The Host Cancer Interface:
Obesity and Diabetes Promote Cancer Development and may Reduce Treatment Efficacy

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Conflict of Interest

None

Objectives

1. **Discuss host metabolism (obesity and diabetes) as risk and prognostic factors for human cancer.**

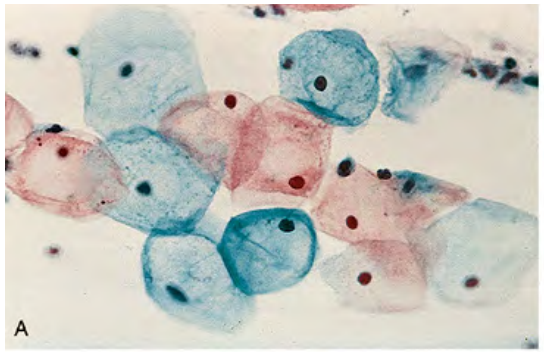
2. **Targeting metabolic dysregulation through our treatment of obesity and diabetes, to prevent and treat cancer**

Cancer

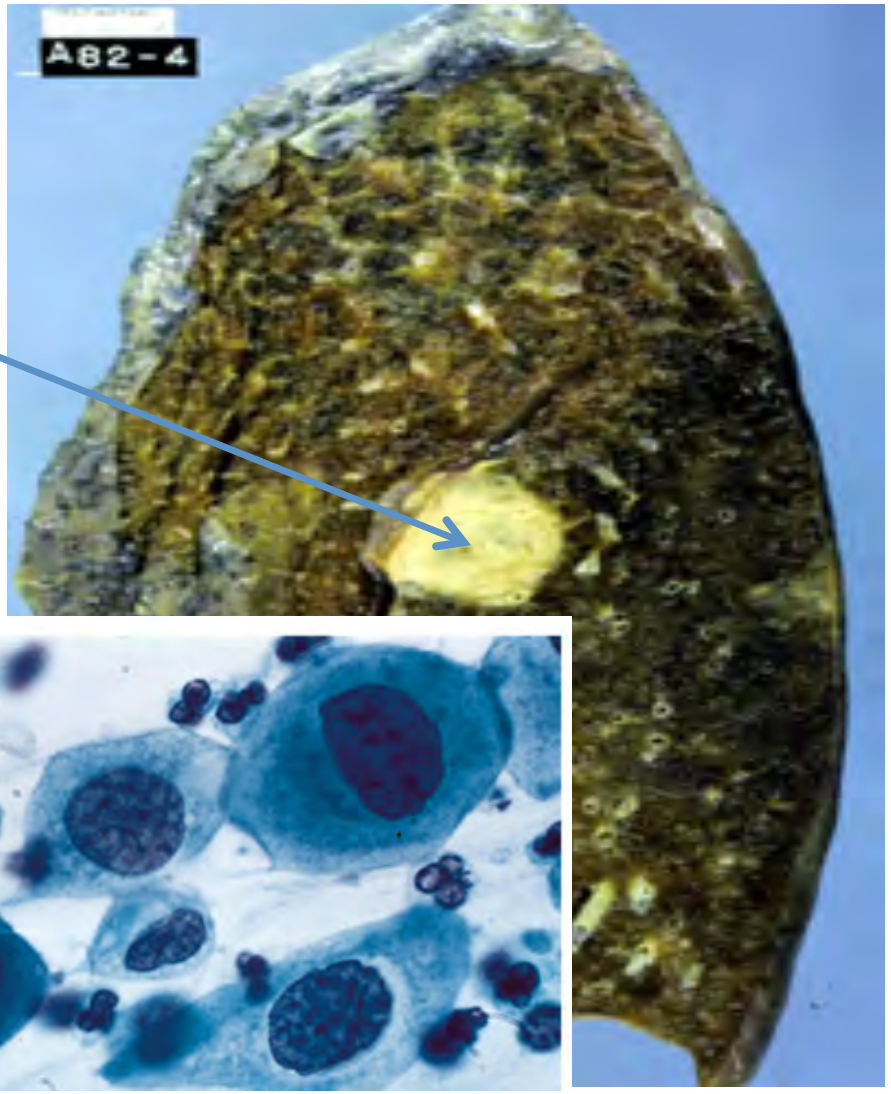
- Multistep process, often taking years
- Variable subtypes, even for the same organ of origin
- Unrestrained growth
- Inability to undergo cell induced death
- Adaptable through clonal progression
- Ability to invade normal tissues-into the neighborhood
- Ability to spread via vessels-to other organs and sites
- Can send and receive local and distant signals to other cells
- Can evade natural immunity

What does Cancer Look Like?

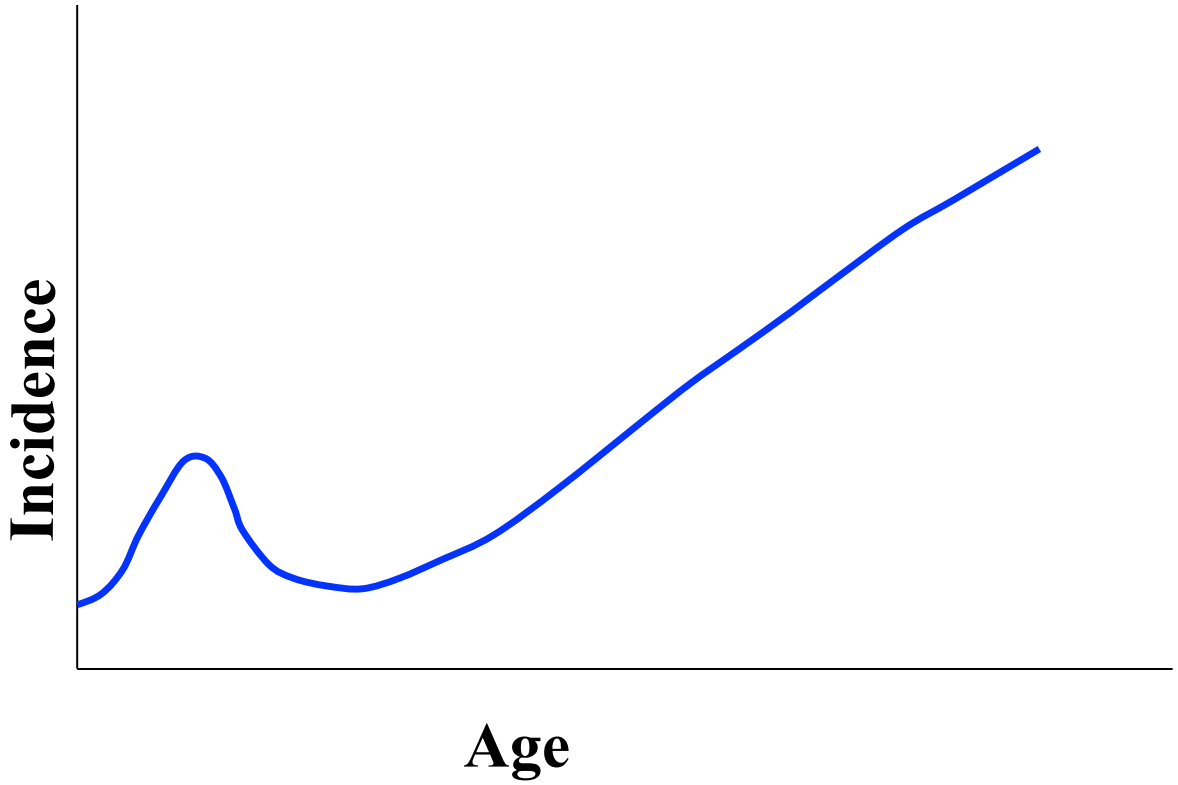
normal



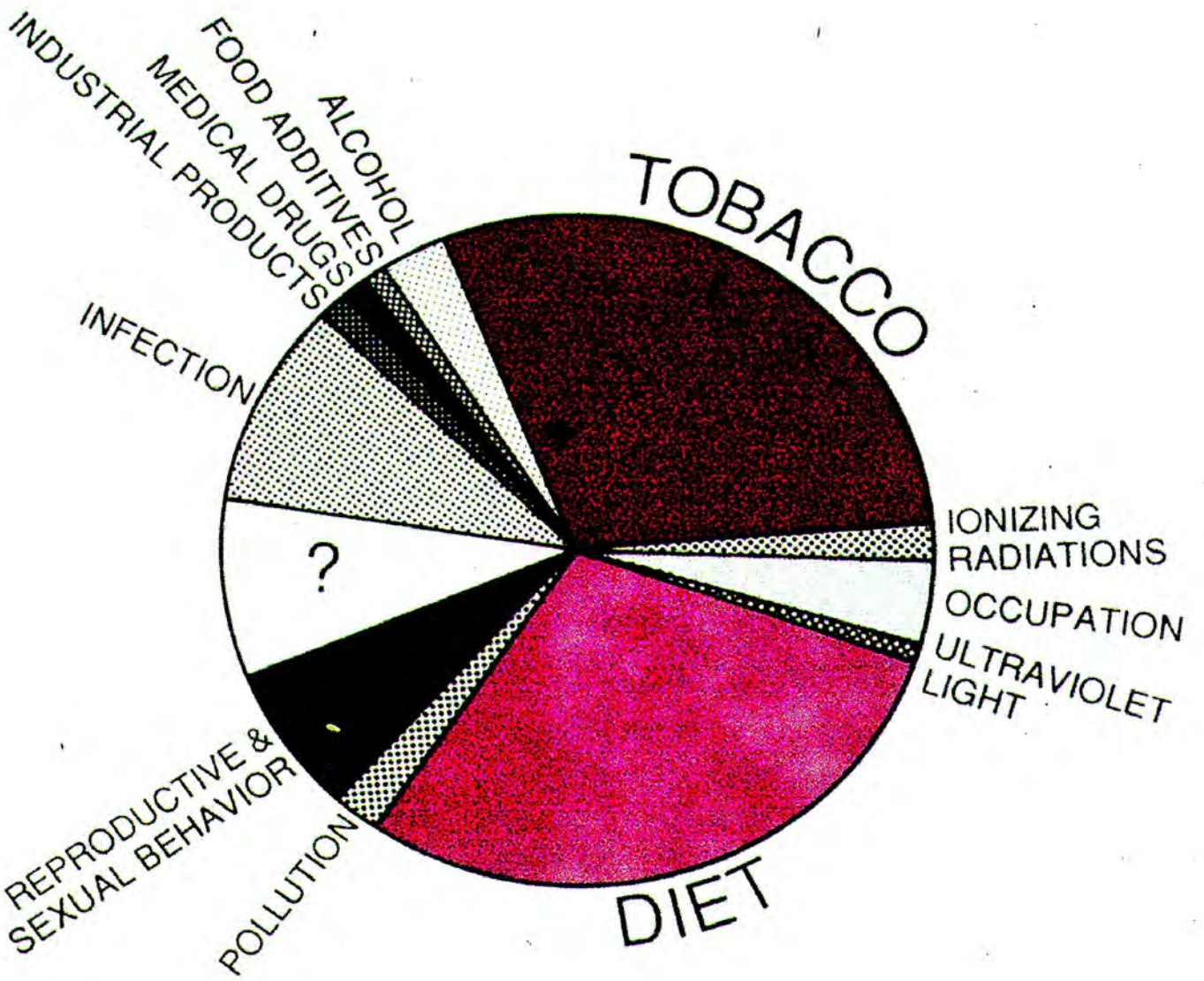
Lung Cancer



Age a Potent Risk Factor for Cancer



Many Risk Factors Can be Modified



…..is it true?

“Sugar and Fat that’s Where it’s At”

CD Young and SM Anderson, Br Ca Res 2008

Diabetes, Obesity and Cancer

- **Disorders of carbohydrate and lipid metabolism are well recognized risk factors for cardiovascular disease.**

- **Much less recognized by health professionals and patients, metabolic dysregulation is also a major risk factor for cancer.**

- **The incidence of TII diabetes and obesity has risen significantly in the US, even in pediatric patients.**
  - **There are 14 M TII Diabetics, 5 M undiagnosed TII diabetics and 41 M prediabetic adults in the US.**
  - **Two thirds of the US adult population is overweight. Half are obese.**

Cancer Pathogenesis

Endogenous Growth Promotion

- Cytokines, inflammatory factors
- Hyperinsulinemia, IGF
- Hyperglycemia
- Altered Metabolism
- Microbiome
- Hormones

Obesity

Type II Diabetes

Hyperlipidemia

Altered Immunity

- Wound healing-induction of growth factors, altered environment
- Decreased Immune Surveillance, immunodeficiency

Genetics/Transcriptomics/Epigenetics

- Inherited/somatic alterations, polymorphisms
- Acquired genetic instability, mutation
- Epigenetic changes

Exogenous Agents

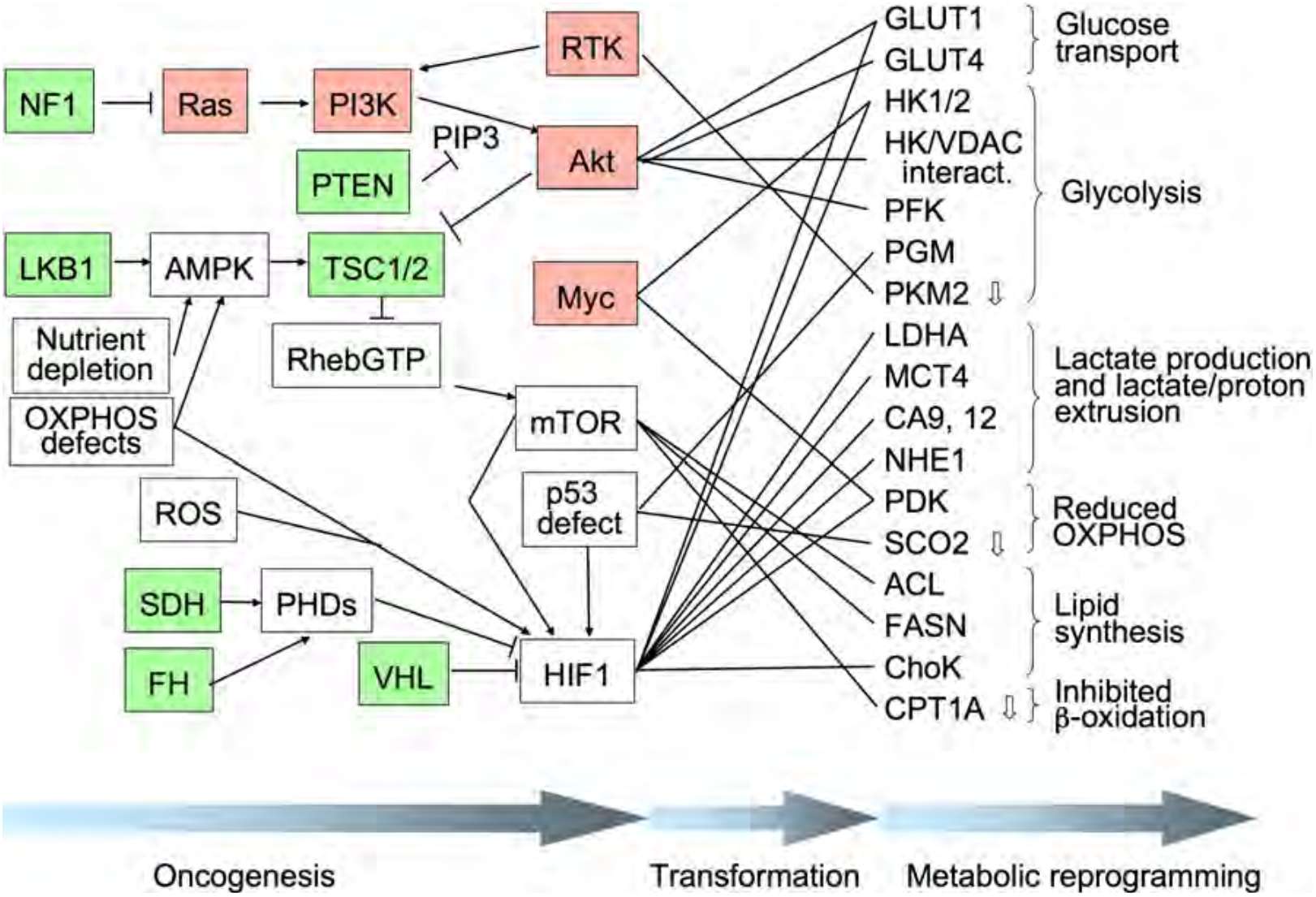
- Viral carcinogenesis (HPV, EBV)
- Chemicals
- Radiation
- Hormone like agents
- Dietary factors

Metabolic Reprogramming in Cancer

- Cancer cells reorganize metabolic pathways to augment anabolic reactions…although the mechanisms that foster this shift are complex

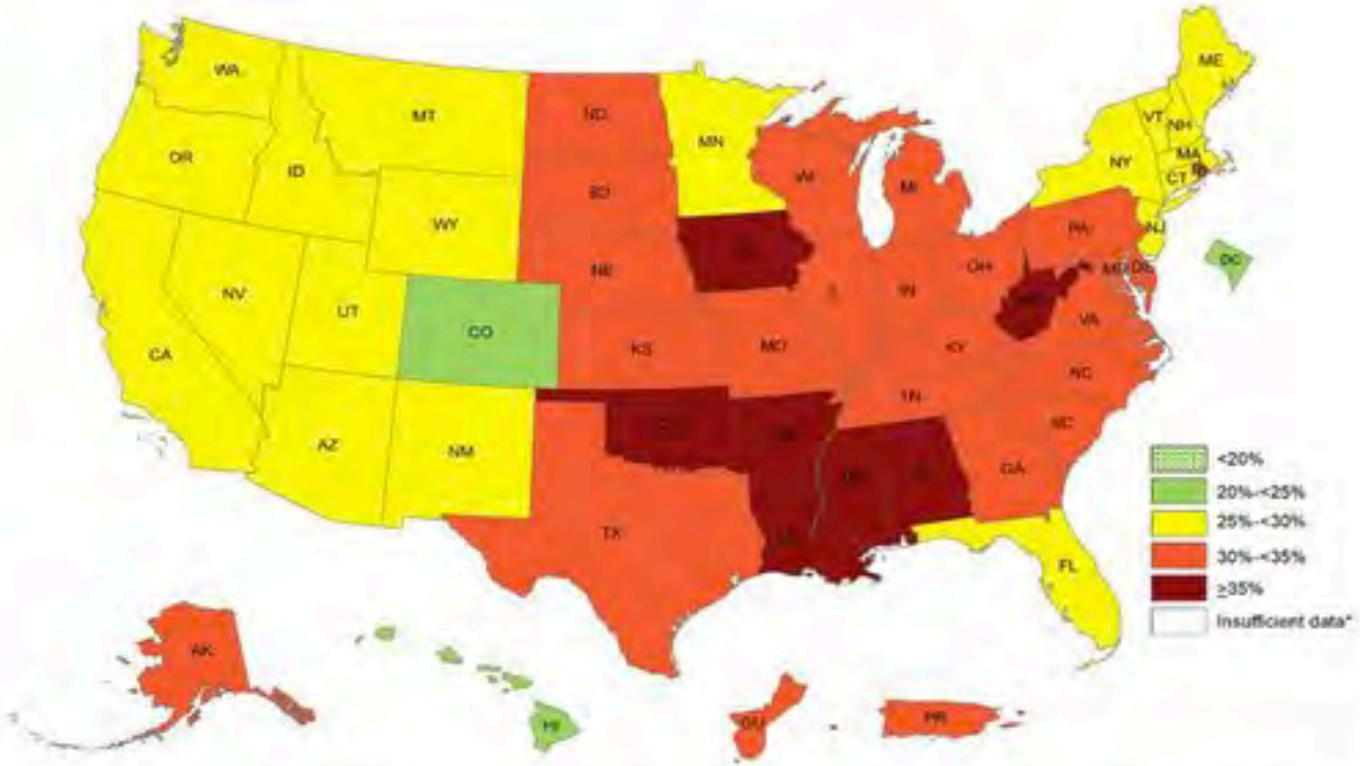
- Intermediates of the glycolytic pathway provide building blocks of anabolic pathways that enable growth and proliferation
    - Amino acids
    - Nucleic acids
    - Lipids

Mechanisms of Cancer Specific Metabolic Reprogramming

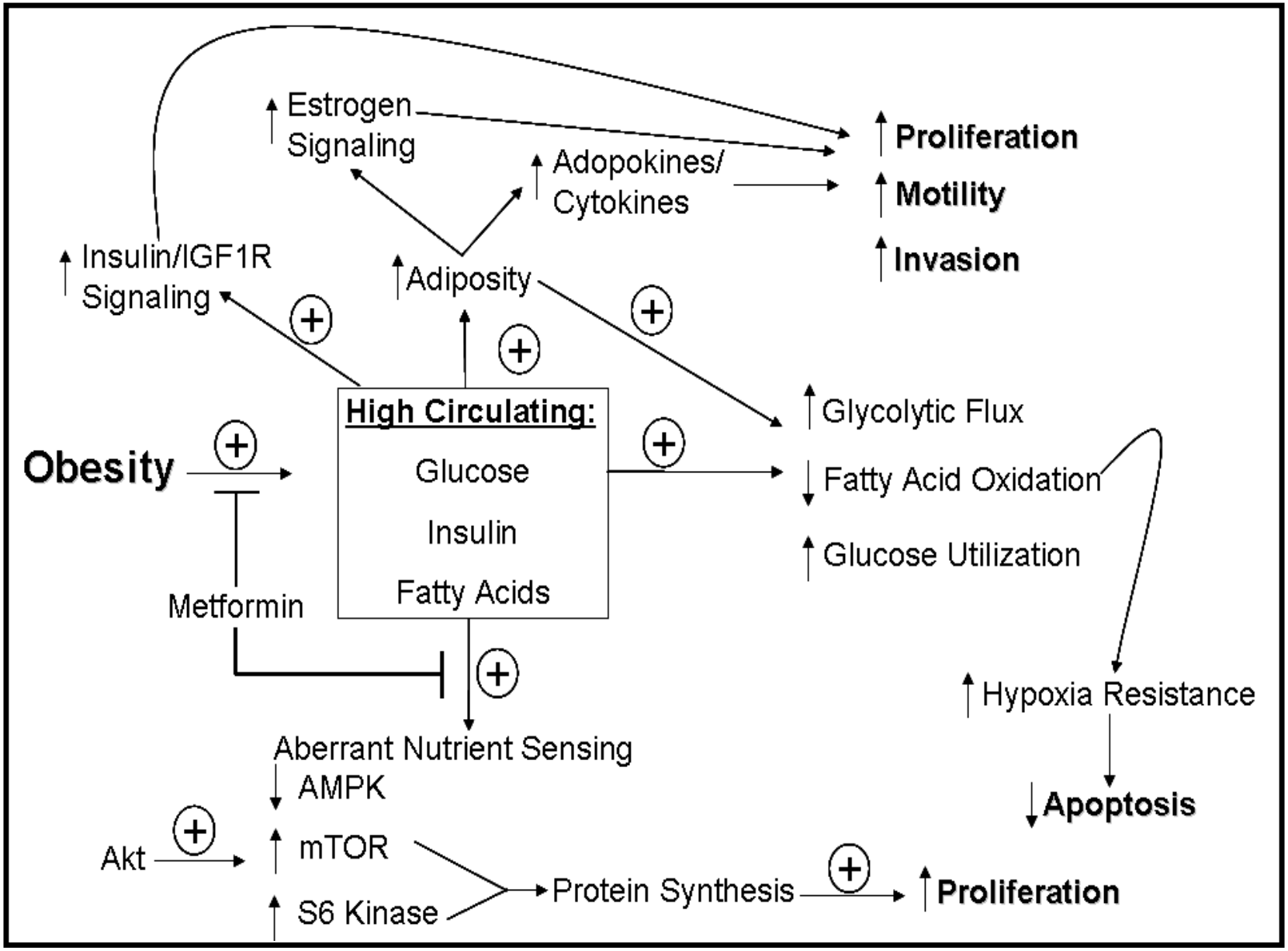


Cancer Cell 13: 2008

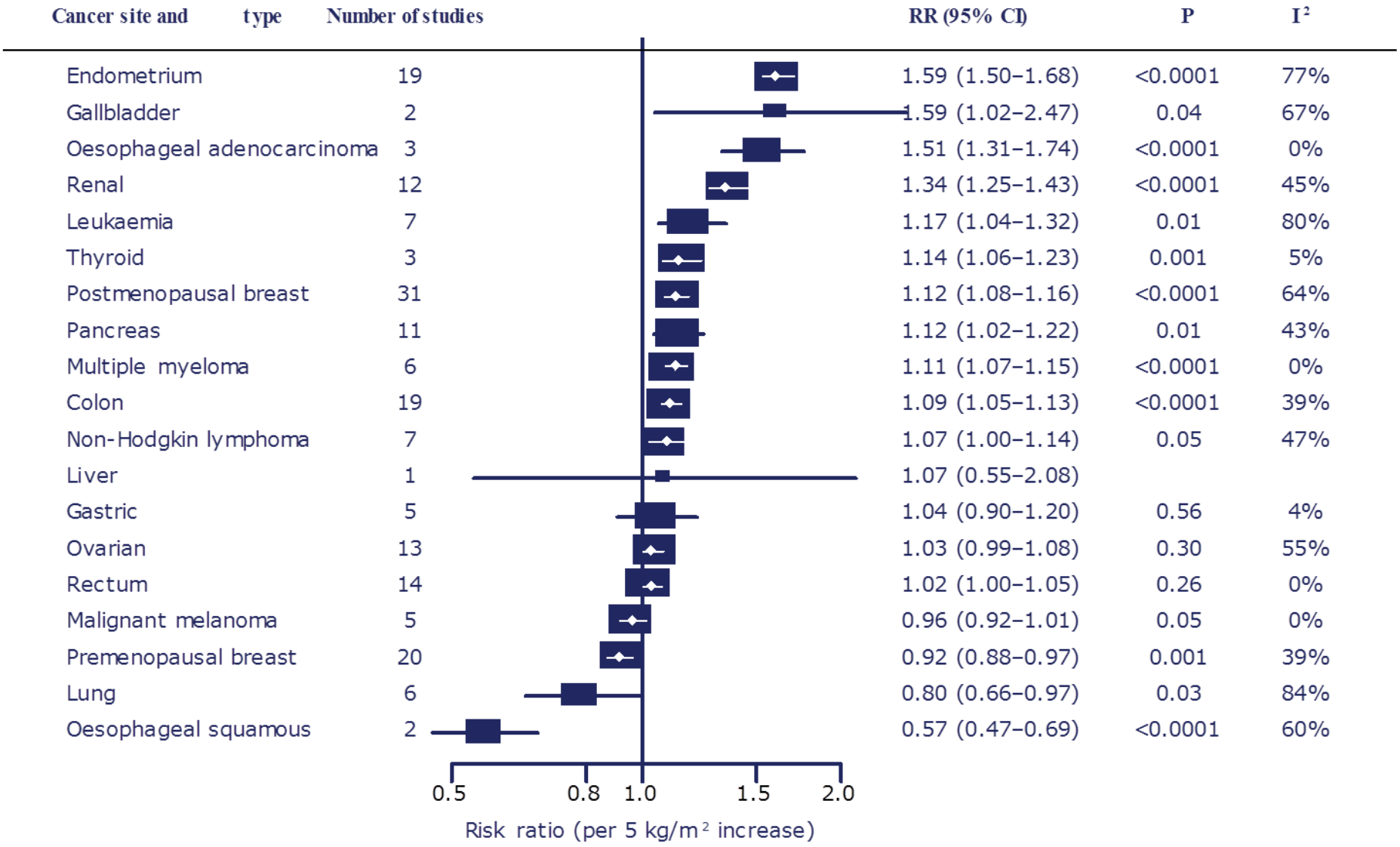
Prevalence[1] of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2017



*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.


↑ Estrogen Signaling
↑ Adopokines/ Cytokines
↑ Proliferation
↑ Motility
↑ Invasion
↑ Insulin/IGF1R Signaling
↑ Adiposity
High Circulating:
Glucose
Insulin
Fatty Acids
Obesity
Metformin
↑ Glycolytic Flux
↓ Fatty Acid Oxidation
↑ Glucose Utilization
↑ Hypoxia Resistance
↓ Apoptosis
Aberrant Nutrient Sensing
↓ AMPK
Akt
↑ mTOR
↑ S6 Kinase
Protein Synthesis
↑ Proliferation

BMI and Cancer Risk: Women



Renehan et al. Lancet 2008;371:569–78

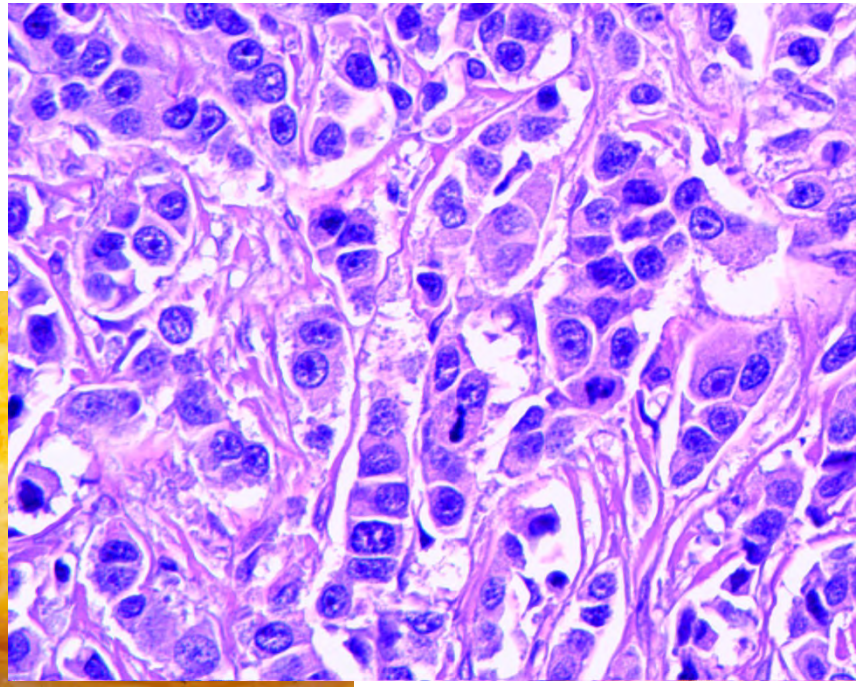
Obesity: an Independent Risk Factor for Breast Cancer

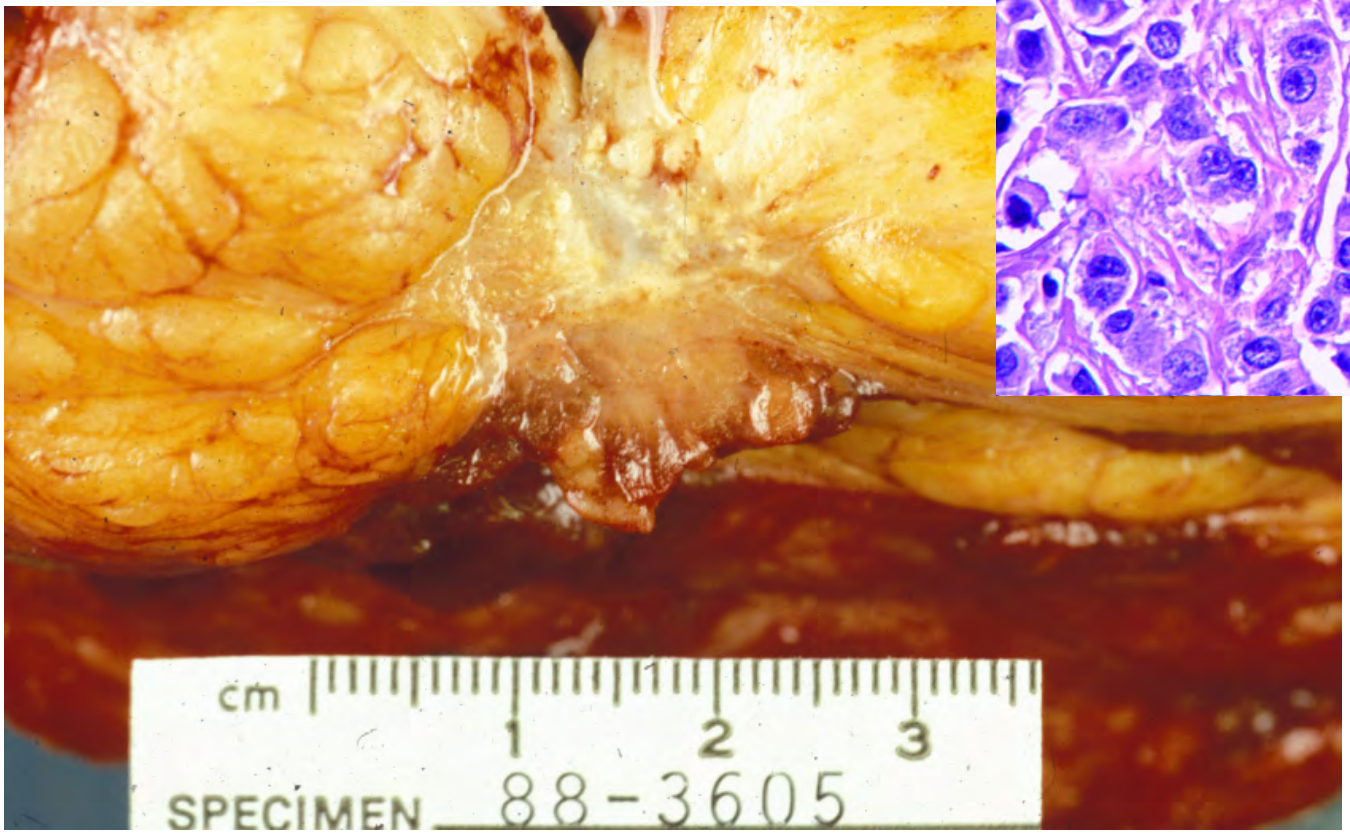
- **The magnitude of risk for obese patients is at least 2 fold…..**
- **In post-menopausal obese women, estrogen levels are increased 50-100 %**
- **Obesity is associated with suppressed fatty acid oxidation, making cells more dependent on glucose and promoting aerobic glycolytic capacity…*The Warburg Effect***
- **Increases with BMI (3% per 1 kg/m^2) post menopausal ER+, PR+ CA**
- **More profound in patients with a strong family history (5-10 fold)**

Breast Cancer and Obesity

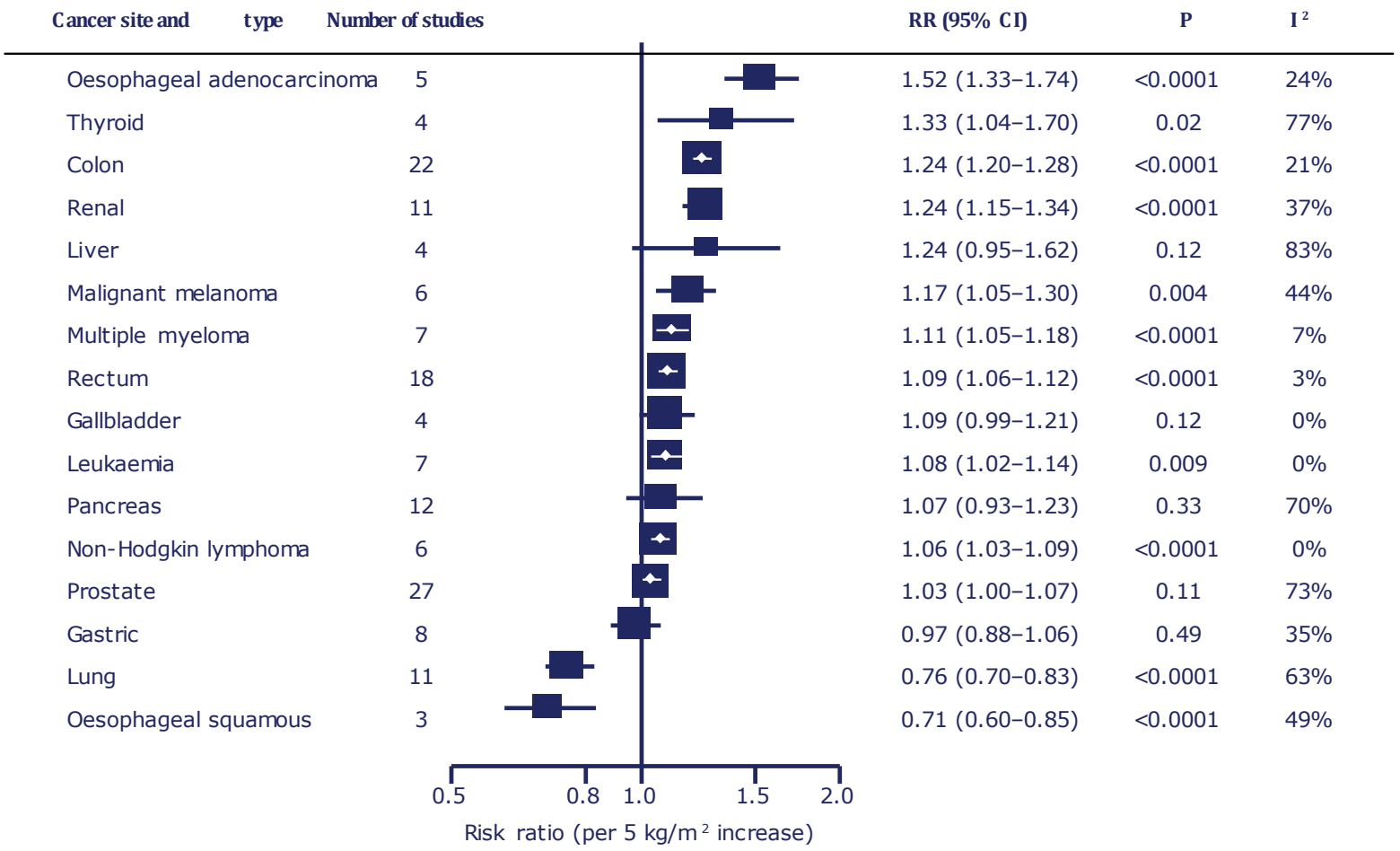
Post-menopausal Caucasian

Pre-menopausal Latino and AA





BMI and CANCER RISK: MEN



Renehan et al. Lancet 2008;371:569–78

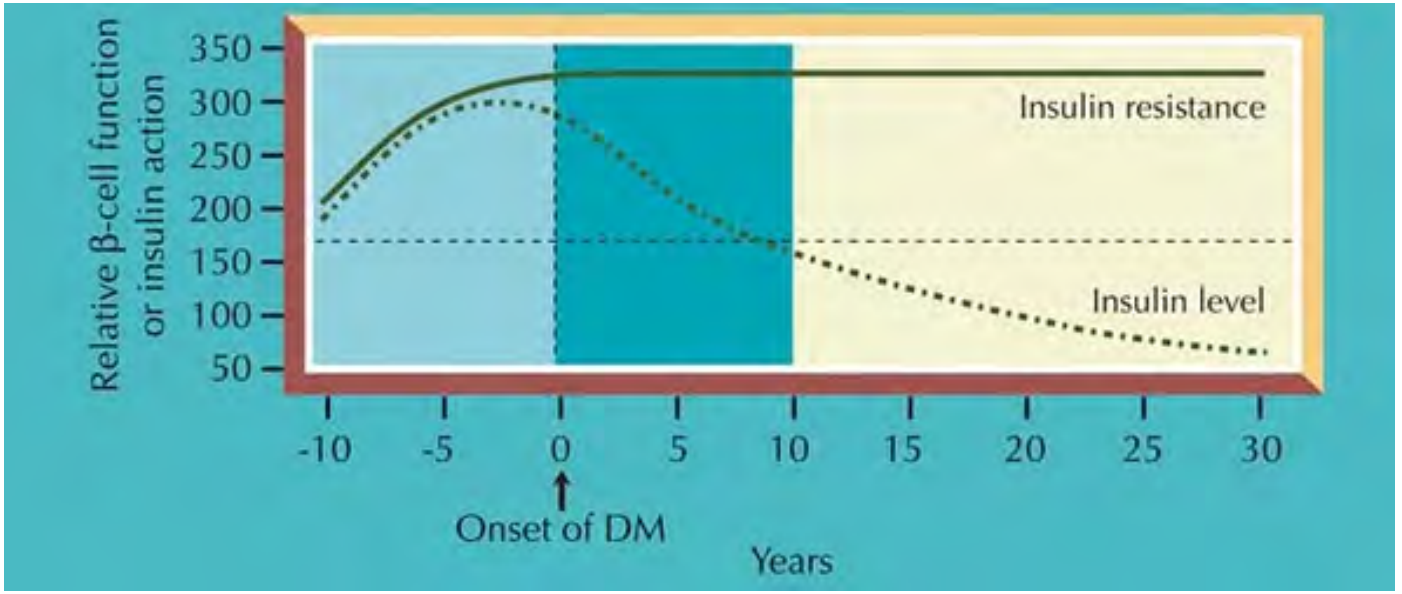
Diabetes and Cancer

"It would appear that either diabetics tend to develop cancer or that cancer patients tend to develop symptoms recognised as diabetic"

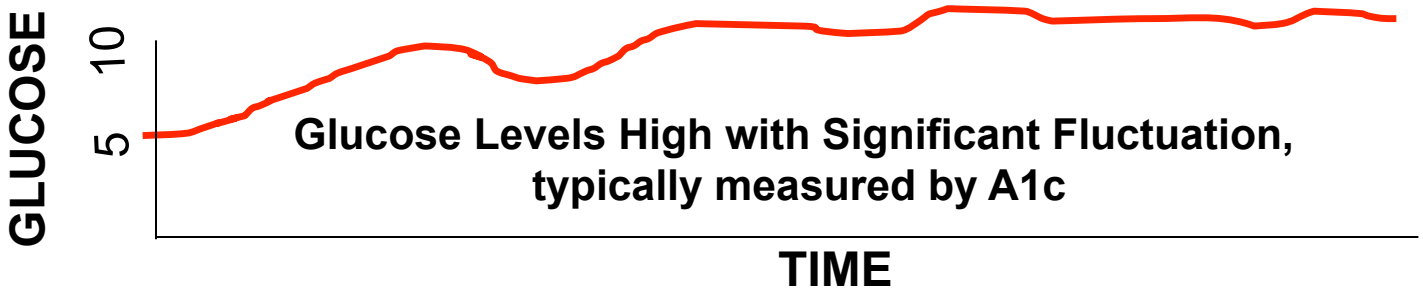
- Wilson and Maher Am J Cancer 1932

Insulin and Glucose Dysregulation with Type 2 Diabetes

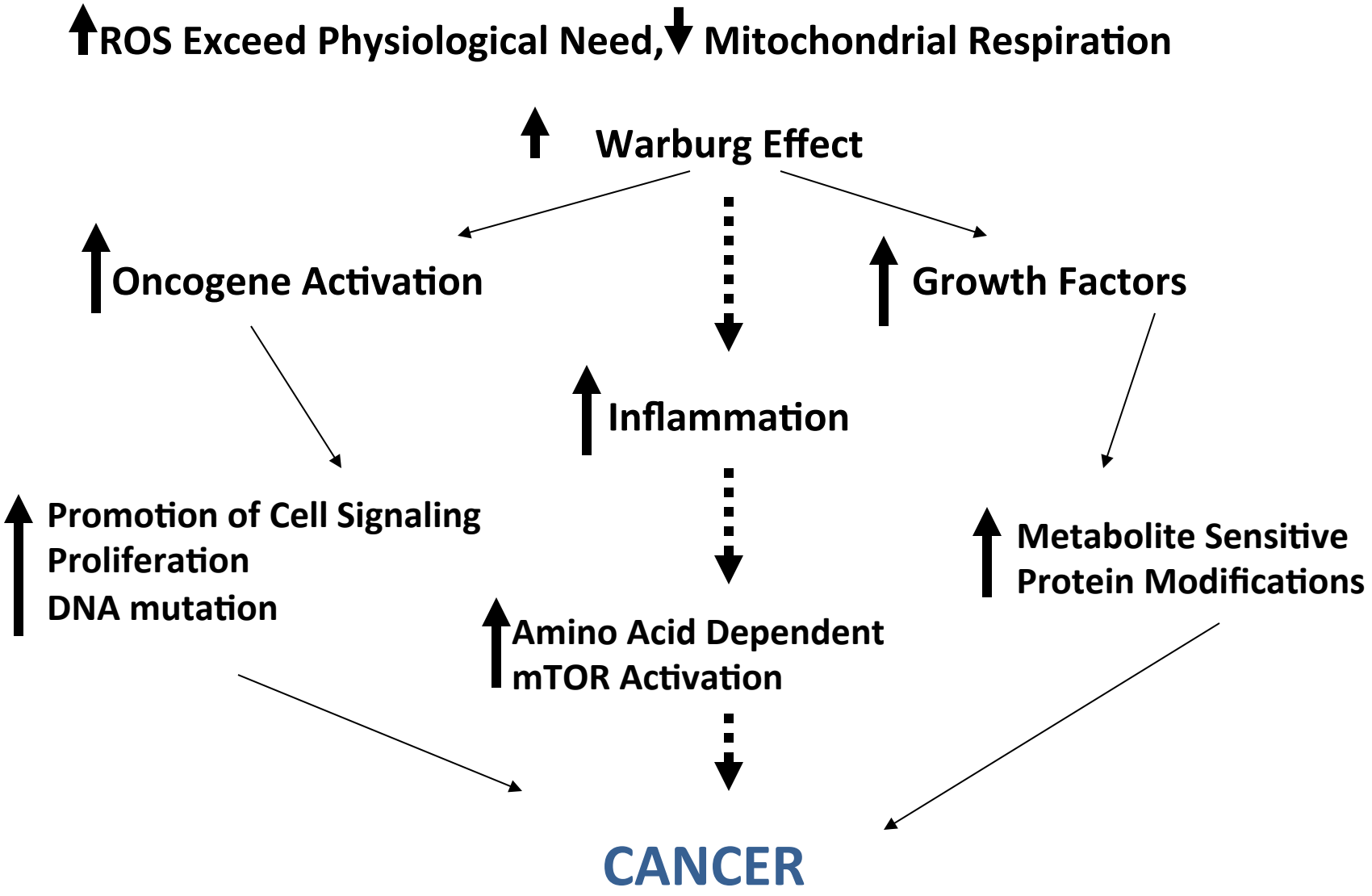
A. Insulin rises over years, then declines with prolonged resistance



B. Glucose fluctuates over years



Nutritional Stress and Cancer



Review: Wellen and Thompson, Mol Cell 40, 2010

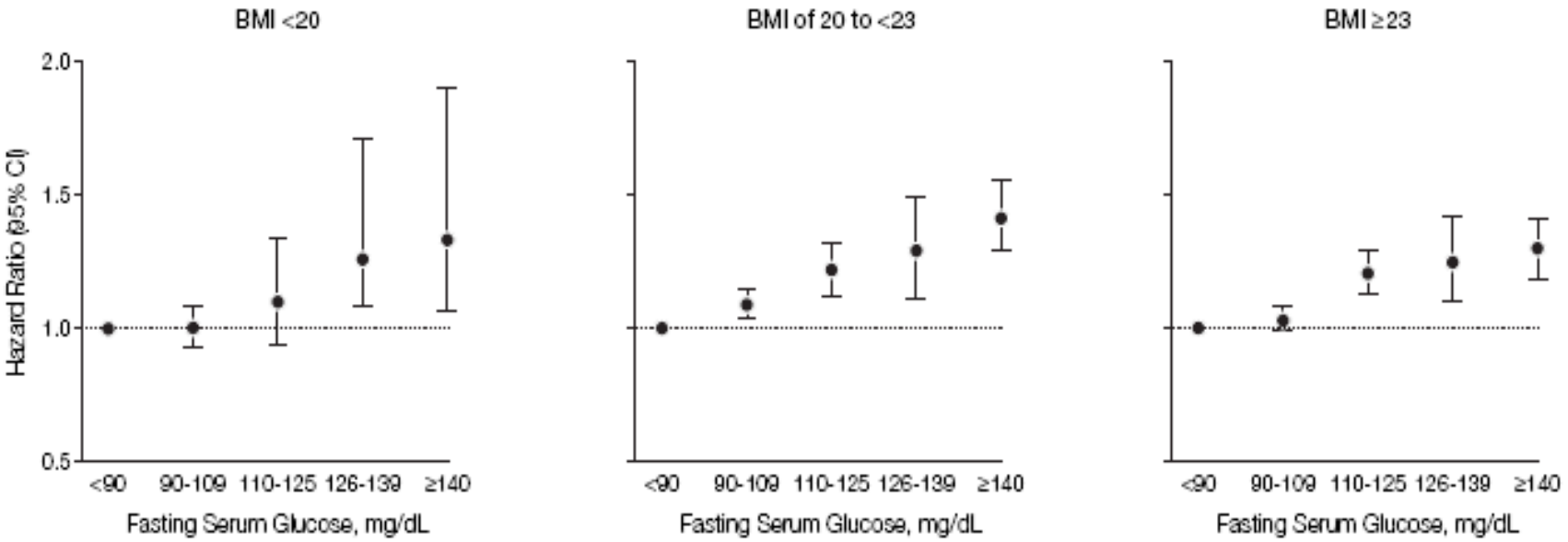
Diabetes and Cancer Incidence

Cancer		RR (95% CI)
Liver (El-Serag *et al.* 2006)	13 case–control studies	2.50 (1.8–3.5)
	7 cohort studies	2.51 (1.9–3.2)
Pancreas (Huxley *et al.* 2005)	17 case–control studies	1.94 (1.53–2.46)
	19 cohort studies	1.73 (1.59–1.88)
Kidney[a] (Lindblad *et al.* 1999, Washio *et al.* 2007)	1 cohort study	1.50 (1.30–1.70)
	1 cohort study	2.22 (1.04–4.70)
Endometrium (Friberg *et al.* 2007)	13 case–control studies	2.22 (1.80–2.74)
	3 cohort studies	1.62 (1.21–2.16)
Colon–rectum (Larsson *et al.* 2005)	6 case–control studies	1.36 (1.23–1.50)
	9 cohort studies	1.29 (1.16–1.43)
Bladder (Larsson *et al.* 2006)	7 case–control studies	1.37 (1.04–1.80)
	3 cohort studies	1.43 (1.18–1.74)
Non-Hodgkin's lymphoma (Mitri *et al.* 2008)	5 cohort studies	1.41 (1.07–1.88)
	11 case–control studies	1.12 (0.95–1.31)
Breast (Larsson *et al.* 2007)	5 case–control studies	1.18 (1.05–1.32)
	15 cohort studies	1.20 (1.11–1.30)
Prostate (Kasper & Giovannucci 2006)	9 case–control studies	0.89 (0.72–1.11)
	10 cohort studies	0.81 (0.71–0.92)

Vigneri et al., Endocrine-Related Cancer 2009; 16 1103–1123

Hyperglycemia and Cancer Mortality

Figure 2. Hazard Ratios for All Cancer Deaths by Fasting Serum Glucose Levels in Korean Men by BMI, 1993-2002

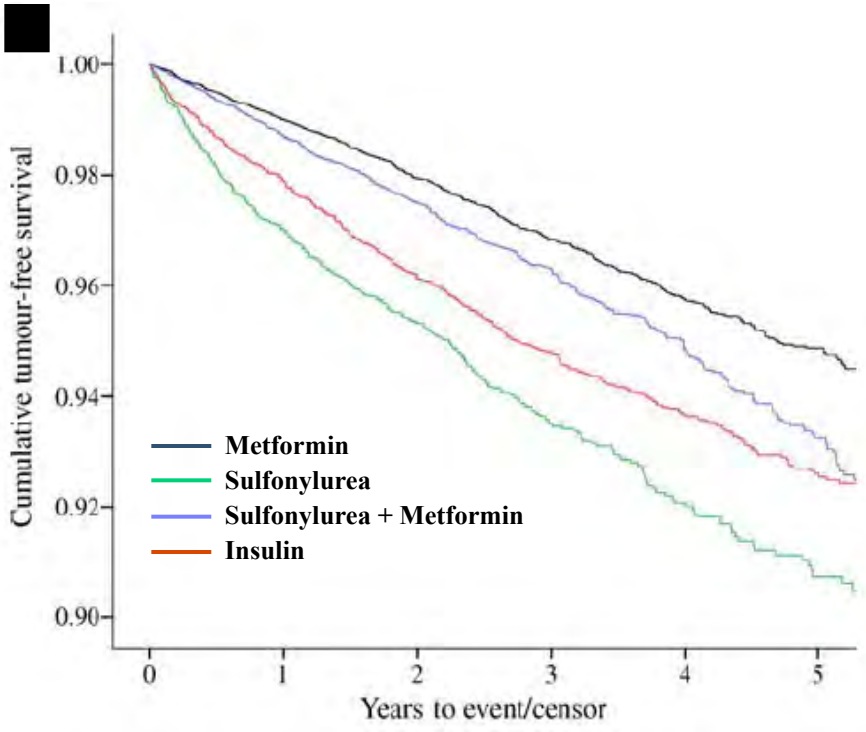


Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. CI indicates confidence interval.

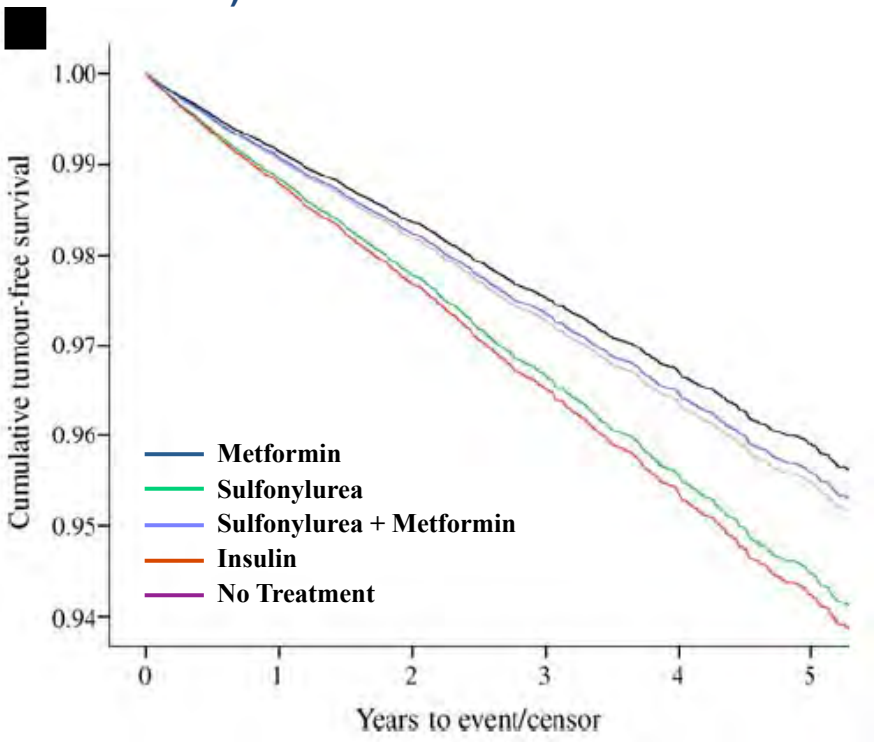
Jee et al. JAMA. 2005;293:194-202

Cancer Risk by Diabetes Treatment over Time

Unadjusted



Adjusted for Confounding Factors (age, sex, smoking status, prior cancer)



Currie et al. Diabetologia 2009; 52:1766-1777

Diabetes and Cancer Prognosis

Table 3. Pooled Hazard Ratios of Long-term, All-Cause Mortality in Cancer Patients With and Without Preexisting Diabetes Mellitus in Selected Cancer Sites

Cancer Site	Studies (Estimates), No.	Total Patients, No.	Patients With Diabetes, No.	Pooled HR (95% CI)[a]	I^2, %
Endometrial	4 (4)[40,42,46,48]	2900	429	1.76 (1.34-2.31)	44.3
Breast	4 (4)[40,41,43,45]	13 019	1107[b]	1.61 (1.46-1.78)	0
Prostate	3 (3)[37,40,47]	6264	555[b]	1.51 (0.94-2.43)	47.1
Gastric	3 (3)[37,40,50]	6200	687[b]	1.36 (0.92-2.01)	83.6
Colorectal	6 (7)[33,34,36,37,39,40]	54 740	8028[b]	1.32 (1.24-1.41)	52.4
Hepatocellular	3 (5)[30,37,44]	3724	848[b]	1.30 (0.99-1.70)	68.9
Lung	4 (5)[29,37,38,40]	11 109	989[c]	1.15 (0.99-1.34)	47.7
Pancreas	4 (4)[28,37,40,49]	1681	477[b]	1.09 (0.70-1.69)	73.4

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Estimates calculated using a random-effects model.
[b] Number is extrapolated because 1 study did not report prevalence of diabetes.
[c] Number is extrapolated because 2 studies did not report prevalence of diabetes.

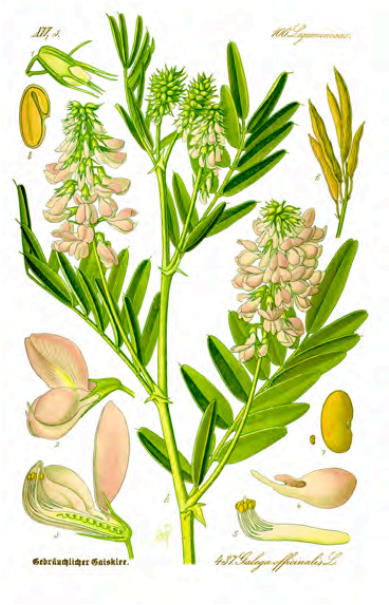
Barone et al. JAMA. 2008;300(23):2754-2764

Lipid Dysregulation Promotes CA

- High cholesterol and lipid dysregulation are associated with a significant and independent risk of cancer, poor outcomes and treatment resistance

- Two patterns of breast CA risk with lipid dysregulation
  - Premenopausal, TNBC, minority women
  - Post menopausal, ER+, PR+, HER2- in Caucasians

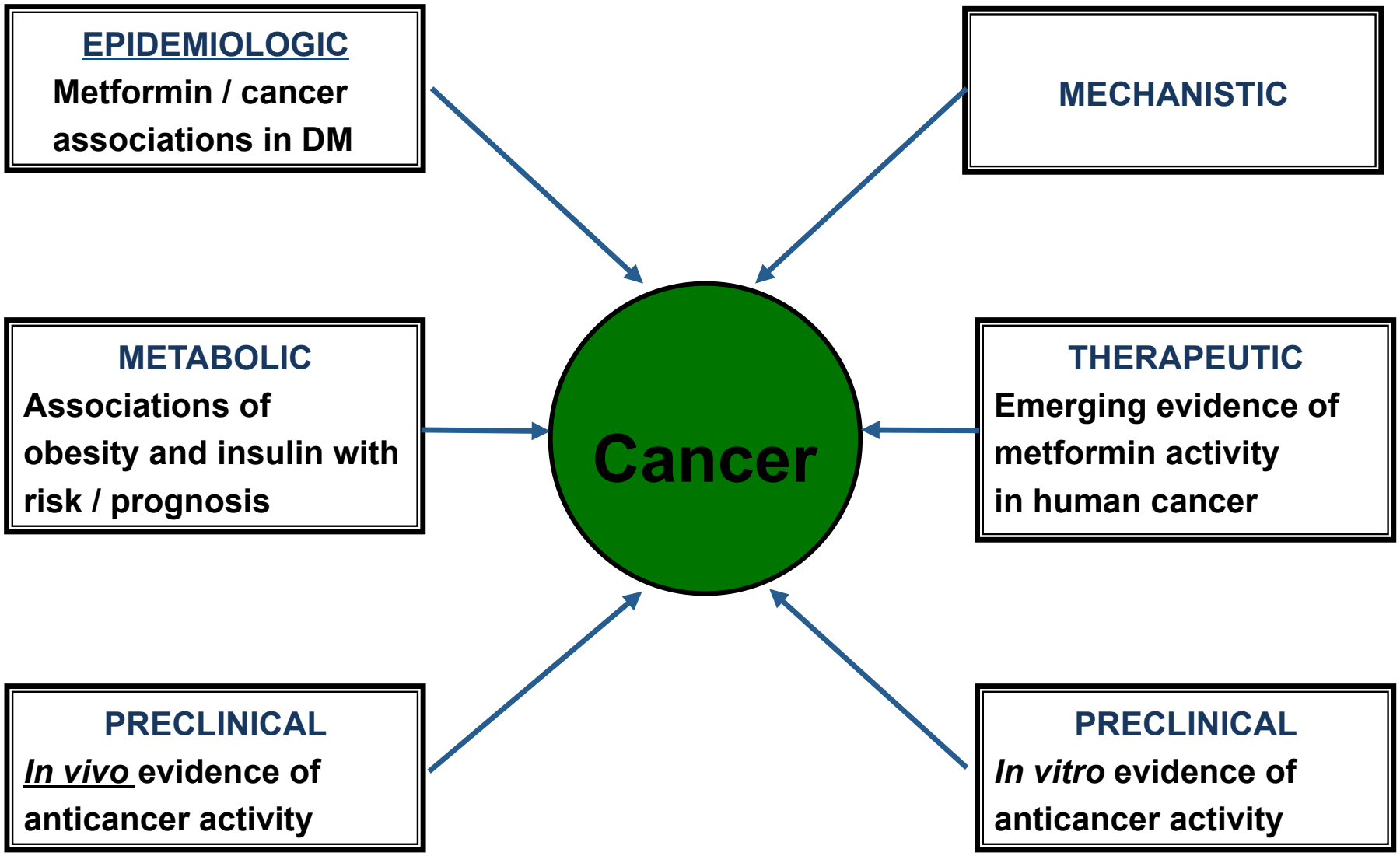
Metformin (Glucophage-Aventis)



Galega officinalis
(Goat's rue, French lilac)

- **The most commonly drug used worldwide to treat type II and pre-diabetic syndromes**
- **Oral, low cost agent**
- **Significant anti-cancer activity**
- **Extremely low toxicity**

Evidence of Metformin's Anti-Cancer Activity



Not seen with other anti-diabetic agents !

Reduction of Incidence of CA with Metformin

Epithelial Derived Cancers

Breast
Prostate
Head and Neck
Colon
Pancreas
Ovary
Endometrium
Liver
Lung
Brain

Soft Tissue and Bone

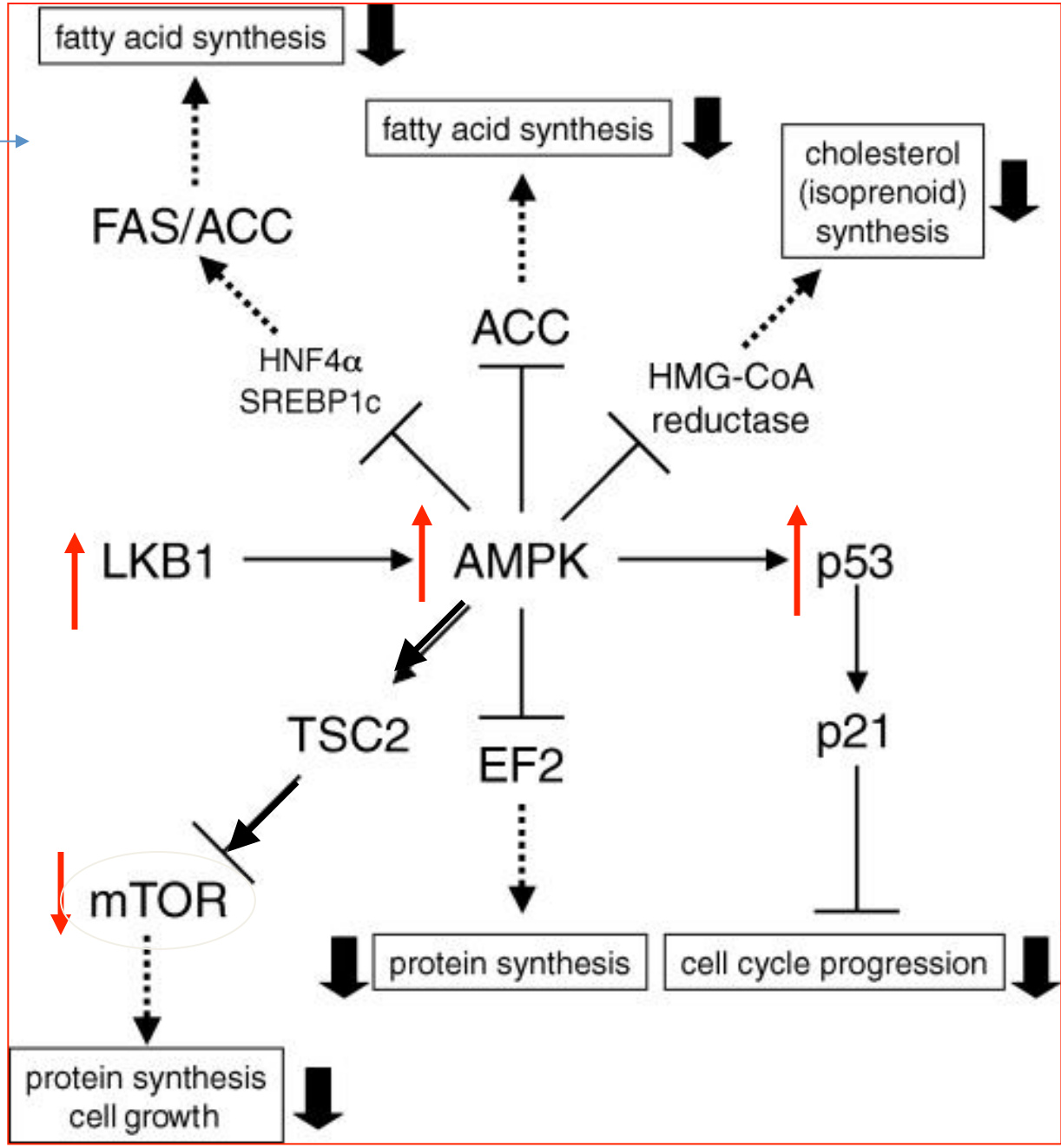
Fibrosarcoma
Osteosarcoma

**** 125 Clinical trials listed with metformin and CA on ClinicalTrials.gov**

IB Sahra et al. Metformin in Cancer Therapy, *Mol Cancer Ther* 9:2010
Del Barco S et al. Metformin: Multi-faceted Protection Against Cancer *Oncotarget* 2: 2011
Kasznicki J et al. Metformin in Cancer Prevention and Therapy, *Ann Transl Med* 2: 2014

Metformin

- **Inhibition of Mitochondrial Complex I**
- **Hepatic gluconeogenesis**
- **Glucose production by liver**
- **Glucose uptake and transport by periphery**



Owen MR et al, Biochem, 2000

Metformin Has Complex Effects *In Vitro* and *In Vivo*

↑ Cell cycle arrest
↓ Cell growth
↓ Protein production (cap dependent translation)
↓ Carcinogen induced transformation
↓ Glycolysis
↑ Glucose transport
↑ Mitochondrial respiration, decrease ROS
↓ Clonogenicity
↓ Fatty acid synthetase (FAS)
↓ Stem cell growth
↑ Apoptosis
↑ Autophagy in p53 competent cells

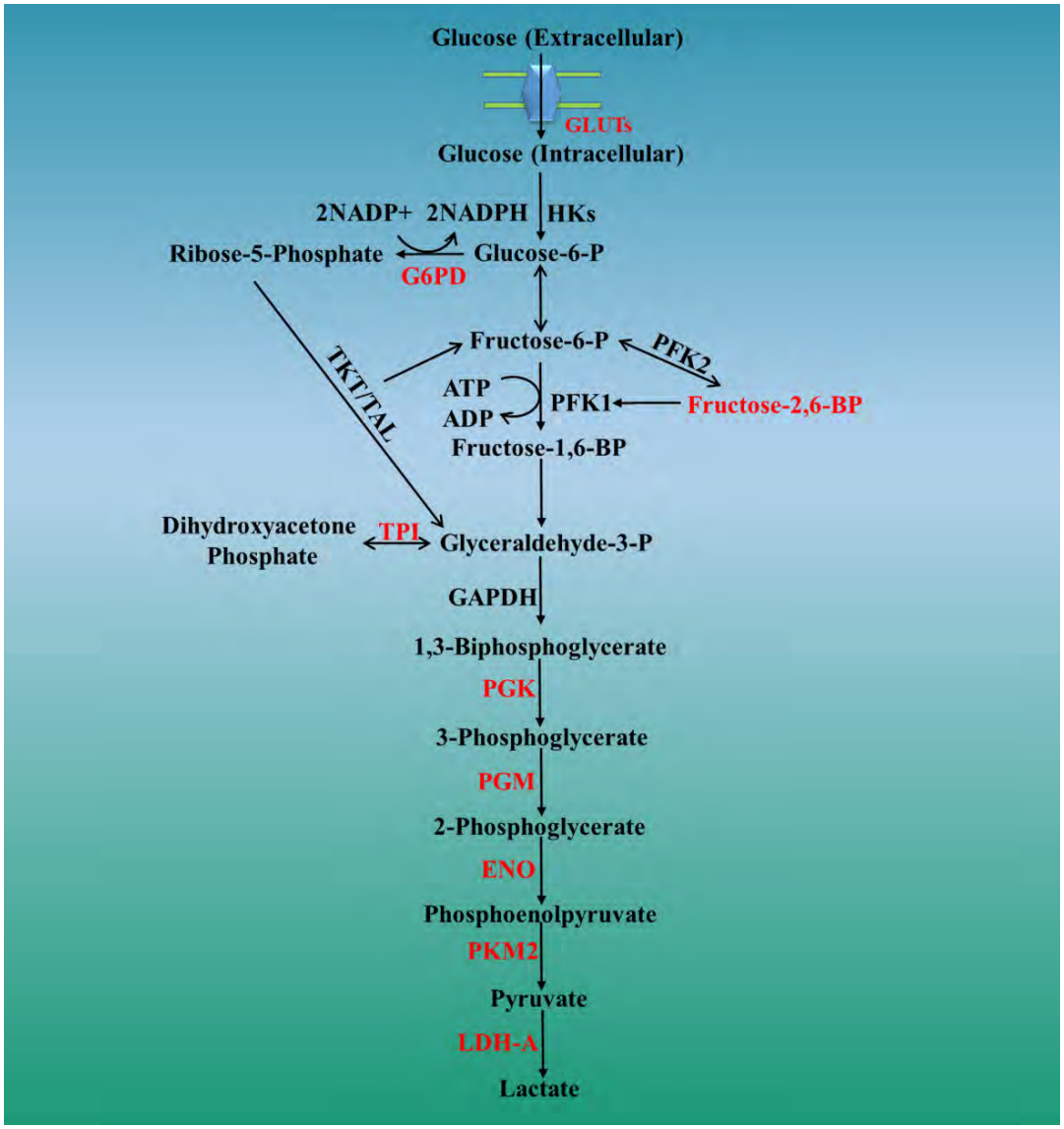
? Angiogenesis

Metformin Acts to Normalize Glucose Metabolism in Cancer

- **Downregulation of Glucose Transport Proteins (Gluts 1, 10, 12, 14)**
- **Downregulation of glucose-6-phosphate transporter, triose phosphate isomerase and 18 other key genes in glucose metabolism**
- **Downregulation of lactose dehydrogenase (LDH), which is a key enzyme catalyzing conversion of pyruvate to lactate.**

Wahdan-Alaswad RS, Edgerton SM, Salem HS, Thor AD. Metformin Targets Glucose Metabolism in Triple Negative Breast Cancer, *J Oncol Transl Res* 4: 129. 2018

Metformin Broadly Inhibits Glycolysis



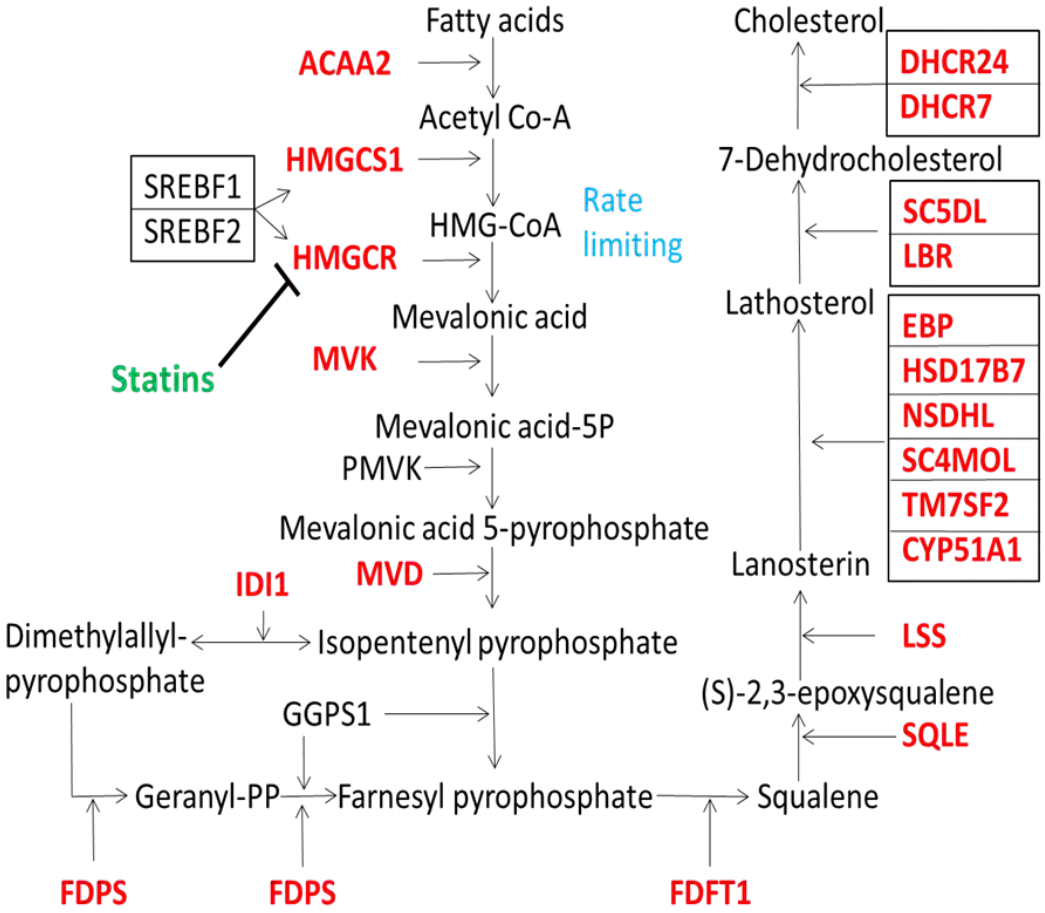
J Oncol Transl Res 4: 129. 2018

Metformin Targets Aberrant Lipid Metabolism in CA: FASN in TNBC

- FASN critical step in fatty acid synthesis.
- FASN one of most downregulated genes in TNBC Rx metformin
- Hypothesis: FASN downregulation facilitates metformin-induced apoptosis.
- Results: Metformin induction of cell death, proliferation and inhibition of stemness mediated by reduction of fatty acid synthase (FASN) via miRNA-193b

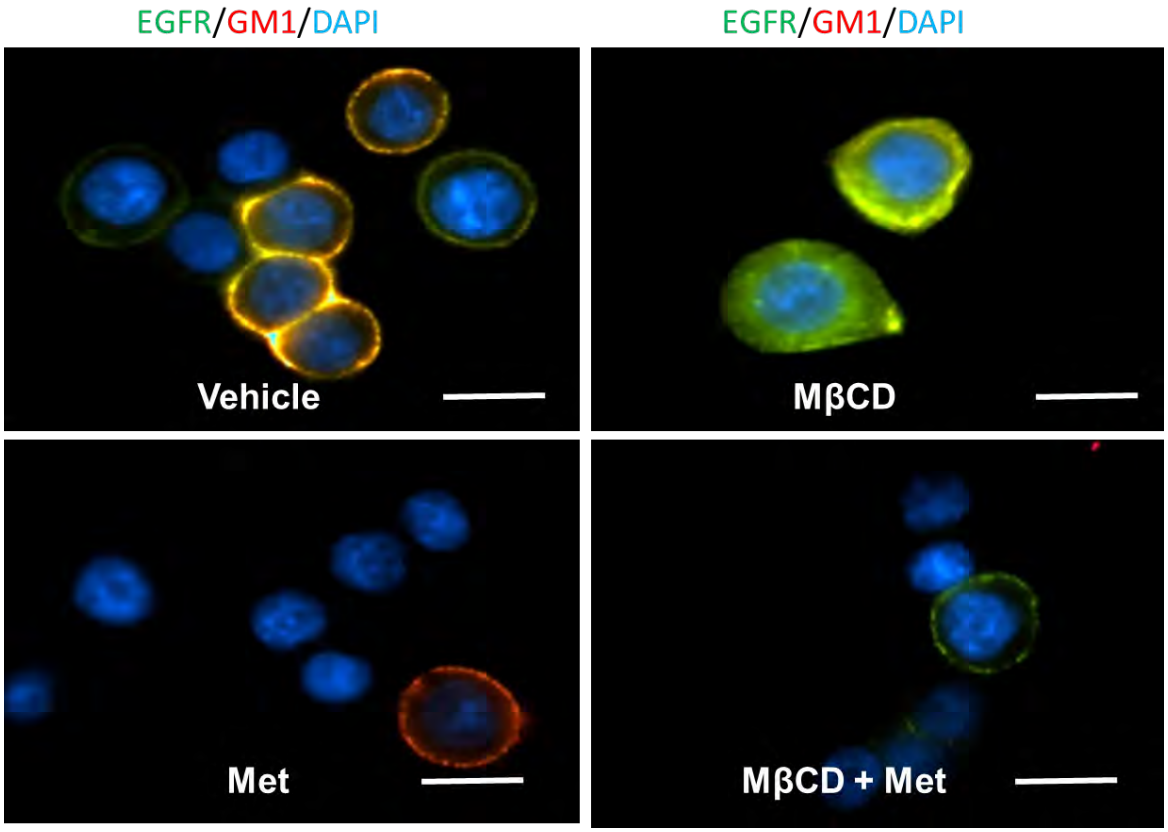
Wahdan-Alaswad RS, Cochrane DR, Spoelstra NS, Howe EN, Edgerton SM, Anderson SM, Thor AD and Richer JK. Metformin-Induced Killing of Triple Negative Breast Cancer Cells is Mediated by Reduction in Fatty Acid Synthase via miRNA-193b ***Hormones and Cancer.*** **5:374-89, 2014**

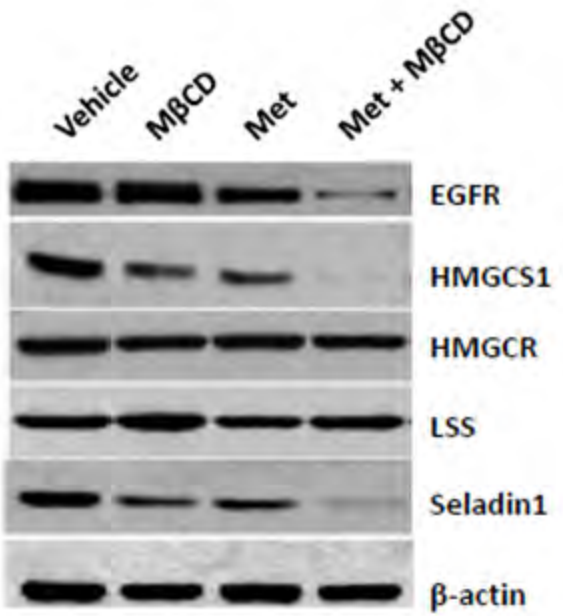
Cholesterol Biosynthesis Targeted by Metformin in TNBC



Wahdan- Alaswad et al., Cancer Therapy and Oncology 2018

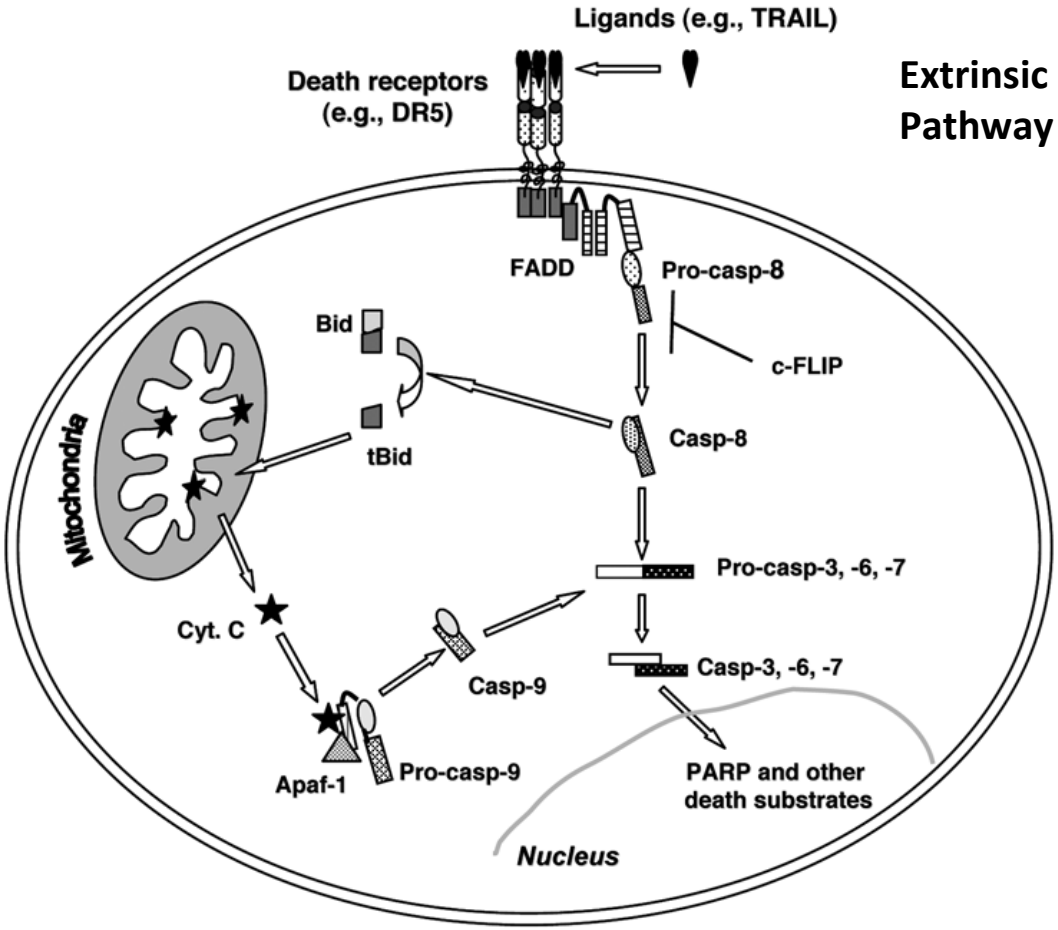
Metformin Downregulates EGFR and Lipid Raft Stabilization: Enhancing Sensitivity to Tyrosine Kinase Inhibitors





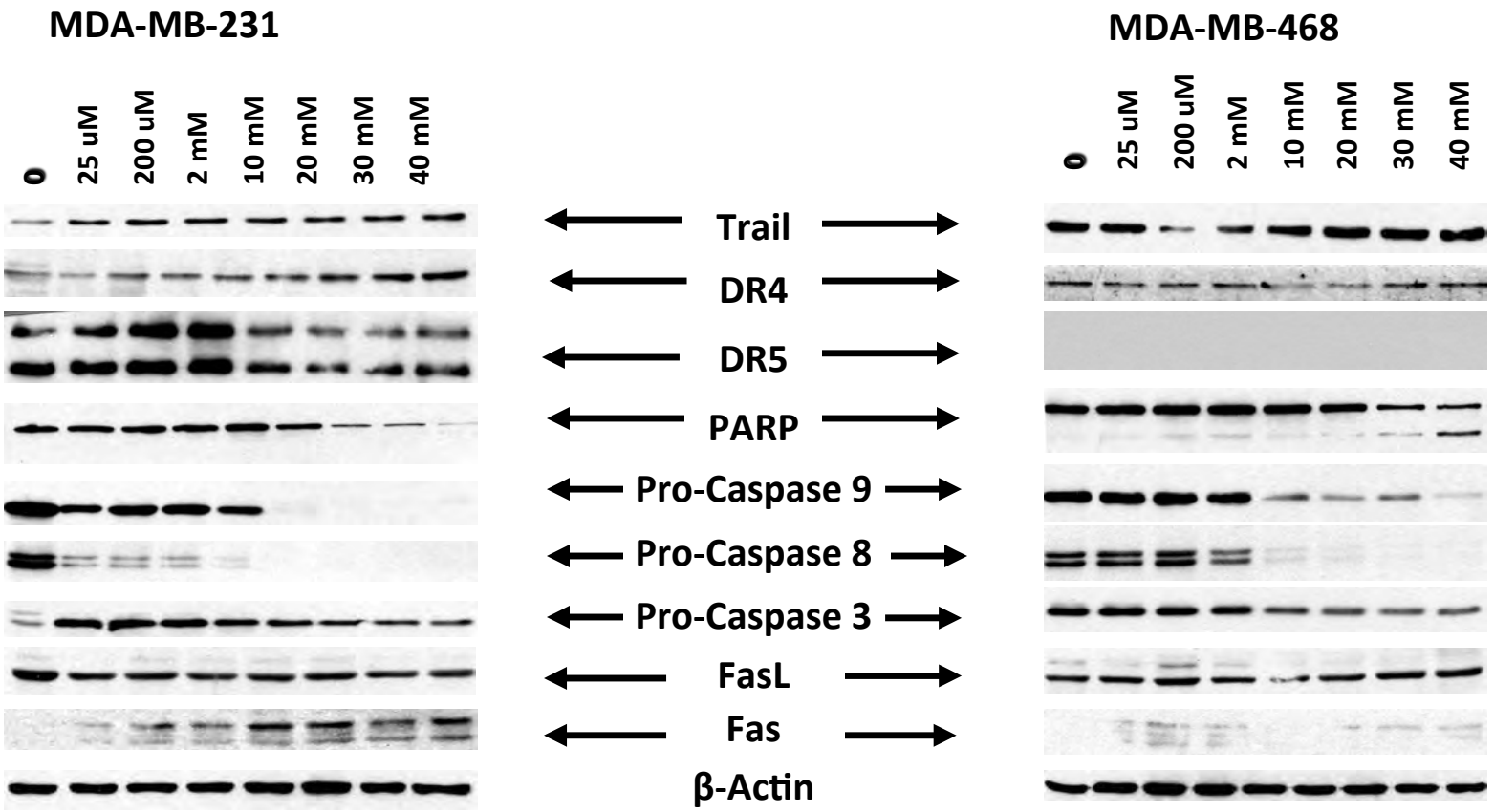
Wahdan-Alaswad RS, Edgerton SM, Salem HS, Thor AD. Metformin targets cholesterol biosynthesis pathway, GM1 lipid raft stabilization, EGFR signaling and proliferation in triple negative breast cancers. Can Therapy Oncol Int J 9:555765 2018

Intrinsic and Extrinsic Pathways of Apoptosis via the Death Receptor TRAIL



Elrod et al., Cancer Biology & Therapy 7: 163

Metformin Induces Cell Death via Intrinsic and Extrinsic Pathways of Apoptosis

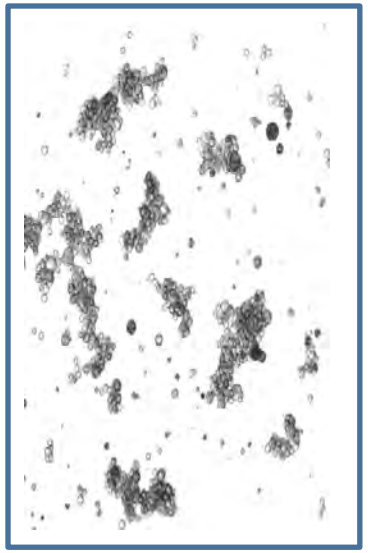


Liu B, Fan Z, Edgerton SM, Deng X-S, Alimova IN, Lind SE, Thor AD. Metformin induces unique biological and molecular responses in triple negative breast cancer cells. *Cell Cycle*, 8:2031-40, 2009

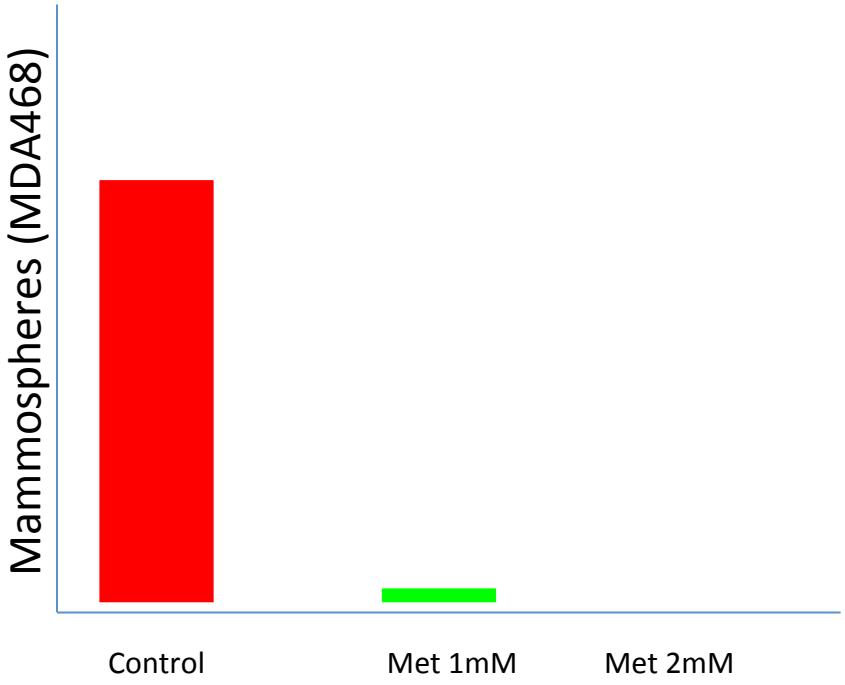
Metformin Targets Stem Cells

- **Metformin selectively kills cancer stem cells/mammospheres**

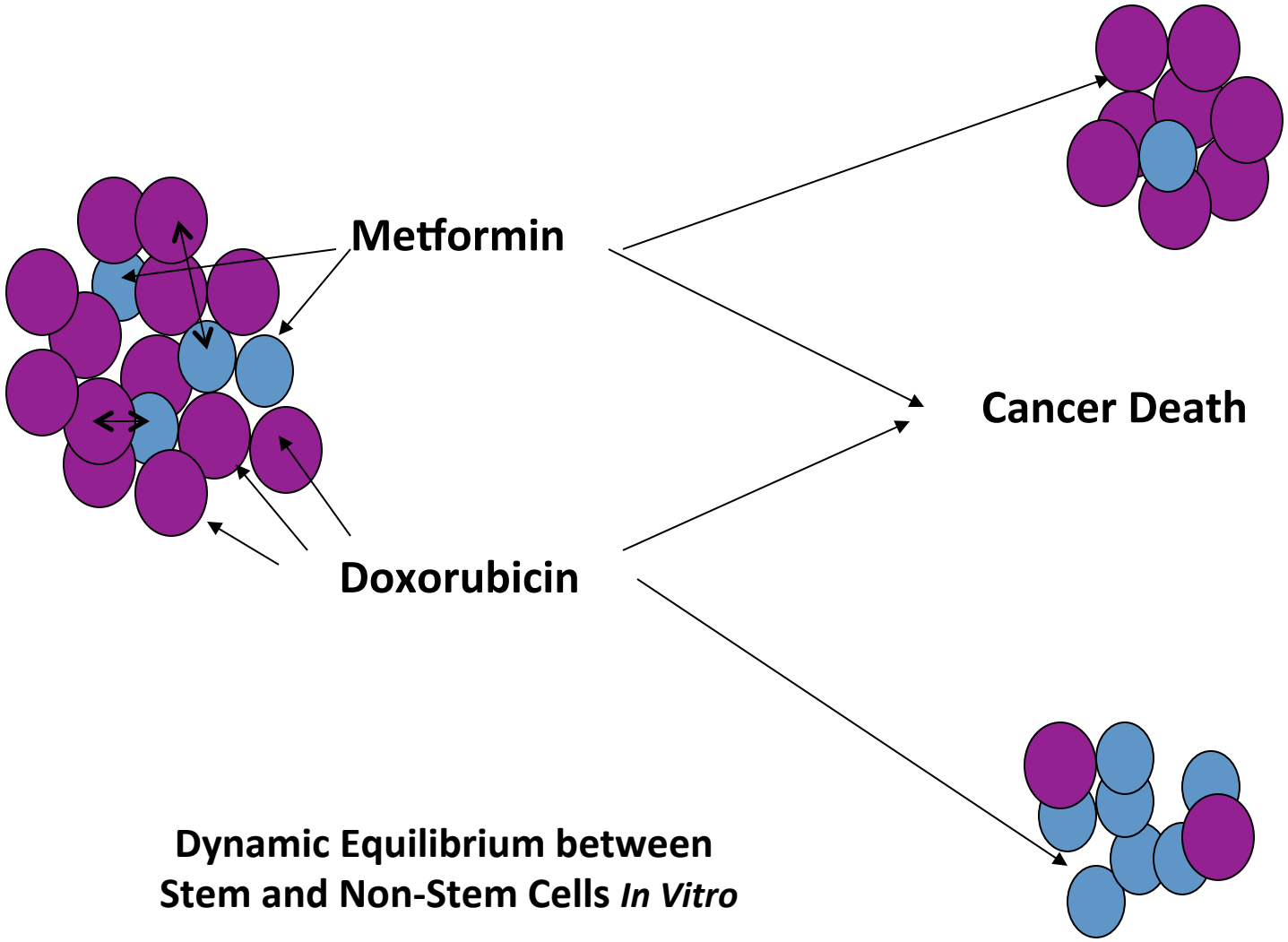
Control
MDA-468



Metformin (1mM)
MDA-468



Metformin Provides Improved Survival if Combined with Chemo



Dynamic Equilibrium between Stem and Non-Stem Cells *In Vitro*

Metformin Inhibits Cancer Motility and Metastasis

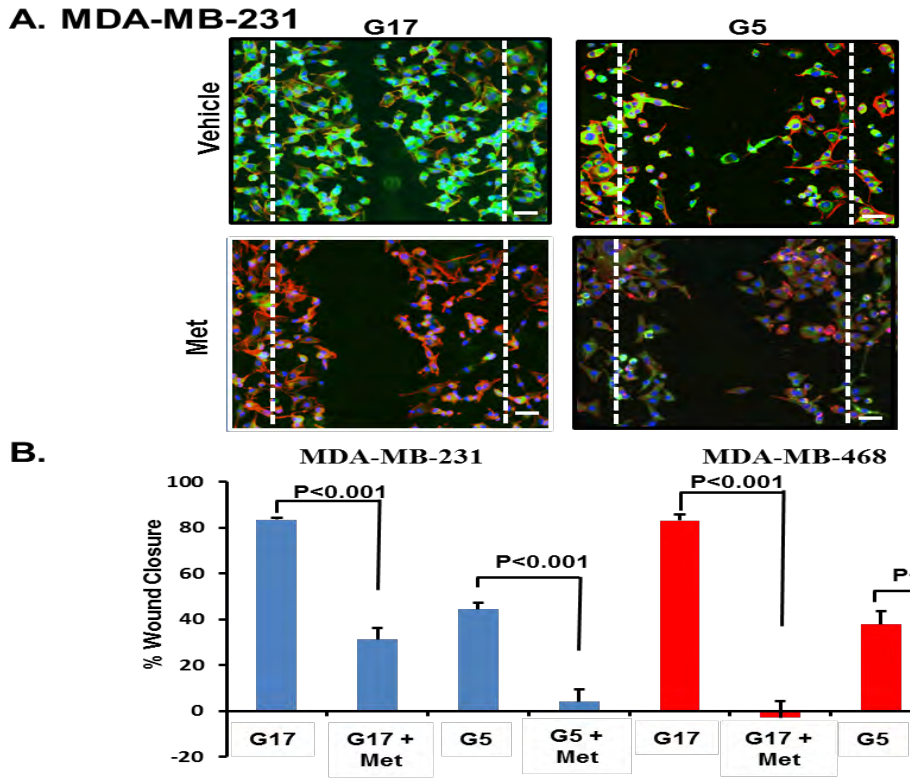
Moesin: Membrane Organizing Extension Spike Protein

- Cross links plasma membranes and actin-based cytoskeleton
- Interacts with CD43, ICAM3, NCF 1,NCF4, VCAM-1, EZR
- Downregulated at least 2 fold in TNBC with Metformin

Moesin and Breast Cancer Cell Motility

Wahdan-Alaswad R….Thor AD. *Cell Cycle* 12:3759-69, 2013.

Figure 4



A. and B. Wound Closure Associated Cell Motility Assay

Moesin Green
F-Actin Red
DAPI Blue

C. High Glucose Drives Co-localization of F-Actin and Moesin in filopodial extensions, Enhancing TNBC Motility

Metformin inhibits Moesin, Actin reassembly and motility

Summary: Metformin

- Metformin has shown potent anti- cancer activity in clinical, preclinical and epidemiologic studies.
- Its effects extend beyond patients with metabolic disease, obesity or diabetes. The potent anti-cancer action likely reflects critical defects in cellular biology of cancer cells, for example, the Warberg effect.
- Metformin can have very different and widespread anti-growth and death inducing effects on molecular subtypes, and subtypes of subtypes of cancer. In general, it appears most potent against cancers that are highly aggressive and more stem like (EMT).
- Metformin's anti-stem activity may be particularly important for reducing dormancy, that promotes recurrence and treatment resistance.
- Its activity can be modified by the environmental milieu, in including extracellular glucose and ligands that bind to specific membrane receptors or transporters.
- Metformin is a well tolerated, inexpensive oral agent administered worldwide with decades of clinical use.
- ~100 clinical trials underway to test its efficacy against cancer.

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E Giles, Ph.D.
Paul McLean, PhD

C Perou
C Harrell, Ph.D.

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American Cancer Society

Additional References on Metformin from Thor et al

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