Carbohydrate Restriction in Cancer Therapy

LOW CARB BRECKENRIDGE

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Disclosures

• Nothing to disclose
Introduction

• What do we know TODAY about diet and cancer?
Many cancers are etiologically unrelated to diet

- (as far as is known)
- Pediatric cancers
- CML—single chromosomal alteration
- Sarcomas
- HPV-related cancers: cervical, anal, vulvar, penile, throat, tongue
- EBV-related cancers: Hodgkin and non-Hodgkin lymphomas
- Acute leukemias
- Testicular…
Common cancers that may be affected by diet

- Breast
- Colon
- Endometrial adenocarcinoma
- Some lung cancers (adenocarcinoma)
- Prostate
- Pancreas
- Gallbladder/biliary
In Diabetes

• Ca risk is higher
• Ca survival lower
• Data are consistent data across preclinical and clinical settings
• Most common cancers in DM are breast and colon
• Exogenous insulin use increases cancer risk
• Metformin decreases risk, may increase survival after diagnosis
• Lipid level inversely associated with cancer incidence in DM(?)
Insulin use assoc w/double cancer risk
Serum Lipid Levels and Cancer

• Higher total and LDL cholesterol, less incidence of certain cancers
• Better response to chemotherapy
• Better cancer-specific survival after diagnosis

• Triglyceride:HDL ratio predicts outcome in triple negative breast cancer
Cancer(s): When to Use

• PART I  Moderate Carbohydrate Restriction
• PART II  Ketogenic Diet
• PART III  Caloric (Energy) Restriction and Fasting
Moderate Carbohydrate Restriction: Breast and Colon Cancer

Part 1
Carbohydrate intake associated with colon cancer survival

• Colon ca stage III: daily glycemic load and total carbohydrate intake are associated with increased risk of recurrence and mortality.

• BUT
Carbohydrate intake associated with colon cancer survival

- Colon ca stage III: daily glycemic load and total carbohydrate intake are associated with increased risk of recurrence and mortality.
- Only if BMI was 25 or higher!
WHELS and WINS Results

• Weak to negligible connection between breast cancer survival and fat restriction

• Little to no connection between high produce intake and breast cancer survival (WHELS)

• Improved survival with weight loss (WINS)
Low Fat intervention improves breast cancer survival in these subgroups:

- if no hot flashes before intervention (WHELS)
- ER-negative subtype (WHELS)
- If weight loss occurred (WINS)
Breast Cancer survival and carbohydrate intake (UCSD)

• N= 265 from WHELS subcohort,

• postmenopausal, tumor ER+, IGF1-receptor expression
Breast Cancer survival and carbohydrate intake (UCSD)

- Decreasing carbohydrate intake by 27 grams/day after diagnosis associated with halving of recurrence.

- Effect strongest if breast tumor expressed IGF1-r

- 40% of Caucasians, 80% Hispanics, 90% of African Americans
Carb limit vs chemo/tamoxifen in older breast cancer patients (50-69yo)

- Historical data on efficacy of br ca treatments
- Chemo: 20% decrease in br ca mortality
- Tamoxifen: 31% decrease in br ca mortality
- Chemo + tamox: 45% decrease in br ca mortality
- Over 15 years

- one less banana a day: 40% decrease in “hazard ratio”
- Over 5.1 years (median)

EBCTCG, Lancet 2005
Interpretation Caveats

• Statistical analysis: HR at 5 years difficult to compare to mortality at 15 years
• Most in WHELS subcohort also treated with chemo and tamoxifen
• Varying levels of tumor tissue IGF1-r expression in positives
• Small, homogeneous sample
Review Part I: Moderate carbohydrate restriction

• ER+ postmenopausal breast cancer

• Stage III colon cancer, if overweight

• Start by restricting carbs to 100 grams/day

• IF/Caloric deficit likely helpful
PART 1.5

• MECHANISM
“Warburg Effect”

• Normal cell
  • 1 glucose molecule nets 38 ATP

• Cancer cell (with Warburg effect)
  • 1 glucose molecule nets 2 ATP

• Massive amounts of glucose needed to keep up with energy demands
Normal PET scan
PET scan: Left lung cancer
PET scan: advanced metastatic cancer
Ketogenic Diet: Glioblastoma and advanced metastatic cancers

Part II
Ketogenesis: “production of ketone bodies”

- Fasting
- Prolonged exercise
- Very low carb intake
- Fatty acids are metabolized in liver into ketone bodies
  - \textit{beta}-hydroxybutyrate, acetoacetate, acetone
Isn’t that fatal?
Etiology of Ketoacidosis

- abnormal increase in blood acid
- uncontrolled type I diabetes
- alcoholism
- Aspirin overdose
- Hyperemesis gravidarum
- Ketone levels 15-25 mmol/L

• Ketoacidosis is not caused by ketogenic diet
Ketogenic diet

- fat 85%
- protein 10%
- carb 5%
Glioblastoma multiforme

• 5-year life expectancy = 0%
• Ketogenic diet in preclinical settings promising
No radiation: KD vs normal diet

Percent Survival

SD
KetoCal®

p = 0.0049

Radiation: KD vs normal diet

Radiation therapy: how ketosis helps

• Differential DNA repair
• Decreased insulin and IGF1 signaling
• Normal cells enter dormancy
• Angiogenesis suppression
• Decreased oxidative damage in normal cells
Cancer cachexia

http://img.medscape.com/thumbnail_library/ps_130821_muscle_atrophy_200x151.jpg
Cause of Cancer Cachexia

- Inflammation
- Generalized inflammatory syndrome—cytokines
Cancer cachexia

• Absent in early cancers—”Adjuvant setting”
• 2/3 of END-STAGE patients with solid tumors
• Weight loss >5%
• BMI <20
• Muscle wasting

• PEARL—can be overweight or obese and have cancer cachexia!
Sarcopenic obesity
BRAF V600E mutation; fat fuels tumor growth
BRAF V600E mutation is common

- melanomas 50%
- hairy-cell leukemia 100%
- colorectal cancer 10%
- prostate cancer 10% (?)
- multiple myeloma 5%

• TEST for it!

Xia et al., Prevention of Dietary-Fat-Fueled Ketogenesis Attenuates BRAF V600E Tumor Growth, Cell Metabolism (2016), http://dx.doi.org/10.1016/j.cmet.2016.12.010
Precision diet based on tumor genetic profiling—statins?

• “Lipid-lowering agents may have a role in cancer prevention or supplemental treatment approaches to reduce cancer progression or improve clinical outcomes in the BRAF V600E-positive premalignancy and cancer settings.”

Jing Chen, MD
Summary Part II: use ketogenic diet

• during radiation
• GBM
• Advanced PET positive cancers
• Cancer cachexia
• To enhance chemotherapy?
• Caution: BRAF v600e
PART III

• CALORIC RESTRICTION AND INTERMITTENT FASTING
Dietary suspects in cancer

• Fat
• Saturated fat
• Meat
• Dairy
• Carbohydrates
• Protein
• Specific amino acids
• Cancer likes FOOD
Human non-small cell lung cancer tumors

• enhanced glucose oxidation

• heterogeneity in glucose metabolism, not only between subjects, but within same subject

• Utilize multiple energy sources

Hensley et al. Cell 2016
Cancers can utilize non-glucose energy sources

- Fructose
- Lipids, choline
- Protein/AAs,
  - Glutamine, Cysteine
- Acetate, Lactate

Glutamine uptake

https://www.mskcc.org/sites/default/files/node/39618/images/dunphy-fig-1.jpg
Chronic caloric restriction

• Cut daily caloric intake 25-40%
• Delays degenerative diseases of aging
  neurologic
  rheumatologic
  malignant
• Extends lifespan in yeast, drosophila, vertebrates, mammals
• Underweight is problem

Intermittent fasting: anything CR can do

• 13 to 24+ hours without calories, many schemas
• Lengthens lifespan even more than chronic caloric restriction
• Maintains normal weight

Intermittent fasting (IF) in cancer

- Animal studies only
- IF sensitizes tumor cells to treatment
- Protects normal cells from treatment side effects
- Slows tumor growth (even without chemo)
- Potentiates chemotherapy

Longo et al. Sci Translational Medicine 2012
Longo et al. Ca Res 2010
Better survival: Fasting 48 h vs Adriamycin

Effect of 48 hours of fasting on survival of DXR-treated mice with metastatic murine melanoma (B16; n = 9 to 10; P < 0.05)

Lee et al. Sci Translational Med 2012
“Differential stress response” DSR

• Dividing cells are more vulnerable to cancer treatment

• When starved, normal cells retreat from division

• When starved cancer cells continue dividing

Adapted from Longo et al.
Fasting in human patients on chemo—USC group

• 10 patient volunteers

• Various malignancies

• Fasted 48-140 hours prior to chemotherapy and 5-56 hours following chemotherapy

Fasting in human patients on chemo—Results

- Well tolerated: mild light-headedness, weakness (temporary)
- Reduced fatigue
- Reduced overall weakness
- Fewer GI side effects

- No adverse effects on tumor volume or serum tumor markers
Fasting reverses certain types of leukemia in animal models

• “...fasting alone robustly inhibits the initiation and reverses the leukemic progression of both B cell and T cell acute lymphoblastic leukemia (B-ALL and T-ALL, respectively), but not acute myeloid leukemia (AML), in mouse models of these tumors....”

• Mechanism: fasting enhances leptin sensitivity
Length of overnight fast affects br ca prognosis

• 1.36 greater risk of breast cancer recurrence if overnight fast less than 13 hours

• Hemoglobin A1c lower with longer overnight fast
Occasional short fasts

• Enhance effectiveness and decrease side effects of cancer therapy
  • Chemotherapy, radiation, targeted therapy (animal studies only)
• Are safe (human studies)
• Are possibly necessary for general health (early human studies)
Isn’t that fatal?
“SNACK OFTEN” – American Cancer Society

- Angel food cake
- Cereal (hot or cold)
- Cookies
- Crackers
- Eggnog (pasteurized)
- Fruit (fresh, frozen, canned, dried)
- Gelatin made with juice, milk, or fruit
- Granola or trail mix
- Ice cream, sherbet, and frozen yogurt
- Juices
- Microwave snacks
- Milk by itself, flavored, or with instant breakfast powder olive oil, dressing, or sauce

Summary

• **Moderate carbohydrate restriction**
  • ER+, PM breast cancer, colon cancer BMI>25

• **Ketogenic diet**
  • glioblastoma, advanced “incurable” cancers of adults; radiation, cancer cachexia

• **Intermittent fasting**
  • select patients during chemotherapy, radiation?
  • Overnight at least 13 hours, most everyone
  • Occasional 24-72 hour fasts may decrease cancer risk
Questions and problems

• KD or exogenous ketones?
• KD plus fasting?
• KD vs fasting?
• Low fat diet or statins with BRAF mutation/amplification?
• Protein or amino acid restriction?
• Diet “cycling”?
THE END
References and Resources 1


References and Resources 4


References and Resources 6


• Hensley et al., Metabolic Heterogeneity in Human Lung Tumors. *Cell 2016; 164*, 1–14 http://dx.doi.org/10.1016/j.cell.2015.12.034


• Zeevi et al., Personalized Nutrition by Prediction of Glycemic Responses, *Cell 2015; 163:1079–1094*
References 8


References


- Brandhorst et al., A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan, Cell Metabolism (2015), http://dx.doi.org/10.1016/j.cmet.2015.05.012

  Note: covers the 5:2 approach


References and Resources 11

• Courneya et al. Med&Sci in Sports&Exercise 2014
• Oechsle et al. Supportive Care Cancer 2014
• Foster et al. Amino Acids 2012
• LeBlanc TW et al. J Pain Symptom Manage. 2015 Apr;49(4):680-9