

Obesity, Energy Balance and Cancer Prevention

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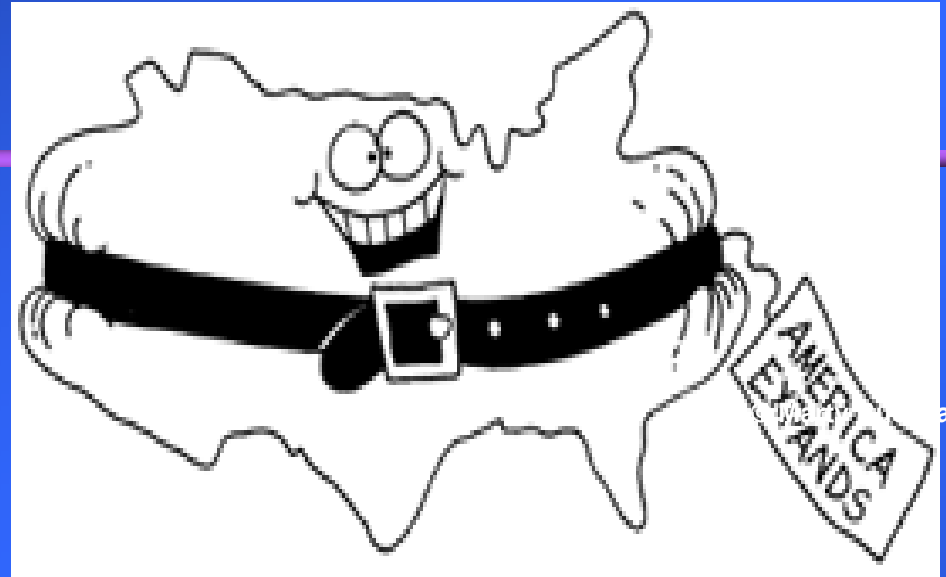
Cancer Chemoprevention

Aim: Inhibit the development of cancer through pharmacological intervention before the appearance of a clinically detectable tumor.



From Greenwald, et. al., *Cancer*, 1990

The US Obesity Epidemic (JAMA 10/9/02)

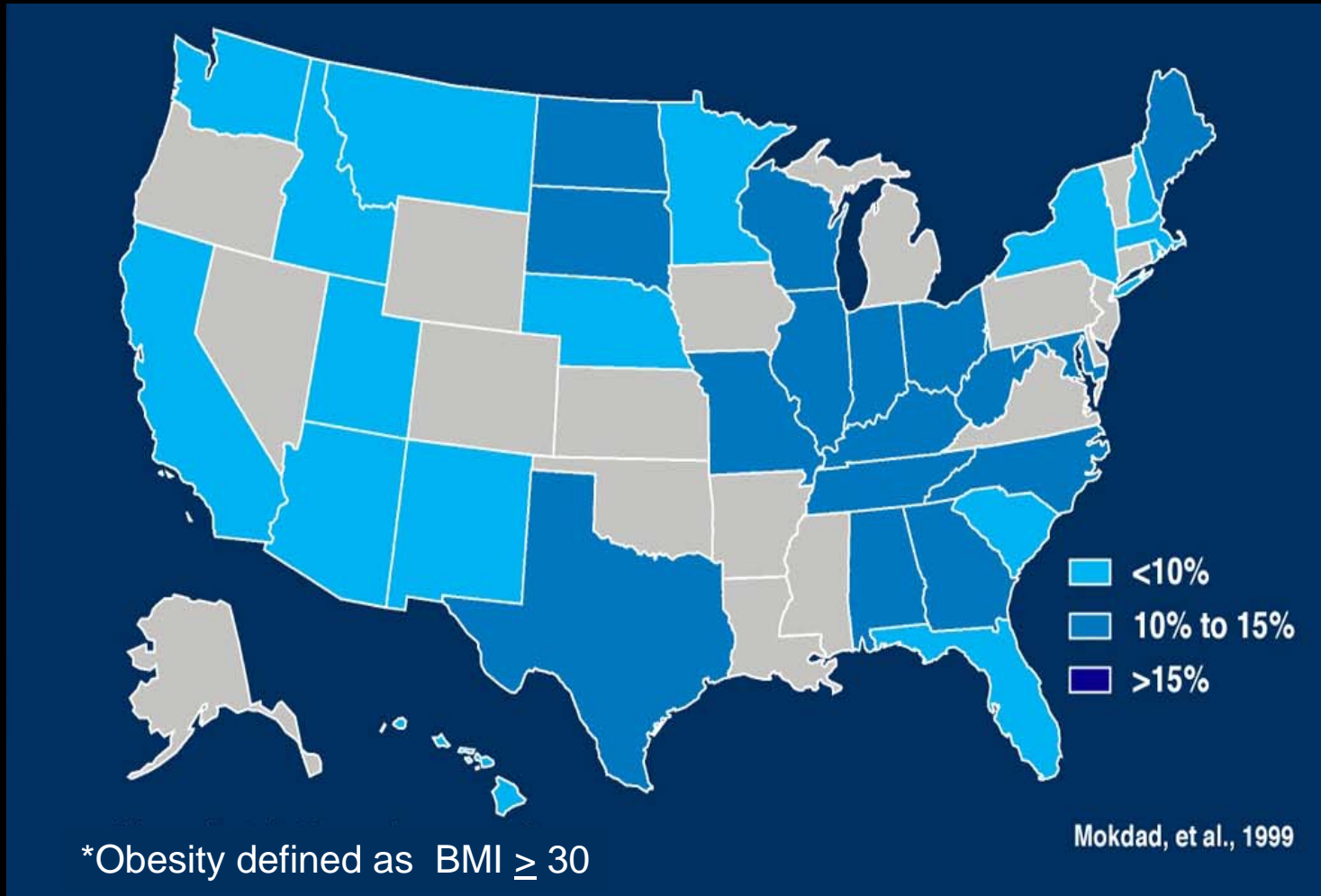


- 64.5% of US Adults Overweight – body mass index (BMI) $>25.0 \text{ kg/m}^2$
- 30.5% US Adults Obese – BMI $> 30.0 \text{ kg/m}^2$
- ~5% US Adults Extremely Obese – BMI $> 40.0 \text{ kg/m}^2$

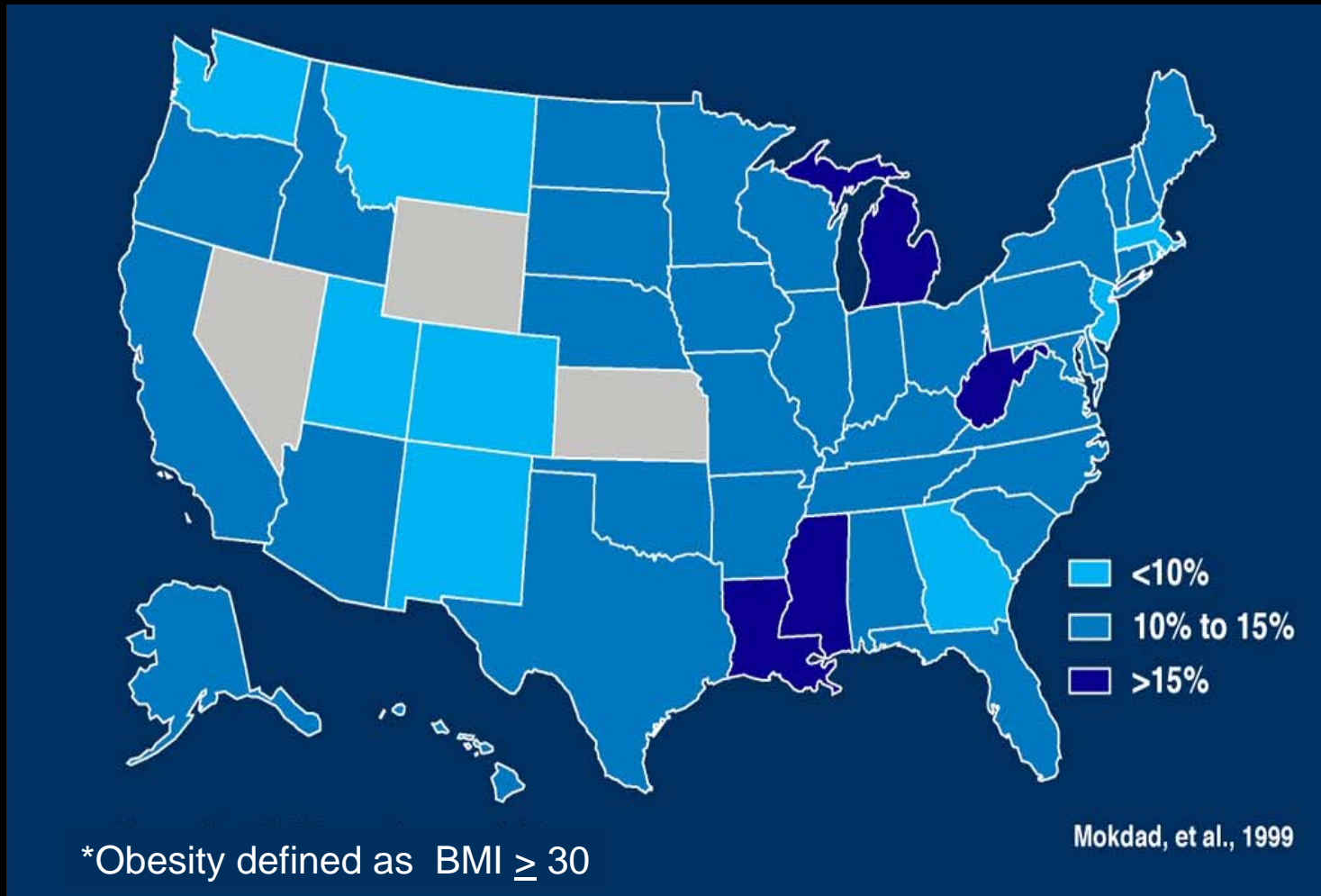
Today's Presentation

- **A nation out of energy balance: the scope of the obesity problem in the US**
- **Energy balance and cancer studies in transgenic mouse models: IGF-1 as a molecular target**
- **Effect of energy balance modulation on gene expression**

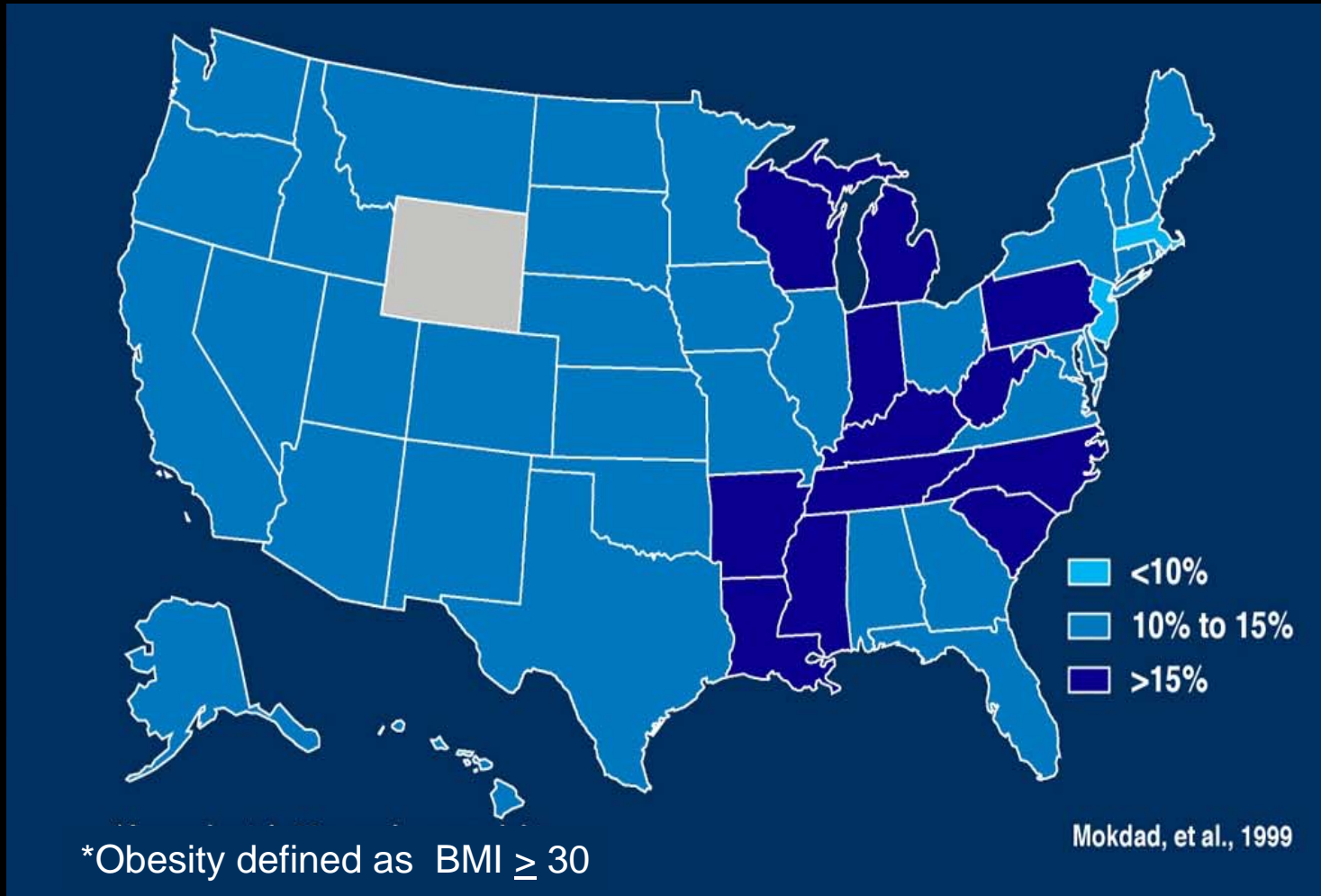
Prevalence of *Obesity Among U.S. Adults BRFSS, 1987



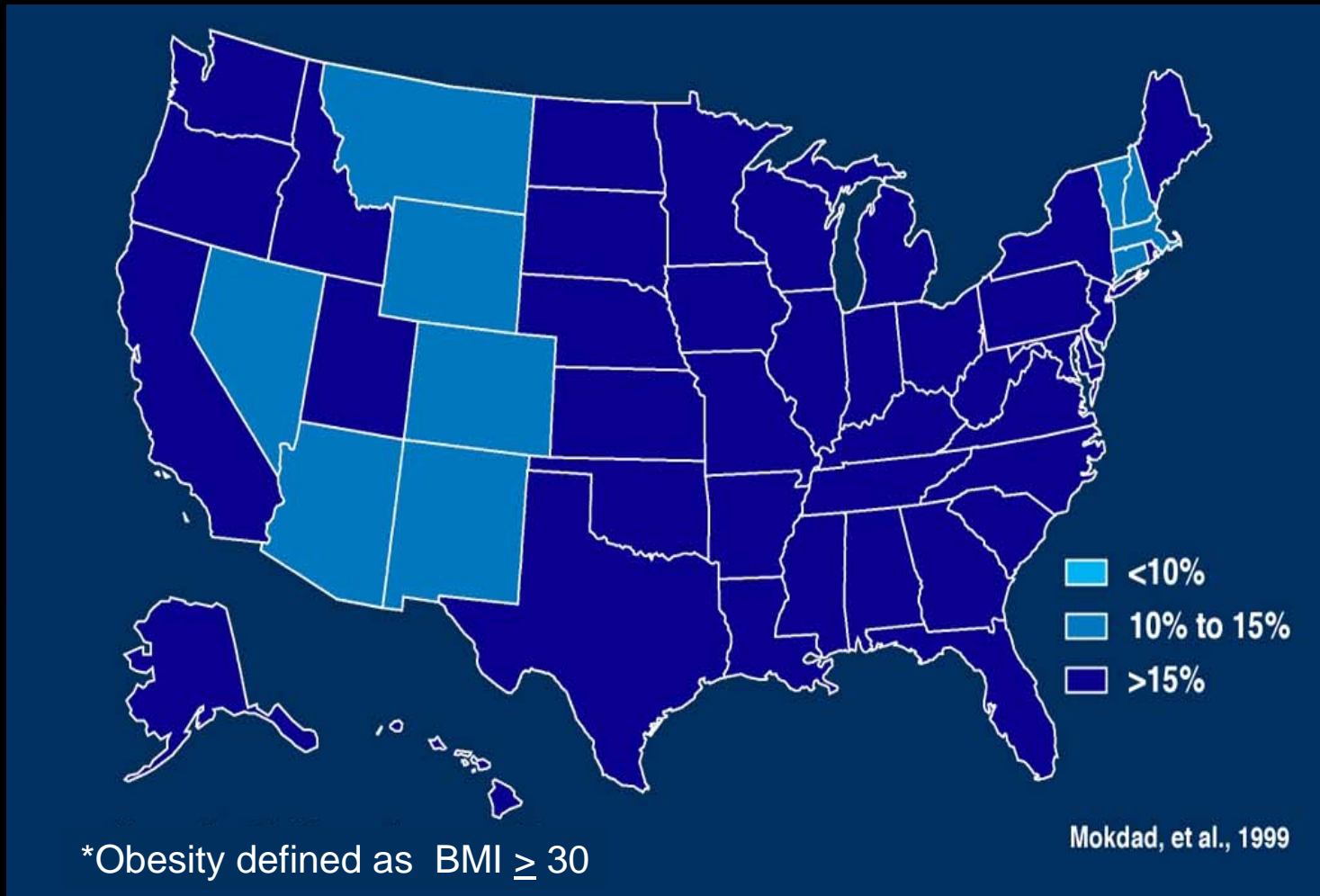
Prevalence of *Obesity Among U.S. Adults BRFSS, 1991



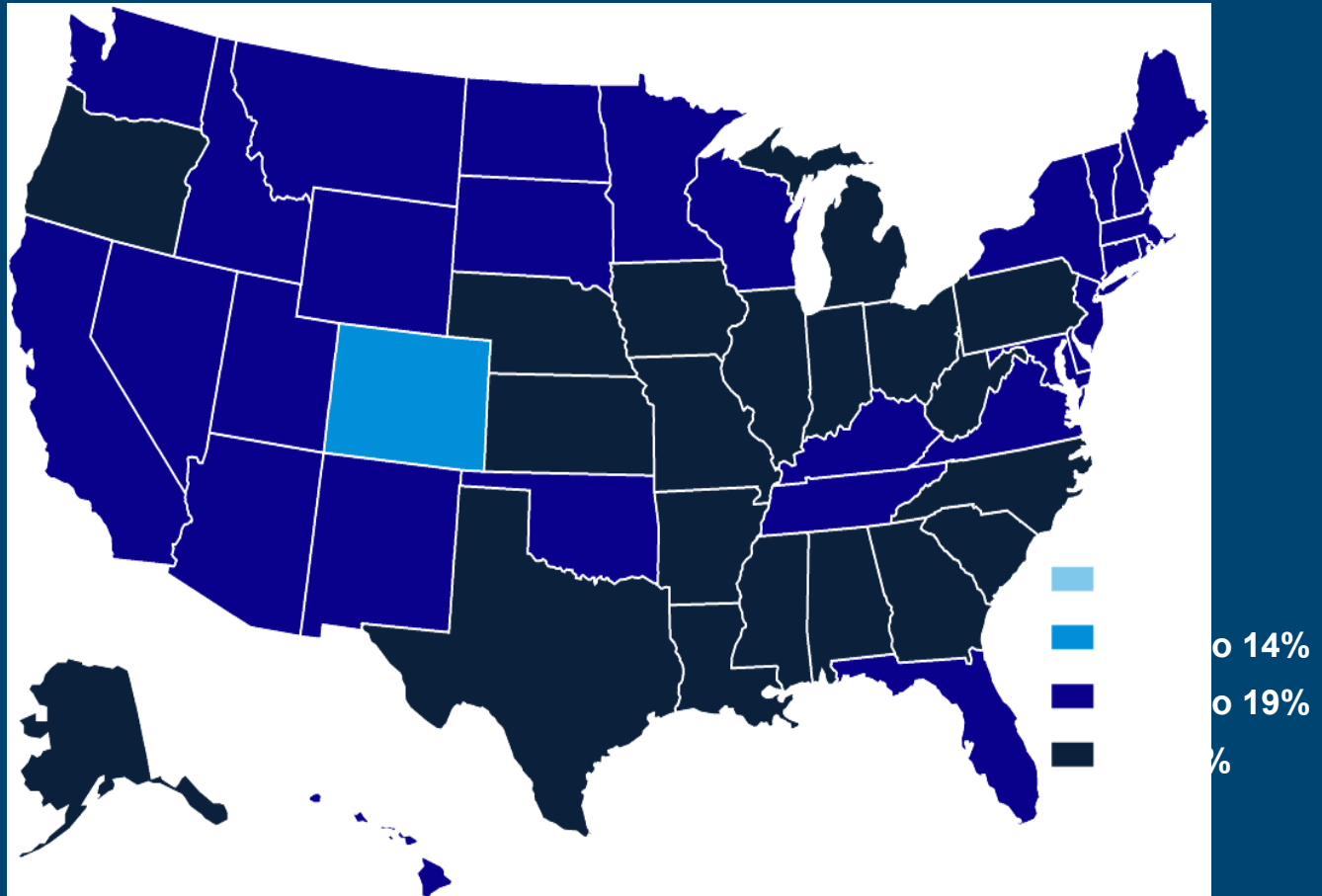
Prevalence of *Obesity Among U.S. Adults BRFSS, 1993



Prevalence of *Obesity Among U.S. Adults BRFSS, 1998



Prevalence of *Obesity Among U.S. Adults BRFSS, 2000



*Obesity defined as BMI \geq 30

Cancers Associated with Obesity

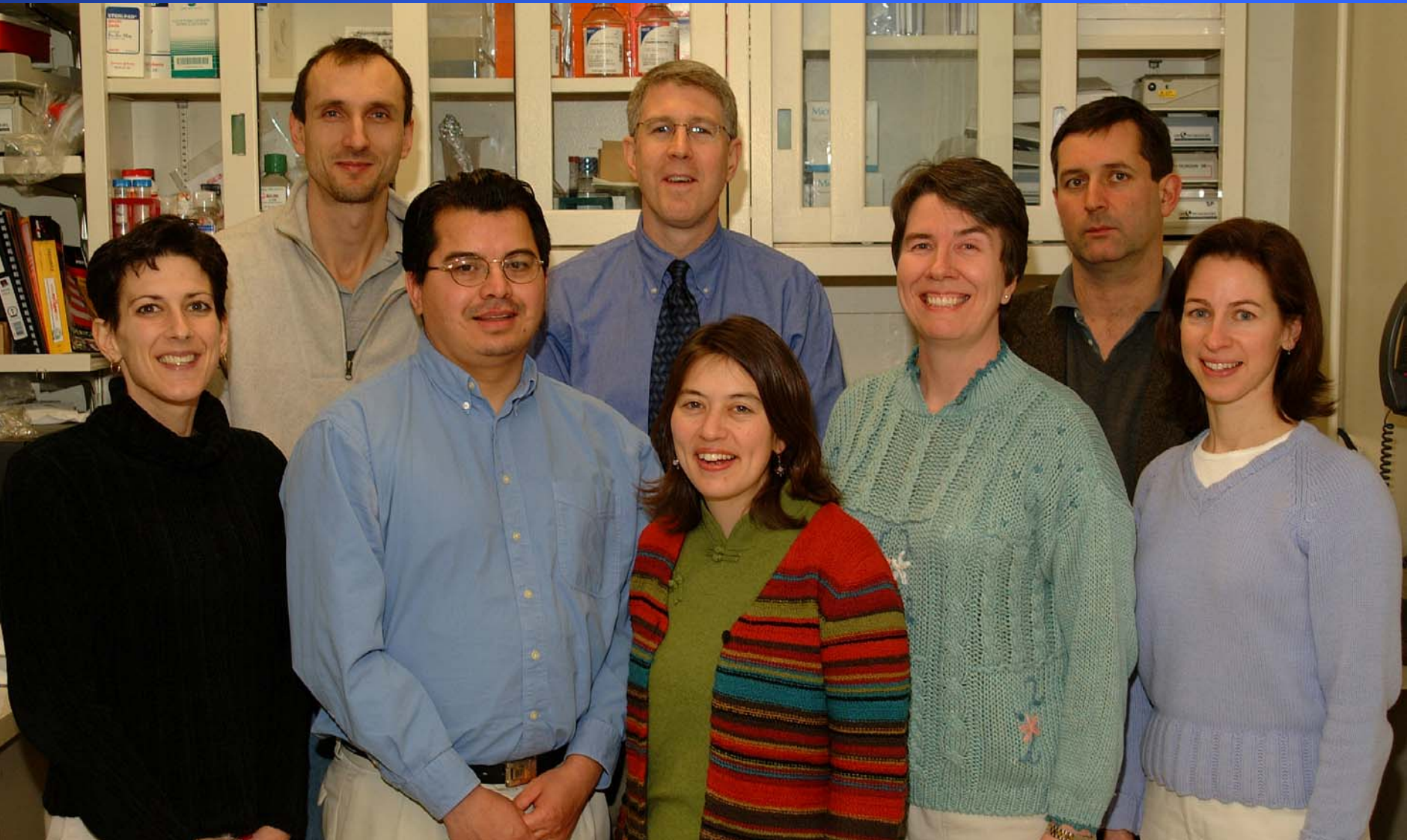
In Women

- Breast (postmenopausal)
- Endometrium
- Cervical
- Ovarian
- Colorectal
- Kidney
- Liver/ Gall Bladder
- Pancreatic
- Esophageal
- Hematopoietic

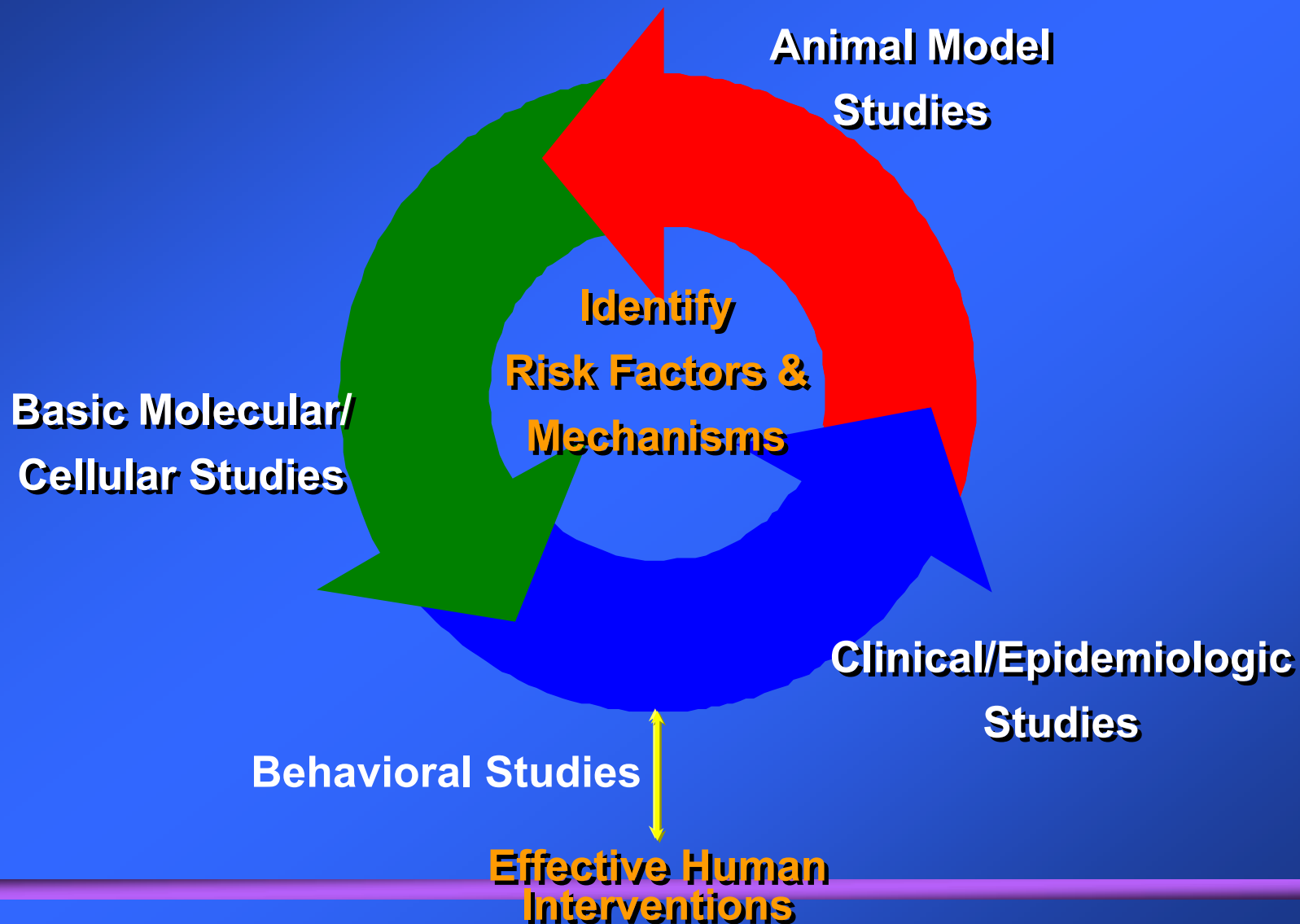
In Men

- Prostate
- Colorectal
- Kidney
- Liver/Gall Bladder
- Pancreatic
- Esophageal
- Hematopoietic

Nutrition and Molecular Carcinogenesis Section, NCI Laboratory of Biosystems and Cancer



The Multi-Disciplinary Approach to Cancer Prevention Research

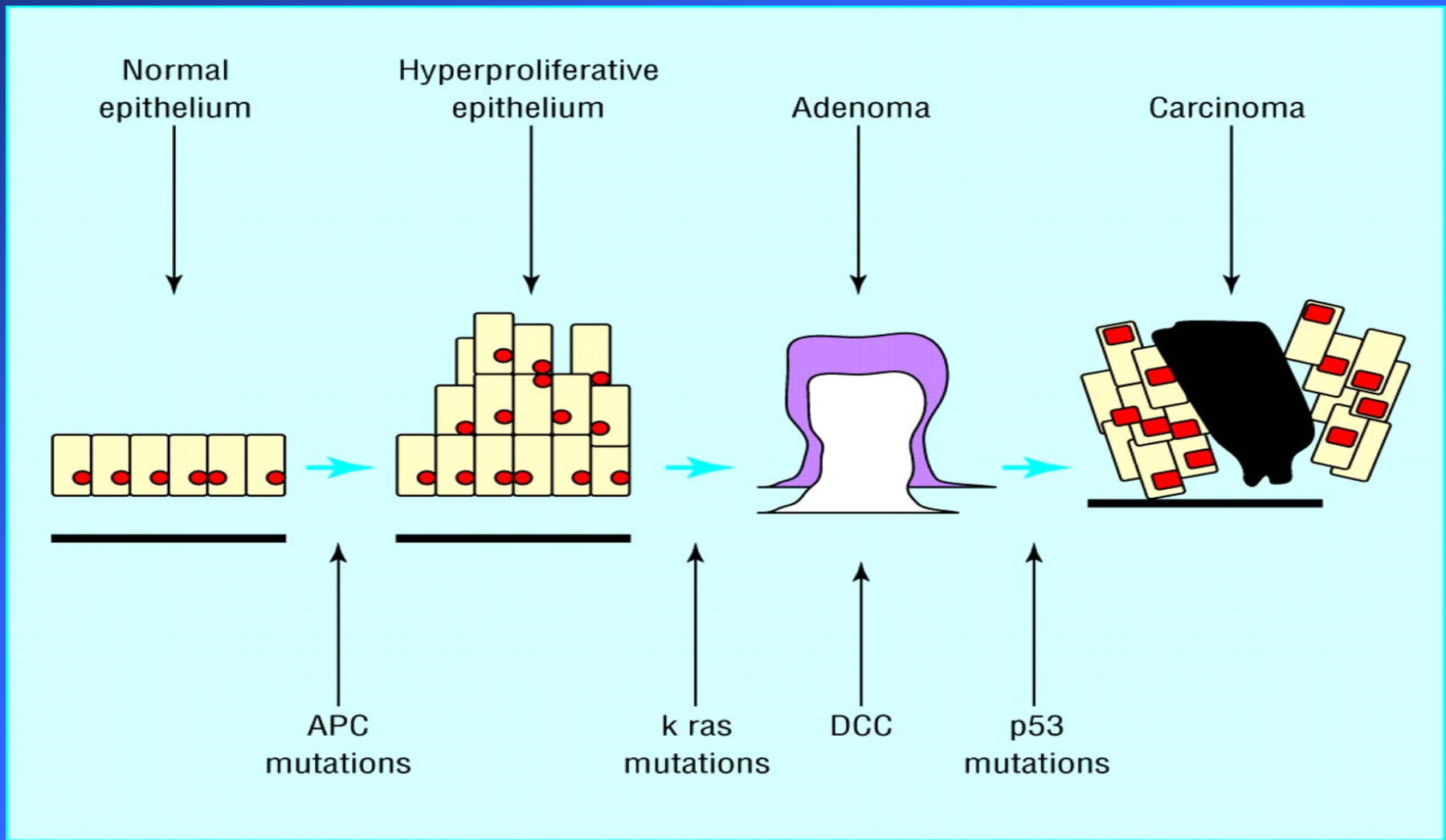


Central Question

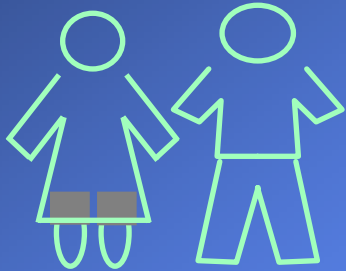
Can we offset increased cancer risk due to a genetic lesion (e.g., loss of p53 tumor suppressor function) by preventive approaches?

(Focus: diet, energy balance)

The Accumulation of Genetic Alterations in Human Colon Carcinogenesis

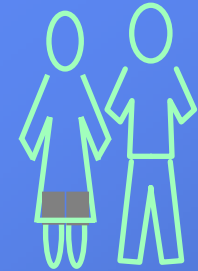


Energy Balance and Cancer Prevention



Energy in

- Amount
- Type
- Pattern



Energy out

- Physical Activity
- Growth
- Storage
- Routine Metabolism
- Thermoregulation

Energy
Balance

A dark blue triangle pointing downwards, containing a smaller version of the woman and man icon. Below the icon, the words "Energy" and "Balance" are written in a light blue font, stacked vertically.

p53-/- Mice

Attractive tumorigenesis model since tumor development is:

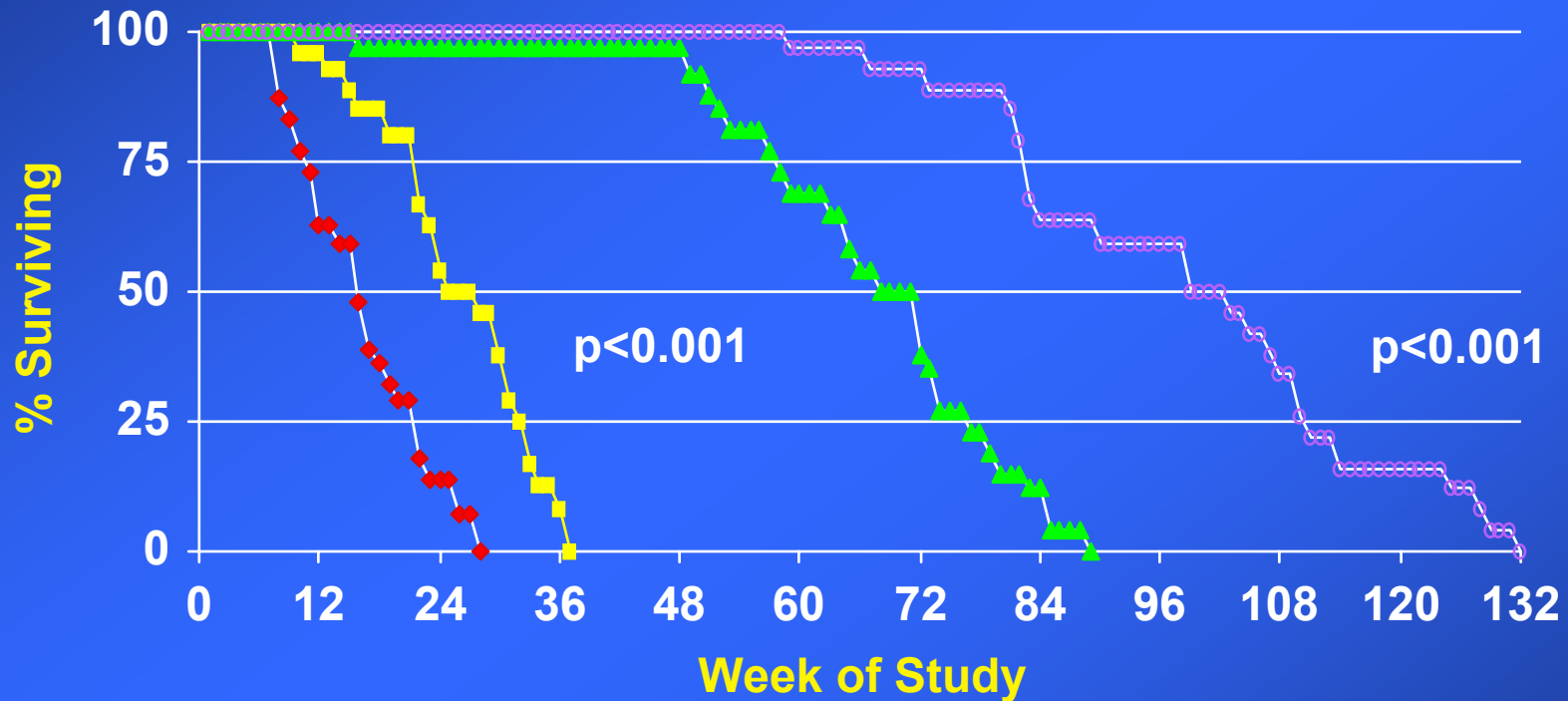
- spontaneous
- rapid
- relevant to human cancer
- *responsive to interventions?*

The Effect of 40% Calorie Restriction on Body Size in p53^{-/-} Mice



p53-knockout (p53^{-/-}) mice fed *ad libitum* (AL) or calorie restricted (CR) for 4 weeks.

The Effect of 40% Calorie Restriction on Survival in p53^{-/-} and p53^{+/+} Mice



—◆— AL:p53^{-/-} —■— CR:p53^{-/-} —▲— AL:p53^{+/+} —○— CR:p53^{+/+}

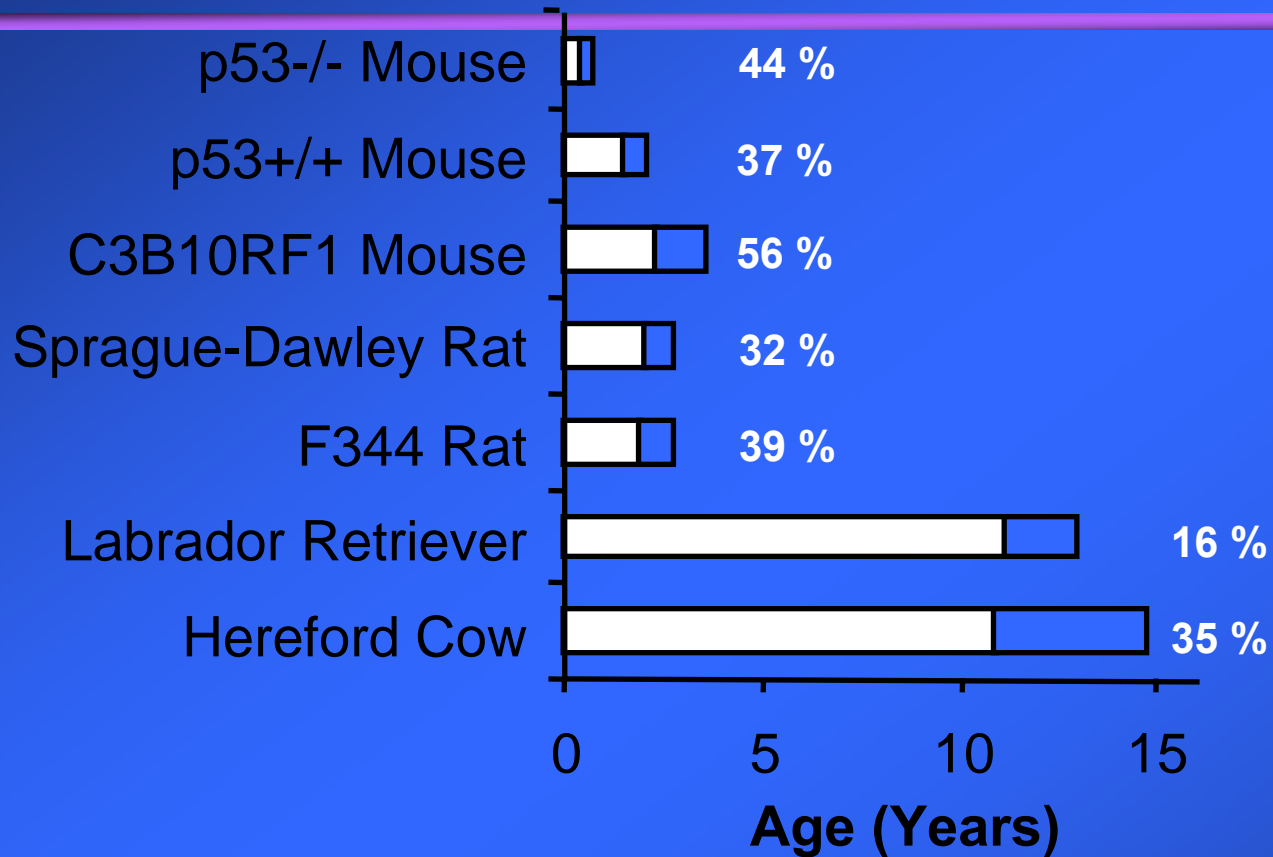
IGF-1 (ng/ml) : 648

373

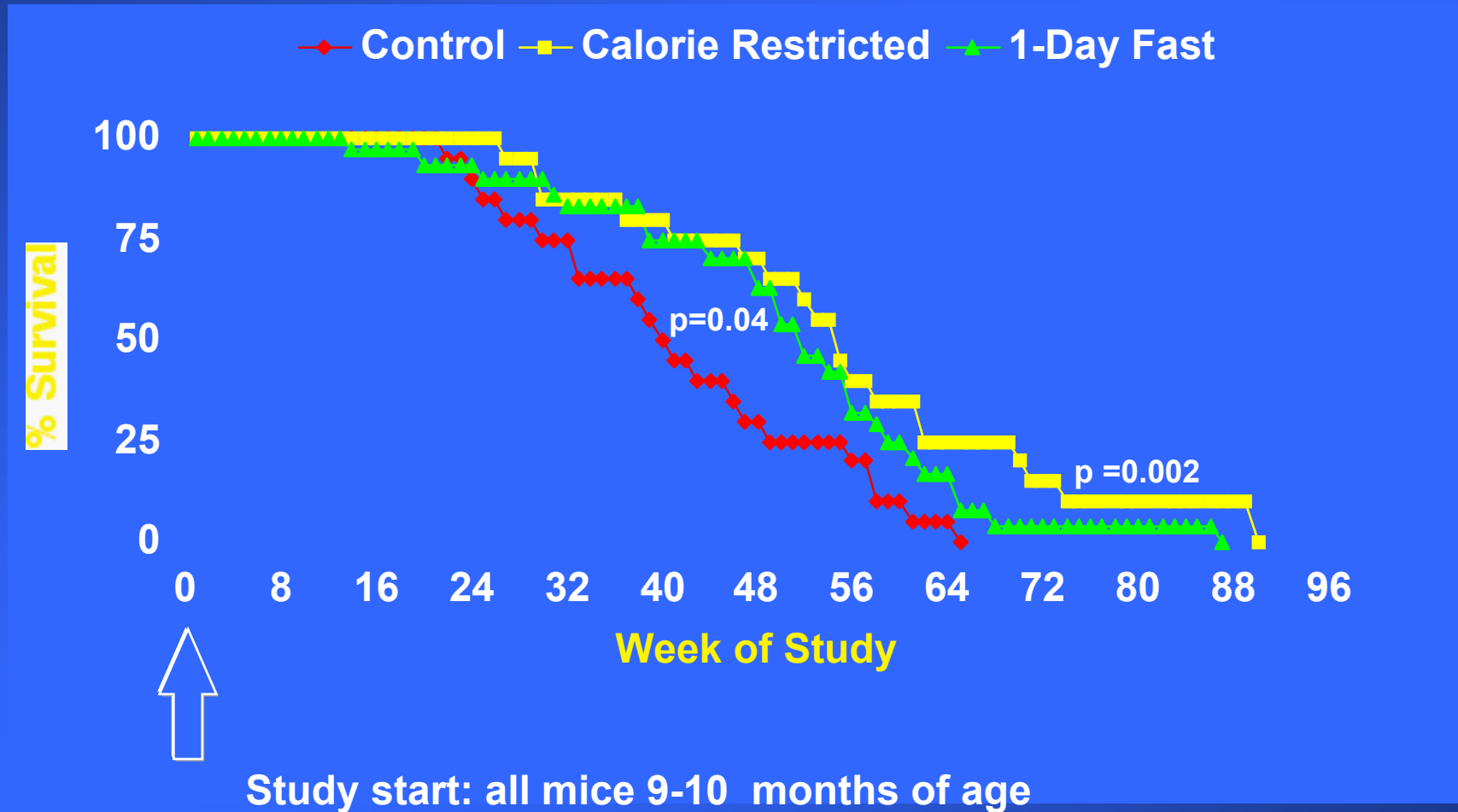
660

365

Calorie Restriction Extends Lifespan and Delays Neoplasia in Multiple Species



The Effect of Dietary Restriction on Spontaneous Tumorigenesis in Aged Male p53+/- Mice



Treatment Effects on Serum IGF-1 and Leptin Levels in p53+/- Mice

Treatment	Mean \pm SE	
	IGF-1 (ng/ml)	Leptin (ng/ml)
Control	514 \pm 14	15.9 \pm 1.9
Calorie Restriction	387* \pm 30	4.9* \pm 1.1
1-Day/Week Fast	463* \pm 17	19.6 \pm 1.5

* p (versus control) < 0.05

Summary: Models Responsive to Anti-Obesity Interventions

- p53^{-/-}, p53^{+/-}, p53^{+/+} (spontaneous HN's, sarcomas)
- p53^{+/-}: *p*-cresidine (6-month bladder model)
- BK5.IGF-1 TG:*p*-cresidine (6-month bladder model)
- p53^{+/-} x MMTV-*Wnt-1* TG (spont. mammary tumors)
- C3(1) -Large T Antigen TG (spont. mammary tumors)
- p53^{+/-}: AOM (chemically-induced intestinal tumors)
- APC^{Min} mice (spontaneous intestinal tumors)

Insulin-like Growth Factor (IGF)-1 and Cancer

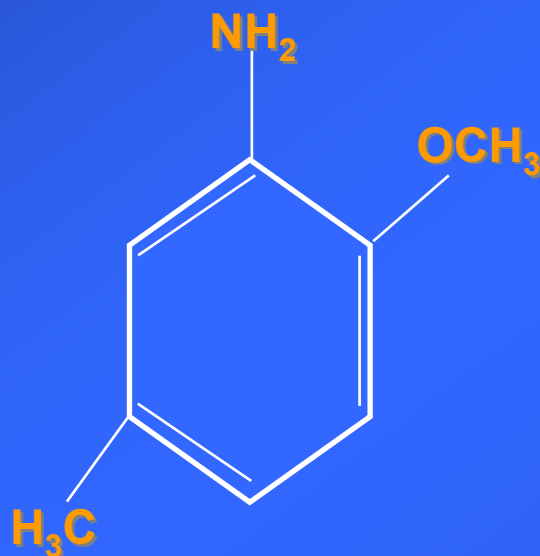
- **IGF-1 regulates mitogenic and apoptotic rates of epithelial cells**
- **High serum levels of IGF-1 are significantly associated with risk of several cancers: prostate (Chan, et al., *Science* 1998); premenopausal breast (Hankinson, et al., *Lancet*, 1998); lung (Wu, et al., *JNCI*, 1999); leukemia (Petridou, et al. *Int J Cancer*, 1999); bladder (acromegaly; Higuchi, et al., *Endocr J*, 2000)**
- **Calorie restriction inhibits cancer in multiple models; lowers plasma IGF-1; IGF-1 replacement reverses anti-cancer effects (Hursting et al., *Cancer Res* 1993; Dunn, et al., *Cancer Res*, 1997; Hursting et al., *Ann Rev Med*, 2003)**

New Model Development in p53-Deficient Mice

Approach: Low-dose carcinogen induction
in p53+/- mice

- ***p*-cresidine**, 4-aminobiphenyl (bladder)
- azoxymethane (colon)
- PhIP (colon, prostate)
- MNU (mammary; lymphoma)

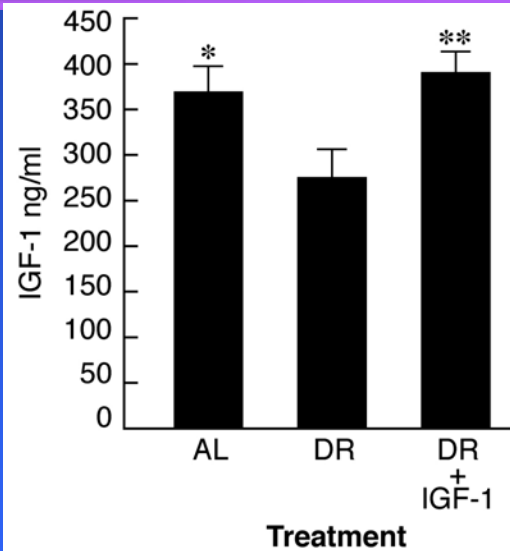
p-Cresidine



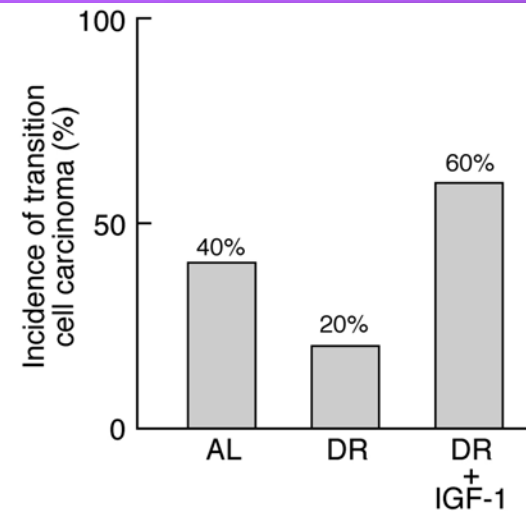
- 2-methoxy-5-methylbenzeneamine
- intermediate in azo dyes
- dye industry: high bladder cancer rate

The Effect of Diet Restriction (+/- IGF-1) in p-Cresidine-Treated p53-Deficient Mice

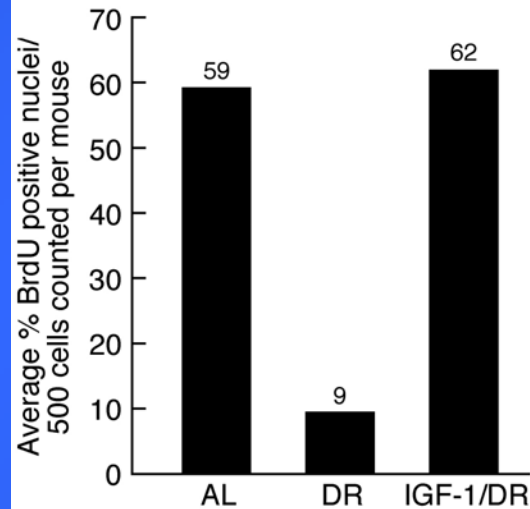
A.



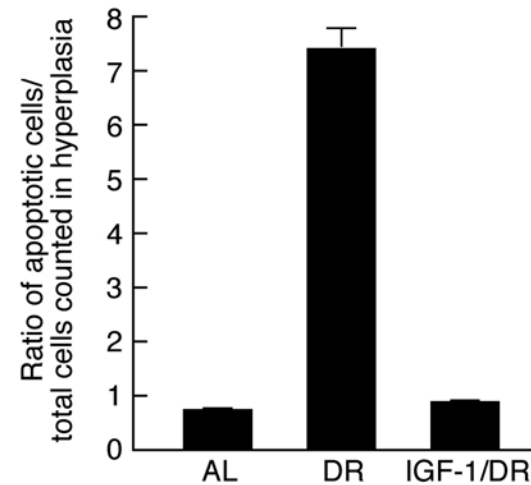
B.



C.

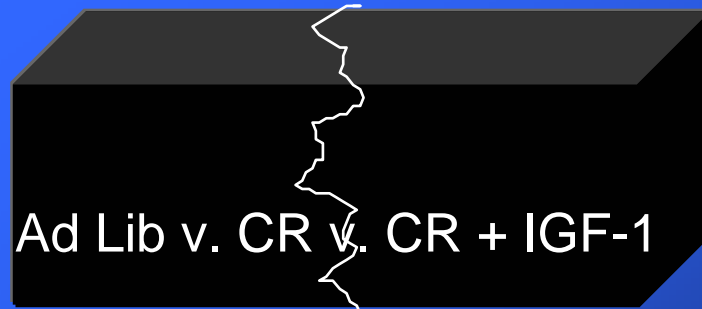
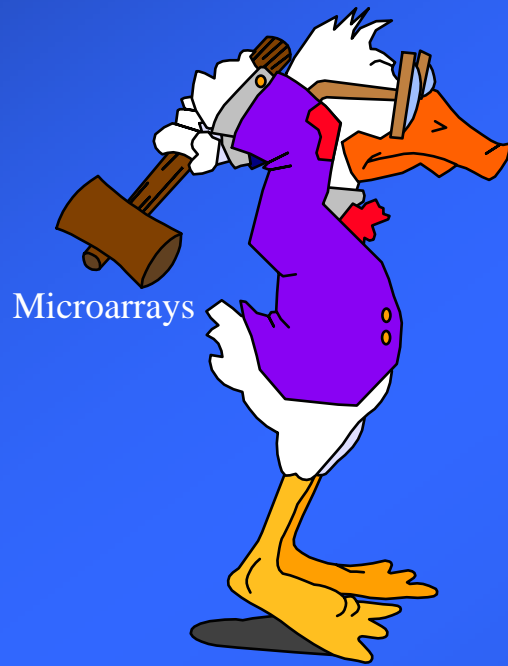


D.



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Breaking Open the Black Box



Effects of CR + IGF-1 on Gene Expression

% Calorie Restriction

<i>IGF-I ($\mu\text{g/day}$)</i>	0	20	30	40
0	X _(AL)	X	X	X
2	X	X	X	X
0 40	X			X
80				X

5 mice per group, all females, 5 wks old at surgery

Number of Genes Changed with Increasing CR

Percent Calorie Restriction	Mean of number of genes changed >2-fold and statistically significantly different
20%	955
30%	1092
40%	1222

Gene Expression Changes: Increasing CR

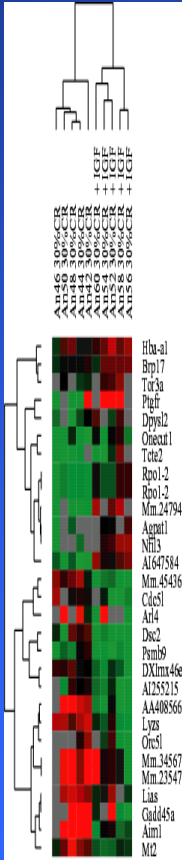
Increased by CR:

Sultn	N-sulfotransferase
Sth2	Sulfotransferase, hydroxysteroid preferring
Mgst3	Microsomal GST 3
Gstt2	GST theta
Gsta2	GST alpha
Amd1	S-adenosylmethionine decarboxylase
Mt1/2	Metallothionein 1 and 2
Gadd45	Growth arrest with DNA damage
Igfbp1	IGF-I binding protein 1

Decreased by CR:

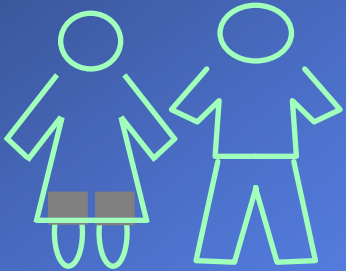
Hsd3b5	Hydroxysteroid dehydrogenase 3b5
Hsd17b2	17b Hydroxysteroid dehydrogenase
EGFR	Epidermal growth factor
COMT	Catechol O-Methyltransferase
CycD1	Cyclin D1

IGF-1-Dependent Gene Expression Changes (30% CR versus 30% CR + IGF-I)



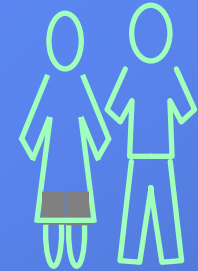
- 58 genes differentially expressed
- 27 restored to ~AL control level
- Examples of IGF-I-Dependent Changes
 - promote cell survival (Gadd45a; CycD1)
 - promote gene transcription (Onecut1, Foxa2)
 - decreased cell adhesion (dsc2)
 - IGF pathway (IGF BP1)

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A simple line-art icon of a woman and a man standing side-by-side, identical to the ones above. The woman is on the left, wearing a dress, and the man is on the right, wearing a shirt and pants. They are both facing forward.

Energy
Balance

QuickTime™ and a
Photo - JPEG decompressor
are needed to see this picture.

Summary: Interventions

- Calorie restriction (chronic) \pm IGF, leptin
- 1-day/week fast (cyclical restriction)
- Treadmill/ running wheel exercise
- Chemopreventive steroids (DHEA, fluasterone)
- Chemopreventive nutrients/agents (soy, 4-HPR, Se, NSAIDs/COX inhibitors)
- Combinations? (CR + exercise; CR + chemopreventives; chemopreventives + vaccines)

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