Obesity, Energy Balance and Colorectal Cancer Survivorship

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Colorectal Cancer Epidemiology

- **Estimated 141,210 cases of CRC in 2011**
  - Fourth most common cancer in US
    - Third most commonly diagnosed cancer in men
    - Third most commonly diagnosed cancer in women
- **Estimated 49,380 deaths from CRC in 2011**
  - Second leading cause of cancer deaths in US

Siegel Ca Cancer J Clin 2011

Adiposity and Colorectal Cancer Risk

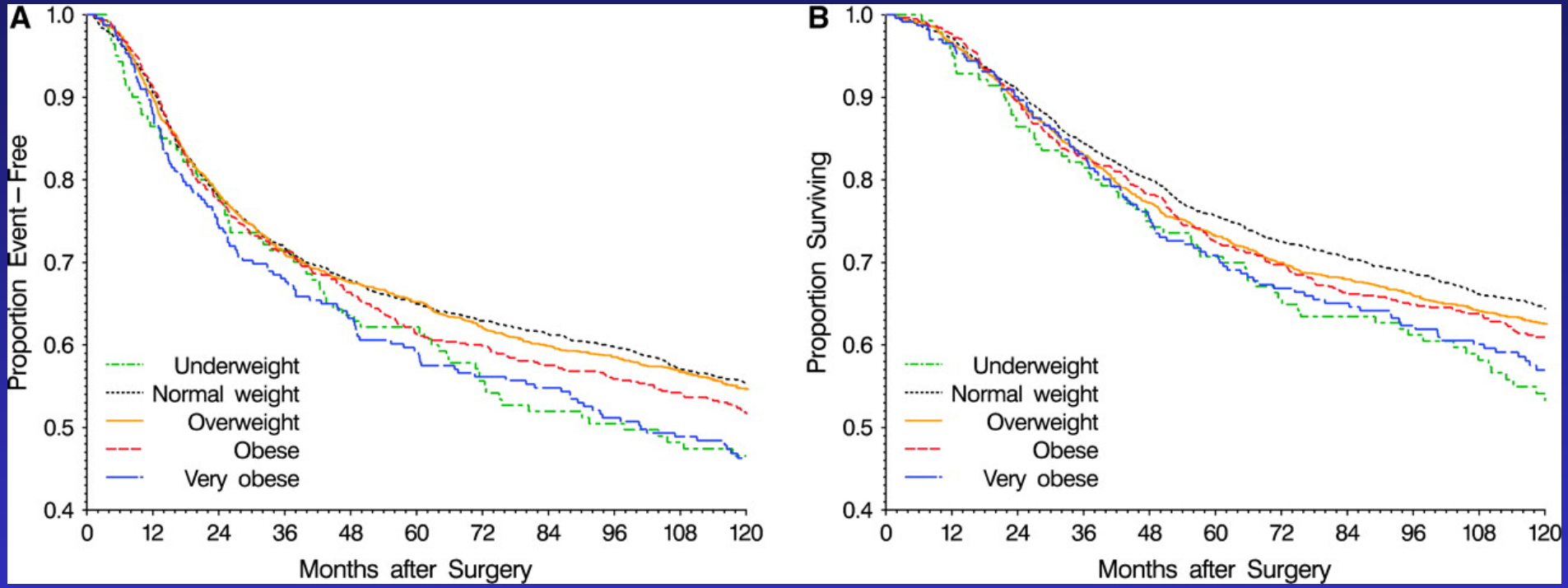
- **Meta-analysis of 28 cohort studies demonstrated 3% increased risk of colorectal cancer for every 1 kg/m2 increase in BMI**
  - **Stronger association for colon cancer than rectal cancer in most studies**

World Cancer Research Forum / AICR 2nd Expert Report on Food, Nutrition, Physical Activity and Prevention of Cancer

Adiposity and Colorectal Cancer Recurrence and Progression

- Data only starting to emerge in past 8 years
- Early stage disease
  - Micrometastases may be present and effects of obesity or other energy balance factors may impact on growth
- Advanced disease
  - Similar effects on growth and further metastatic potential

NSABP and Body Mass Index



Disease-free and overall survival by body mass index (BMI) category in 4288 patients from National Surgical Adjuvant Breast and Bowel Project randomized clinical trials for Dukes B and C colon cancer

Dignam, J. J. et al. J. Natl. Cancer Inst. 2006 98:1647-1654

Author	Years	N	Outcome	Hazard Ratio (95% CI) or P value (compared to normal weight)
Tartter	1976-1979	279	Recur Rate	P = 0.003 for above median weight
Meyerhardt	1988-1992	3759	DFS	1.11 (0.94-1.30) BMI $\geq$ 30 kg/m^2
			OS	1.11 (0.96-1.29) BMI $\geq$ 30 kg/m
Meyerhardt	1990-1992	1792 rectal	DFS	1.10 (0.91-1.32) BMI $\geq$ 30 kg/m^2
			OS	1.09 (0.90-1.33) BMI $\geq$ 30 kg/m^2
			Local Recur	1.31 (0.91-1.88) BMI $\geq$ 30 kg/m^2
Dignam	1989-1994	4288	DFS	1.06 (0.93-1.21) BMI 30-34.9 kg/m^2 1.27 (1.05-1.53) BMI $\geq$ 35 kg/m^2
Meyerhardt	1999-2001	1053	DFS	1.00 (0.72-1.40) BMI 30-34.9 kg/m^2 1.24 (0.84-1.83) BMI $\geq$ 35 kg/m^2
			OS	0.90 (0.61-1.34) BMI 30-34.9 kg/m^2 0.87 (0.54-1.42) BMI $\geq$ 35 kg/m^2
Hines	1981-2001	496	OS	0.77 (0.61-0.97) BMI $\geq$ 25 all stages 0.92 (0.65-1.30) stage I-II 0.92 (0.59-1.45) stage III 0.58 (0.37-0.90) stage IV

89803 and Change in Weight

	Adjusted Hazard ratio (95% CI)	
> 5 kg weight loss	1.39 (0.69 – 2.79)	$P_{trend} = 0.13$
2.1 – 5 kg weight loss	1.15 (0.54 – 2.44)	
+/- 2 kg change	Referent	$P_{trend} = 0.90$
2 – 4.9 kg weight gain	1.11 (0.66 – 2.06)	
> 5 kg weight gain	1.19 (0.73 – 1.94)	

Meyerhardt J Clin Oncol. 2008 Sep 1;26(25):4109-15.

Body Mass Index in Colon Cancer Patients over Past Decade

	< 21	21-24.9	25-29.9	30-34.9	≥ 35
INT-0089 (1988-92)	14 %	34 %	34 %	13 %	5 %
89803 (1999-2001)	8 %	26 %	36 %	20 %	10 %
% change in a decade	- 43%	- 24%	+ 6%	+ 54%	+ 100%

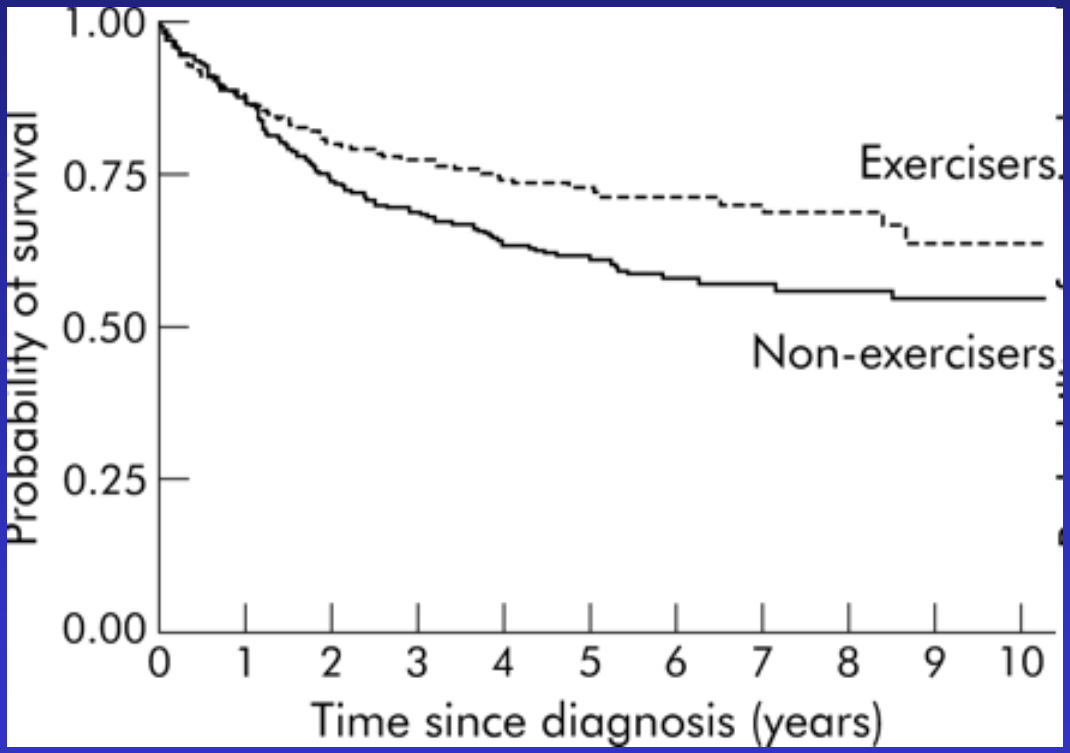
Other Energy Balance Factors and Colorectal Cancer Outcomes

Physical Activity and Colorectal Cancer

- Many studies have looked at physical activity and quality of life during treatment or beyond treatment for colorectal cancer patients
  - Most observational
  - Few intervention (single arm or different ways of intervening)
  - Only 1 RCT of exercise intervention v control specific to colorectal cancer patients – contamination of control limits conclusions

Physical Activity and Colorectal Cancer

- Cohort study from Australia of 526 colorectal cancer patients with pre-diagnosis physical activity assessment

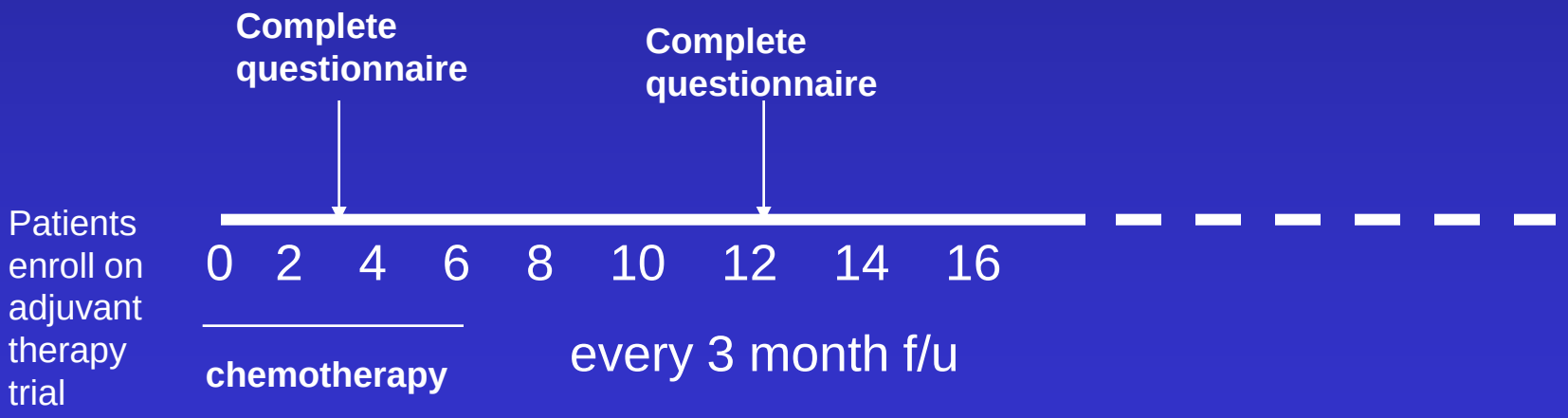


Colorectal cancer specific survival

Haydon Gut. 2006 Jan;55(1):62-7

CALGB 89803

- NCI-sponsored adjuvant therapy trial for stage III colon cancer
- Patients randomized to Roswell Park 5-FU/LV or IFL (bolus 5-FU/LV/Irinotecan)
- 1264 enrolled between 1999 and 2001



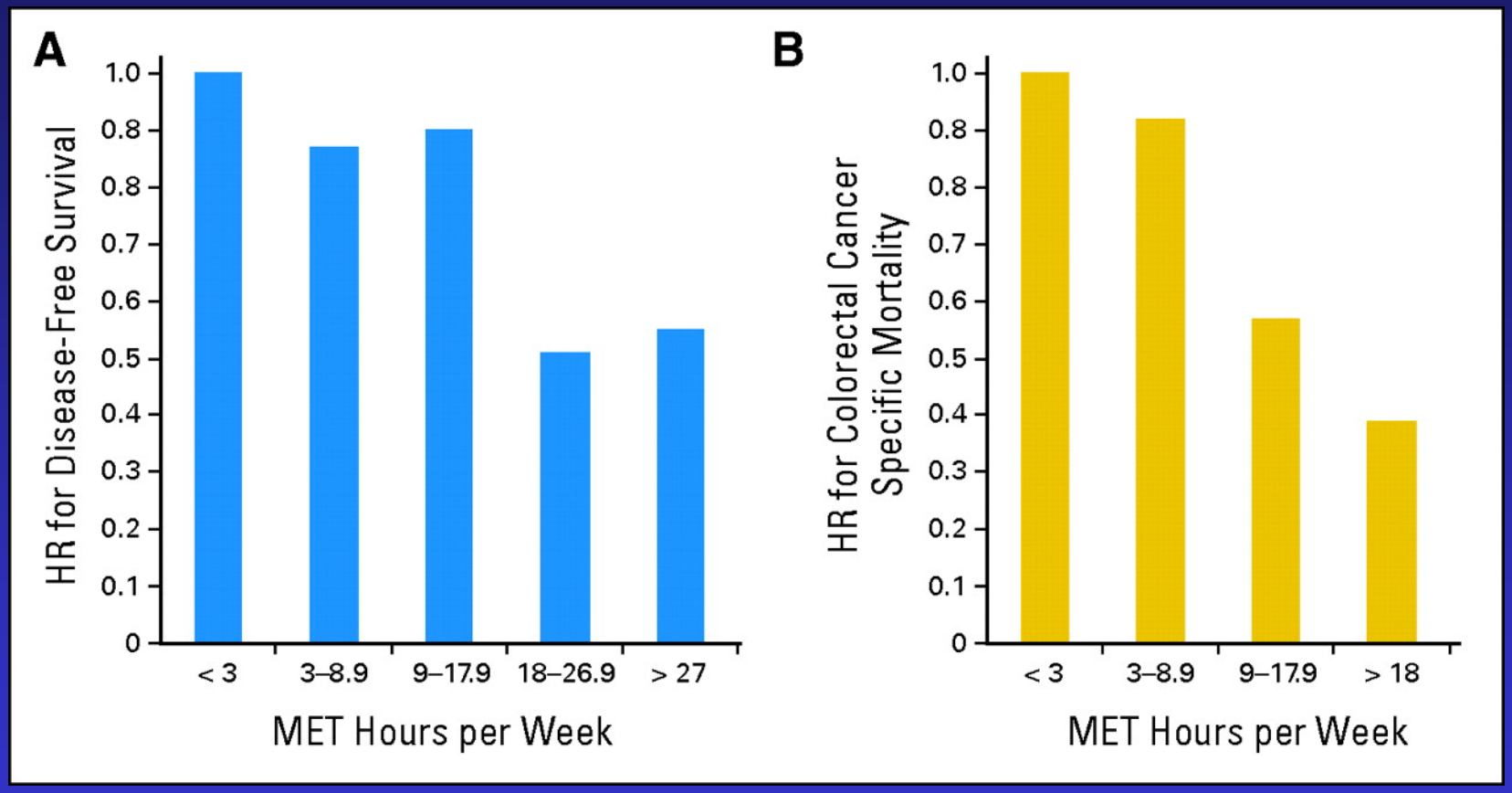
Saltz, L. B. et al. J Clin Oncol; 25:3456-3461 2007

Statistical Considerations

- Reverse causality
  - Is the exposure changing outcomes or the outcome changing exposure
  - Restrict to events at least 90 days from exposure
  - Sensitivity analyses to extend restriction to 6 months and 12 months

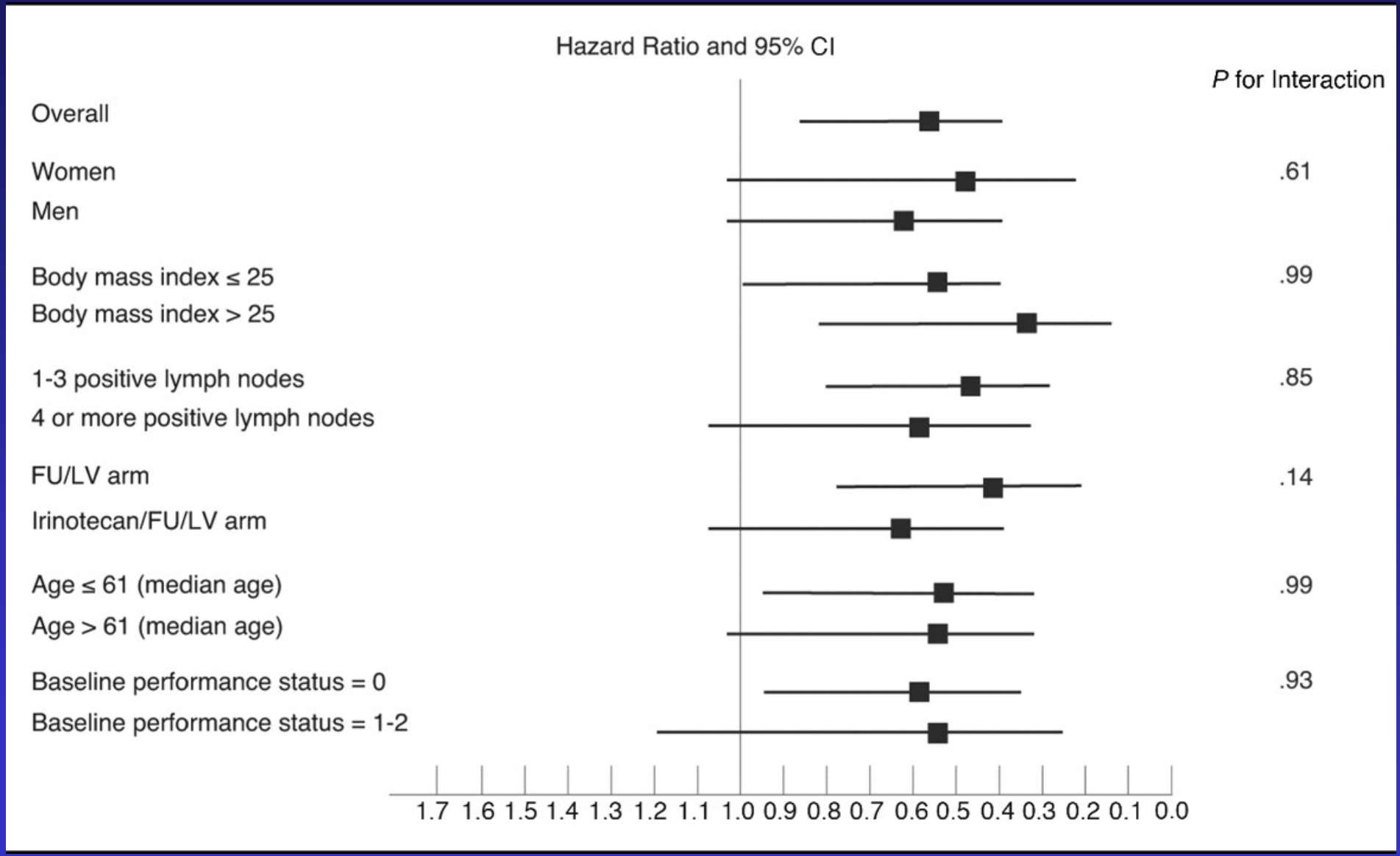
- Recall bias
  - The clock starts at time of questionnaire completion – all events are prospective beyond the exposure data
  - Limits generalizability – data speak to those that get to point of questionnaire

Physical activity after Diagnosis in Colorectal Cancer Survivors



Meyerhardt J A et al. JCO 2010;28:4066-4073

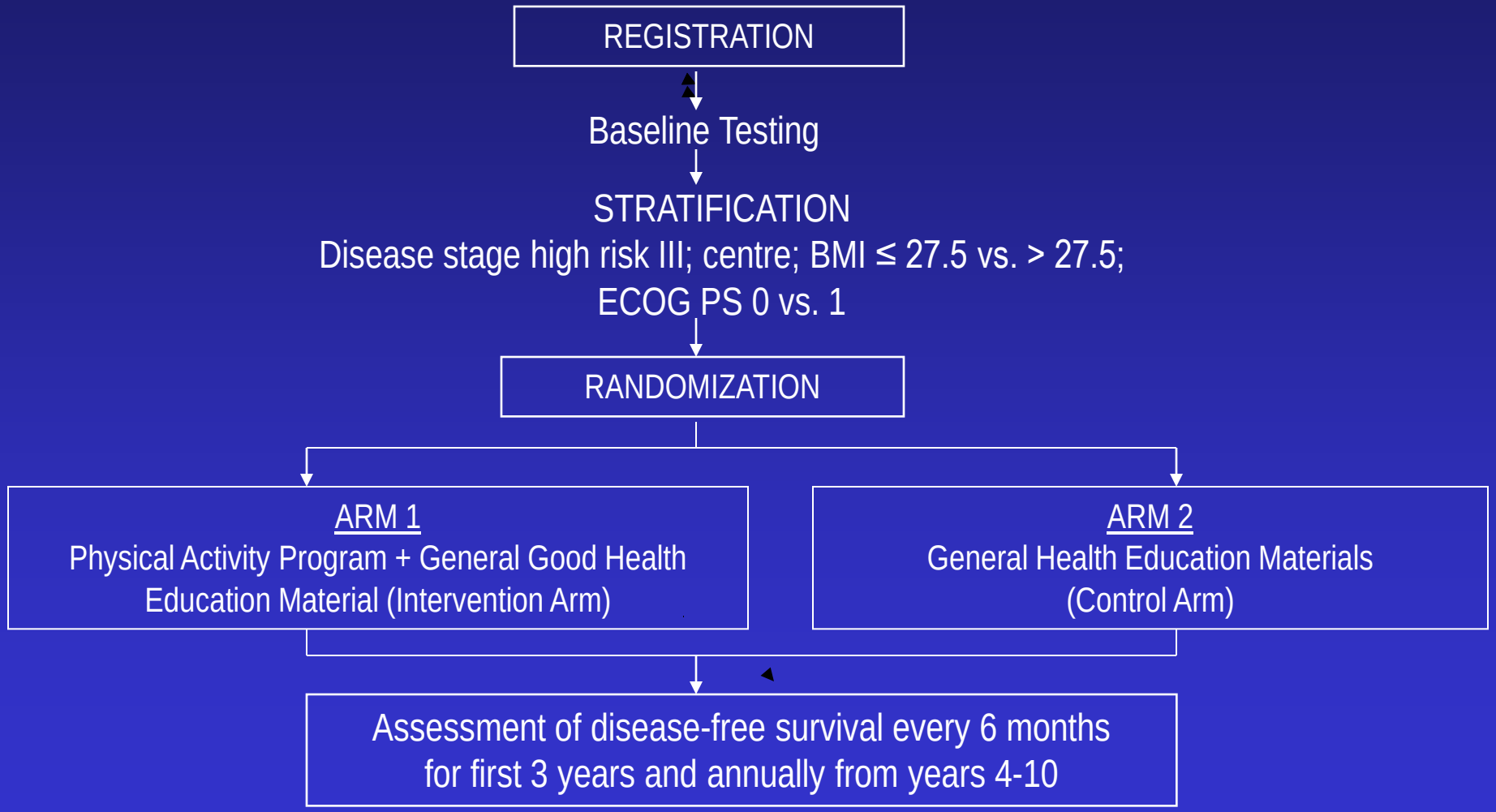
89803 and Exercise: Stratification



Meyerhardt, J. A. et al. J Clin Oncol; 24:3535-3541 2006

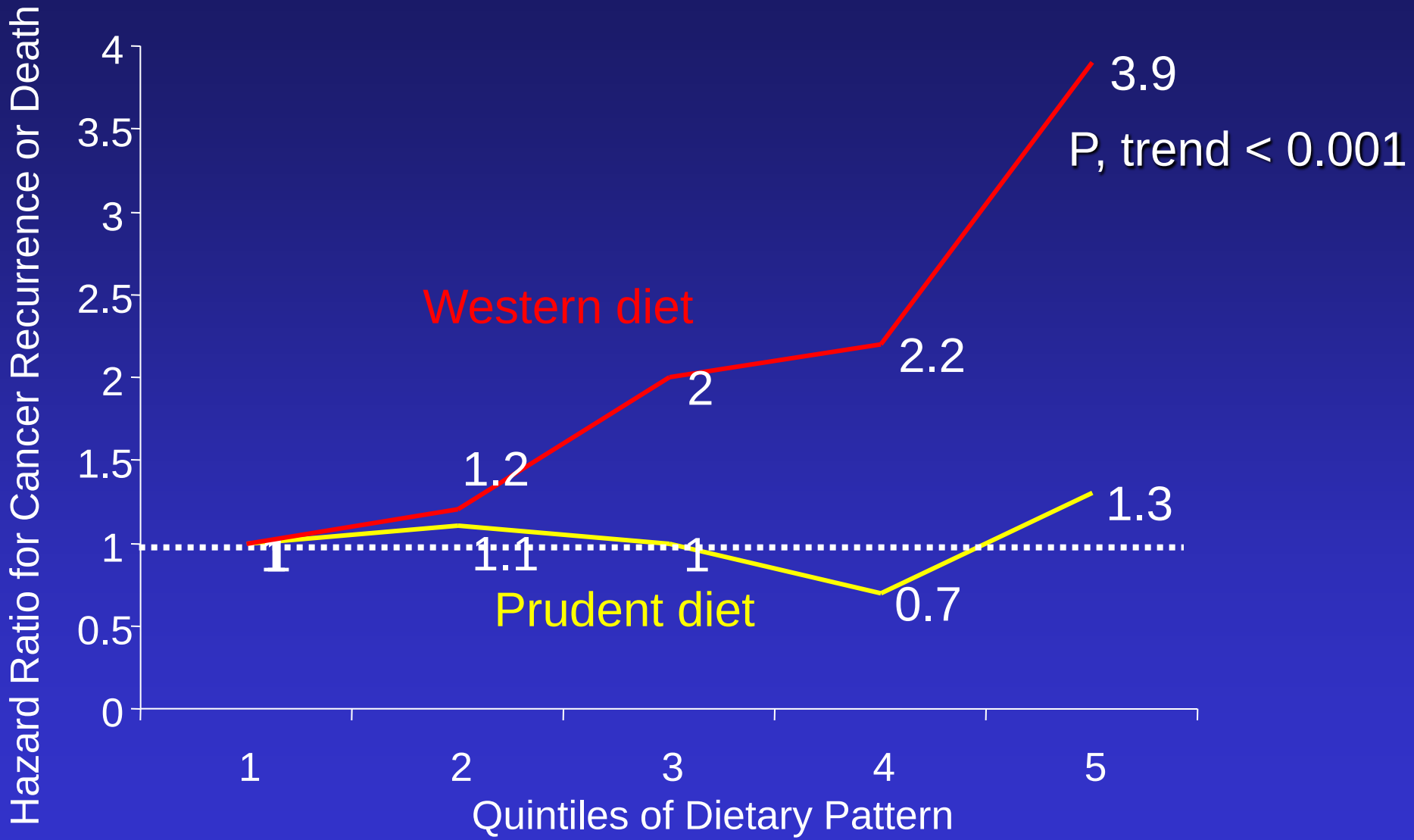
CHALLENGE: Colon Health and Life-Long Exercise Change trial

High risk Stage II or stage III colon cancer - completed adjuvant chemotherapy within 2-6 months



Courneya Curr Oncol.2008 Dec;15(6):271-8.

CALGB 89803: DFS By Dietary Pattern



Meyerhardt, J. et al. JAMA 2007298(7):754-764.

CALGB 89803: Dietary Pattern

	Mean (SD) Intake by Quintile				
	1 (n = 201)	2 (n = 202)	3 (n = 202)	4 (n = 202)	5 (n = 202)
Red meat, servings/wk	2.3 (1.5)	3.1 (1.8)	3.7 (2.1)	4.7 (2.5)	6.1 (3.0)
Processed meats, servings/wk	1.8 (1.7)	2.3 (1.8)	3.0 (2.6)	4.2 (2.9)	5.6 (4.1)
Refined grains, servings/d	2.0 (1.3)	2.8 (1.6)	3.5 (1.8)	4.2 (2.2)	5.8 (2.7)
Dessert, servings/d	0.7 (0.6)	1.1 (0.8)	1.3 (0.9)	1.6 (1.0)	2.5 (1.6)
Total fat, g/d	69 (15)	72 (18)	73 (13)	77 (15)	80 (13)

[a] Values are rounded to nearest 0.5. The median total servings of poultry and fish were similar across each quintile (approximately 2 servings per week of poultry and 1.5 servings per week of fish).

Meyerhardt, J. et al. JAMA 2007;298:2263-a.

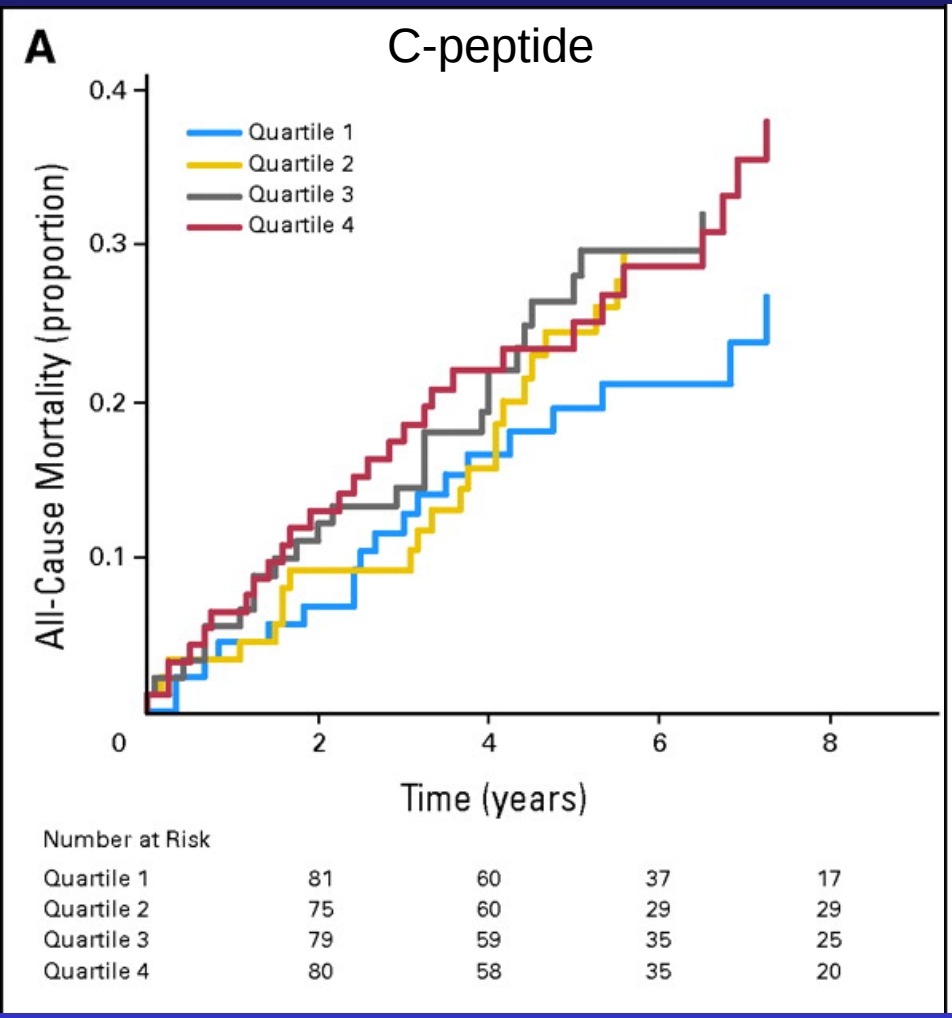
Molecular Markers of Hyperinsulinemia and Colorectal Cancer Outcomes

Insulin-related Growth Factors and Outcomes

- Nested case-control of 373 patients nonmetastatic colorectal cancer 1991-2004
- Prediagnosis circulating C-peptide, insulin-like growth factor-I (IGF-I), IGFBP-1, and IGFBP-3
- Colorectal cancer-specific mortality and overall mortality

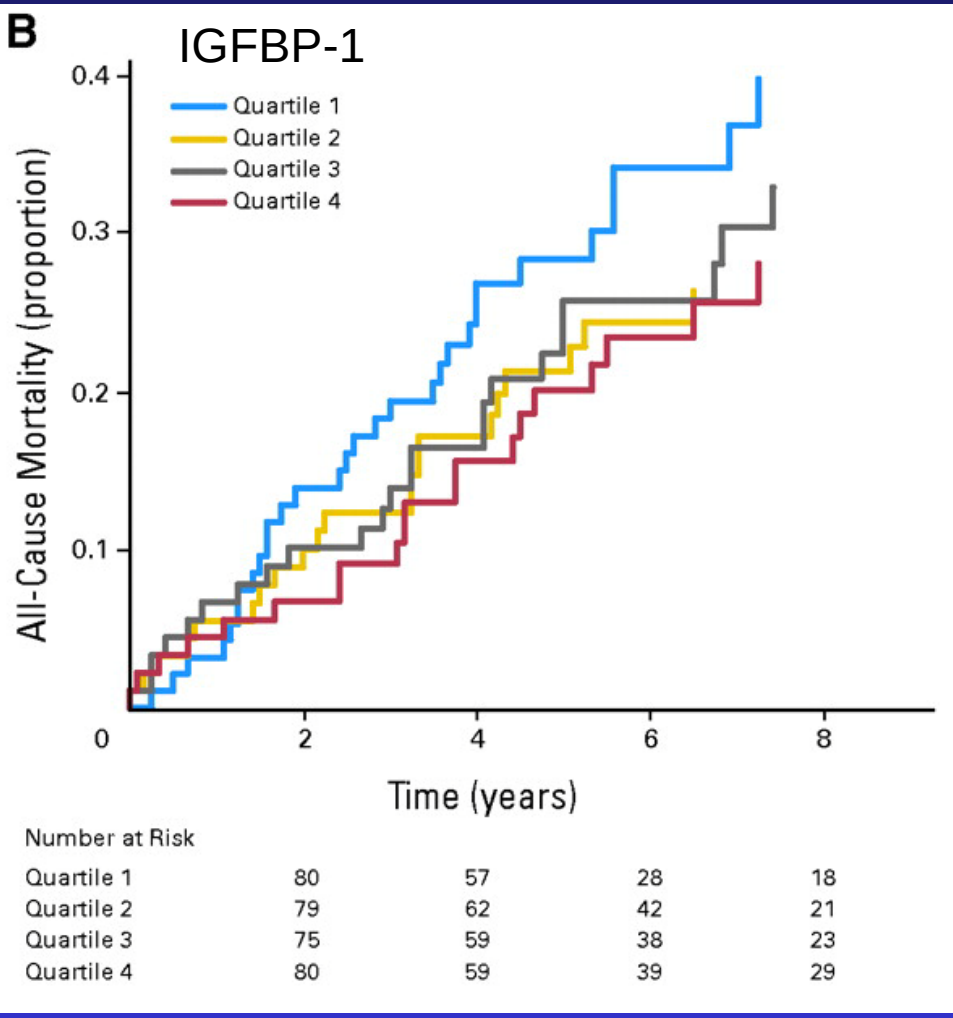
Wolpin B M et al. JCO 2009;27:176-185

Insulin-related Growth Factors and Outcomes



Number at Risk

Quartile 1	81	60	37	17
Quartile 2	75	60	29	29
Quartile 3	79	59	35	25
Quartile 4	80	58	35	20

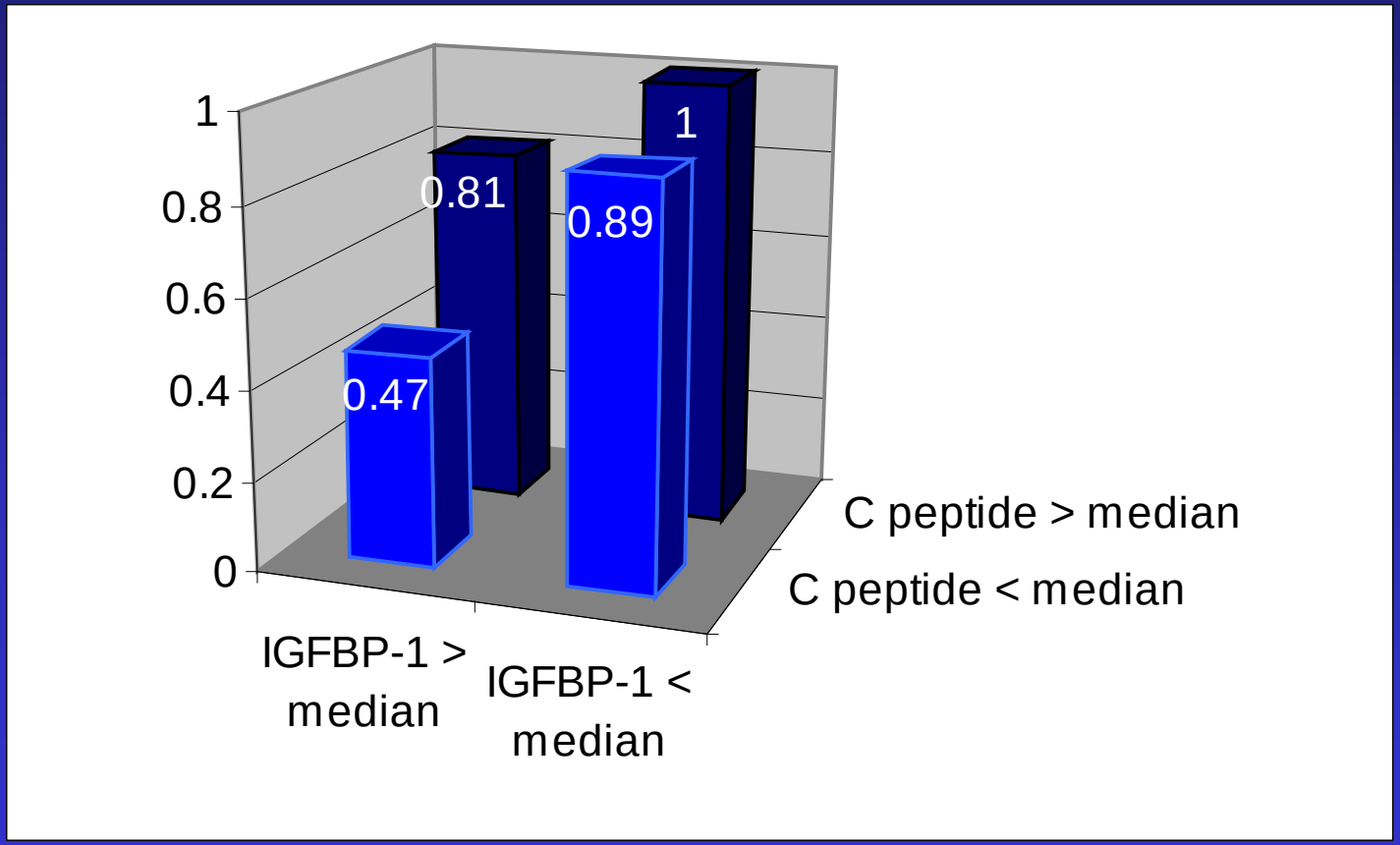


Number at Risk

Quartile 1	80	57	28	18
Quartile 2	79	62	42	21
Quartile 3	75	59	38	23
Quartile 4	80	59	39	29

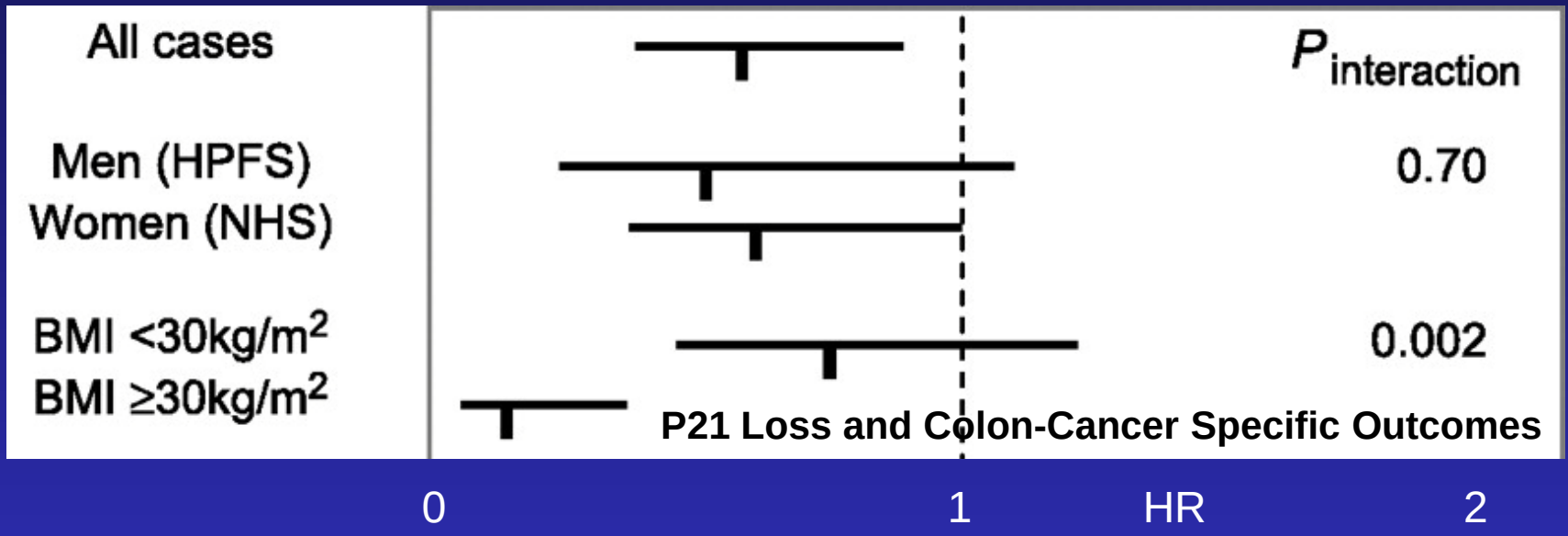
Wolpin B M et al. JCO 2009;27:176-185

Insulin-related Growth Factors and Outcomes



Wolpin B M et al. JCO 2009;27:176-185

P21 Expression/Loss Influencing Association Between BMI and Outcomes



	Colon cancer–specific mortality		
	No. of deaths/cases	Stage-matched HR (95% CI)	Multivariate HR (95% CI)
p21-Expressing cases			
BMI < 30 kg/m^2	28/113	1 (reference)	1 (reference)
BMI ≥ 30 kg/m^2	8/20	7.24 (3.09-17.0)	5.85 (2.28-15.0)
p21-Lost cases			
BMI < 30 kg/m^2	99/400	1 (reference)	1 (reference)
BMI ≥ 30 kg/m^2	18/89	1.08 (0.64-1.80)	1.05 (0.60-1.83)
P for interaction (p21 and BMI)		0.0002	0.002

Ogino
CEBP 3009

Cumulative Incidence Curves of Colorectal Cancer and Overall Mortality for Level of Physical Activity by CTNNB1 (b catenin) Status

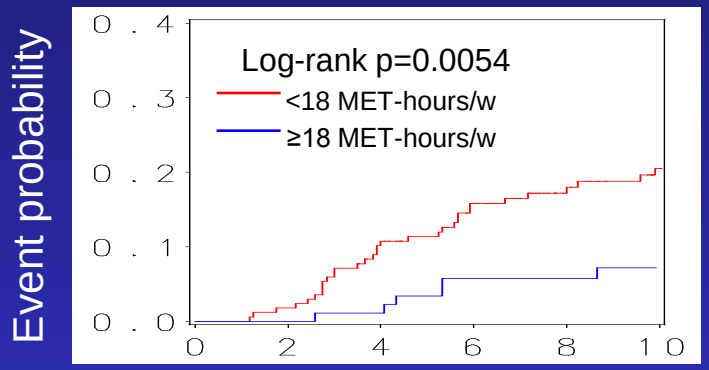
Main Effect Positive Nuclear CTNNB1 Adjusted HR

0.24

(0.12-0.49)

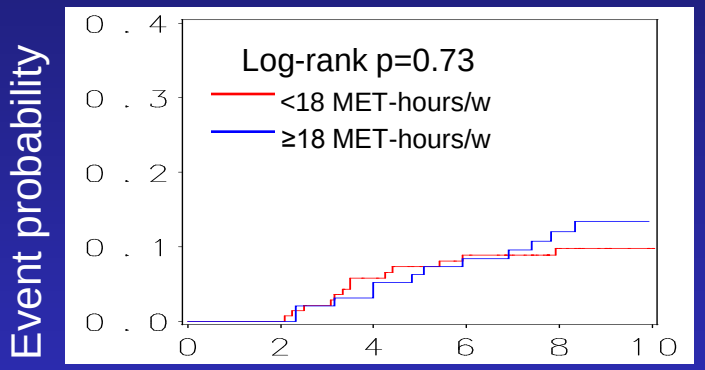
A

All stage I-III cases with nuclear CTNNB1(-)

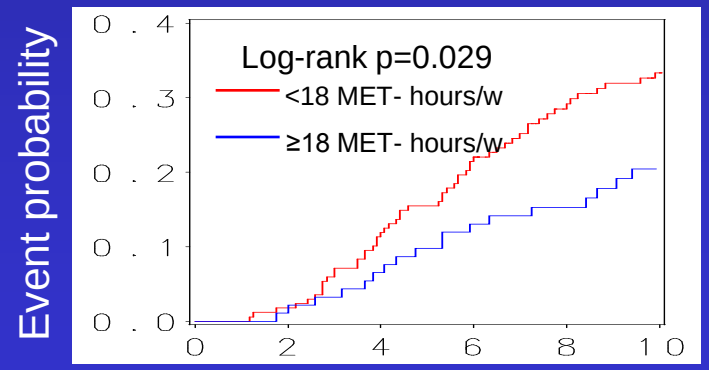


C

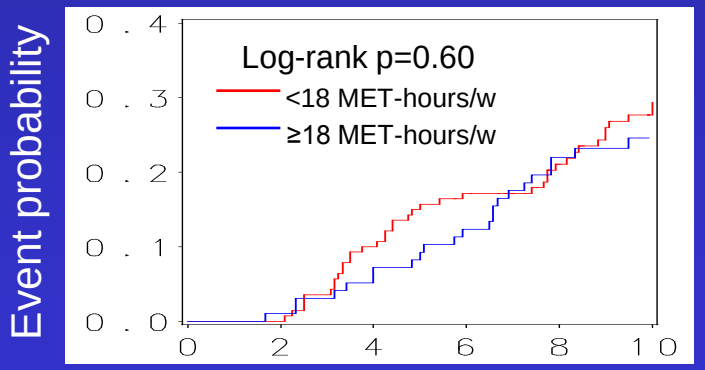
All stage I-III cases with nuclear CTNNB1(+)



B



D



Morikawa et al JAMA 2011

Where Do We Go From Here – Energy Balance Factors and Tertiary Prevention / Survivorship

- Are observational data enough?
- What if we do a randomized trial of better diet or increased physical activity and result is negative – what's the message?
- Survivorship raises issues of addressing other diseases down the road
- Better biomarkers to study effects – decrease sample size?
- Single exposure v multiple exposure intervention