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Ovarian Cancer: Possible Role of Nutrition and Energy Metabolism

Barbara M. Buttin, MD
Practice Leader, Gynecologic Oncology
Northwestern Medicine Regional Medical Group
Central DuPage Hospital and Warrenville Cancer Center

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Metabolic Abnormalities and Cancer Risk

- **What is metabolism?**
  - A set of life-sustaining chemical transformations within the cells of living organisms
- **Catabolism:** the *breaking down* of organic matter for example, the breaking down of glucose to pyruvate, by cellular respiration
- **Anabolism:** the *building up* of components of cells such as proteins and nucleic acids
- Usually, breaking down releases energy and building up consumes energy.

Metabolic Abnormalities and Cancer Risk

- **Disorders of abnormal metabolism**
- **Inborn errors of metabolism**
  - Born with genetic abnormality resulting in:
    - Lack of enzymes needed to process certain foods
    - Lack of enzymes needed to excrete toxins
    - Many are serious, some lethal
- **Acquired metabolic disorders**
  - Diabetes
  - Metabolic Syndrome
  - Obesity
  - Alzheimer's disease?

Metabolic Abnormalities and Cancer Risk

- **Obesity:**
  - 71% of Americans are overweight or obese
  - Body Fatness, poor nutrition, physical inactivity and excess alcohol consumption lead to
    - ➢ *1 in 5 cancer deaths*
  - Being overweight or obese likely raises a person's risk of getting at least
    - ➢ *13 types of cancer*

American Cancer Society, 2016

Metabolic Abnormalities and Cancer Risk

- **Diabetes:**
  - 10% of Americans are diabetic
    - More than 25% of Americans over age 65
  - Associated with cardiovascular disease, renal disease
  - Associated with upwards of 20% of cancers in the U.S.
  - Associated with shorter overall and disease-free survival in ovarian cancer (Shah MM et al., Gynecol Oncol 2014)

Metabolic Abnormalities and Cancer Risk

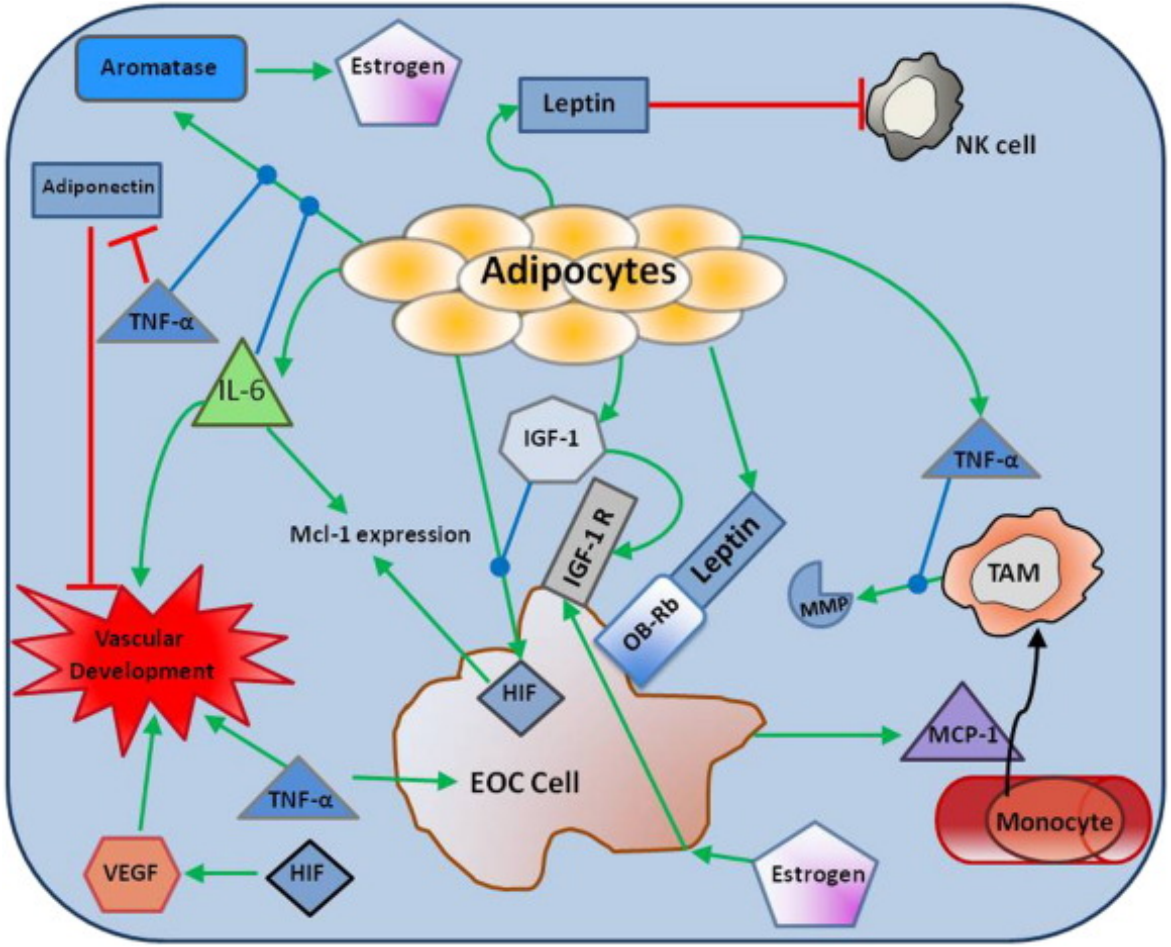
- **Metabolic Syndrome**
  - Must have 3 of 5:
    - Increased waist circumference/fat around the middle
    - Elevated triglycerides (>150 mg/dl)
    - Hypertension (SBP > 130, DBP > 85)
    - Elevated fasting blood glucose (> 100 mg/dl)
    - Decreased HDL cholesterol (< 50 mg/dl in women)
  - 38% of U.S. adult females
  - Increased risk of developing diabetes and heart disease, increased risk for several cancers

Epithelial Ovarian Cancer (EOC) and Metabolic Abnormalities

- Obesity:
  - Million Women Study (UK) found higher incidence of EOC with increasing BMI (> 27.5) *Reeves GK et al. 2007*
  - Meta-analysis showed increased risk for EOC in BMI > 30 *Olsen CM et al. 2007*
  - Multiple studies: high BMI in adolescence or early adulthood increases risk for developing EOC
  - Multiple studies: decreased overall and cancer-specific survival in obese women with EOC *Protani MM et al. 2012, Nagle CM et al.2015*
- Diabetes:
  - Independent risk factor for poor outcomes/mortality in EOC
  - Higher incidence of dose limiting toxicities
  - If co-exists with obesity, may be even more high risk

Proposed Mechanisms Linking Metabolic Abnormalities and EOC

- Abnormal adipokine and cytokine levels increase tumor evasion of immune response
- Altered endocrine function can influence pro-tumor signaling pathways, higher androgen and estrogen levels
- Abnormal tumor associated macrophages (TAM) increase tissue remodeling and angiogenesis
- Higher IGF-1 production stimulates cell differentiation and angiogenesis, correlates with poor outcome



Craig ER et al, Gynecol Oncol 2016

Cytokine/Growth factor	Change under abnormal metabolic condition	Mechanism contributing to EOC development/ progression
IL-6 (from fat cells, macrophages, tumor cells)	Upregulated in obesity and DM	Promotes angiogenesis, induces aromatase, chemoresistance
TNF-α (same sources)	Same	Increases tumor invasiveness, angiogenesis
Leptin (from fat cells)	Increased in obesity	Immune suppression, increases proliferation
Adiponectin (from fat cells)	Decreased in obesity, DM	Inhibits TNFα signaling , angiogenesis
HIF	Increased in obesity	Upregulates IL-6, TNF, angiogenesis, fibrosis
VEGF	Increased in obesity	Promotes vascular growth
Insulin/IGF-1	Increased in obesity, DM	Increases HIF, tumor growth, decreases SHBG, increases bioavailable estrogen
Estrogen	Increased in obesity	Induces IGF-1 receptor, acts as mitogen (pro-cell division)

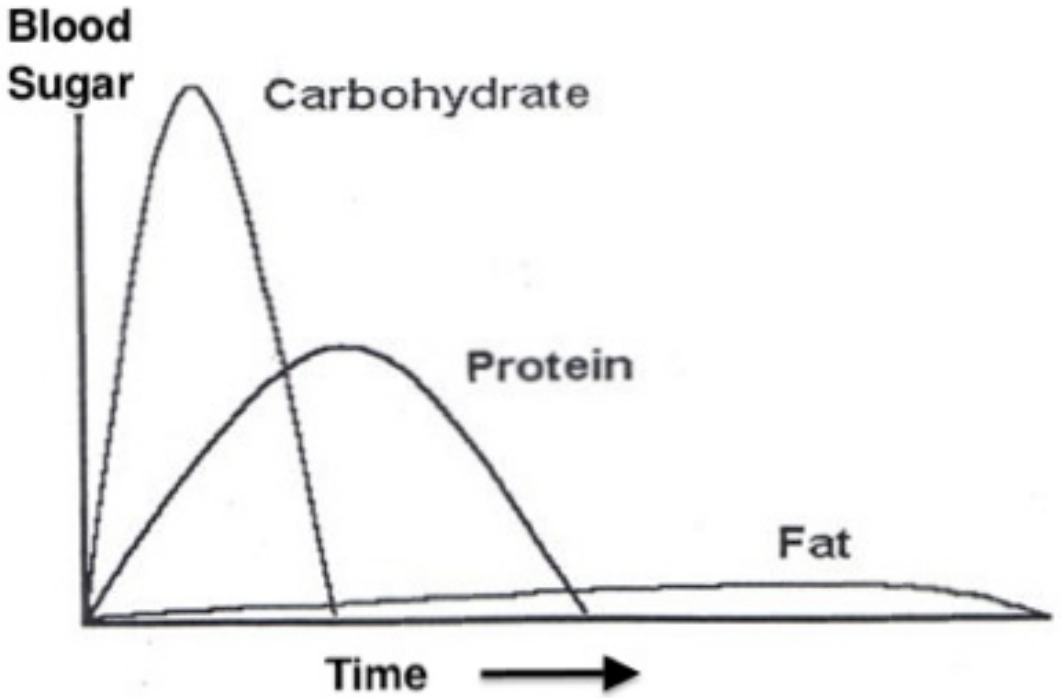
The Standard American Diet

- Food and Nutrition Board of the Institute of Medicine (2005, revised 2016):
  - 45-65% carbohydrates
  - 10-35% protein
  - 20-35% fat
- Most Americans eat refined carbs, processed foods and processed meats, and few fresh fruits and vegetables
- Most Americans eat a high carbohydrate ***and*** moderate-high fat diet (mostly unhealthy fats)
  - This pattern of eating leads to **hyperglycemia** and resultant **hyperinsulinemia** (high blood sugars provoke high levels of insulin being secreted by the pancreas in order to drive the sugar from the blood into the cells)
  - In chronic amounts, this pattern can lead to ***insulin resistance (IR)***

Hyperinsulinemia

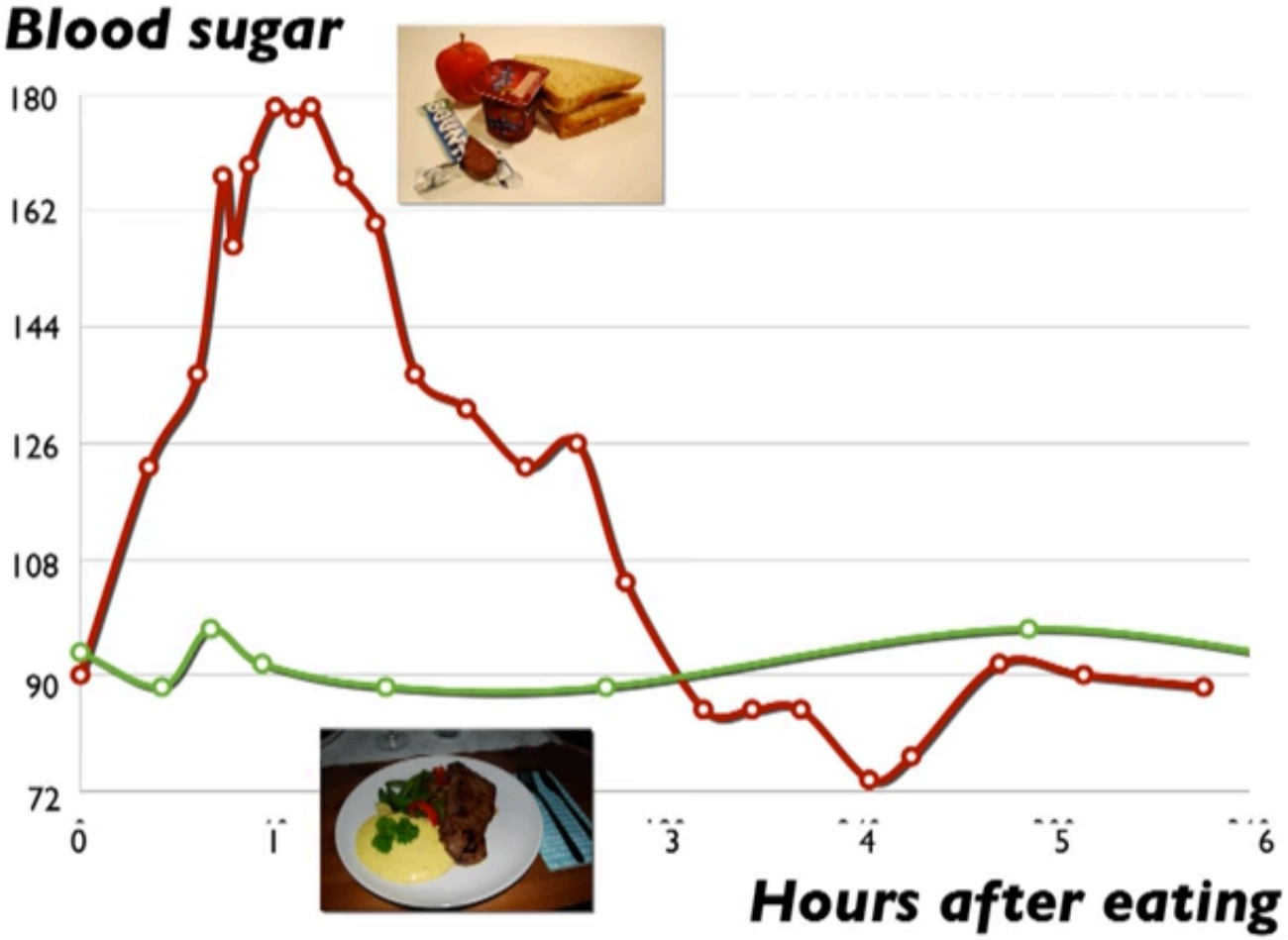
- Insulin and weight
  - Insulin is *lipogenic and anabolic* (a fat storage and weight gain hormone)
  - Insulin shuts down the release of fatty acids from body fat while it manages the intake of food
  - When insulin turns off, you go back to burning stored fat (lipolysis) until you eat again
  - Insulin goes up in relation to the macronutrient intake/glycemic index
  - Most people eat 4-5 times a day and keep insulin high most of the time

Blood Sugar Levels in Response to Different Macronutrients

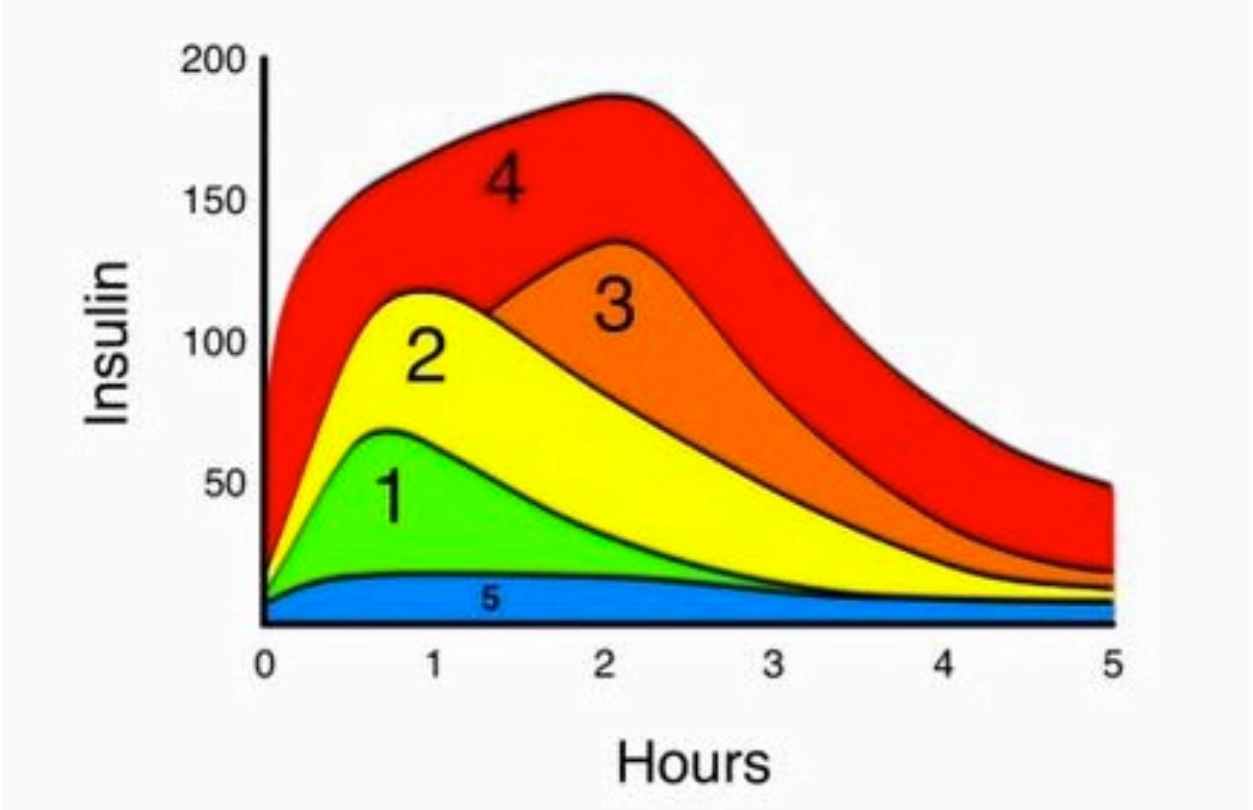


Post-Prandial Blood Glucose Levels in Insulin-Sensitive Individual

(Andreas Eenfeldt, MD, dietdoctor.com)



Kraft Patterns:
Insulin response to OGTT
(14,000 people: patterns 2,3 and 4 = insulin resistant= 75% of population “Diabetes-in-situ” or frank DM)



75gm carb load

The Metabolic Theory of Cancer

Otto Heinrich Warburg

German Cell Biologist

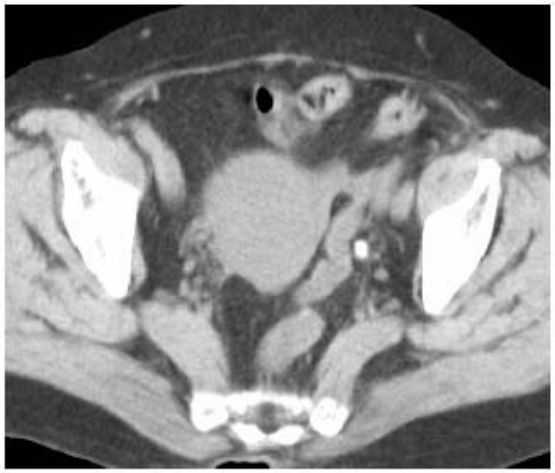
Nobel Prize in Physiology or Medicine in 1931

- Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there **is only one prime cause**. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar.

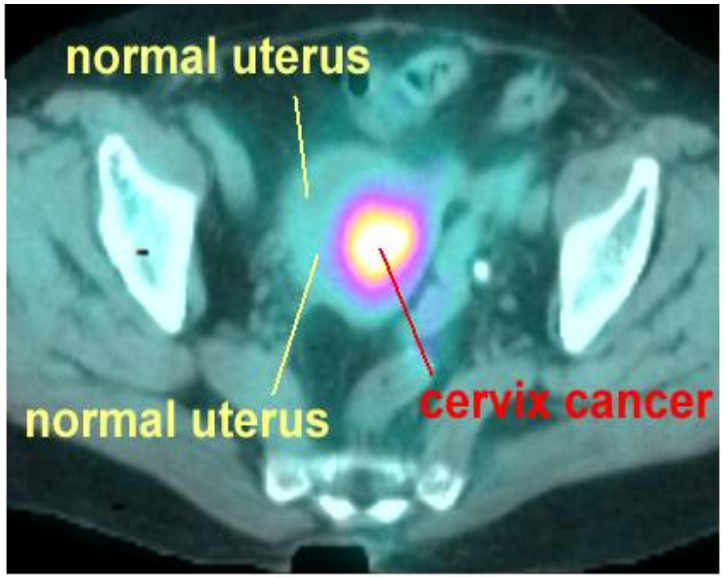
- Otto H. Warburg

Example: PET Scans

- Patients are injected with radioactive glucose
- Cancer cells that are dividing (growing and active) preferentially take up the labeled glucose
- Many types of cancer “light up” on PET scan for this reason
- Cancer cells produce energy primarily through glycolysis, needing lots of glucose for fuel

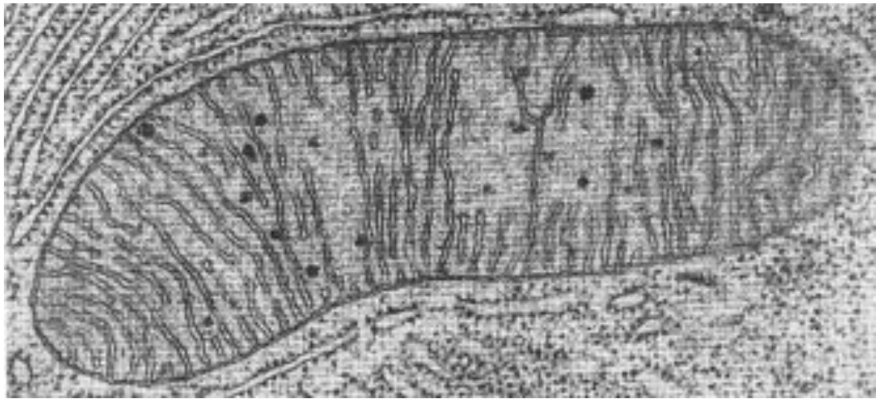


On CT difficult to separate uterus from cervix cancer



On PET scan it is easy

Mitochondrial Damage



Healthy Mitochondria. Note the abundant looping structures inside the mitochondria (cristae), this is where all energy is produced through oxidative pathways.

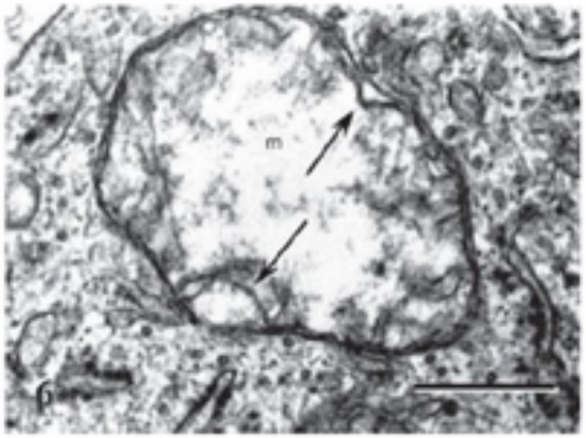


Image of a mitochondria from a cancer cell. Note the almost compete absence of cristae.

- Mitochondria are the cell's energy-producing organelles
- Mitochondrial function and oxidative phosphorylation is impaired in tumor cells
- Pathologic changes in mitochondrial function have been linked to
  - Metabolic and neurodegenerative diseases
  - Epilepsy
  - Cancer

Cancer as a Genetic Disease

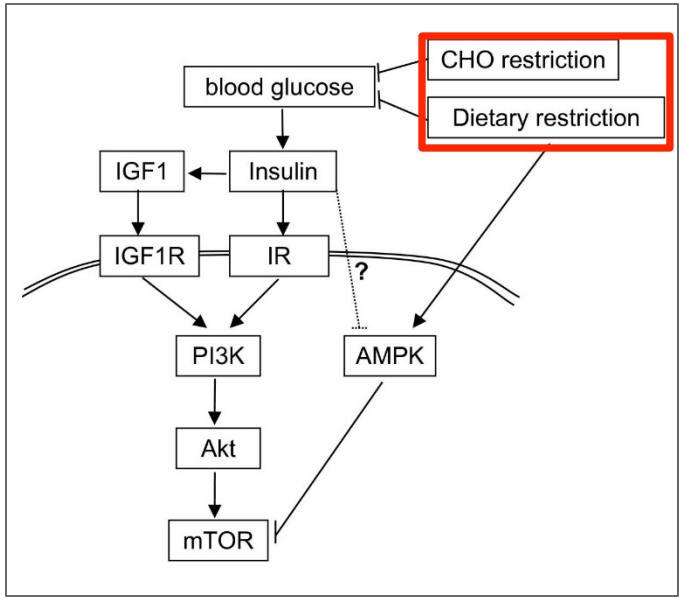
- 1953: Watson and Crick discover DNA

- What are Epigenetics?
- Genetics load the gun, but diet and life style pull the trigger!

Compare Modern Humans to Uncivilized Hunter-Gatherer Societies

- Caveman's diet (foraging and nomadism):
  - Mostly fat, meat
  - Only occasional roots, berries, and other sources of CHO
- Modern civilization's diet (agriculture and settlement): in use for < 1% of human history!
  - Easily digestible CHO, high glycemic index foods
  - Grains
- Most recent changes (last 100 years) also include:
  - increase in sedentary lifestyle
  - less sun
  - more stress
  - insufficient sleep
- **High CHO loads, high blood sugar, high insulin levels seem to be linked to many modern diseases, including cancer**

Tumor Cell Metabolism: It's All About Glucose



Therapeutic opportunity?

- Malignant cells:
  - utilize aerobic glycolysis which is inefficient (glucose as substrate)
  - Upregulate key enzymes to help in glycolysis (GLUT1, GLUT3)
  - Have mitochondrial dysfunction and therefore can't use OXPHOS
  - Upregulate genes that aid in inactivation of tumor suppressors (p53, PTEN) and activation of mTOR pathway
  - mTOR causes cell growth and proliferation with input from insulin and other growth factors

Metabolic Syndrome, Central Obesity and Insulin Resistance are Associated with Adverse Pathological Features in Postmenopausal Breast Cancer

- 150 post-menopausal women with breast cancer
- Patients with a later pathological stage (II-IV) were significantly more likely to be centrally obese, hyperglycemic and hyperinsulinemic
- 51% of later stage patients had metabolic syndrome compared with 12% for early stage disease.
- Patients with node-positive disease were significantly more likely to be hyperinsulinemic and have metabolic syndrome than patients with node-negative disease.

Clin Oncol (R Coll Radiol). 2010 May;22(4):281-8, LA Healy,et al

Pretreatment Insulin Levels as a Prognostic Factor for Breast Cancer Progression

- **RESULTS:**
- Fasting blood glucose level, insulin level, and HOMA index, but not HbA1c level, were significantly elevated in Breast Cancer patients compared with control subjects.
- Insulin had the best specificity (92%) and sensitivity (41%), was significantly associated with disease stage, and acted as a negative prognostic marker of progression-free survival independently of menopausal status, disease stage, hormone receptor status, and Her 2 and Ki67 expression.

Oncologist 2016 Sep;21(9):1041-9 by Ferroni, et al

What is a Low Carb High Fat (LCHF)/ Ketogenic Diet?

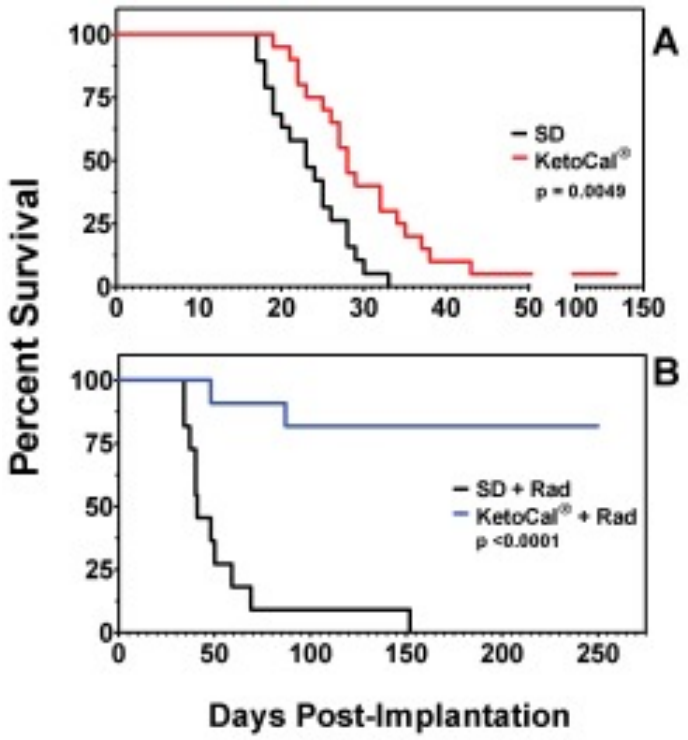
- A high fat, moderate protein, low carbohydrate diet
- It lowers blood glucose and thus insulin levels
- Allows the body to burn fat for fuel (body fat and/or dietary)
- When fat is burned for fuel, fatty acids and ketone bodies are produced (thus “ketogenic”)
- Keeps blood sugars stable
- Maintains or builds muscle mass
- Mimics the metabolic effect of “starvation” without starving the person

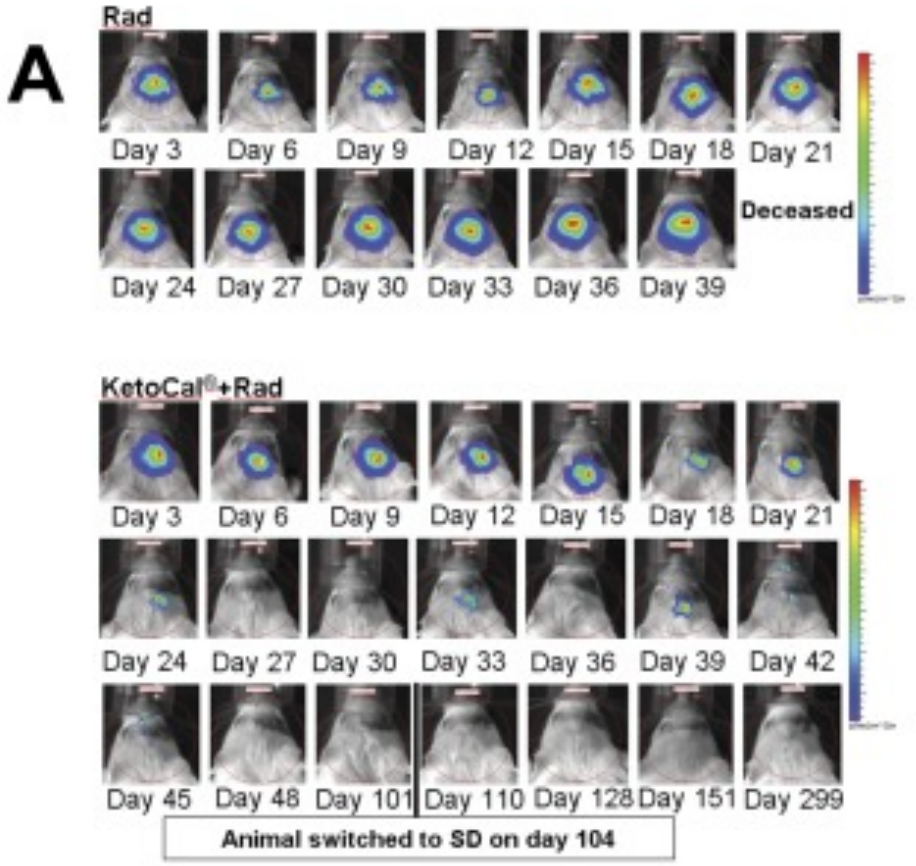
What Happens in a Ketogenic State?

- Decreased insulin and IGF-1 signaling
- Angiogenesis suppression
- Differential DNA repair
- Normal cells enter dormancy
- Decreased oxidative damage in normal cells

The Ketogenic Diet Is an Effective Adjuvant to Radiation Therapy for the Treatment of Malignant Glioma

Mohammed G. Abdelwahab,[1] Kathryn E. Fenton,[1] Mark C. Preul,[2] Jong M. Rho,[3,¤] Andrew Lynch,[4] Phillip Stafford,[5] and Adrienne C. Scheck[1,2,*]





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Targeting insulin inhibition as a metabolic therapy in advanced cancer: a pilot safety and feasibility dietary trial in 10 patients.

Fine EJ, Segal-Isaacson CJ, Feinman RD, Herszkopf S, Romano MC, Tomuta N, Bontempo AF, Negassa A, Sparano JA.

Nutrition. **2012** Oct;28(10):1028-35. doi: 10.1016/j.nut.**2012**.05.001. Epub **2012** Jul 26.
PMID: 22840388

- 10 patients with advanced incurable cancers
- 5 had stable disease or PR in 28 days by PET
- 4 had progressive disease and lower ketone levels
- No weight loss or cachexia
- Lowered insulin levels in those with higher level of ketosis

Modified Atkins diet in advanced malignancies - final results of a safety and feasibility trial within the Veterans Affairs Pittsburgh Healthcare System.

Nutr Metab (Lond). 2016 Aug 12;13:52. doi: 10.1186/s12986-016-0113-y. eCollection 2016.

Tan-Shalaby JL[1], Carrick J[2], Edinger K[1], Genovese D[1], Liman AD[1], Passero VA[1], Shah RB[2].

Several clinical trials are currently recruiting patients studying a ketogenic diet as adjunct to standard therapy

In Summary…

- Tumor cells have a **high demand for glucose** and conduct glycolysis for energy production even in the presence of oxygen (Warburg Effect)
- Many cancer cells over-express insulin receptors and hyper-activate the IGF1-IR pathway
- Chronic hyperglycemia and hyperinsulinemia facilitate tumorigenesis and worsen outcomes in cancer patients
- These findings also likely explain the association of metabolic syndrome with increased risk for several types of cancer
- CHO restriction has a beneficial effect on metabolic syndrome, could also be beneficial in decreasing cancer risk
- Cancer patients, especially those with advanced disease, have a multitude of metabolic aberrations including increased levels of inflammation and altered energy utilization
- Low carbohydrate and high fat diets can mimic the metabolic effect of calories restriction or (ketogenic diet) fasting
- Ketone bodies themselves may have direct anti-tumor potential as shown in various animal studies

Take Away

- The idea of using a ketogenic diet as a therapeutic adjunct to standard cancer treatment (surgery, radiation, chemotherapy, biologic therapy) is appealing and should be studied in all gynecologic cancers
- Stay tuned for **clinical trials** using this very interesting modality in the near future!