin + Gemcitabine (see labs pdf)

Summary of Recent and Current Treatments

Medical Oncology Care *(surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)*

None as of November 2017

Integrative Oncology Care *(nutraceutical, botanical, phytochemical, acupuncture, energy medicine, other)*

Neurofeedback + Trauma therapy (lost a daughter to SIDS 8 years ago) - still affecting his nervous system based on quantitative EEG evaluation. AHCC, zinc picolinate, IV glutathione, vitamin C, artemisinin, and curcumin

Your 2 Core Questions (stated clearly and succinctly)

1. What is a tumour of this origin most responsive to for treatment in regards to conventional and CAM

2. What would be other forms of therapy to add or recommend above and beyond what is currently being done.

Attached Medical Records for Reference (with patient identifying information removed)

See attached pdf's

PROPOSED TREATMENT PLAN Your case will not be reviewed without a completed proposed treatment plan

Nutriceutical, Phytochemical and Botanical Supplements (name of supplement, dosing)

Foundation Nutrition Supplements:

Zinc picolinate, Vitamin C, Glutathione, High dose probiotic (250 billion CFU per day), Magnesium bisglycinate, Curcumin, P5P NAC, L-glutamine, Honokiol, Dessicated adrenal, Modified Citrus pectin powder, Melatonin, Astragalus, Ox bile + taurine - due to gall bladder involvement, Herbal liver support - milk thistle, rosemary

Targeted Supplements:

AHCC, Transfer factor - enviro + PlasMyc, Black cumin oil, Fibrinolytic enzyme - Lumbrokinase + Nattokinase, Zeolite + charcoal, Anti-viral tincture, Gamma linoleic acid - due to low omega-6 in testing

Functional Foods and/or Therapeutic Shake

Originally started with ketogenic diet
Has recently switched to OutSmart Cancer Plan

Dietary Guidelines

Looking for guidance here

Lifestyle Guidelines

Exercise (moderate-high intensity interval training 2x per week), Infrared Sauna, Meditation, Neurofeedback, Other spiritual practices

Recommended Diagnostics

Continue addressing mycotoxins - reduce VEGF, ACTH & MMP-9 (if elevated)

Referrals to specialists

Neurofeedback + trauma therapy
Not sure who else to involve other than an acupuncturist

Other Notes (please do not include additional notes in your email – notate them here within the case study)