Personalizing One's Diet for Cancer Prevention

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National Cancer Institute

Sponsored by the University of Arizona College of Medicine at the Arizona Health Sciences Center
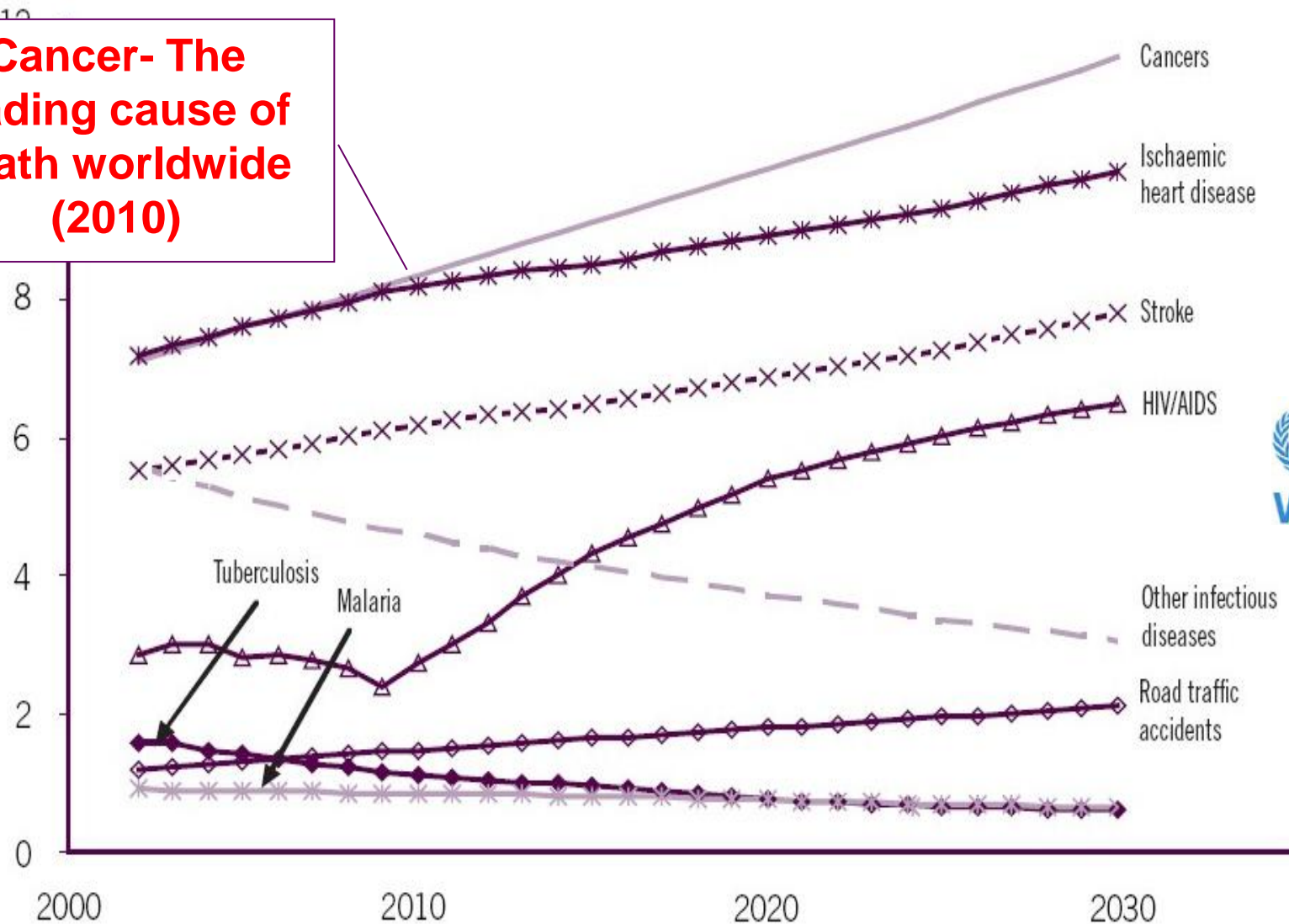
THE UNIVERSITY OF ARIZONA.

Arizona Health Sciences Center

No Disclosures

The World Is Changing: Projected Deaths

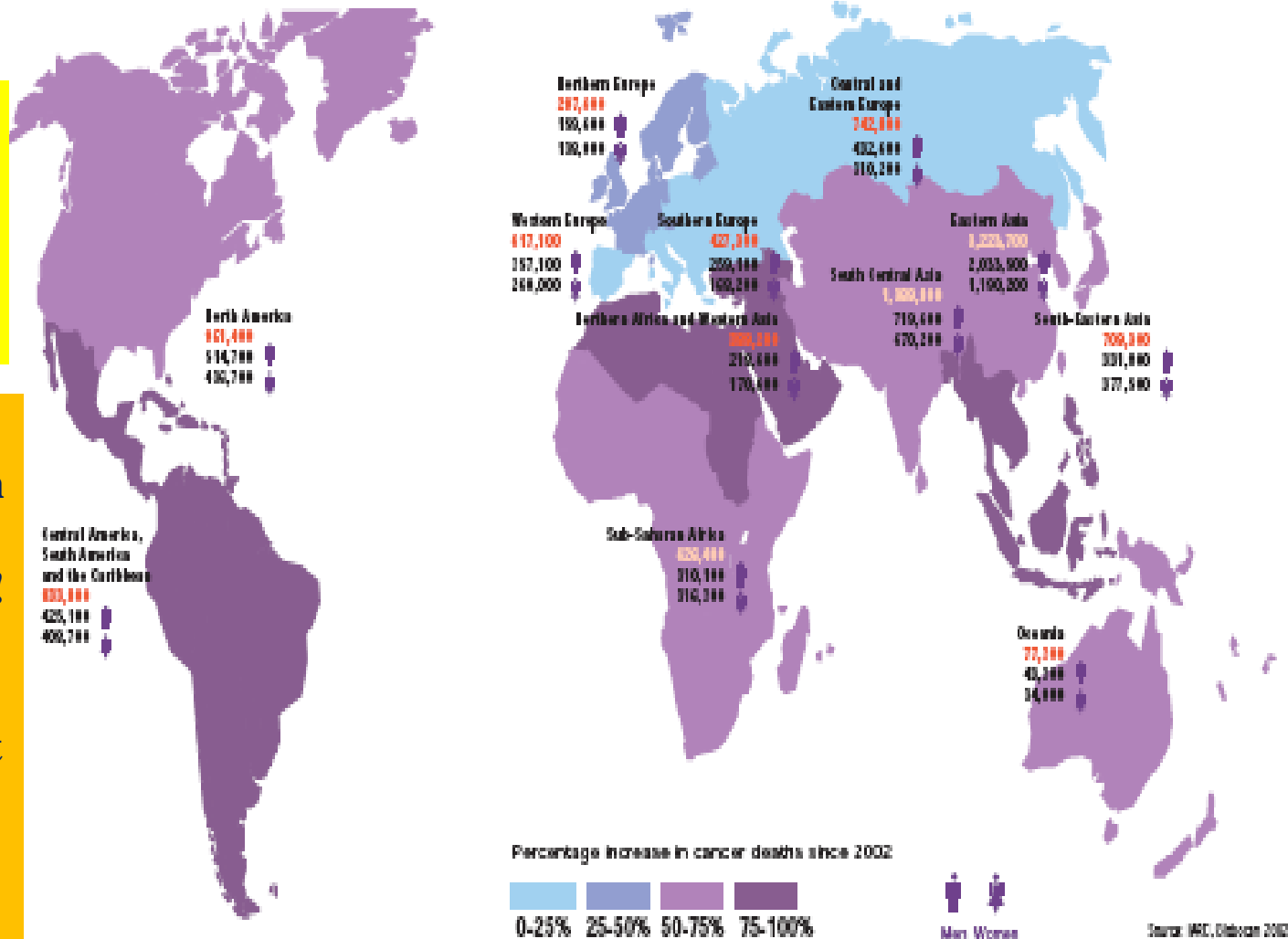**Cancer- The leading cause of death worldwide (2010)**

By **2020**, cancer **could kill** **10.3 million** people per year unless we act
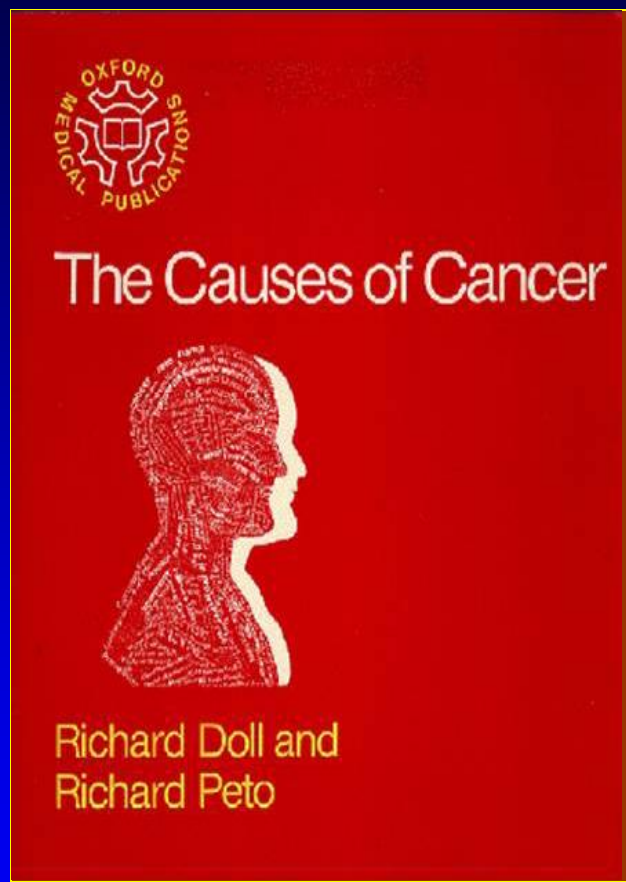
Increase partially due to aging & growing society!

Do we have the infrastructure in place to deal with this crises?! What dietary change is best? Who will benefit and will anyone will be placed at risk??
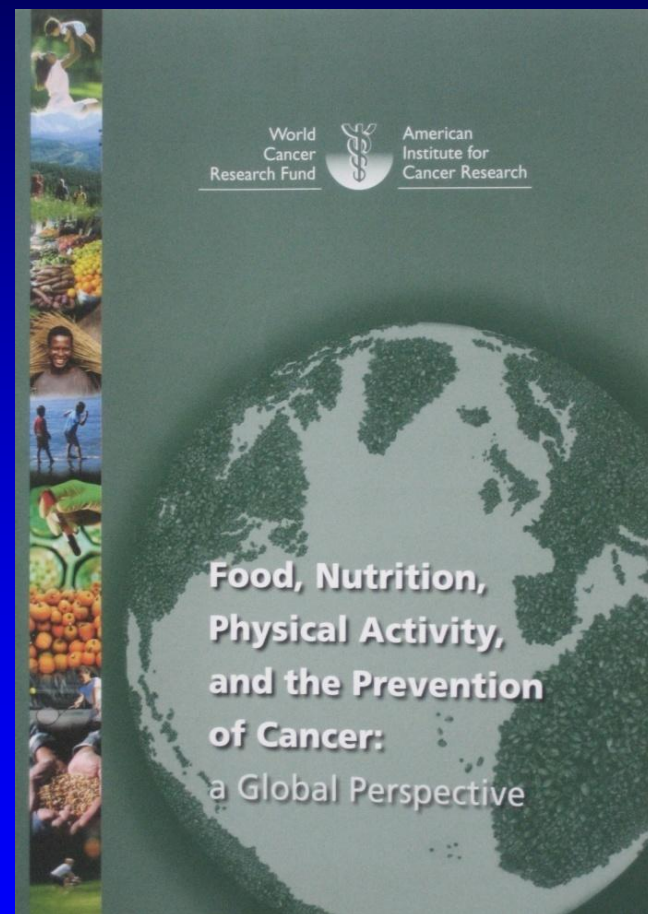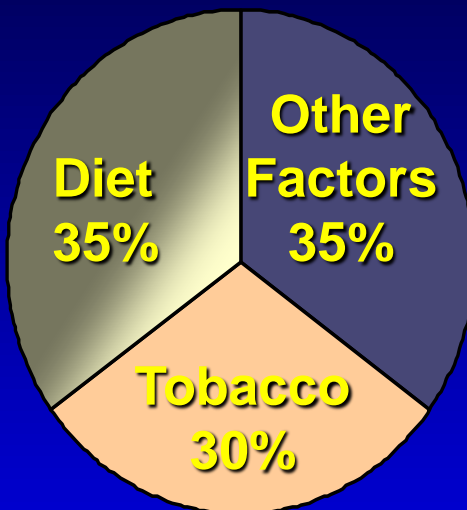
Dr. Lee Jong-wook, Director General WHO

It has been estimated that about 1/3 of all cancer deaths may be attributable to dietary factors.

The Causes of Cancer
– Richard Doll & Richard Peto, 1981

Diet 35%

Other Factors 35%

Tobacco 30%

WCRF/AICR Report
- Released Nov. 1-2, 2007

Suspect Functional Foods With Health Benefits

- Soy
- Tomatoes
- Spinach
- Broccoli
- Garlic
- Nuts
- Salmon
- Oats
- Blueberries
- Curcumin
- Green tea
- Red wine

Modified Time Magazine: January 21, 2002

Numerous Dietary Components Can Protect Against Cancer

- Essential Nutrients- Ca, Zn, Se, Folate, C, E
- Non-Essential

   Phytochemicals- Carotenoids, Flavonoids, Indoles, Isothiocyanates, Allyl Sulfur

   Zoochemicals - Conjugated linoleic acid, n-3 fatty acids

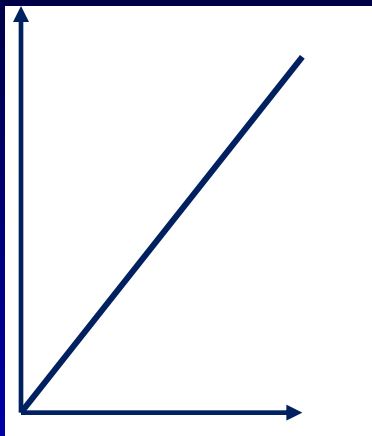   Fungochemicals - Several compounds in mushrooms

   Bacteriochemical - Those formed from food fermentations and those resulting from intestinal flora

Bacteria Can Generate New Metabolites from Dietary Components

Food Component	Bacterial Metabolite
Soy	Equol
Fiber	Butyrate
Plant Lignans	Enterodiol, Enterolactone
Ellagic Acid	Urolithins A and B
Hops	8-Prenylnaringenin
Linoleic Acid	Conjugated Linoleic Acid

Always Questions About How Much Is Needed!

Better / **More**
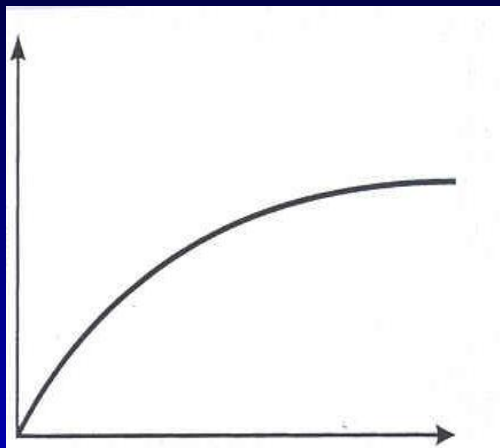
As progress the response gets better and better, with no end in sight (real life is seldom, if ever, like this. People often assume that if X is good, then 10X is better.
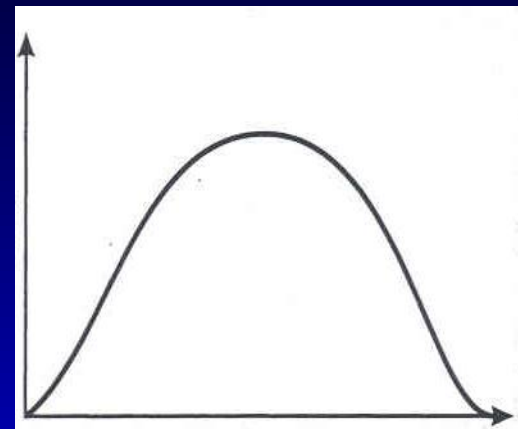

Better / **More**

As increase the effect reaches a plateau, becoming no better with higher doses. This is common with many nutrients. Any excess is not absorbed and excreted (expensive urine / feces)
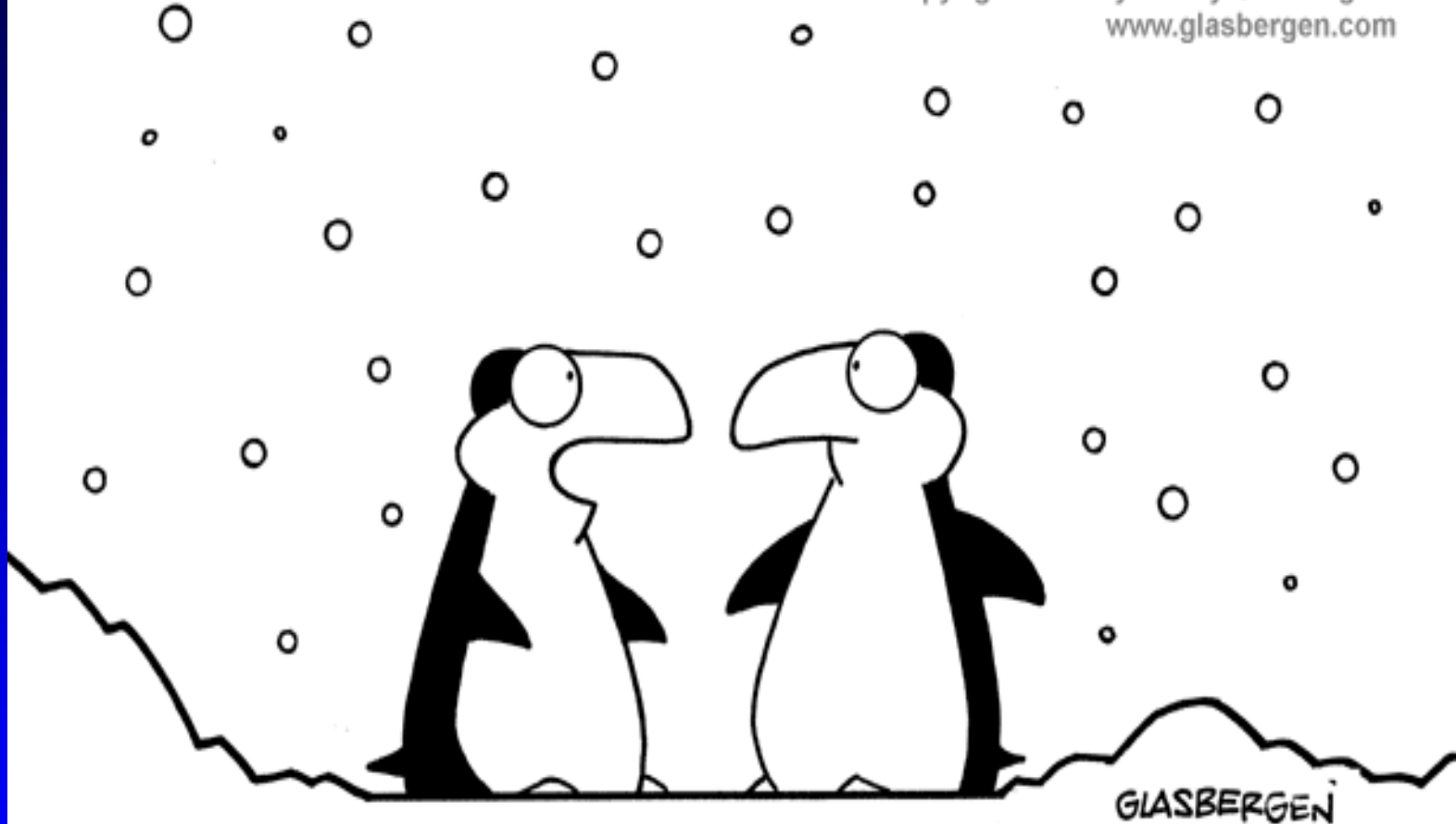

Better / **More**

As increase effect reaches optimum At some dose it declines, showing that more is better up to a point and then harmful. Applies to some nutrients, e.g. Na^+ high blood pressure, Fe, Se.

While Diet Linked to Cancer, Much Confusion Exists About What to Eat and Under What Circumstances!!

"Low fat diets don't work. I eat fish every day and my butt still drags on the ground!"

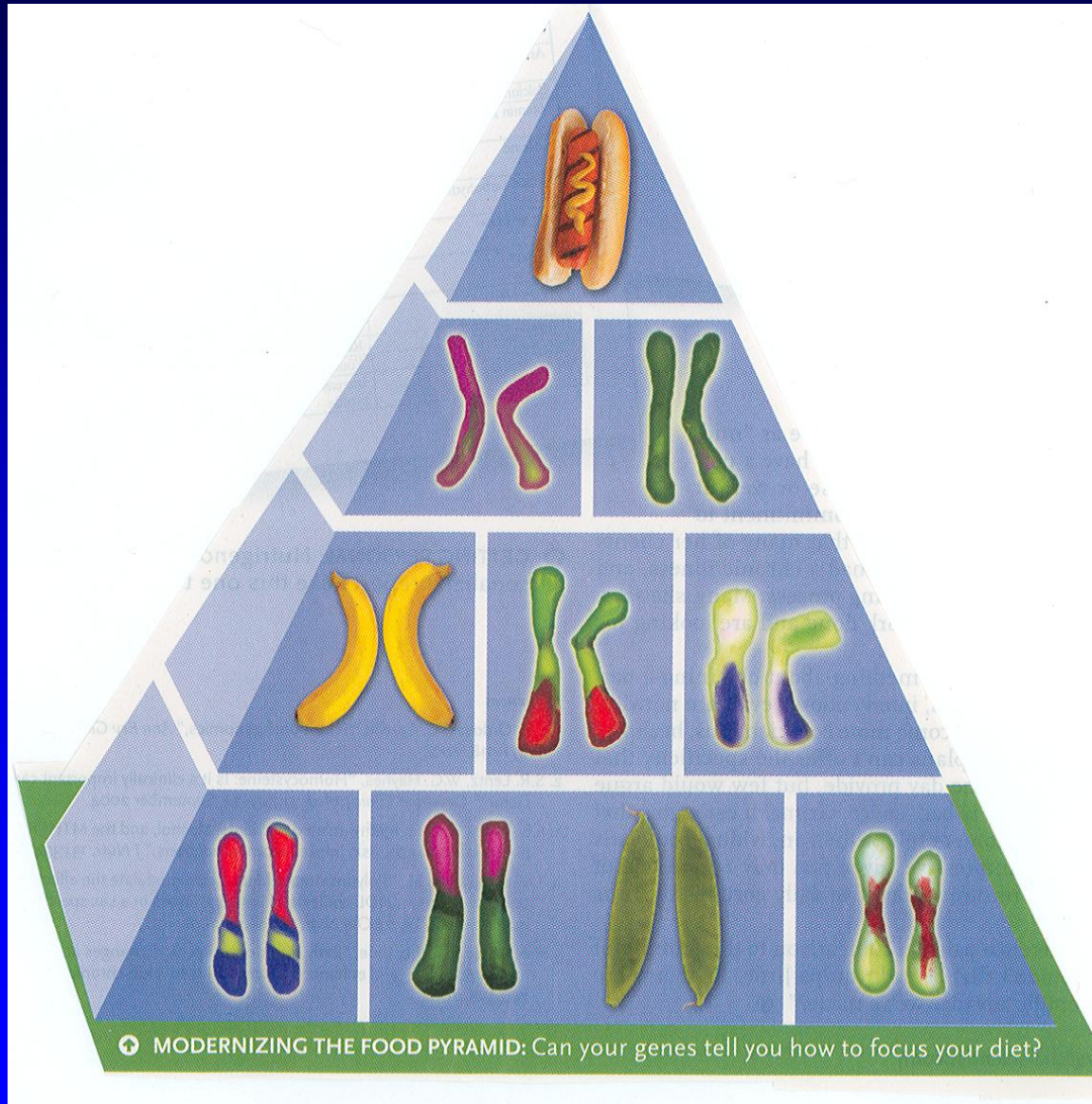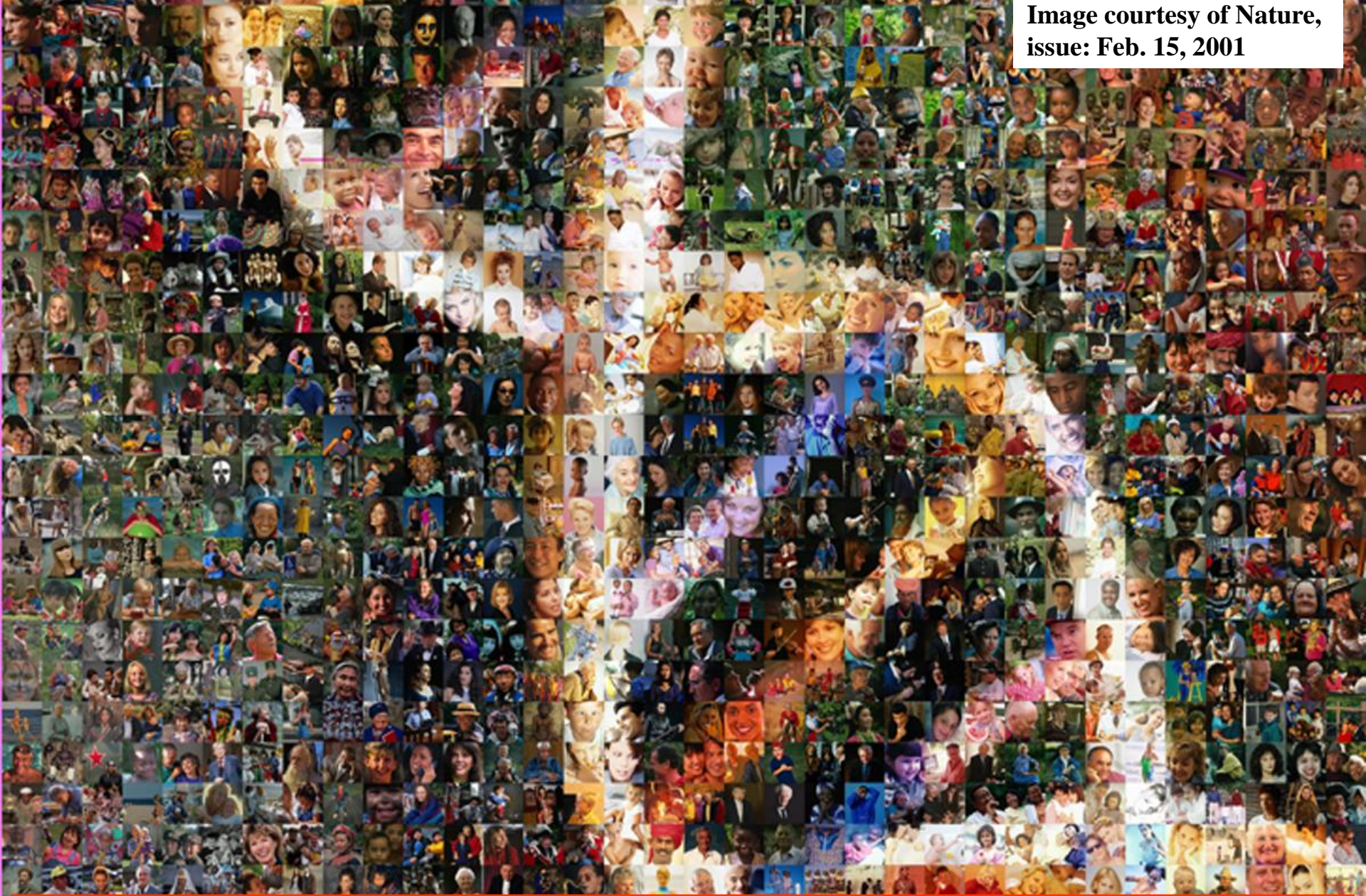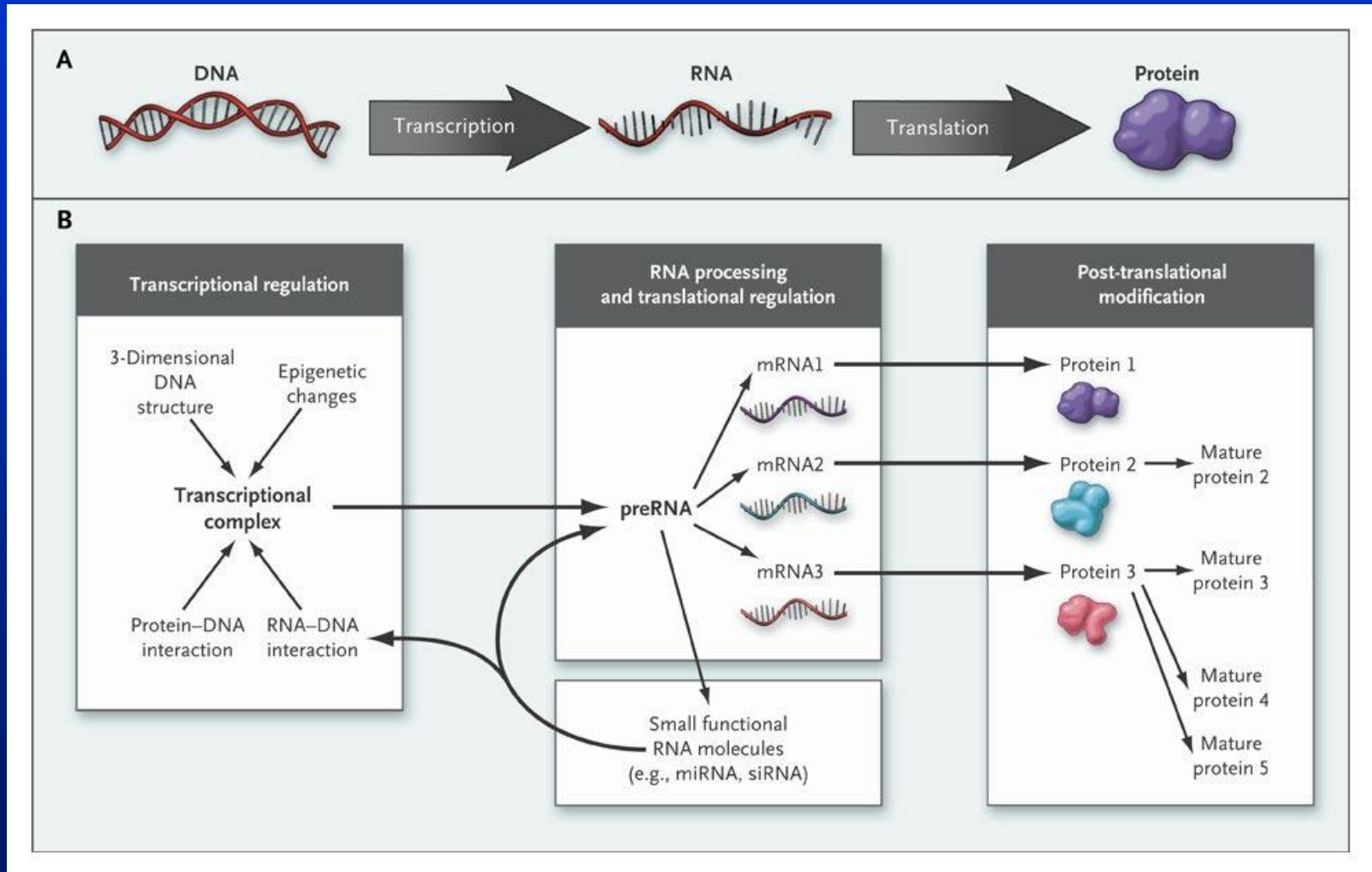# Can your genes tell you how to focus your diet for cancer prevention?

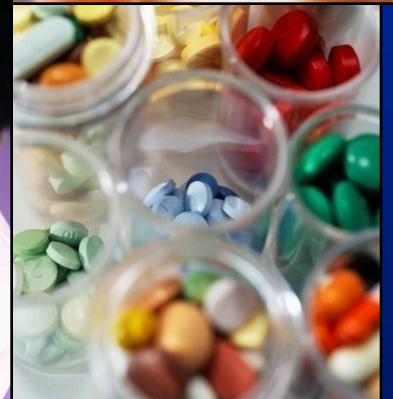MODERNIZING THE FOOD PYRAMID: Can your genes tell you how to focus your diet?

The Genetic Revolution is Providing New Insights into a Number of Health Issues Including the Role of Diet in Cancer Prevention

The Increasing Complexity of the Central Dogma of Molecular Biology

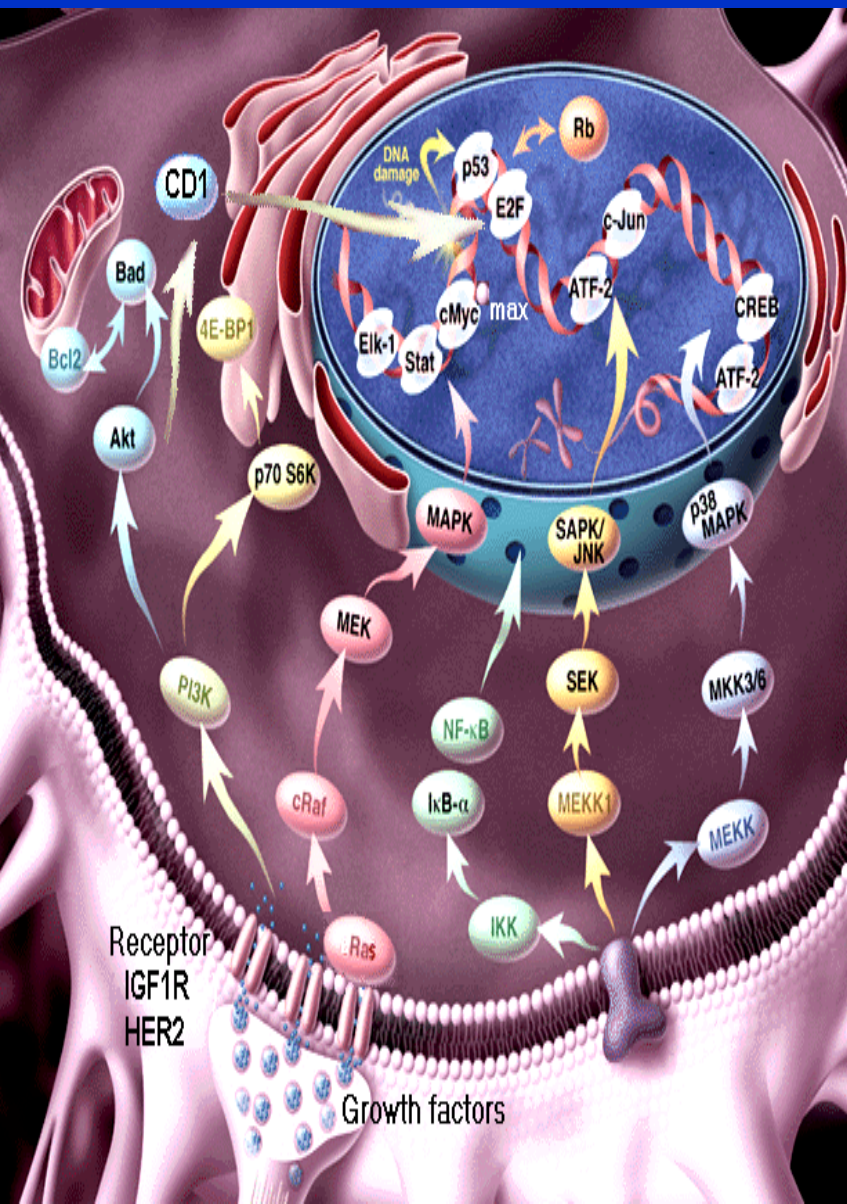Feero W et al. N Engl J Med 2010;362:2001-2011

What is Personalized Medicine?

- ➢ **Using information about a person's genetic makeup to tailor strategies for the detection, treatment, or prevention of disease.**

- ➢ **Using molecular profiling technologies to assess DNA, RNA, protein, and metabolites to tailor medical care.**

- ➢ **Approach has the promise of delivering the right dose for the right indication to the right patient at the right time.**
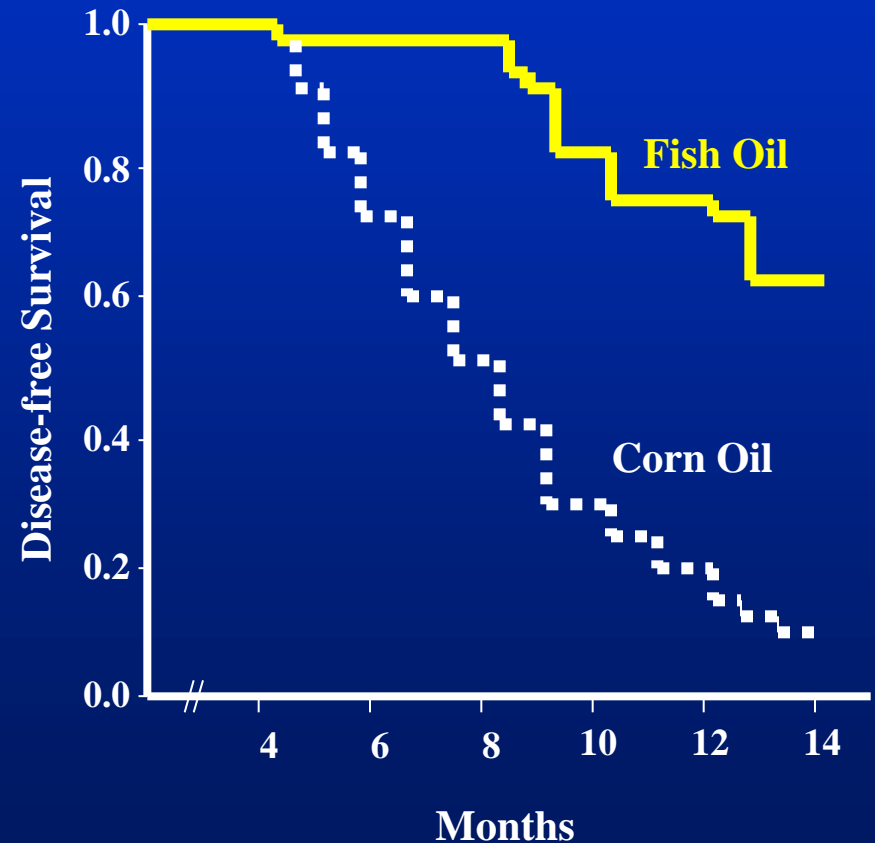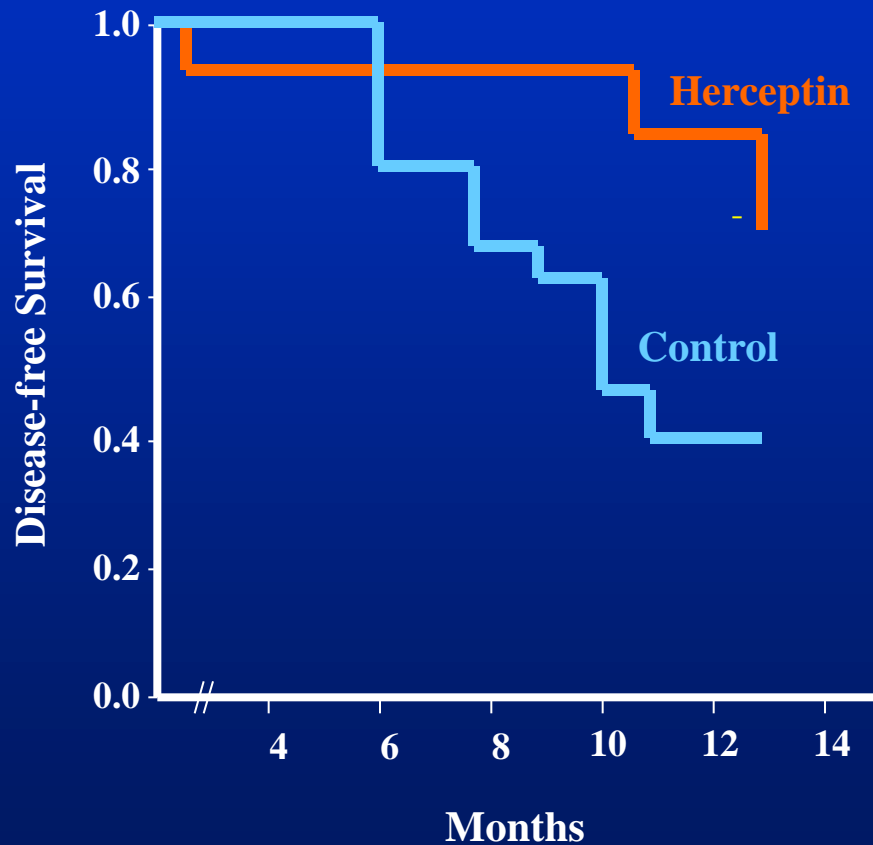
Personalized Medicine versus Personalized Nutrition

Recent advances:

Herceptin is a Novel Pioneering Drug for Personalized Medicine Approach Based on Pharmacogenomics to block Her2-neu expression.

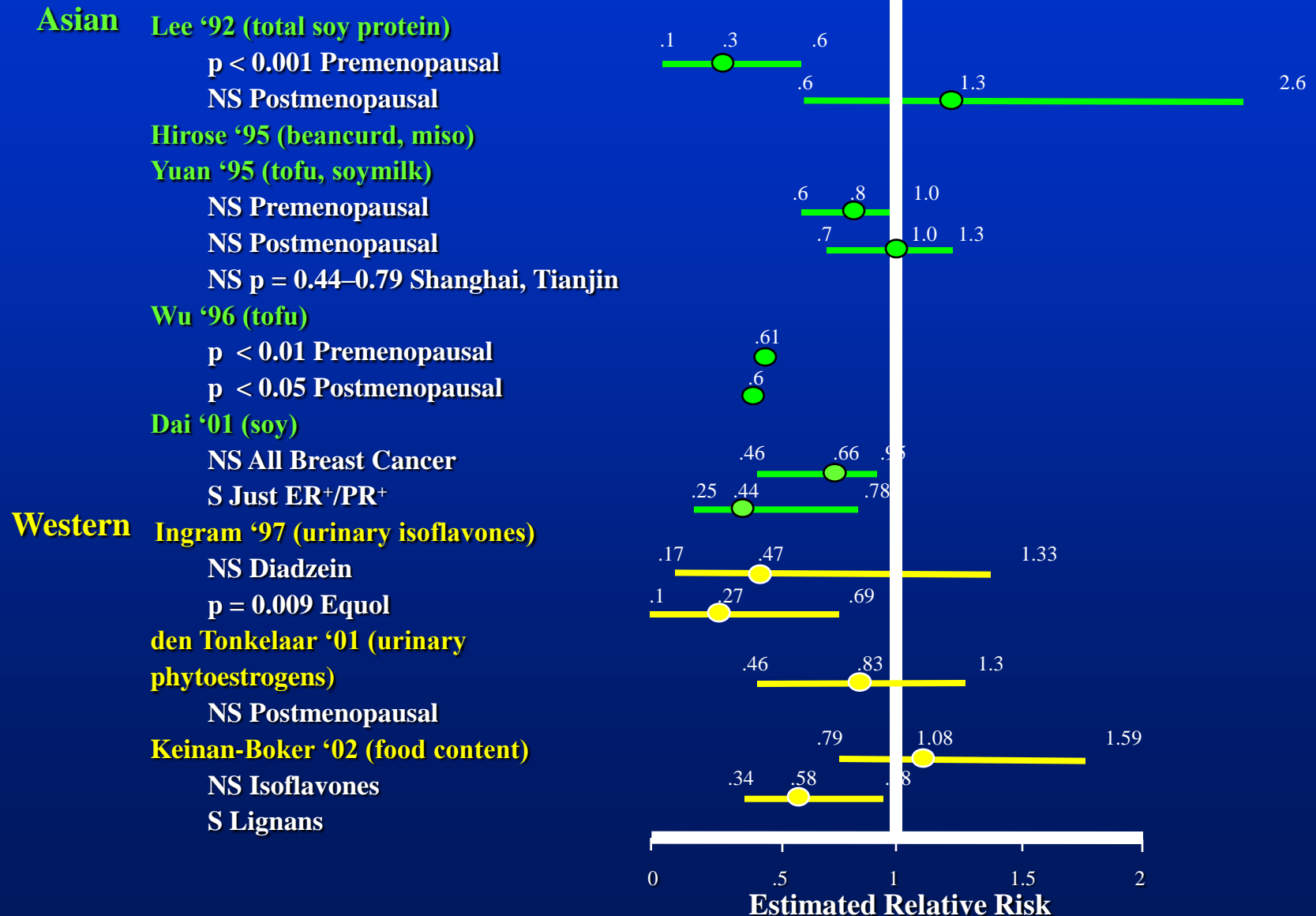## Evidence Has Existed for Some Time:

EGCG from Green Tea, Oleic Acid from Olive Oil, n-3 fatty acids from Fish Oil and Apigenin from parsley, thyme, and peppermint may also significantly influence HER2neu expression!

Herceptin and Dietary fish oil increased the latency time to mammary gland tumor development in the HER-2 transgenic mice

Finkle D et al Clin Cancer Res 10: 2499-511, 2004

Yee LD et al J Nutr 135: 983-8, 2005

The Literature Provides Mixed Conclusions.
Epidemiologic Studies of Dietary Soy Components and Breast Cancer Risk

Asian

Lee '92 (total soy protein)
  p < 0.001 Premenopausal — .1 .3 .6
  NS Postmenopausal — .6 1.3 2.6
Hirose '95 (beancurd, miso)
Yuan '95 (tofu, soymilk)
  NS Premenopausal — .6 .8 1.0
  NS Postmenopausal — .7 1.0 1.3
  NS p = 0.44–0.79 Shanghai, Tianjin
Wu '96 (tofu)
  p < 0.01 Premenopausal — .61
  p < 0.05 Postmenopausal — .6
Dai '01 (soy)
  NS All Breast Cancer — .46 .66 .95
  S Just ER+/PR+ — .25 .44 .78

Western

Ingram '97 (urinary isoflavones)
  NS Diadzein — .17 .47 1.33
  p = 0.009 Equol — .1 .27 .69
den Tonkelaar '01 (urinary phytoestrogens)
  NS Postmenopausal — .46 .83 1.3
Keinan-Boker '02 (food content)
  NS Isoflavones — .79 1.08 1.59
  S Lignans — .34 .58 .8

Estimated Relative Risk: 0 | .5 | 1 | 1.5 | 2

Part of Confusion Arises from Trying to Use Population Information to Predict Individual Responses

If only cancer prevention was this easy…

Using the "Omics" of Nutrition to Identify Responders from Non-Responders

Human Genetic Variation

Genomics Can Influence the Response to Diet at Multiple Points

- ➤ Food preference
- ➤ Food tolerance
- ➤ Absorption
- ➤ Transport
- ➤ Metabolism
- ➤ Effect in target tissue

Lampe and Potter, in *Gene-Envir Interactions* (2006)

Genetics Can Influence What Types of Foods Are Consumed

Food group	Additive genetic effect	Shared environment effect
Meat and fish	0.78 (.63-.92)	0.12 (.00-.27)
Vegetables	0.37 (.20-.58)	0.51 (.30-.66)
Fruits	0.51 (.37-.68)	0.32 (.16-.46)
Desserts	0.20 (.04-.38)	0.64 (.46-.77)

n= 103 MZ and 111 DZ twin pairs

Specific Genes Can Influence What We Like to Eat

Knockout Suggest Glucose Transporter Type-2 (GLUT2) Involved

Esophagus
Gallbladder
Liver
Stomach
Sigmoid colon
Duodenum
Pancreas
Colon
Small Intestine
Anus
Rectum

GLUT2 Polymorphism

Thr 110 **Ile**

Sugar (g/d)

125
100
75
50

*

Thr/Thr

Thr/Ille + Ille/Ille

Single Nucleotide Polymorphisms in the VDR gene

5'　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　3'

1f　　1e 1a 1d 1b　　1c　2　　3　　4 5　6　　7 8 9 3'UTR

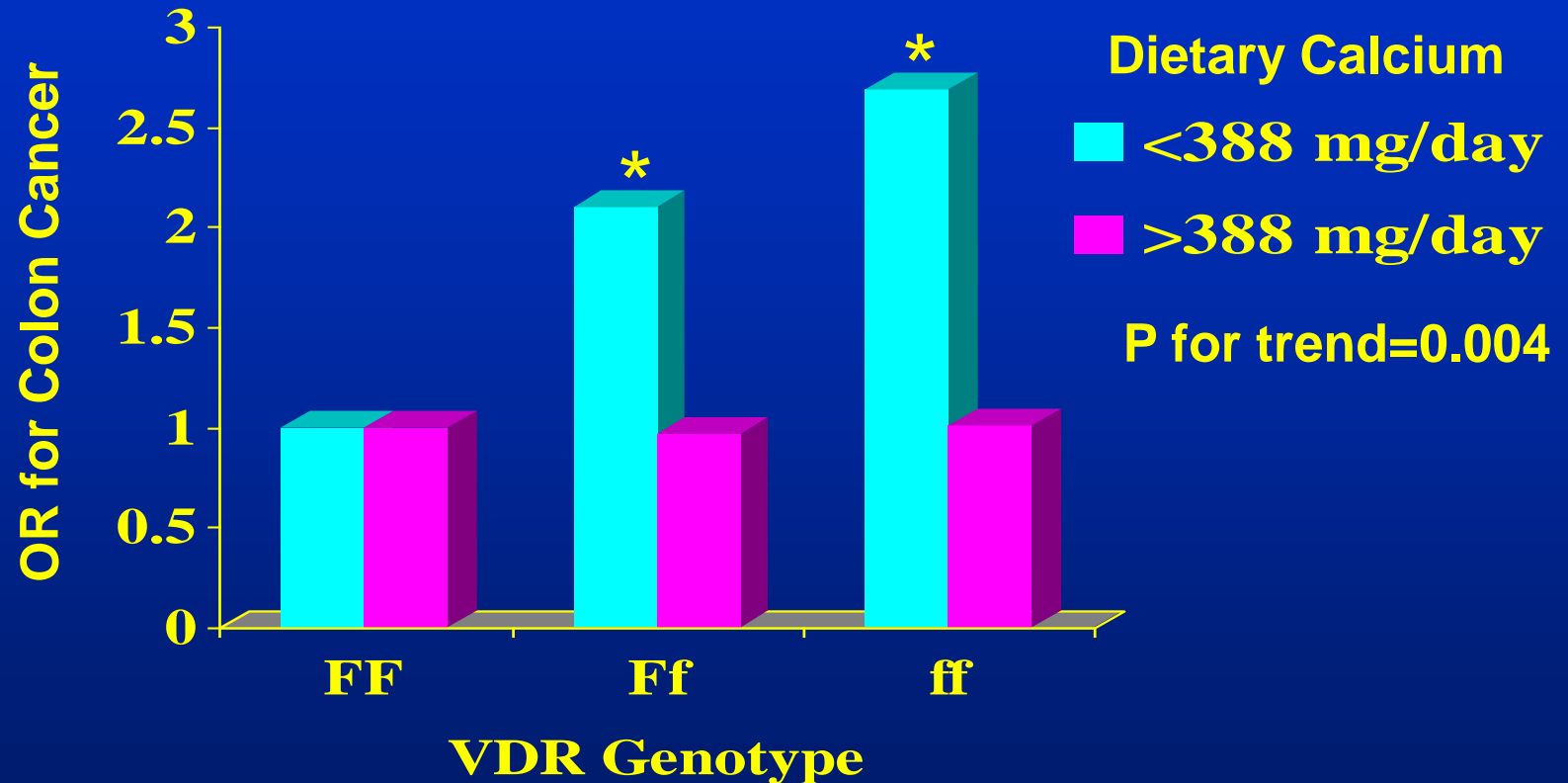Cdx-2 *GATA*　　　　　　*Fok1*　　　　　　*Taq Apa1* Poly *A*

Human VDR >470 reported SNPs
Distribution and frequency varies among ethnic groups

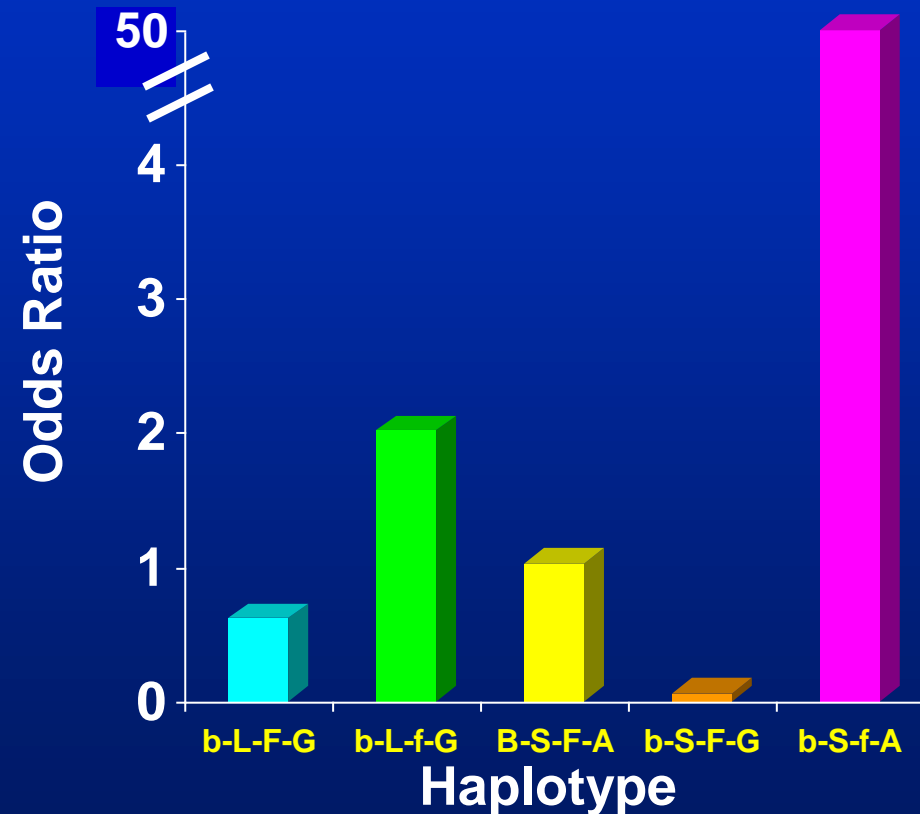# VDR *FokI* Polymorphism Affects Calcium Homeostasis in Adolescence

Abrams et al. (2005) J. Bone Mineral Res. 20: 945-953.

Dietary Calcium, VDR *FokI* Genotype and Colon Cancer Risk

Wong et al. Carcinogenesis, 24: 1091-1095, 2003

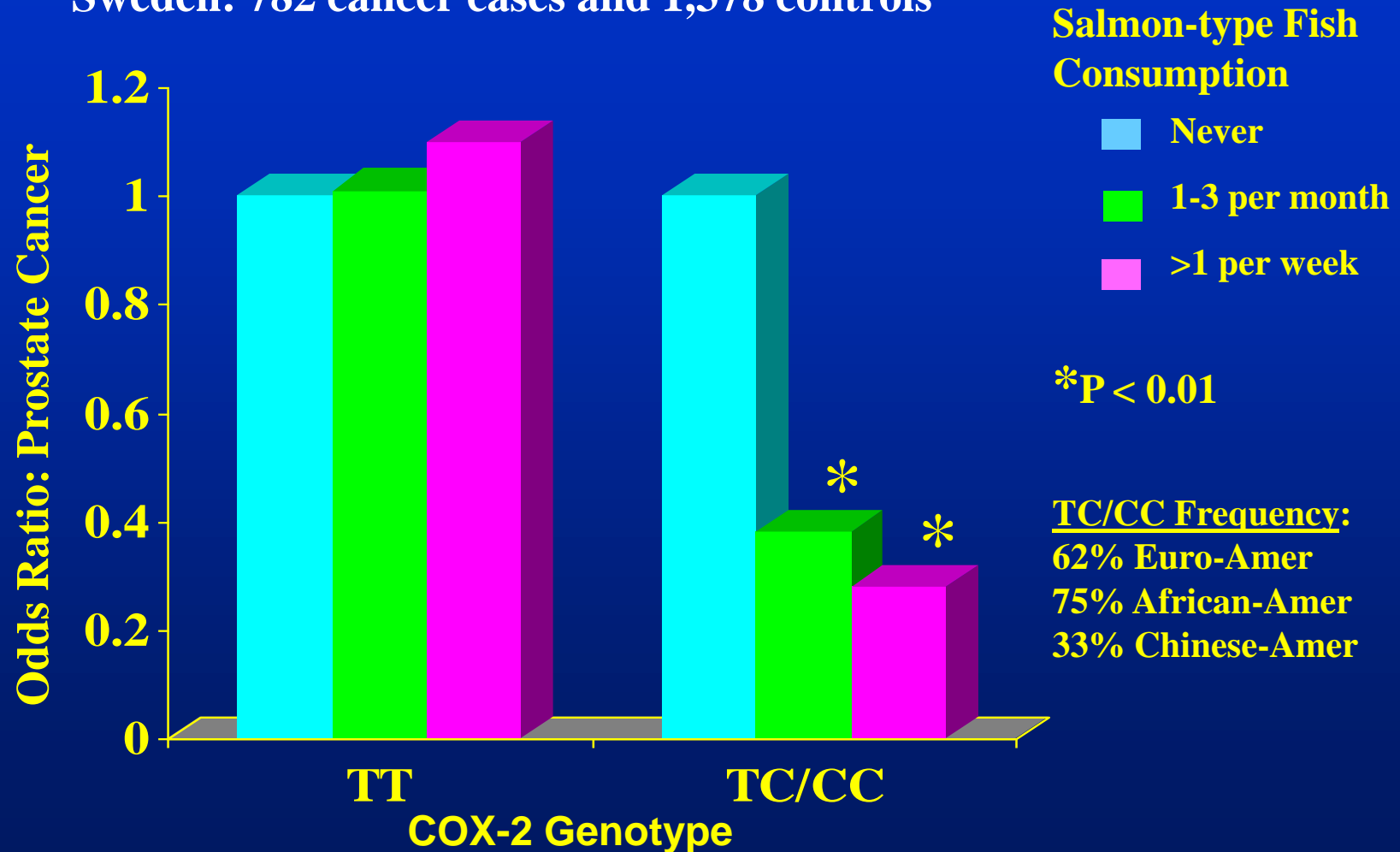# Haplotypes in the VDR Gene Influence Colon Cancer Risk

Bsml (b or B), poly (A) S or L, *Fok I* (f or F) and CDX2 (G or A); 1574 cases and 1970 controls

- ➤ **Haplotype frequencies varied by ethnic group**
- ➤ **OR for colon cancer varied from 0.06 to 51.12 depending on haplotype**

Slattery et al. Cancer Epidemiol Barmark Prev. 16:2752-5, 2007

Genetic Information May Assist in Identifying Those Who Will Benefit from Supplemental Intake

COX-2 (rs5275+6365 T/C) and prostate cancer risk
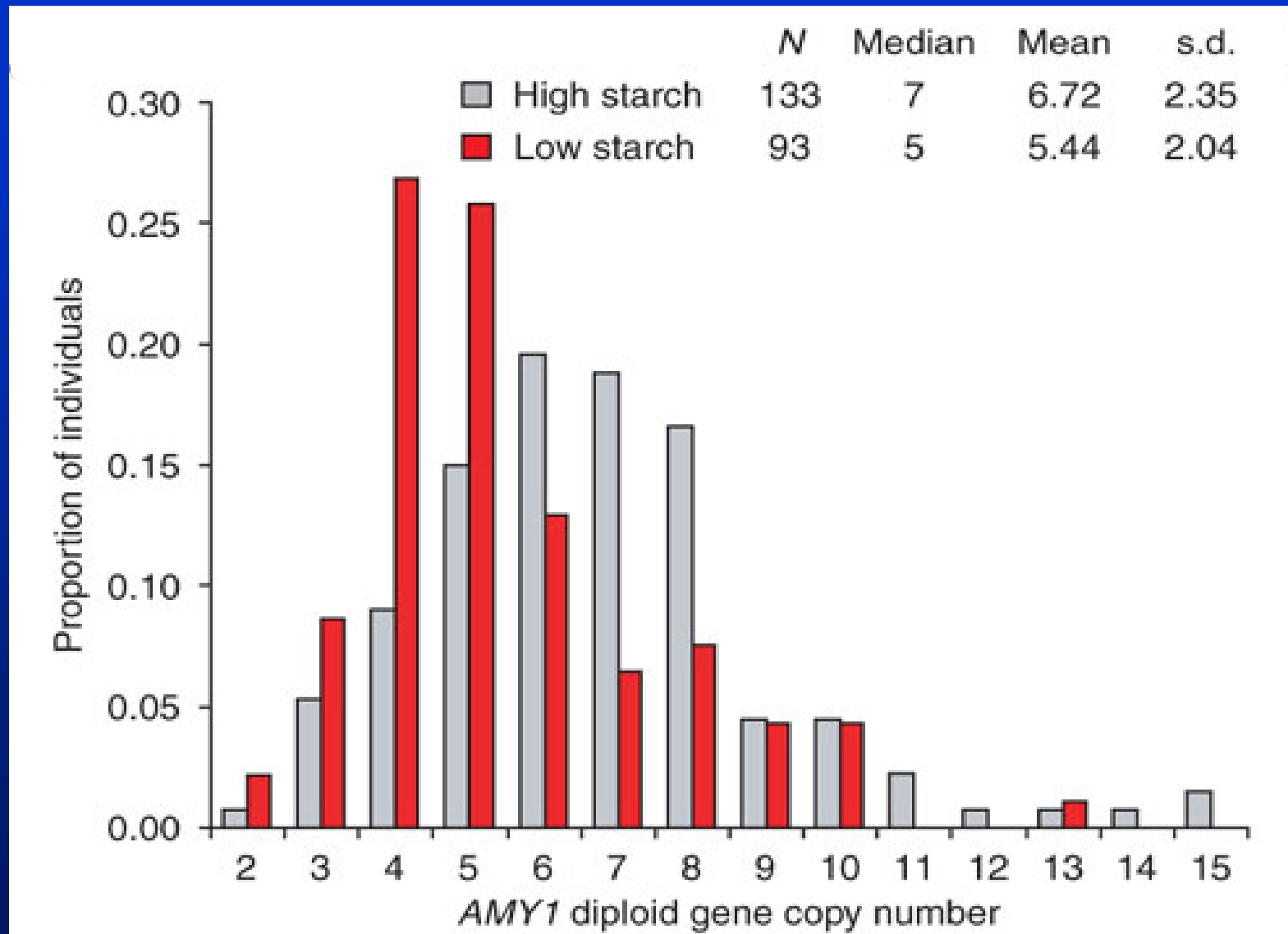Sweden: 782 cancer cases and 1,378 controls

Salmon-type Fish Consumption
- Never
- 1-3 per month
- >1 per week

*P < 0.01

TC/CC Frequency:
62% Euro-Amer
75% African-Amer
33% Chinese-Amer

Odds Ratio: Prostate Cancer

COX-2 Genotype

TT   TC/CC

Hedlin et al. (2006) Int. J. Cancer, 120:398-405.

Genetic Information May Also Identify Those at Risk from High Intakes

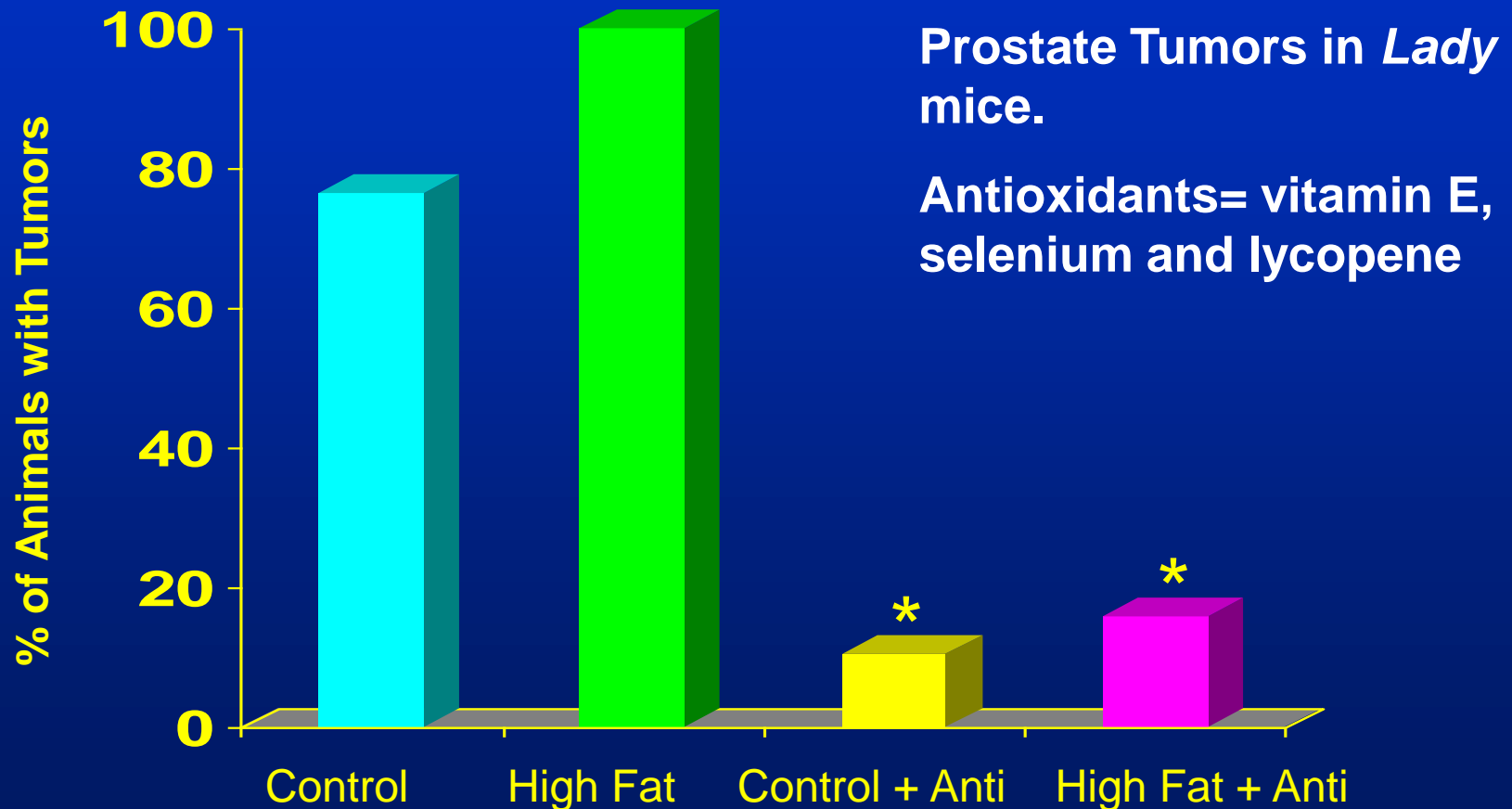**PPAR⊠ Genotype, Fish Consumption and Colon Cancer Risk**

Siezen et al., Carcinogenesis 26:229-457, 2005

Diet and Human Amylase Gene Copy Number

	N	Median	Mean	s.d.
High starch	133	7	6.72	2.35
Low starch	93	5	5.44	2.04

Perry et al. (2007) Nature Genetics 39(10):1256-60.

Diet Can Modify Genetic Susceptibility to Cancer

Prostate Tumors in *Lady* mice.

Antioxidants= vitamin E, selenium and lycopene

Venkateswaran et al., Cancer Research 64: 5891-5896, 2004

Gene-Nutrient Interactions and Colon Cancer

Percent survival vs Weeks survival curves:
- p21+/+ AIN-76A Diet
- p21+/- AIN-76A Diet
- p21+/+ Western Diet
- p21-/- AIN-76A Diet
- p21+/- Western Diet
- p21-/- Western Diet

One Size Does Not Fit All! Genetic Background May Determine Who Will Respond to Specific Bioactive Dietary Ingredients or Foods

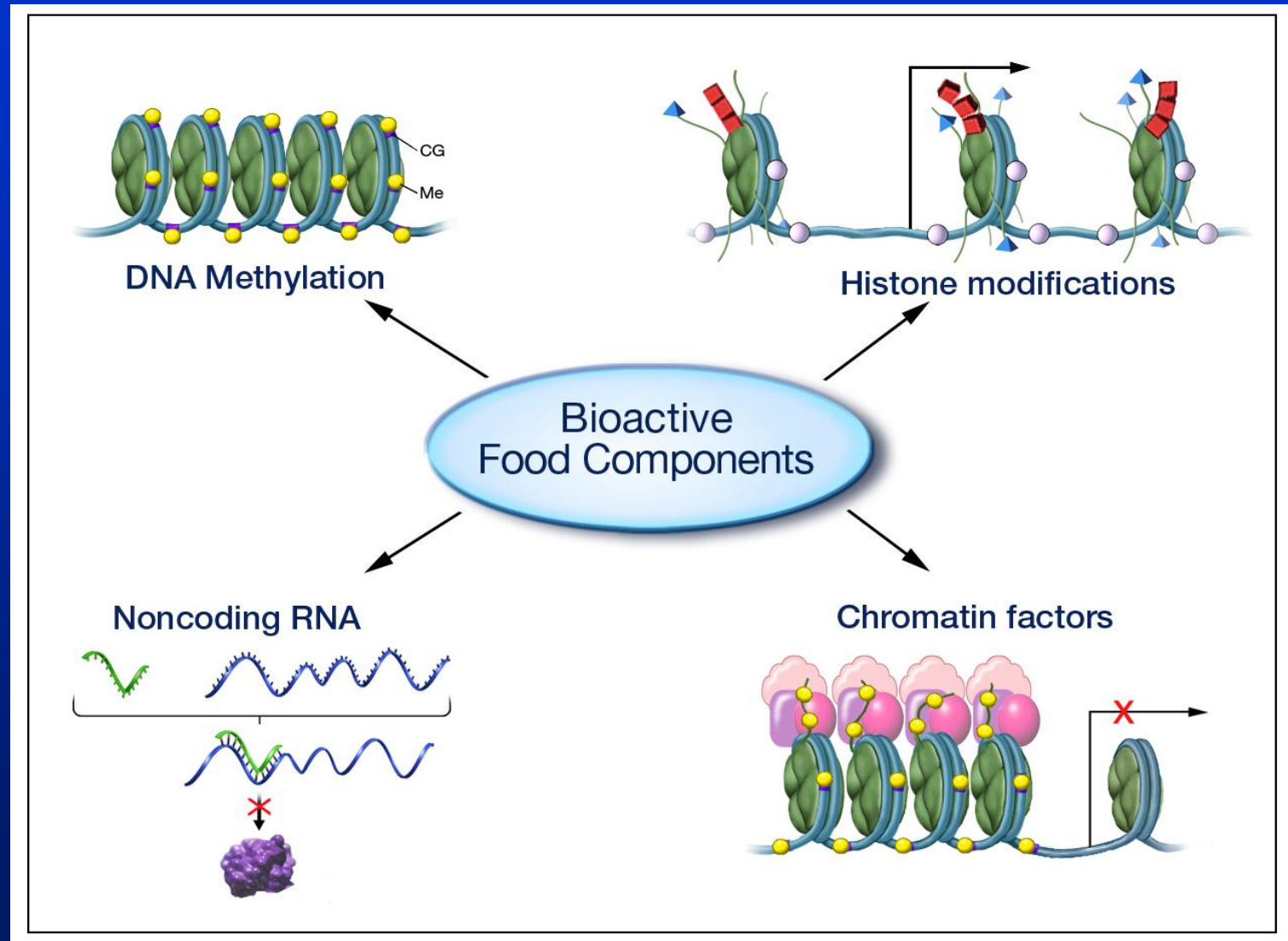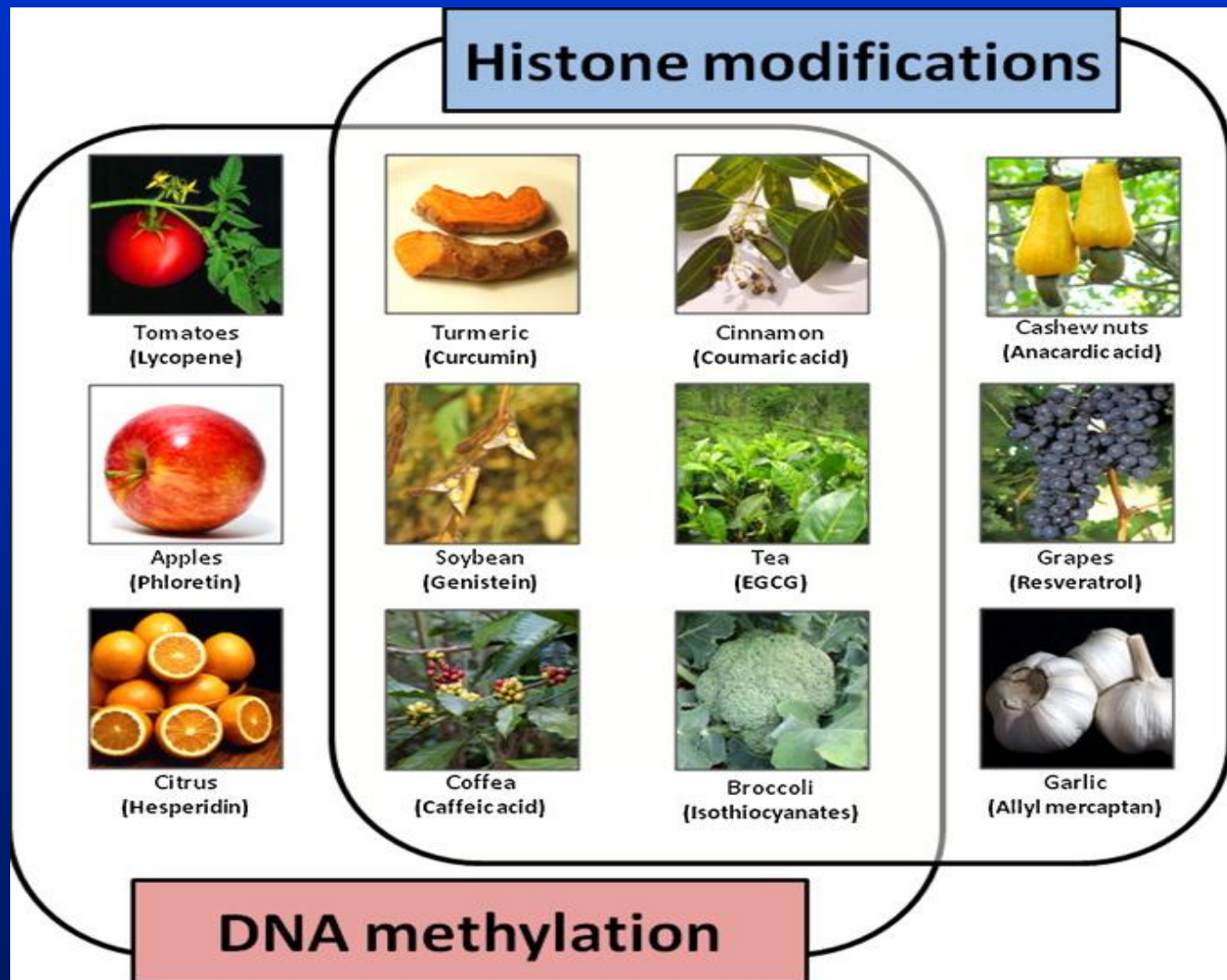# Genes Are Only Part Of The Equation

*Epi*genetics Definition

- **genetics**: the study of heritable changes in gene function that occur with a change in the DNA sequence

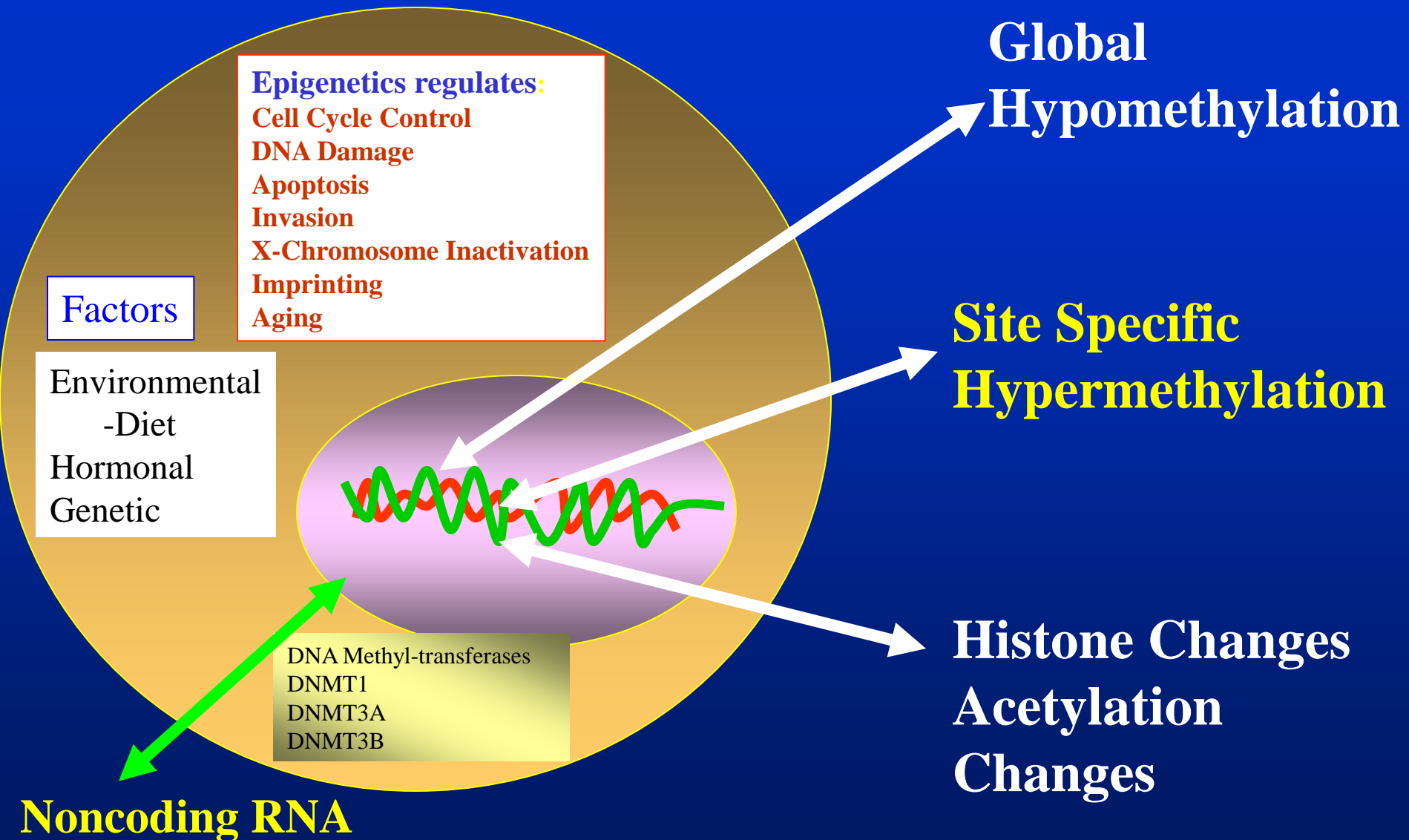- *Epi*genetics: the study of heritable changes in gene function that occur without a change in DNA sequence.

Foods Can Also Influence Epigenetics

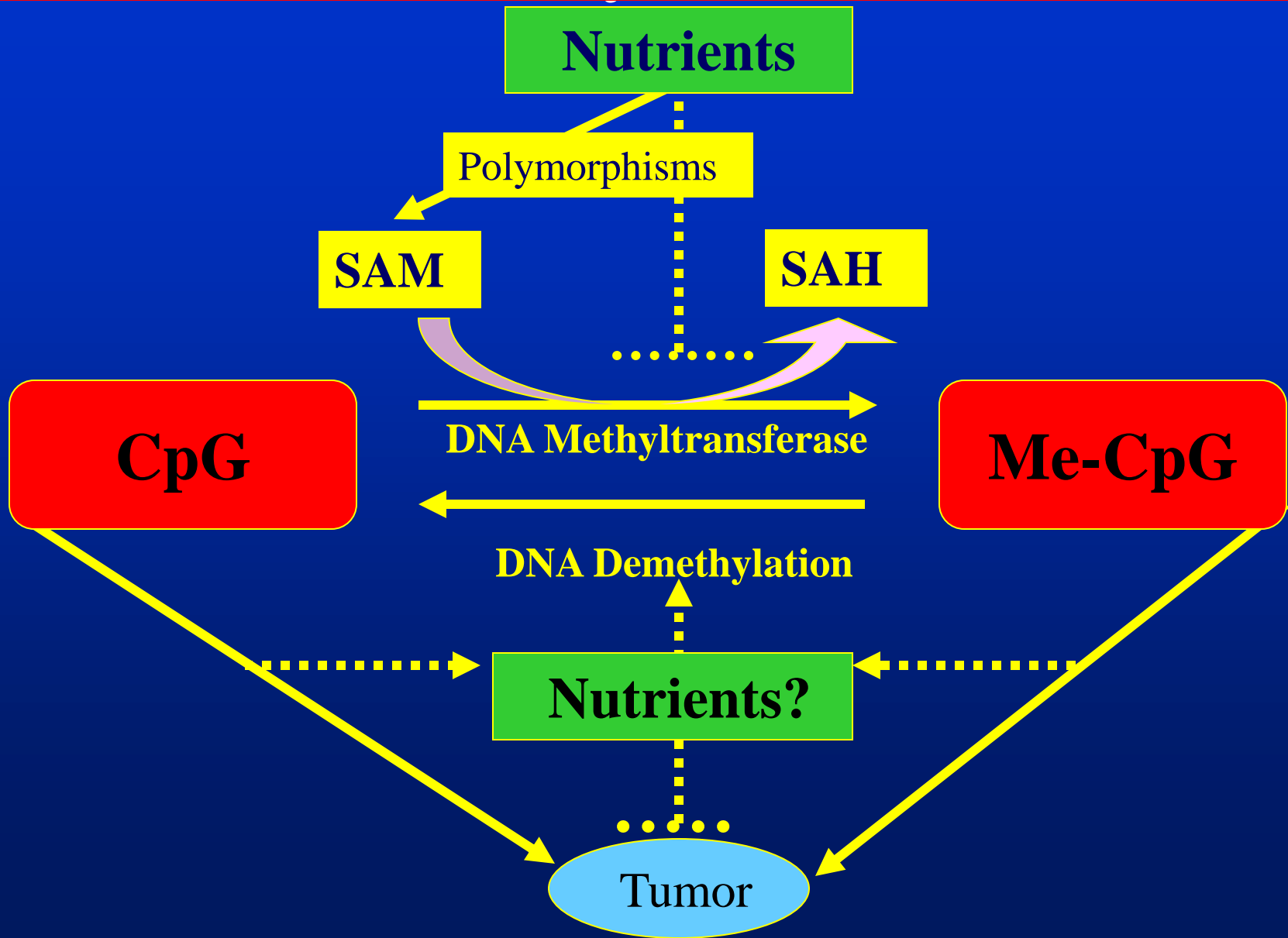# Major plants (constituents) with evidence for epigenetic modifications

Epigenetic Regulation of Cancer

Epigenetics regulates:
Cell Cycle Control
DNA Damage
Apoptosis
Invasion
X-Chromosome Inactivation
Imprinting
Aging

Factors

Environmental
-Diet
Hormonal
Genetic

DNA Methyl-transferases
DNMT1
DNMT3A
DNMT3B

Noncoding RNA

Global Hypomethylation

Site Specific Hypermethylation

Histone Changes Acetylation Changes

Verma and Srivastava (2002) Lancet Oncology 3:755-63.

Bioactive Food Components in the DNA Methylation Process

LTR Hypomethylated

LTR Hypermethylated

Maternal Supplements

zinc
methionine
betaine
choline,
folate
B_{12}

Yellow Mouse

Agouti Mouse

High risk cancer, diabetes, obesity & reduced lifespan

Lower risk of cancer, diabetes, obesity and prolonged life

Cooney et al. J Nutr 132:2393S (2002)

Genistein Can Also Influence Agouti Phenotype
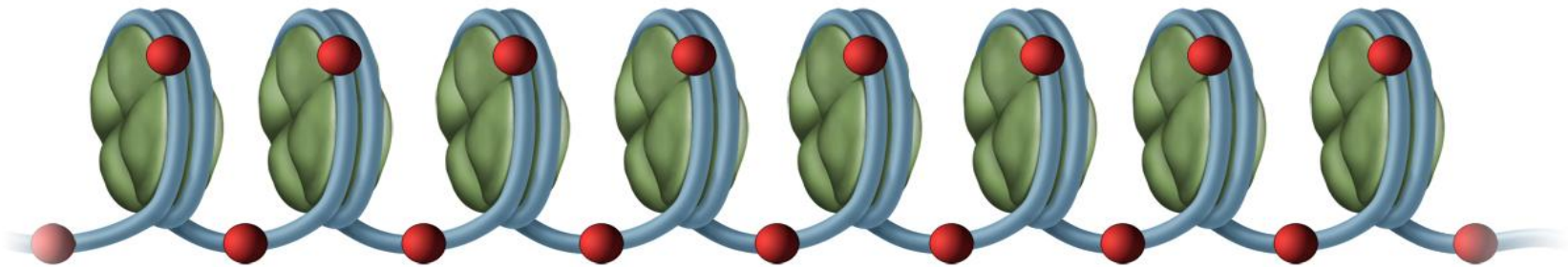## *Viable yellow Agouti (A^{vy}) Locus*

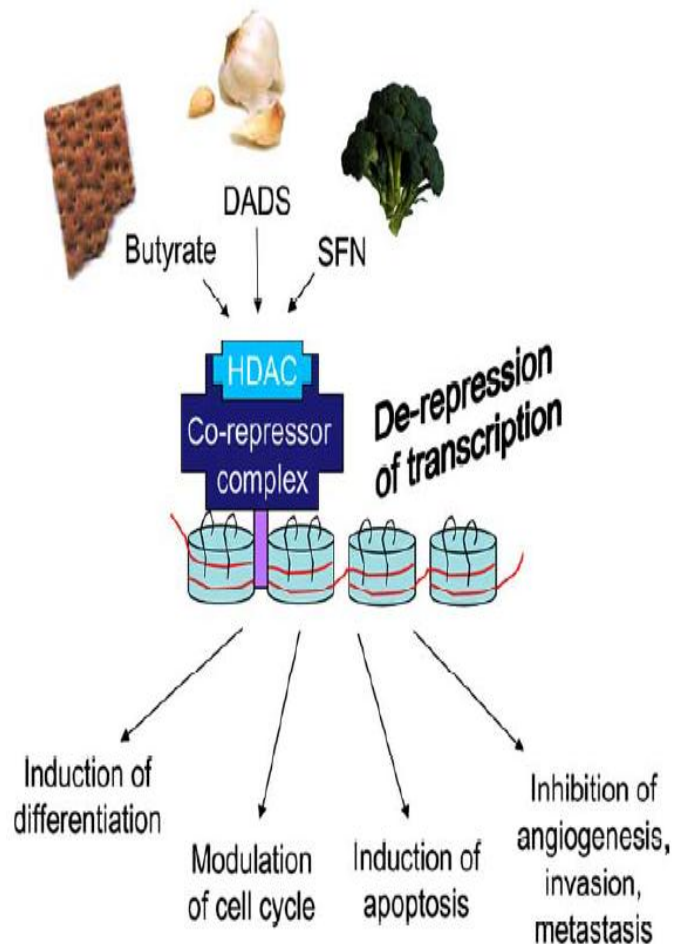# Histone Modifications Influence Gene Expression

Gene "switched on": open chromatin, unmethylated cytosines, acetylated histones

Gene "switched off": closed chromatin, methylated cytosines, deacetylated histones

Histone Modifications Can Be Regulated by Butyrate, Diallyl Disulfide, and Sulforaphane

Acetylated histones H3 and H4 associated with *P21* and *Bax* promoters
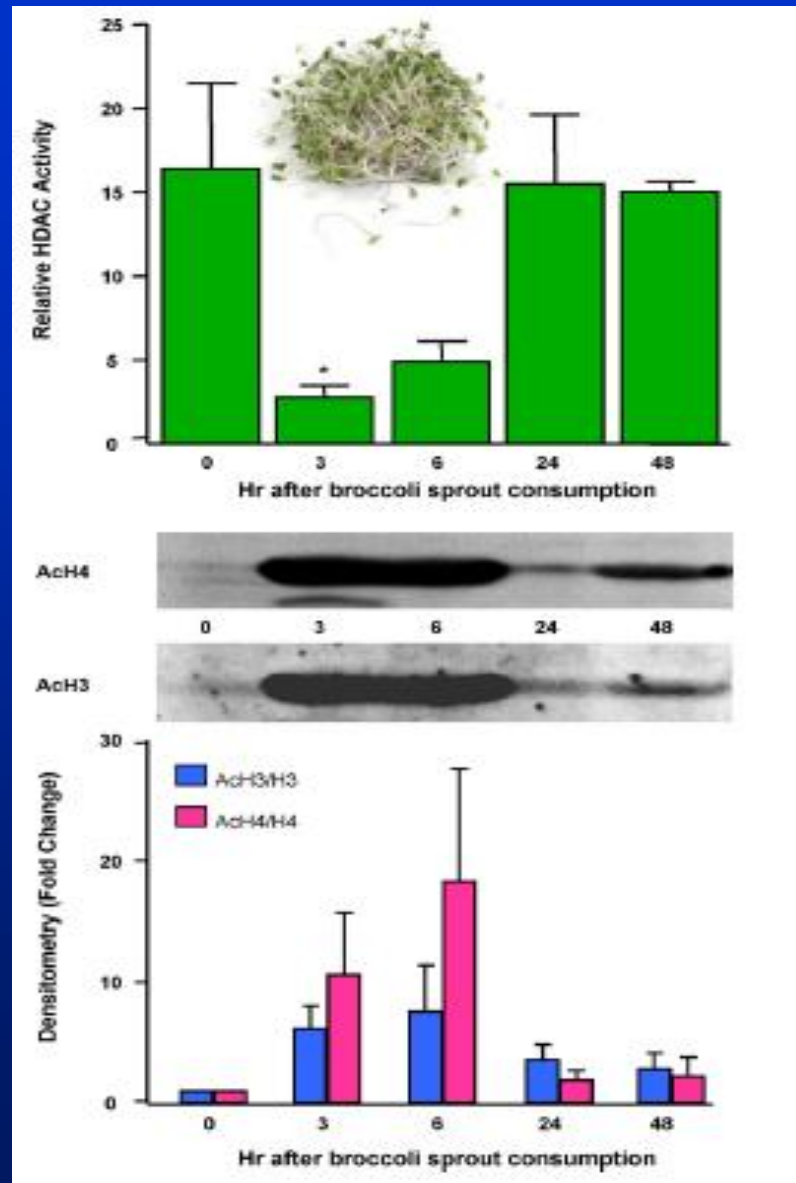
Transcription of *P21* and *Bax* mRNA

p21 and Bax protein levels increased
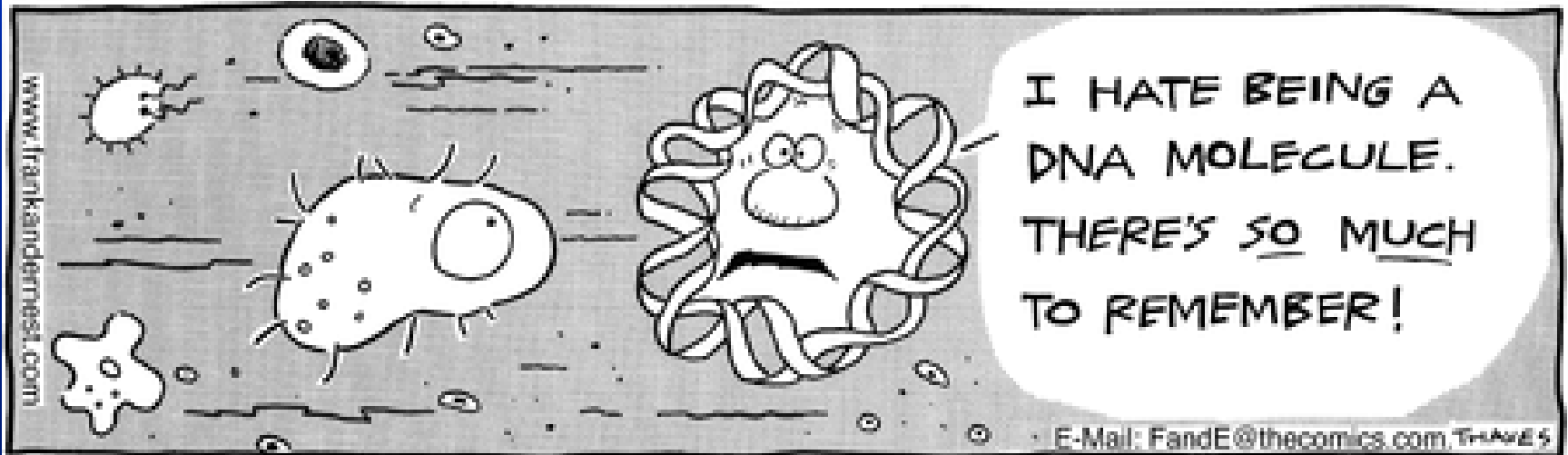
Cell cycle arrest   Caspase activation

APOPTOSIS

HDAC Inhibition by Sulforaphane-rich Broccoli Sprouts in Human Volunteers

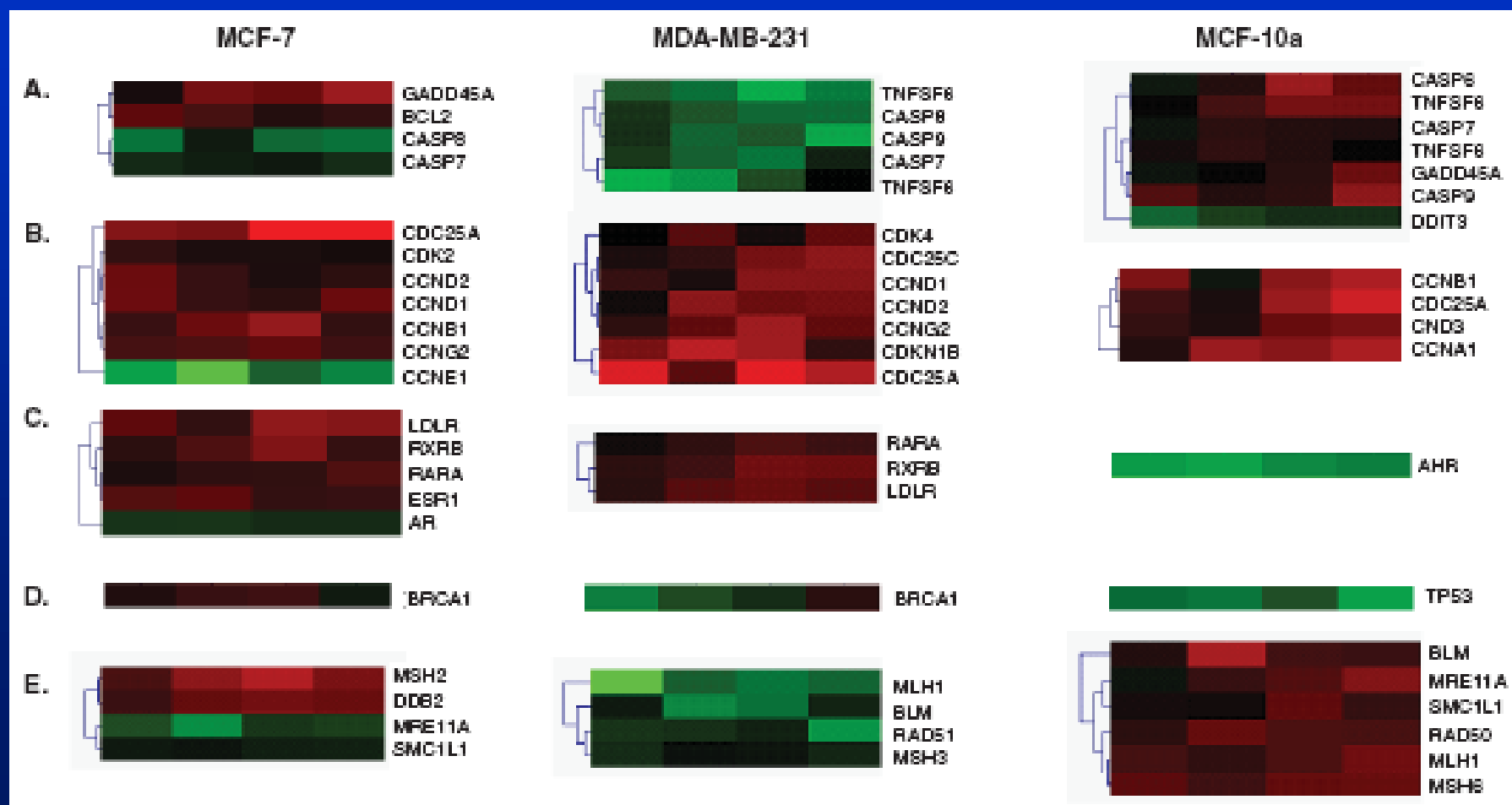# Genetic and Epigenetic Events Can Effect DNA and Therefore Gene Expression

Low-Fat Feeding and Gene Expression in Human Prostate Epithelium

HUGO	NAME	PRE-DIET				POST-DIET				AVERAGE RELATIVE EXPRESSION
		1	2	3	4	1	2	3	4	
MMP7	Matrix metalloproteinase 7									13.1
OLFM4	Olfactomedin 4									6.9
BF	B-factor properdin									6.4
IGF-2R	Insulin-like growth factor-2 receptor									3.5
VMP1	Likely ortholog of rat vacuole membrane protein 1									3.3
TGFB1I4	Transforming growth factor beta 1 induced transcript 4									3.2
IER3	Immediate early response 3									3.2
CCT2	Chaperonin containing TCP1, subunit 2 (beta)									3.1
HLA-DRB5	Major histocompatibility complex class II DR beta 4									3.1
CXCR4	Chemokine (C-X-C motif) receptor 4									2.8
LUM	Lumican									2.8
CCL2	Chemokine (C-C motif) ligand 2									2.7
DUSP1	Dual specificity phosphatase 1									2.6
IER2	Immediate early response 2									2.5
SPARCL1	SPARC-like 1									2.3
TBX3	T-box 3									2.1
ETS1	V-ets erythroblastosis virus E26 oncogene homolog 1									2.0
SLC25A3	Solute carrier family 25 member 3									0.6
PRDX1	Peroxiredoxin 1									0.5
ABAT	4-aminobutyrate aminotransferase									0.4
FOLH1	Folate hydrolase (prostate-specific membrane antigen)									0.4
BPGM	23-bisphosphoglycerate mutase									0.4
MGC15937	Similar to RIKEN cDNA 0610008P16 gene									0.3

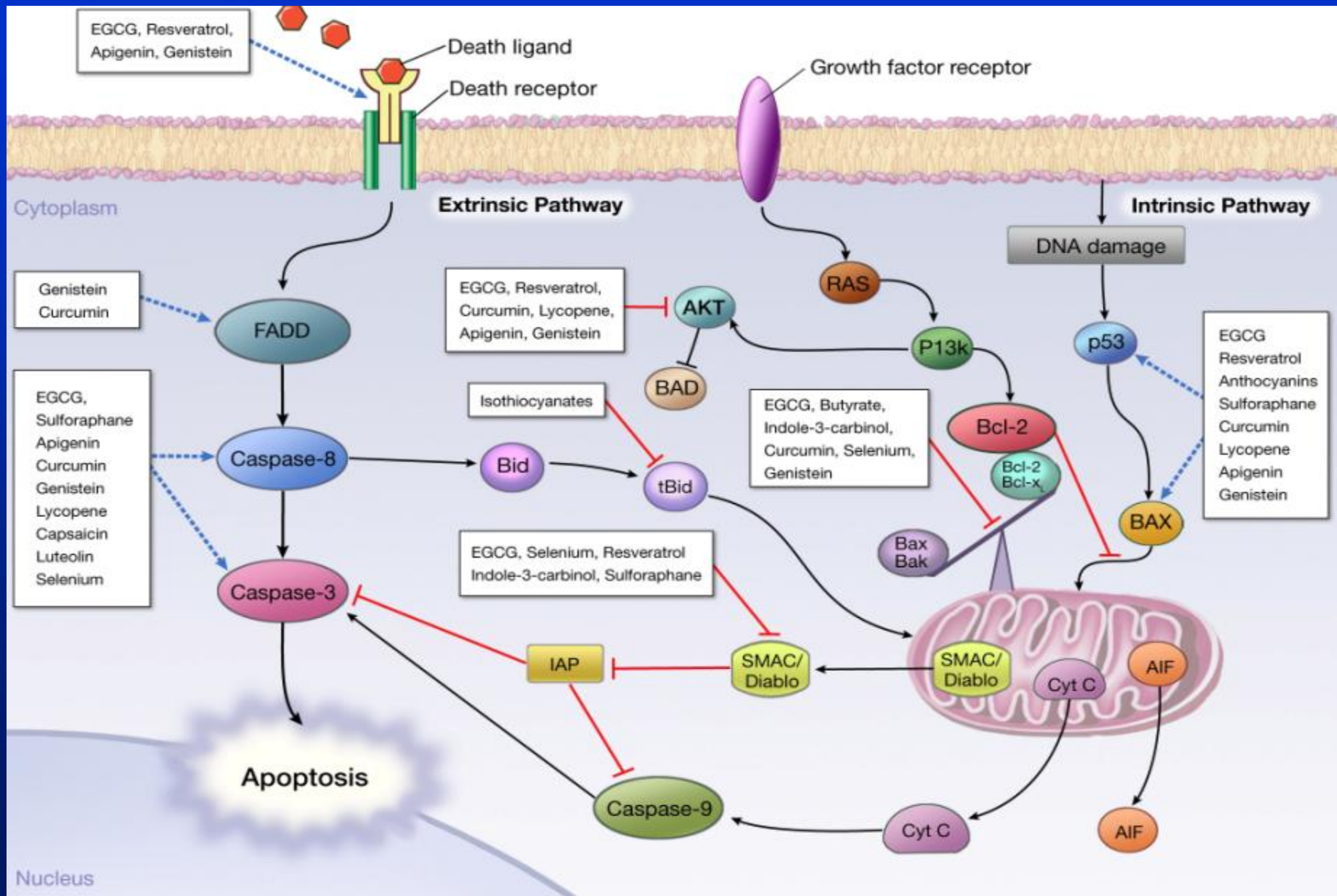# Gene Expression Changes in Breast Cancer Cell Lines Treated with Lycopene

A=apoptosis; B= cell cycle; C= receptors; D= oncogenes; E= DNA repair

Future is to Focus on the Process Needing Modification

Dietary Components and Apoptosis

Multiple Food Constituents Can Influence One Nuclear Transcription Factor

Garlic, fish, broccoli, tomatoes

Active Intermediate (radical??)

HS   SH

keap-1   nrf2

Caloric Restriction

Agent

S ⋯ S

keap-1

Cytoplasm

nrf2

small maf   nrf2

Nucleus

ARE

Increased GST, QR

"antioxidant responsive element"

Is There a Best Time for Intervention?

Genistein & Mammary Cancer:

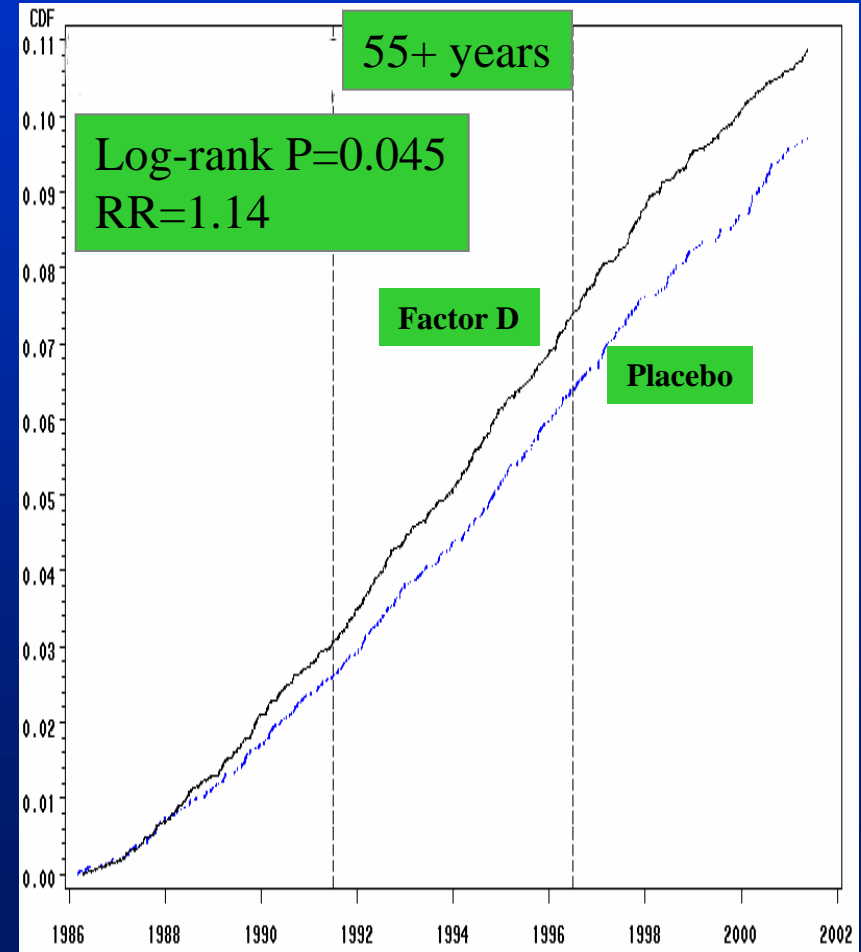| Exposure Period	Tumors/Rat
None	8.9
Prenatal	8.8
Adult	8.2
Prepubertal	4.3
Prepubertal + Adult	2.8

Timing Is Very Important

Linxian Nutrition Intervention Trial
Esophageal cancer mortality by factor D (N=1515)
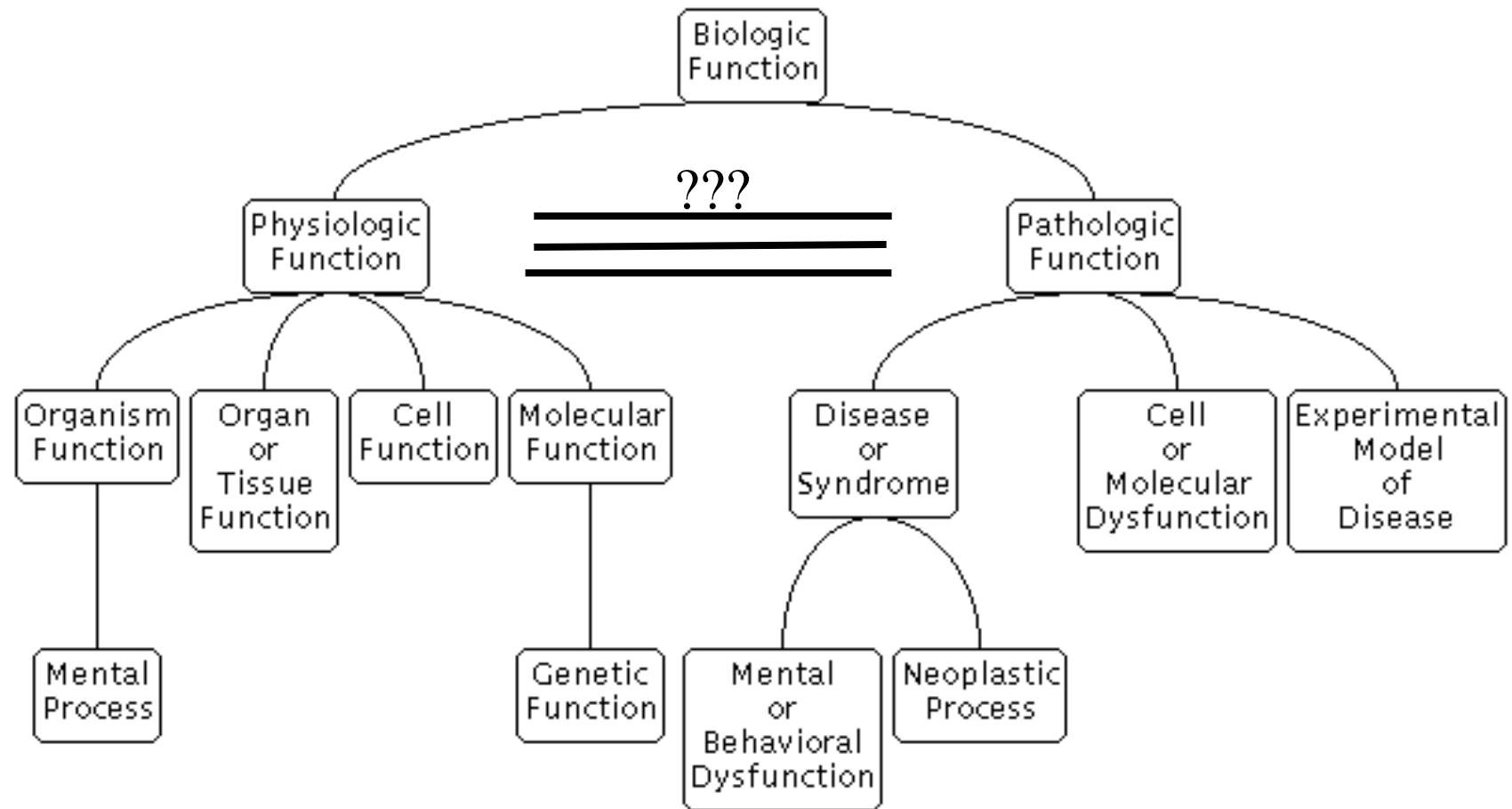### Factor D= Selenium, β-carotene, vitamin E

Esophageal Cancer Death Time (Year)　**Esophageal Cancer Death Time (Year)**
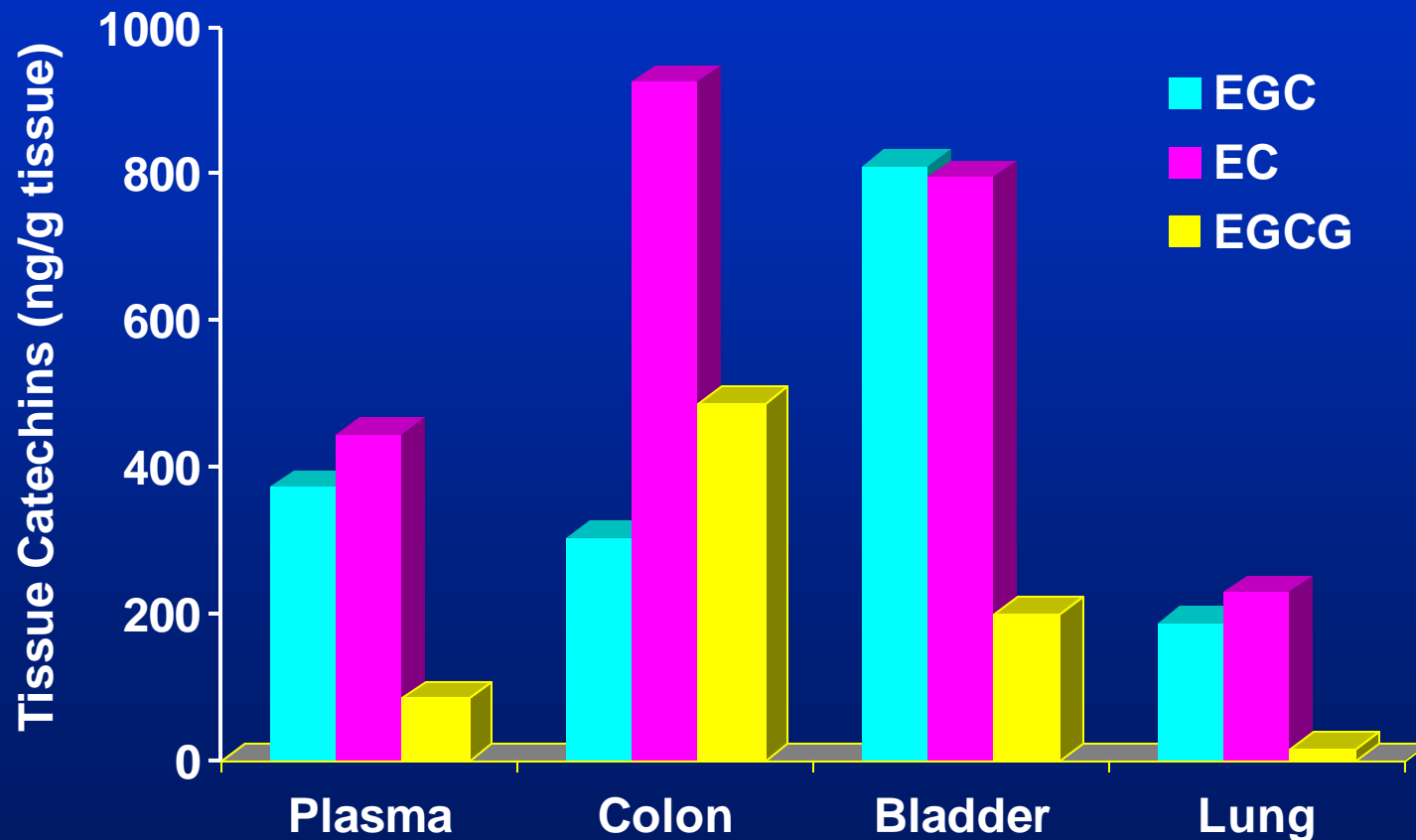
Qiao YL et al. J. Natl Cancer Inst. 101, 507-518, 2009

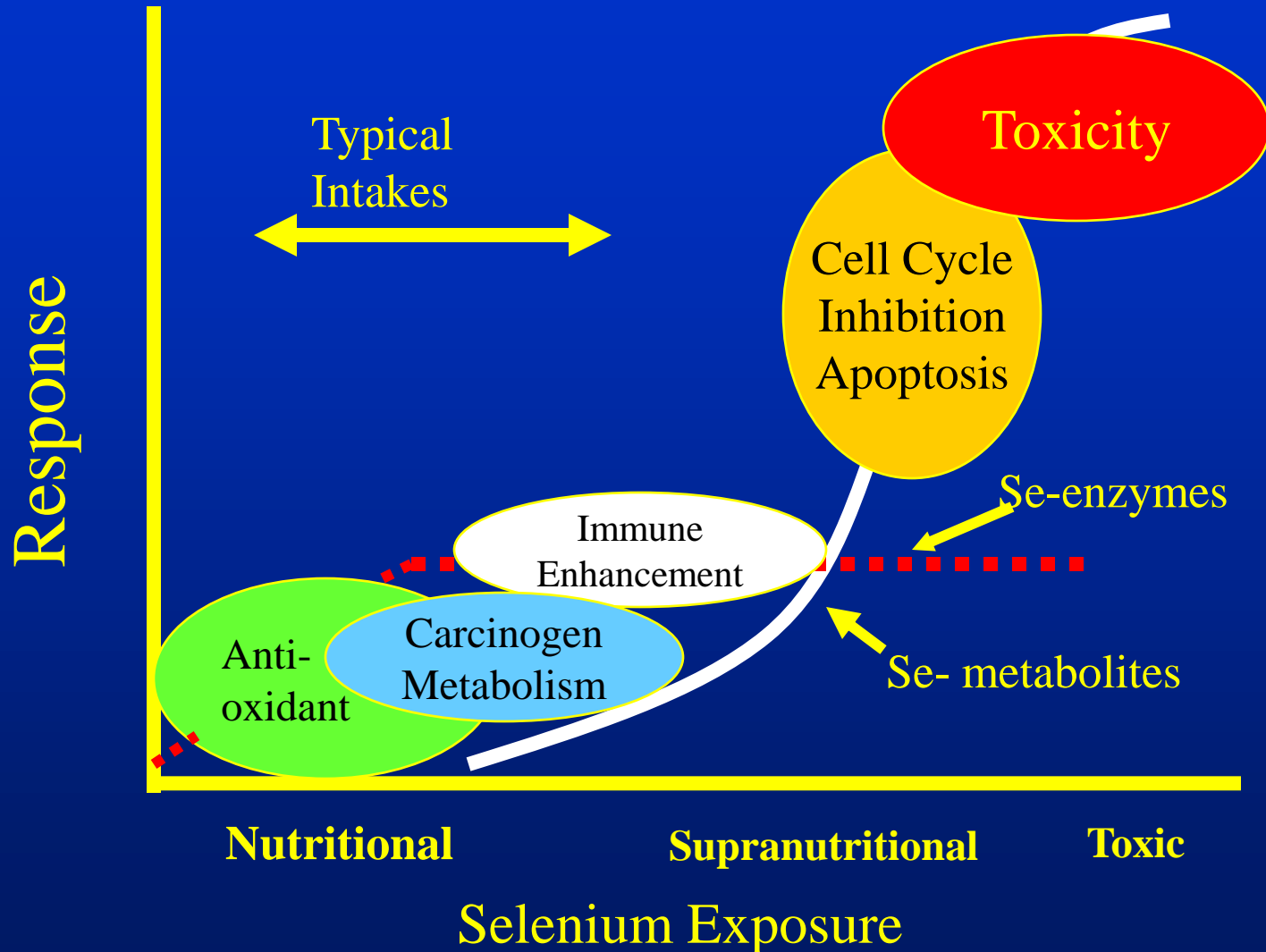# Fundamental Question Remains if Pathologic Evaluations Reflects What Occurs Normally??

Not All Tissues Respond the Same

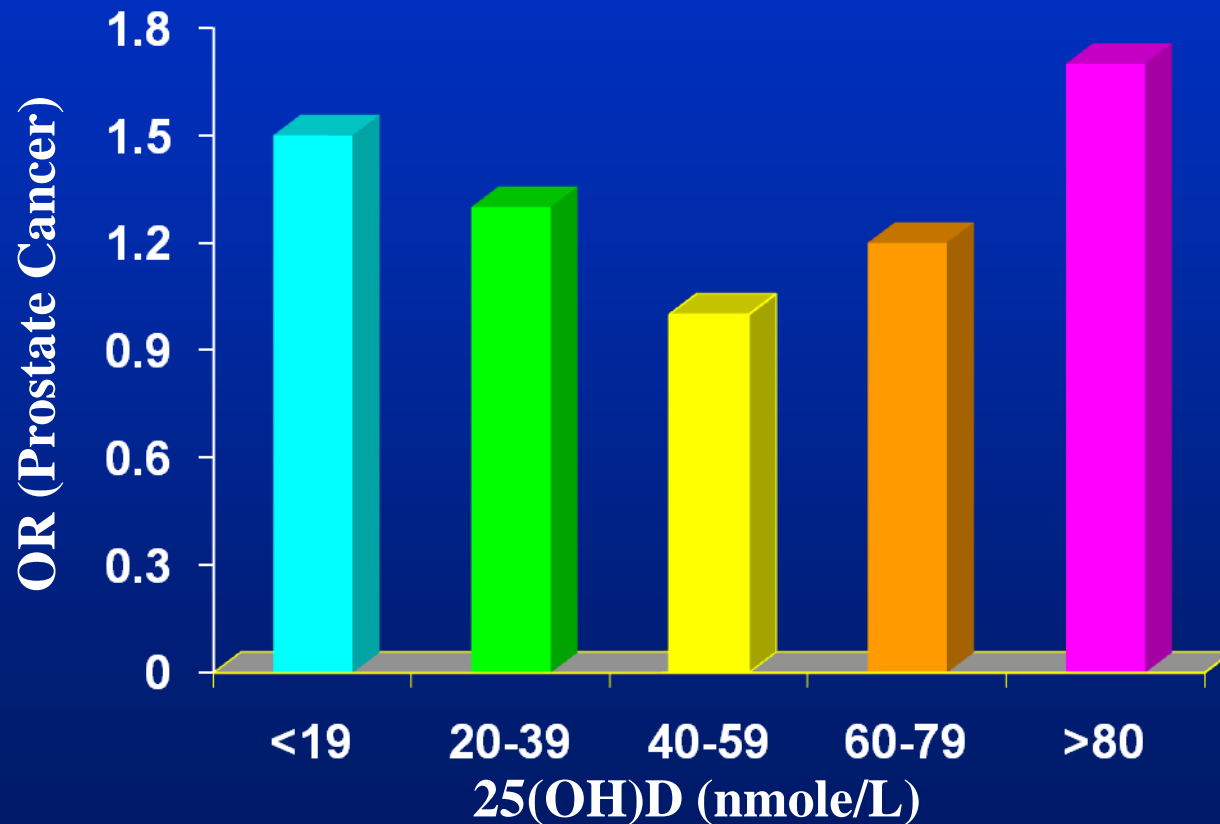Plasma and Tissue Levels of Tea Catechins During Chronic Consumption of Tea Polyphenols

Kim et al., Nutrition and Cancer 37: 41-48, 2000

Biological Response Depends on the Quantity Consumed

Combs and Gray, Parmacol. Ther. 79: 179-192, 1998.

How Much Is Enough and Too Much?

Nested Case-Control Prostate Study in Nordic Men (622 cases and 1451 controls)
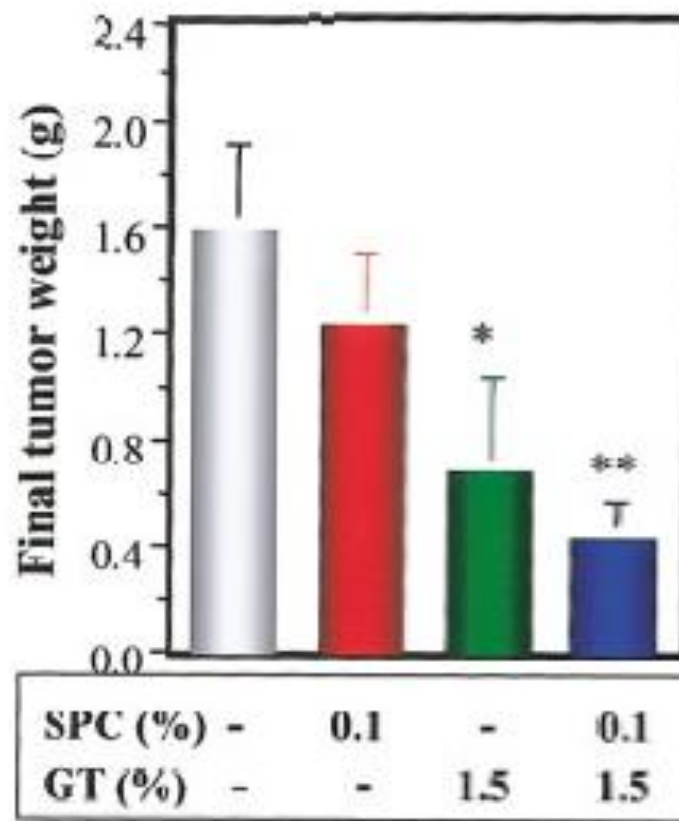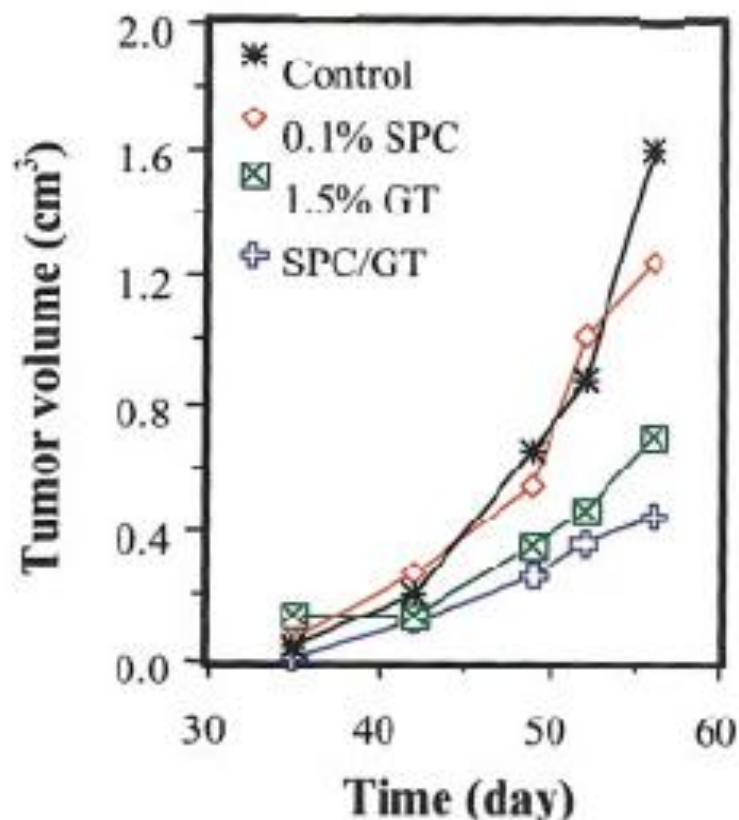

50 nM = 20 ng/ml

Tuohimaa et al. Int J Cancer 108: 104-108, 2004

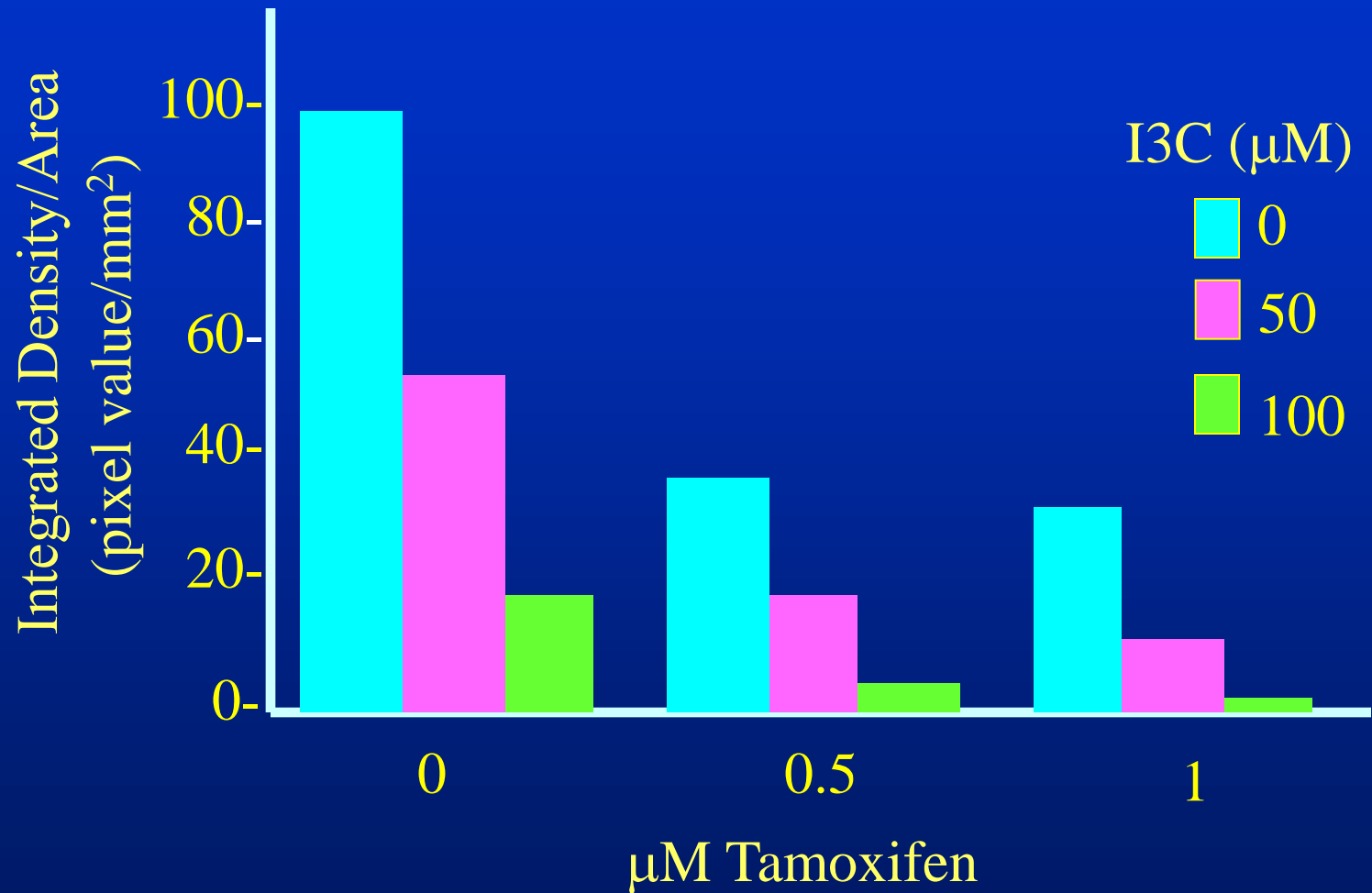# Foods are "complex mixtures"
- act synergistically

"Caution: This tomato soup combined with our chicken noodle soup can form a lethal nerve gas."

Soy Phytochemicals and Green Tea Inhibit Human Mammary Tumors in Mice

Need to Consider Nutrient-Drug Interactions

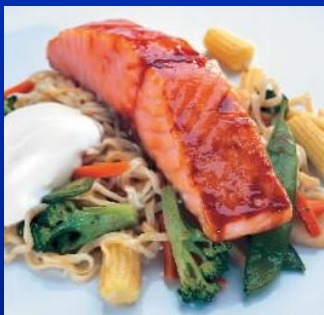## Indole 3-Carbinol and Tamoxifen In MCF-7 Cells

Cover et al. Cancer Research 59:1244, 1999.

Polymeals May Offer Special Attributes

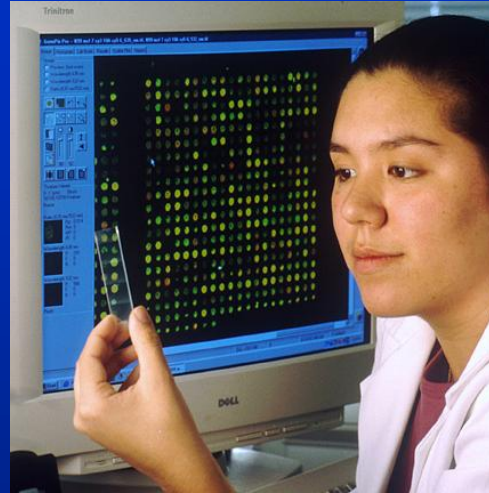| Dietary Component	% Reduction
➢ Wine (150 ml/day)	32%
➢ Fish (114 g 4x/week)	14%
➢ Dark Chocolate (100 g/day)	21%
➢ Fruits and Vegetables (400 g/day)	21%
➢ Garlic (2.7 g/day)	25%
➢ Almonds (68 g/day)	12%

76% decreased risk of CVD

Franco et al. BMJ 329:1447-1450, 2004

While I have raise lots of Concerns: There Is Light At the End of the Tunnel!

The Future: Personalization

Predictive ⟷ Personalized ⟷ Preemptive

Participatory