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…

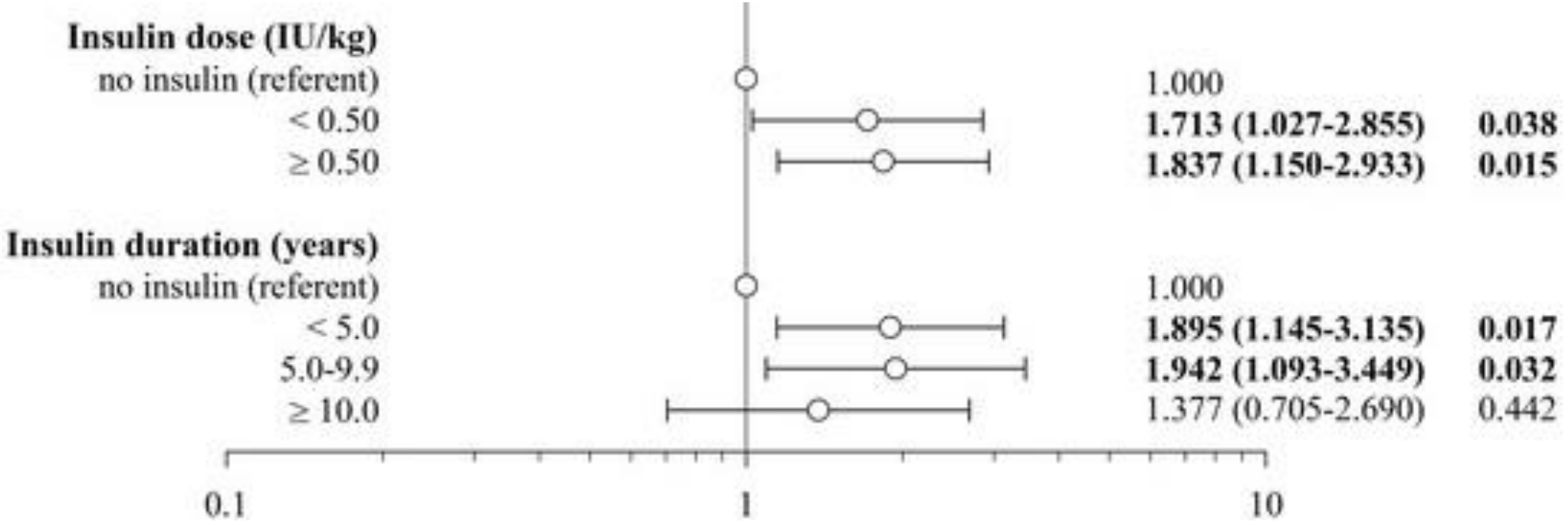
Common cancers that may be affected by diet

- 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

Meyerhardt, JNCI 2012

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!

Meyerhardt, JNCI 2012

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

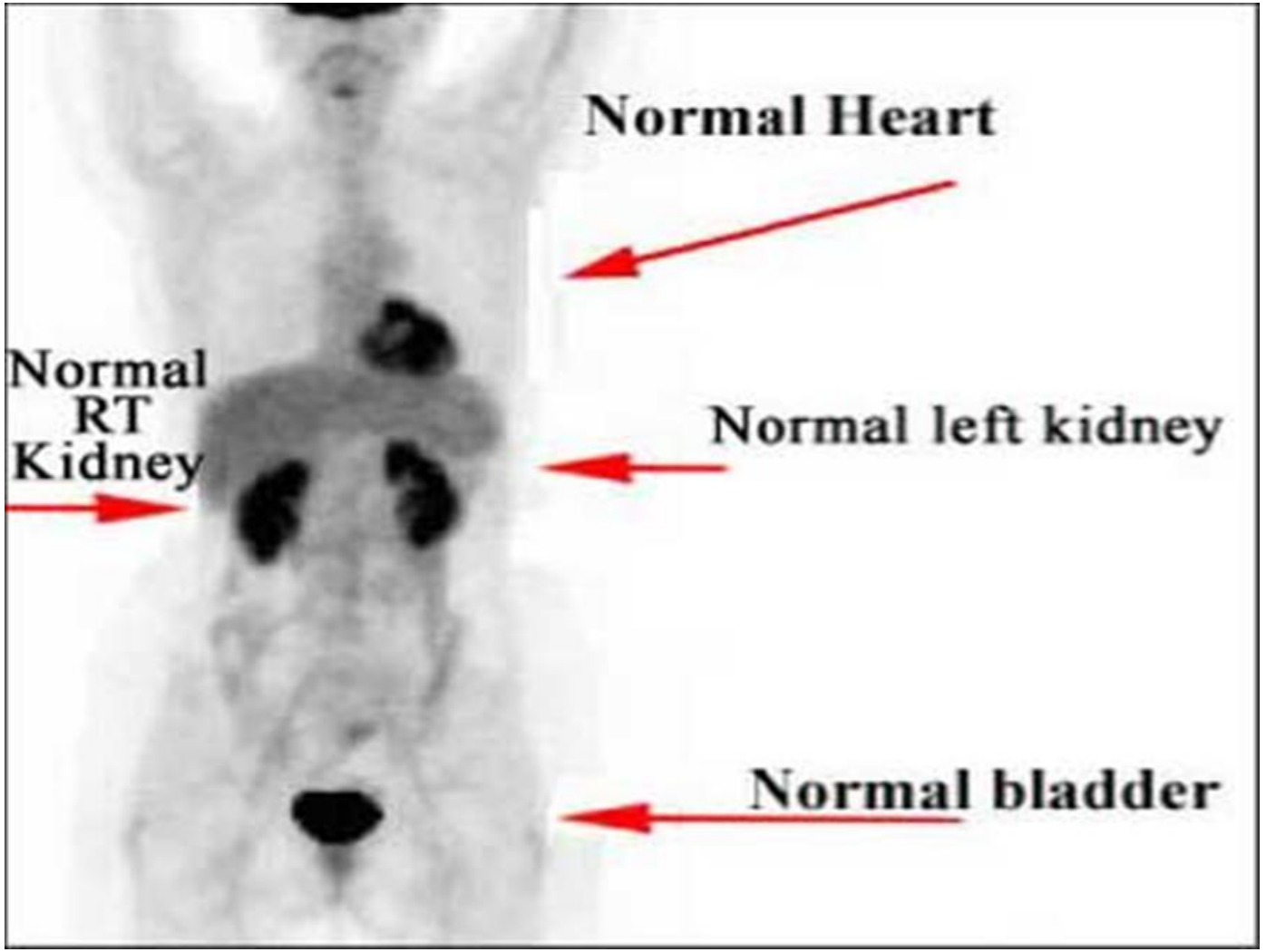
“Warburg Effect”

- Normal cell
- 1 glucose molecule nets 38 ATP

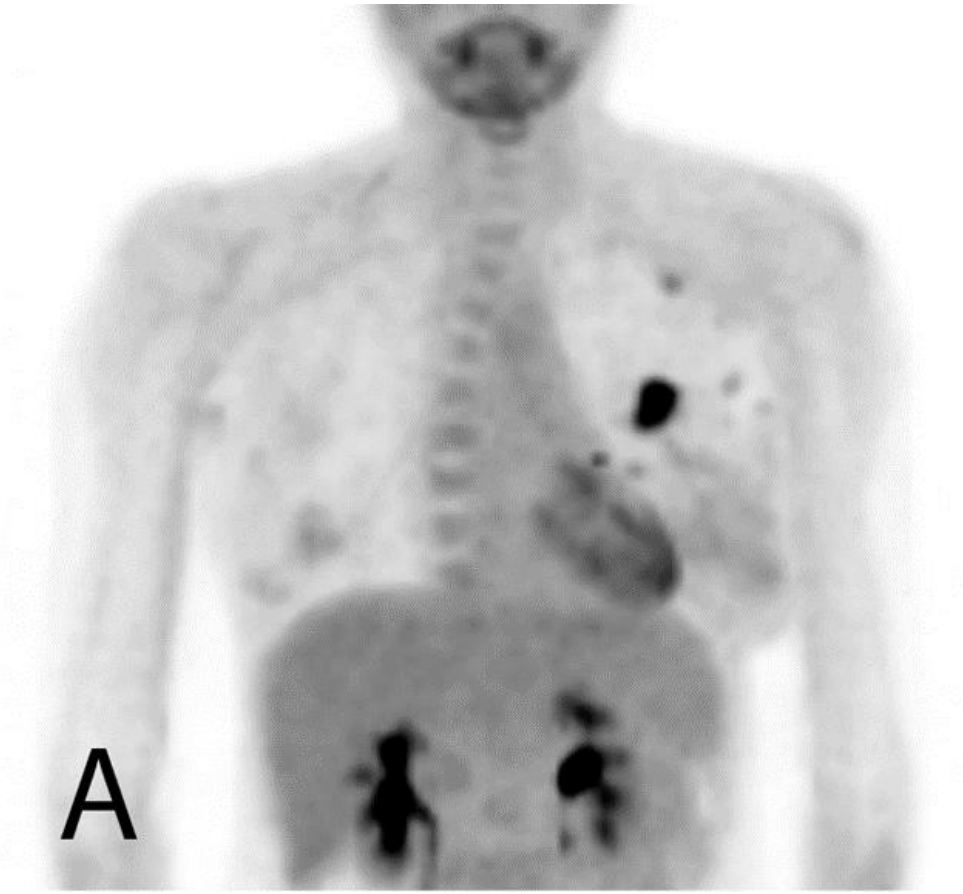
- Cancer cell (with Warburg effect)
- 1 glucose molecule nets 2 ATP

- Massive amounts of glucose needed to keep up with energy demands

Normal PET scan



PET scan: Left lung cancer



PET scan: advanced metastatic cancer

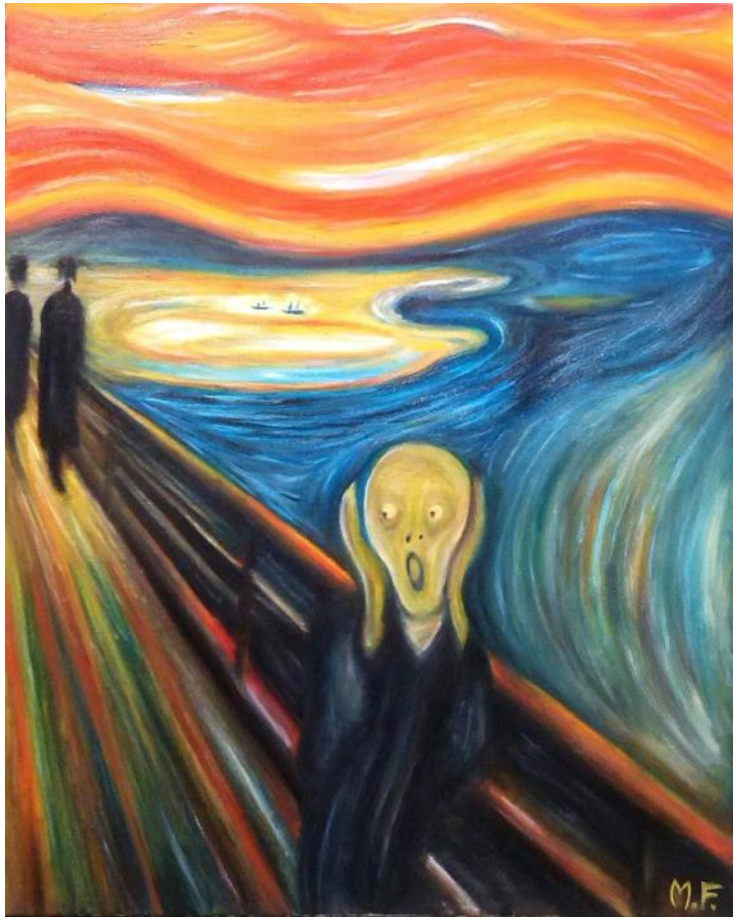
Ketogenic Diet: Glioblastoma and advanced metastatic cancers

Part II

Ketogenesis: “production of ketone bodies”

- Fasting
- Prolonged exercise
- Very low carb intake
- Fatty acids are metabolized in liver into ketone bodies
- *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

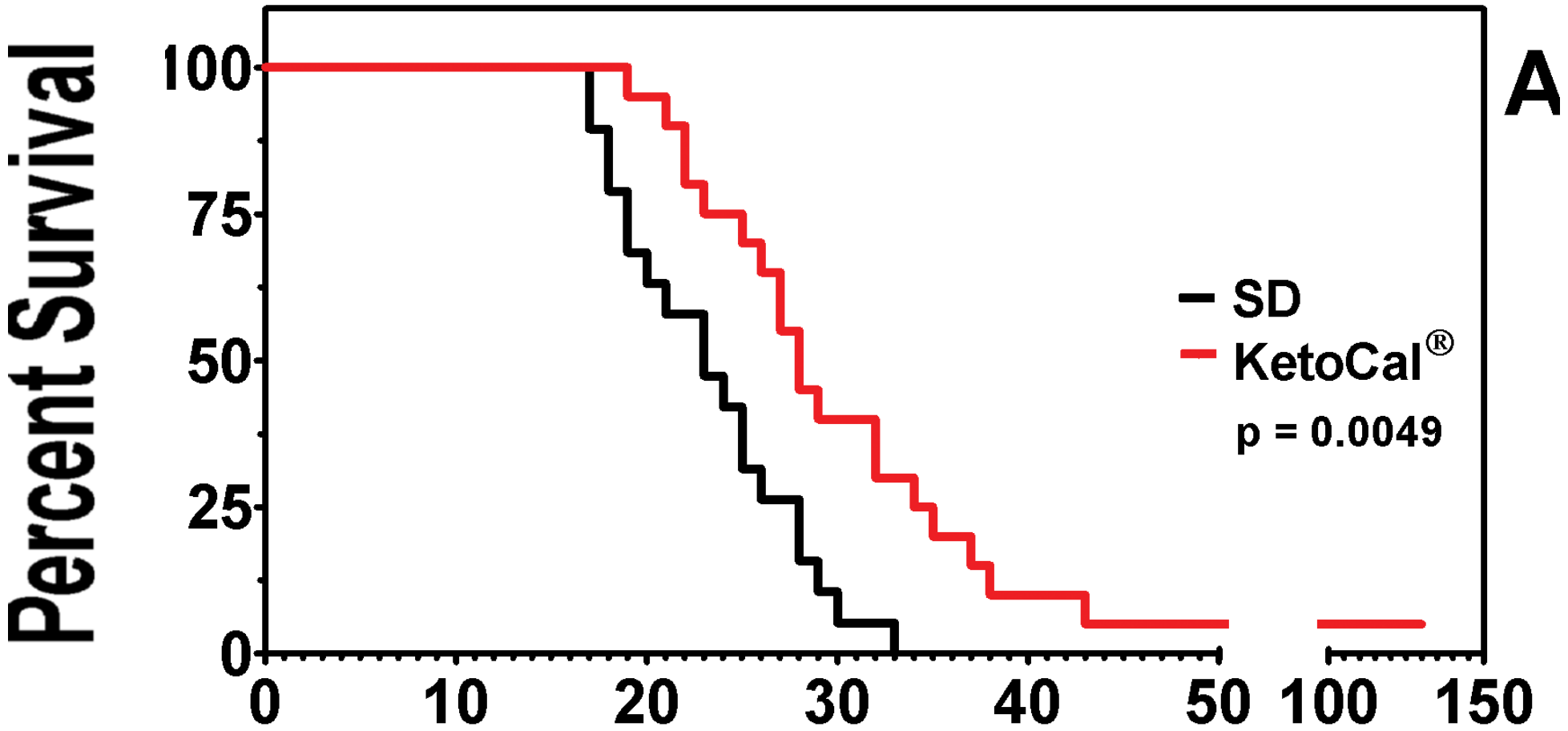
Ketogenic diet

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

Glioblastoma multiforme

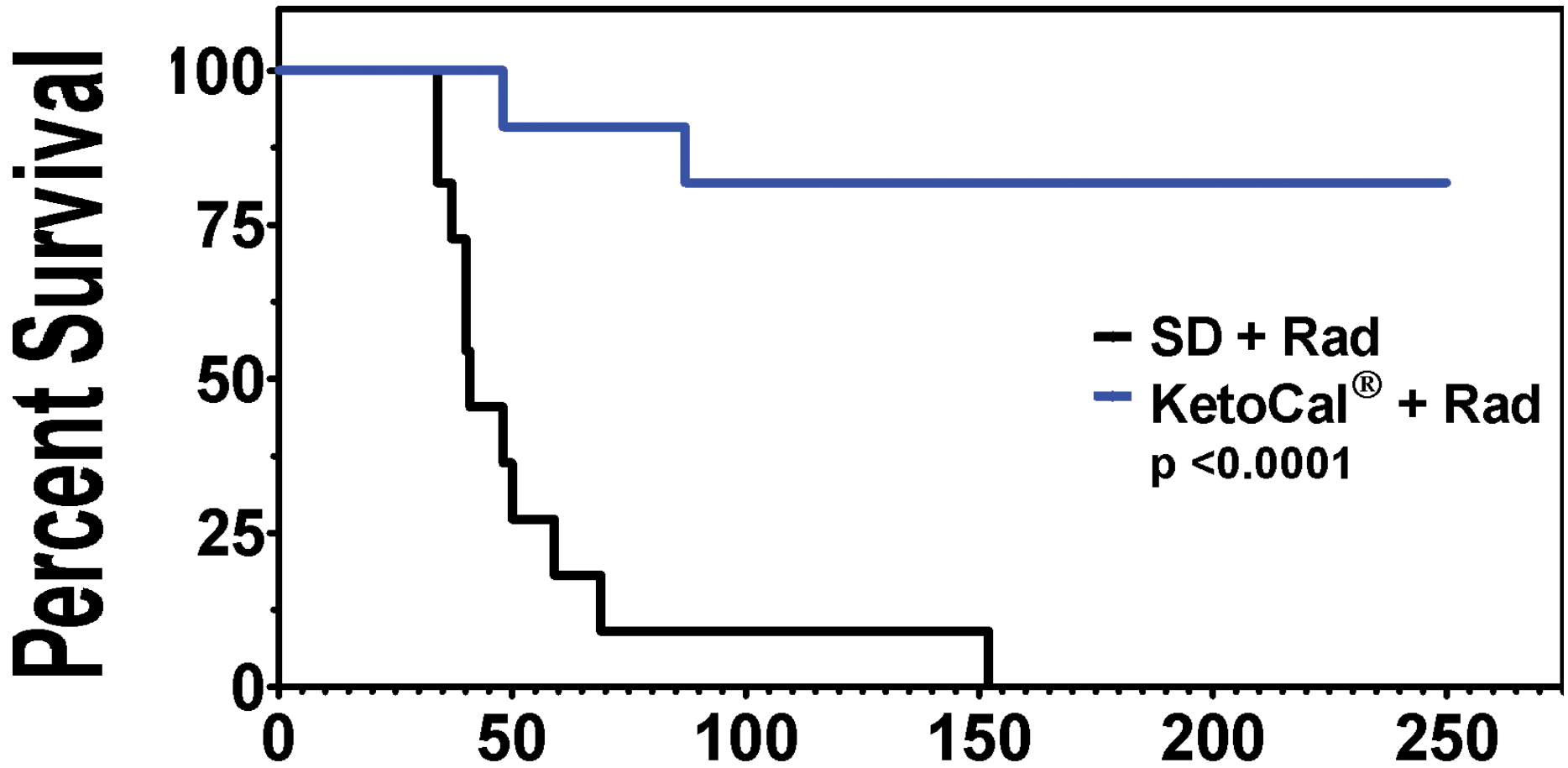
- 5-year life expectancy = 0%
- Ketogenic diet in preclinical settings promising

No radiation: KD vs normal diet



Abdelwahab et al. PLoS One 2012

Radiation: KD vs normal diet



Abdelwahab et al. PLoS One 2012

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

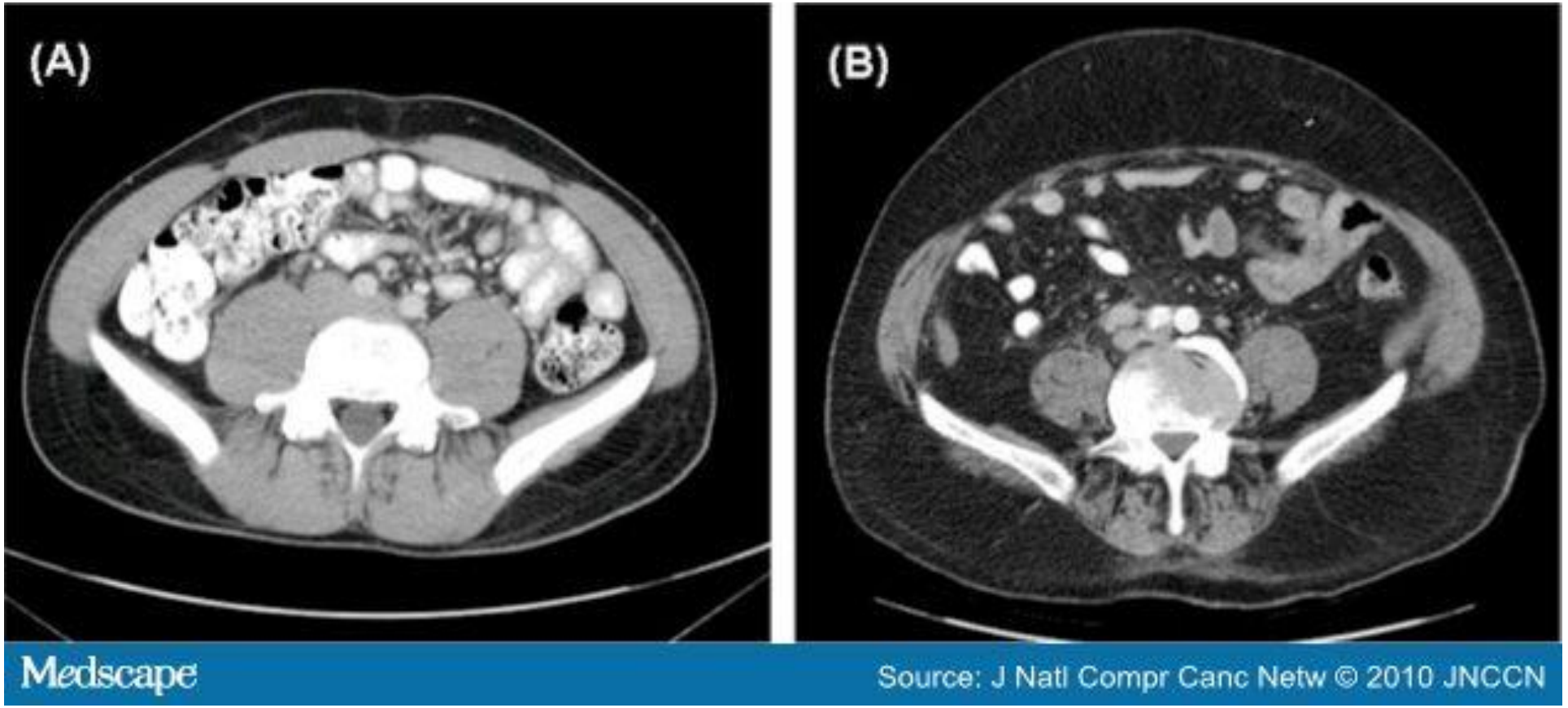
Cancer cachexia

- 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!

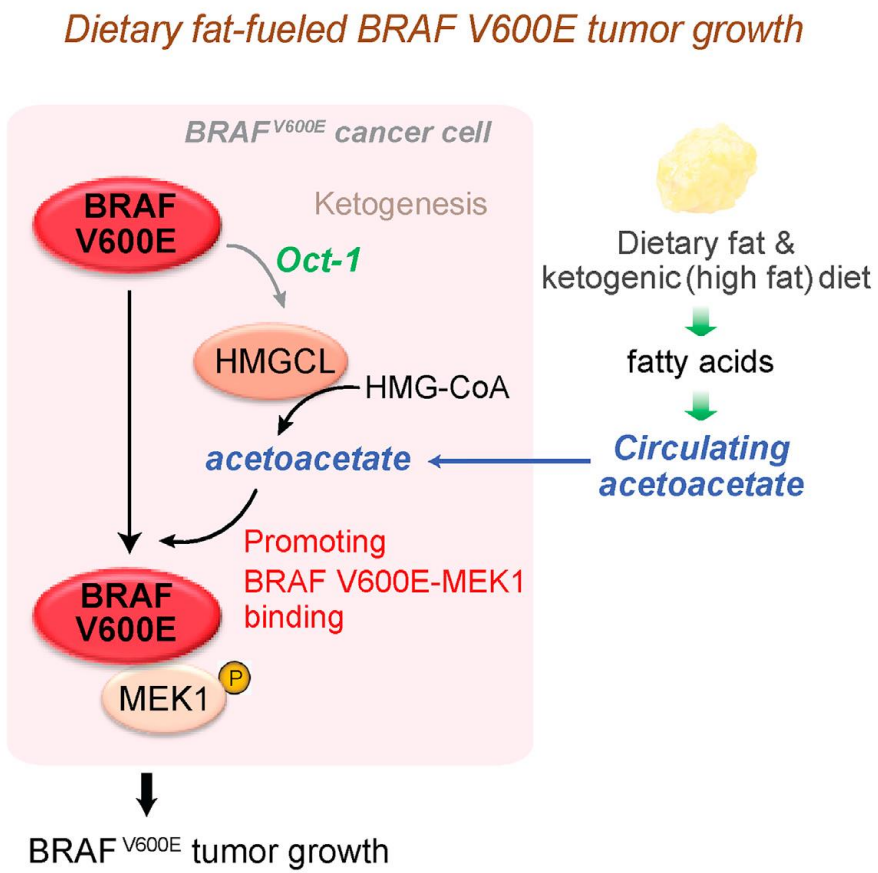
LeBlanc TW et al. J Pain Symptom Manage. 2015 Apr;49(4):680-9

Sarcopenic obesity



http://img.medscape.com/article/716/542/716542-fig2.jpg

BRAF V600E mutation; fat fuels tumor growth



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

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

Pouliot, Cancer Forum 2014; Lyssiotas, Cell 2014; Cao, BMC Cancer 2014; Thompson, Trends Biochem Sci 2010.

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

Longo and Mattson, Fasting: Molecular Mechanisms and Clinical Applications, Cell Metabolism (2014), http://dx.doi.org/10.1016/j.cmet.2013.12.008

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

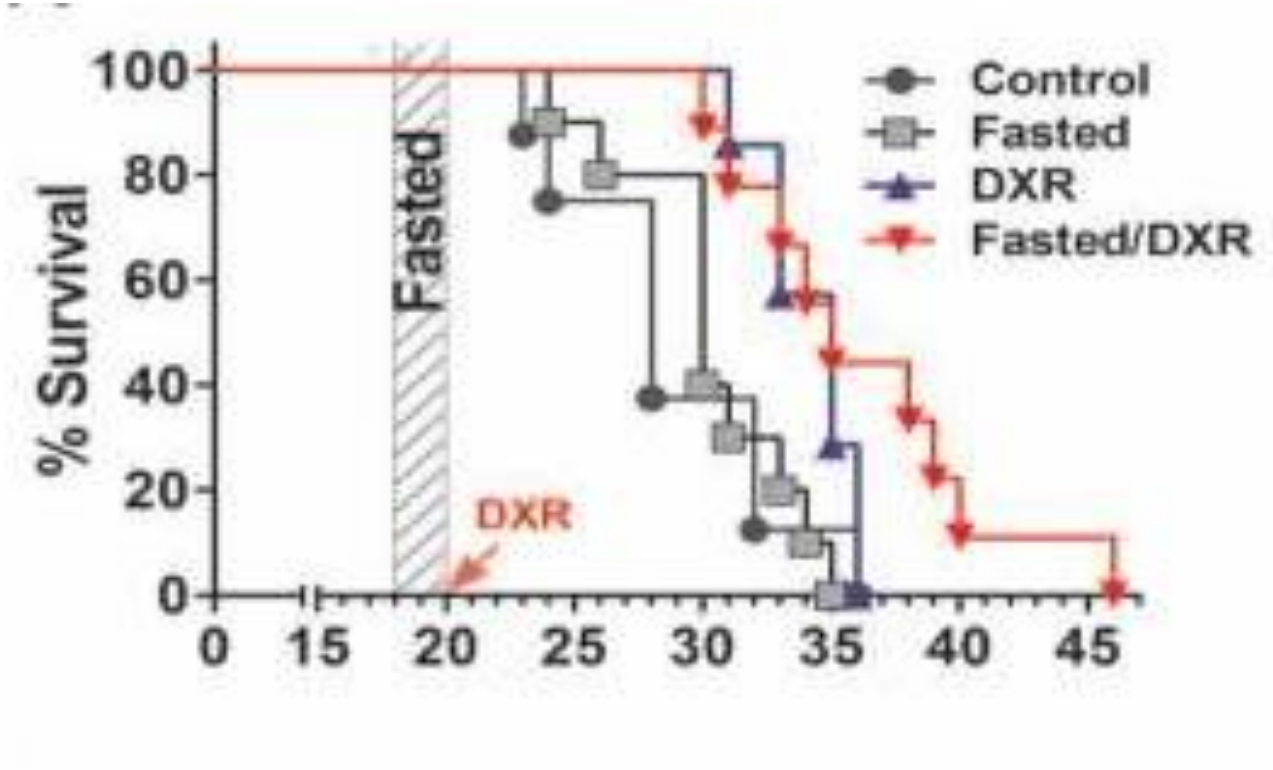
Mendelsohn and Larrick, Rejuvenation Res 2014; Longo et al. Sci Translational Medicine 2012; Longo et al. Ca Res 2010

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

Safdie et al. Aging 2009;1(12):988-1007.

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

Safdie et al. Aging 2009;1(12):988-1007.

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

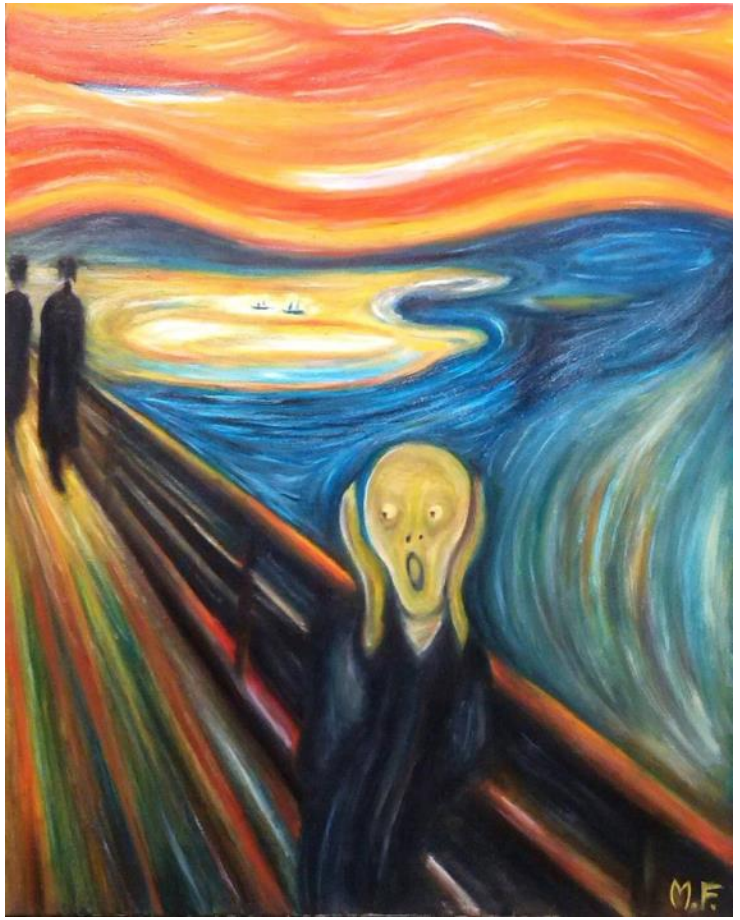
- 1.36 greater risk of breast cancer recurrence if overnight fast less than 13 hours

- 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**

https://www.cancer.org/treatment/survivorship-during-and-after-treatment/staying-active/nutrition/nutrition-during-treatment/once-treatment-starts.html accessed 02/24/2017; excerpted

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

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- Note: covers the 5:2 approach

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