

Nutrition and Cancer

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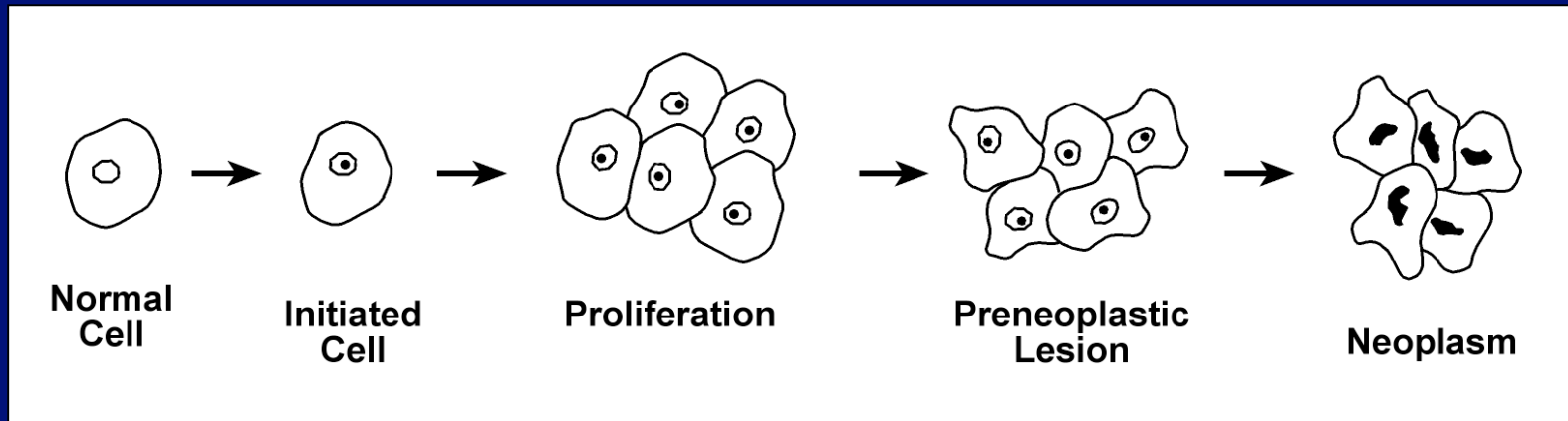
Talk Outline

1. Cancer biology
2. What is the evidence that diet matters?
3. How might diet cause or prevent cancer?
4. What is the evidence for the diet—prostate cancer link
5. Why don't the experts agree?
6. Are dietary supplements helpful ?
 - What led to SELECT?
7. What are reasonable recommendations for dietary patterns to reduce cancer risk?

1

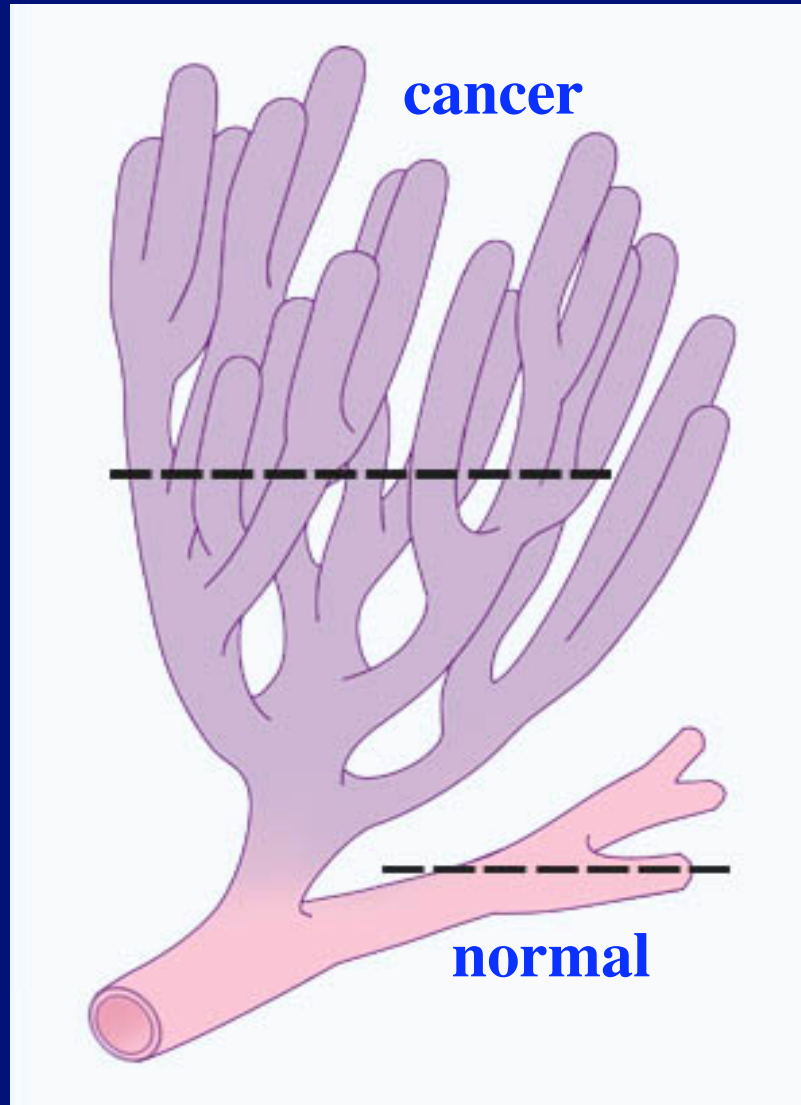
Cancer Biology

Cancer is Caused by an Accumulation of DNA Damage



- DNA Damage (accumulation of somatic mutations)
- Uncontrolled cell growth (proliferation)
- Decreased cell death (apoptosis)
- Recruit blood supply (angiogenesis)
- Grow in distant organs (metastasis)

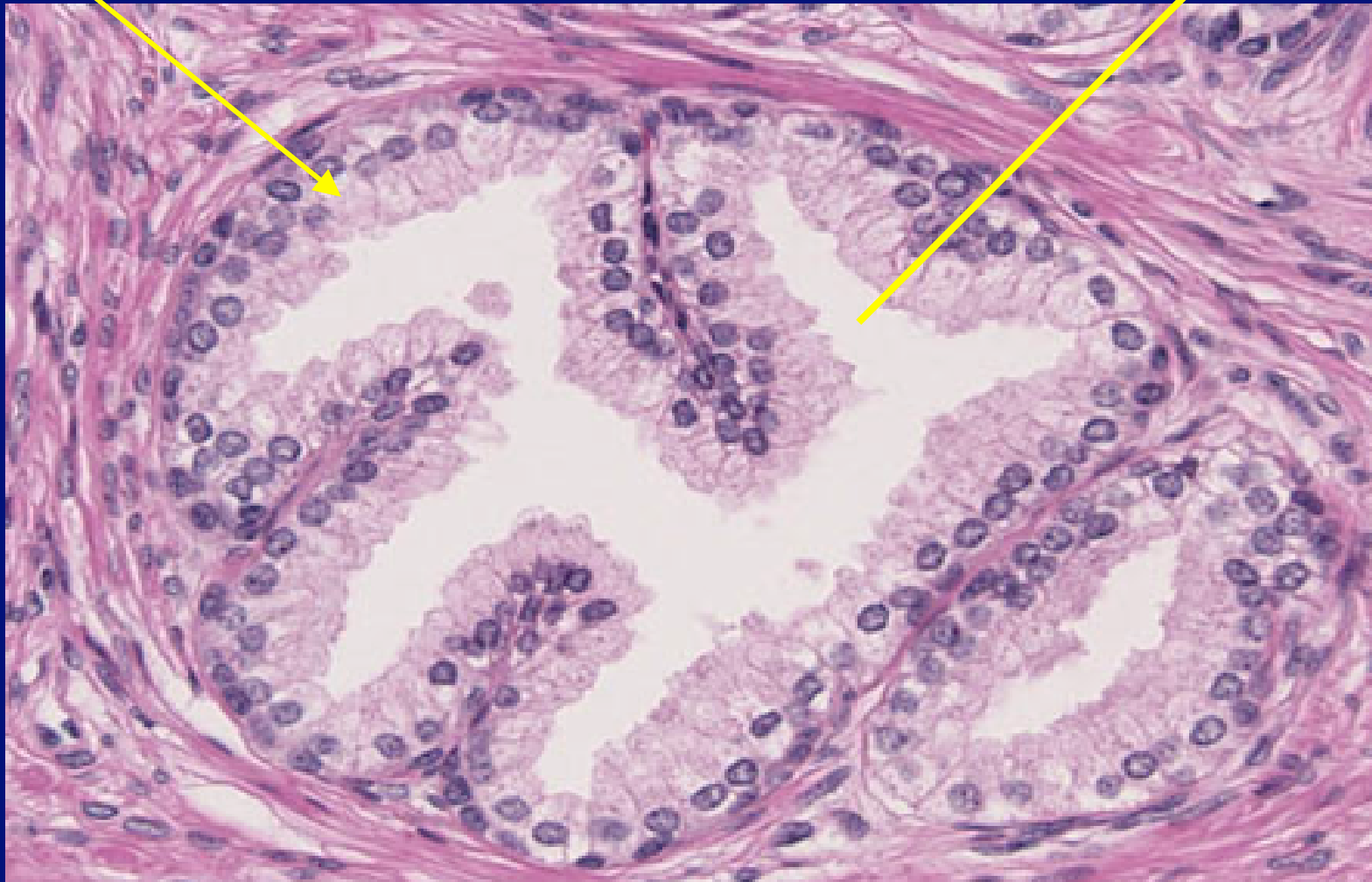
Prostate Ducts in Cancer Become Branched and Small



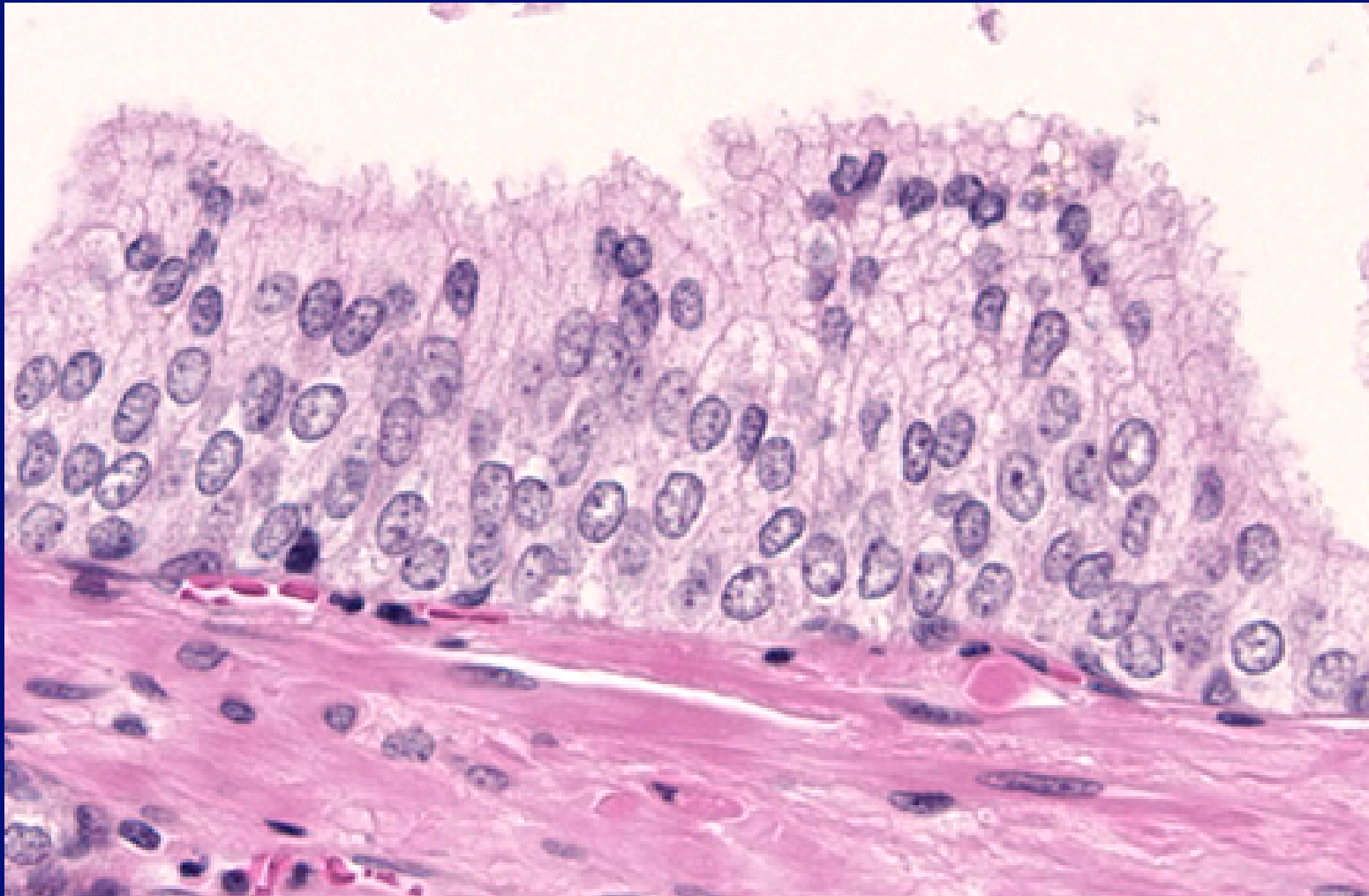
Normal Prostate Tissue

Secretory cells

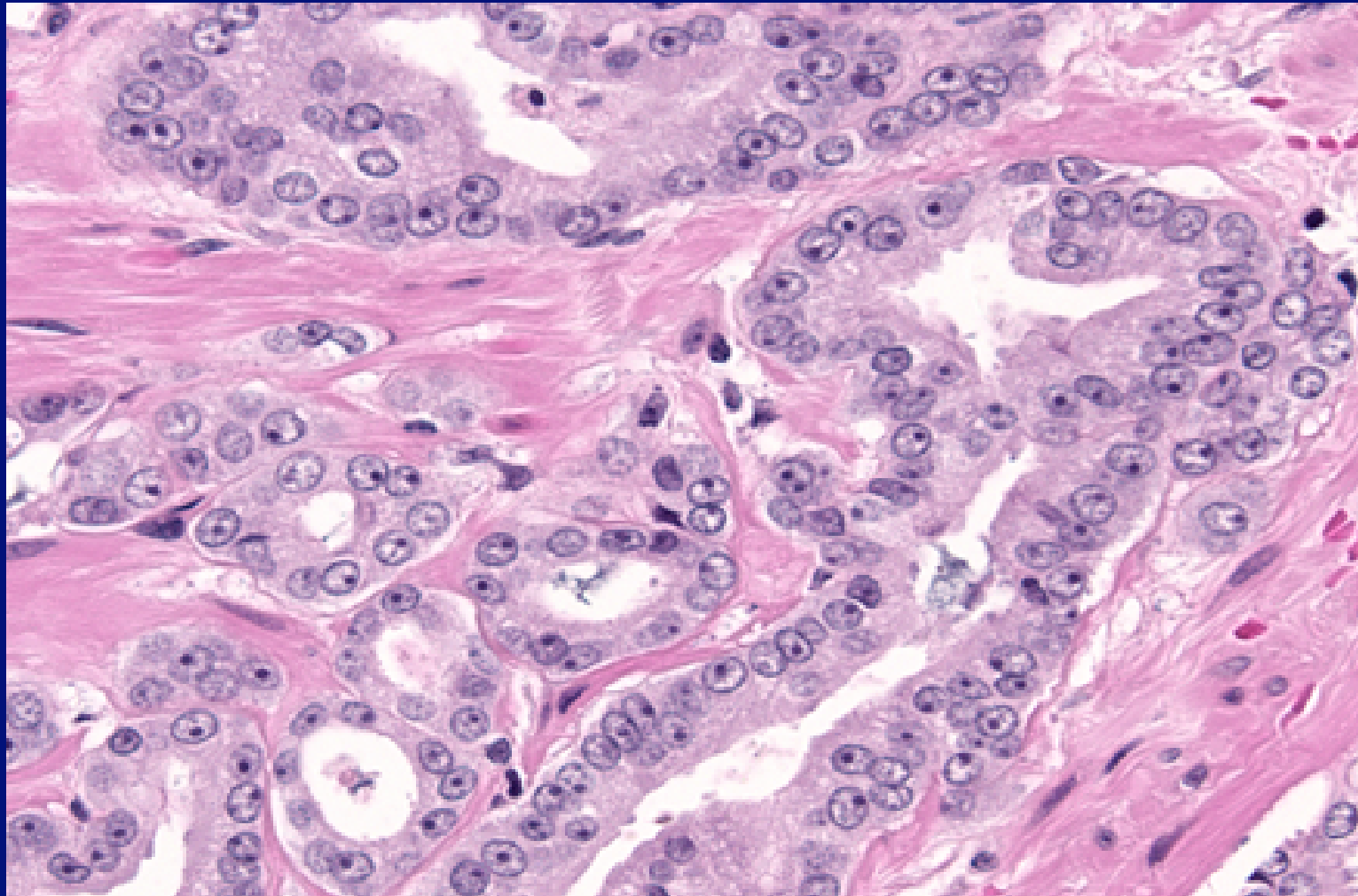
duct



Uncontrolled Prostate Cell Growth Prostatic Intraepithelial Neoplasia (PIN)



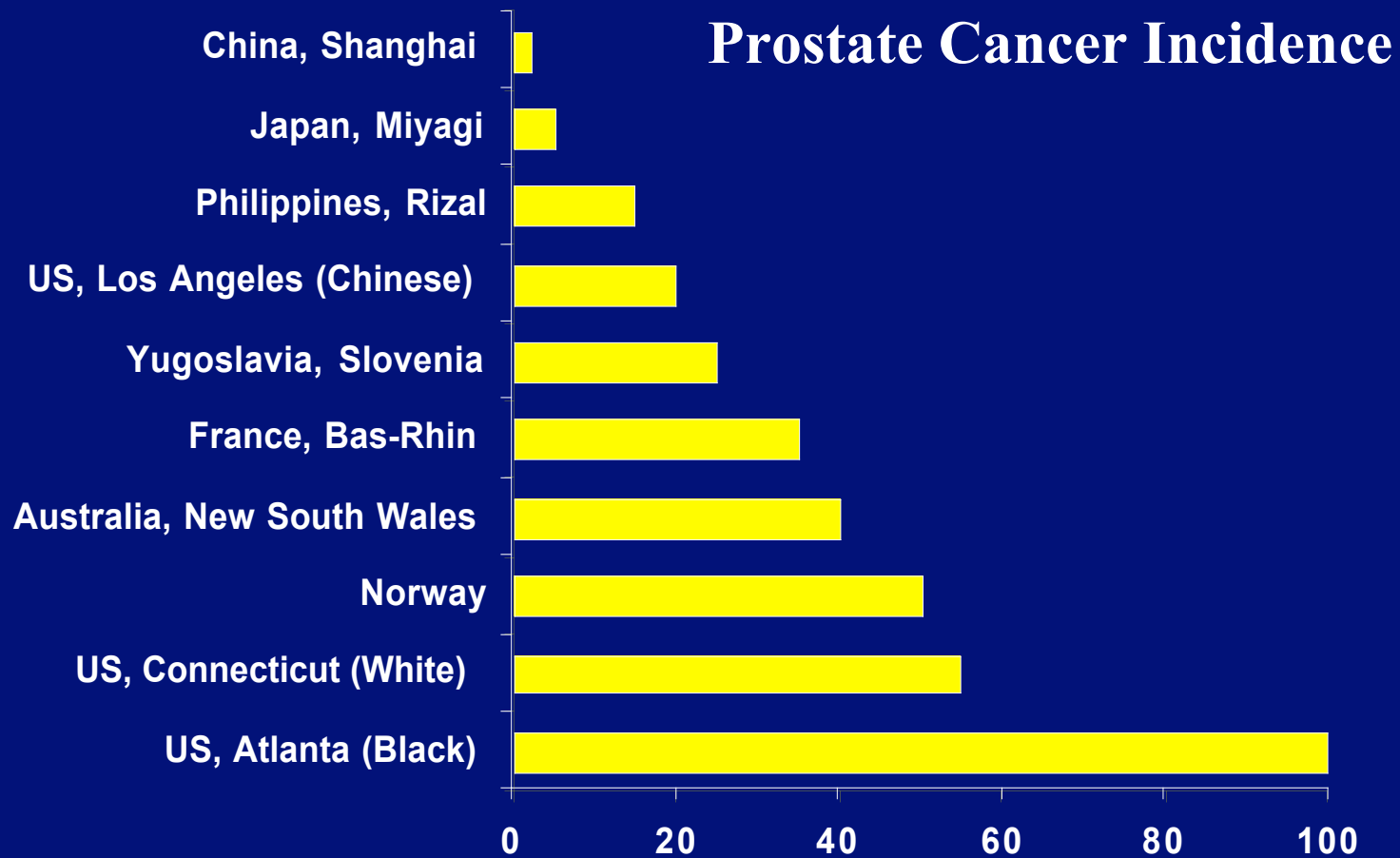
Prostate Cancer



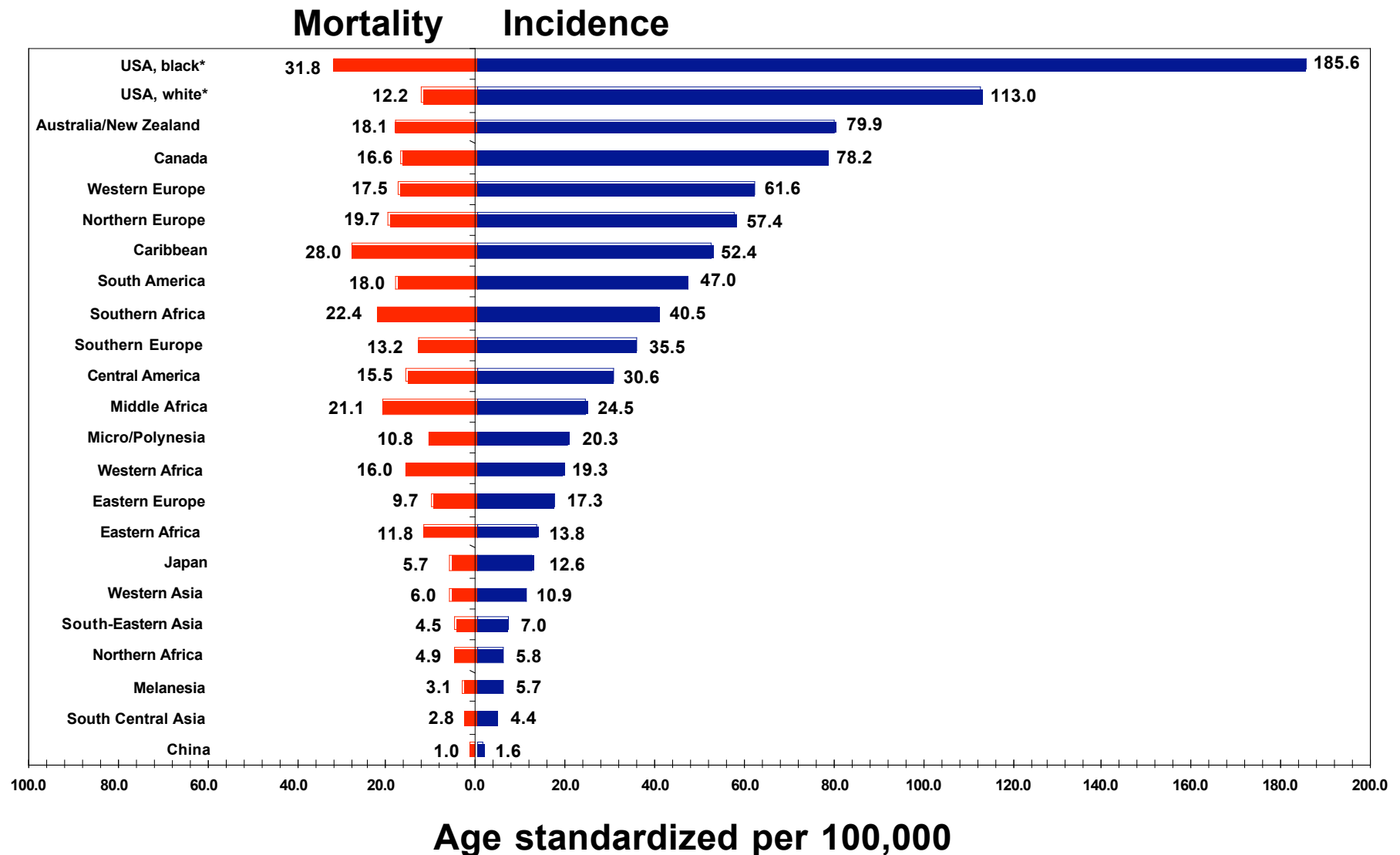
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What is the evidence that diet matters?

Rates of Many Cancers Differ 100-fold Across Countries

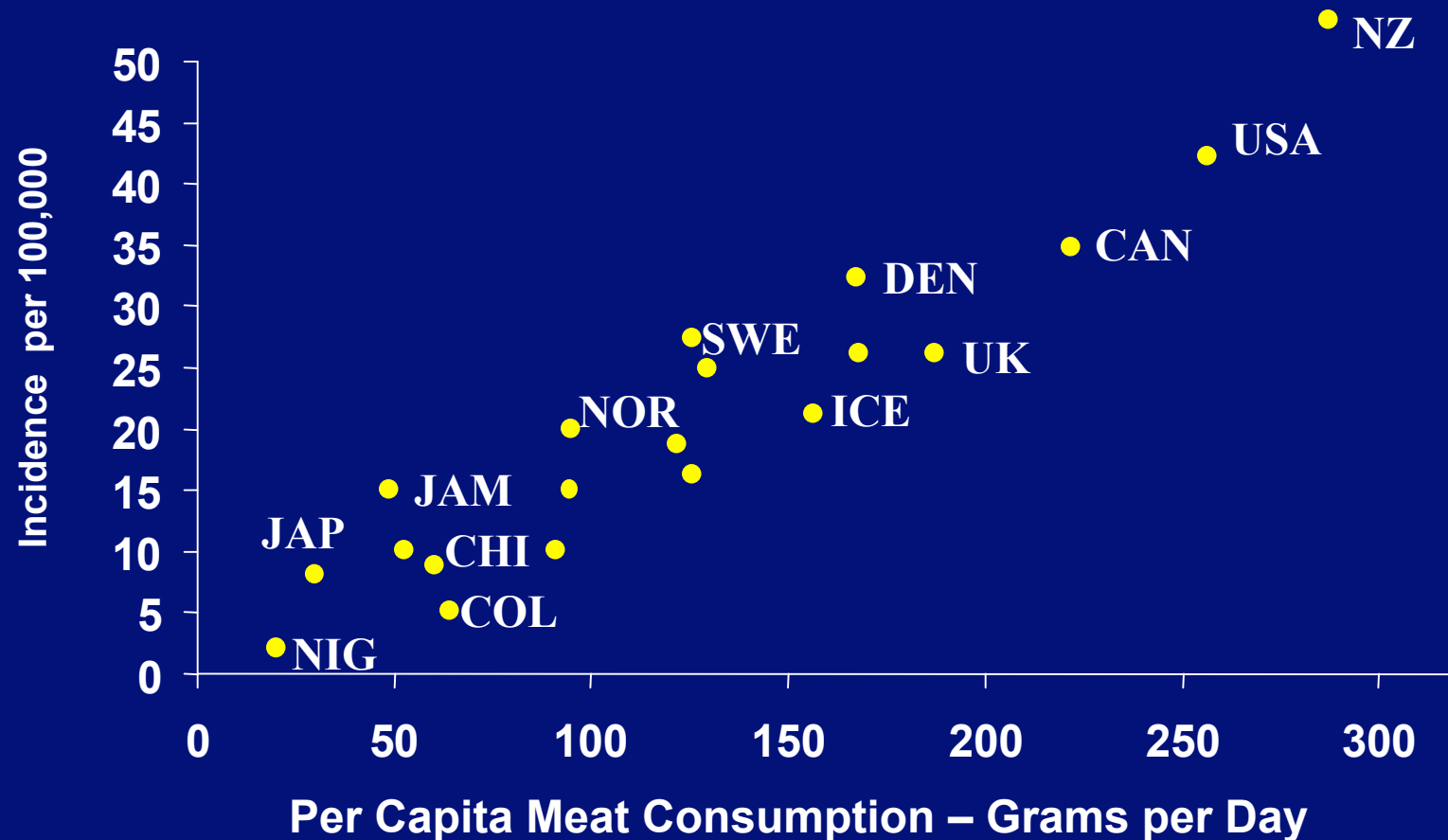


Prostate Cancer Across the Globe





Per-Capita Meat Consumption Correlates Strongly with Colon Cancer Incidence (1970s)



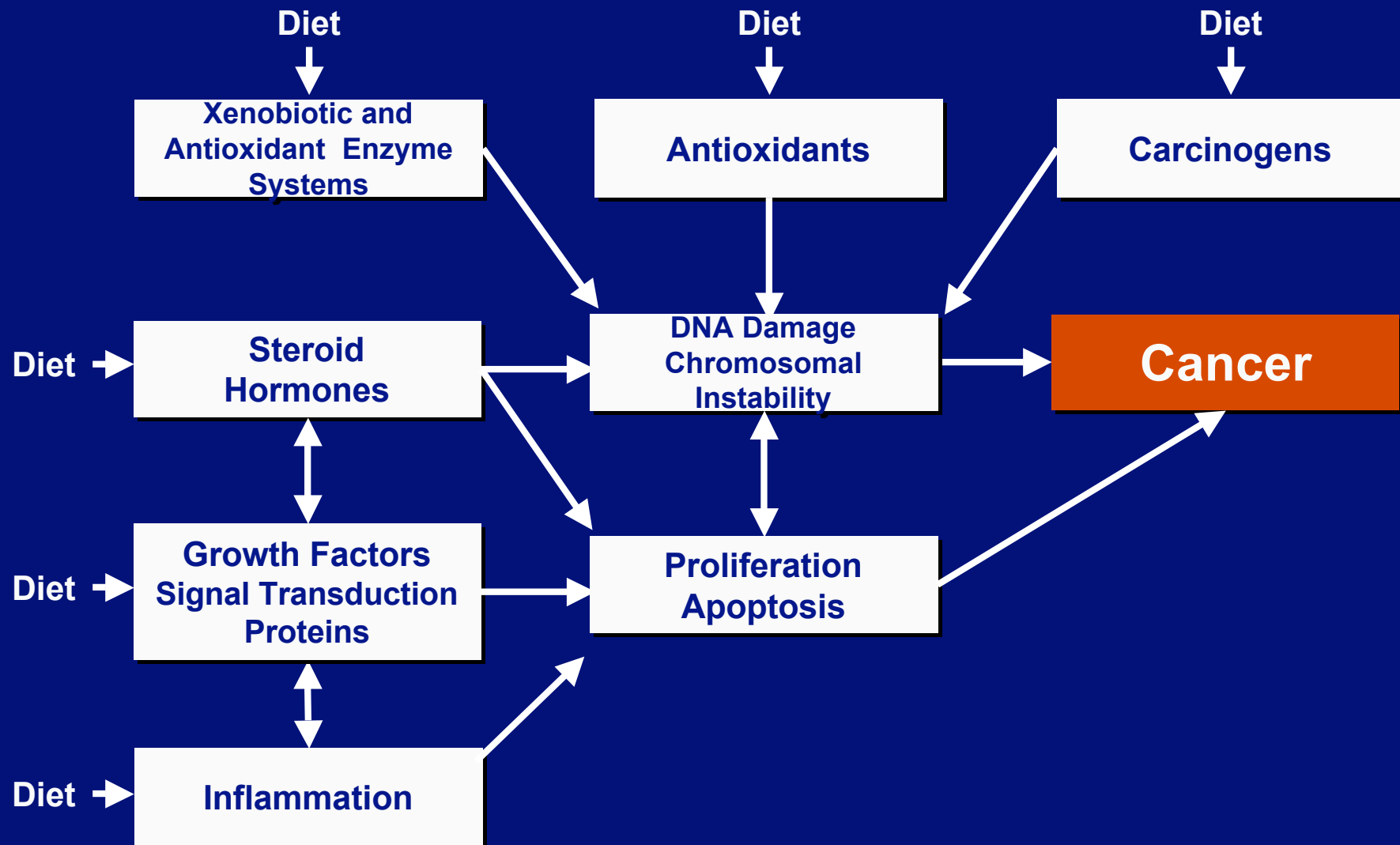
Proportion of Cancer Deaths Attributable to Diet

- **1977 Wynder and Gori**
40% men, 57% women
- **1981 Doll and Peto**
35% overall, range 10%-70%
- **1990 Prentice and Sheppard**
_50% fat \Rightarrow _33% women _17% men

3

How Might Diet Cause or Prevent Cancer?

Diet Affects Many Factors Related to Cancer Risk



Abundant Indirect Evidence Supports Associations of Diet with Reduced Cancer Risk

**Diet
Supplements
Obesity**

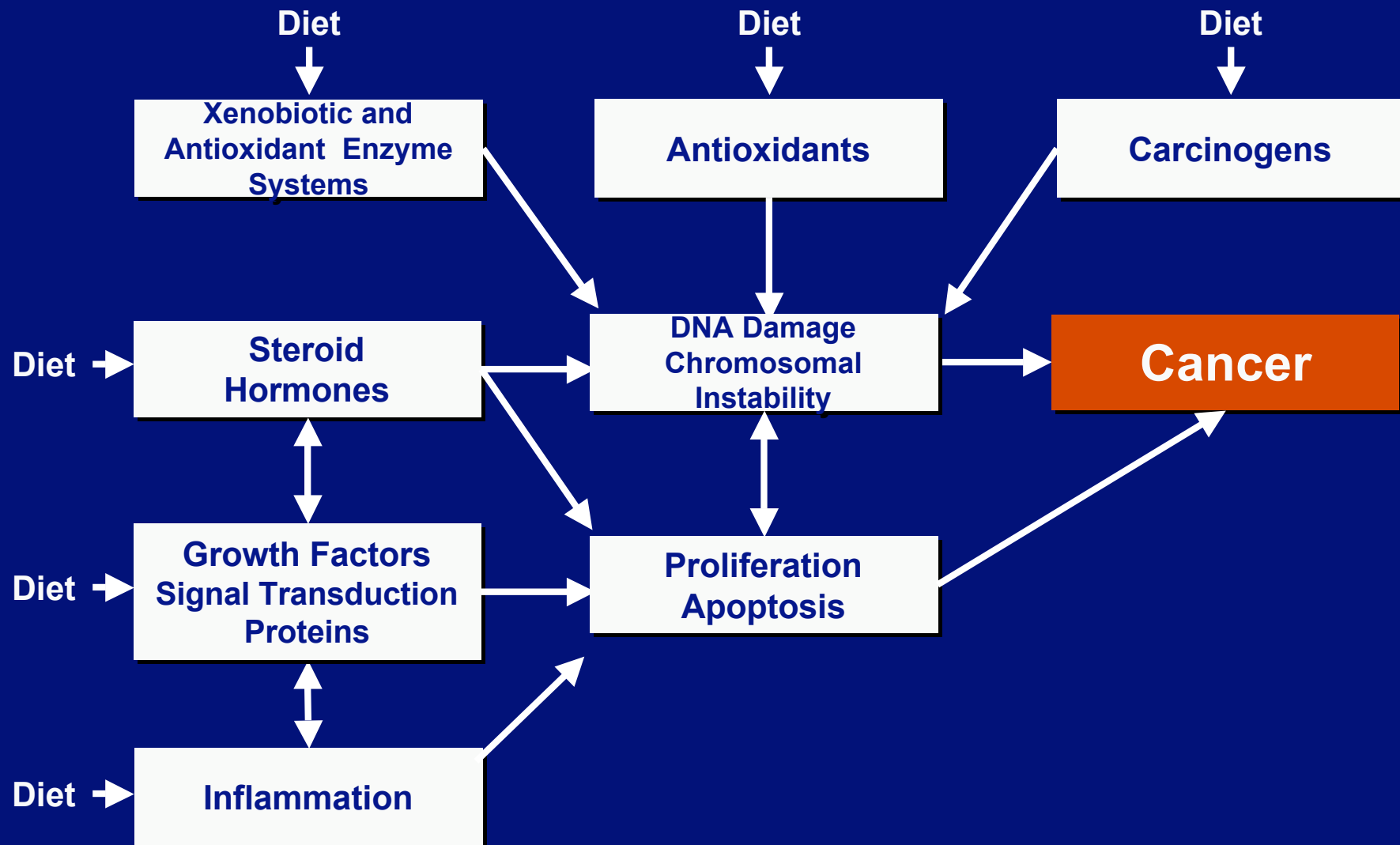


**Biological
Intermediate**



Cancer Risk

Diet Affects Many Factors Related to Cancer Risk



Xenobiotic Metabolism

Xenos, foreign

**Enzyme systems that converts
nonpolar organic compounds to polar
compounds that can be concentrated
and excreted by the kidneys**

Xenobiotic Enzymes

- Phase 1** **“Activate” compounds to make them water soluble, strong electrophiles (P450 enzymes)**
- Phase 2** **“Detoxify” activated compounds by conjugation or conversion to stable metabolites (Glutathione-S-transferases [GST])**

Xenobiotic Enzymes

Dietary compounds are strong inducers of Phase 1 and Phase 2 enzymes

Isothiocyanates
(Cruciferous vegetables)

↑↓ CYP450
↑ GST

Flavonoids
(Grapefruit juice)

↓ CYP1A2

Allyl sulfides
(Garlic, onions)

↑ NAT

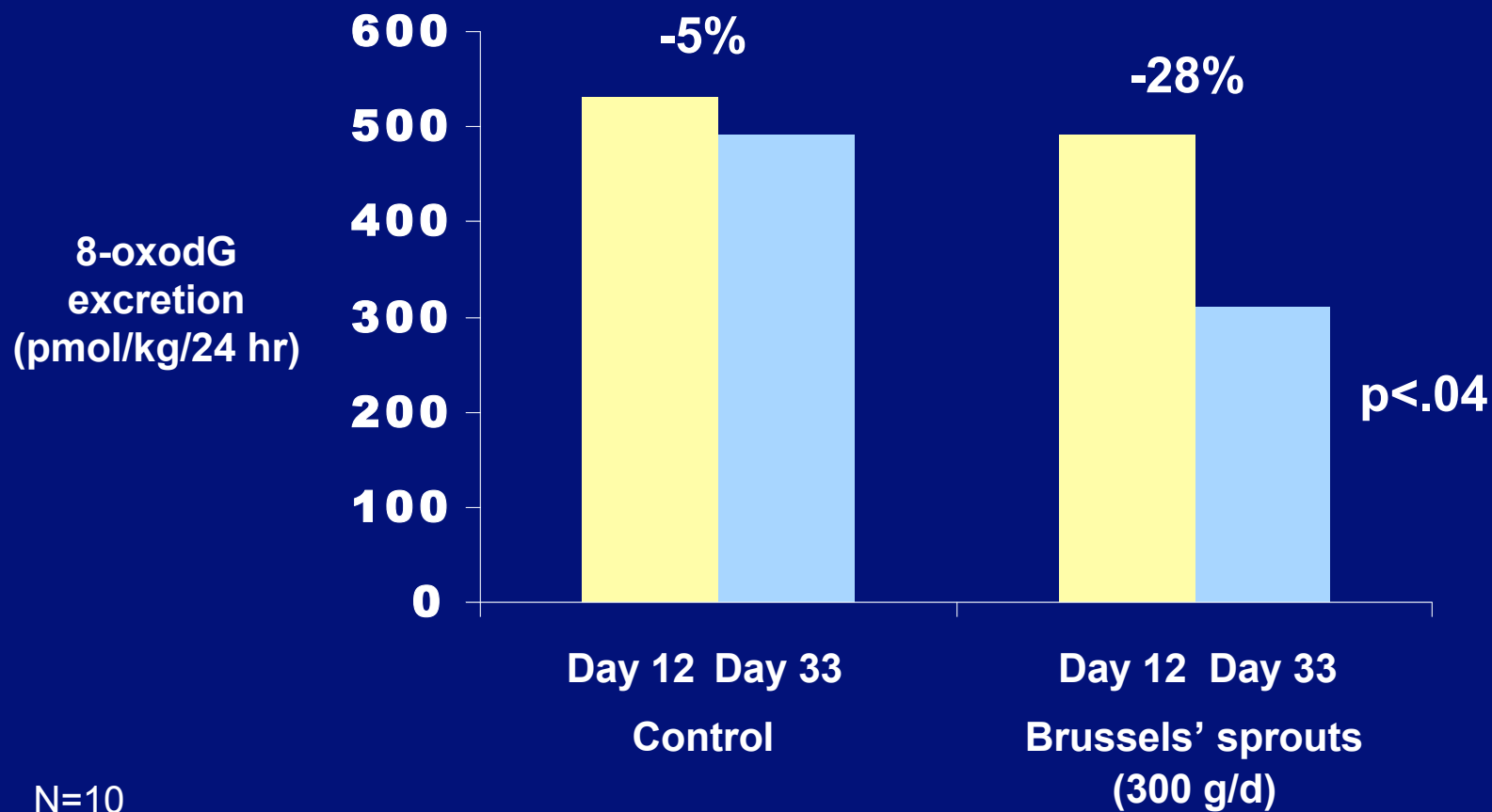


Biological Activities of Isothiocyanates in Cruciferous Vegetables

- **Steroid hormone metabolism**
 - Decreases potency of estrogens
- **Carcinogen metabolizing enzymes**
 - Increase activity of enzymes that detoxify carcinogens
- **DNA structure**
 - Inhibit enzymes that unwind DNA and make it accessible for building protein

Brussels' Sprouts

Reduce Oxidative DNA Damage

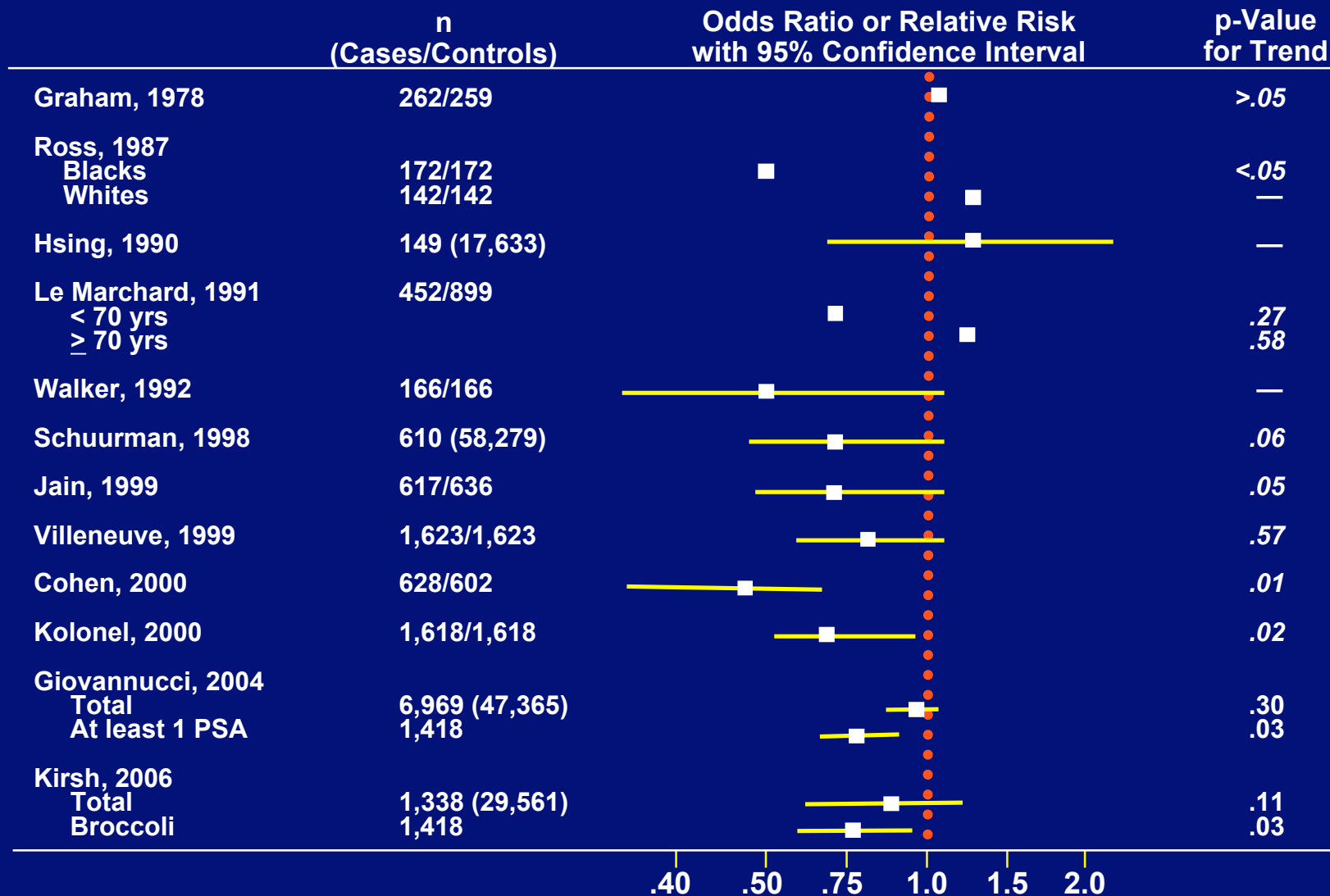


N=10
Verhagen, 1995

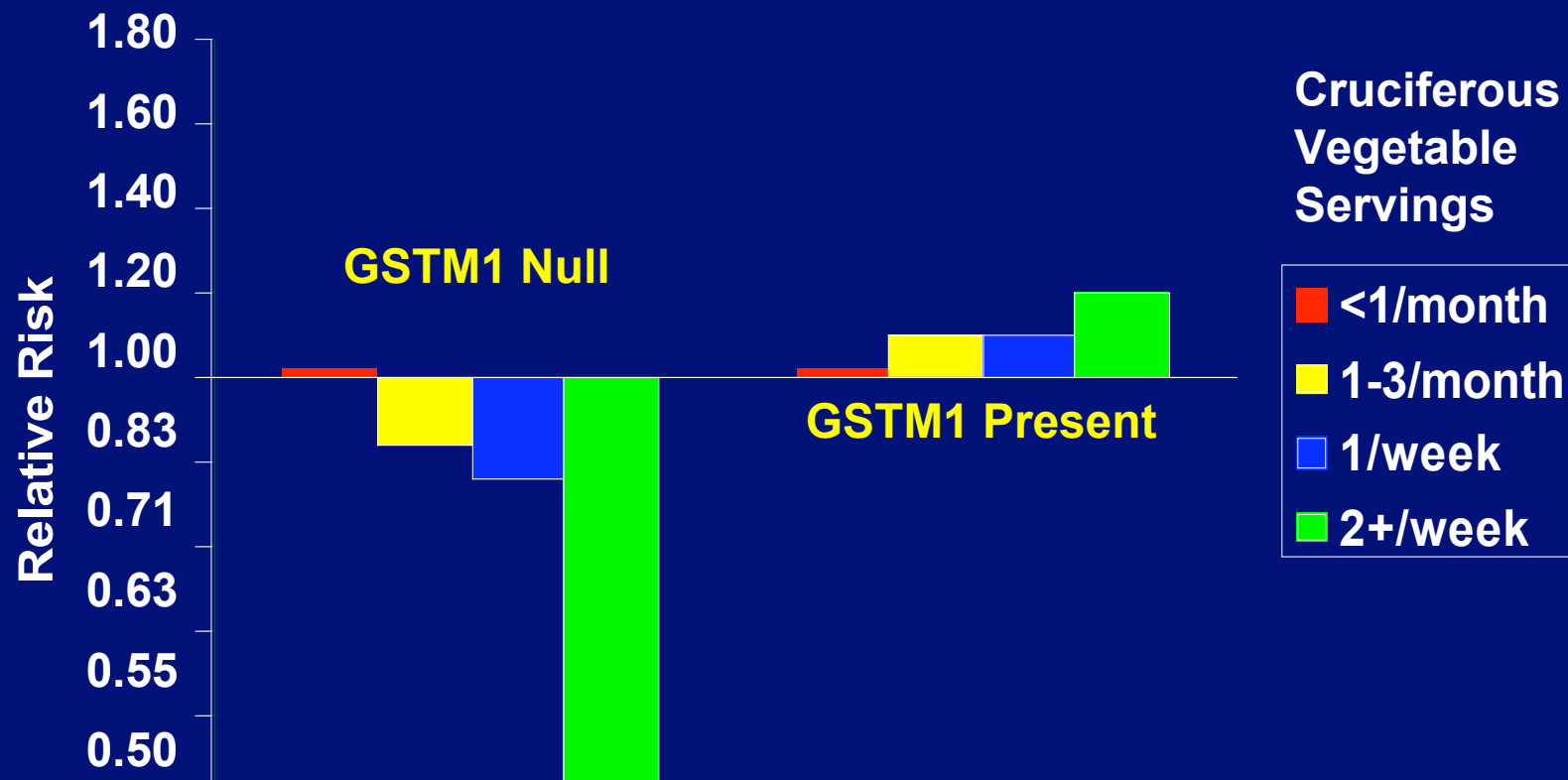
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Evidence for diet—prostate cancer link

Cruciferous Vegetables are Consistently Associated with Lower Prostate Cancer Risk

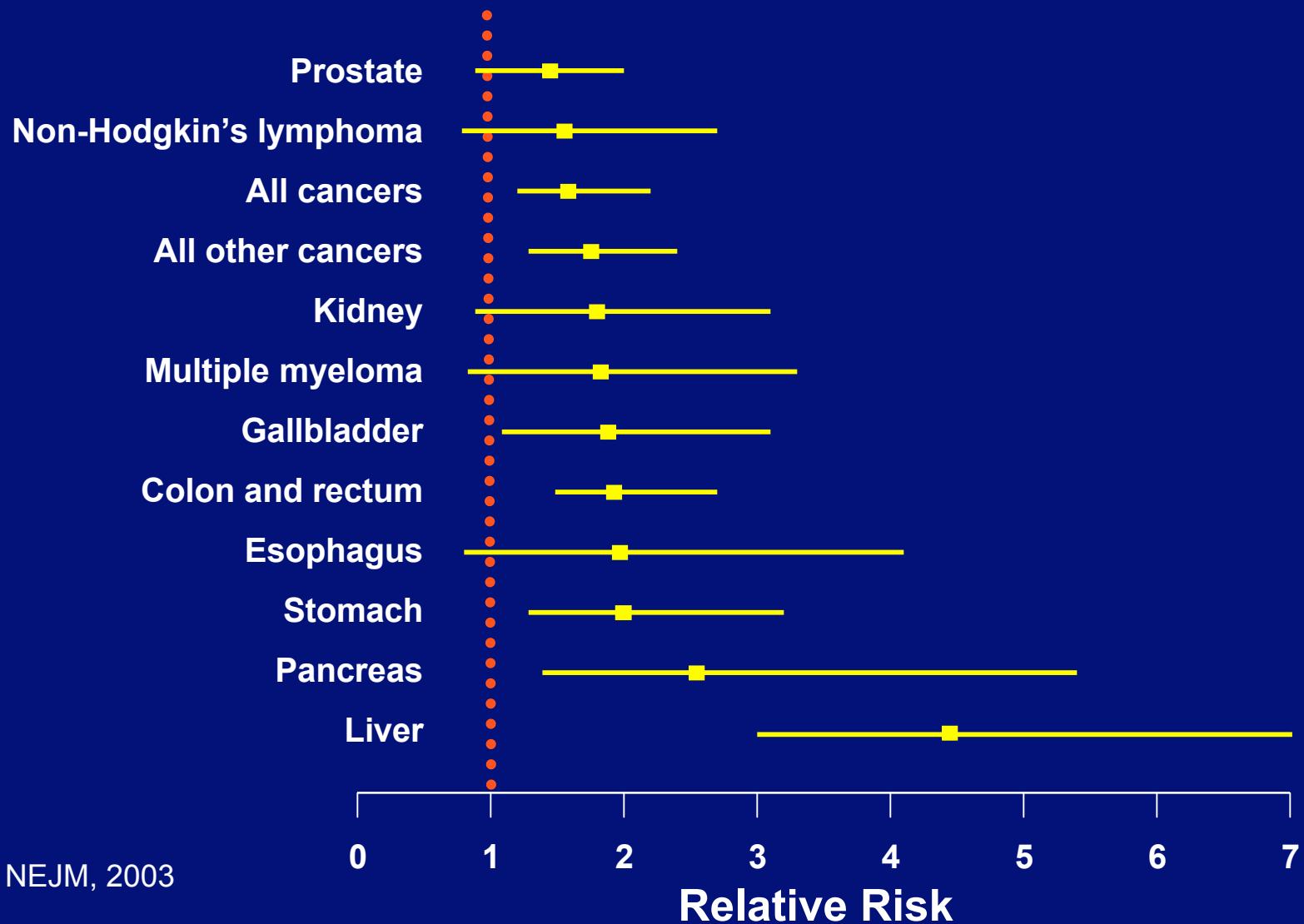


Cruciferous Vegetables Prevent Prostate Cancer Only if GSTM1 Null



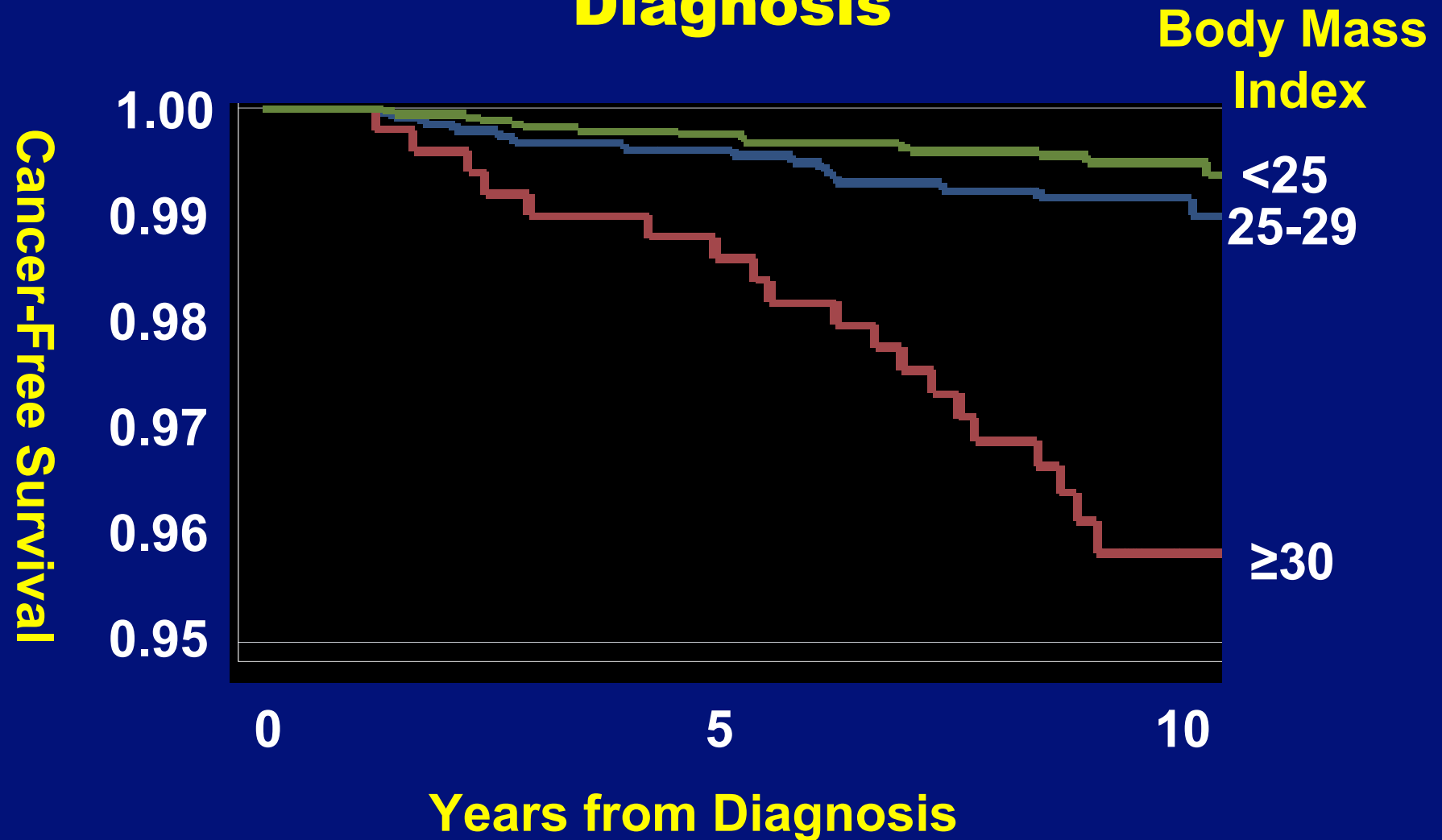
820 cases, 820 controls, Carotene and Retinol Efficacy Study, Kristal 2005.

Obesity and Cancer Mortality in Men



Calle, NEJM, 2003

Obese Men Have an Increased Risk of Prostate Cancer Death Following Diagnosis



Part 5

Why Don't the Experts Agree?

Direct Evidence in Humans Requires Epidemiological Studies



Why Do Experts Disagree?

Diet is Very Difficult to Measure

Diet varies day-to-day and year-to-year

Self-report of diet is inaccurate

Dietary measures typically used in epidemiological studies may not do a very good job!

☐ Amended data Ppt Initials (L,F,M): Site #: Participant ID:

SPAGHETTI, MIXED DISHES and SOUPS

	HOW OFTEN DID YOU EAT THESE FOODS LAST YEAR?									Medium Serving Size	Amount?		
	Never or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day		S	M	L
Stew, pot pie, curries and casseroles with meat or chicken	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chili with meat and beans	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spaghetti, lasagna and other pasta with meat sauce	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spaghetti and other pasta with tomato sauce (no meat)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spaghetti and other pasta with oil, cheese or cream sauce, including macaroni and cheese	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Asian-style (stir-fried) noodles and rice, such as chow mein, fried rice and Pad Thai	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pizza	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1/2 of a 12" pizza	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tofu, tempeh and products such as tofu hot dogs, soy burgers and tofu cheese	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4 ounces, 2 hot dogs or 1 burger	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Burritos, tacos, tostadas and quesadillas	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 medium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Enchiladas and tamales	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 medium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vegetable, minestrone and tomato soup	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cream soups such as chowders, potato and cheese	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bean soups such as pea, lentil and black bean	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Miso soup	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ramen noodle soup	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other soups such as chicken noodle	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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Prostate Cancer Prevention Trial

Food Frequency Questionnaire

Can you answer this question?

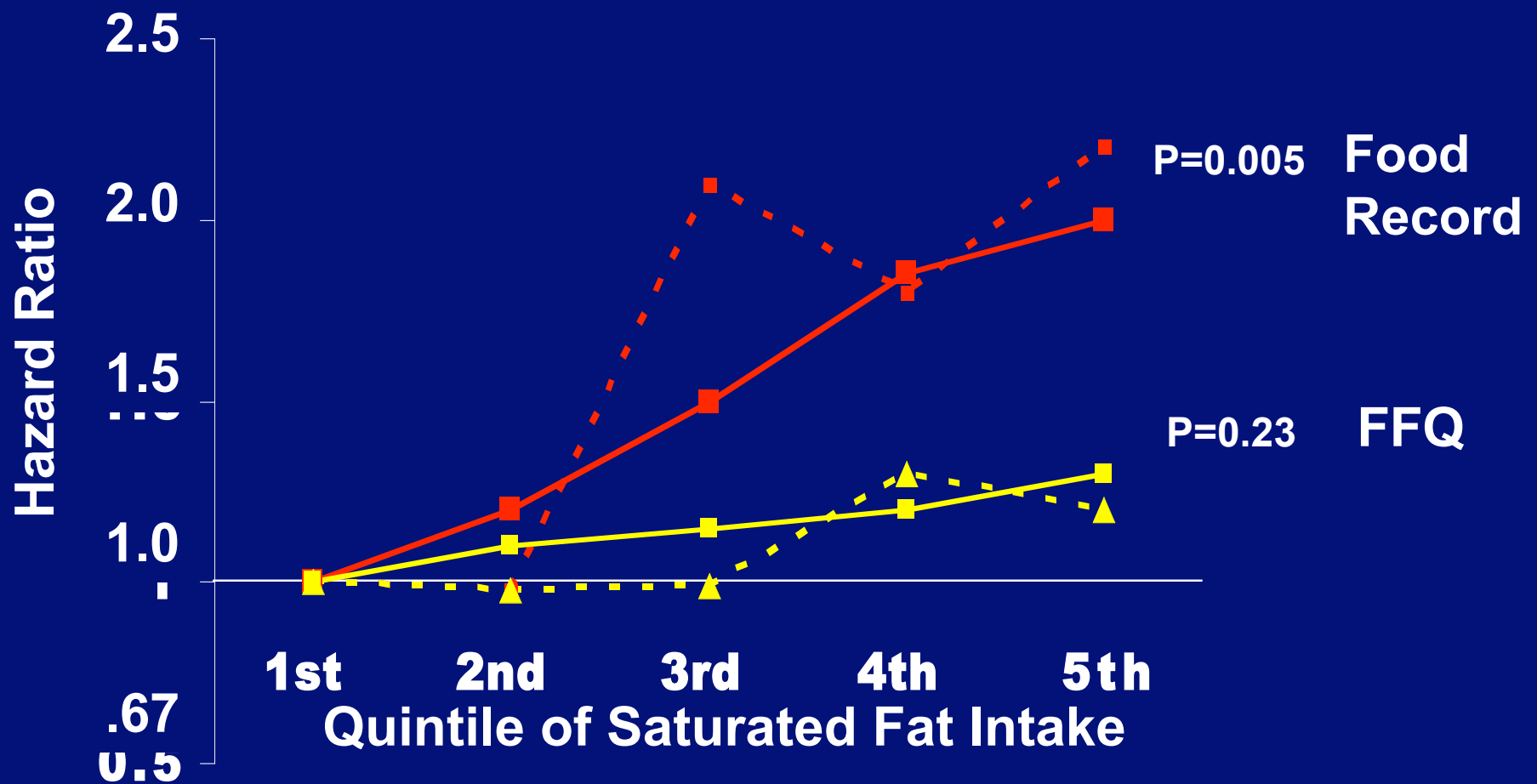
How could you analyze it?

SPAGHETTI, MIXED DISHES and SOUPS

	<u>HOW OFTEN DID YOU EAT THESE FOODS LAST YEAR?</u>										<u>Amount?</u>		
	Never or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium Serving Size	S	M	L
Stew, pot pie, curries and casseroles with meat or chicken	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chili with meat and beans	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spaghetti, lasagna and other pasta with meat sauce	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spaghetti and other pasta with tomato sauce (no meat)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spaghetti and other pasta with oil, cheese or cream sauce, including macaroni and cheese	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Asian-style (stir-fried) noodles and rice, such as chow mein, fried rice and Pad Thai	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 cups	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pizza	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	½ of a 12" pizza	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Dietary Fat is Associated with Breast Cancer Risk When Measured by Food Records

Norfolk, UK



Bingham, Lancet, 2003 EPIC Norfolk (UK) 168 Cases

Why Do Experts Disagree?

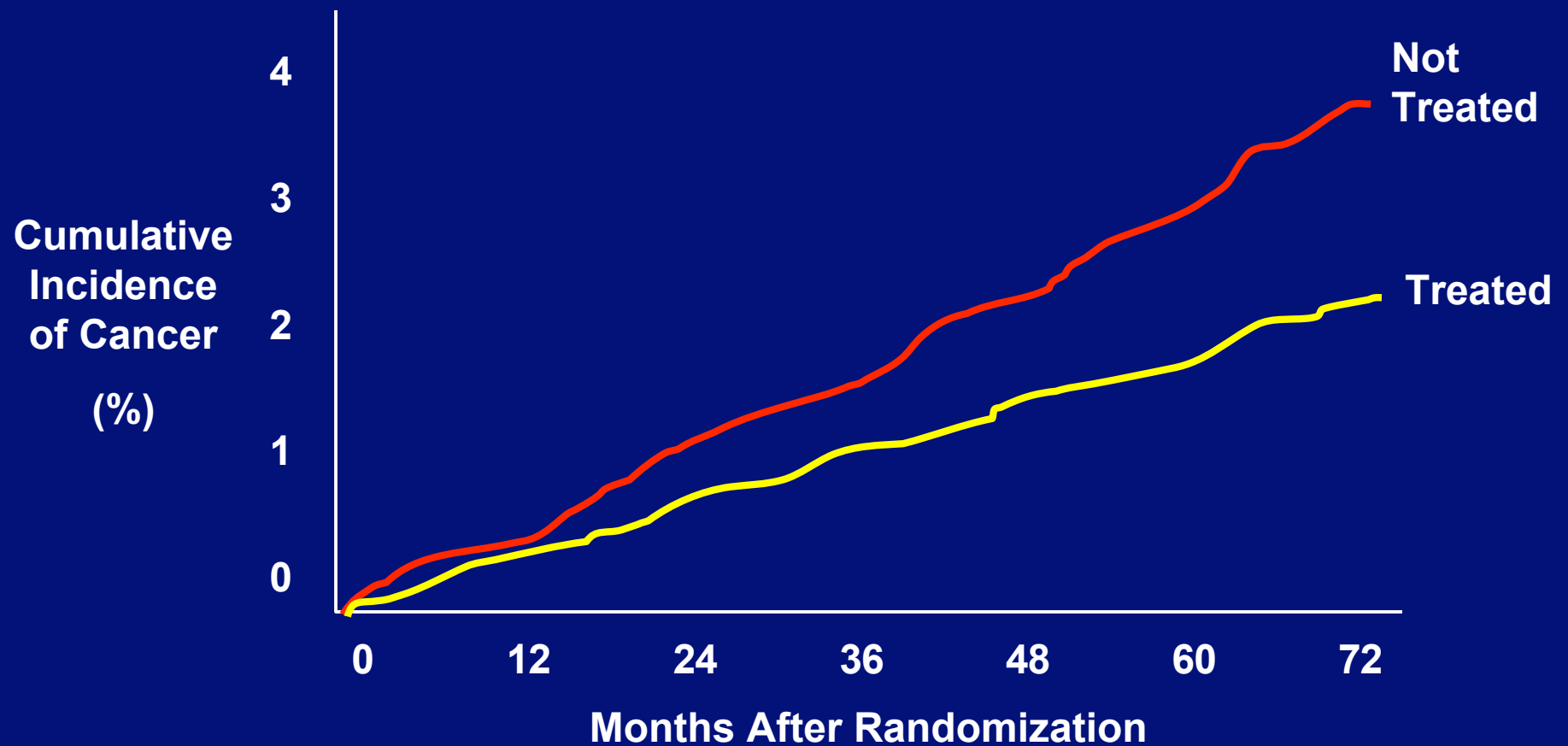
Randomized Trials for Cancer Prevention Have Limitations

Randomized trials cannot test effects of long-term dietary exposure

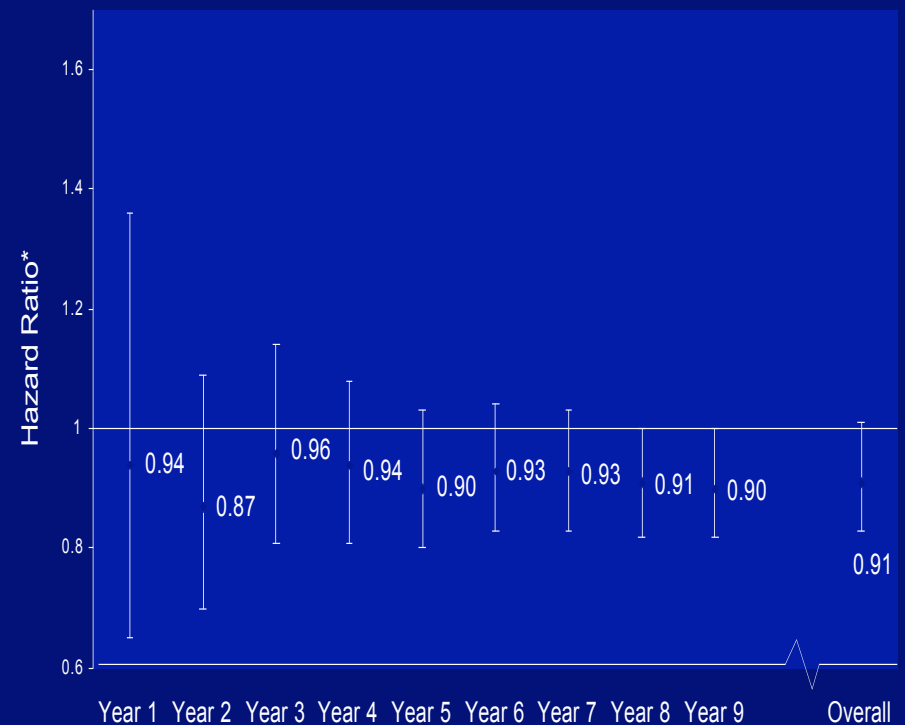
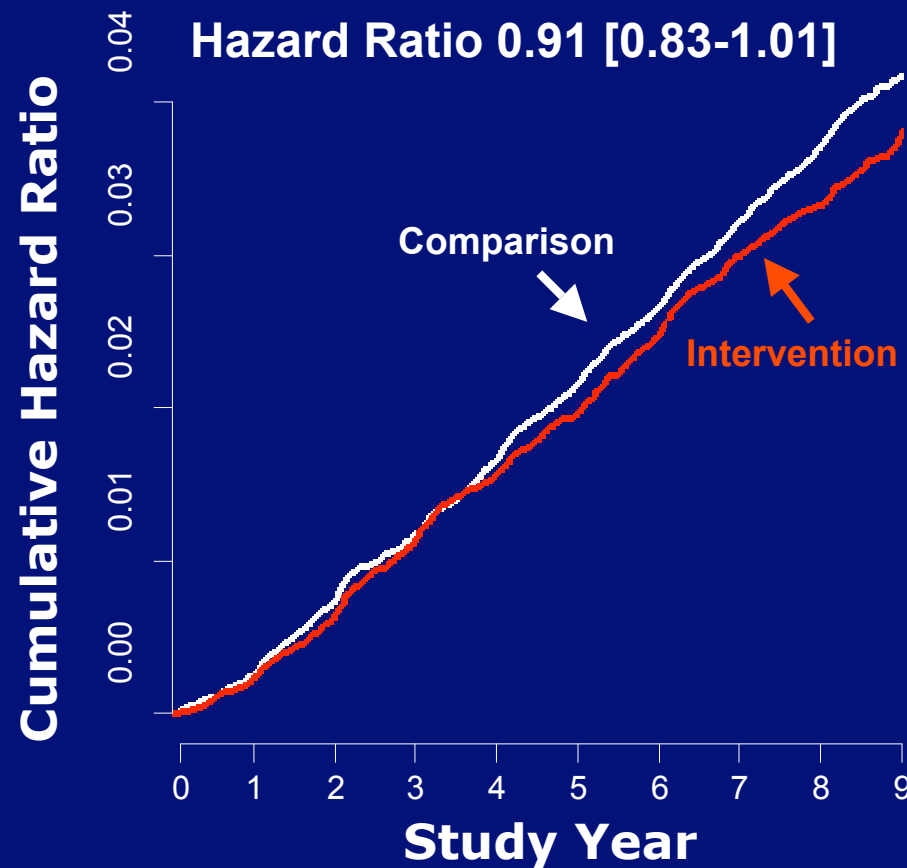
Long-term adherence to dietary change interventions is modest

Randomized trials cost \$50-\$200 million

Randomized Trial of Diet and Cancer Prevention



Women's Health Initiative Low-Fat Diet and Breast Cancer



JAMA 2006; 295; 629-642

The New York Times:
LOW-FAT DIET DOES NOT CUT HEALTH RISKS

The Atlanta Journal-Constitution:
REDUCING FAT MAY NOT CURB DISEASE

The Boston Globe:
STUDY FINDS NO MAJOR BENEFIT OF A LOW-FAT DIET

The Los Angeles Times:
EATING LEAN DOESN'T CUT RISK

Low Fat, High Fiber, Fruit and Vegetable Diet Has No Effect on Colorectal Adenoma Recurrence

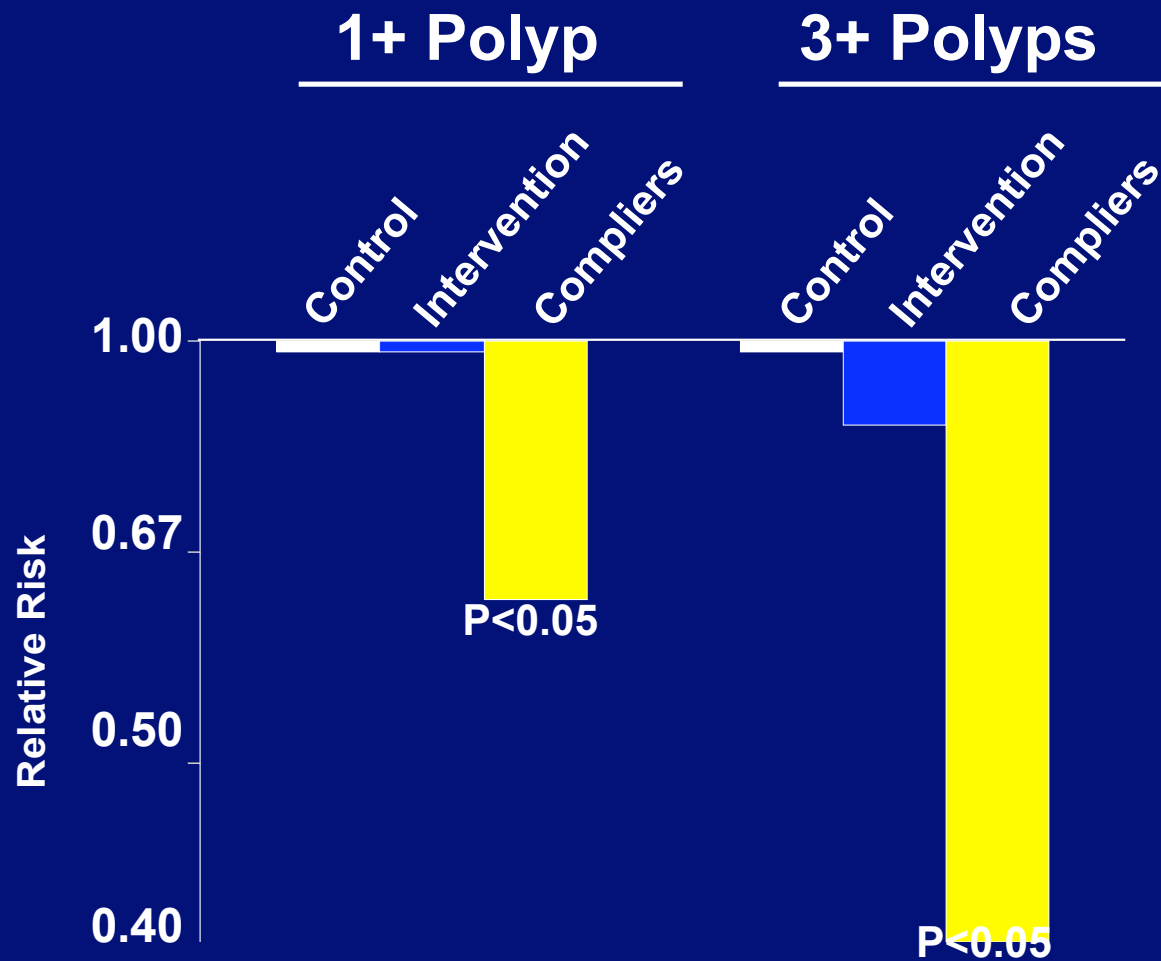
Number of Adenomas	Adenoma Recurrence (%)		Risk Ratio
	Intervention (n=958)	Control (n=947)	
1+	39.7	39.5	1.00 (0.9 – 1.12)
3+	7.6	7.9	0.96 (0.71 – 1.31)

Adherence to Fruit and Vegetable Component of the ~~Polyp Prevention Trial Dietary Intervention~~

	Intervention		Control		Intervention Effect
	Baseline	Year 4	Baseline	Year 4	
Fruits and Veggies (Svgs/1000Kcal)	2.0	3.4	2.0	2.2	+52%
Serum Carotenoids (mg/dl)	4.46	4.50	4.45	4.42	+1.3%
Predicted by Feeding Studies					≥+45%

Reduced Risk of Polyp Recurrence

Dietary Intervention Compliers



Compliers

Fat <20 %energy

Fiber 18 g/1000 kcal

Fruit & Vegetables
3.5 svgs/1000 kcal

Why the Experts Don't Agree

Poor dietary measurement leads to irreproducible and chance findings

Randomized trials of diet and cancer are likely to give false-negative answers

Our understanding of cancer risk is rudimentary, so we often do not know how to ask the right question

Part 6

Do Dietary Supplements Prevent Cancer?

Supplement Use in the United States

- **48-55% of adults use vitamin/mineral supplements**
- **20% of adults use herbal supplements**
- **\$17,700,000,000 (17.7 billion) spent per year**

If Dietary Antioxidants Prevent Cancer Are Supplements the Answer?

There is little evidence that dietary antioxidants prevent cancer. Evidence is stronger for enzyme systems.

There is little evidence that antioxidant supplements prevent DNA damage

There is little evidence that antioxidant supplements prevent cancer, and strong evidence that they can induce cancer



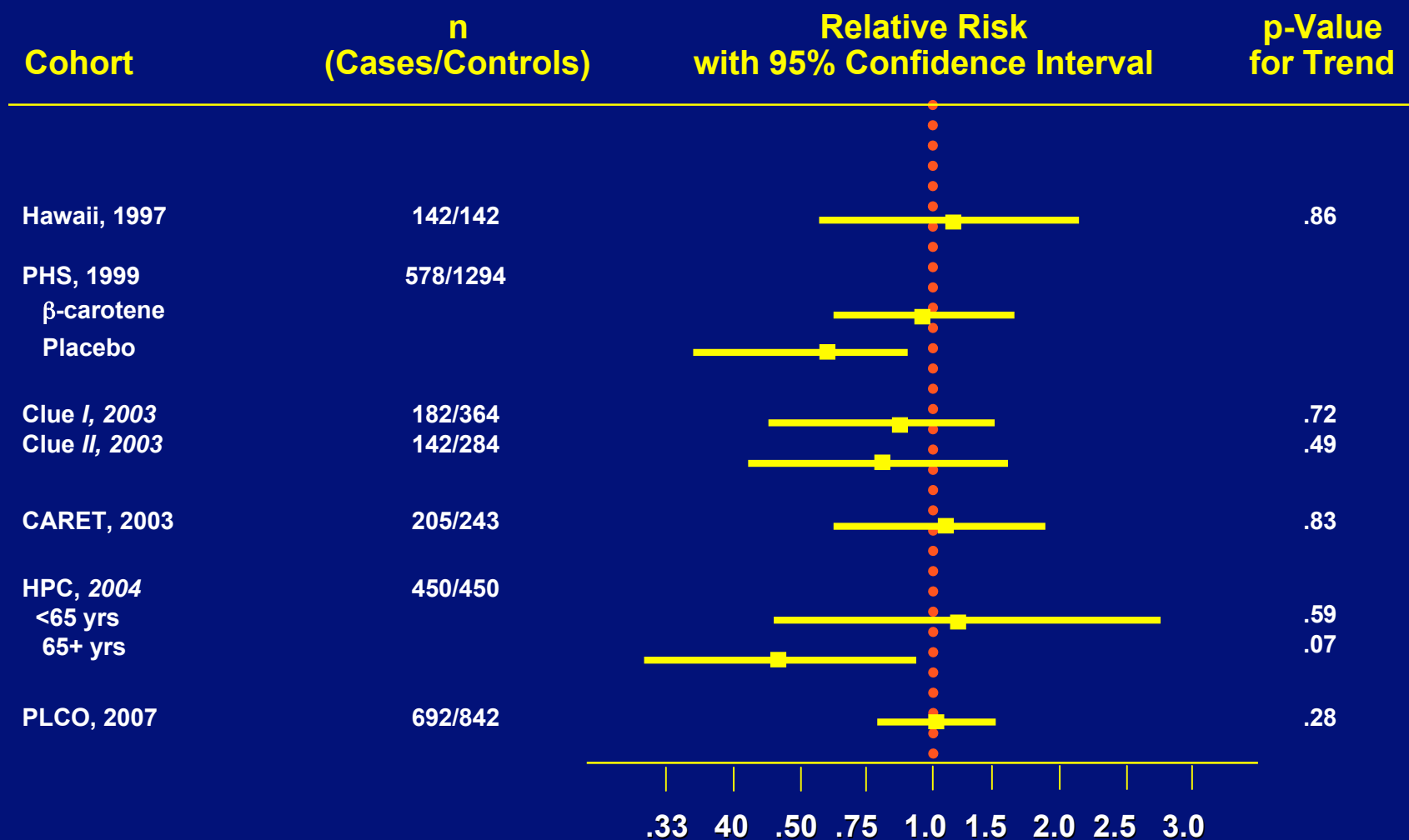
First (1995) Finding that Eating Tomato Products Reduces Prostate Cancer Risk

Relative Risk

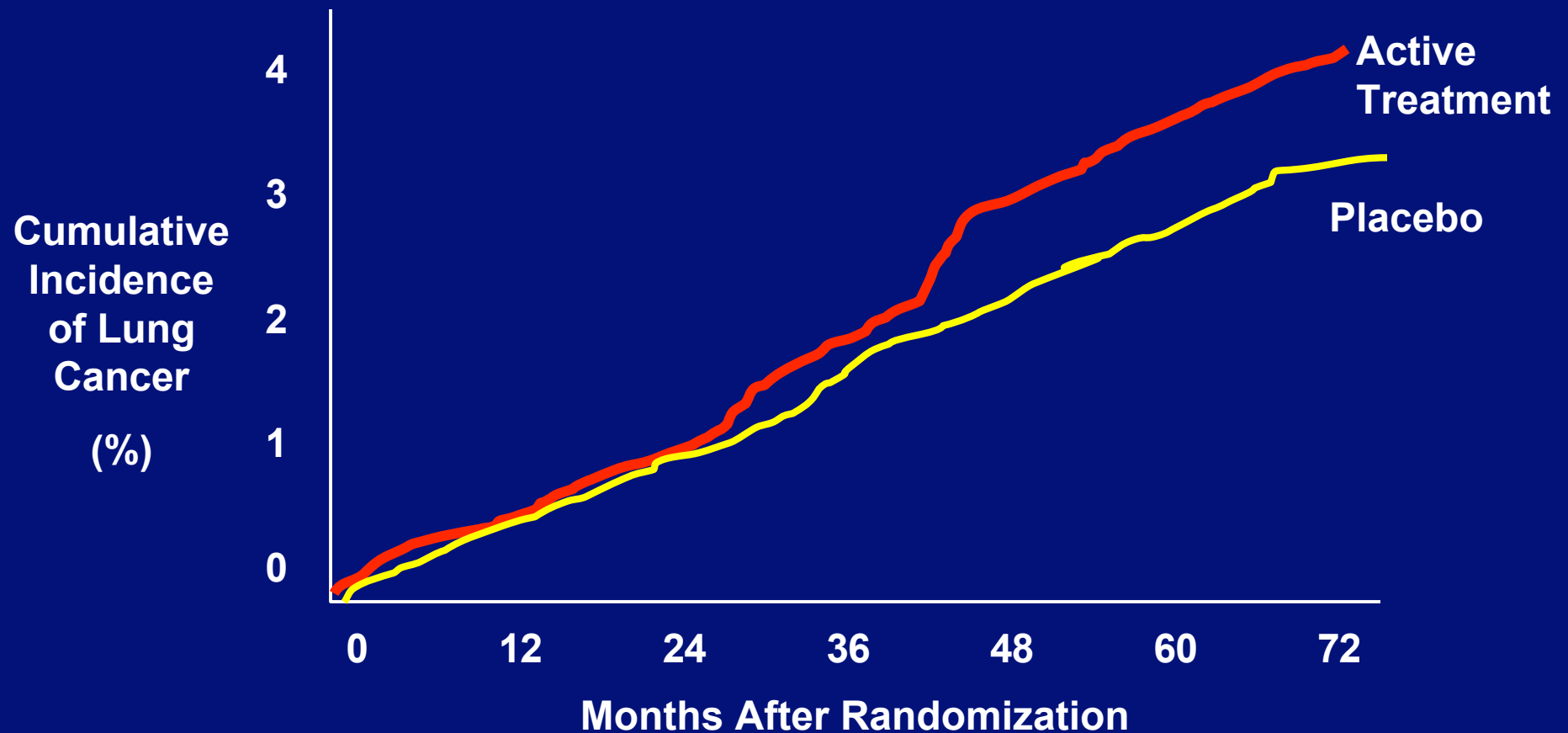
	Quintiles of Intake					<i>P for trend</i>
	Low				High	
Lycopene	1.00	0.90	0.94	0.89	0.79*	.04
Tomato sauce	1.00	0.85	0.77*	0.66*		.001
Tomatoes	1.00	0.90	0.91	0.74*		.03
Pizza	1.00	0.94	0.76	0.85		.05

773 cases, Health Professionals Follow-up Study, N=47,894.
Giovanucci, 1995

Serum Lycopene is Not Associated with Reduced Prostate Cancer Risk



β -Carotene Increases Lung Cancer Incidence in Smokers



Omenn, et al., 1996

Could Other Supplements Prevent Cancer?

There is good evidence that folate (multivitamin) prevents increased breast cancer risk in alcohol drinkers

There is fair evidence that selenium prevents several cancers, at least among persons with low serum selenium level

There is good evidence that calcium decreases risk of colon cancer, but it may increase risk of high-grade and fatal prostate cancer

Part 6

Do Dietary Supplements Prevent Cancer?

The SELECT trial

Selenium Supplementation (200 μ g) Decreases Risk of Many Cancers

Site	Relative risk	p-value
Lung	0.54	.04
Prostate	0.37	.002
Colorectal	0.42	.03
Breast	2.88	.09
Total cancer	0.63	.001

Nutritional Prevention of Cancer Trial, N=1,312.
Clark, 1996

Selenium Supplementation (200 μ g) Reduces Prostate Cancer Risk in Men with Low Serum Selenium

Baseline serum selenium (Tertiles)	Treatment vs. Placebo (Relative Risk)
Low	0.08
Medium	0.30
High	0.85

Nutritional Prevention of Cancer Trial, N=1,312.
Clark, 1998.

Selenium and Vitamin E Cancer Prevention Trial

Calendar Year
2001-2004

Pre-Randomization Period
(Minimum 28 Days)

Randomized
(N=35,200)

Calendar
Year
2001-2013

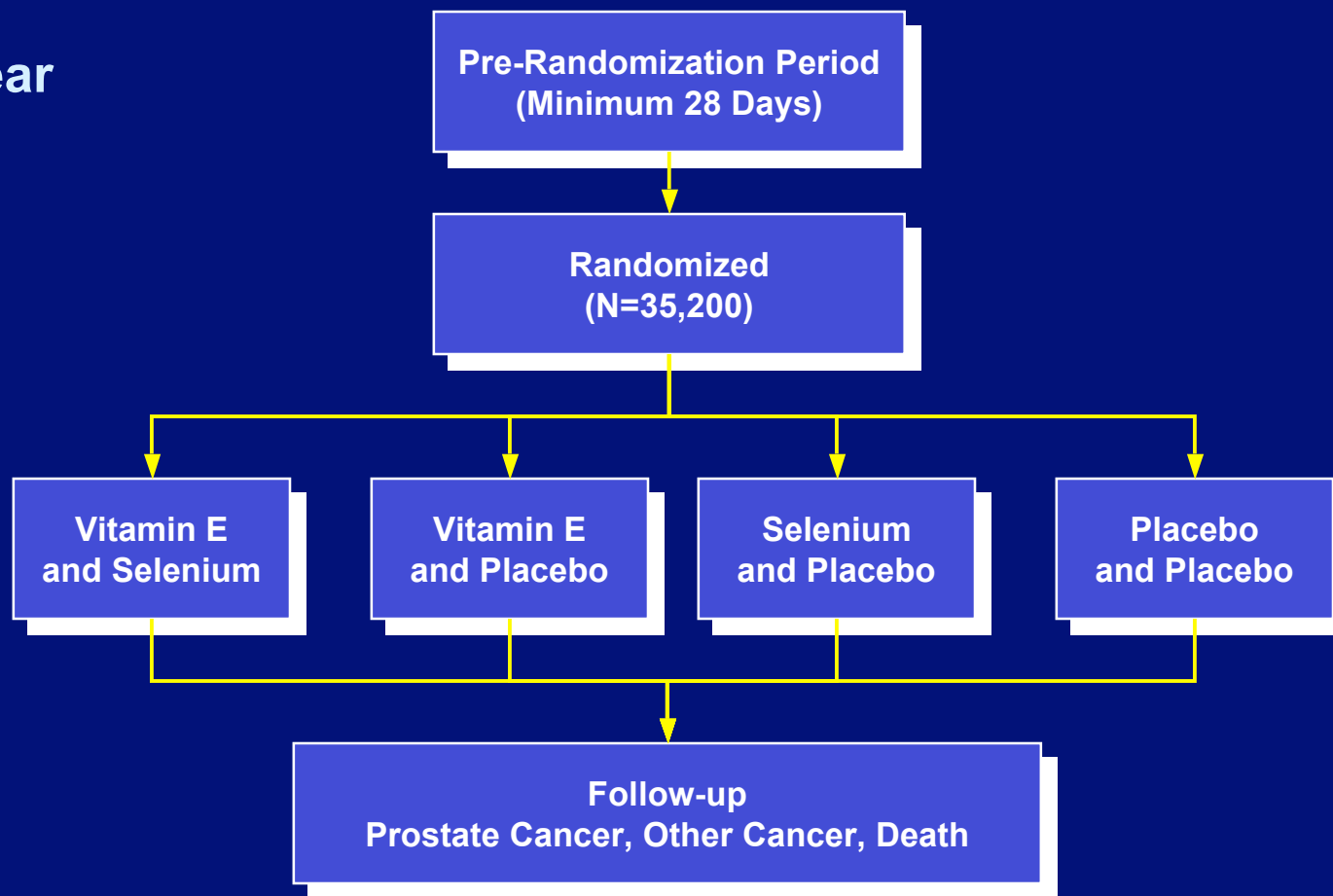
Vitamin E
and Selenium

Vitamin E
and Placebo

Selenium
and Placebo

Placebo
and Placebo

Follow-up
Prostate Cancer, Other Cancer, Death



Supplements or Diet for Disease Prevention?

Supplements

High (pharmacological) dose of specific agent

Feasible to measure and test (placebo-controlled trial)

Food

Low dose of agent delivered in complex matrix of other
biologically-active compounds

Difficult to measure and even more difficult to test

As More and More Evidence Accumulates

**Dietary Supplements Have
Little or No Role in Cancer Prevention**

Part 7

What are reasonable recommendations for dietary patterns to reduce cancer risk?

Not Controversial

Alcohol: Increases risk of oral, esophageal, breast and liver cancers

Obesity: Increases risk of many cancers

Likely Associations but Controversial!

Selenium: Decreases prostate, lung, colon,
and esophagus cancers

Fruits and Vegetables:
Decreases many cancers

Well-Done, Flame-Broiled or Fried Meat
Increases breast and colon
cancers

Fat: Increases breast and prostate
cancers

Calcium: Decreases colon and increases
prostate cancers

What is it About Vegetables?

Plant Anti-Carcinogens

Allium compounds - found in onions, garlic, etc.
diallyl sulfide; allyl methyl trisulfide

Dithiolthiones - found in cruciferous vegetables

Flavonoids - found in a variety of vegetables and fruit
quercetin; kaempferol

Isothiocyanates - found in cruciferous vegetables
sulphorophane; others

Lignans - derived from fiber by colonic bacteria

Biologically-Active Compounds in Vegetables Stimulate Metabolizing Enzymes

Compounds in vegetables must be “detoxified” and excreted

The same enzyme systems that metabolize drugs and detoxify carcinogens also metabolize dietary compounds

By increasing the activity of metabolizing enzymes, vegetables indirectly increase the detoxification of carcinogens

Dietary Recommendations for Cancer Prevention

- **Maintain an optimal weight**
 - *Remain or become physically active*
 - *Eat moderate portions*
 - *Avoid high-calorie beverages*
- **Eat a variety of fruits and vegetables**
 - *Raw and cooked, 5-9 servings per day*
 - *Include broccoli and Brussels' sprouts*

Dietary Recommendations for Cancer Prevention

- **Moderate consumption of fat**
 - *Use low fat salad dressings and reduced fat milk products*
 - *Bake, broil, boil but don't fry*
 - *Avoid margarine, commercial baked goods and fast food made with trans-fats*
- **Moderate consumption of meat**
 - *Choose lean varieties and trim fat*
 - *Eat sensible (3-4 oz) portion*
 - *Avoid pan-fried and charcoal-broiled meats*

Dietary Recommendations for Cancer Prevention

- **Supplements**

- *Multivitamin with minerals for folate and selenium*

Clear Thinking about Diet and Cancer

Dietary patterns do affect cancer risk, but our understanding is not precise

Scientific evidence is for foods, not supplements

Single studies reported in the newspaper can be misleading. Focus on the big picture.

There are no “magic bullets”

1 Apple Every 8 Hours will keep 3 Doctors Away

