Epidemiology of Lifestyle Factors and Colorectal Cancer

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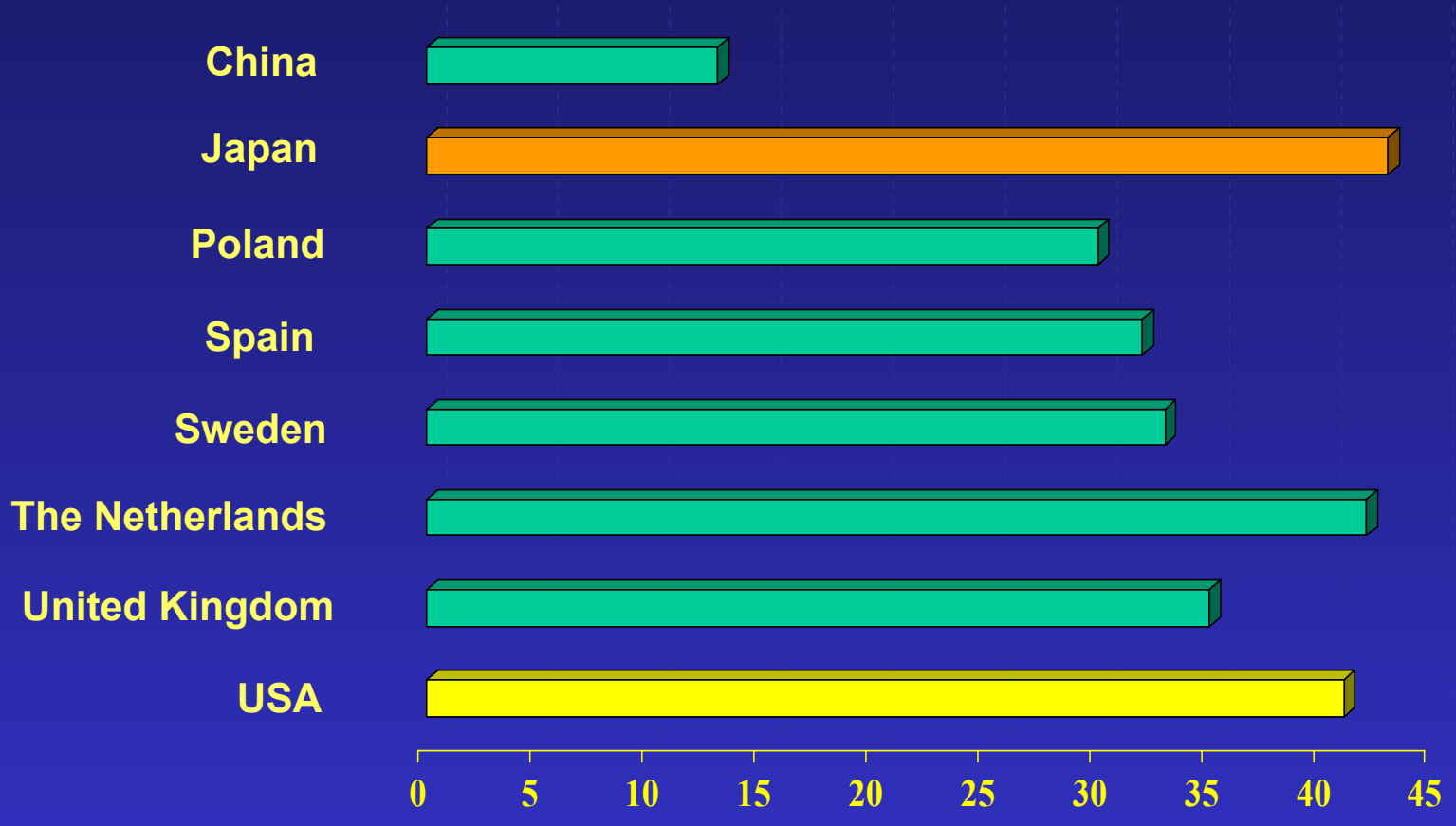
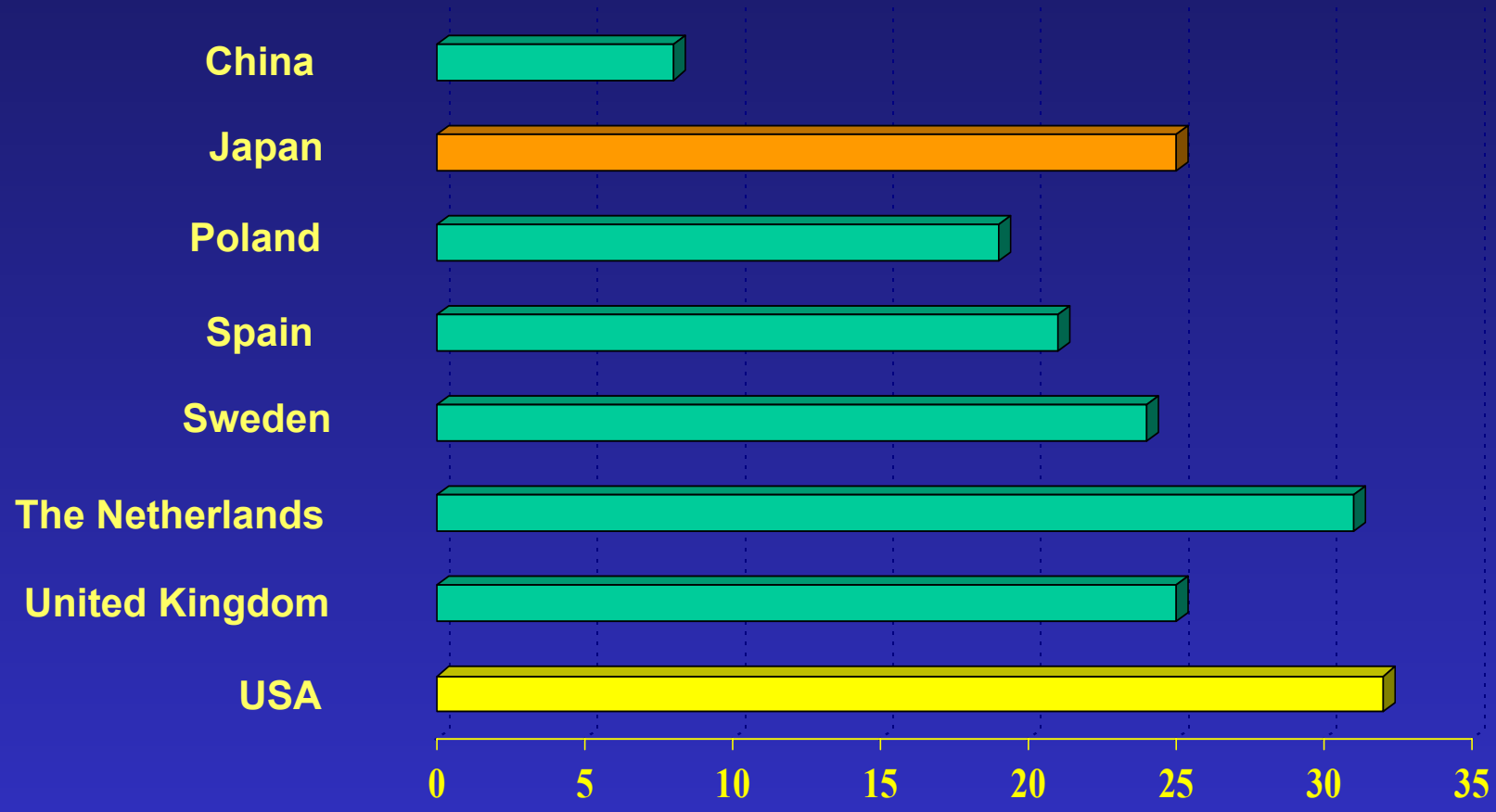
- There is relatively little racial / ethnic variation in colorectal cancer (CRC) mortality in U.S.
- However, worldwide incidence rates vary approximately 20-fold, with the lowest rates in India and the highest in U.S. and Japan
- International differences and migrant data show that CRC is highly sensitive to changes in lifestyle

Age-standardized Incidence Rates of CRC (Men)



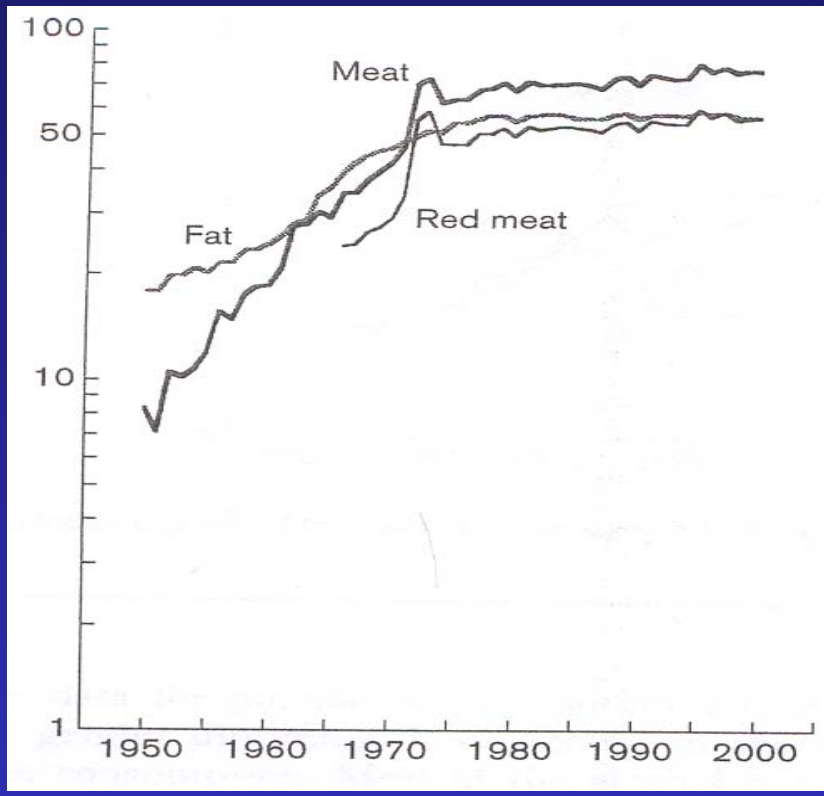
Ferlay et al, 2001.

Age-standardized Incidence Rates of CRC (Women)

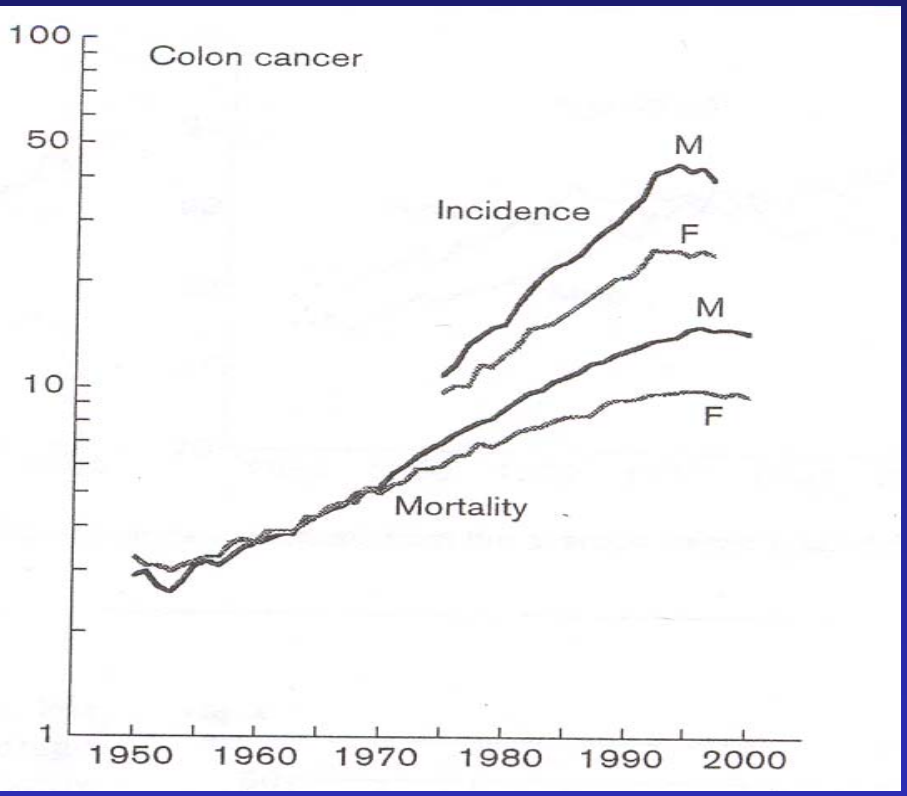


Ferlay et al, 2001.

Consumptions of Fat & Meat in Japan



Incidence and Mortality Rates In Japan



Kono, S. Eur J Can Prev 2004

Western Diet & Lifestyle

↓

Energy Imbalance

High energy intake
Western Diet Pattern
Obesity

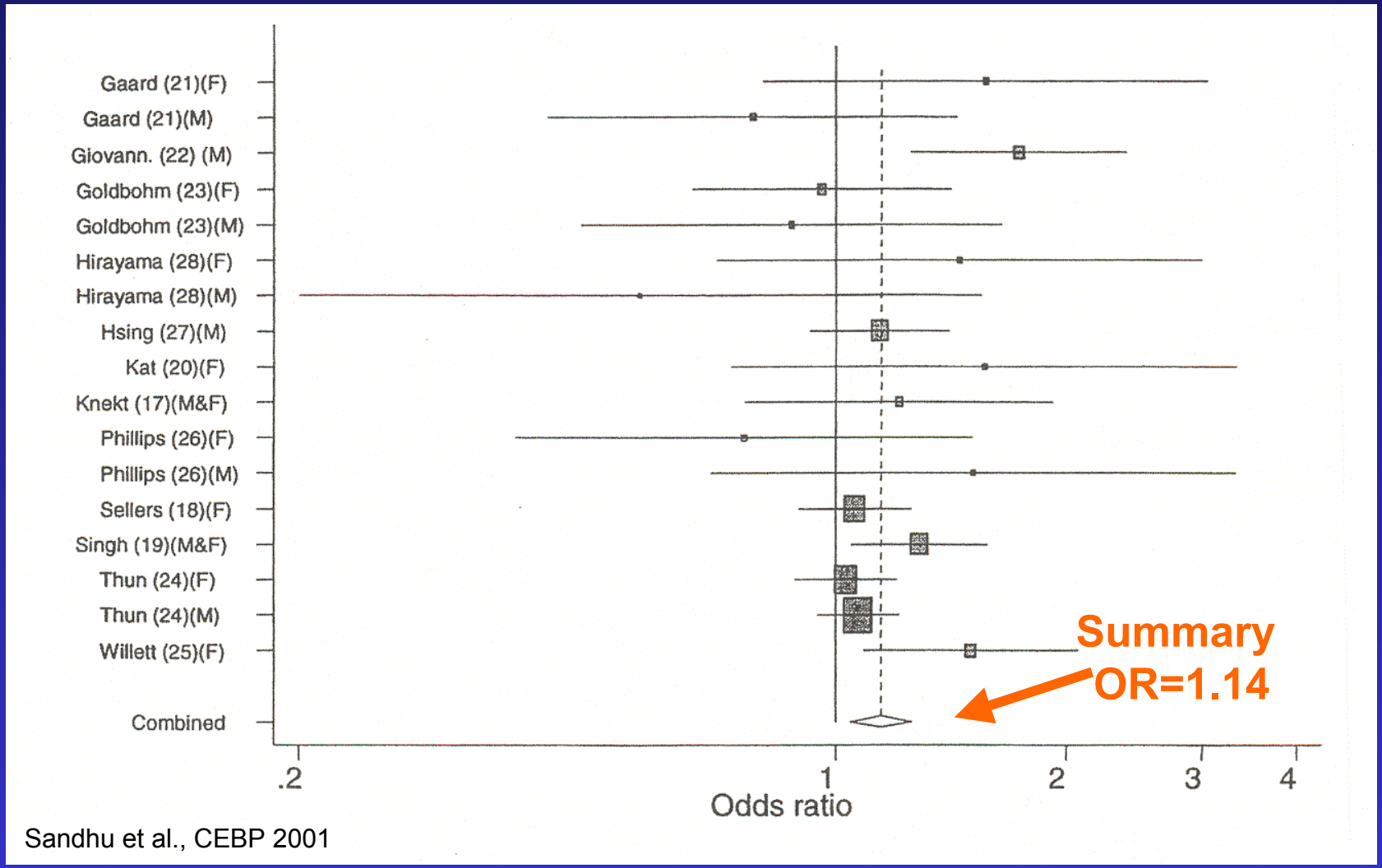
Physical
Activity

Western Dietary Pattern*

- Red meat
- Processed meats
- High fat dairy
- Sweets
- Refined grain products
- Less whole grain fiber

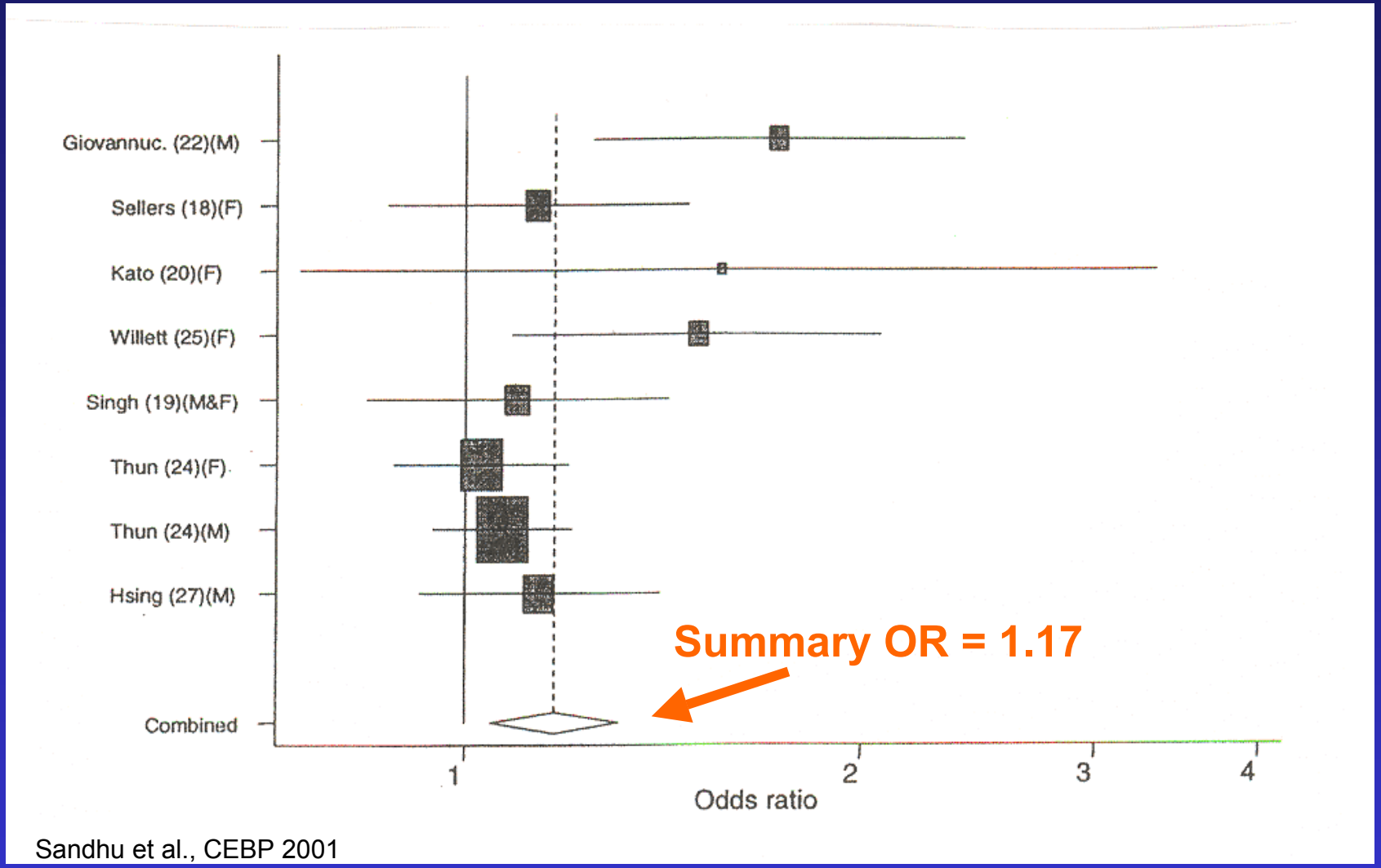
* Factor analysis (principal components)

Meta-Analysis of Risk of CRC for an Increase of 1 Portion of All Meat



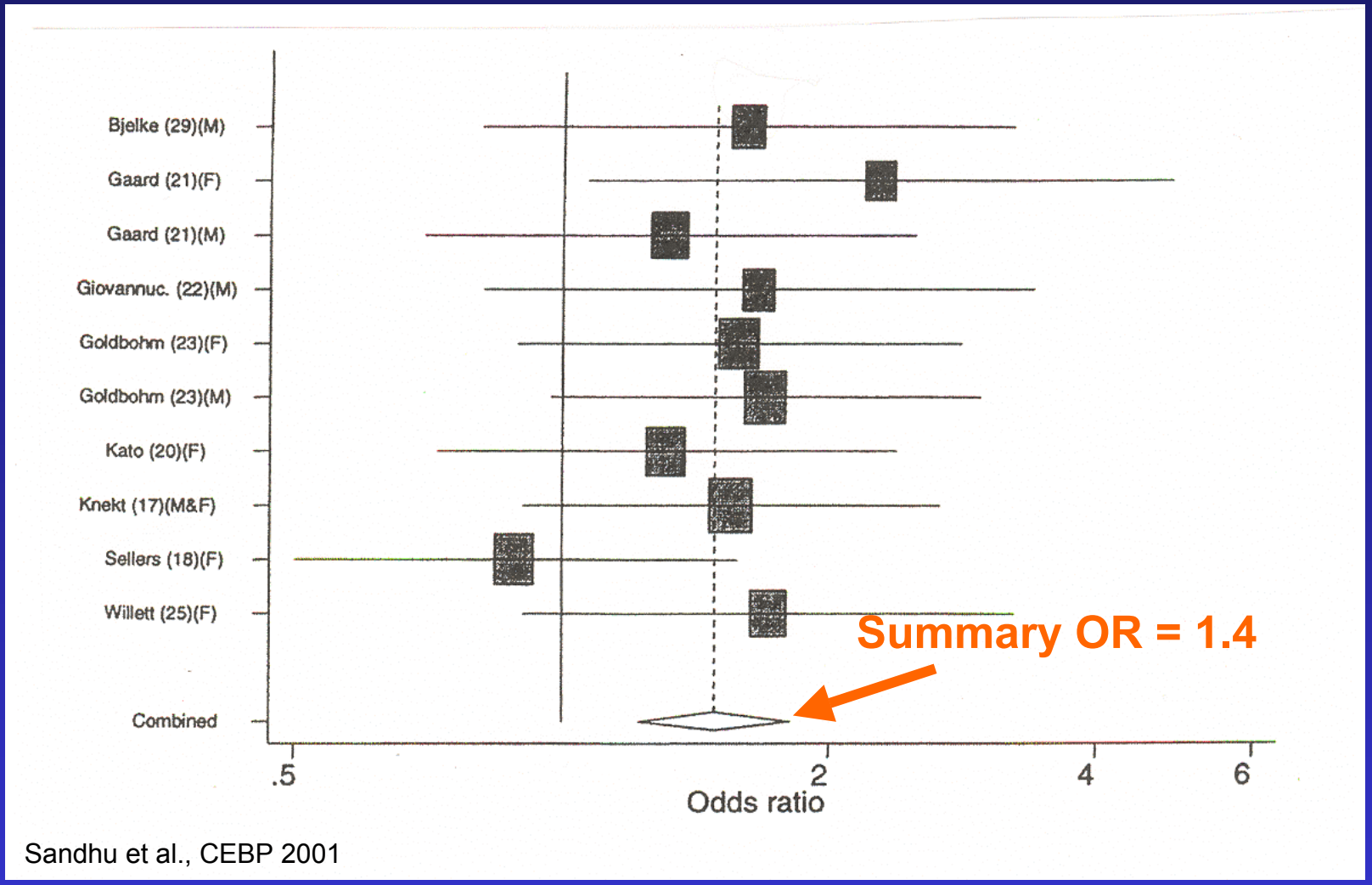
Sandhu et al., CEBP 2001

Meta-Analysis of Risk of CRC for an Increase for 1 Portion of Red Meat



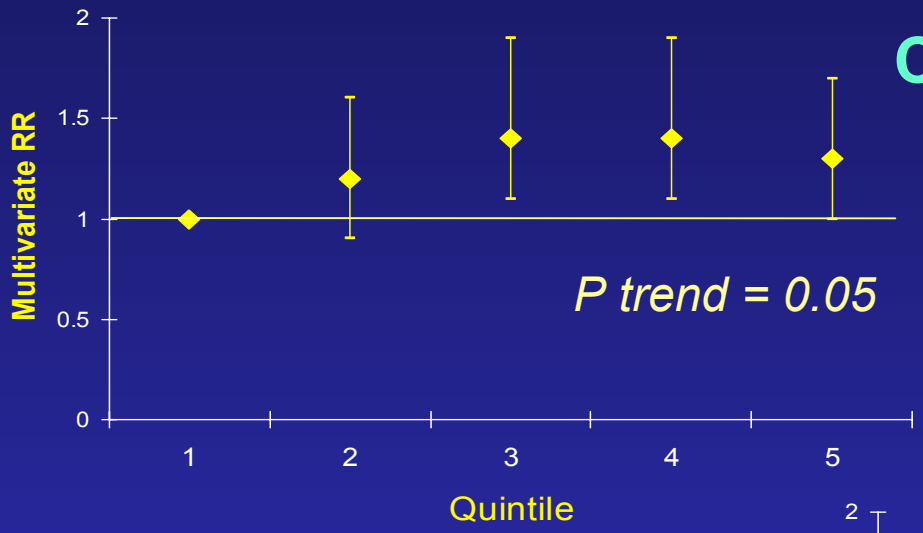
Sandhu et al., CEBP 2001

Meta-Analysis of Risk of CRC for an Increase of 1 Portion of Processed Meat



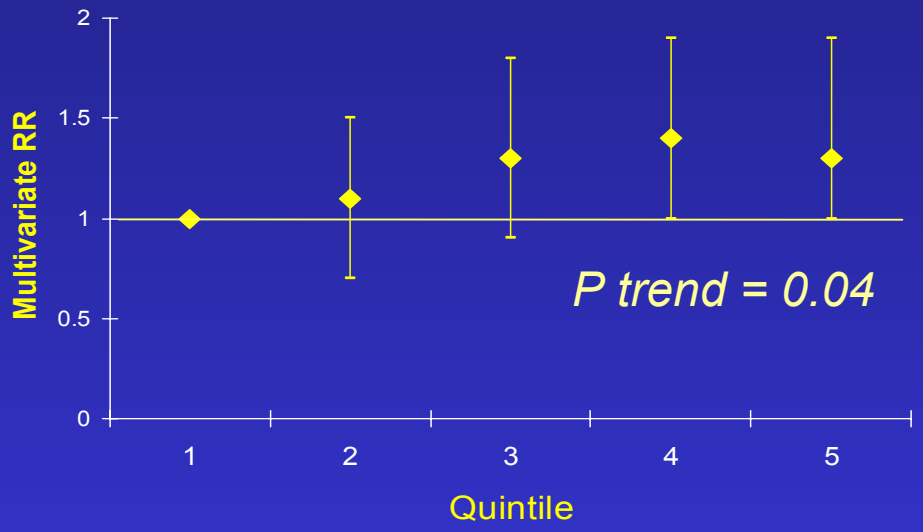
Sandhu et al., CEBP 2001

Western Dietary Pattern and Risk of Adenomas and Colon Cancer In Men (HPFS)



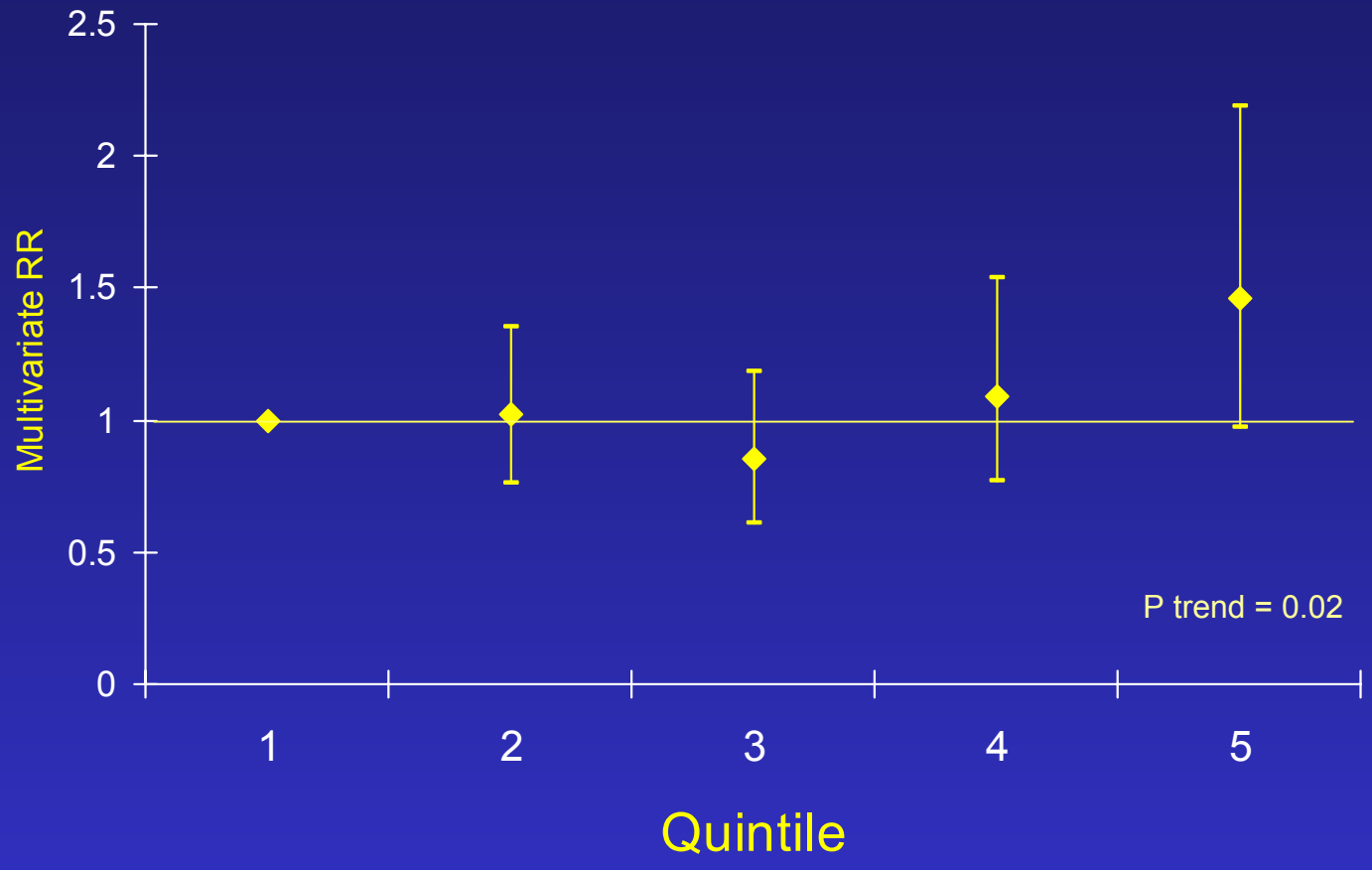
Colon cancer

Large distal adenomas



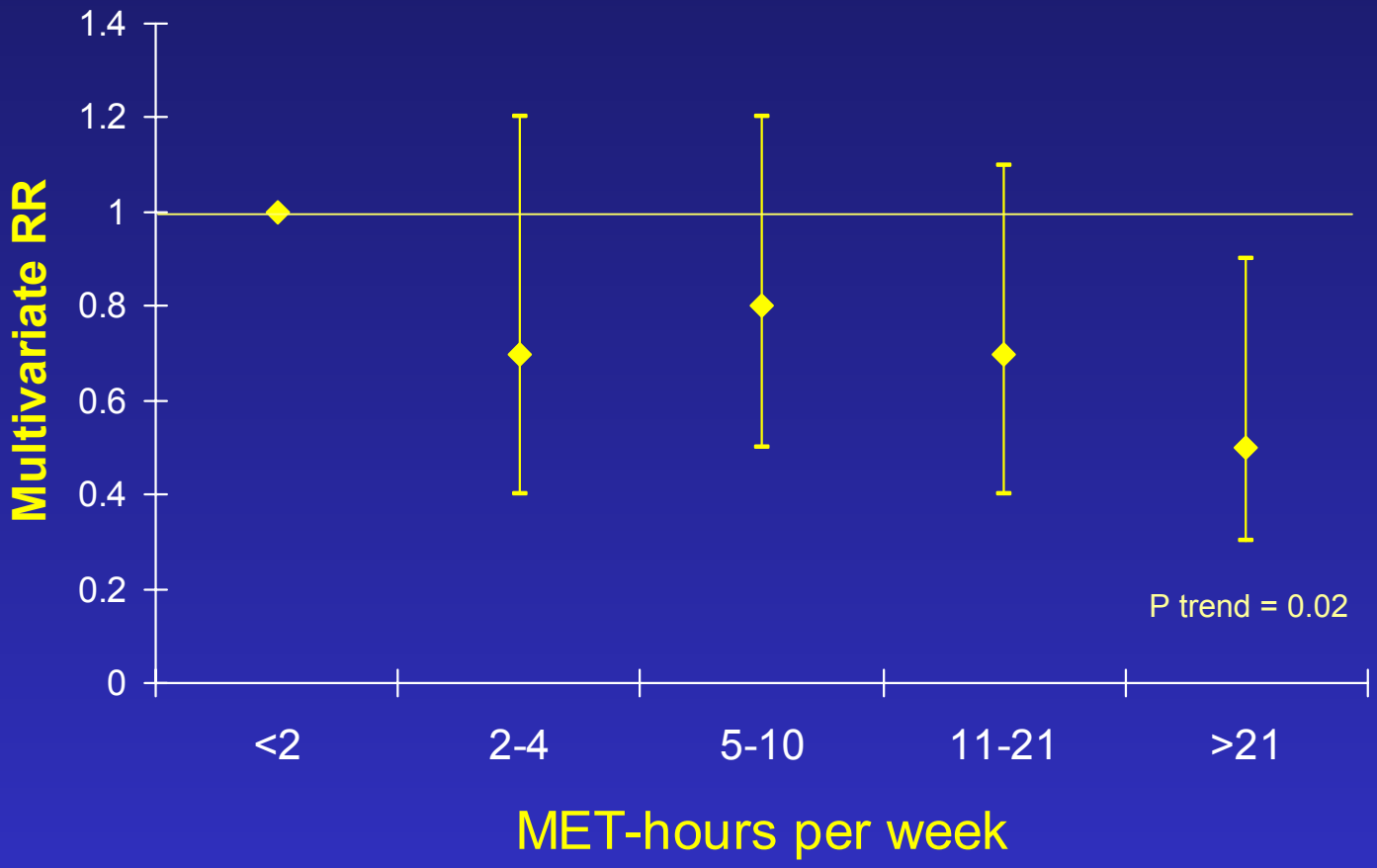
Wu et al. Cancer Causes & Control 2004

Western Dietary Pattern and Colon Cancer Risk In Women, The Nurses' Health Study (NHS)



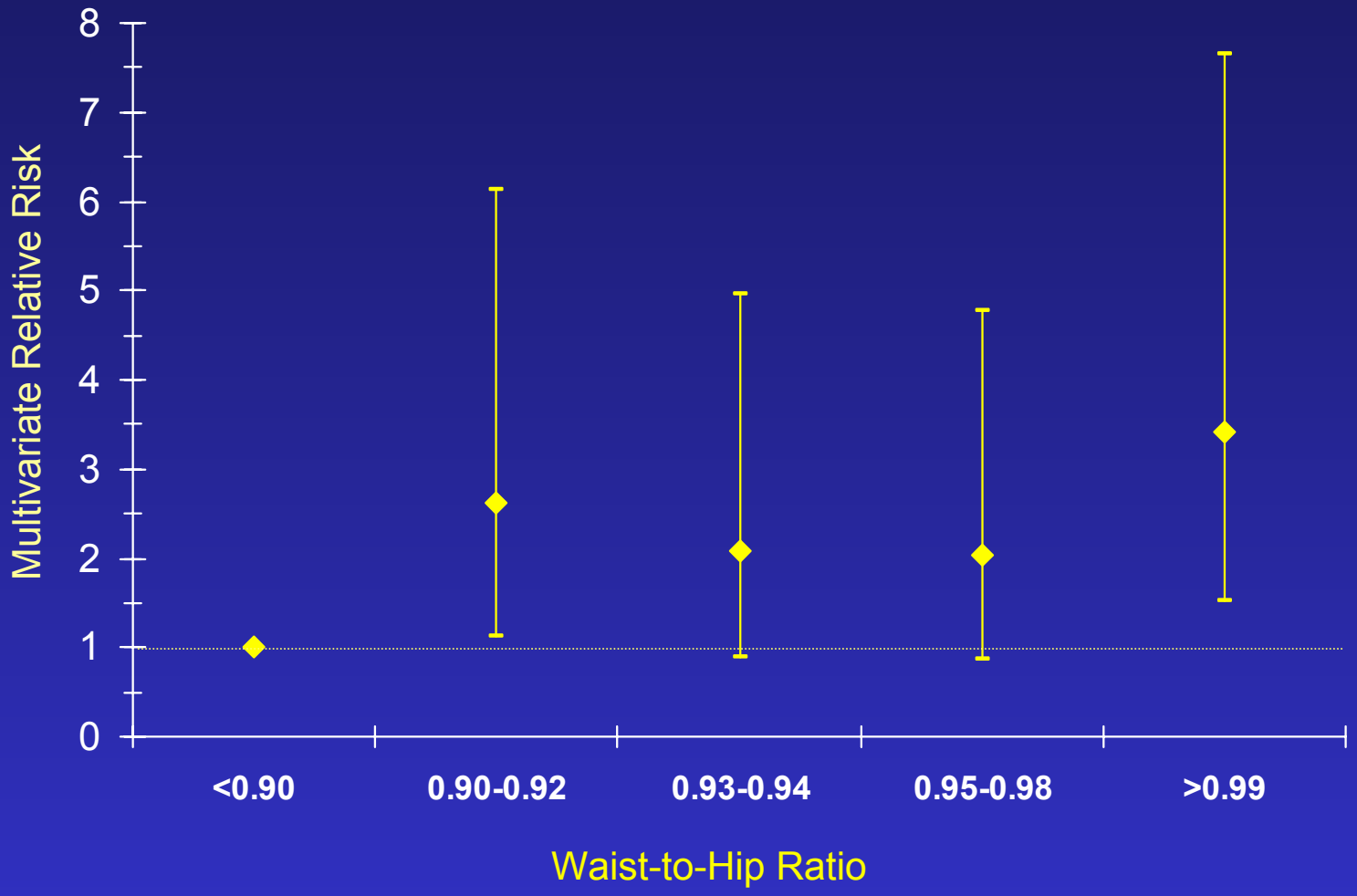
Fung et al., *Arch Intern Med* (in press)

Leisure-Time Physical Activity and Colon Cancer Risk in Women (NHS)

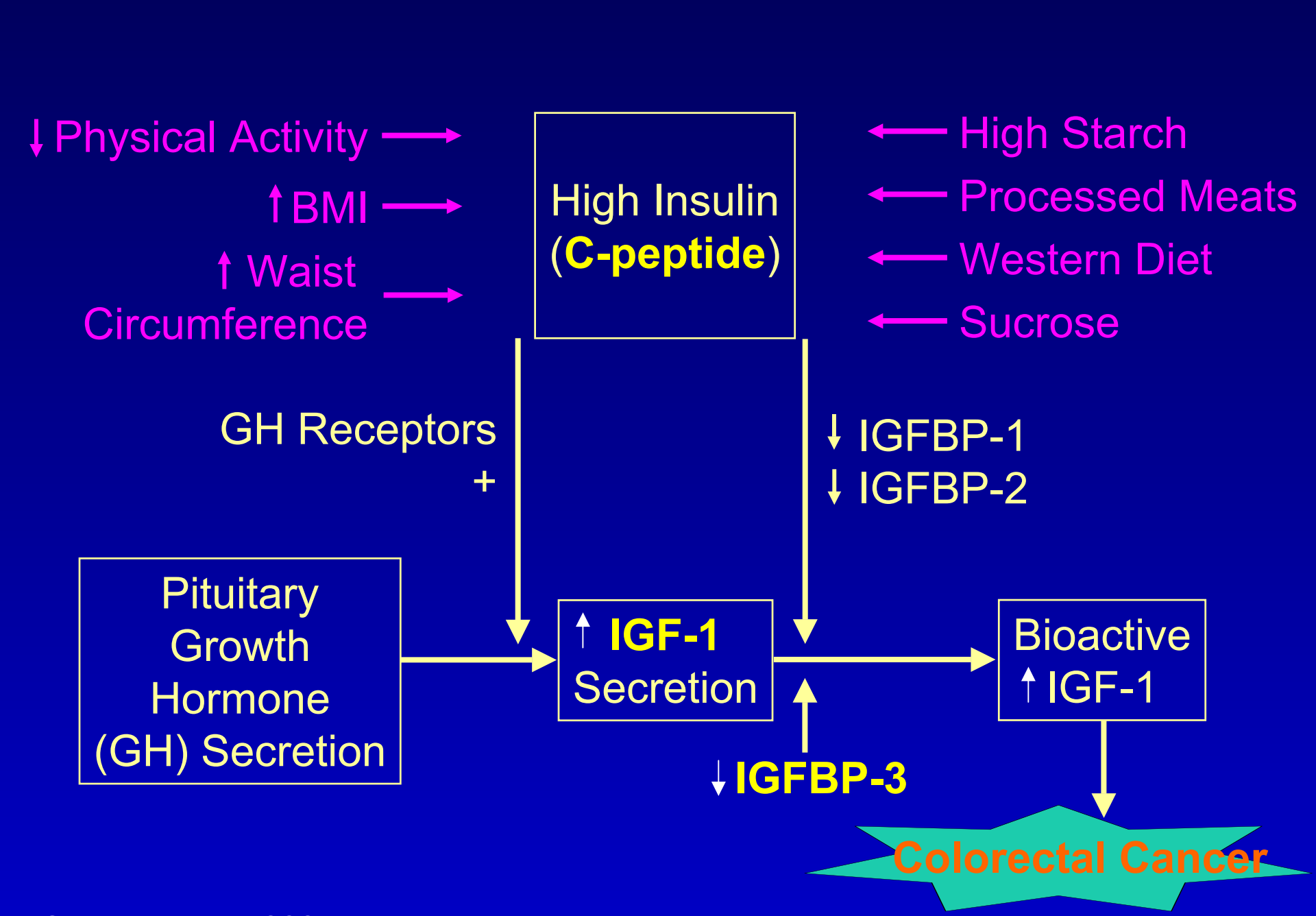


Martimez et al. JNCI1997

Waist to Hip Ratio and Colon Cancer Risk in Men
HPFS

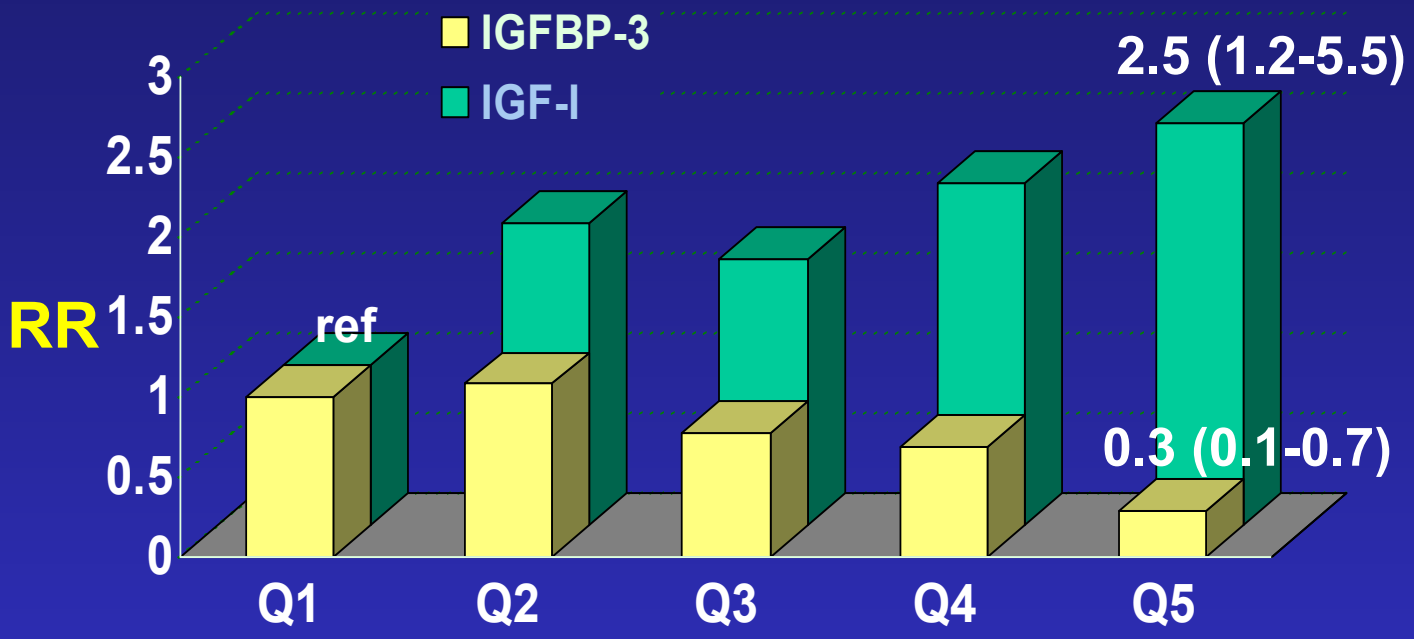


Giovannucci et al., JNCI 1995



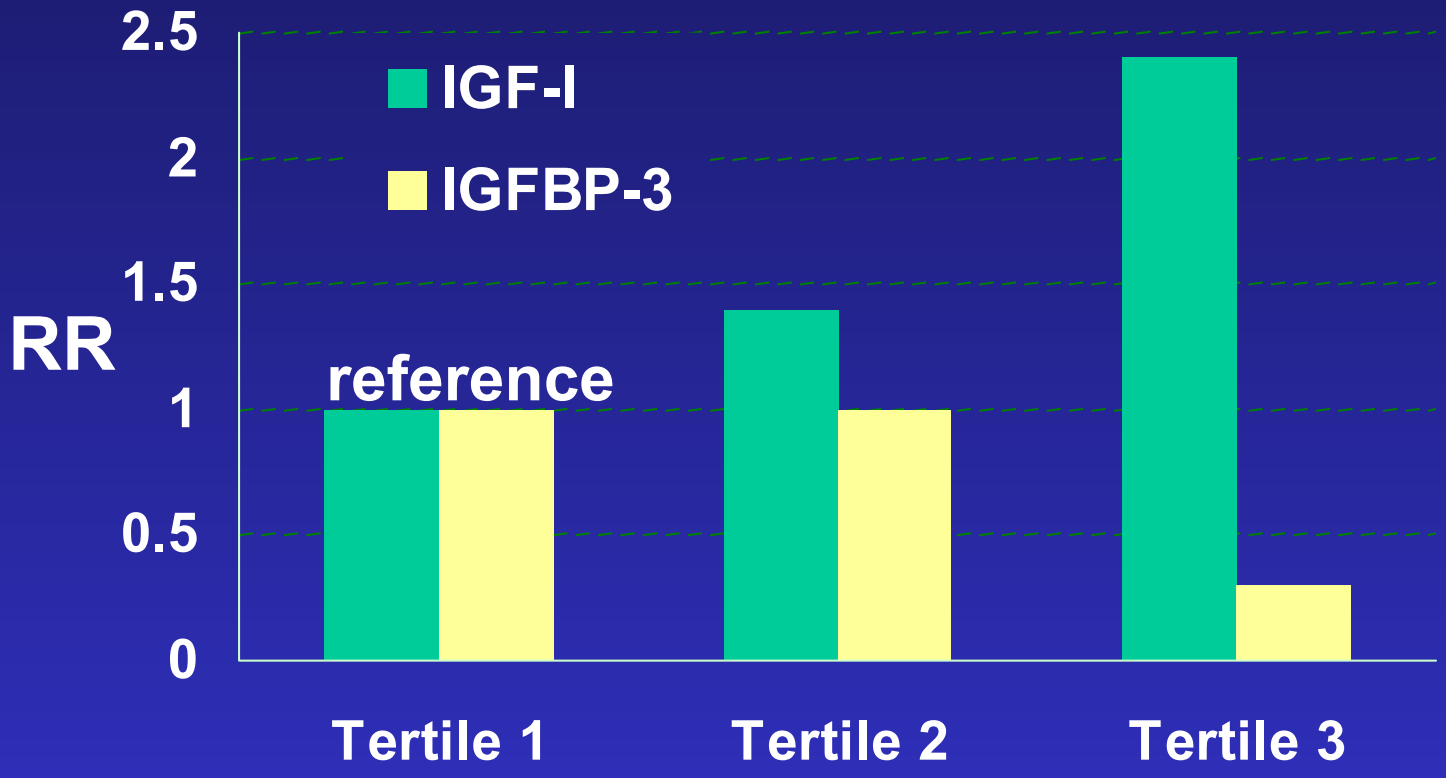
Giovannucci et al., *CCC* 1995; *J Nutr* 2002

Relative Risk of Colorectal Cancer in Men (PHS)



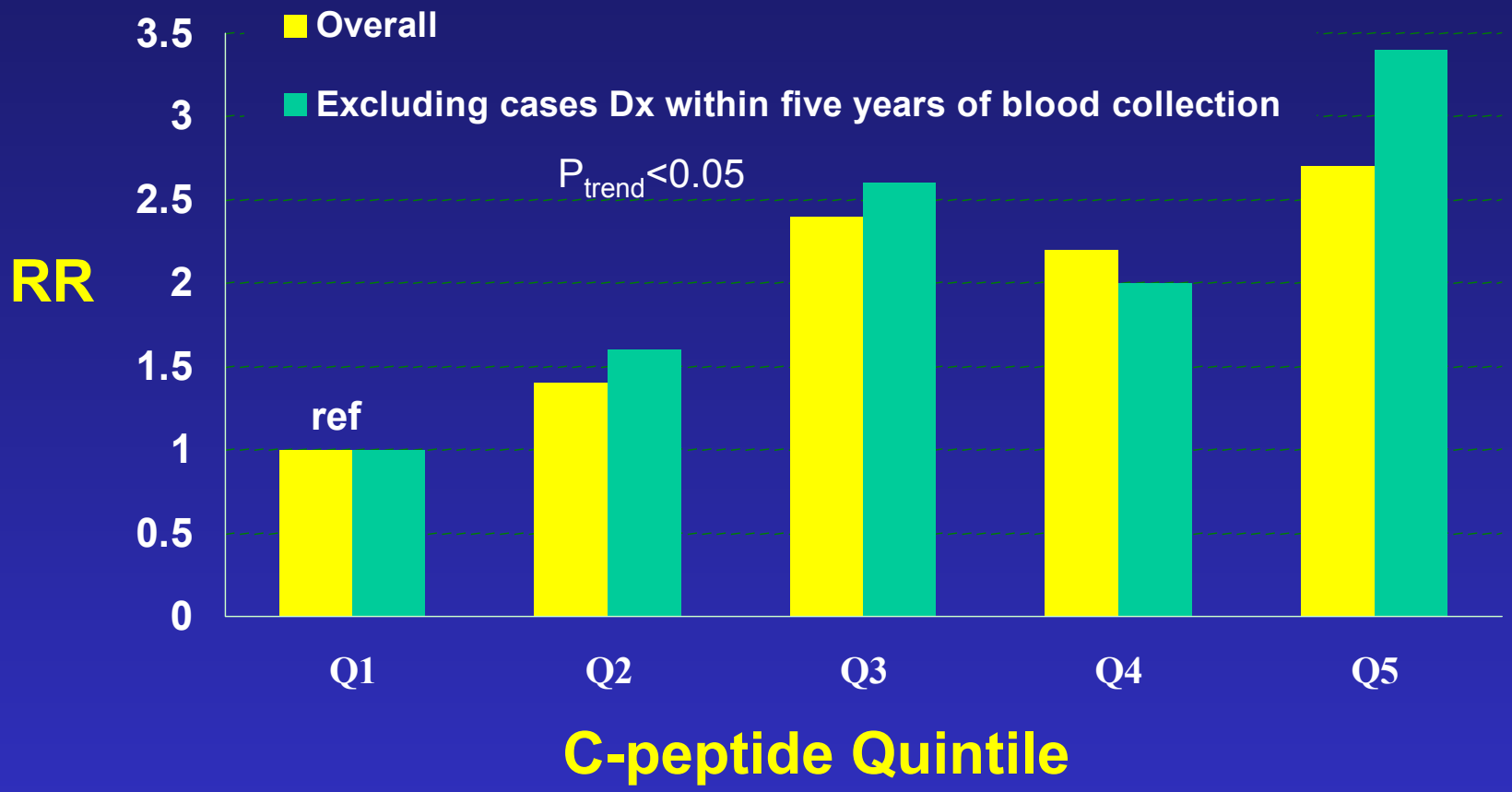
Ma J, et al. *J Natl Cancer Inst* 1999

RR of Colorectal Cancer and High Risk Adenoma in Women (NHS)



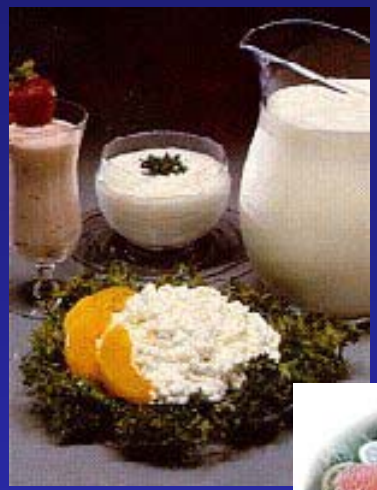
Giovannucci E, et al. *CEBP* 2000

C-peptide Levels (a marker of insulin production) and Risk of Colorectal Cancer in Men (PHS)

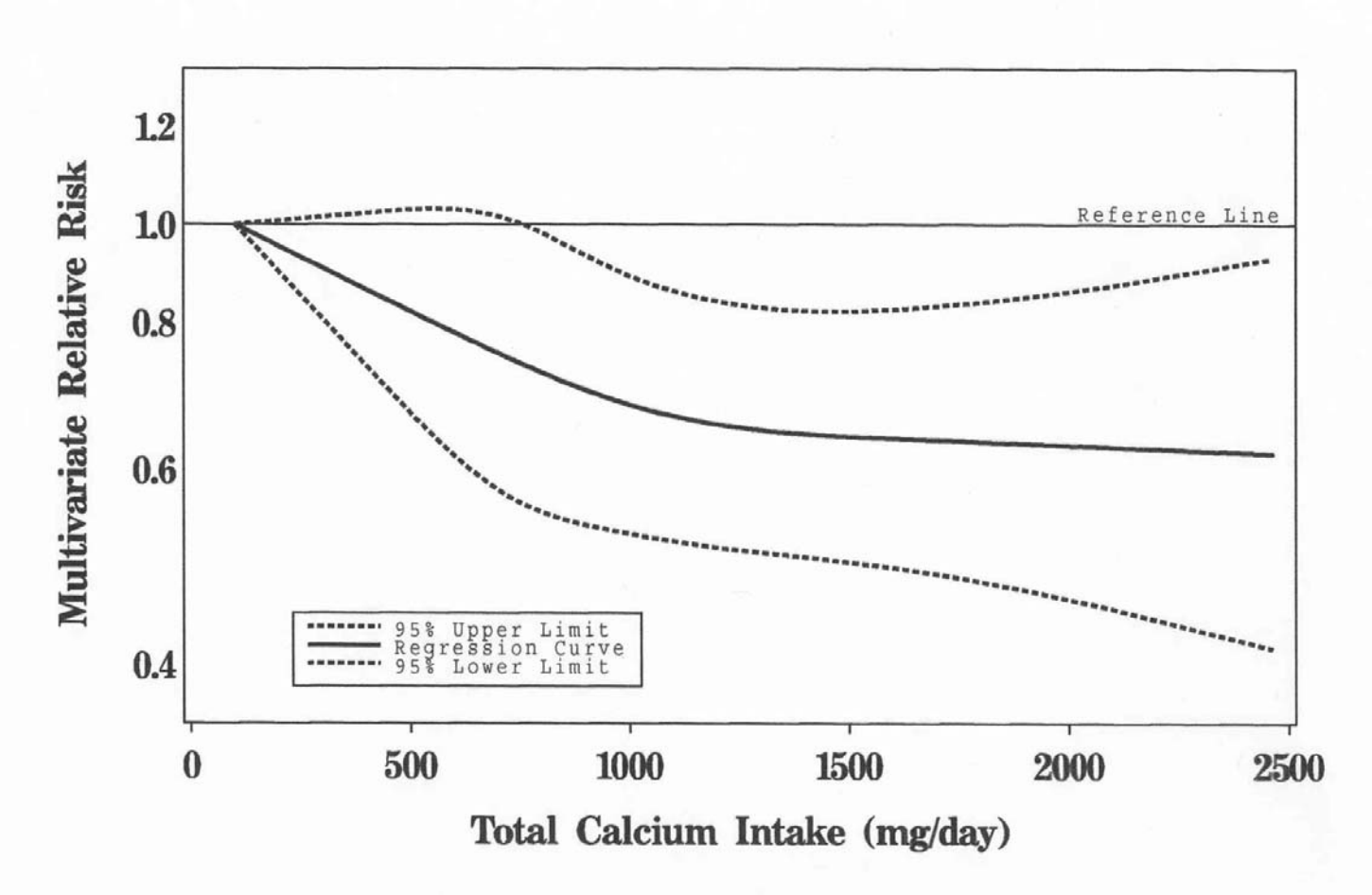


Ma, et al. *J Natl Cancer Inst 2004*

Calcium & vitamin D

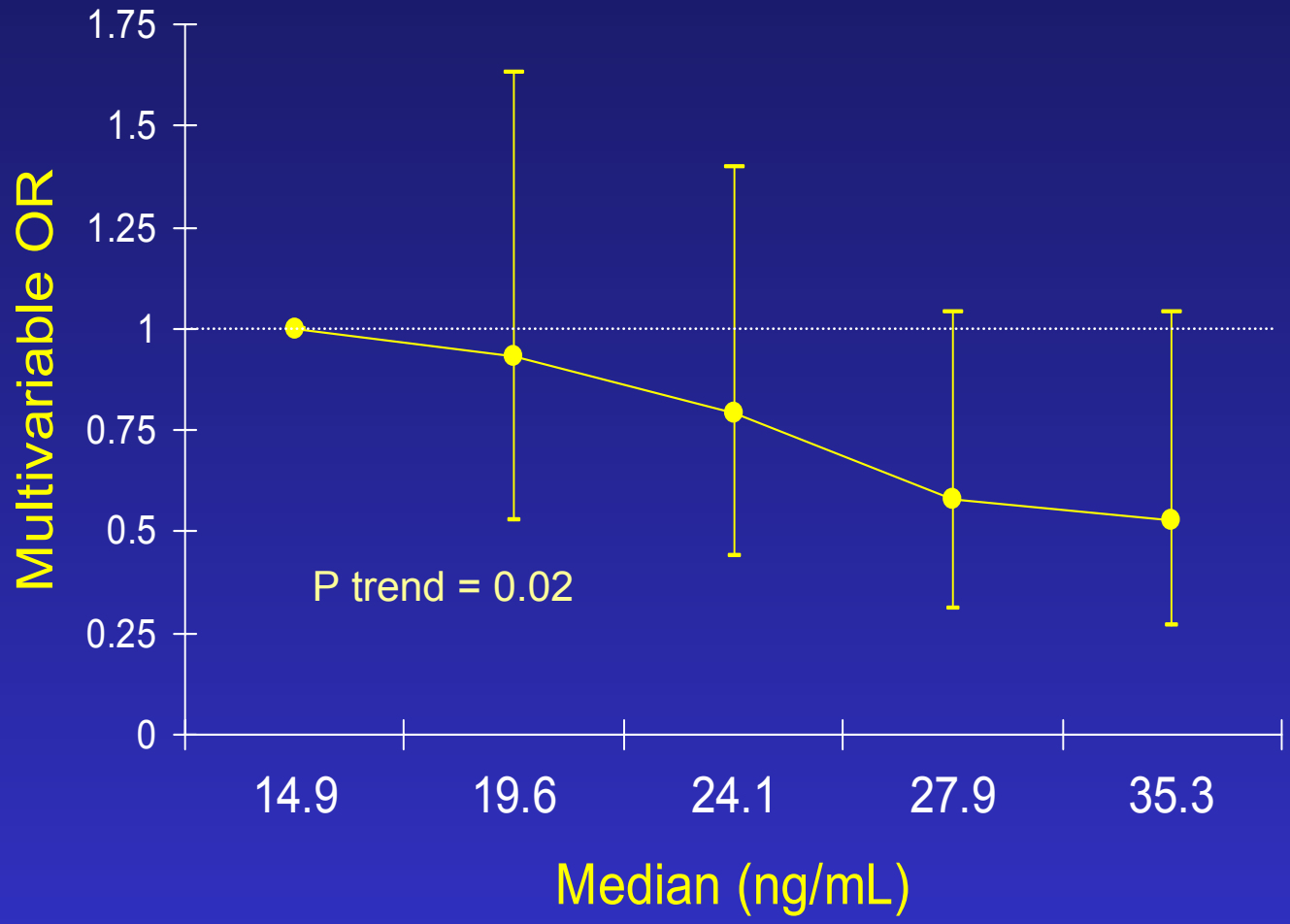


Total Calcium Intake and Colorectal Cancer Pooled Analysis from 10 Cohorts



Cho et al., *JNCI* 2004

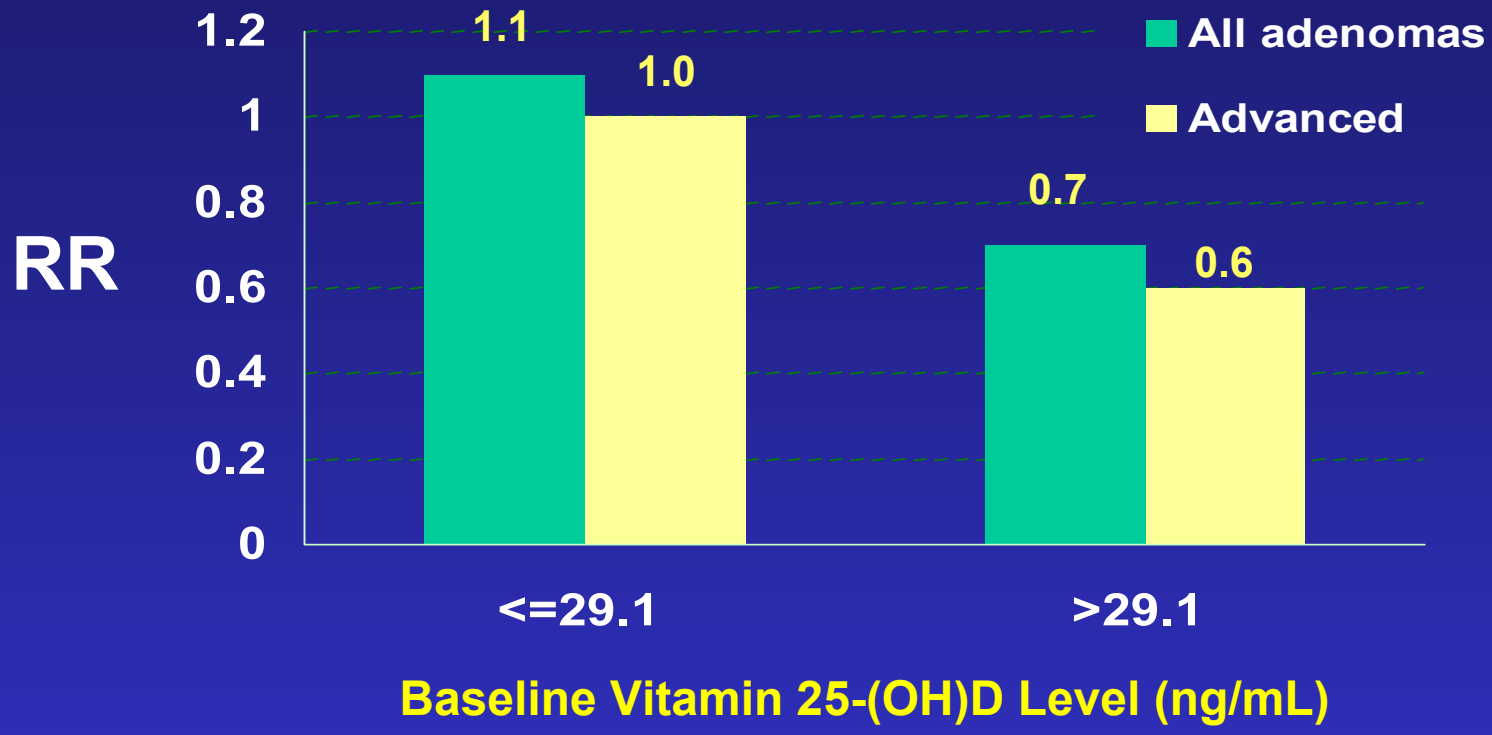
Plasma 25(OH) Vitamin D and Colorectal Cancer
Nurses' Health Study



Feskanich D. et al., *CEBP* 2004

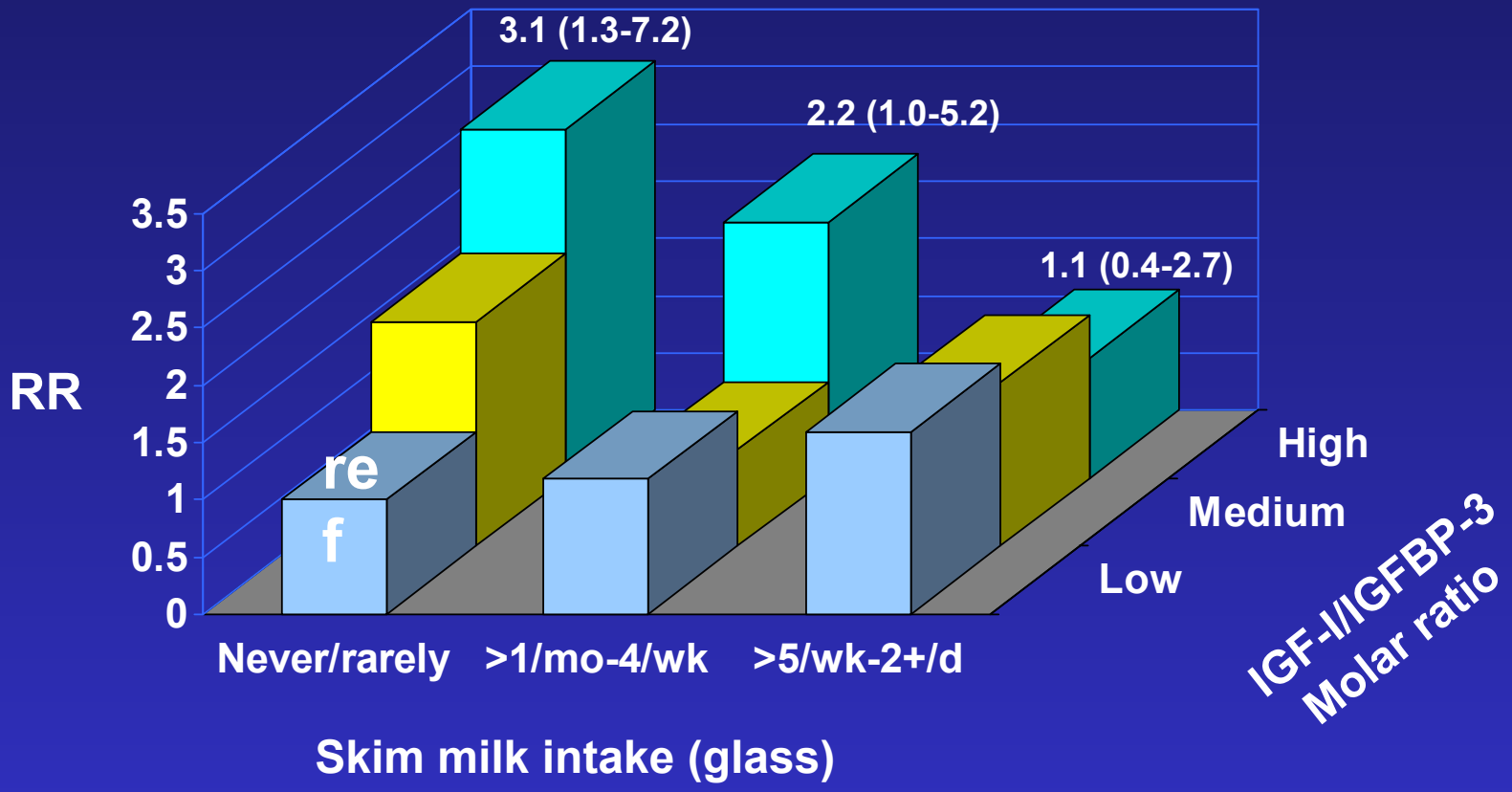
Vitamin D Status Modify the Effect of Calcium on Adenoma Recurrence

(The Calcium Polyp Prevention Study)



Grau MV et al. *J Natl Cancer Inst* 2003

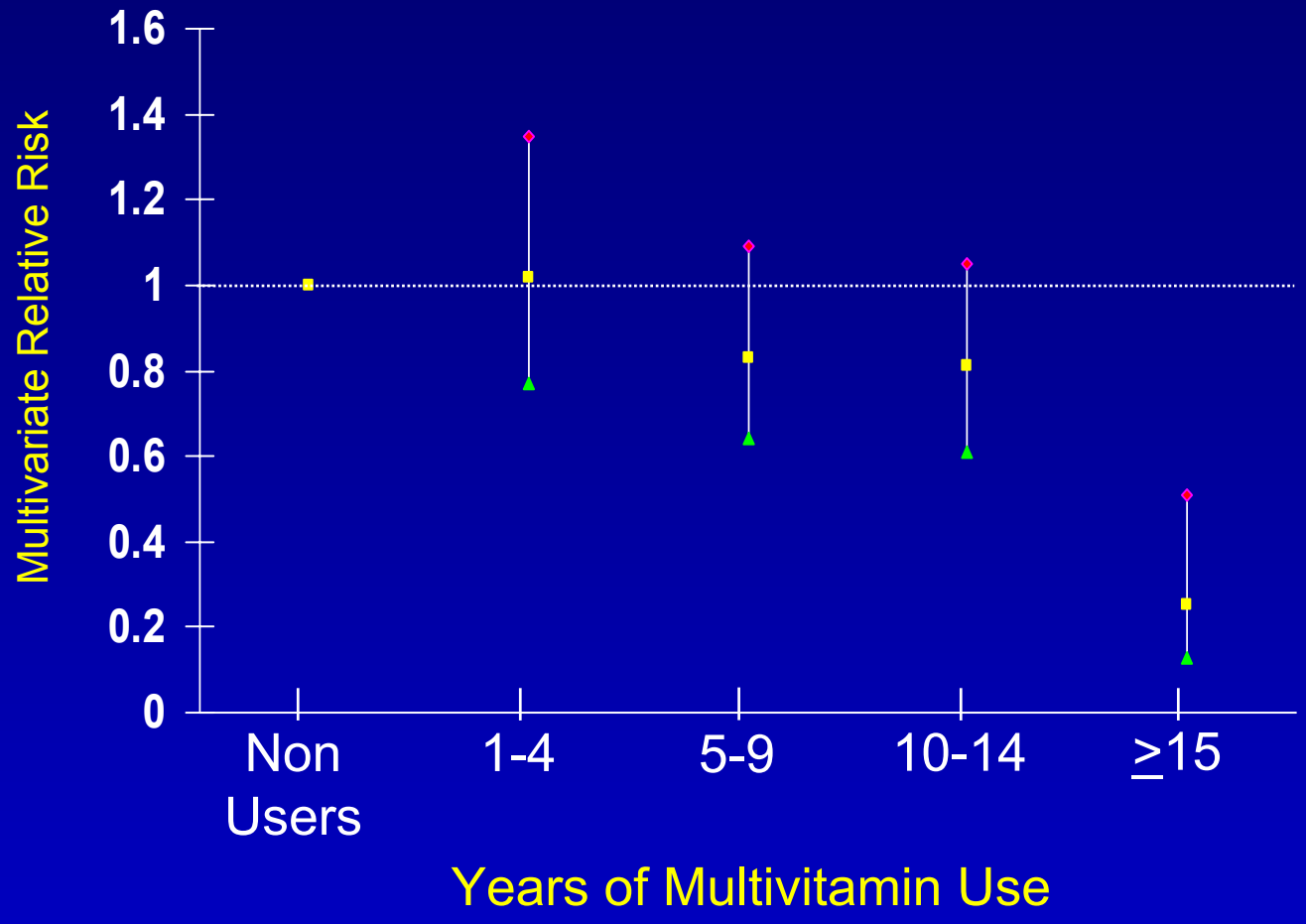
RR of colorectal cancer in Men (PHS)



Ma J, et al. *J Natl Cancer Inst* 2001

Folate
&
Related Genetic Factor

Relative Risk and 95% CI of Colon Cancer in Women (NHS)



Giovannucci et al., *Ann Intern Med* 1998

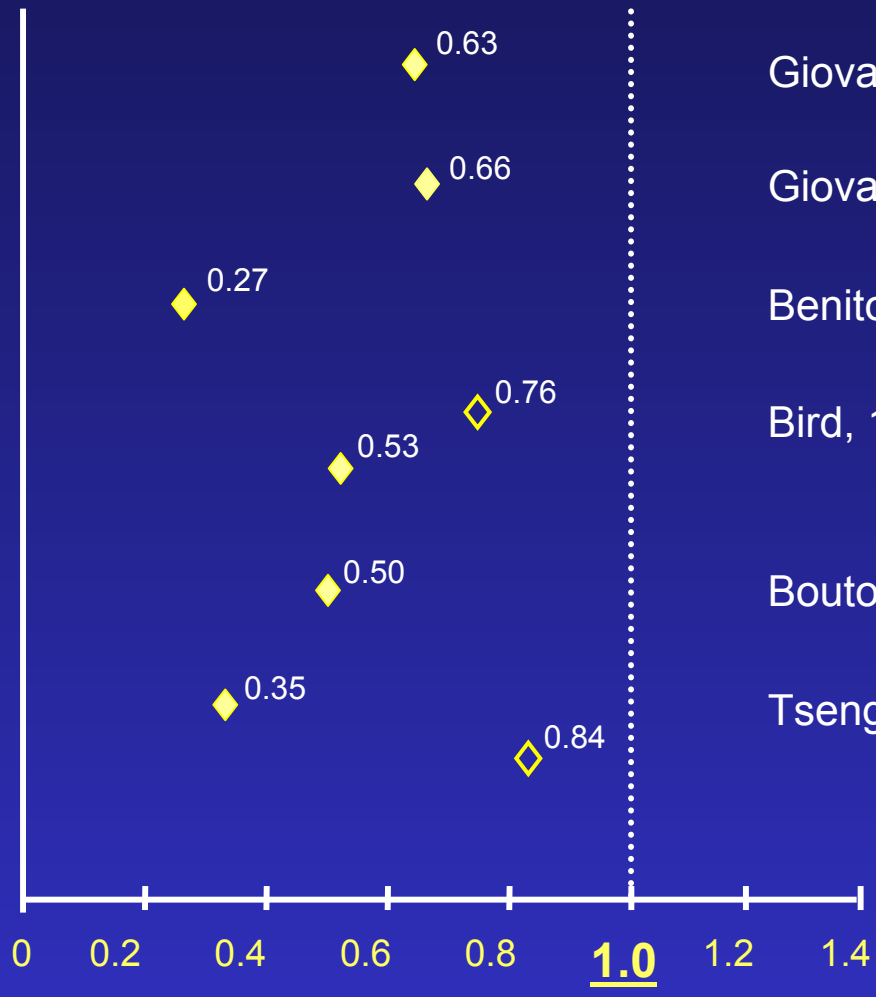
RR of colonic adenoma for high to low quintiles of folate and the specified nutrient intake* in Men and Women (NHS & HPFS)

	RR	95% CI	
Vitamin A	0.96	0.69-1.33	
Folate	**0.68**	**0.50-0.93†**	**P ≤ .05**
Vitamin C	1.05	0.78-1.40	
Folate	**0.64**	**0.47-0.87‡**	**P ≤ .01**
Vitamin D	1.24	0.90-1.71	
Folate	**0.53**	**0.38-0.76§**	**P ≤ .001**
Vitamin E	1.05	0.78-1.41	
Folate	**0.62**	**0.45-0.86‡**	**P ≤ .01**
β-Carotene	0.79	0.58-1.06	
Folate	**0.68**	**0.51-0.89‡**	**P ≤ .01**

* Model included folate and specified nutrient, age, sex, total energy intake, BMI, alcohol consumption, family history, saturated fat and dietary fiber intake, indications of endoscopy, and prior history of endoscopy.

Giovannucci, *JNCI,* 1993

Folate Intake and Adenoma Studies



Giovannucci, 1993 (M)

Giovannucci, 1993 (F)

Benito, 1993

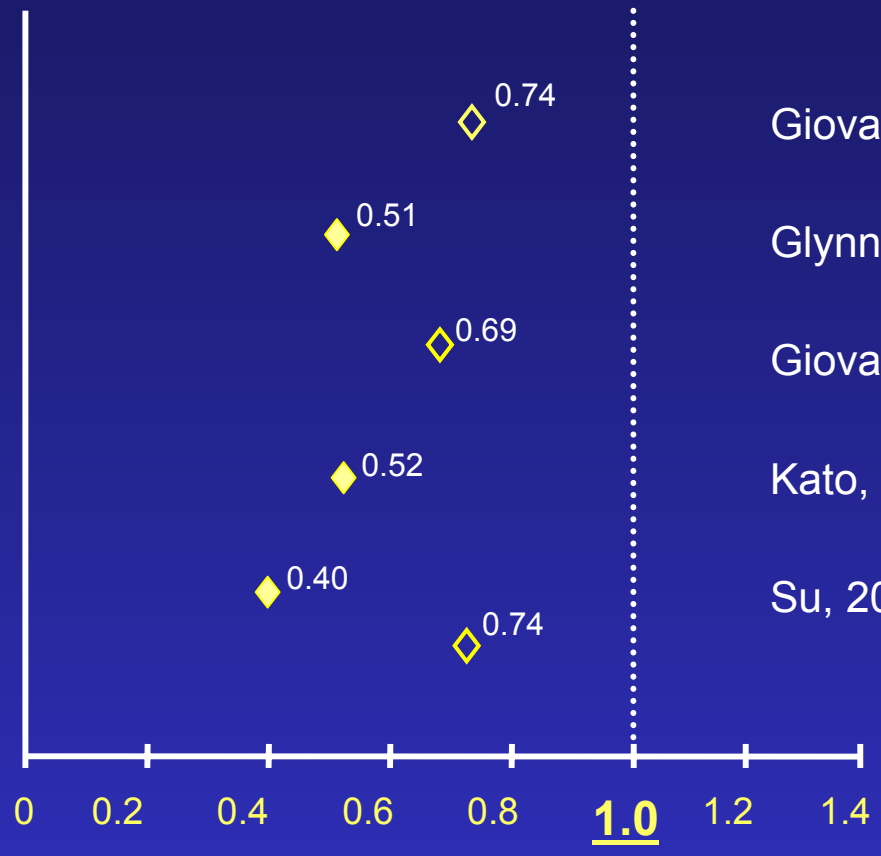
Bird, 1995 (M & F, diet)
(M, RBC)

Bouton-Rualt, 1996 (F)

Tseng, 1996 (F)
(M)

◆ significant
◇ non-significant

Cohort Studies of Folate & Colon Cancer



Giovannucci, 1995 (M)

Glynn, 1996 (M)**

Giovannucci, 1998 (F)

Kato, 1999 (F)

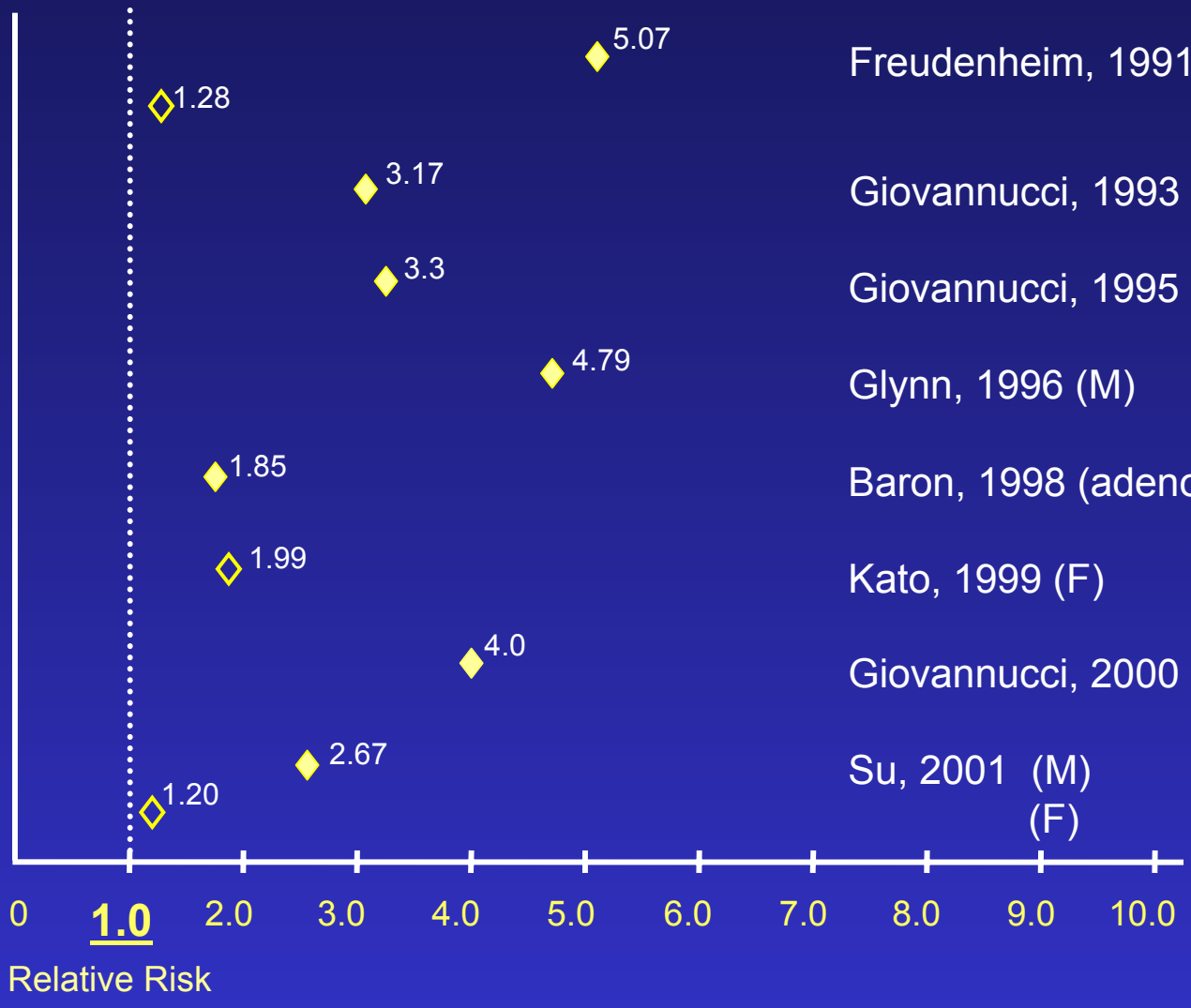
Su, 2001 (M)
(F)

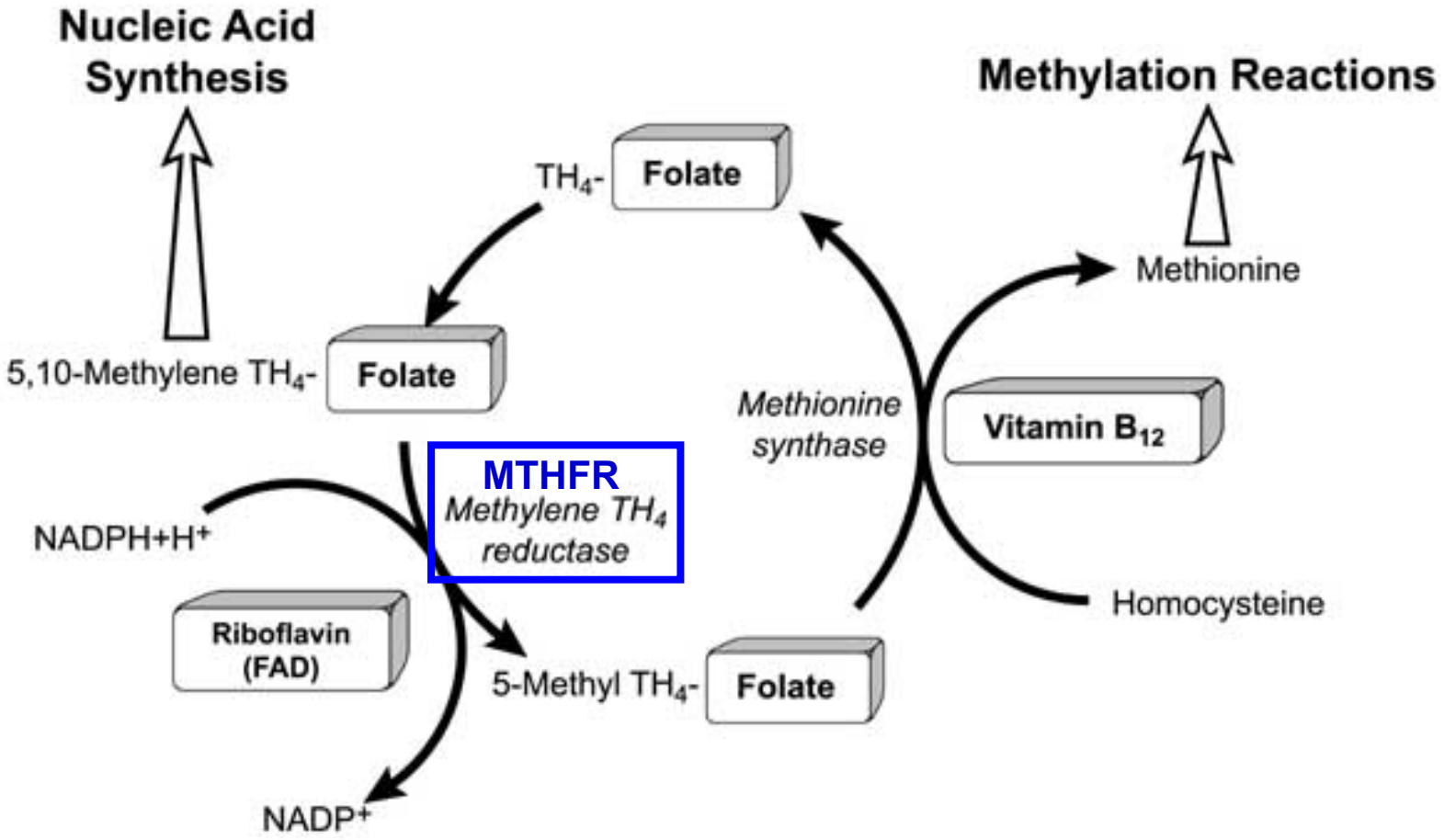
RR for high vs. low category for folate

♦ significant
◇ non-significant

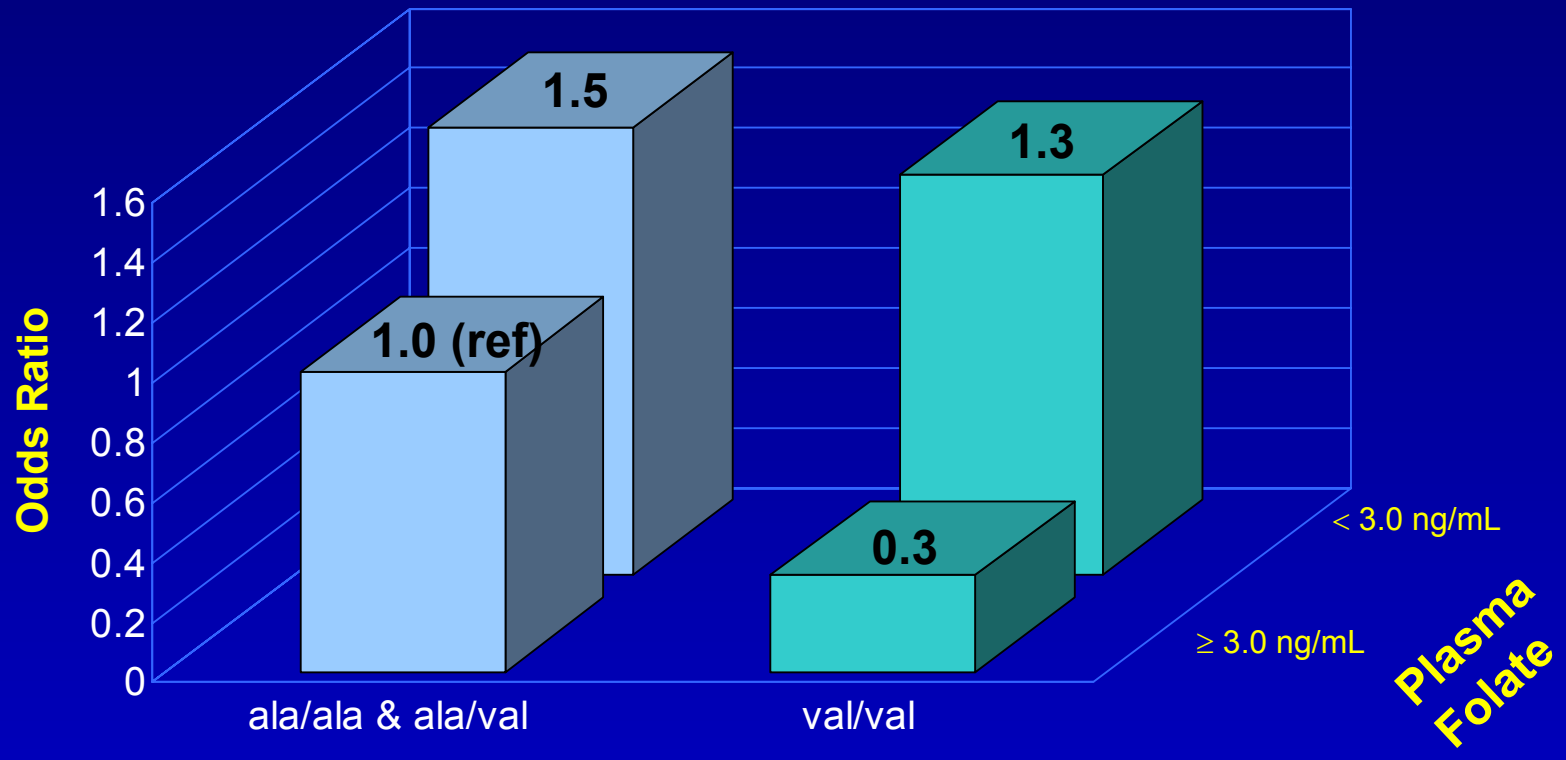
** plasma-based;
other studies dietary based

High Alcohol / Low Folate vs. Low Alcohol / High Folate



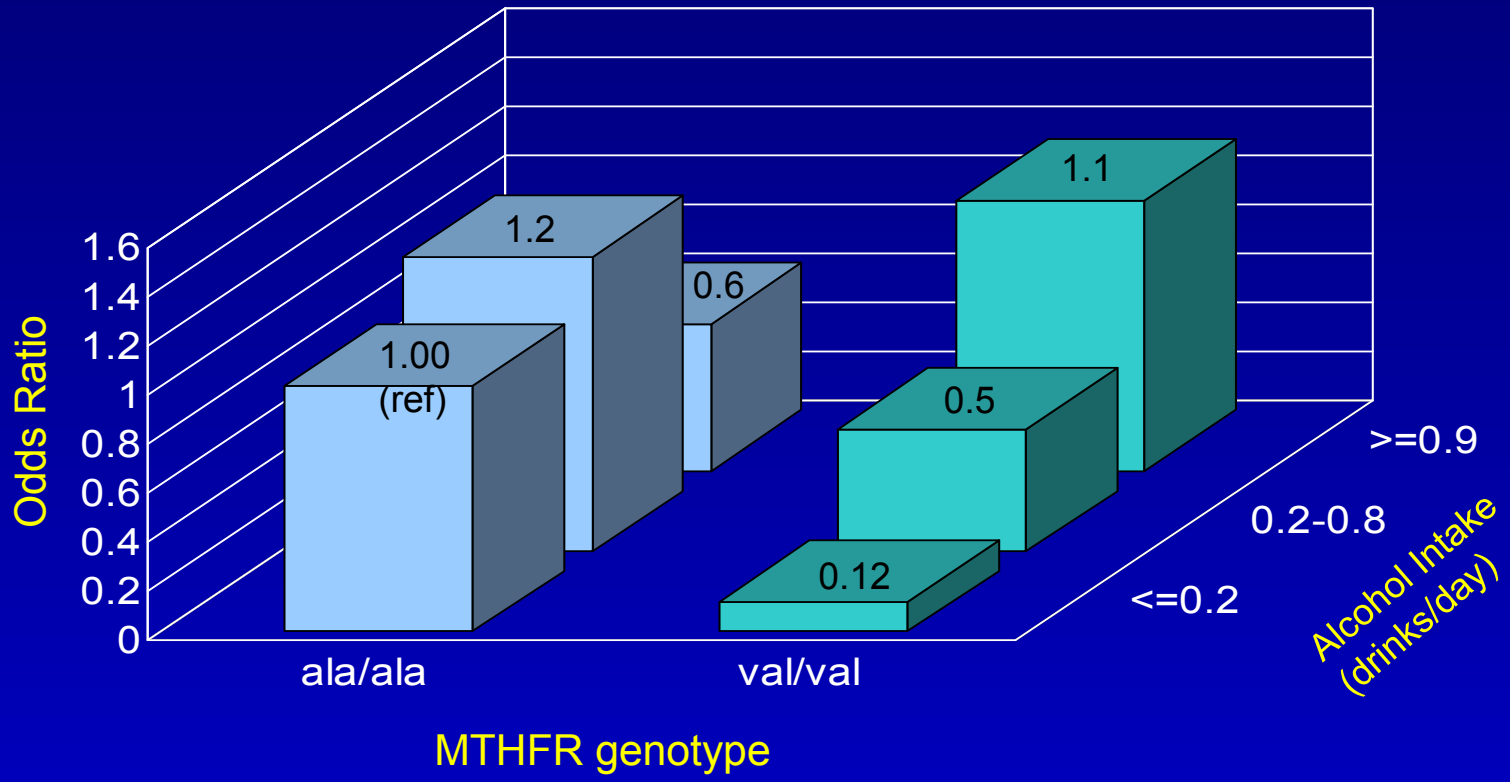

Nucleic Acid Synthesis
Methylation Reactions
TH4- Folate
5,10-Methylene TH4- Folate
Methionine
Methionine synthase
Vitamin B12
MTHFR
Methylene TH4 reductase
NADPH+H+
Riboflavin (FAD)
5-Methyl TH4- Folate
Homocysteine
NADP+

OR of Colorectal Cancer by MTHFR Genotype and Plasma Folate Status PHS



Ma et al., *Cancer Res 1997*

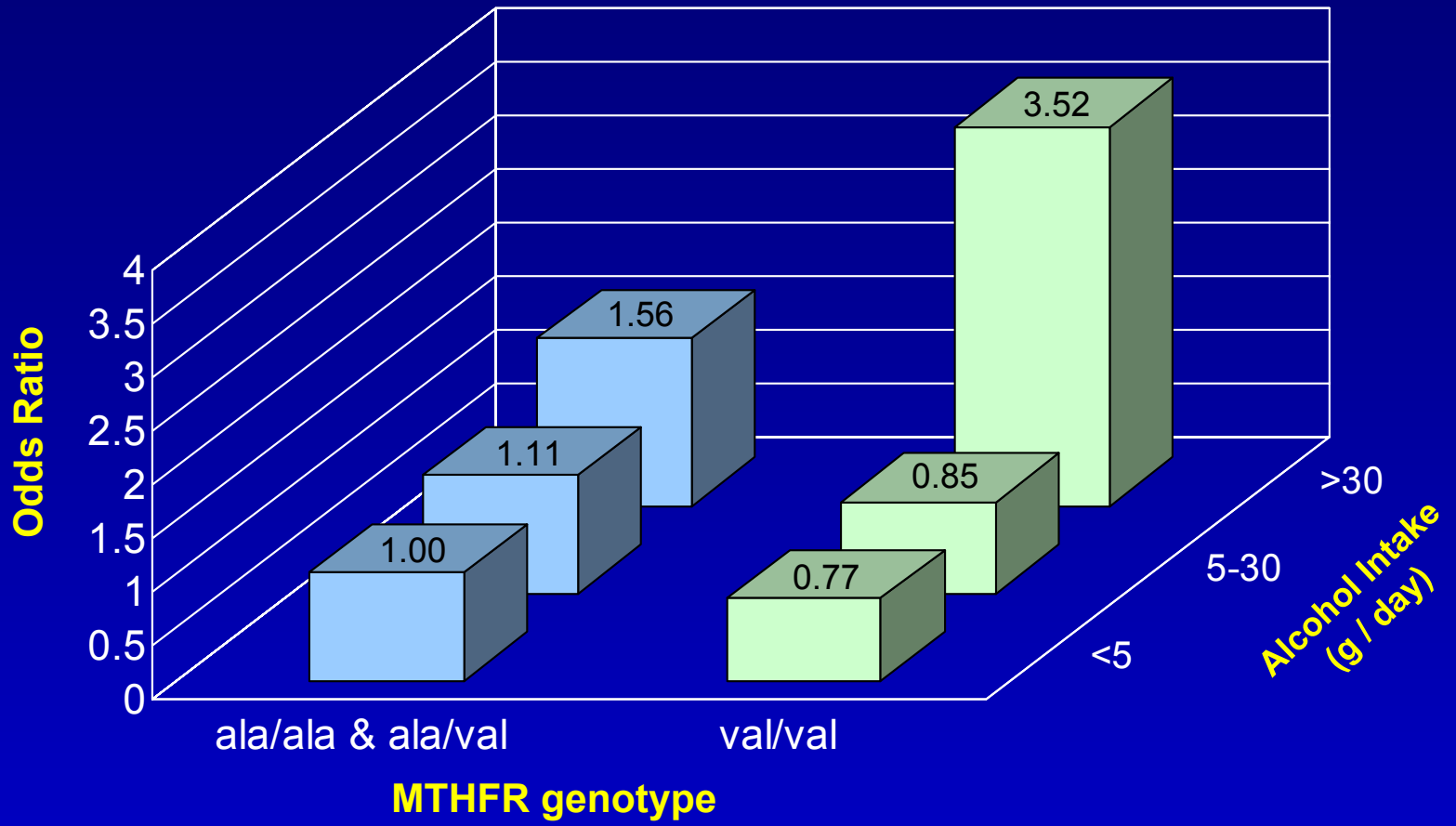
Age-adjusted OR of colorectal cancer by MTHFR genotype and alcohol intake PHS



P, interaction= 0.01

Ma et al., *Cancer Res 1997*

Multivariate OR of Colorectal Adenoma by MTHFR Genotype and Alcohol Intake HPFS

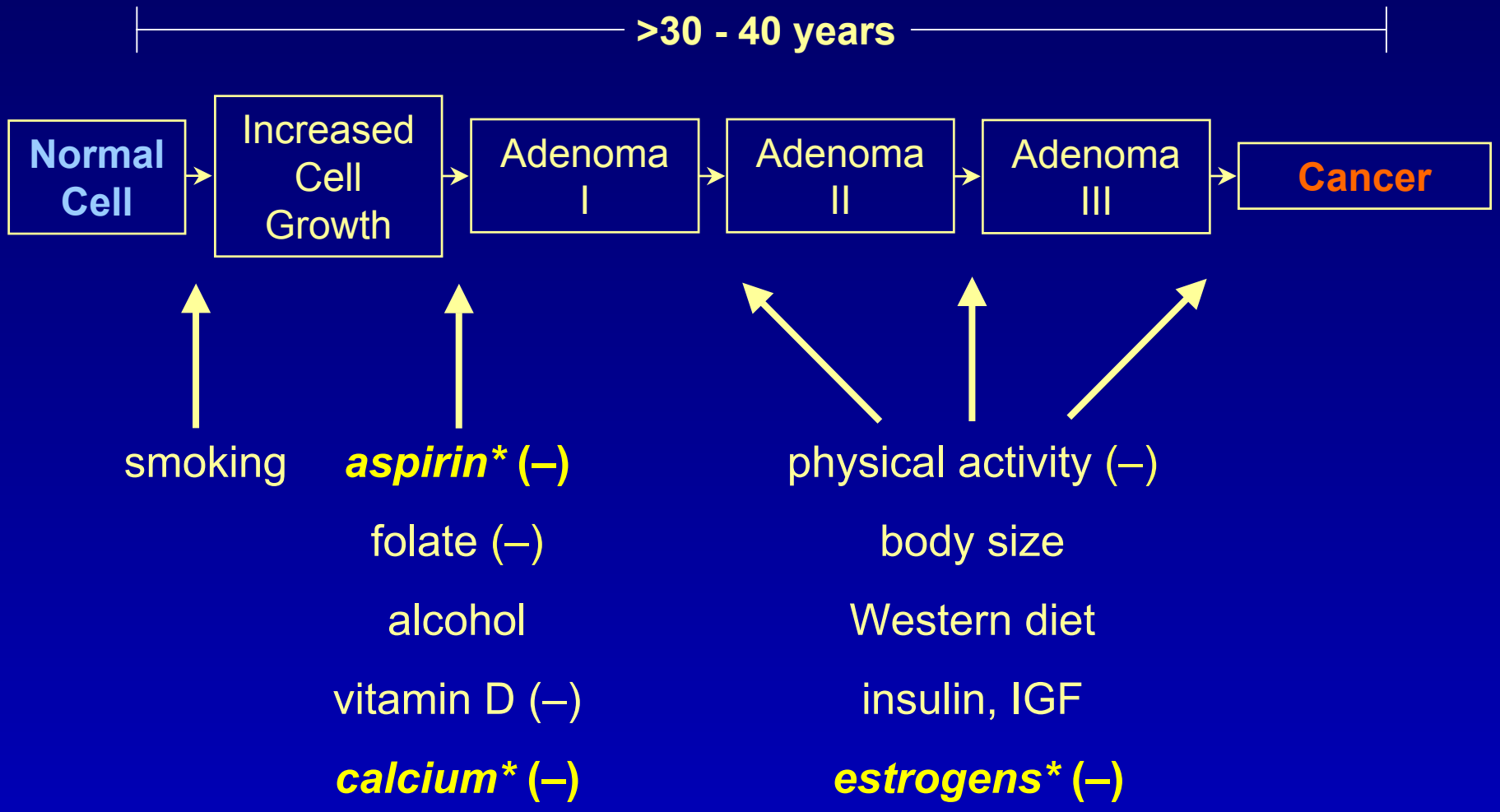


P, interaction=0.09

Giovannucci, unpublished

Summary: Epidemiologic Evidence Supporting a Role of Folate and Alcohol

- Adenoma studies; case-control and cohort studies of cancer
- Low folate status with high alcohol intake (an anti-folate) -> highest risk
- *677C→T* polymorphism of a key metabolic enzyme in MTHFR provide evidence on a role of folate in DNA synthesis and DNA methylation and tumor development
- Recent evidence suggests that vitamin B6 is also protective



*Results supported by randomized trial