# Overview of the Interaction between Obesity, Diabetes and Cancer Therapy

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# Potential Conflicts

Consult with:

- Astrazeneca
- Johnson and Johnson
- Mannkind

# Multistage Carcinogenesis

Targets for Cancer Prevention

Biological Links Between Obesity, T2DM and Cancer

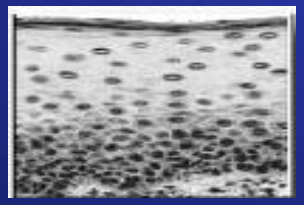
Chemotherapy
Radiation
Surgery

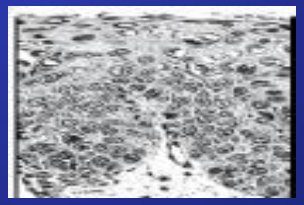
Progression

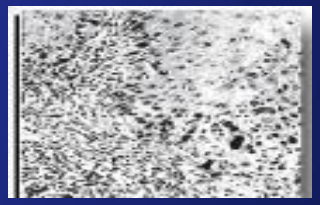
Promotion

Initiation

Normal

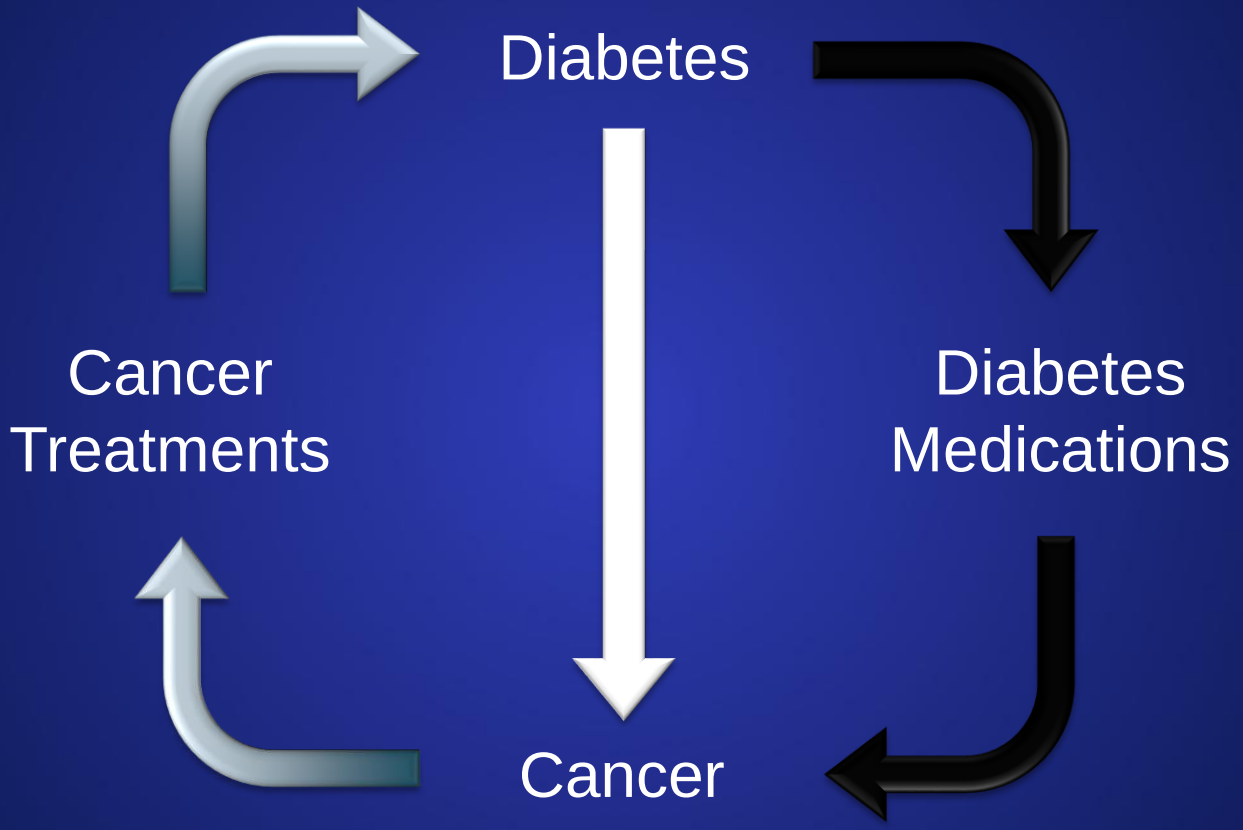






Adapted from Hursting, DiGiovanni, et al. *JNCI*, 1999

# Cancer and Diabetes

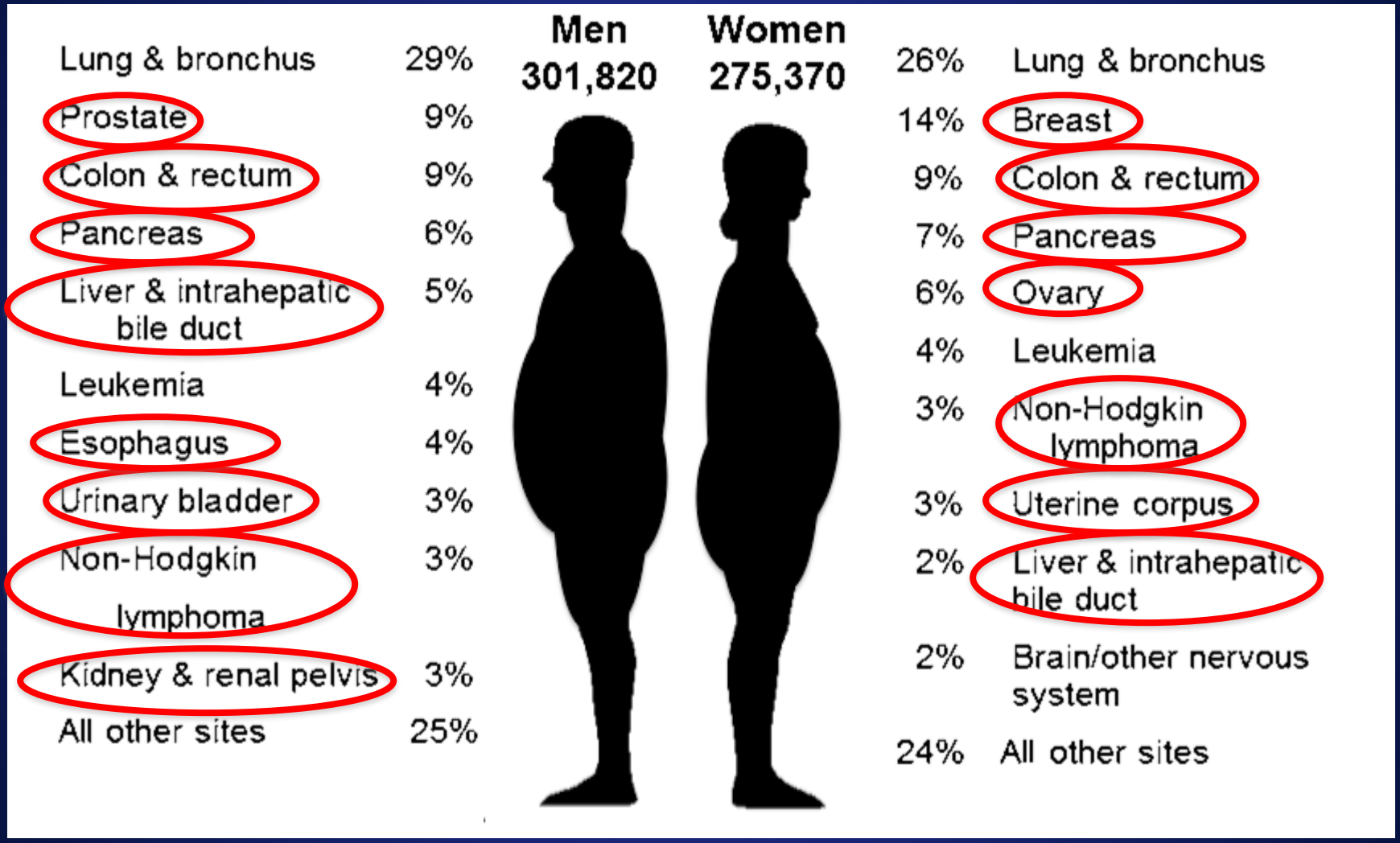


# Outline

- Epidemiology of Diabetes and the increased Cancer risk

- Potential mechanisms explaining this association

# Cancer Deaths Associated with Obesity



# Does Bariatric Surgery Affect Mortality?

## Utah Obesity Surgery Study

- Retrospective cohort study
  - 9949 gastric bypass patients
  - 9628 severely obese driver's license applicants (BMI ≥35 kg/m2)

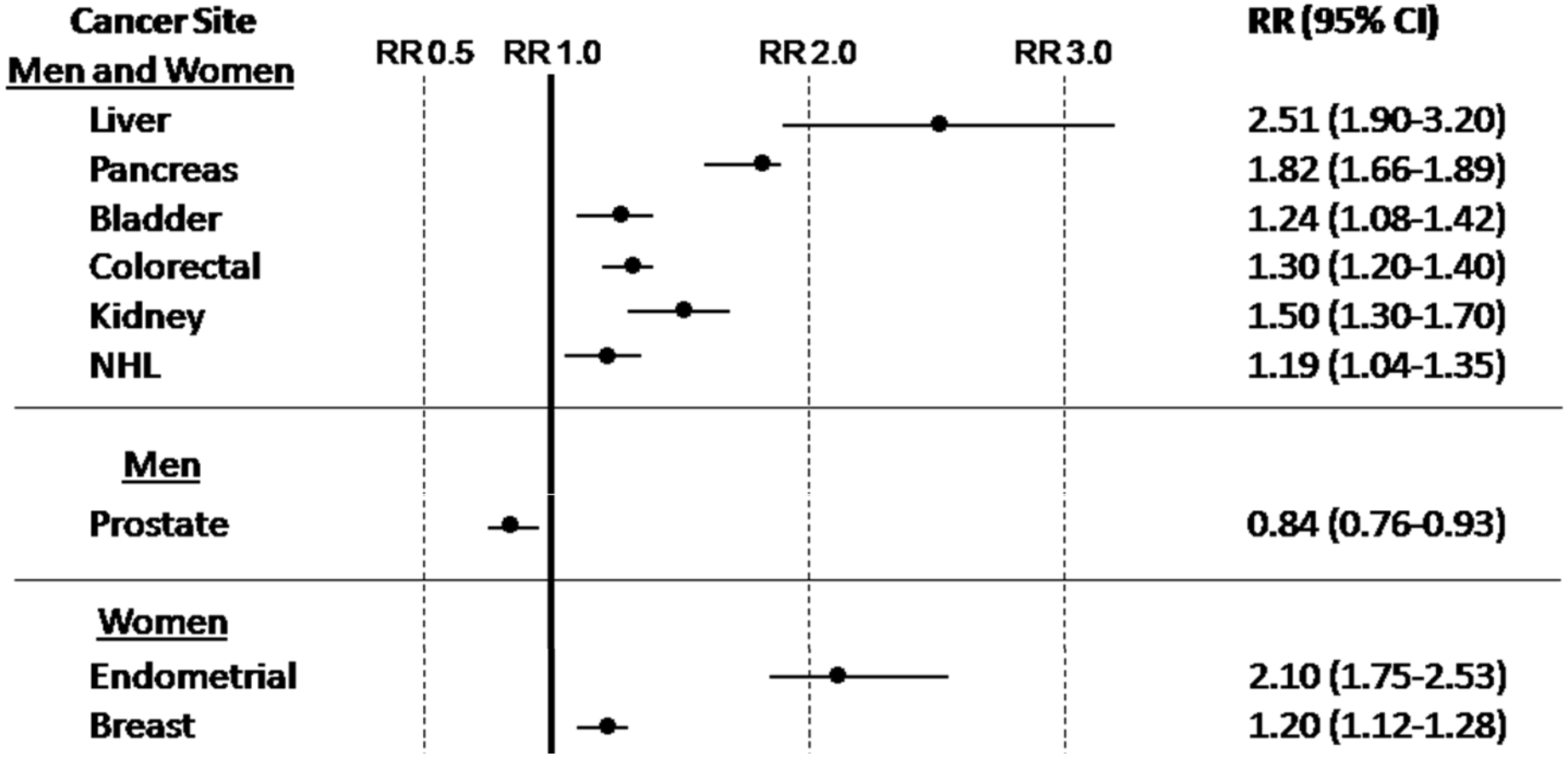
Adams TD et al. *N Engl J Med* 2007;357:753-761.

# Does Bariatric Surgery Affect Mortality?

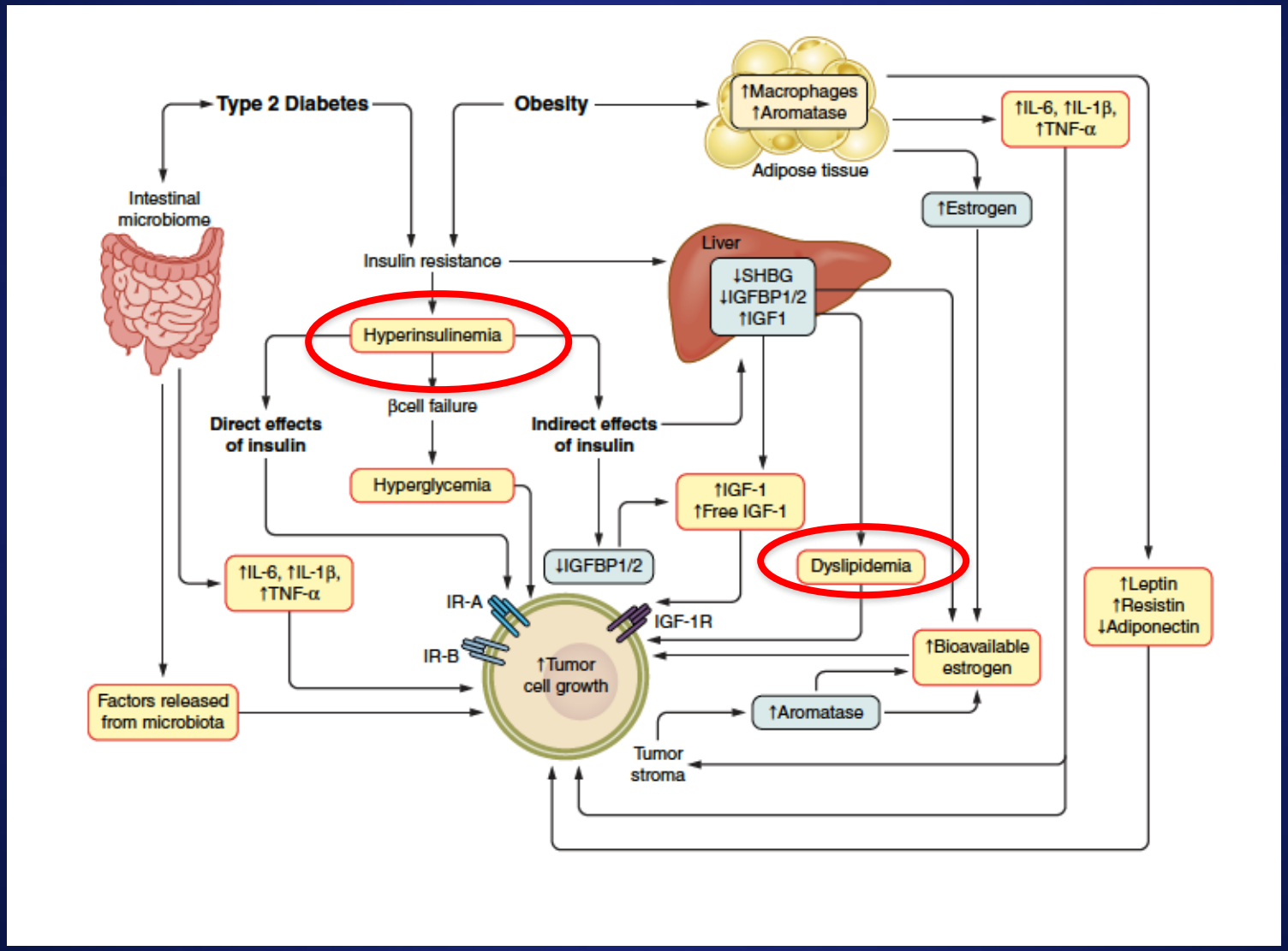
| | Surgery Group (#/10,000 person-yr) | Control Group (#/10,000 person-yr) |
|---|---|---|
| **All causes of death** | 37.2 | 61.1 |
| CV disease | 8.5 | 19.3 |
| Diabetes | 0.3 | 3.5 |
| **Cancer** | **5.4** | **15** |
| Other disease | 11.4 | 17 |
| **Non-disease causes** | | |
| Accident | 3.7 | 2.7 |
| Poisoning | 1.9 | 0.6 |
| Suicide | 2.7 | 1.2 |

Adams TD et al. *N Engl J Med* 2007;357:753-761.

# T2DM is associated with an increased risk of cancer at specific sites

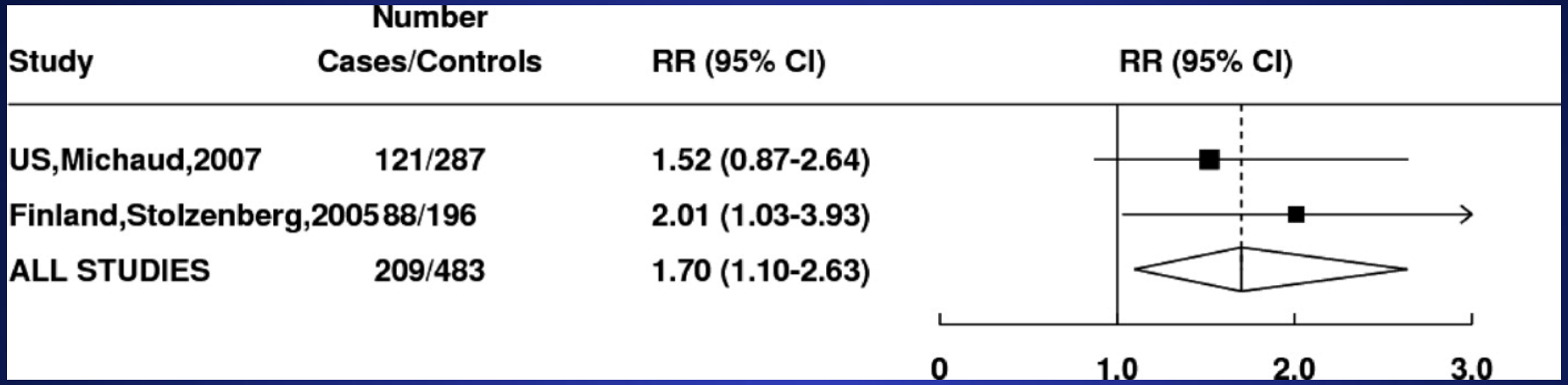


# Potential Mechanisms Linking Type 2 Diabetes and Cancer



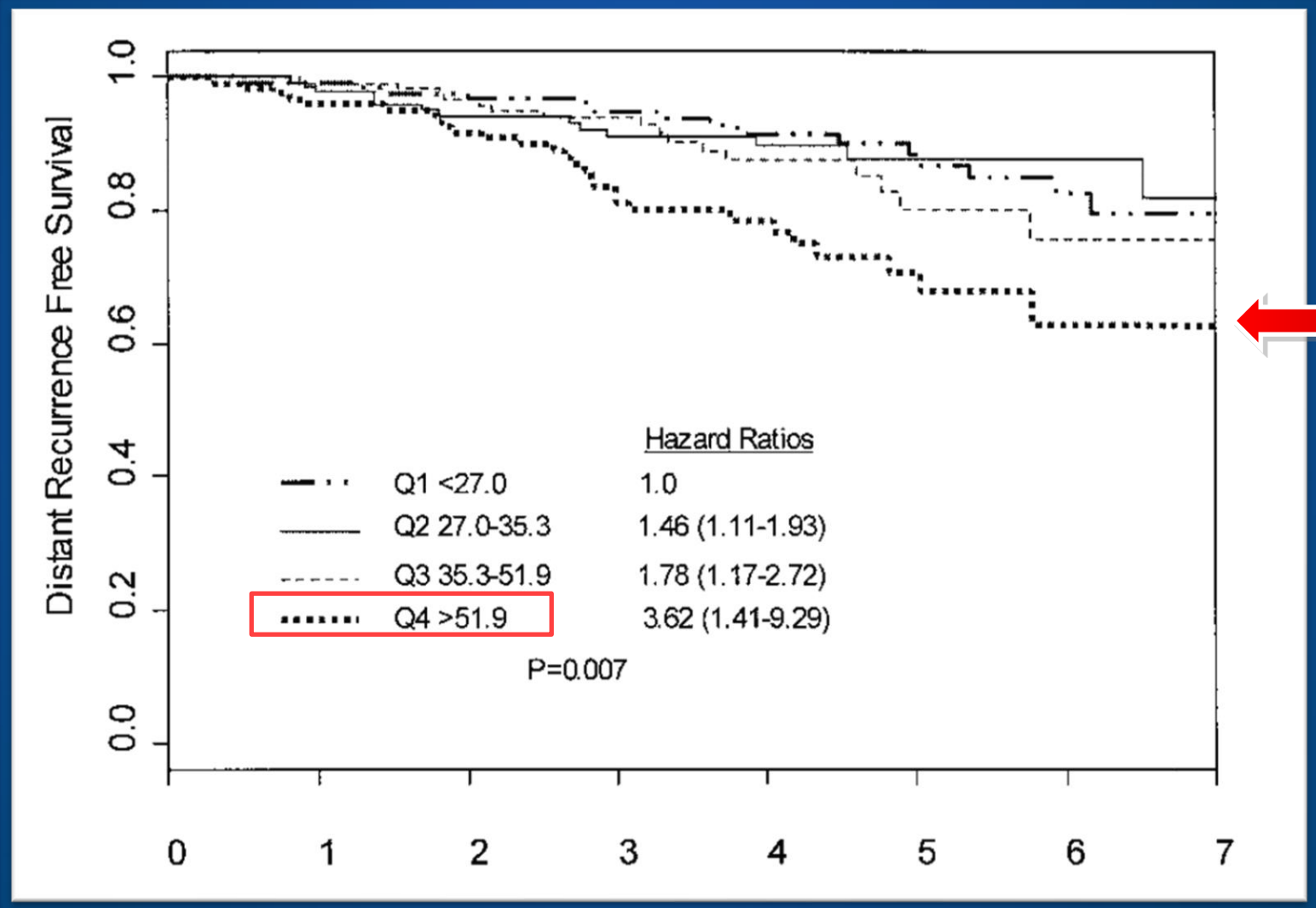

Adapted from: Gallagher EJ, LeRoith D. Curr Opin Endo Diab Obes 2013; 20(5) 485-94

# Relative risk of pancreatic cancer and Insulin / C-peptidelevel



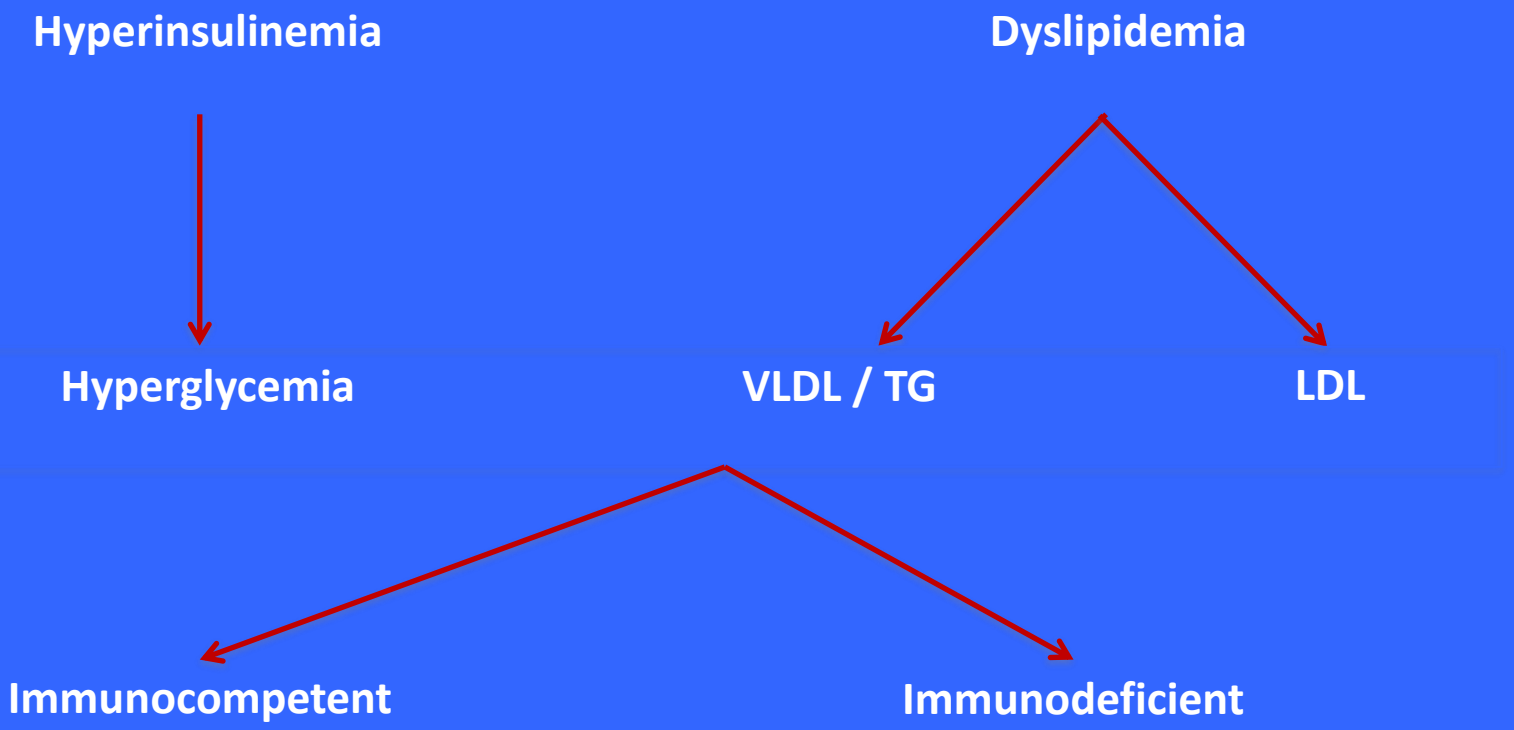

Pisani et al. Archives of Physiology and Biochemistry 2008; 114(1): 63-70

# Breast Cancer and Endogenous Insulin Levels



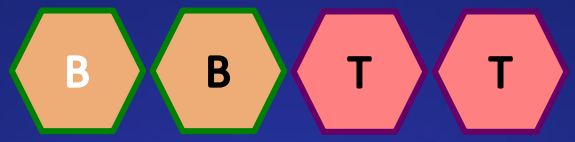

Goodwin et al. *J Clin Oncol* 2002; 20 (1): 42-51

# Animal Models of Metabolic Disease and Cancer

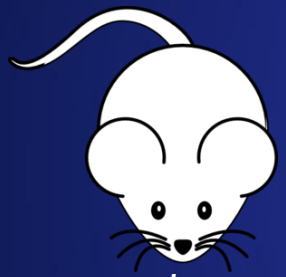


# $Rag1^{-/-}/MKR^{+/+}$ Mouse: Immunodeficient model

Wild-Type Mouse




Immunocompetent



$Rag1^{-/-}$ Mouse

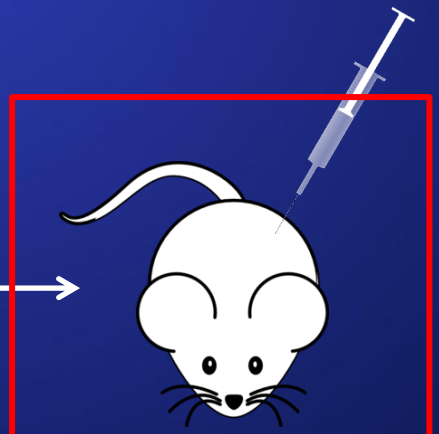
No mature B and T cells

Immunodeficient

$Rag1^{-/-}$ Mouse
Rag/WT

X

MKR Mouse



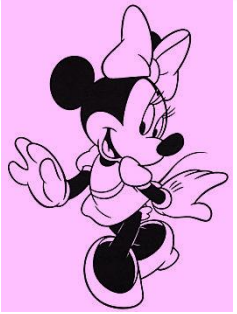
$Rag1^{-/-}$; MKR Mouse
Rag/MKR

$4^{th}$ Mammary Fat Pad

Human Triple Negative
ER-, PR-, HER2-

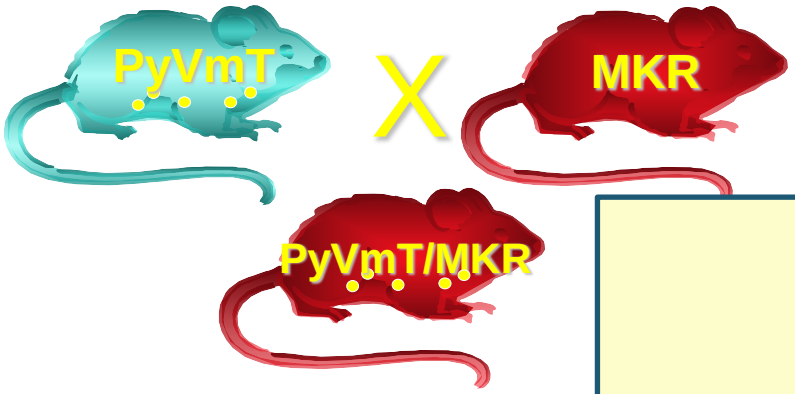
# Metabolic Abnormalities in MKR Mice

| | Males | Females |
|---|---|---|
| Hyperglycemia | ++ | - |
| Hyperinsulinemia | +++ | +++ |
| Insulin resistance | +++ | +++ |
| Hyperlipidemia | ++ | - |
| Obesity | - | - |

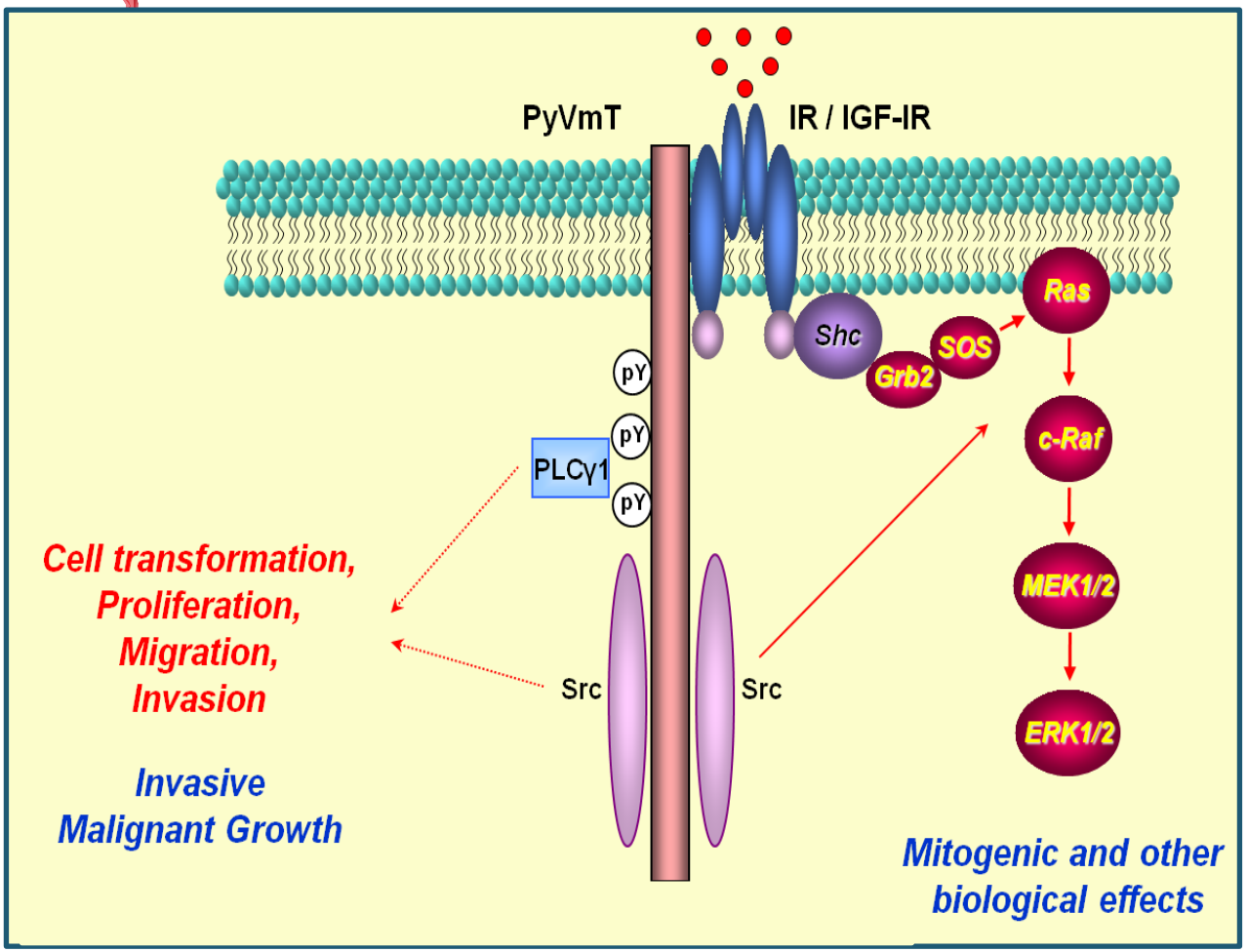


# Mouse Models of Breast Cancer

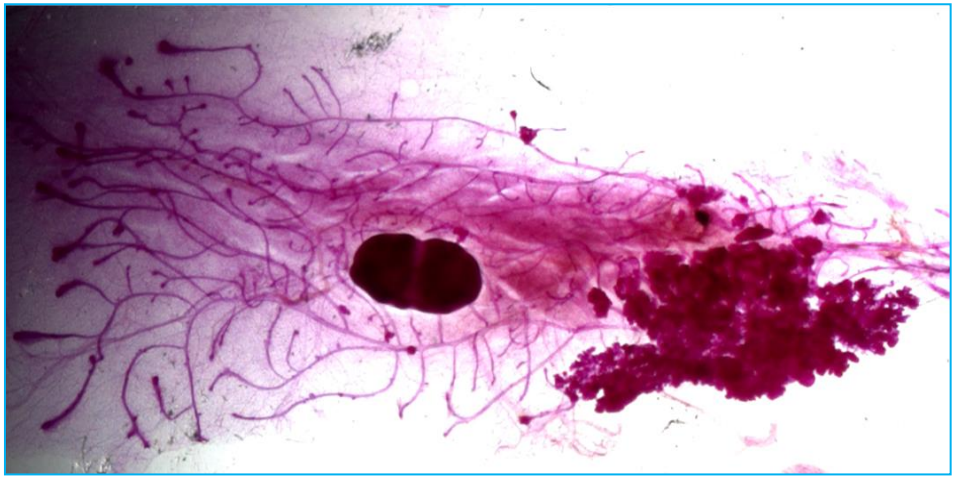
***Transgenic Model***



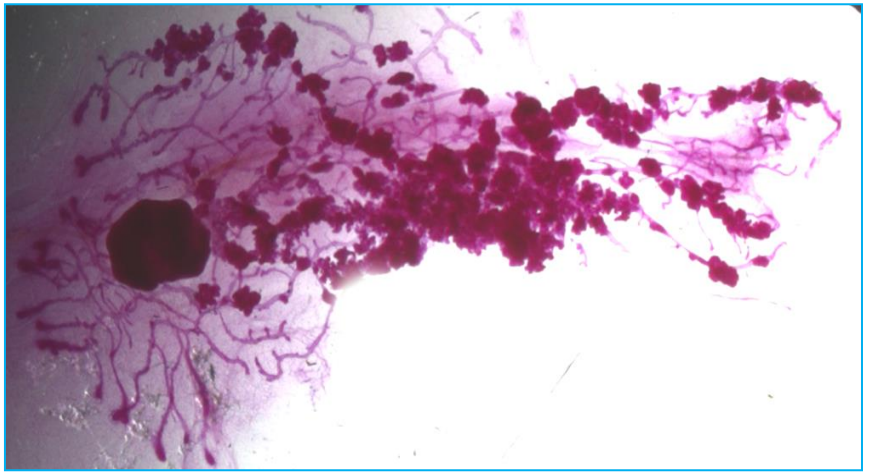

Polyoma Middle T Ag
(PyVmT)



# Mammary Tumorigenesis
# the effect of endogenous hyperinsulinemia



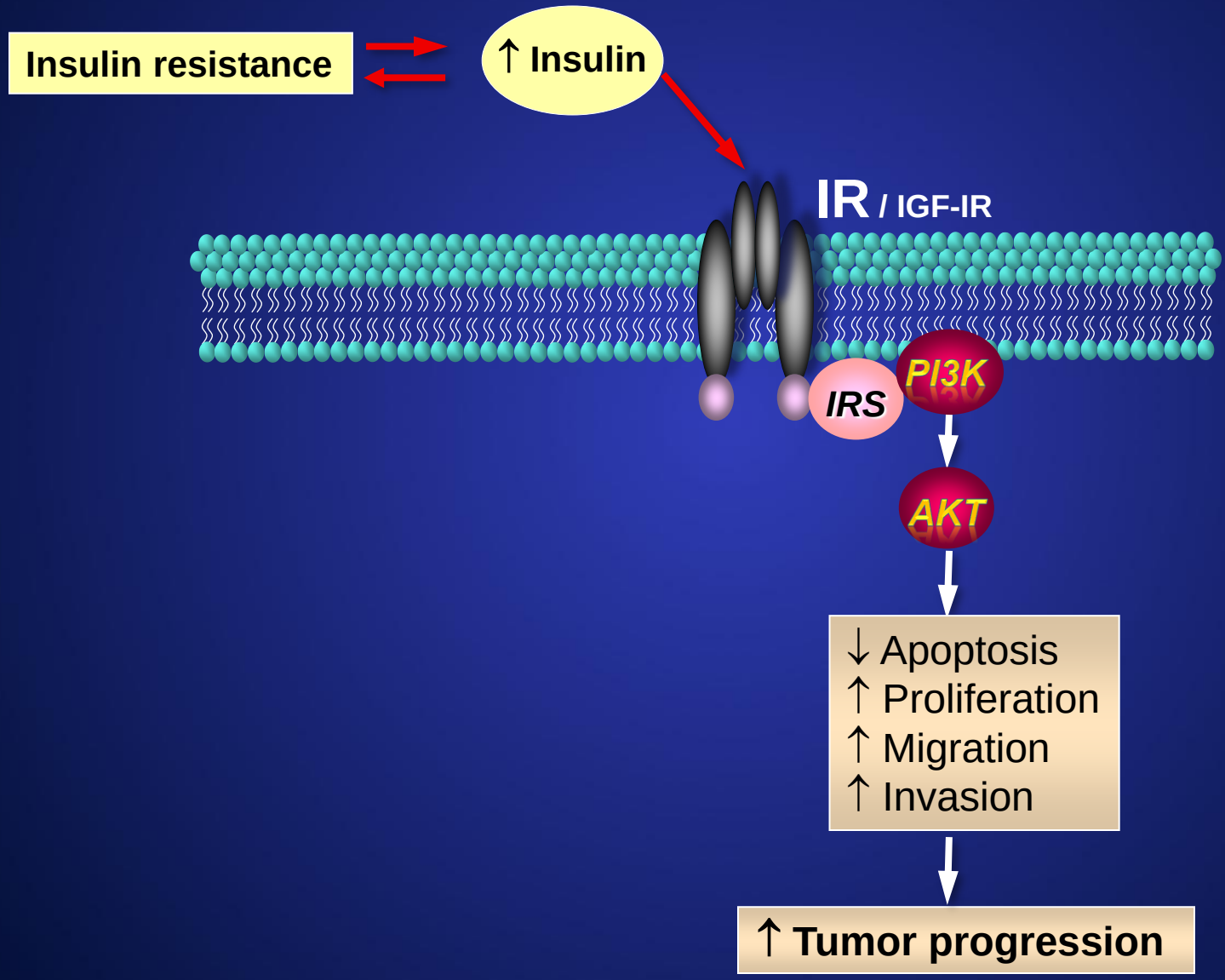
**PyVmT at 6 weeks**



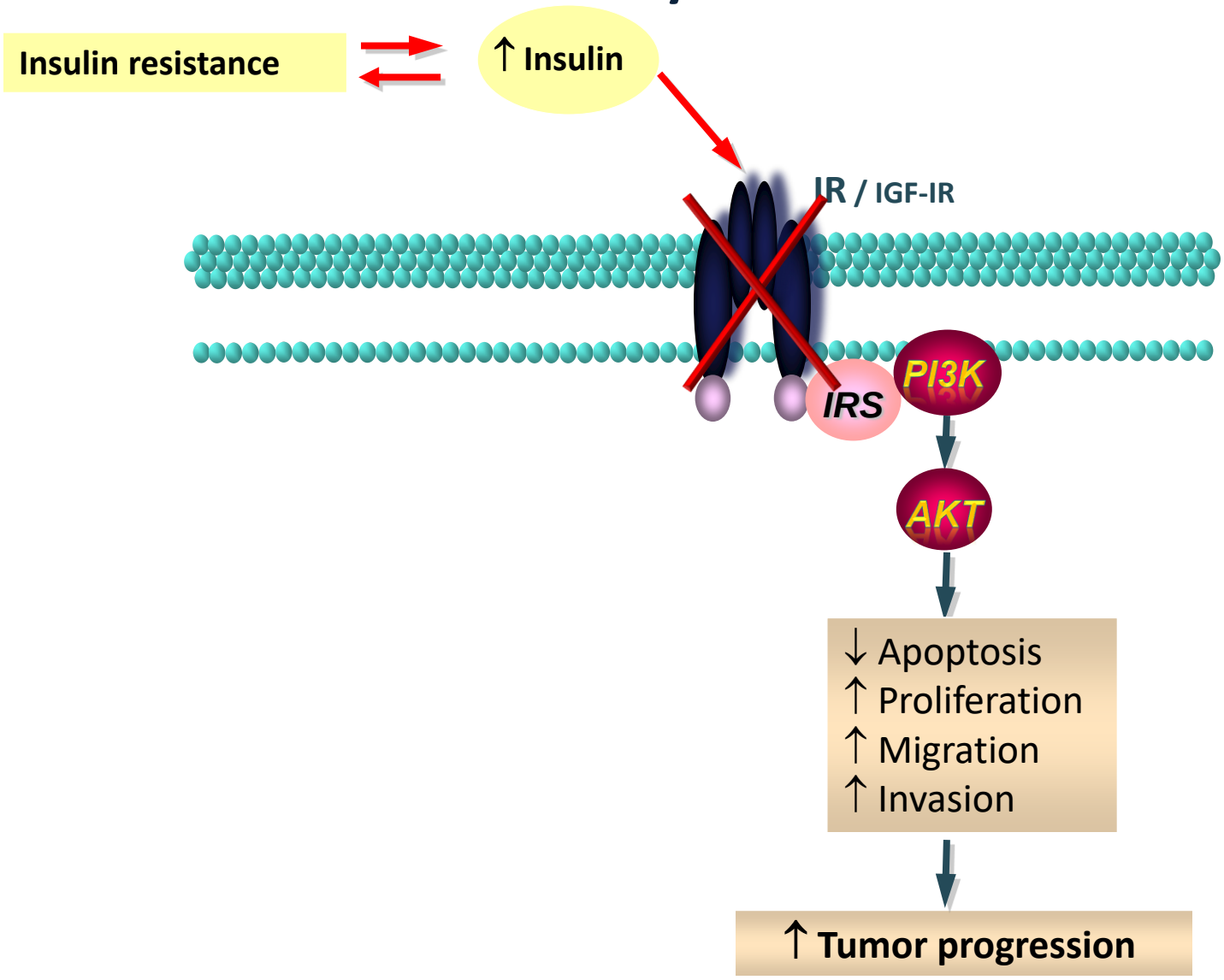
**PyVmT/MKR at 6 weeks**

Polyoma Middle T Ag
(PyVmT)

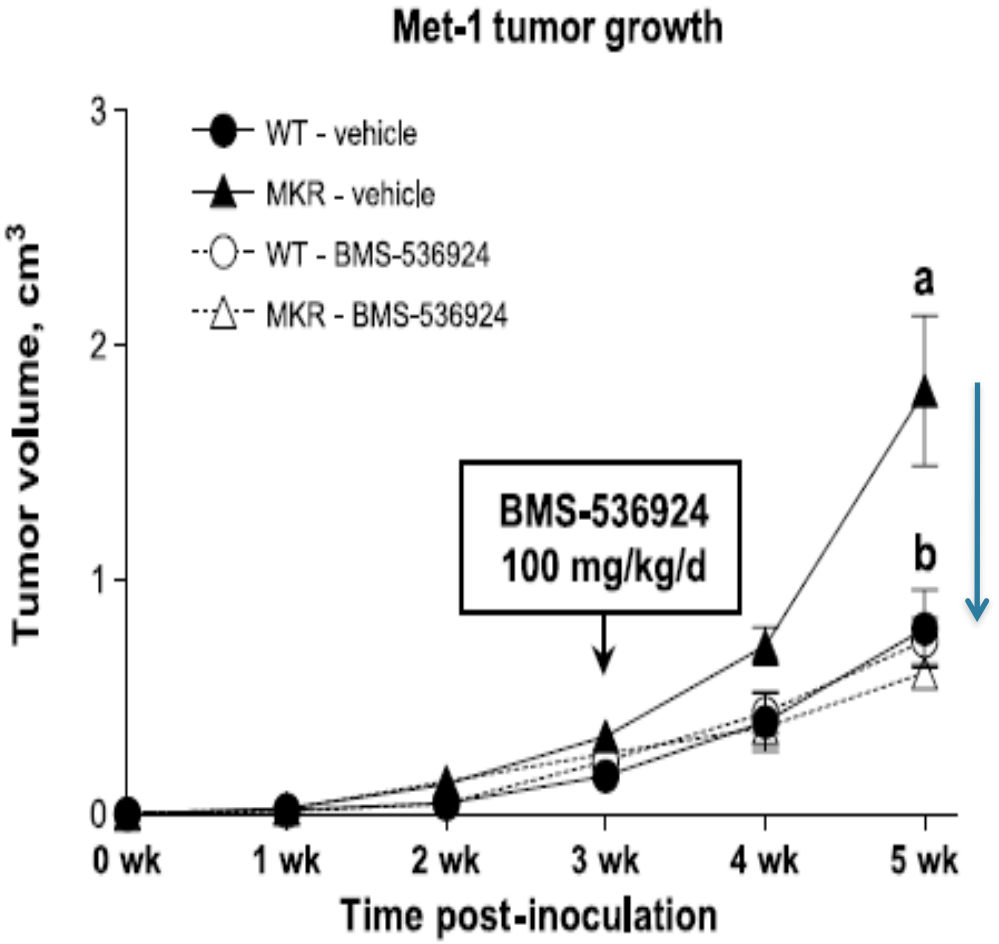
# Molecular Mechanisms Underlying Tumor-Promoting Activity in T2DM

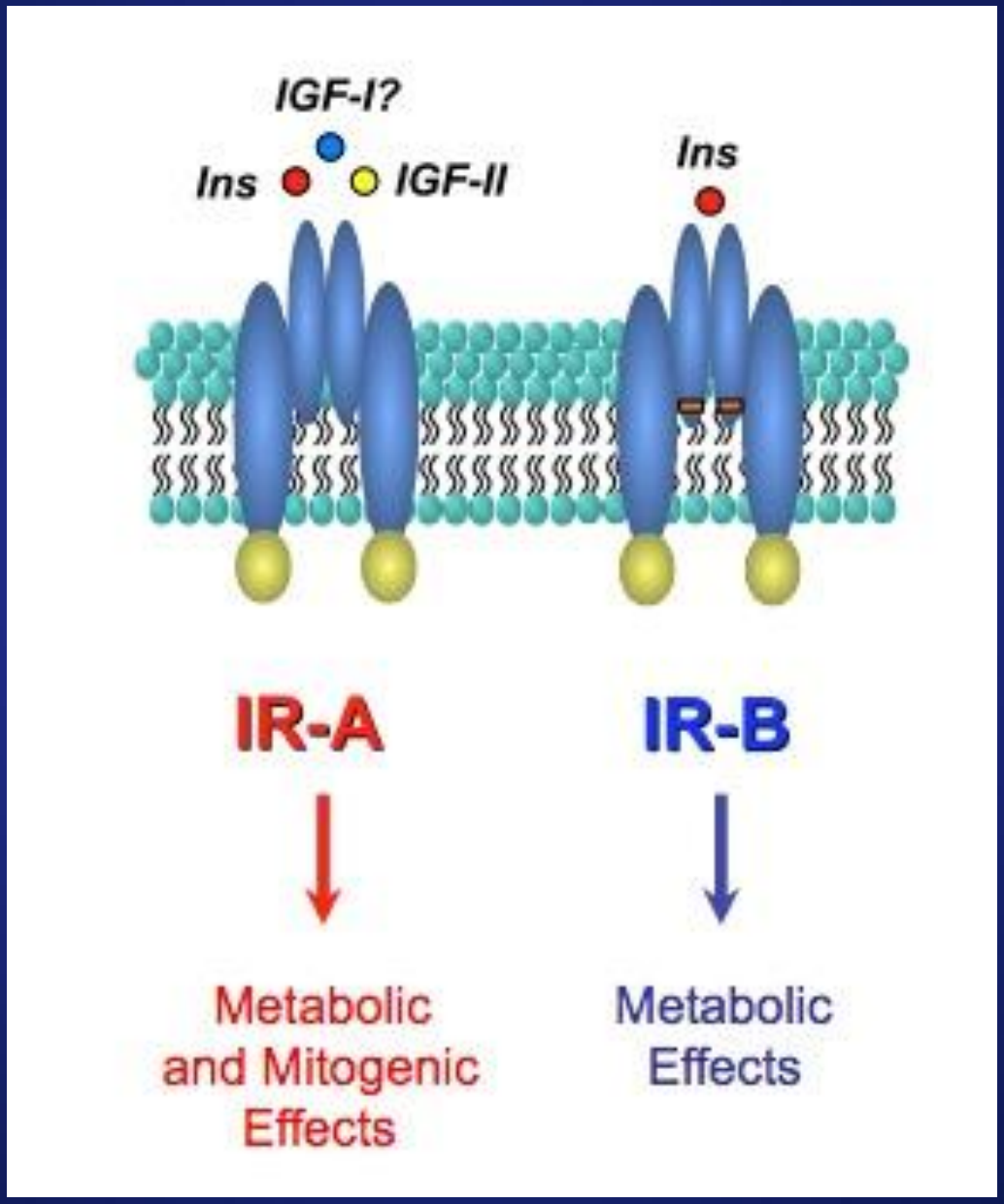


# Strategies to Reduce Tumor-Promoting Activity in T2DM



# Reduction of Mammary Tumors Using a Tyrosine Kinase Inhibitor, Despite the Marked Hyperinsulinemia




IGF-I?
Ins
IGF-II
Ins
IR-A
IR-B
Metabolic and Mitogenic Effects
Metabolic Effects

| Study | Number of participants | Association studied | OR/HR |
|---|---|---|---|
| Framingham Offspring Cohort | 3,278 | VLDL-C and overall cancer risk | 1.54 |
| Atherosclerosis Risk in Communities (ARIC) | 7,575 | Low HDL-C (<50 mg/dL) and breast cancer incidence | 1.67* |
| Malmö Preventive Project (Sweden) | 9,738 | Total cholesterol and breast cancer risk | 1.64** |
| Furberg et al., 2004 (Norway) | 38,823 | HDL-C (>1.64 mmol/L vs <1.20 mmol/L) and breast cancer risk | 0.43** |
| EBBA study (Norway) | 206 | HDL-C, TC, LDL-C/HDL-C and mammographic parenchymal pattern | 1.77 (HDL-C)<br>0.54 (TC)<br>0.60 (L/H) |
| ATBC Cancer Prevention Study (Finland) | 27,074 | HDL-C (highest vs lowest quintile) and risk of Non-Hodgkin Lymphoma | 0.35 |
| Andreotti et al., 2008 (China) | 460+858 | HDL-C (lowest vs median quintile) and gallbladder/bile duct cancer risk | 11.63/16.81 |
| Magura et al., 2008 (North Dakota) | 312+319 | Total cholesterol, LDL-C (high vs normal), HDL-C (low vs normal) and prostate cancer risk | 1.64 (TC)<br>1.60 (LDL-C)<br>1.57 (HDL-C) |
| Atherosclerosis Risk in Communities (ARIC) | 14,547 | Low HDL-C and lung cancer incidence | 1.45 |

# Does dyslipidemia affect breast carcinogenesis independently of insulin resistance?

Epidemiological studies have shown an association between hyperlipidemia and cancer risk

Recent NEJM article demonstrated that statins reduce cancer-mortality.

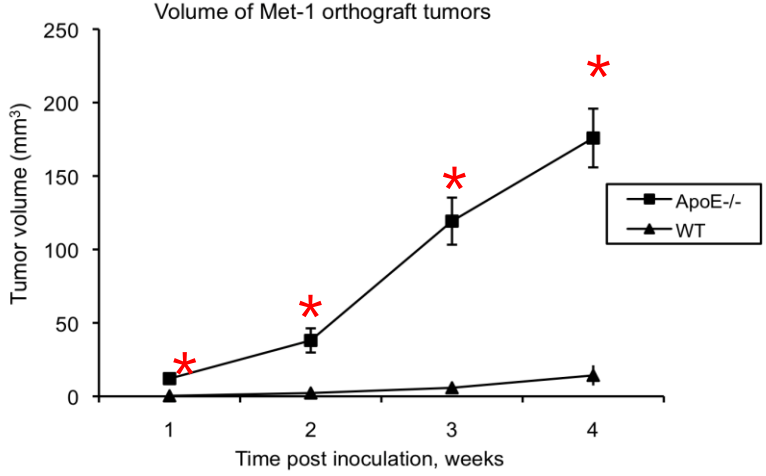
Nielsen NEJM 2013

**Animal Model of Hyperlipidemia**

ApoE-/- mice cannot take up TG and Chol into tissues, therefore have increased circulating chol and TG in blood stream, but are insulin sensitive and do no have hyperinsulinemia.

# ApoE-/- Mice with Orthotopic Tumors

A

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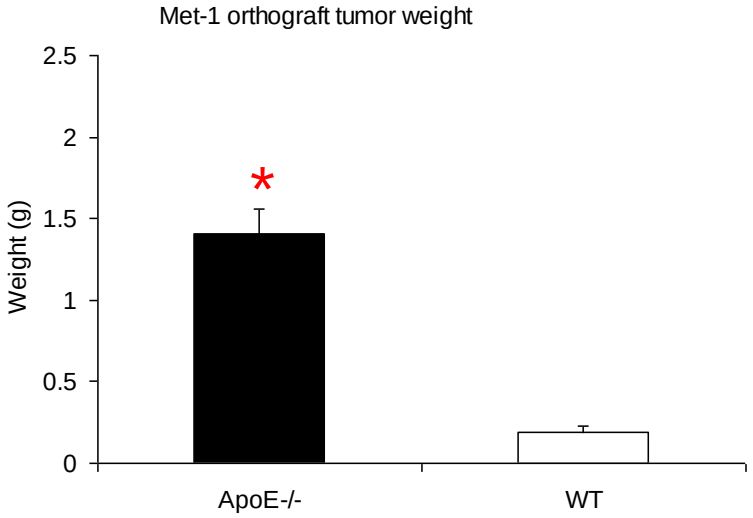


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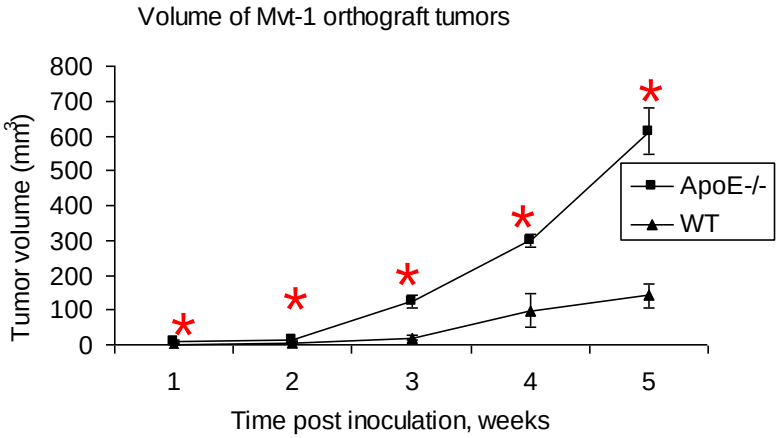


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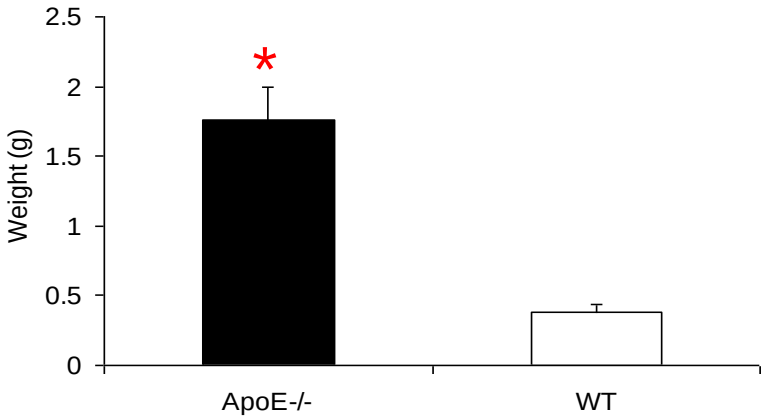
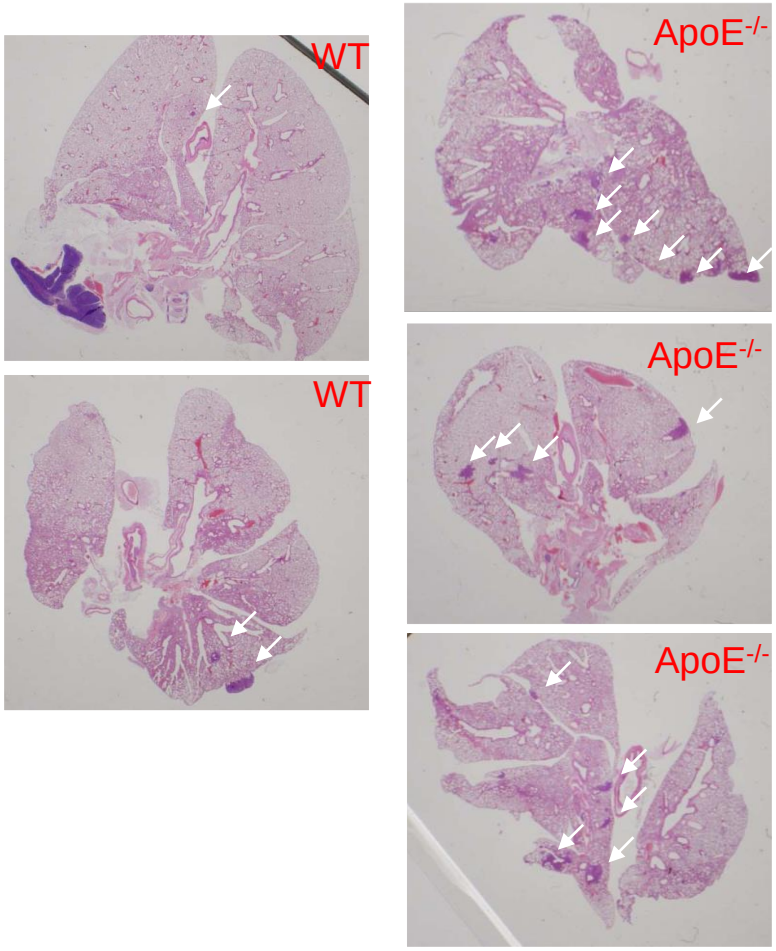


# Lung Metastasis after Orthotopic and Intravenous Injection of Tumor Cells in ApoE-/- Mice

A

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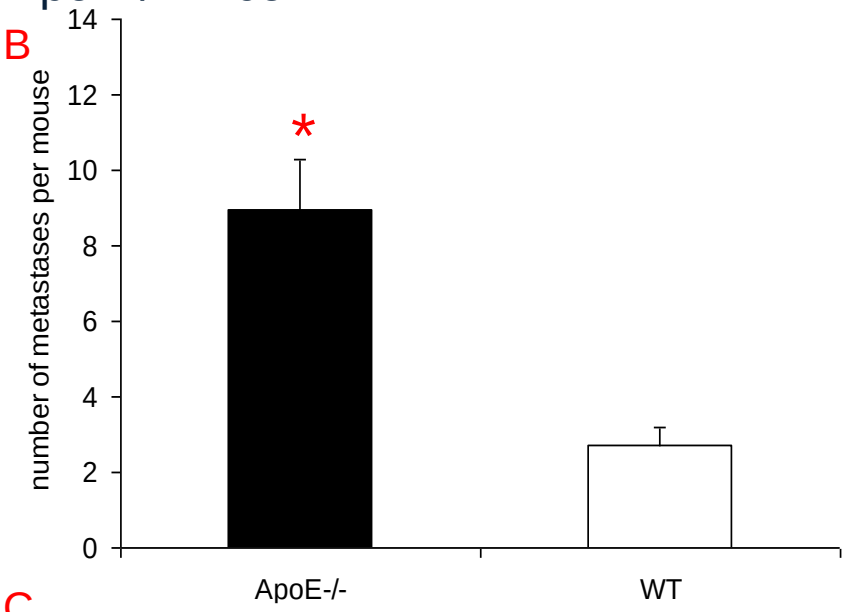


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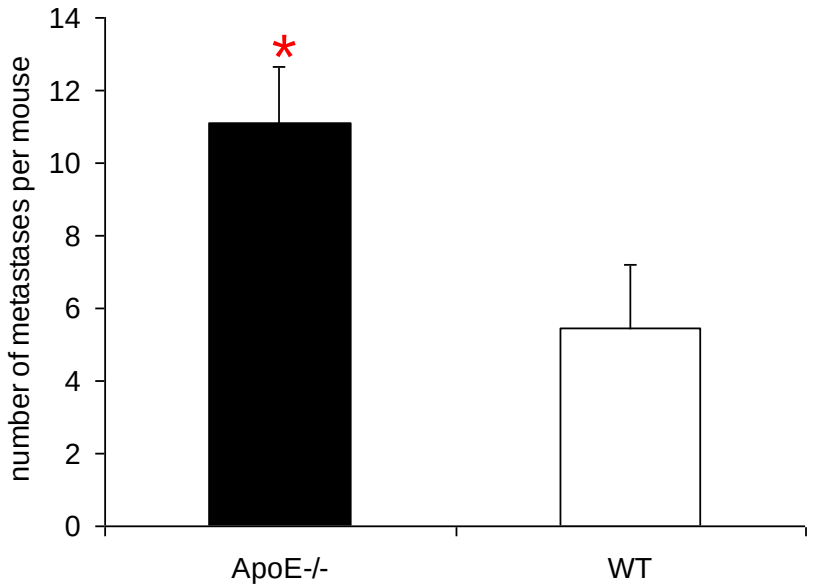
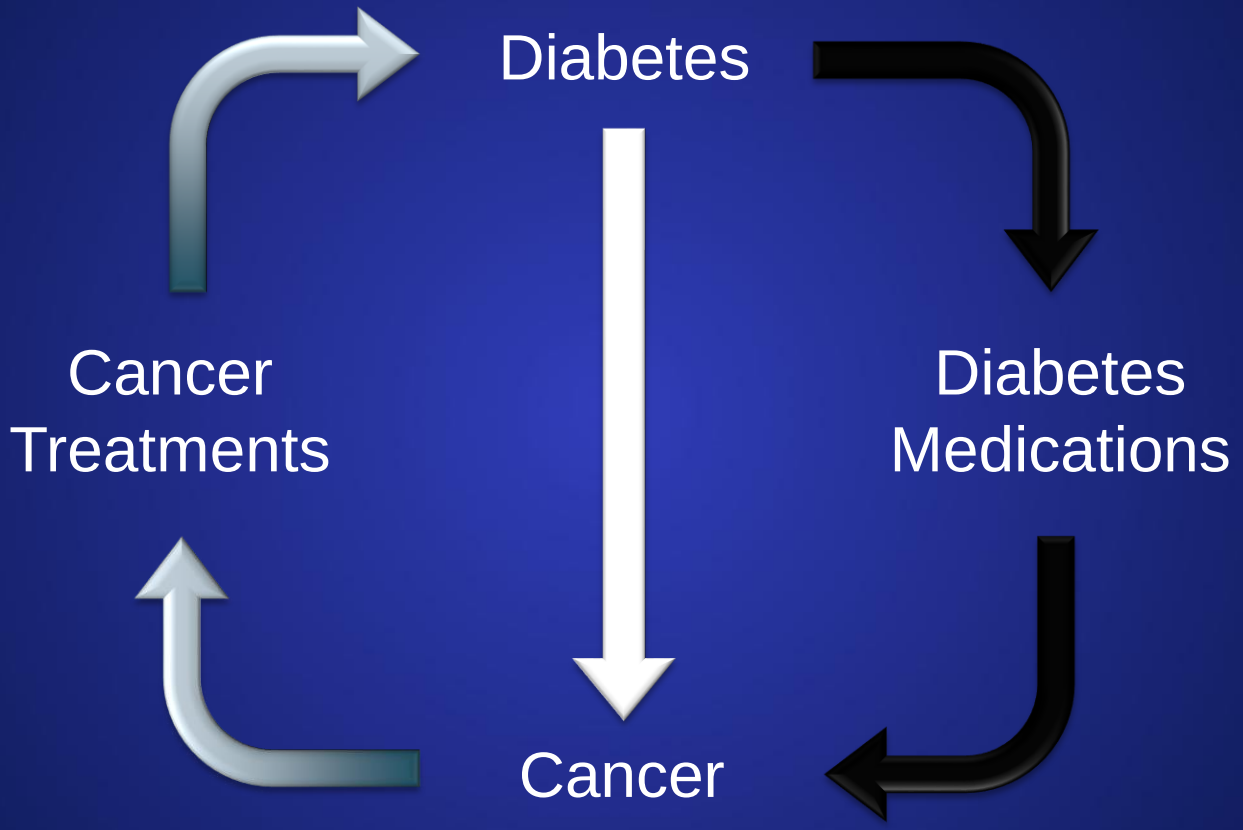
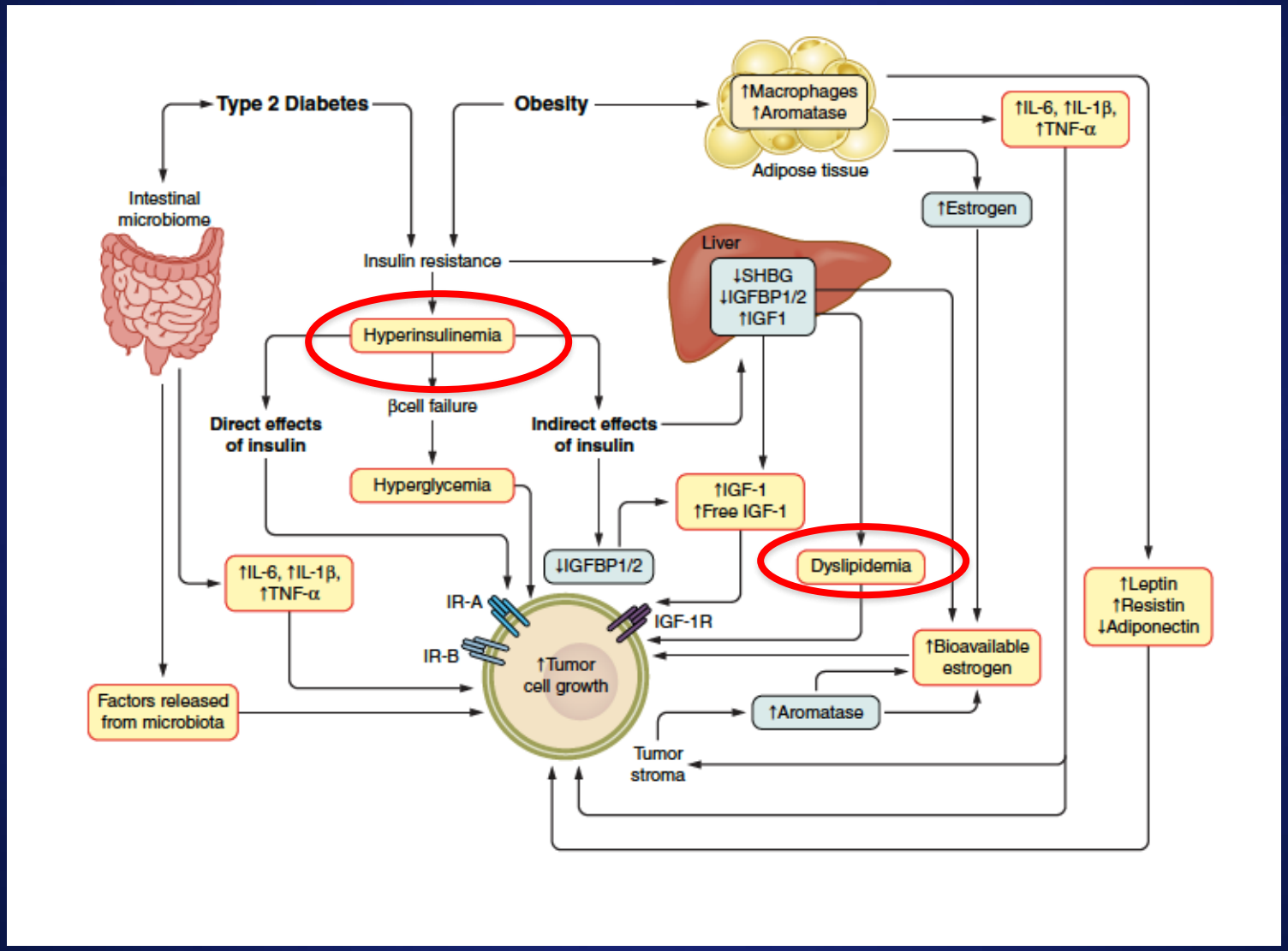


# Cancer and Diabetes



# Potential Mechanisms Linking Type 2 Diabetes and Cancer

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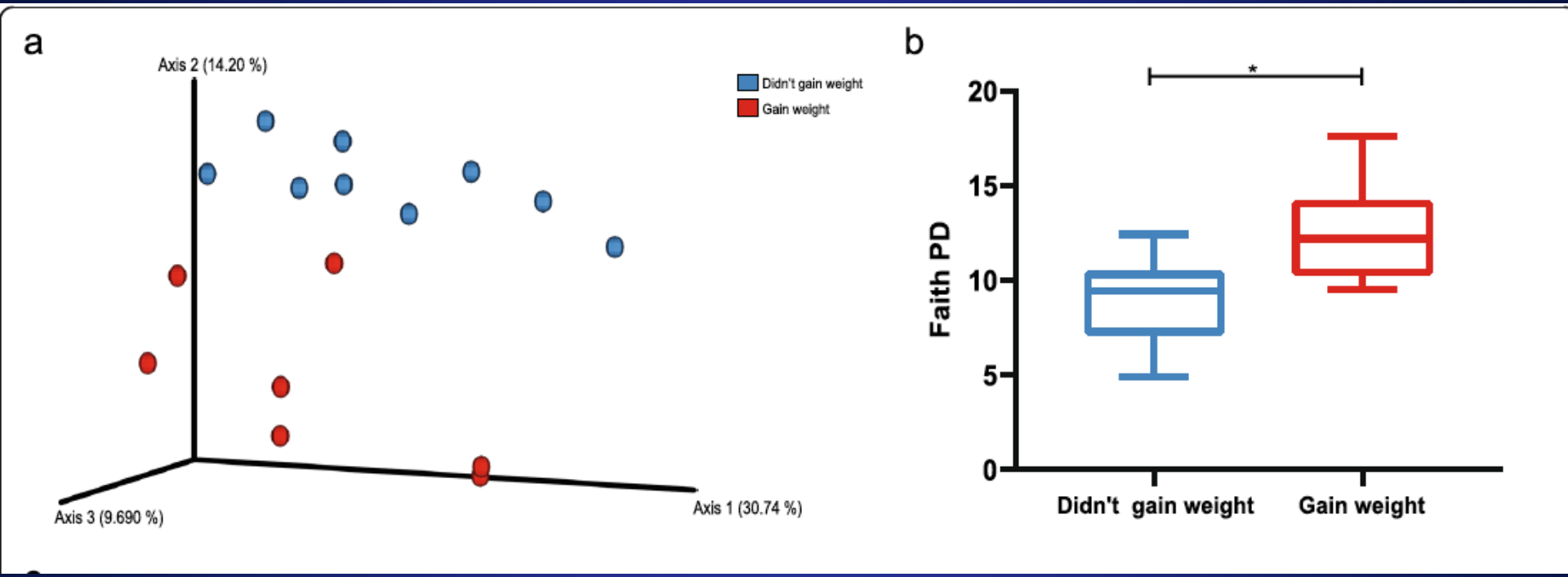
# The intestinal microbiome, weight, and metabolic changes in women treated by adjuvant chemotherapy for breast and gynecological malignancies




Uzan-Yulzari *et al. BMC Medicine* (2020) 18:281
https://doi.org/10.1186/s12916-020-01751-2

# Thanks

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