The Role of Observational Studies

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Disclosure Information

As required, I would like to report that

I have no financial relationships to disclose,

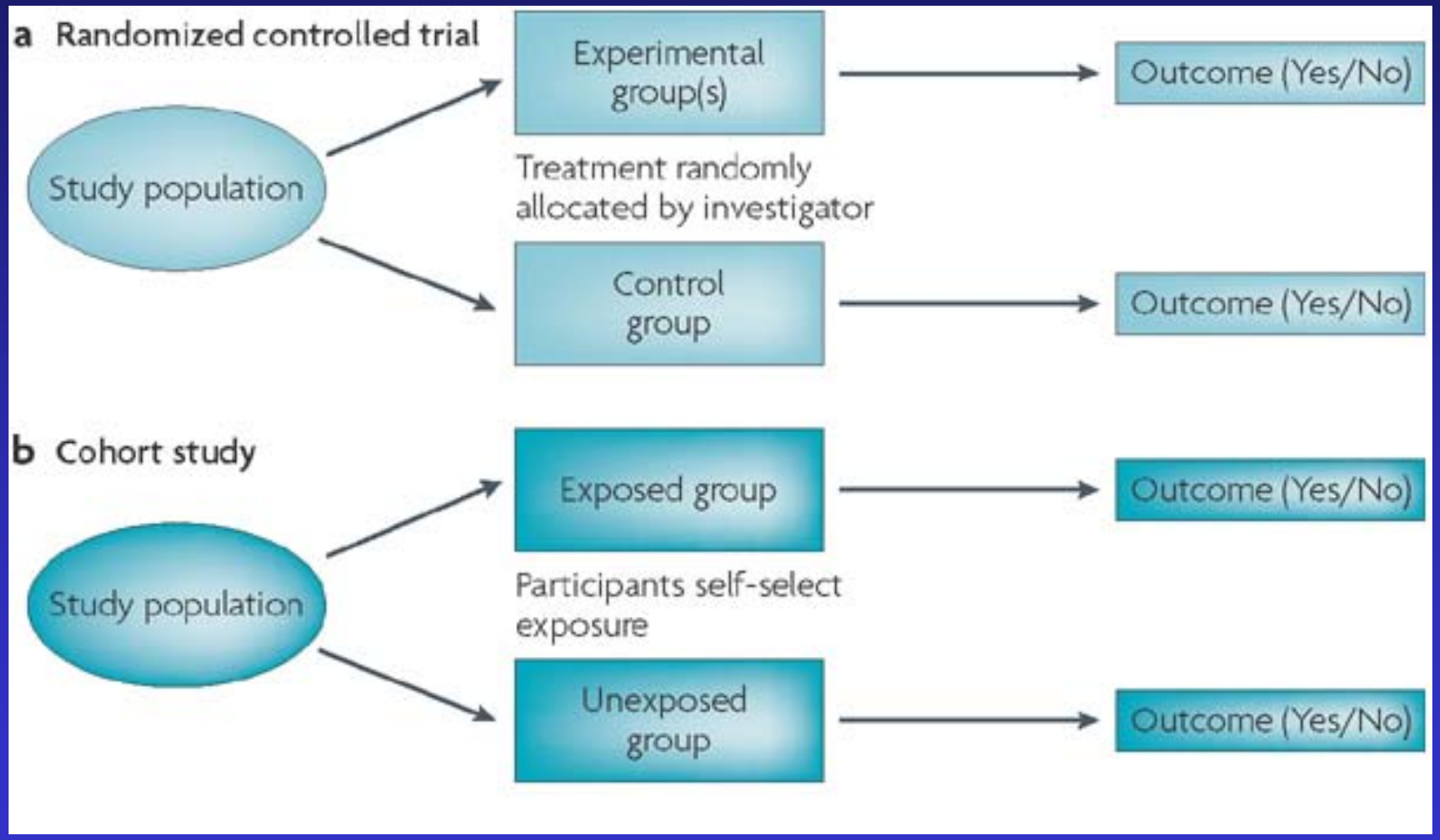
nor will I discuss off-label or investigational

usage of drugs.

Nutritional Epidemiology

- Correlational (ecologic) studies
- Migrant studies
- Secular trend studies
- Case-control (retrospective)
- Cohort studies (prospective)
- Interventions

Randomized Controlled Trials vs. Observational Studies of Cancer



Martinez M.E. et al (2008) Nat Rev Cancer

Observational Studies

Each individual study is limited to some degree by weaknesses in size, dietary assessment, potential biases, and (most importantly) the potential for uncontrolled confounding.

The main strength of observational studies is the ability to examine an association in various circumstances, in diverse populations, using multiple approaches (correlational, secular, migrant studies, case-control and cohort studies), combined with understanding of biology, which allows us to construct a “model” that coherently explains most of the data.

4 Critical Issues

- Timing of association
- Dose-response
- Complexity of diet in influencing carcinogenic pathways
- Inter-correlation among single nutrients

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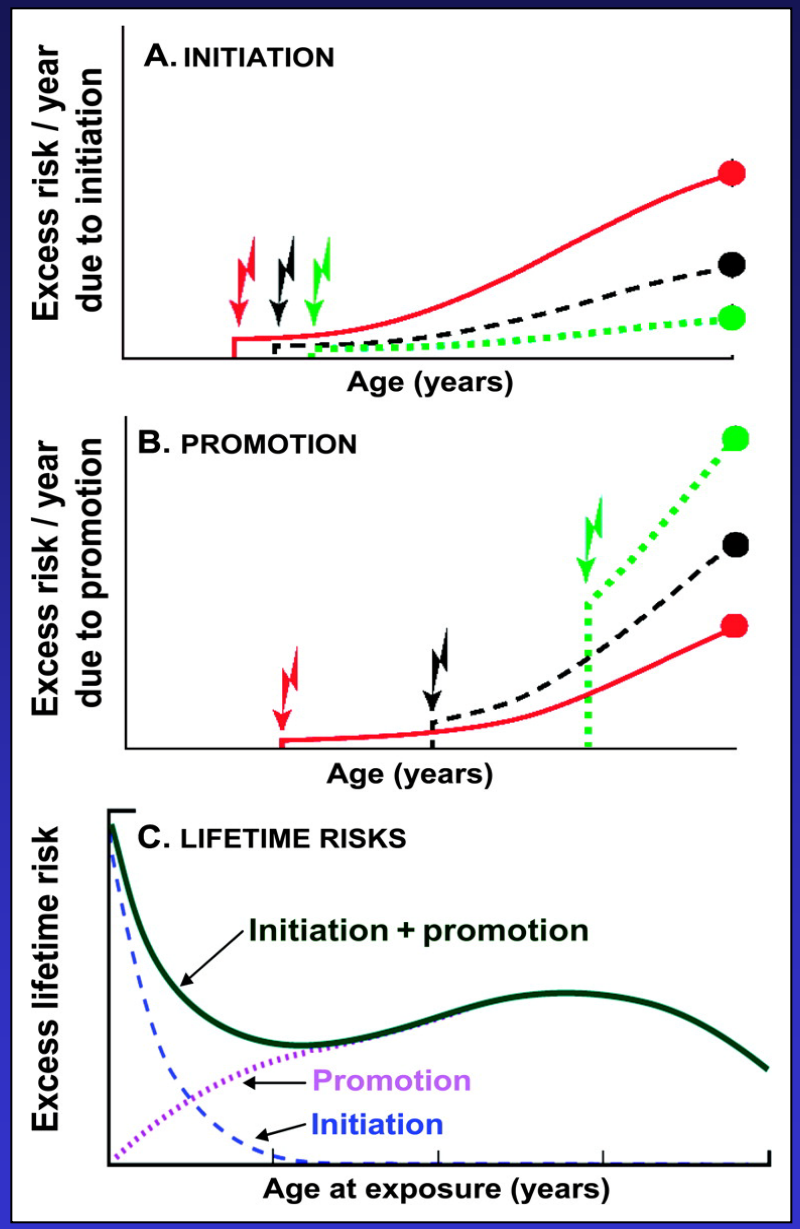
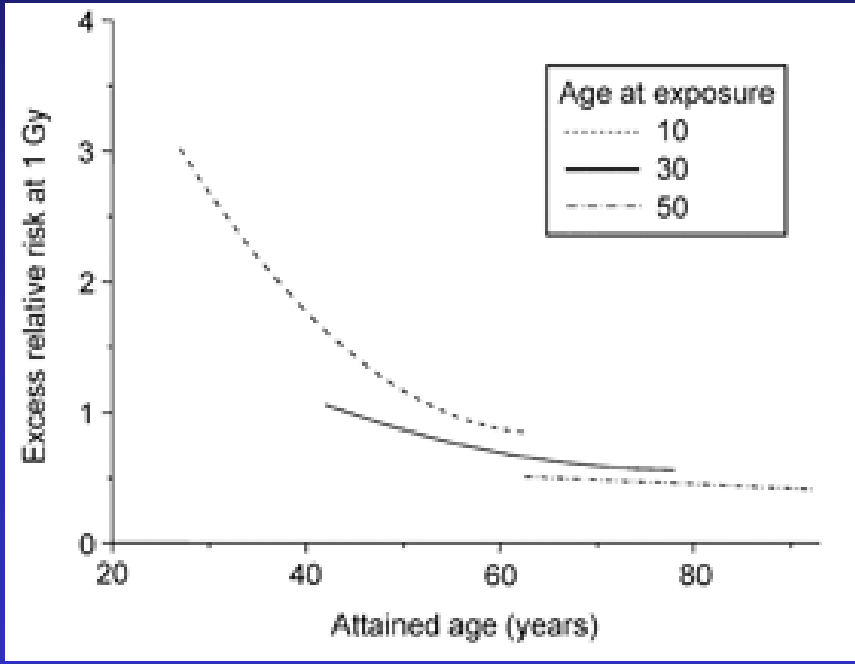


Schematic of dominant factors determining the variation in radiation-induced cancer risk with age at exposure.

Shuryak I. et al.(2010) J Natl Cancer Inst

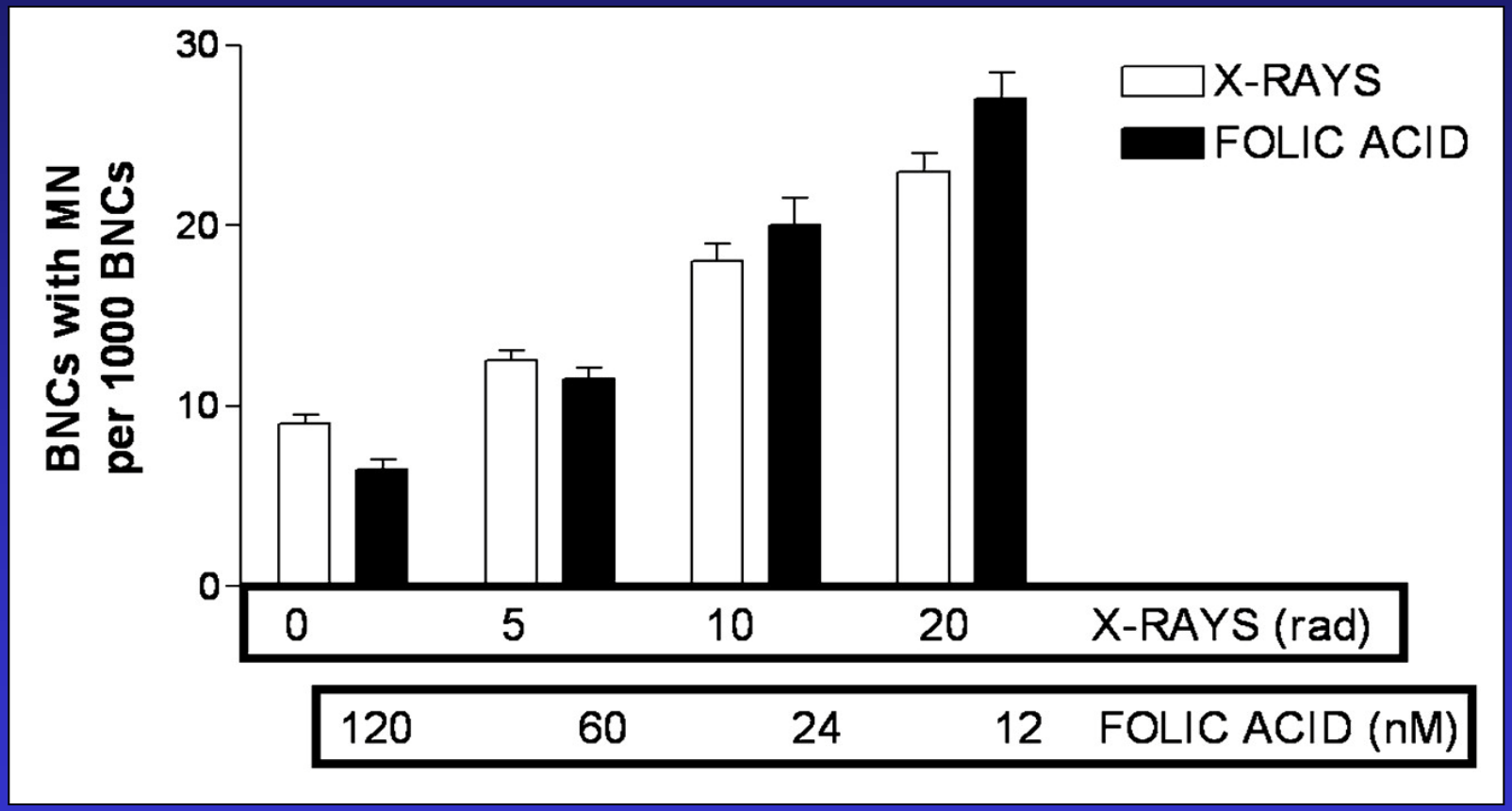
Effects of Age at Exposure and Attained Age on the Excess Risk of Solid Cancer Incidence Following Exposure to 1 Gy.



Excess Relative Risk (ERR)

Radiation Effects Research Foundation, 2011

Comparison of the dose-response effect on micronucleus induction in cytokinesis-blocked cultured lymphocytes caused by acute exposure to X-rays up to a maximum dose of 20 rad with folic acid



Fenech M. F. (2010) Am J Clin Nutr

Nutrient factors that influence genomic integrity

are likely to act very early in carcinogenesis,

especially for some cancers (e.g. breast cancer)

Nurses' Health Study

(n=121,700, age 30-55 yr)

1976	1978	1980	1982	1984	1986	1988	1990	1992	1994	1996	1998	2000	2002	2004	2006	2008	2010
▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
		Diet		Diet	Diet		Diet		Diet		Diet		Diet		Diet		Diet

Smoking
Weight/Ht
Med. Hist.

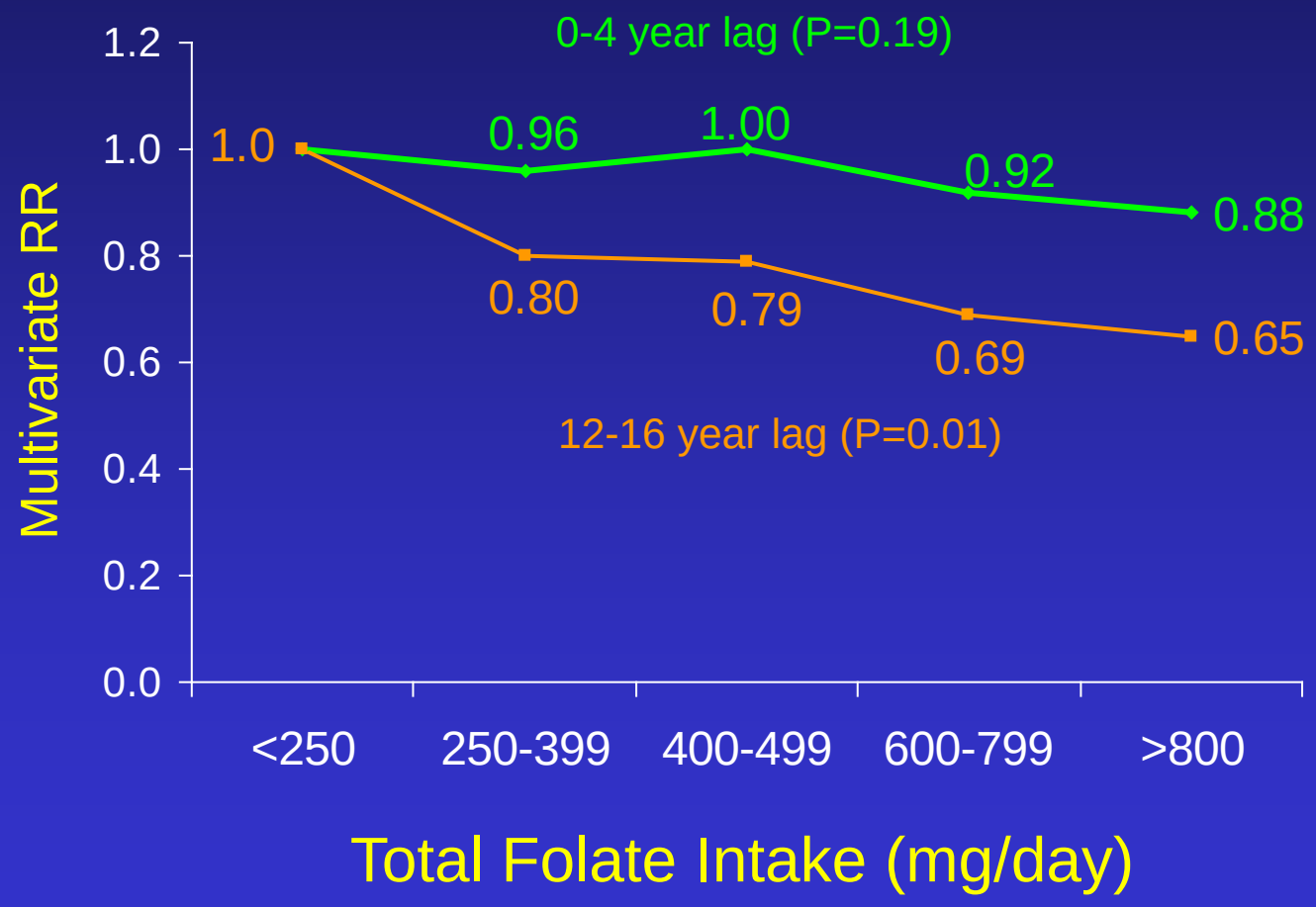
Health Professionals Follow-up Study

(n=51,529, age 40-75 yr)

1986	1988	1990	1992	1994	1996	1998	2000	2002	2004	2006	2008	2010
▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
Diet		Diet		Diet		Diet		Diet		Diet		Diet

Smoking
Weight/Ht
Med. Hist.

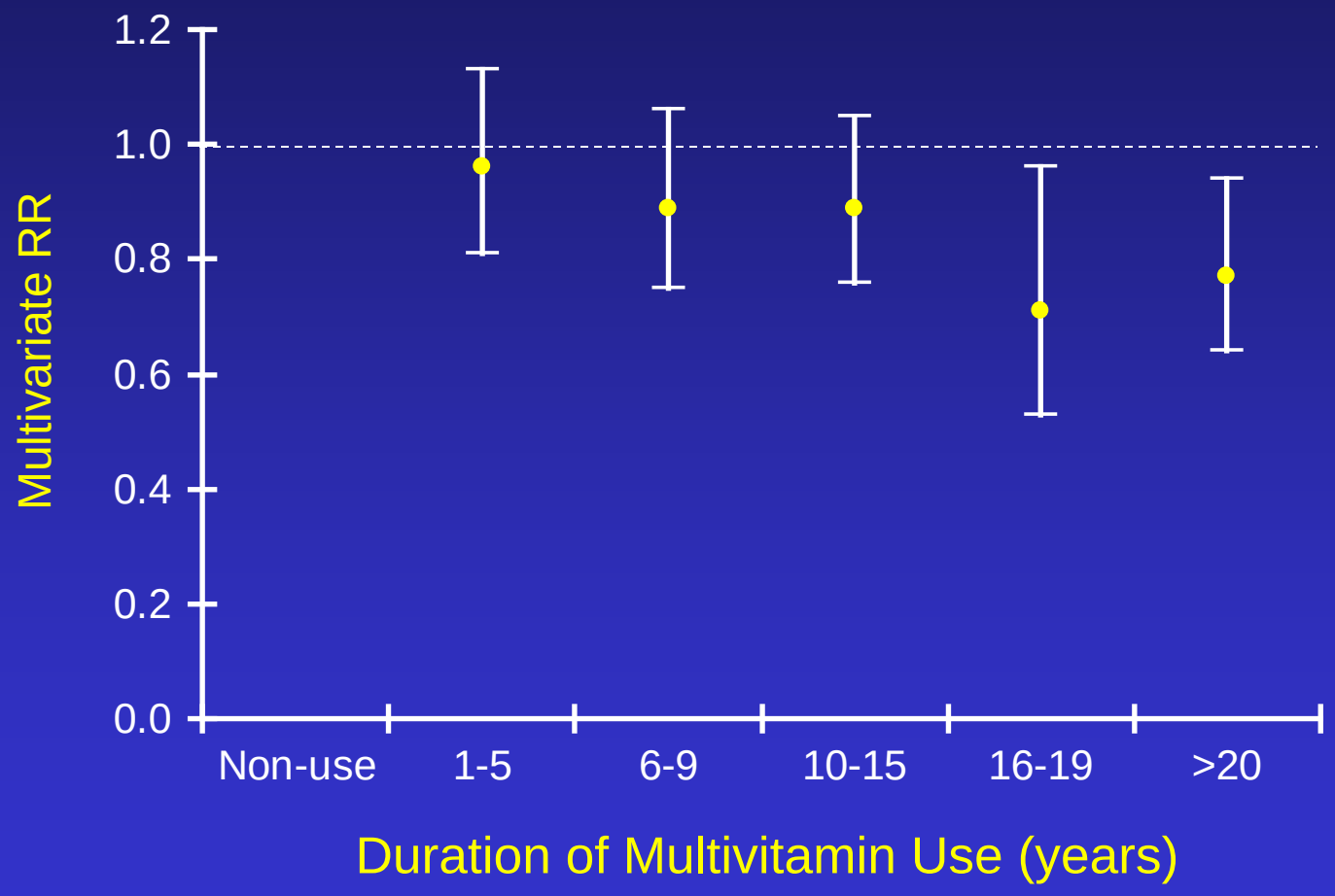
Colorectal Cancer Risk
(NHS, HPFS)



Lee J.E., et al. (2010) Am J Clin Nutr

Colorectal Cancer

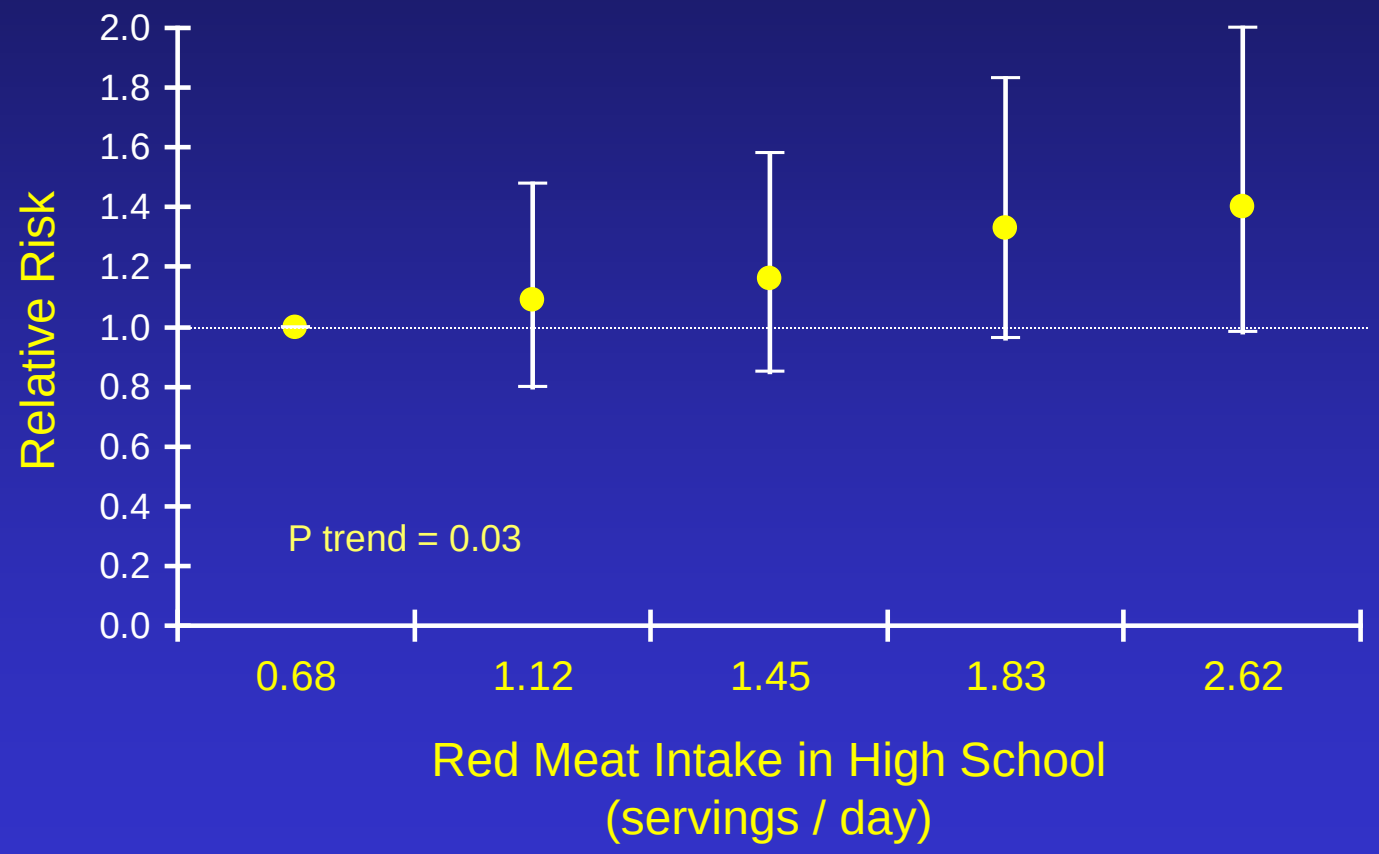
(NHS, HPFS)



Lee J.E., et al. (2010) Am J Clin Nutr

Breast Cancer

(NHS II, ages 33-53 yrs)



Linos E., et al. (2008) Cancer Epidemiol Biomarkers Prev

The association of

milk / calcium intake and colon cancer risk

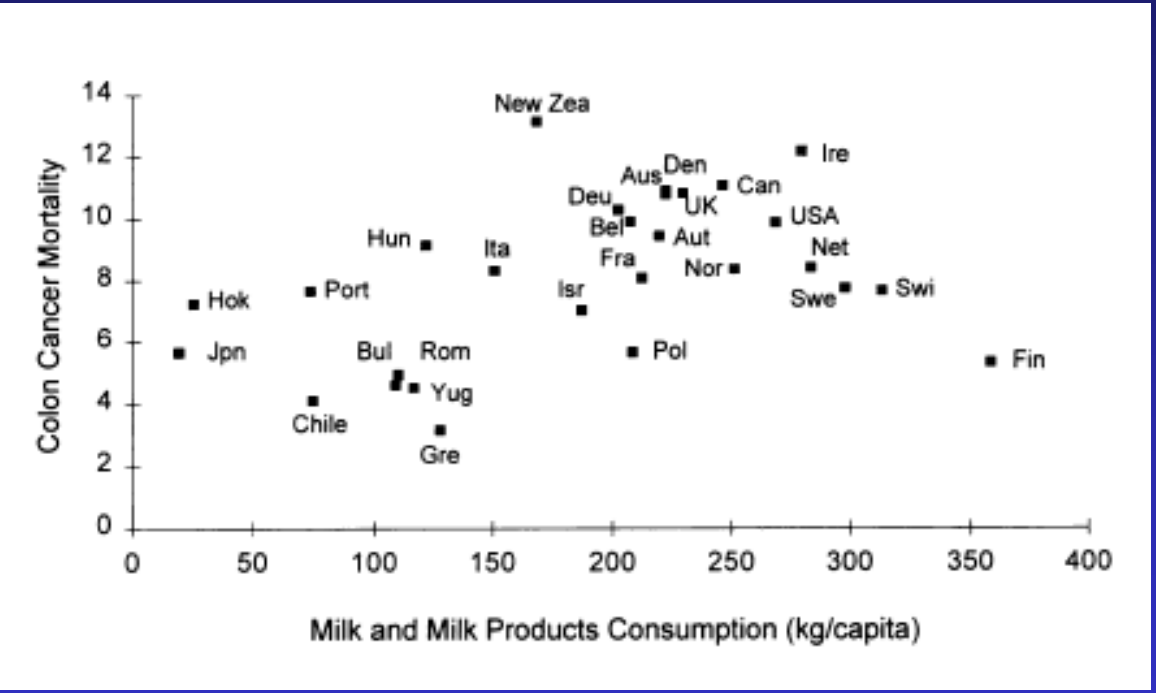
demonstrates the complexity of one dietary factor

acting at different points in the lifespan

Study Design	Factor	Association with Risk of Colon Cancer
Ecologic	milk	↑
Case-control	milk / calcium	↓
Cohort	milk / calcium	↓
Intervention (adenoma)	calcium	↓

Colon Cancer Mortality

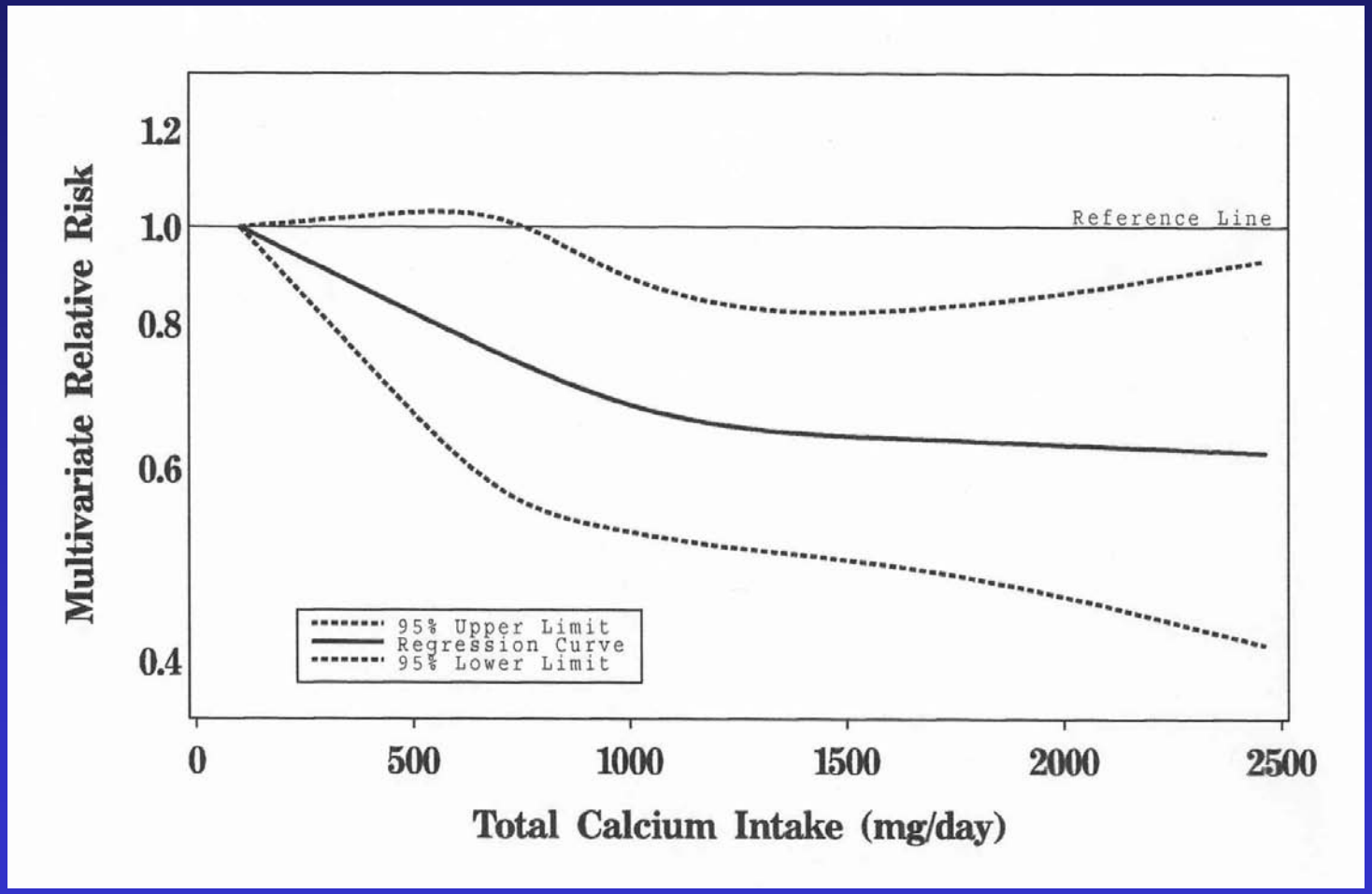
by Milk and Milk Product Consumption*



*WHO Food and Health Indicators in Europe for 1971 per 100,00 population, ages 0-64

Martinez ME & Willett WC (1998) Cancer Epidemiol Biomarkers Prev

Nonparametric Regression Curve for the Relationship between Total Calcium Intake and Colorectal Cancer Pooled Cohort Analysis



Cho et al., *JNCI* 2004

Hypothesis:

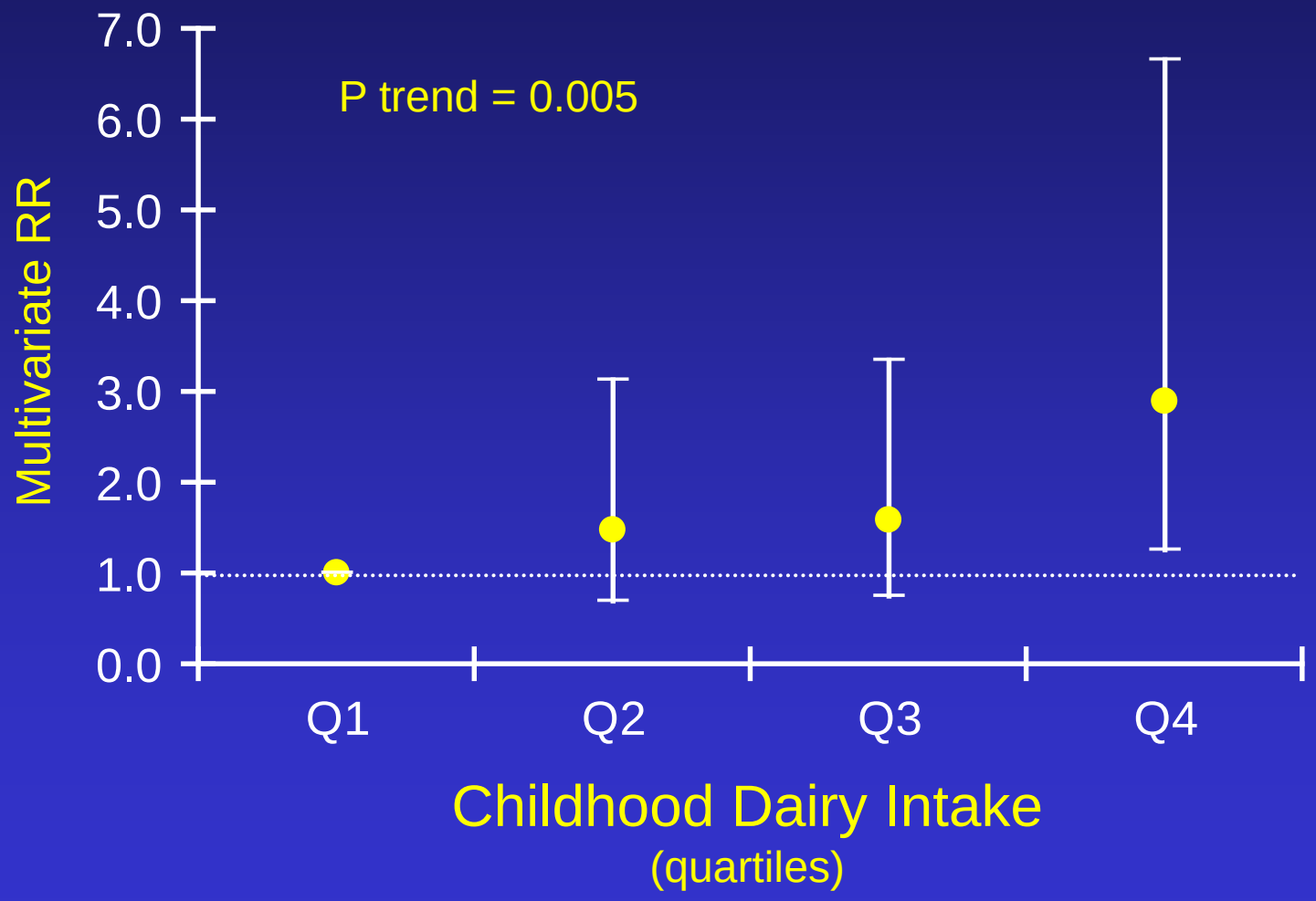
Western (meat, dairy) diet ↓ ↑ IGF-1

dairy (calcium) ↓ ↑ apoptosis

In Utero | Birth | Childhood | Adolescence | Adulthood

Colorectal Cancer Risk: ↑↑ ↓

Boyd Orr Study Cohort (1948-2005)
Colorectal Cancer (n = 76)



van der Pols J.C., et al. (2007) Am J Clin Nutr

4 Critical Issues

- Timing of association
- ➢ *Dose-response*
- Complexity of diet in influencing carcinogenic pathways
- Inter-correlation among single nutrients

If a nutrient is causally associated

with cancer risk, the effect is likely to occur

over a specific range (dose-response)

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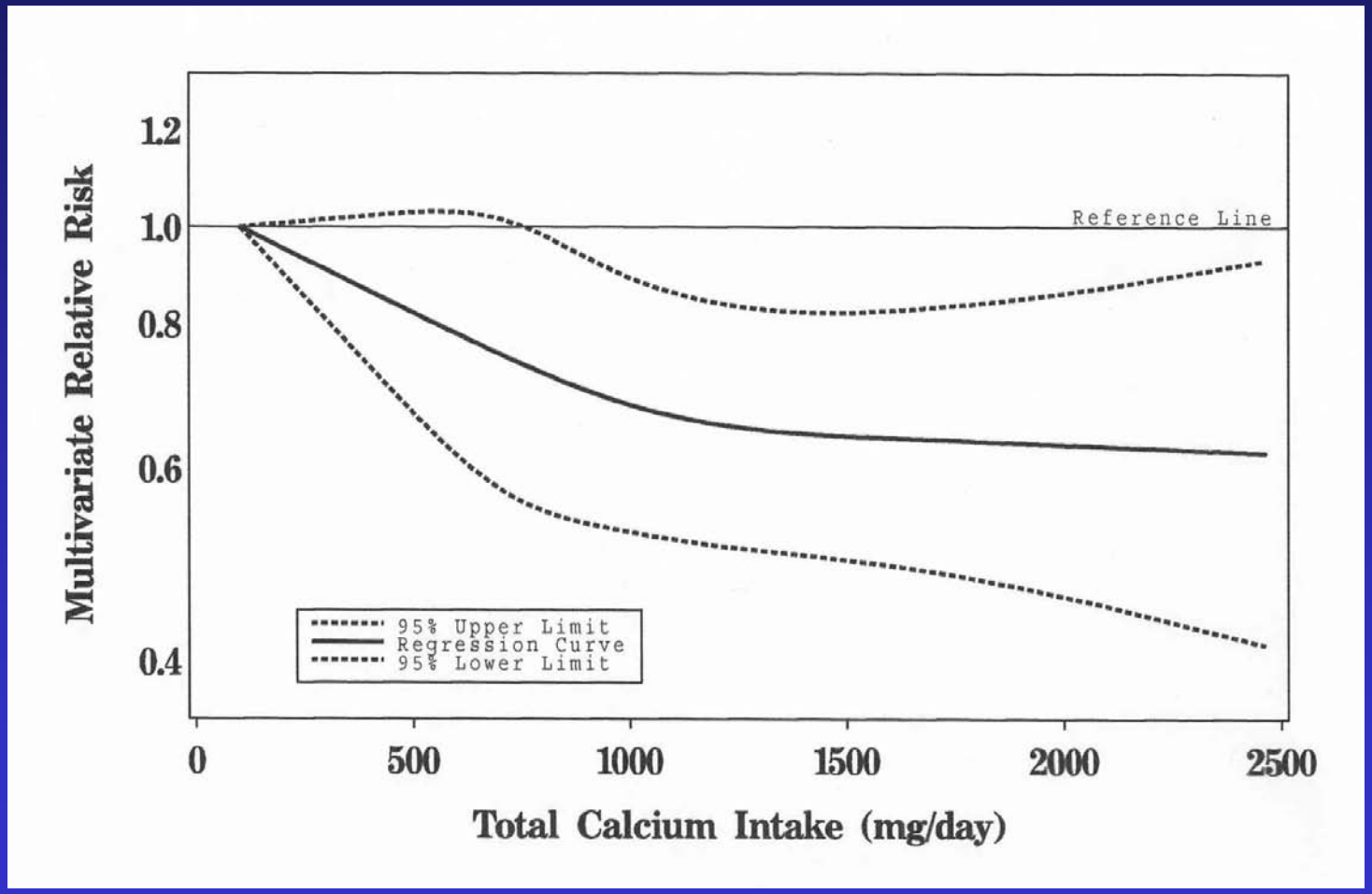
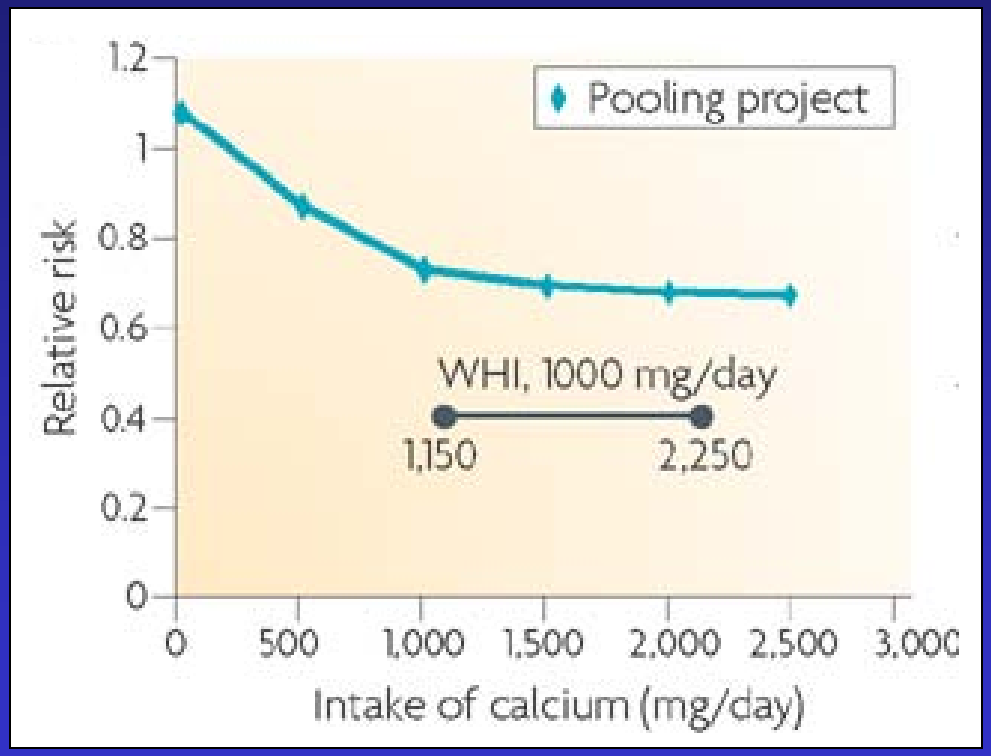
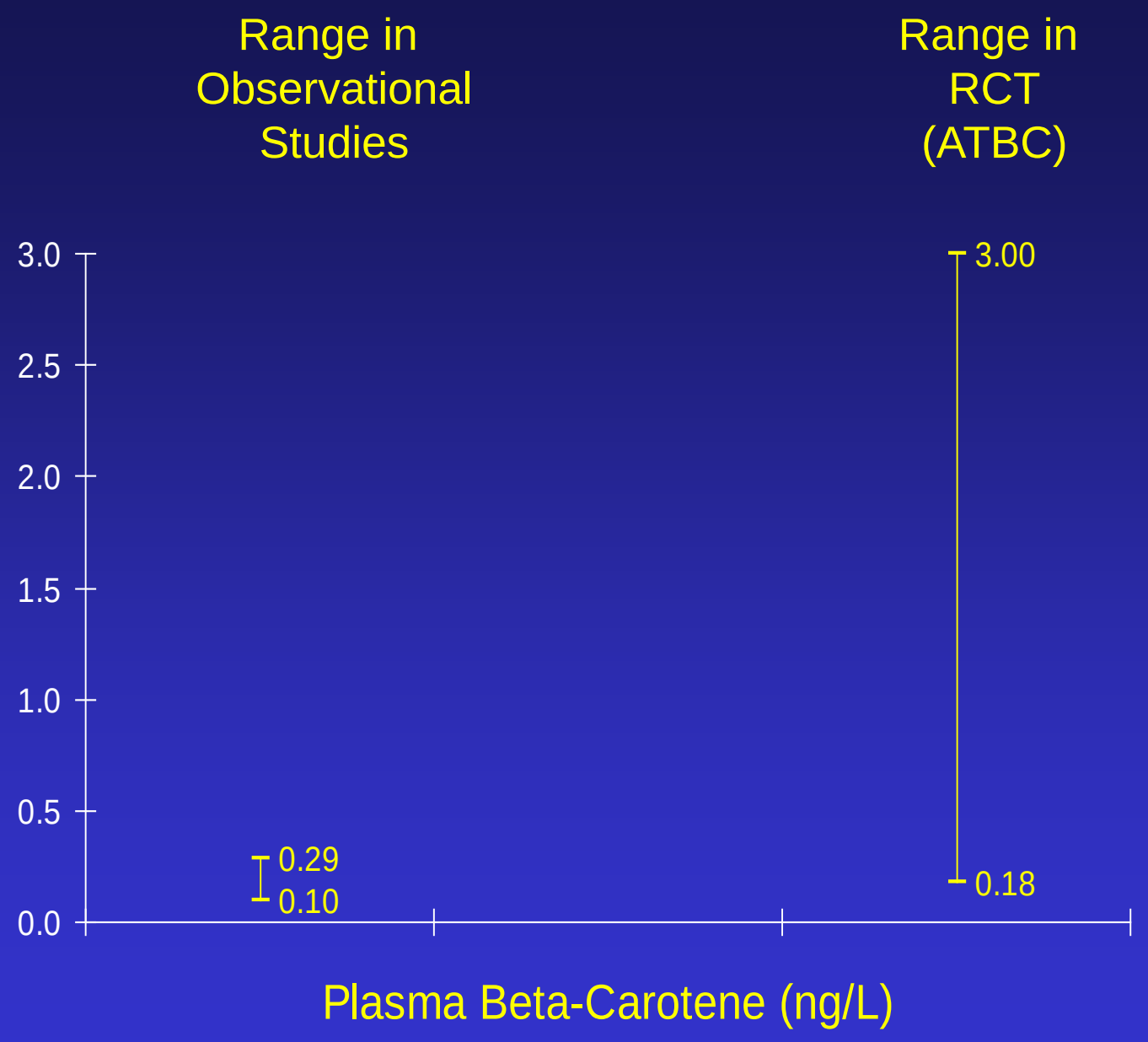


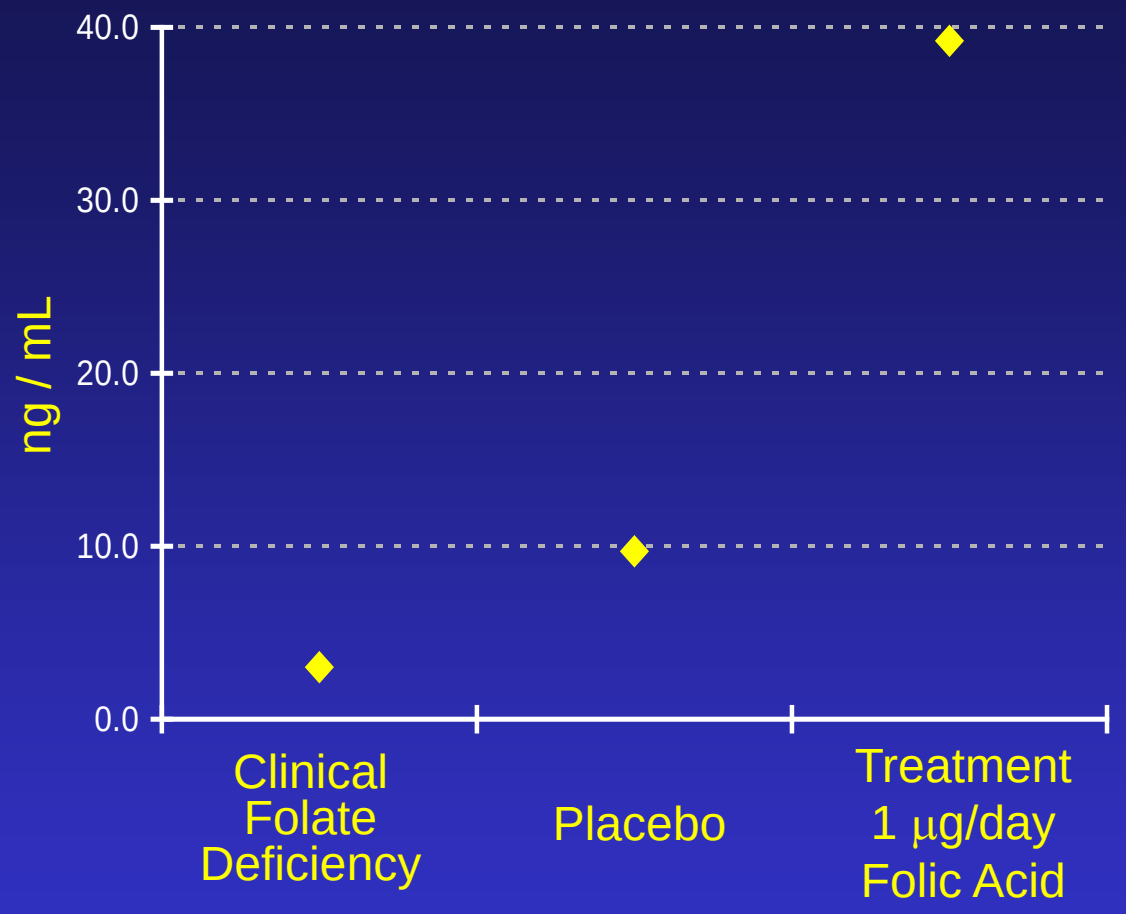
Cho et al., *JNCI* 2004

Ranges of Nutrient Intakes Tested in Observational and Randomized Controlled Trials (RCTs) of Calcium



Martinez M.E., et al. (2008) Nat Rev Cancer


Range in Observational Studies
Range in RCT (ATBC)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.29
0.10
3.00
0.18
Plasma Beta-Carotene (ng/L)



RCT of Folic Acid and Colorectal Adenoma

Wu K., et al. (2009) Am J Clin Nutr

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Two Examples:

- Energy balance (insulin)
- One-carbon metabolism

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WCRF / AICR Cancer Prevention Recommendations:

- Be as lean as possible
- Be physically active
- Avoid sugary drinks, energy-dense foods
- Eat more variety of vegetables, fruits, whole grains and legumes
- Limit red meats and processed meats
- Limit alcoholic drinks
- Limit consumption of salt
- Don't use supplements to protect against cancer
- * Breastfeed exclusively for up to 6 months
- * Cancer survivors should follow the recommendations for cancer prevention

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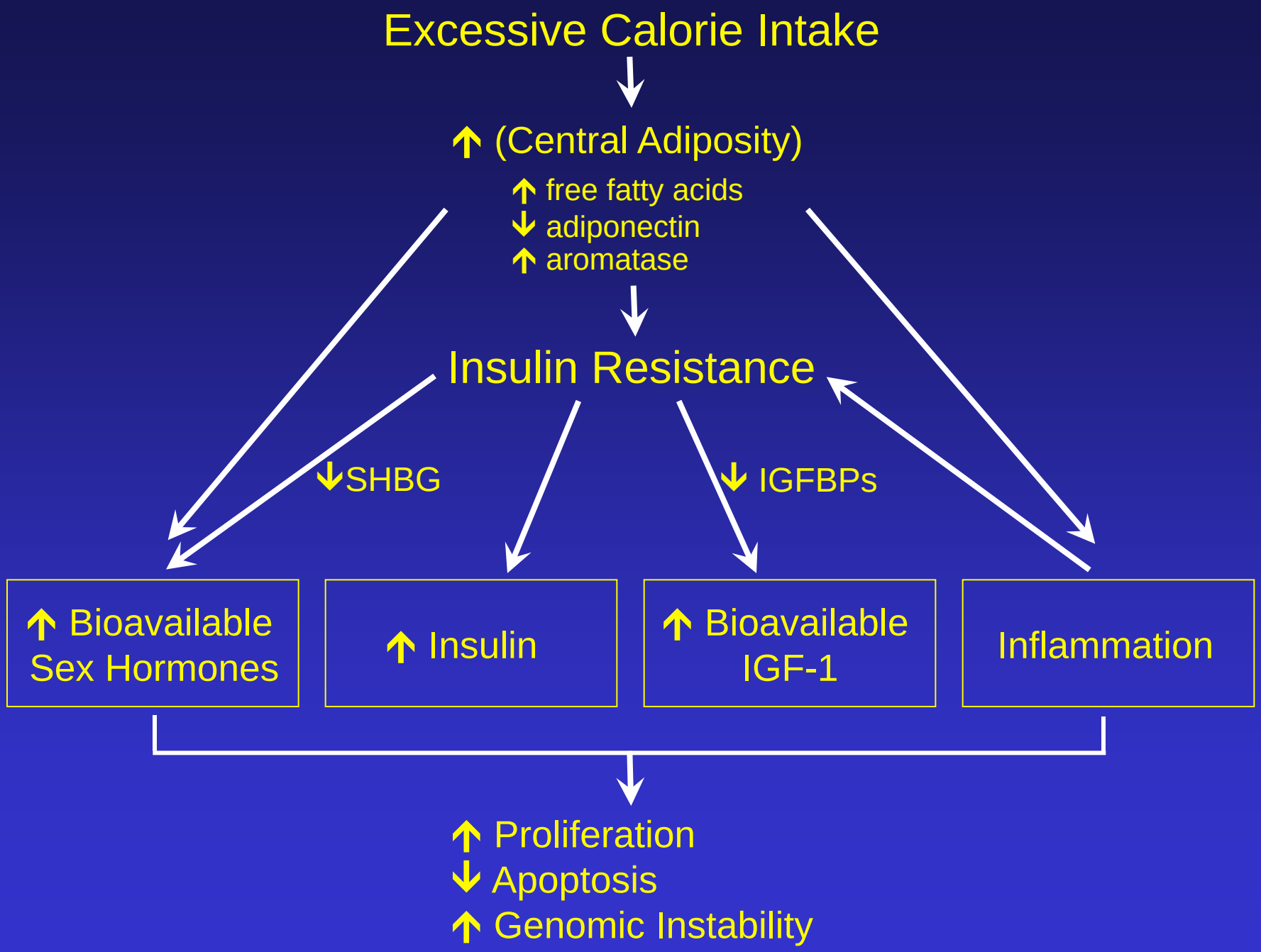
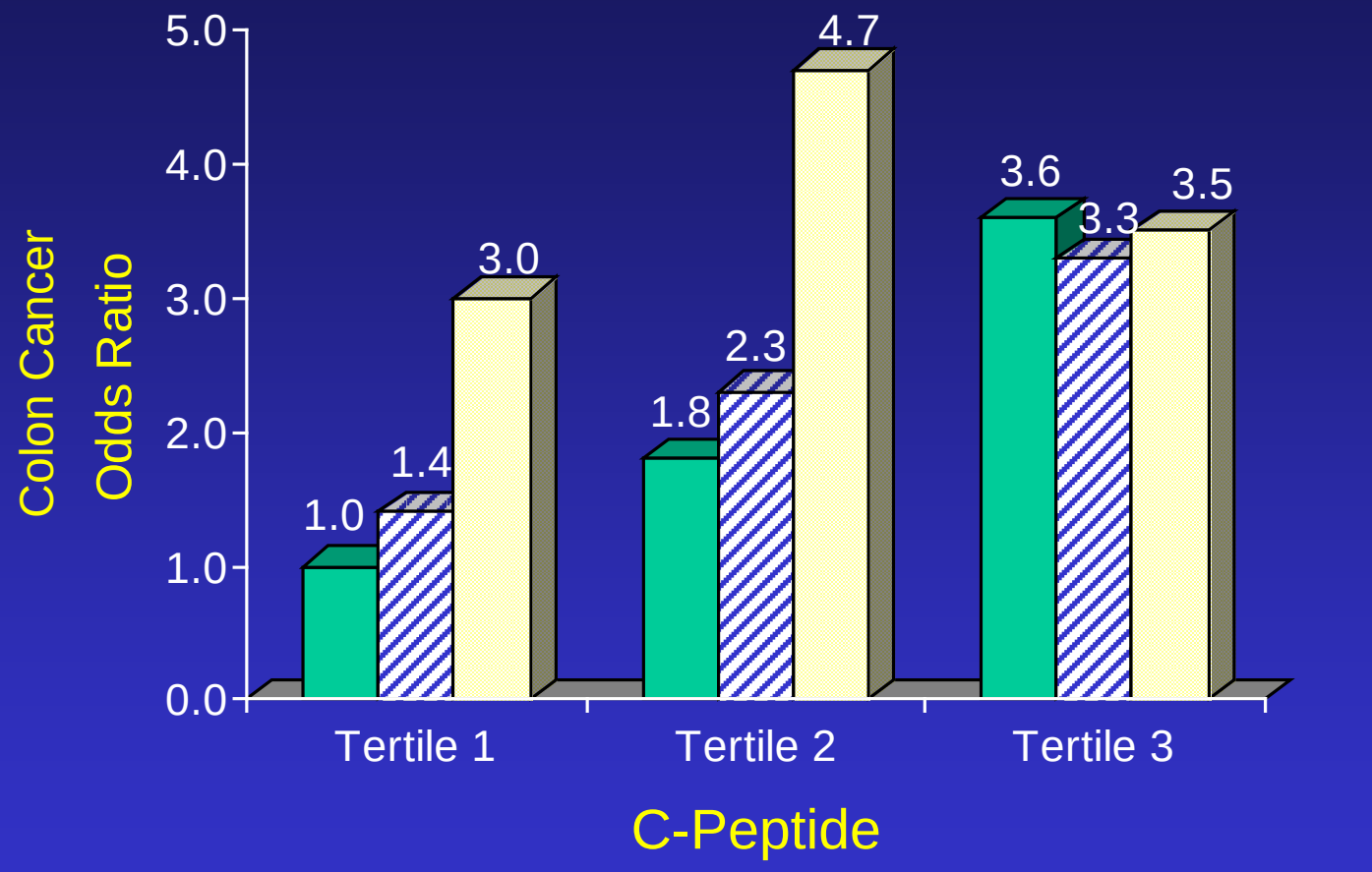

Excessive Calorie Intake
↑ (Central Adiposity)
↑ free fatty acids
↓ adiponectin
↑ aromatase
Insulin Resistance
↓SHBG
↓ IGFBPs
↑ Bioavailable Sex Hormones
↑ Insulin
↑ Bioavailable IGF-1
Inflammation
↑ Proliferation
↓ Apoptosis
↑ Genomic Instability

Risk Factors* for Colon Cancer and Adenoma Compatible with Insulin/IGF Hypothesis

- ↑ circulating C-peptide / insulin
- ↑ circulating IGF-1 or IGF-1/BP-3
- Acromegaly (↑ IGF, insulin)
- Type 2 diabetes
- Metabolic syndrome (↑ insulin)
- Tallness (↑ IGF-1)
- ↑ BMI
- ↑ waist circumference
- ↓ physical activity
- Western diet (↑ insulin)

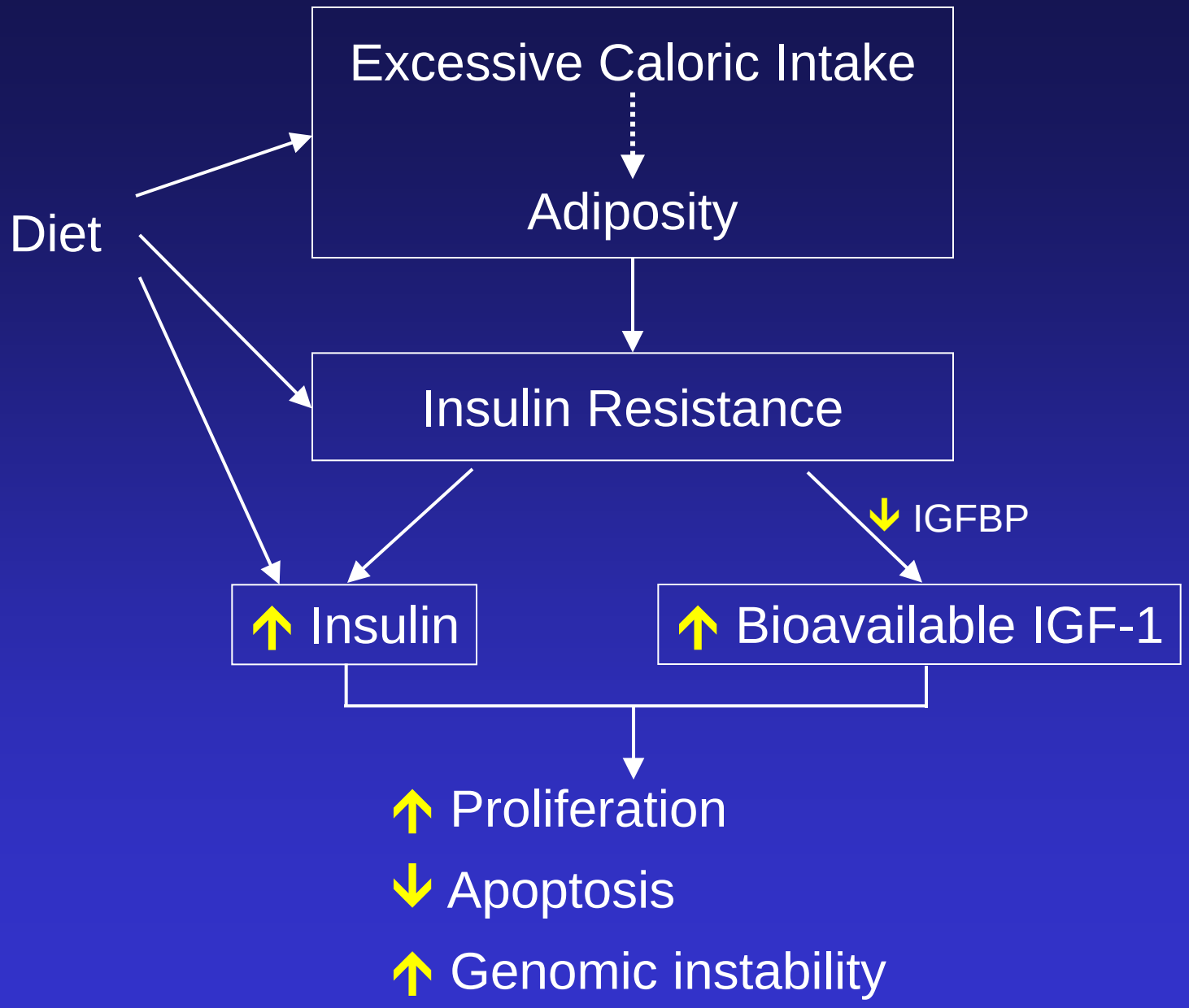
* based on meta-analyses

Physicians' Health Study

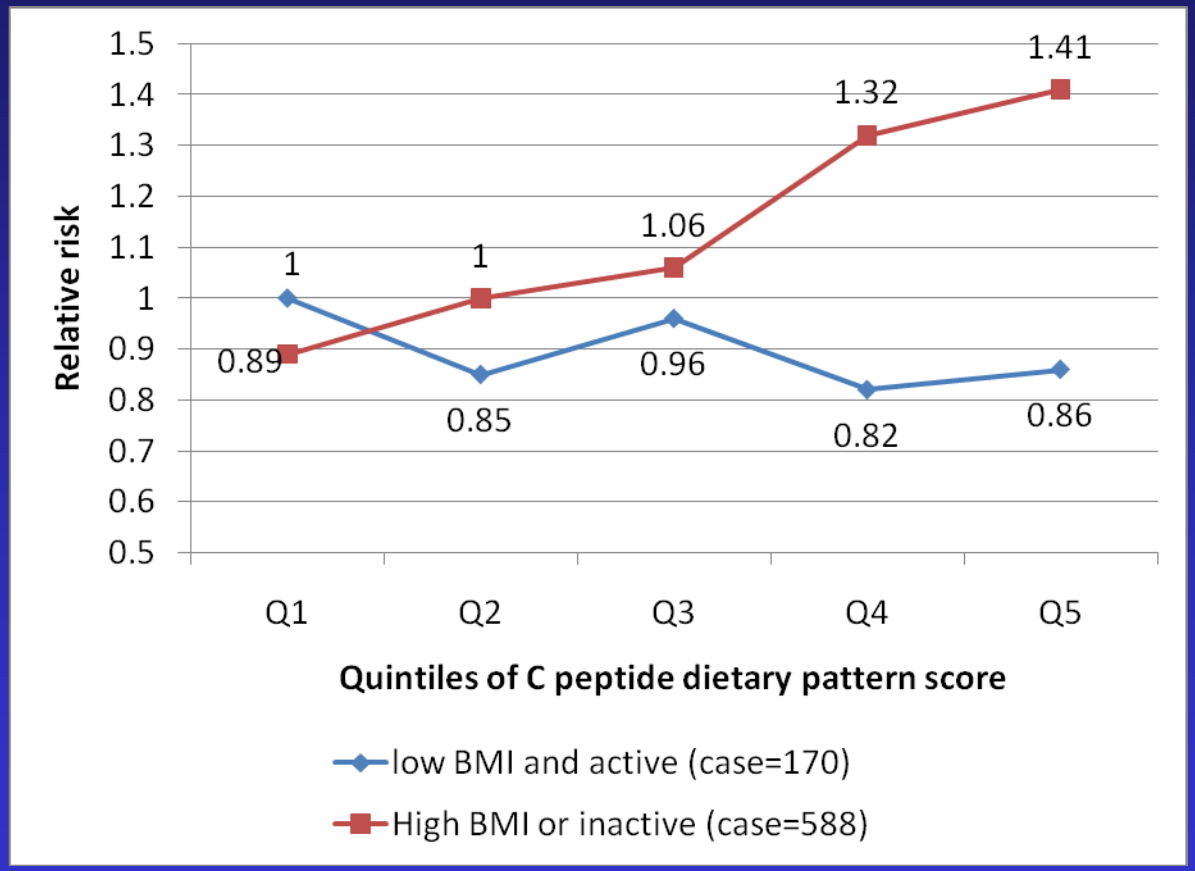


IGF-1 / IGFBP-3: **Tertile 1** **Tertile 1** **Tertile 3**

Ma et al., 2004


Excessive Caloric Intake
Adiposity
Diet
Insulin Resistance
IGFBP
Insulin
Bioavailable IGF-1
Proliferation
Apoptosis
Genomic instability

Multivariate RR for C-Peptide Dietary Pattern Score and Risk of Colon Cancer by BMI and Physical Activity (NHS; n=66,714)



Fung T.T. et al., submitted.

Dietary factors that predict hyperinsulinemia will likely differ across populations.

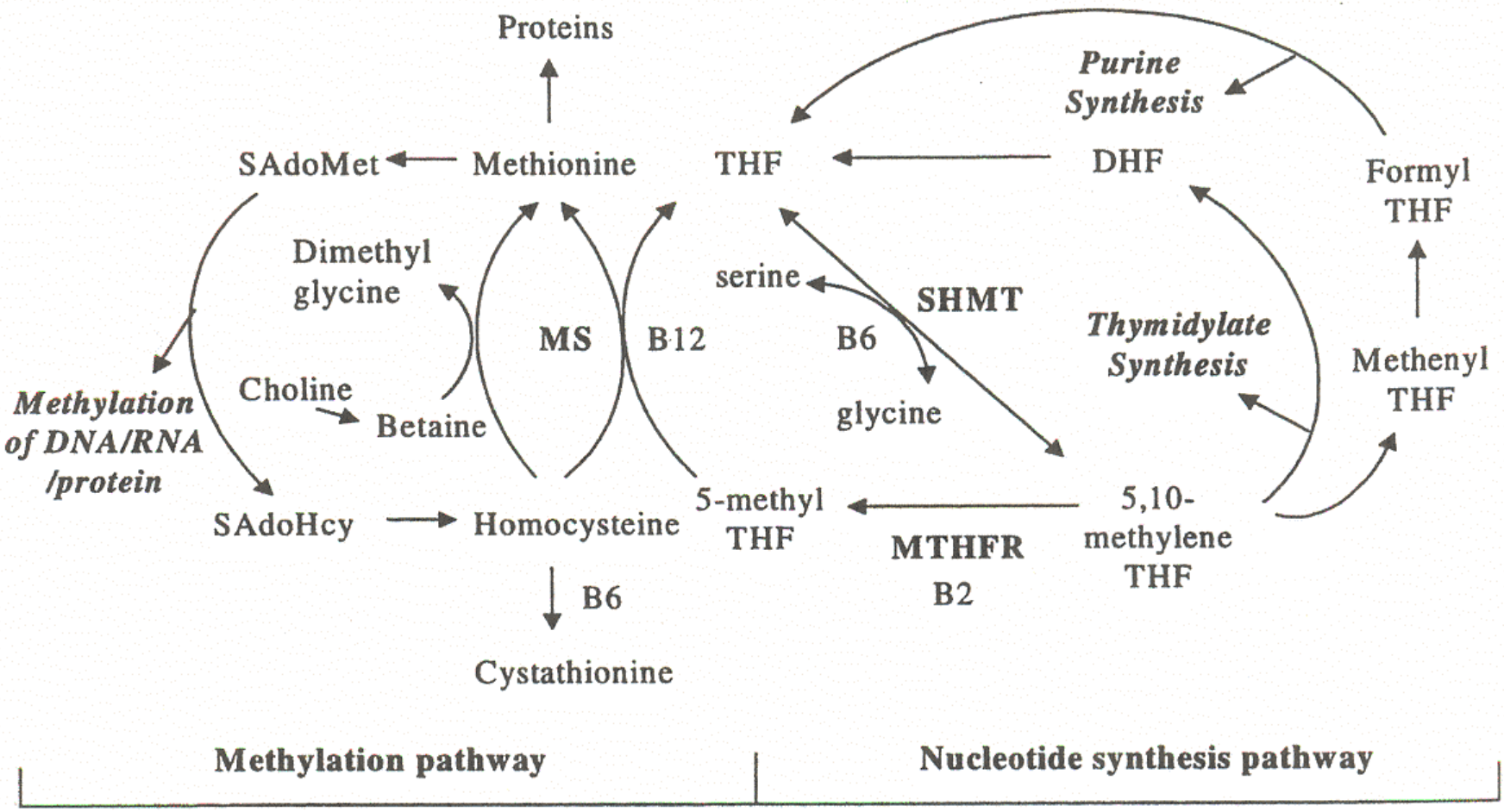
Examples:

- U.S. → red meat, sweetened beverages ↑; coffee ↓
- Sweden → rye bread (lignans) ↓
- Costa Rica → beans / white rice ratio ↓

Two Examples:

- Energy balance (insulin)

➢ *One-carbon metabolism*


Proteins
Purine Synthesis
SAdoMet
Methionine
THF
DHF
Formyl THF
Dimethyl glycine
serine
SHMT
MS
B12
B6
Thymidylate Synthesis
Methenyl THF
Methylation of DNA/RNA /protein
Choline
Betaine
glycine
SAdoHcy
Homocysteine
5-methyl THF
MTHFR
B2
5,10-methylene THF
B6
Cystathionine
Methylation pathway
Nucleotide synthesis pathway

1-Carbon Sources

methionine
choline
betaine

1-Carbon Carrier

folate

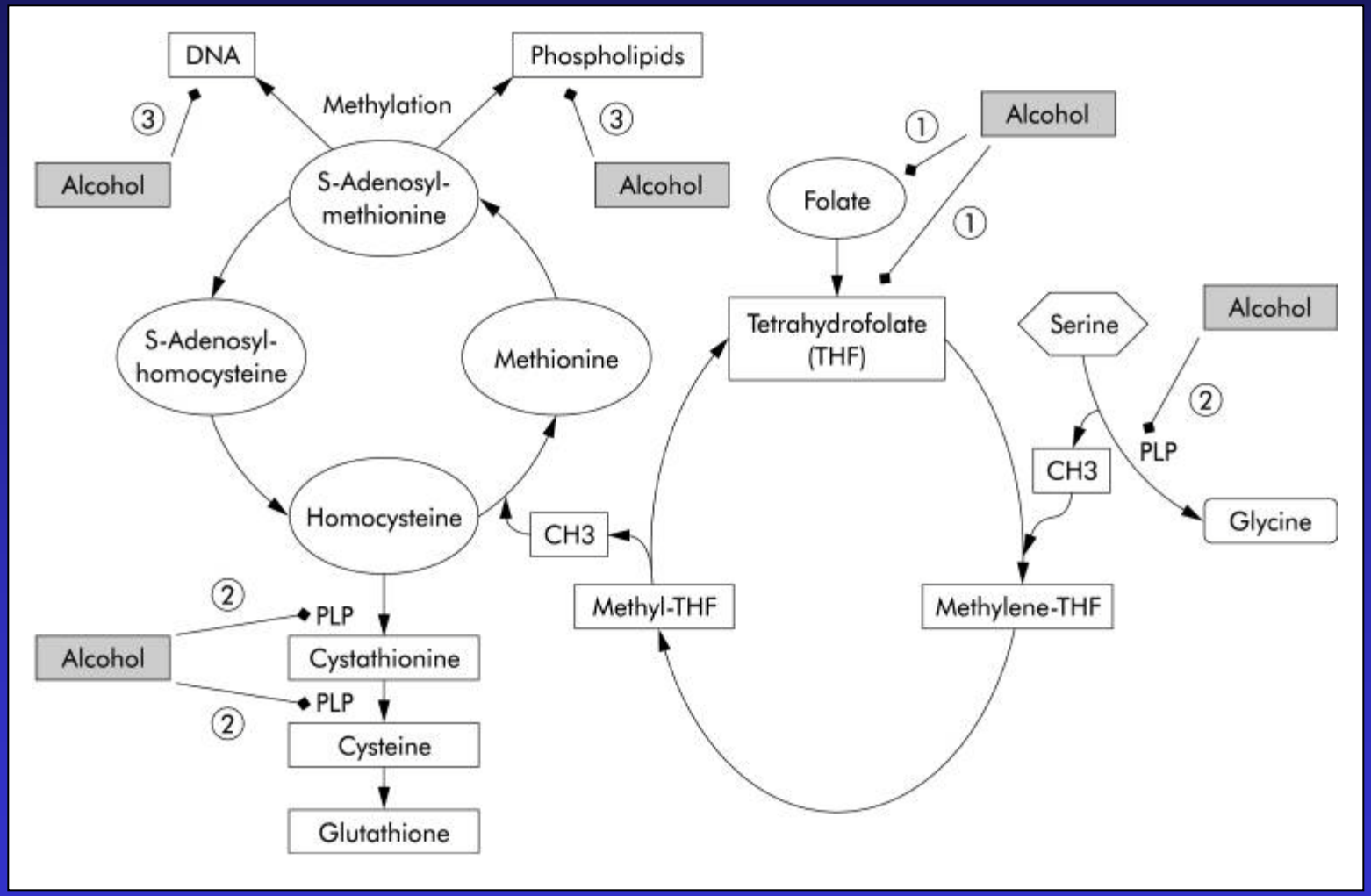
Co-factors

vitamins B2, B6, B12

Antagonists

alcohol

Interaction of Alcohol with Methyl Transfer



Stickel F., et al. (2002) Gut

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- ➢ *Inter-correlation among single nutrients*

Fruits and Vegetables

- Up to the early 1990s, most evidence came from case-control studies
- Suggested benefits led to strong recommendations for total fruit and vegetable intake, and led to focus (including RCTs) on specific nutrients

Evidence of Decreased Risk

	Convincing	Probable	Possible
Vegetables and Fruits	Mouth, pharynx Esophagus Lung Stomach	Larynx Pancreas Breast Bladder	Ovary Endometrium Cervix Thyroid
Vegetables	Colon, rectum		Liver Prostate Kidney

Food, Nutrition and the Prevention of Cancer: A Global Perspective
World Cancer Research Fund, 1997

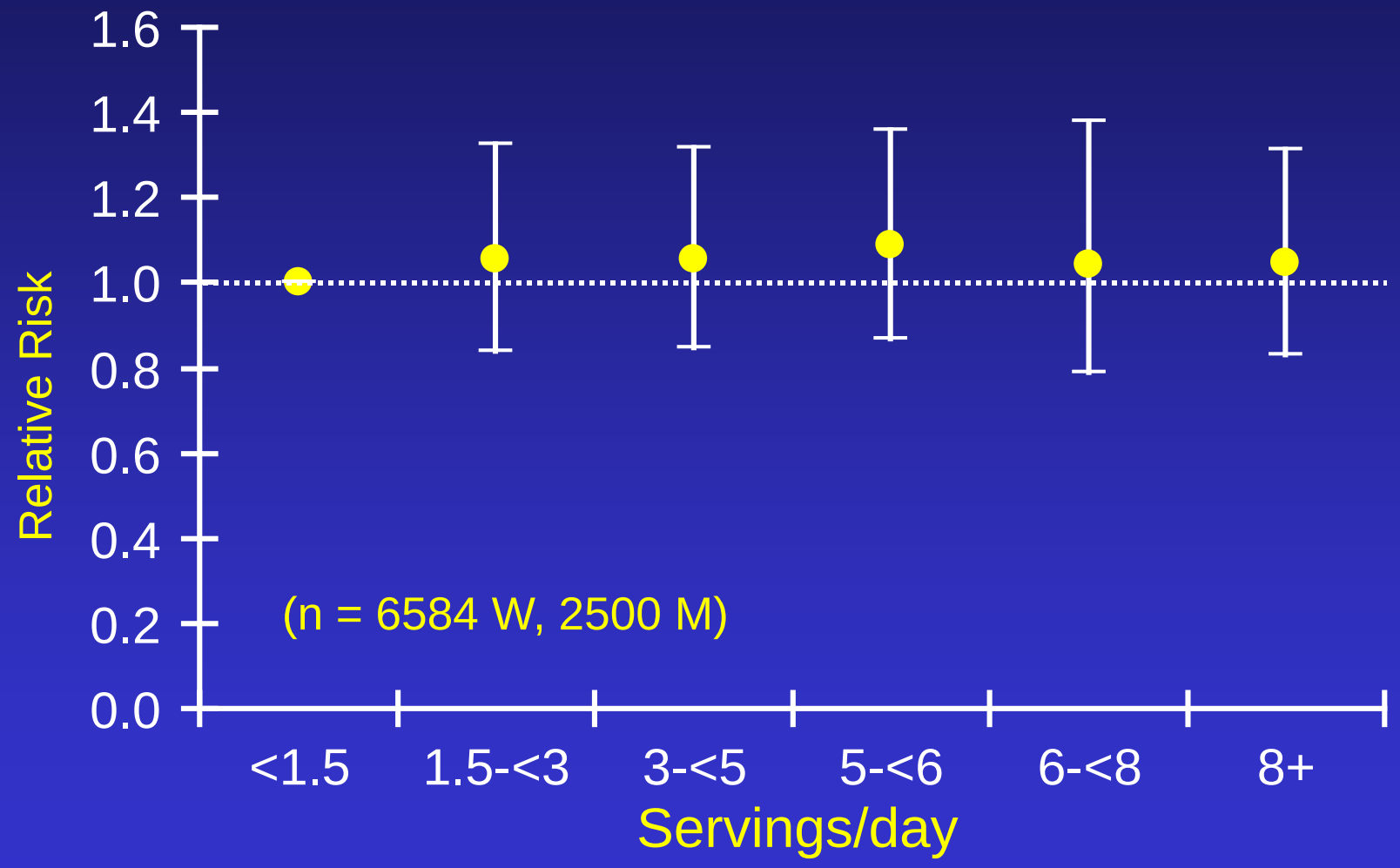
Randomized trials have offered strong evidence against benefits of relatively *high doses* of *selected nutrients* and risk of cancer over approximately a *5-year period before diagnosis*:

- selenium
- vitamin E
- vitamin C
- B vitamins
- β-carotene

Results from prospective studies

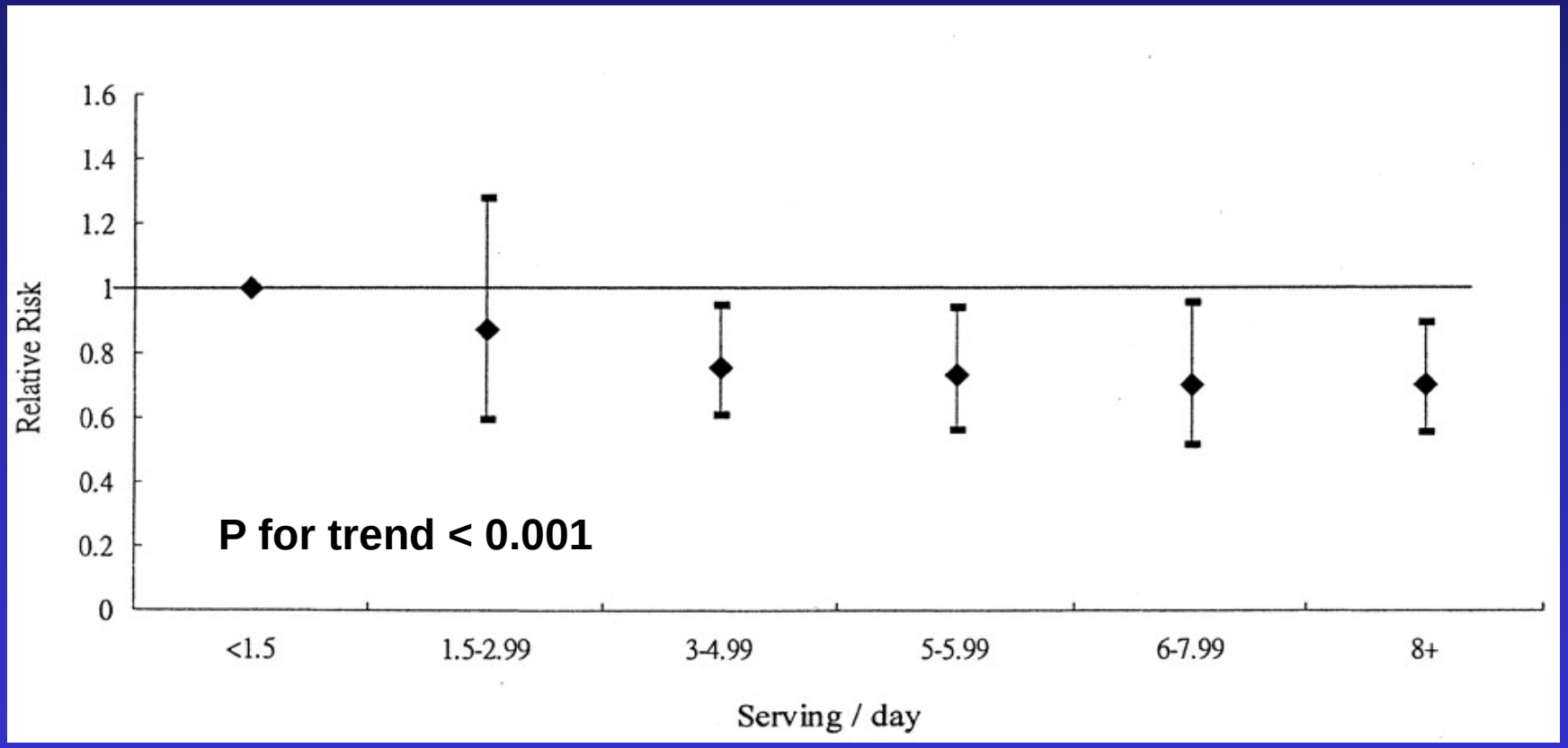
began to be published in the 1990’s

Fruits and Vegetables and Cancer
(NHS and HPFS)



Hung H.C. et al. (2004) J Natl Cancer Inst

Fruits and Vegetables and Cardiovascular Disease
(NHS and HPFS)



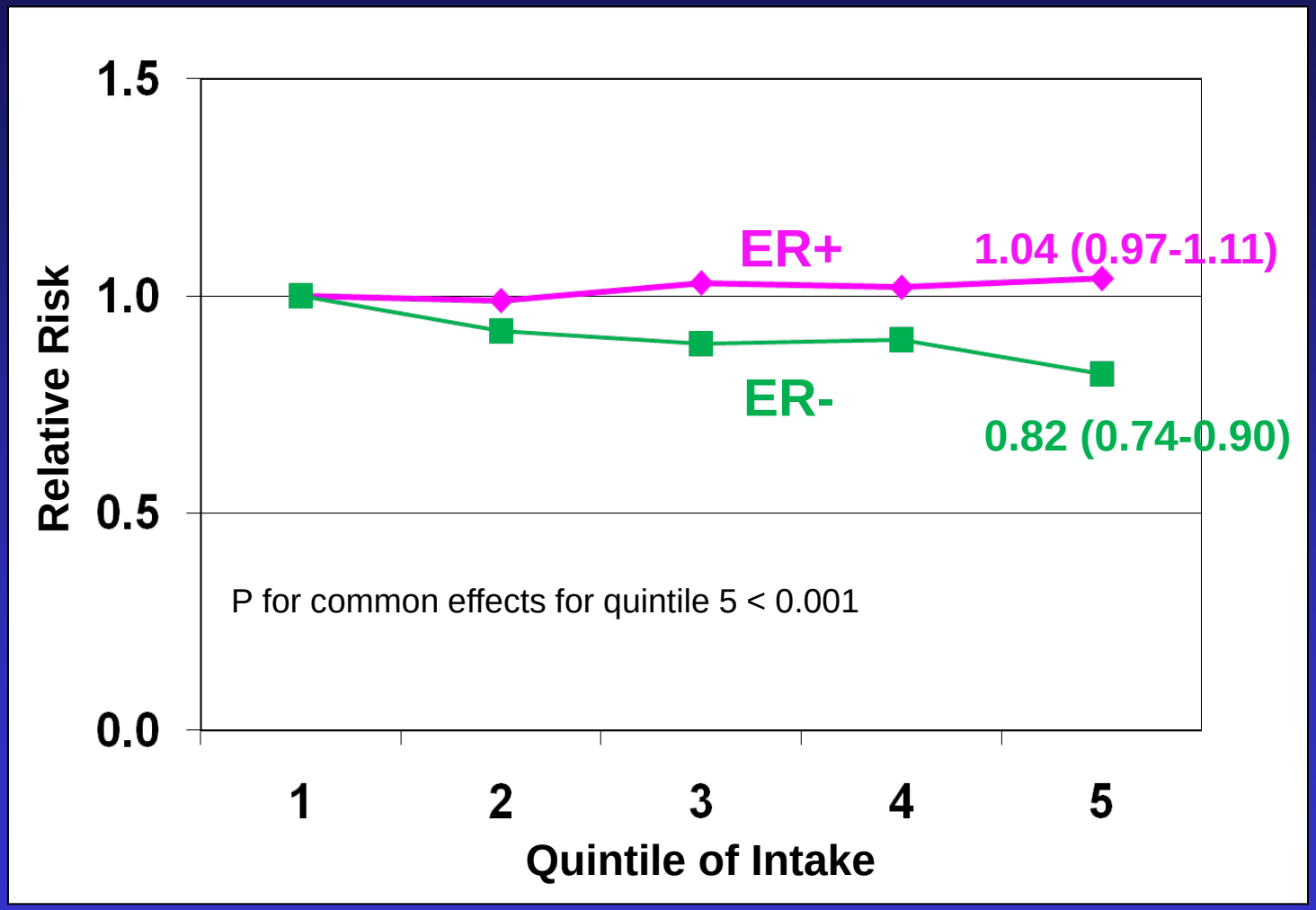
Hung H.C. et al. (2004) j Natl Cancer Inst

Fruits and Vegetables and the Risk of Cancer

Decreases Risk	Exposure	Cancer site
Convincing	---	---
Probable	Non-starchy vegetables	Mouth, pharynx, larynx Esophagus Stomach)
	Allium vegetables	Stomach
	Garlic	Colorectum
	Fruits	Mouth, pharynx, larynx Esophagus Lung Stomach
	Foods with folate	Pancreas
	Foods with carotenoids	Mouth, pharynx, larynx Lung
	Foods with beta-carotene	Esophagus
	Foods with lycopene	Prostate
	Foods with vitamin C	Esophagus
	Foods with selenium	Prostate

WCRF / AICR, 2007

Total Vegetables and Breast Cancer by ER Status



n = 19,869 ER+, 4821 ER- breast cancer cases; 21 studies

Courtesy of S.A. Smith-Warner, 2011

S. Jung, unpublished data

Suggestions for Future Observational Studies

- Better assessment of diet
- Better conceptualization of diet into relevant carcinogenic pathways
- Large numbers, long follow-up
- Cancer sub-types
- Early life exposures
- Survivorship studies
- Complementary data (e.g. genetics)