OBESITA' e CANCRO
Geni, alimentazione metabolismo e tumorigenesi

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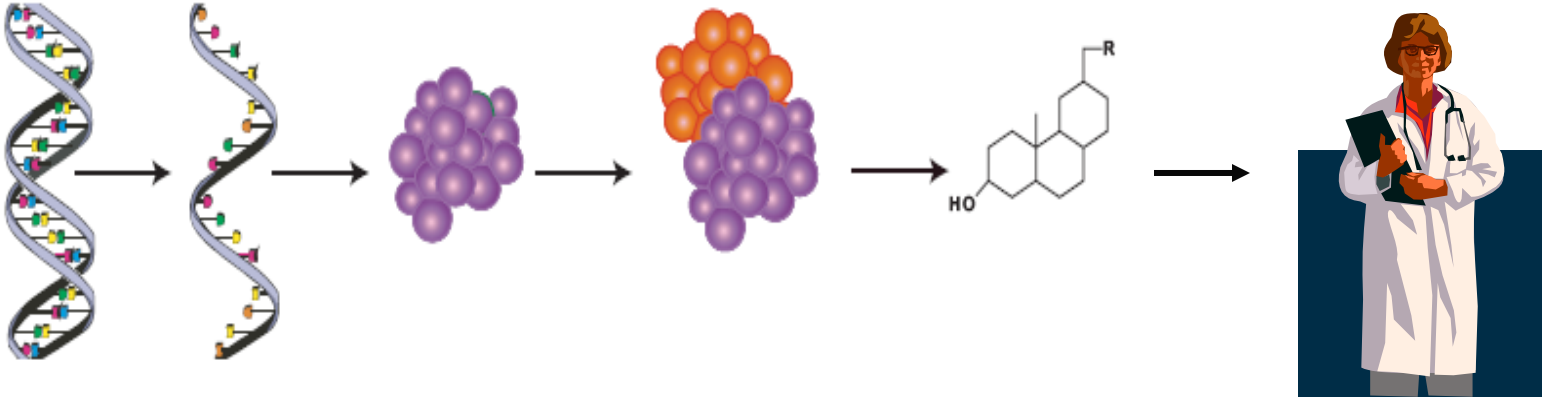
Plan

1. **System Biology**
2. Nuclear Receptors: genes on/off
3. Metabolic Syndrome and Cancer
4. The Concept of Welfare

Systems Biology and Pathobiology



Genomics

Proteomics

Native

Modified

Metabolomics
Metabonomics

Phenomics
Pathophenomics

Transcriptomics

Functional Genomics/Proteomics

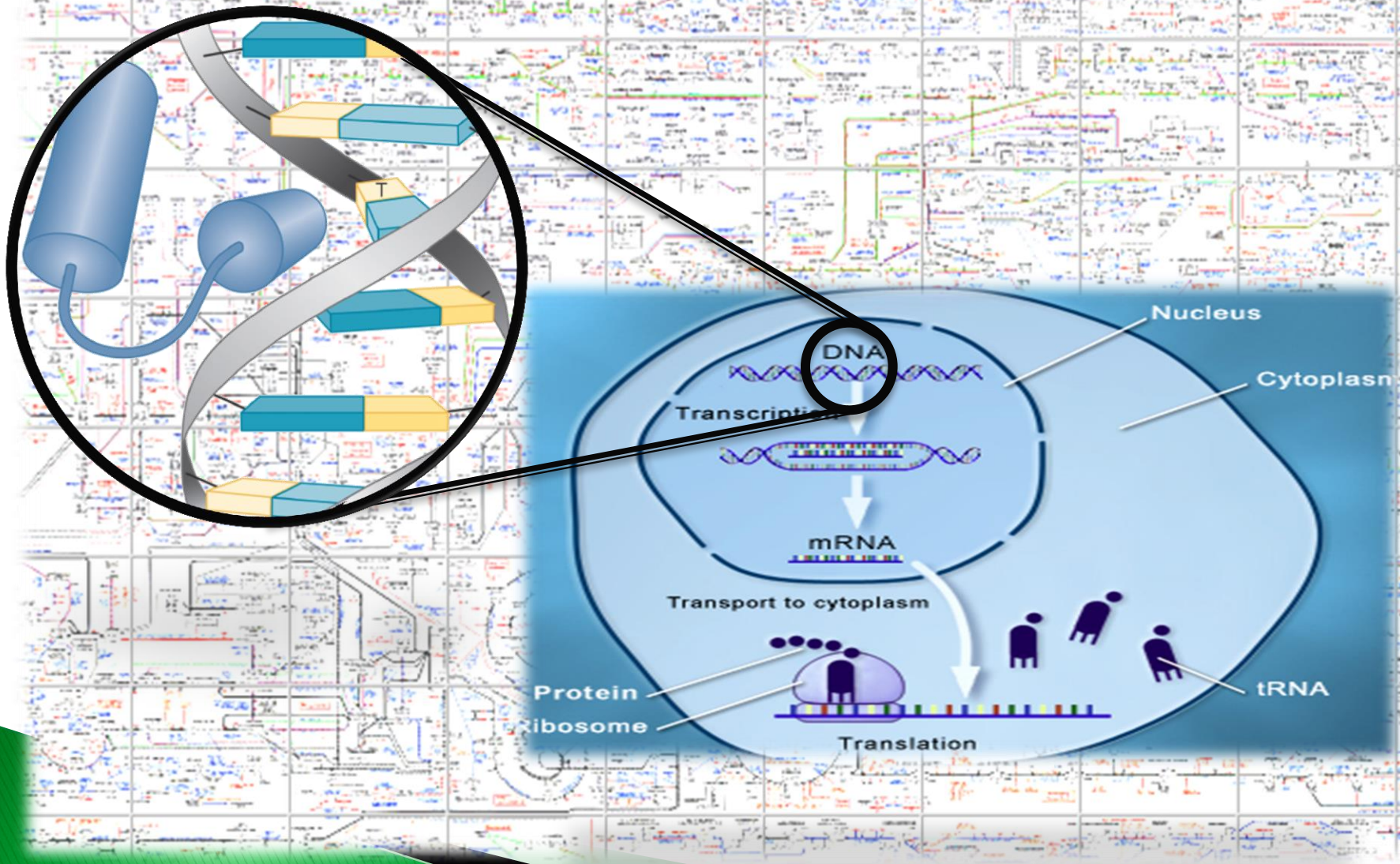
Environmental Perturbations

Systems Biology/Pathobiology

FACTS

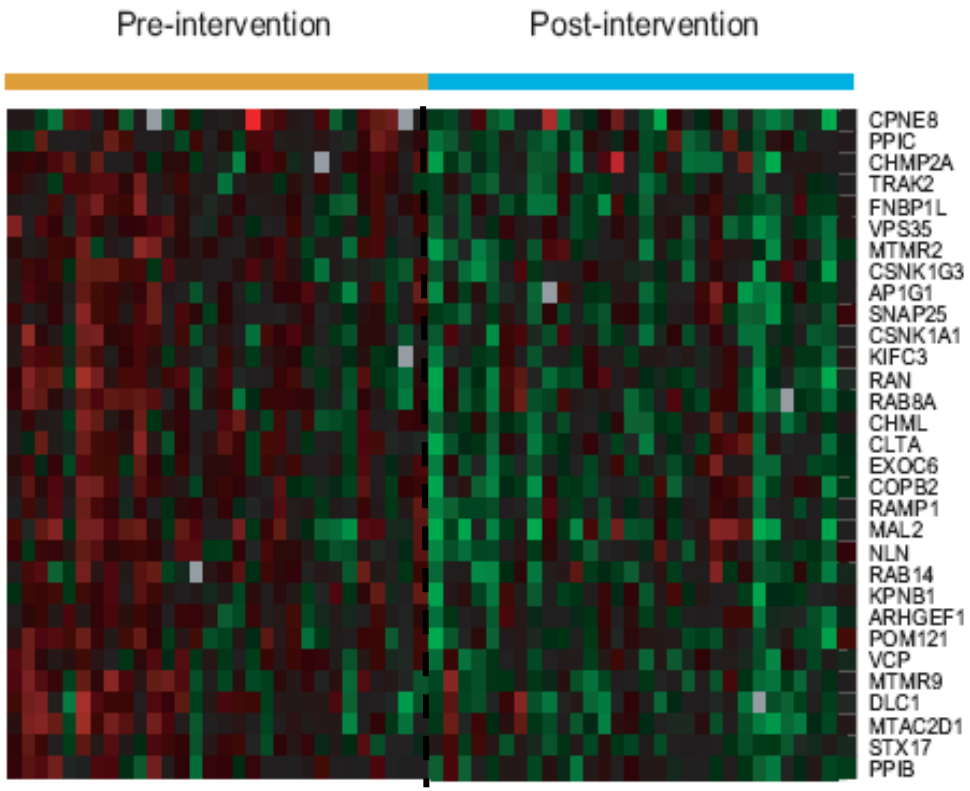
- The DNA sequence brings the “genetic code”
- Phenotype is the interaction of this genetic code with the environment
- Genes are turned “on” or “off” by:
  - Environmental influences
  - Diet (Nutrigenomics)
  - Drugs (Pharmacogenomics)

Nutrients can modify gene transcription



Effects of Lifestyle Changes, Hypocaloric Diet & Physical exercise on gene expression of patients with Prostate Cancer

Risk factor	Change
Body mass index (BMI)	-2.6 kg/m^2
Systolic BP	-9.2 mmHg
Diastolic BP	-5.4 mmHg
Total cholesterol	-45.2 mg/dL
LDL cholesterol	-34.2 mg/dL
HDL cholesterol	-8.3 mg/dL
LDL/HDL ratio	-0.4



Ornish, et al. PNAS 2008

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Nuclear Receptor Superfamily

NH2- AF1 | DNA | Ligand | AF2 -COOH

Endocrine

(Endocrine lipid sensors)

GR	*glucocorticoids*
MR	*mineralocorticoid*
PR	*progesterone*
AR	*androgens*
ERα,β	*estrogens*

RARα,β,γ	*retinoic acids*
TRα,β	*thyroid hormone*
VDR	*vitamin D, LCA*

Adopted Orphan

(Dietary & endogenous lipid sensors)

RXRα,β,γ	*9-cis RA, DHA*
PPARα,δ,γ	*fatty acids*
LXRα,β	*oxysterols*
FXR	*bile acids*
PXR	*xenobiotics*
CAR	*xenobiotics*

Orphan

(Endogenous ligands uncertain)

ERRα,β,γ	*synthetic steroids*
HNF-4α,γ	*fatty acids?*
RORα,β,γ	*fatty acid, sterols?*
SF-1	*phospholipids?*
LRH-1	*phospholipids?*
GCNF	?
PNR	?
TLX	?
TR2,4	?
NGFI-Bα,β,γ	?
COUP-TFα,β,γ	?
RVRα,β	?
DAX-1	?
SHP	?

Moschetta & Mangelsdorf. Nature Medicine 2004
Kliewer & Moschetta. J Clinical Investigation 2004
Choi & Moschetta. Nature Medicine 2006

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The NEW ENGLAND JOURNAL of MEDICINE

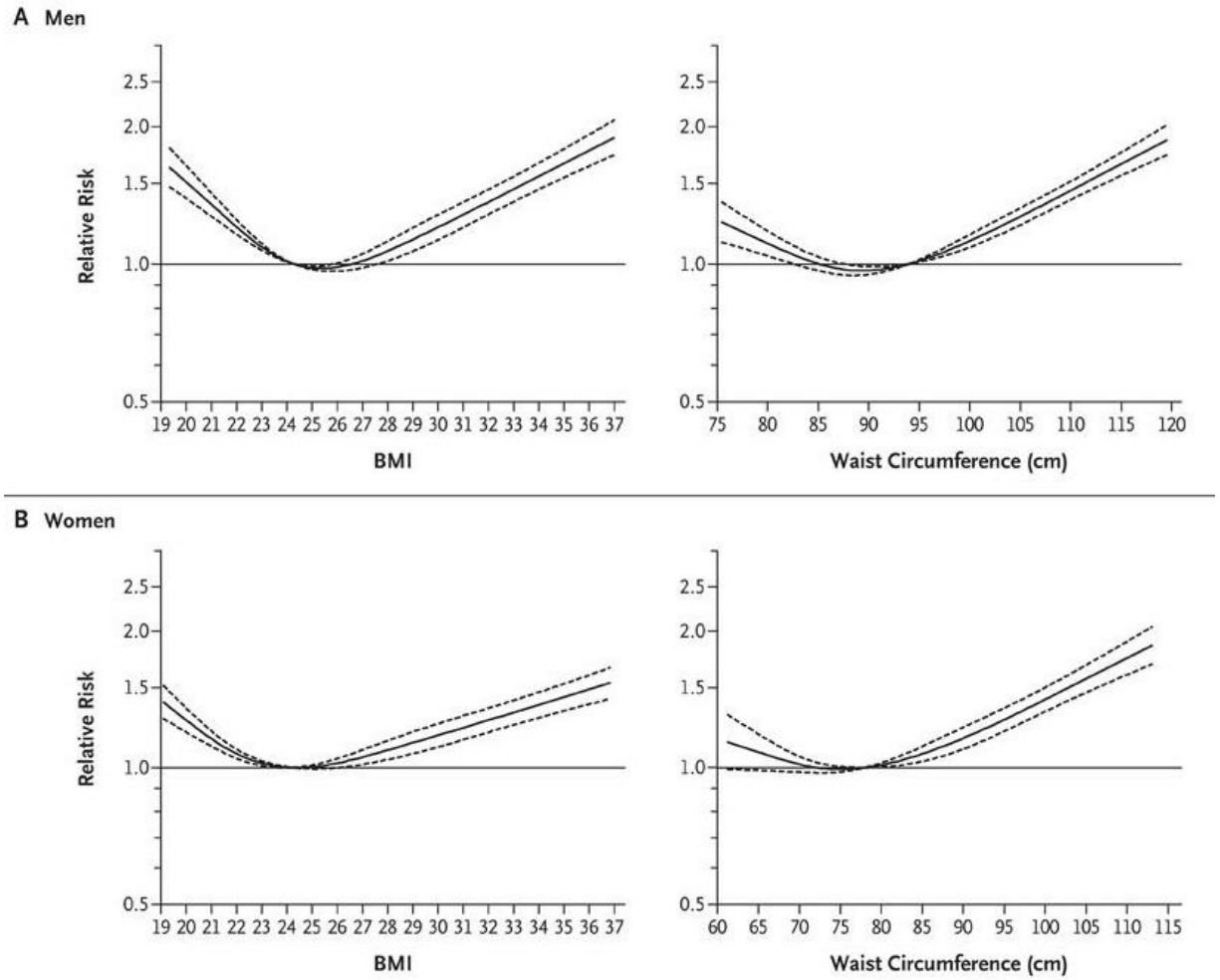
ORIGINAL ARTICLE

General and Abdominal Adiposity and Risk of Death in Europe

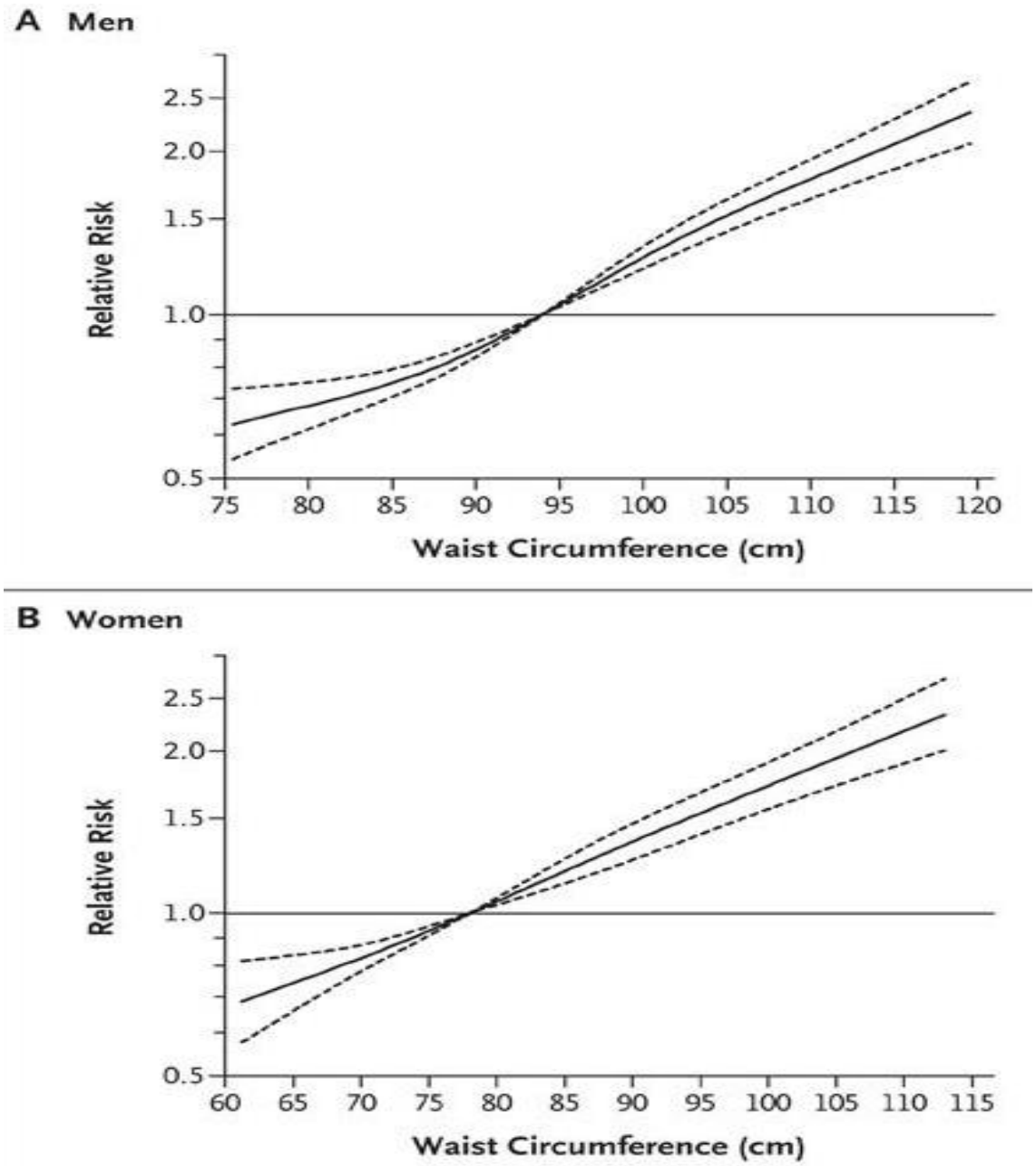
T. Pischon, M.D., M.P.H., H. Boeing, Ph.D., M.S.P.H., K. Hoffmann, Ph.D.,*
M. Bergmann, Ph.D., M.B. Schulze, Dr.P.H., K. Overvad, M.D., Ph.D.,
Y.T. van der Schouw, Ph.D., E. Spencer, Ph.D., K.G.M. Moons, Ph.D.,
A. Tjønneland, M.D., Ph.D., Dr.Med.Sci., J. Halkjaer, Ph.D., M.K. Jensen, Ph.D.,
J. Stegger, M.D., F. Clavel-Chapelon, Ph.D., M.-C. Boutron-Ruault, Ph.D.,
V. Chajes, Ph.D., J. Linseisen, Ph.D., R. Kaaks, Ph.D., A. Trichopoulou, M.D., Ph.D.,
D. Trichopoulos, M.D., Ph.D., C. Bamia, Ph.D., S. Sieri, Ph.D., D. Palli, M.D.,
R. Tumino, M.D., P. Vineis, M.D., M.P.H., S. Panico, M.D., M.Sc.,
P.H.M. Peeters, M.D., Ph.D., A.M. May, Ph.D.,
H.B. Bueno-de-Mesquita, M.D., Ph.D., M.P.H., F.J.B. van Duijnhoven, Ph.D.,
G. Hallmans, M.D., L. Weinehall, M.D., Ph.D., J. Manjer, M.D., Ph.D.,
B. Hedblad, M.D., Ph.D., E. Lund, M.D., Ph.D., A. Agudo, Ph.D., L. Arriola, Ph.D.,
A. Barricarte, Ph.D., C. Navarro, M.D., Ph.D., C. Martinez, M.D., J.R. Quirós, M.D.,
T. Key, D.Phil., S. Bingham, Ph.D., K.T. Khaw, M.B., B.Chir., P. Boffetta, M.D., M.P.H.,
M. Jenab, Ph.D., P. Ferrari, Ph.D., and E. Riboli, M.D., M.P.H., Sc.M.

369K subjects
9,7 yrs follow-up

Mortalità secondo BMI e circonferenza vita



Mortalità secondo circonferenza vita, a parità di indice di massa corporea

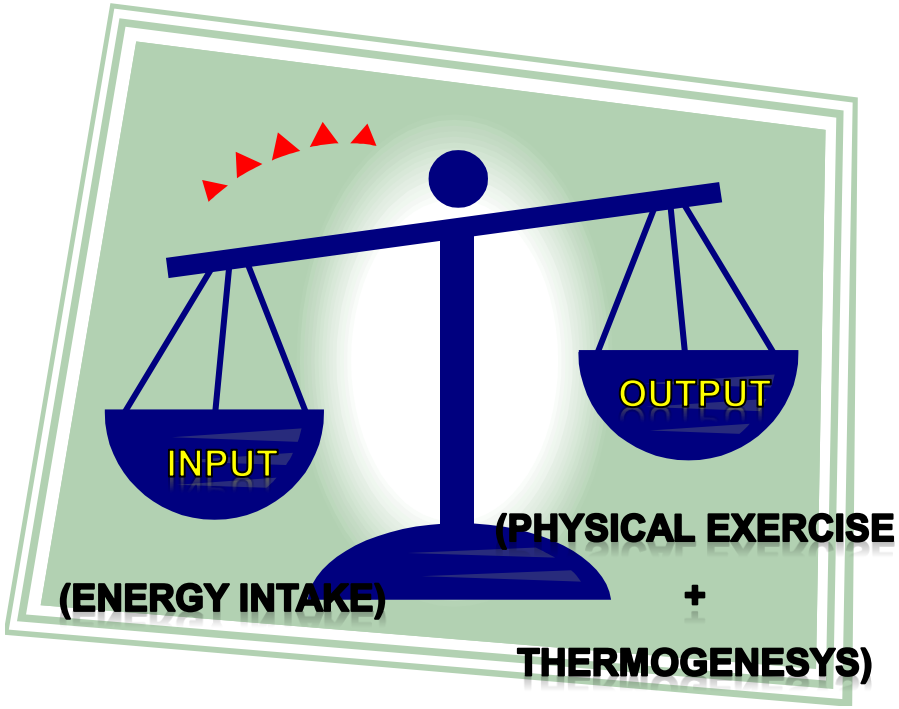


Metabolic Syndrome

Definition

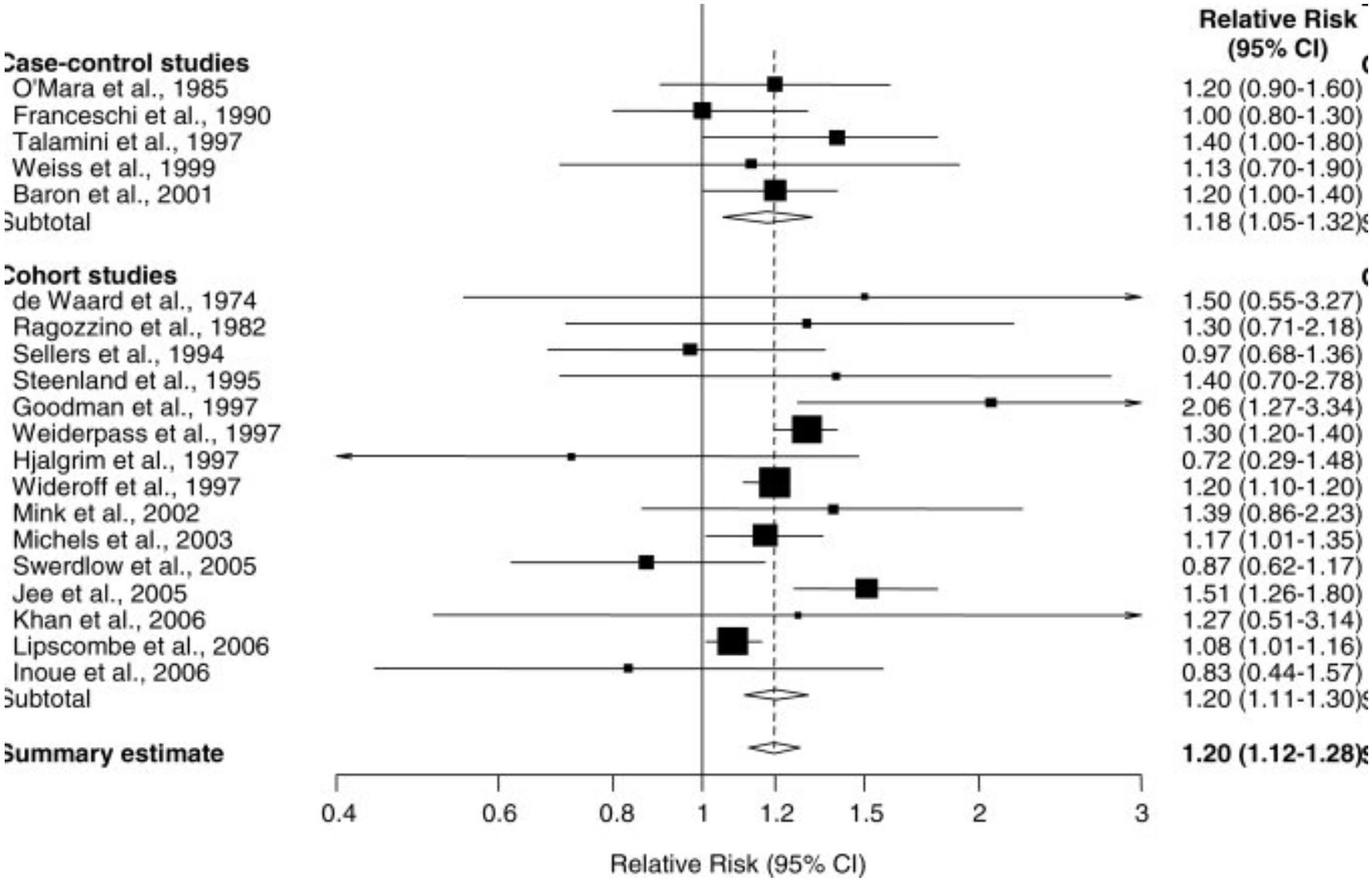
	ATP III 2001 (Rev 2004-2005)
Ab. Circumference	>102 cm (M) >88 cm (F)
Triglycerides	≥150 mg/dl
HDL Cholesterol	<40 mg/dl (M) <50 mg/dl (F)
Arterial Blood Pression	≥135/85 mmHg (or Therapy)
Glucose	≥100 mg/dl (or Therapy)

Aetiology



Energetic Balance

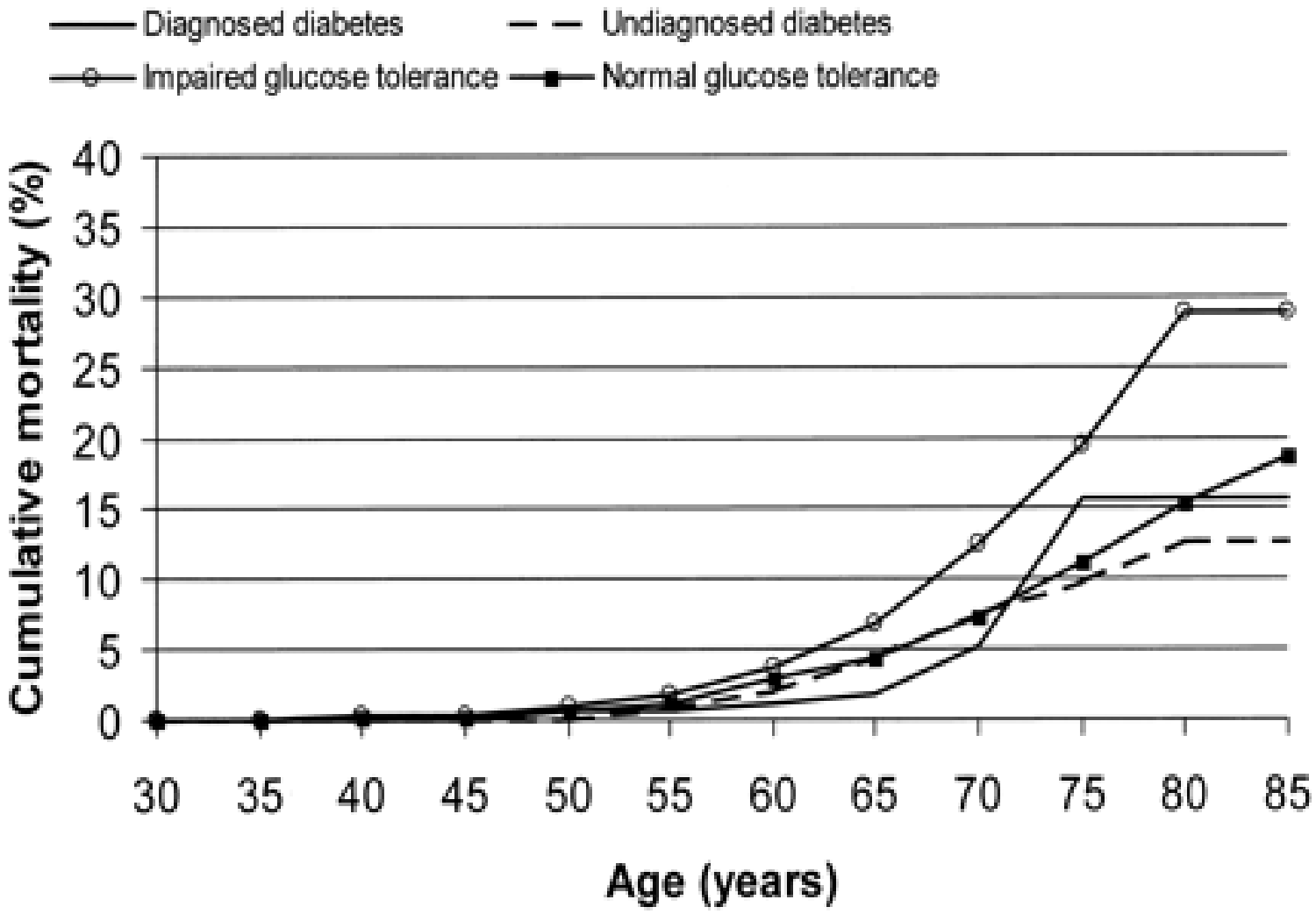
Eckel RH et al Lancet 2005 ; NCEP JAMA 2001; IDF 2005



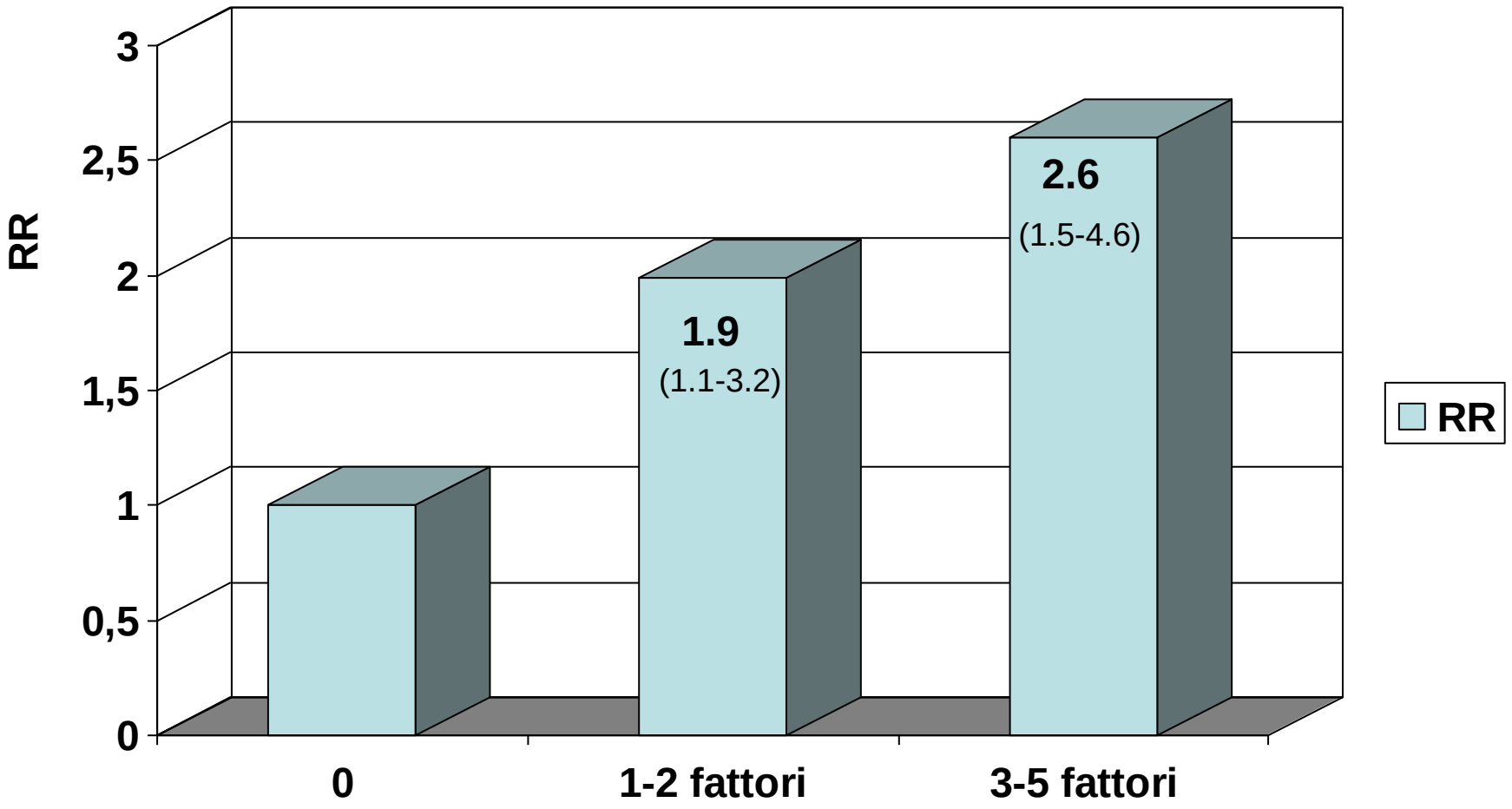
Diabete e cancro mammario. Larsson S, Wolk A 2007 int J Cancer 121:856

Intolleranza al glucosio e mortalità per cancro nel 2° National Health & Nutrition Examination Survey

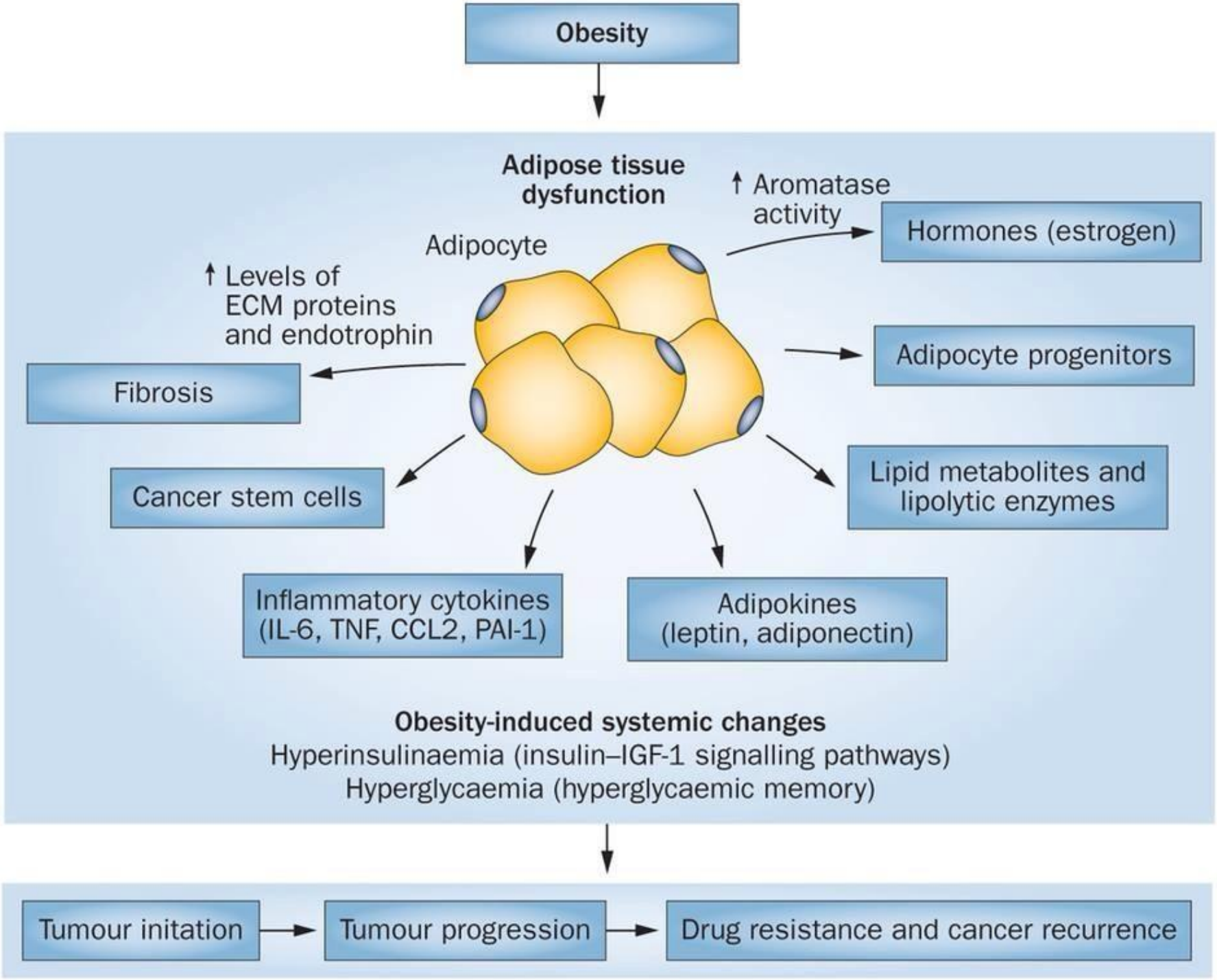
S. Saydah et al. 2003 Am J Epidemiol 157: 1092



RISCHIO DI CANCRO MAMMARIO IN FUNZIONE DEL NUMERO DI FATTORI DI SINDROME METABOLICA



Progetto ORDET (postmenopausa). Agnoli et al. 2009


Obesity
Adipose tissue dysfunction
↑ Aromatase activity
Hormones (estrogen)
Adipocyte
↑ Levels of ECM proteins and endotrophin
Fibrosis
Adipocyte progenitors
Cancer stem cells
Lipid metabolites and lipolytic enzymes
Inflammatory cytokines (IL-6, TNF, CCL2, PAI-1)
Adipokines (leptin, adiponectin)
Obesity-induced systemic changes
Hyperinsulinaemia (insulin–IGF-1 signalling pathways)
Hyperglycaemia (hyperglycaemic memory)
Tumour initation
Tumour progression
Drug resistance and cancer recurrence

The Metabolic Program of Tumor Cells

Dr. Otto Heinrich Warburg

1931 Nobel Prize Winner

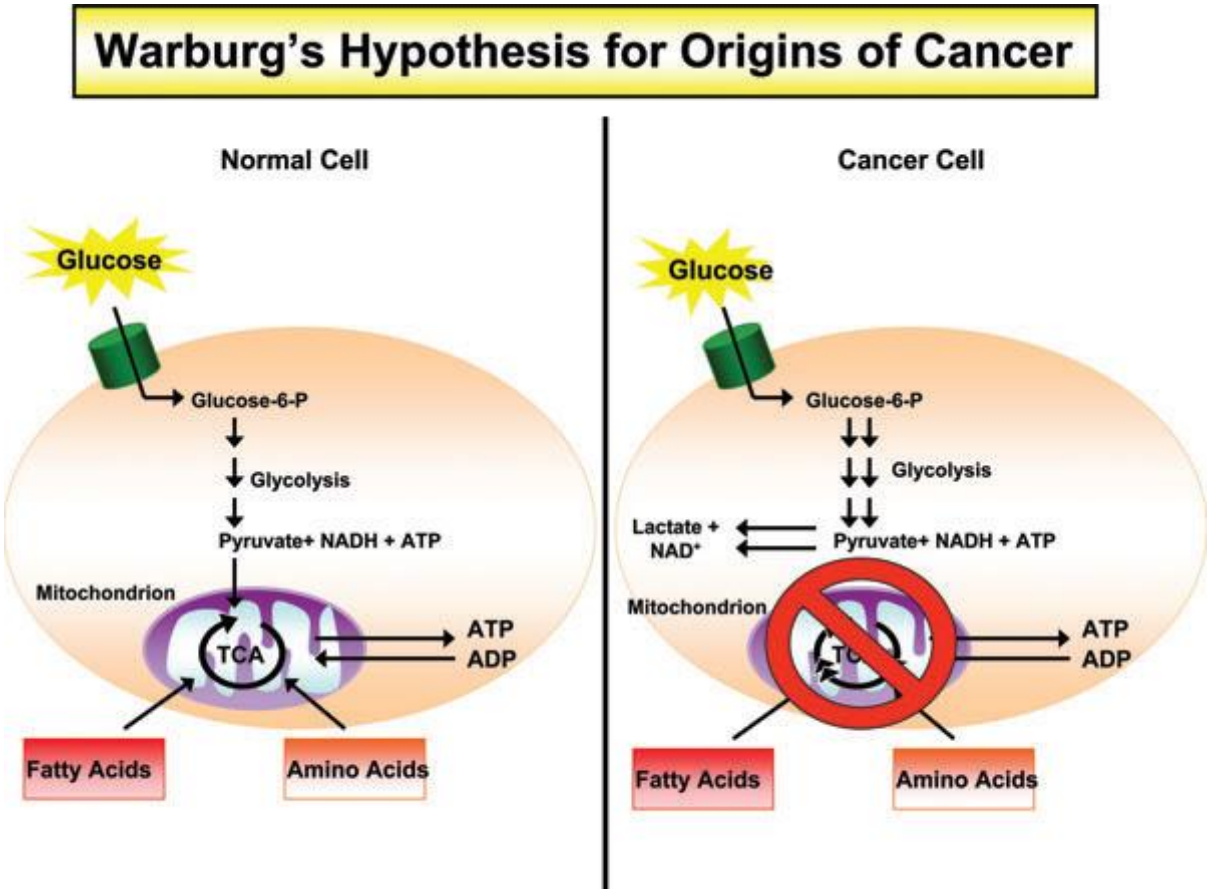
The Root Cause of Cancer

Dr. Otto Warburg discovered the root cause of cancer in 1923 and he received the Nobel Prize for doing so in 1931. Dr. Warburg was director of the Kaiser Wilhelm Institute (now Max Planck Institute) for cell physiology at Berlin. He investigated the metabolism of tumors and the respiration of cells, particularly cancer cells. Below are some direct quotes by Dr. Warburg during medical lectures where he was the keynote speaker:

"Cancerous tissues are acidic, whereas healthy tissues are alkaline. Water splits into H+ and OH- ions, if there is an excess of H+, it is acidic; if there is an excess of OH- ions, then it is alkaline."

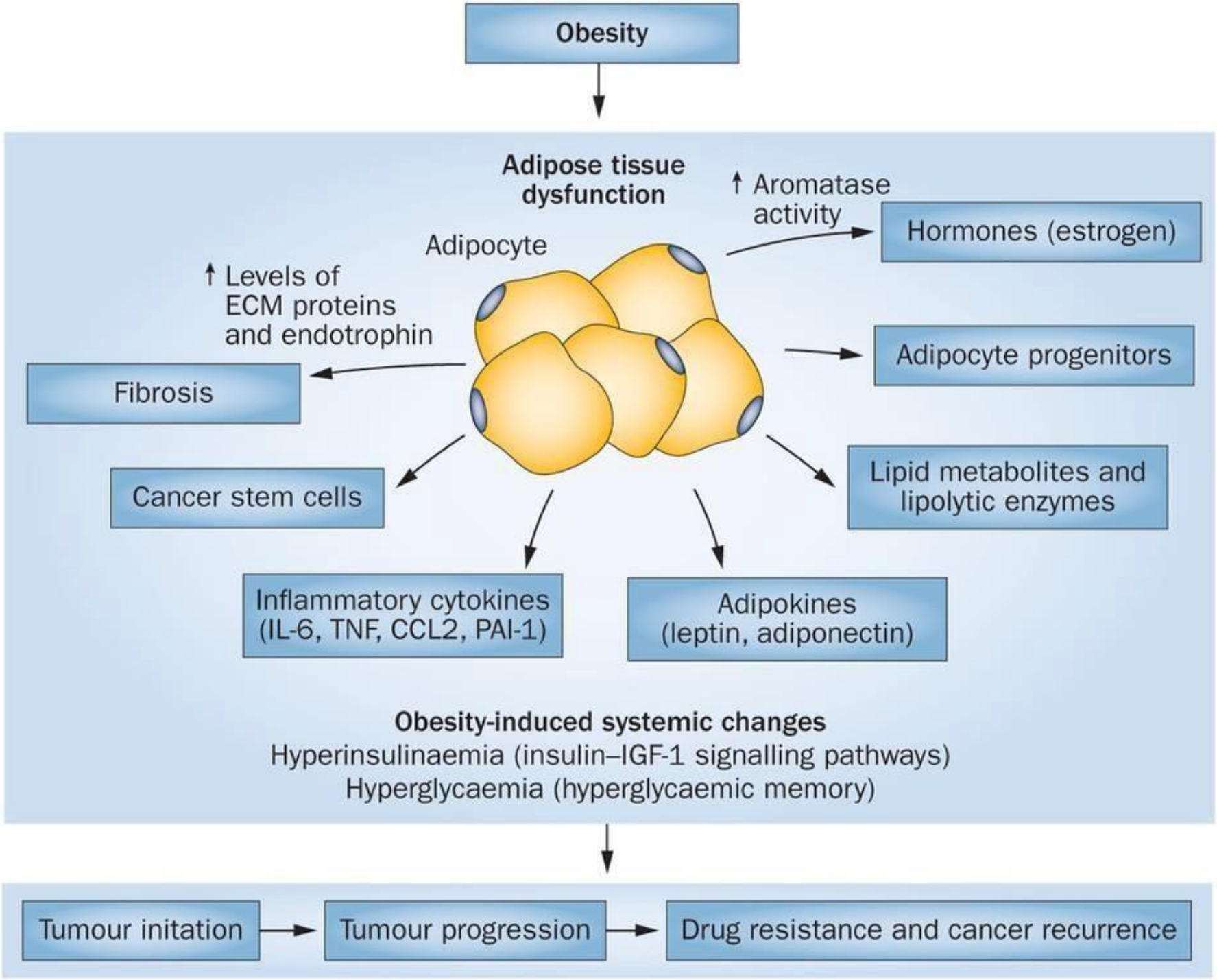
In his work *The Metabolism of Tumours* he demonstrated that all forms of cancer are characterized by two basic conditions: acidosis and hypoxia (lack of oxygen). Lack of oxygen and acidosis are two sides of the same coin: where you have one, you have the other.

"All normal cells have an absolute requirement for oxygen, but cancer cells can live without oxygen - a rule without exception." – Dr. Otto Warburg

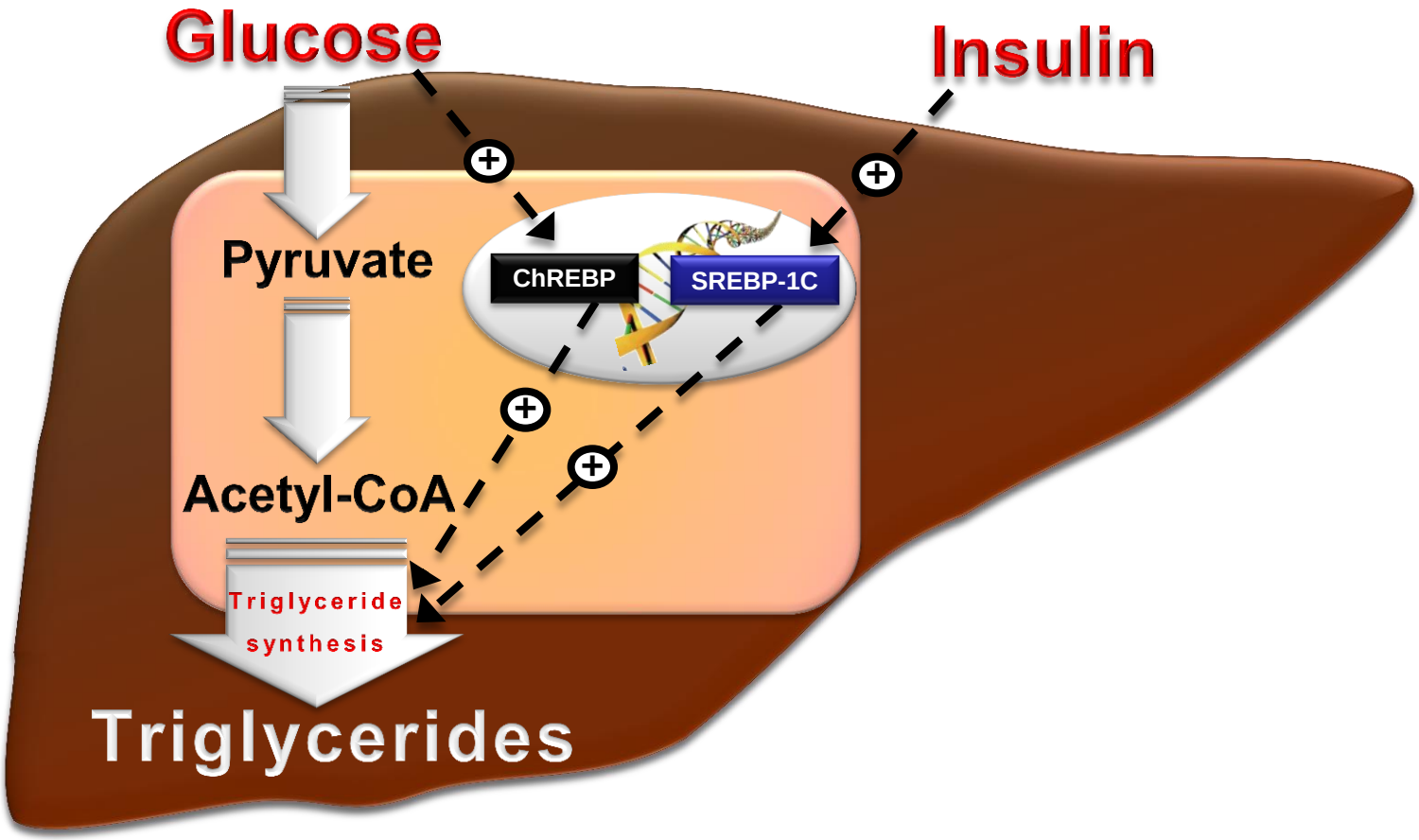


Even if tumor cells have functional mitochondria, a decrease in mitochondrial metabolism and respiratory rate is essential for tumor cell proliferation

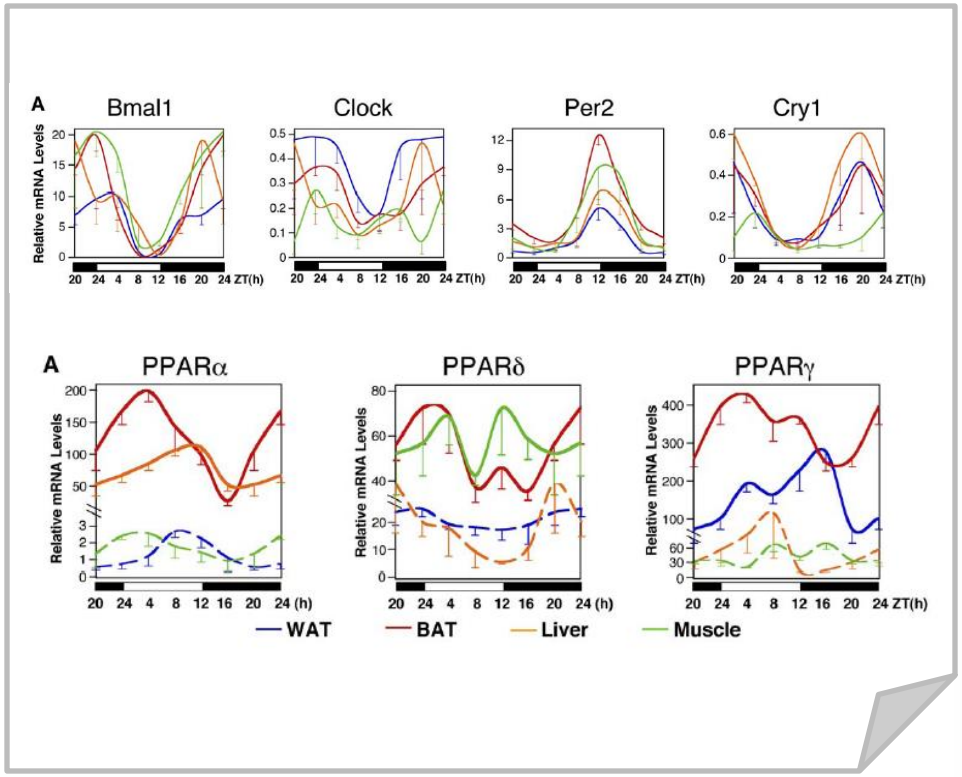
Perhaps increasing mitochondrial metabolism could be a strategy to prevent tumor growth

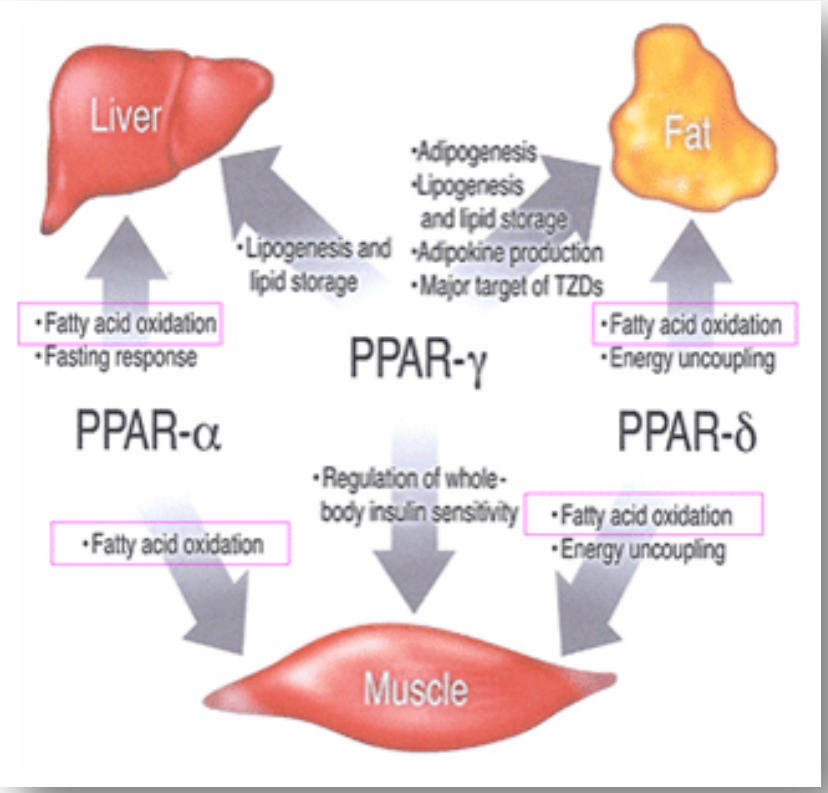

Obesity
Adipose tissue dysfunction
↑ Aromatase activity
Hormones (estrogen)
Adipocyte
↑ Levels of ECM proteins and endotrophin
Fibrosis
Adipocyte progenitors
Cancer stem cells
Lipid metabolites and lipolytic enzymes
Inflammatory cytokines (IL-6, TNF, CCL2, PAI-1)
Adipokines (leptin, adiponectin)
Obesity-induced systemic changes
Hyperinsulinaemia (insulin–IGF-1 signalling pathways)
Hyperglycaemia (hyperglycaemic memory)
Tumour initation
Tumour progression
Drug resistance and cancer recurrence

Carbohydrate Overload



MS is a disease of the “Biological Clock” Implications at the level of the genome





Xiaoyong Yang, Cell 2006
Lemartelot Plos Biol 2009

Take Home Messages

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AIRC
European Research Council, European Science Foundation,
FP7 Lipidomicnet, MIUR, Ministero della Salute, UNIBA