

CAPP 3 ??

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Possibilities for CAPP 3

What do Previous Trials Suggest?

- NSAIDs
- Antioxidants
- Other micronutrients
- Others

DOUBLE BLIND STUDY

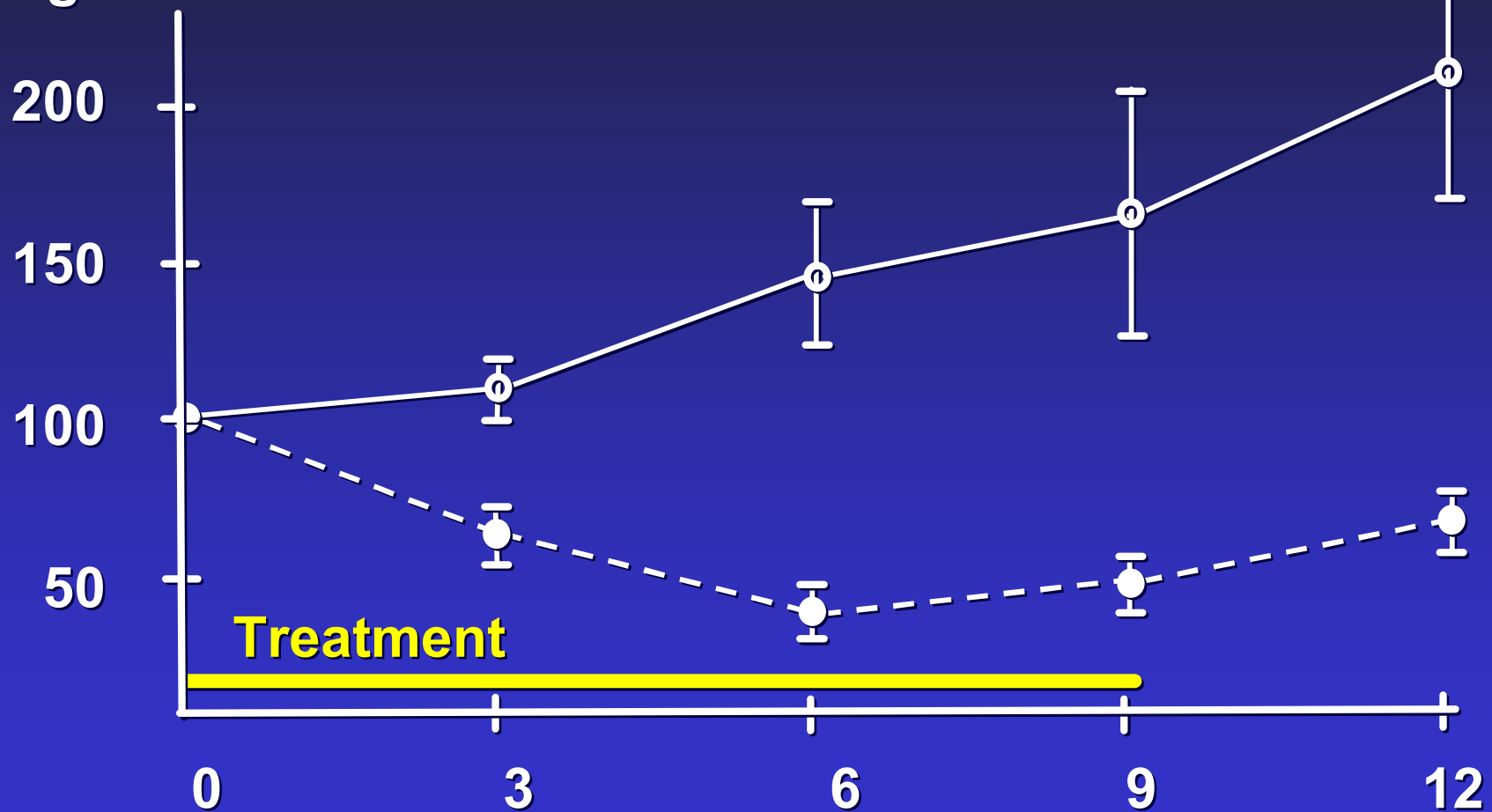


NSAIDS



Sulindac in FAP

polyps
% change

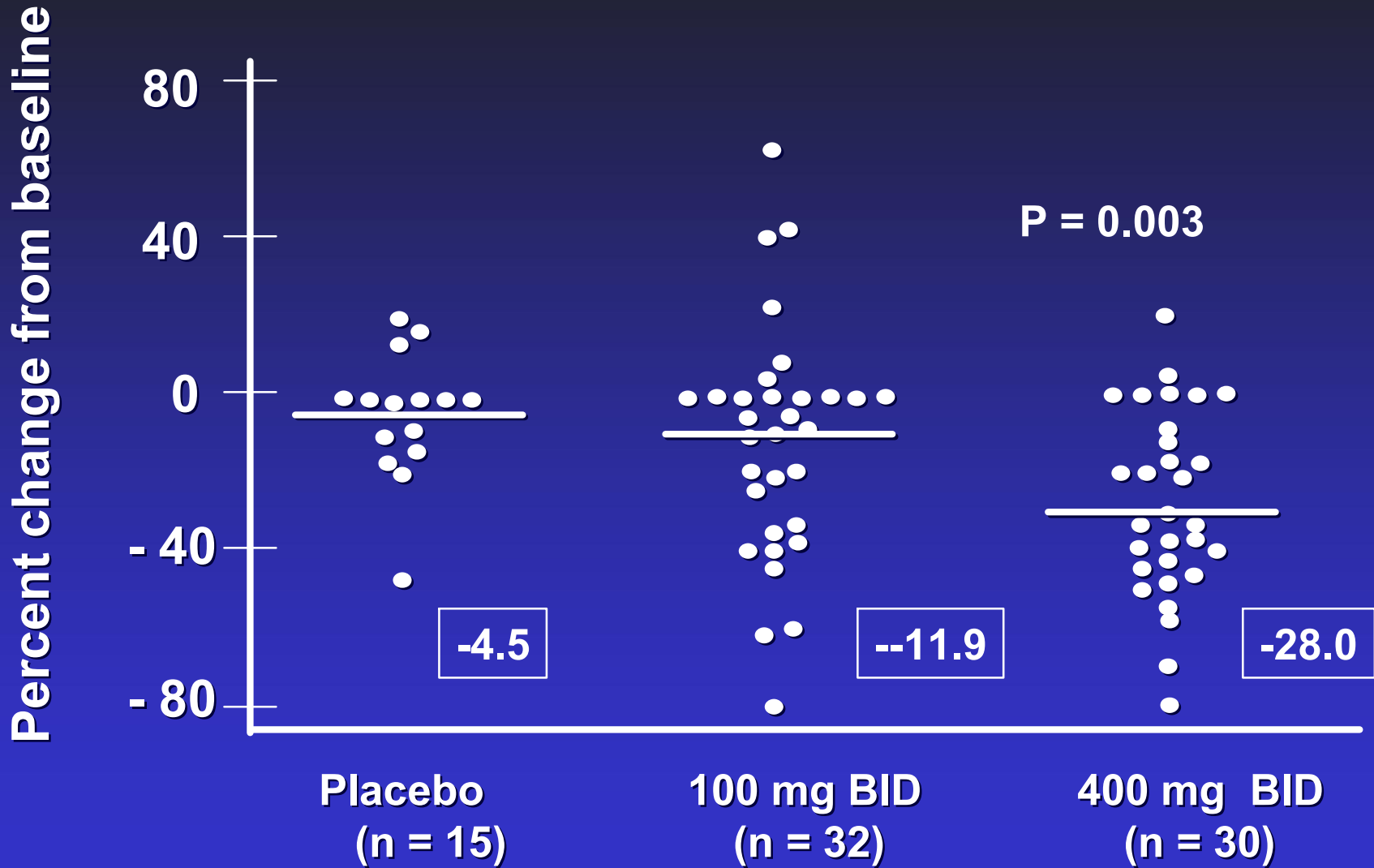


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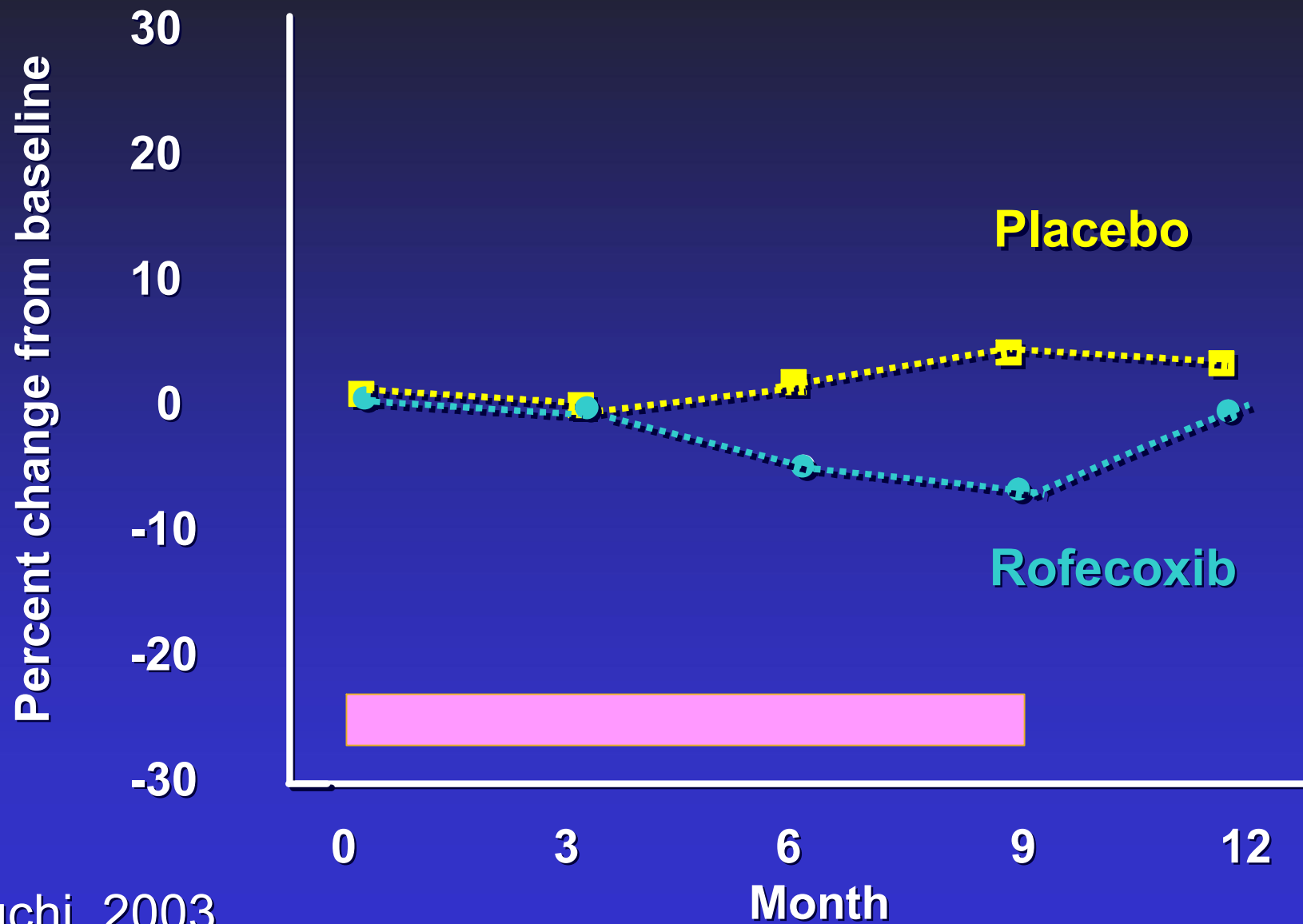
Giardiello et al, 1993

Time (months)

Celecoxib in FAP



Rofecoxib in FAP



Higuchi, 2003

Vioxx and Colorectal Adenomas

APPROVe Trial Efficacy Analysis

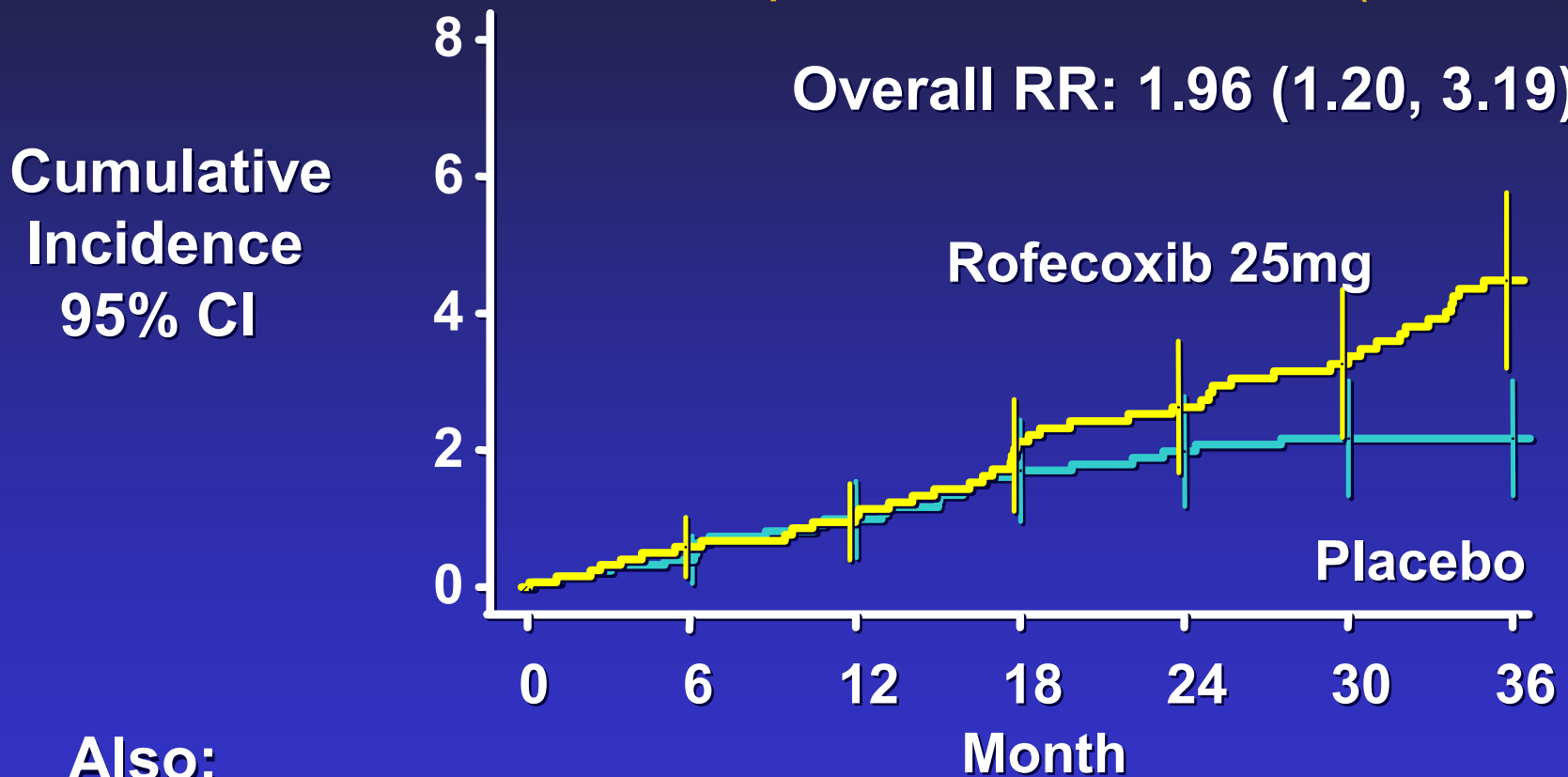
Rofecoxib RR* All Subjects

All Adenomas	0.76 (0.69-0.83)
Advanced Adenomas	0.75 (0.61-0.93)

*unadjusted

Confirmed Thrombotic Events

Kaplan-Meier Estimates (95% CI)

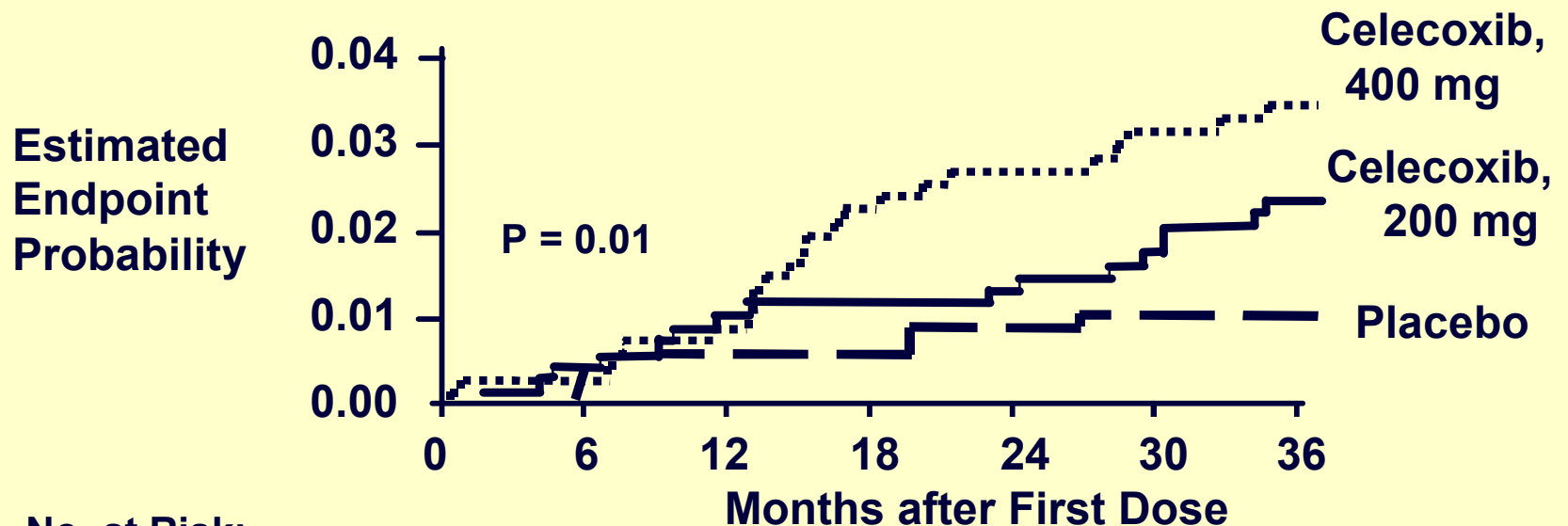


Also:

RR CHF/PE/Cardiac Failure 4.29 (1.43, 12.8)

Celecoxib & Cardiovascular Disease

Composite Endpoint



No. at Risk:

Celecoxib 400 mg	671	576
Celecoxib 200 mg	685	595
Placebo	679	585

From Solomon et al, 2005

Aspirin & Colorectal Neoplasia

Adenoma Trials



	<u>Dose</u>	<u>Duration</u>	<u>Relative Risk</u>
Baron	81 mg	33 mos	0.83 (0.70 - 0.98)
	325 mg		0.95 (0.80 - 1.12)
Sandler	325 mg	31 mos	0.65 (0.46 - 0.91)*
Ben'zig	160/300 mg	1 yr	0.73 (0.52 - 1.04)

*Cancer patients

Advanced adenomas:

81 mg	0.58 (0.37-0.90)
325 mg	0.83 (0.55-1.23)

Antioxidants



β -Carotene & Cardiovascular Dz

Overview of Large Trials

	<u>Dose</u>	<u>MI</u>	<u>Stroke</u>	<u>Fatal CVD</u>
ATBC	20 mg/d	+11%	+ 20%	
Physicians'	50 mg/qod	- 4%	- 4%	+ 9%
CARET	30 mg/d **			+ 26%

** with retinol

β-Carotene and Mortality

Overview of Large Trials

	<u>Dose</u>	<u>Duration</u>	<u>Relative Risk (CI)</u>
ATBC	20 mg/D	6 yrs	1.1 (1.0 -1.2)
Physicians	50 mg QOD	4 yrs	1.0 (0.9 -1.1)
CARET	30 mg/D*	12 yrs	1.2 (1.0 -1.4)

* with retinol

β -Carotene & Colorectal Neoplasia

Adenoma Trials



	<u>Dose</u>	<u>N</u>	<u>Duration</u>	<u>RR</u>
Greenberg	25 mg	864	4 years	1.0 (0.9-1.2)
Kikendall	15 mg	262	1.5 years	no effect
MacLennan	20 mg	424	2-4 years	1.4 (0.8-2.3)

<u>Non-drinker</u>	<u>Drinker</u>	<u>p</u>
0.7 (0.5-1.0)	1.2 (0.9-1.4)	0.02
<u>Non-smoker</u>	<u>Smoker</u>	<u>p</u>
0.9 (0.8-1.2)	1.4 (1.1-2.0)	0.02

Antioxidants and Bowel Cancer

Very Large Trials

	<u>Dose</u>	<u>N Cases</u>	<u>Relative Risk</u>
β-Carotene			
ATBC	20 mg/d	135	1.05 (0.75-1.47)
CARET	30 mg ^{**} /d	106	1.02 (0.70-1.50)
Physicians'	50 mg qod	341	~0.96
α-Tocopherol			
ATBC	50 mg/d	135	0.78 (0.55-1.09)

^{**}with retinol

Antioxidants & Colorectal Neoplasia

Vitamins C/E Adenoma Trials

- Sporadic: Two negative vitamin C/E trials
- FAP: one suggestive vitamin C trial
one negative vitamin C/E trial

Selenium Chemoprevention?

Skin Cancer Trial

	<u>N</u>	<u>Selenium</u>	<u>RR</u>
Squamous Ca	409	1.14 (0.93 - 1.39)	
Basal Cell Ca	727	1.10 (0.95 - 1.28)	
Lung Ca	40	0.56 (0.31 - 1.01)	
Prostate Ca	48	0.35 (0.18 - 0.65)	
Colorectal Ca	27	0.39 (0.17 - 0.90)	

1312 Patients: hx of non-melanoma skin Ca
200 μ g Selenium vs. placebo
Mean 4.5 year F/U

Other Micronutrients

Calcium & Colorectal Neoplasia

Trials:

<u>Dose</u>	<u>Duration</u>	<u>Relative Risk</u>
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Calcium Polyp Prevention Study

1200 mg	4 yrs	0.81 (0.55-0.98)
	advanced histology:	0.65 (0.46-0.93)

European Trial

2000 mg	3 yrs	0.75 (0.43-1.29)
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Calcium Polyp Prevention Study

Interactions with Vitamin D

<u>Serum 25-OH Vit D</u>	<u>Risk Ratio</u>
Below Median	1.06 (0.88-1.27)
Above Median	0.73 (0.59-0.91)

interaction $p = 0.01$

Folate & Colorectal Adenomas

Aspirin-Folate Polyp Prevention Study

Two Surveillance cycles completed

First three years:

all adenomas	1.04 (0.90 -1.20)
advanced adenomas	1.31 (0.90 -1.89)

Next surveillance cycle:

adenoma multiplicity	1.44 (1.03 - 2.02)
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Other Possibilities

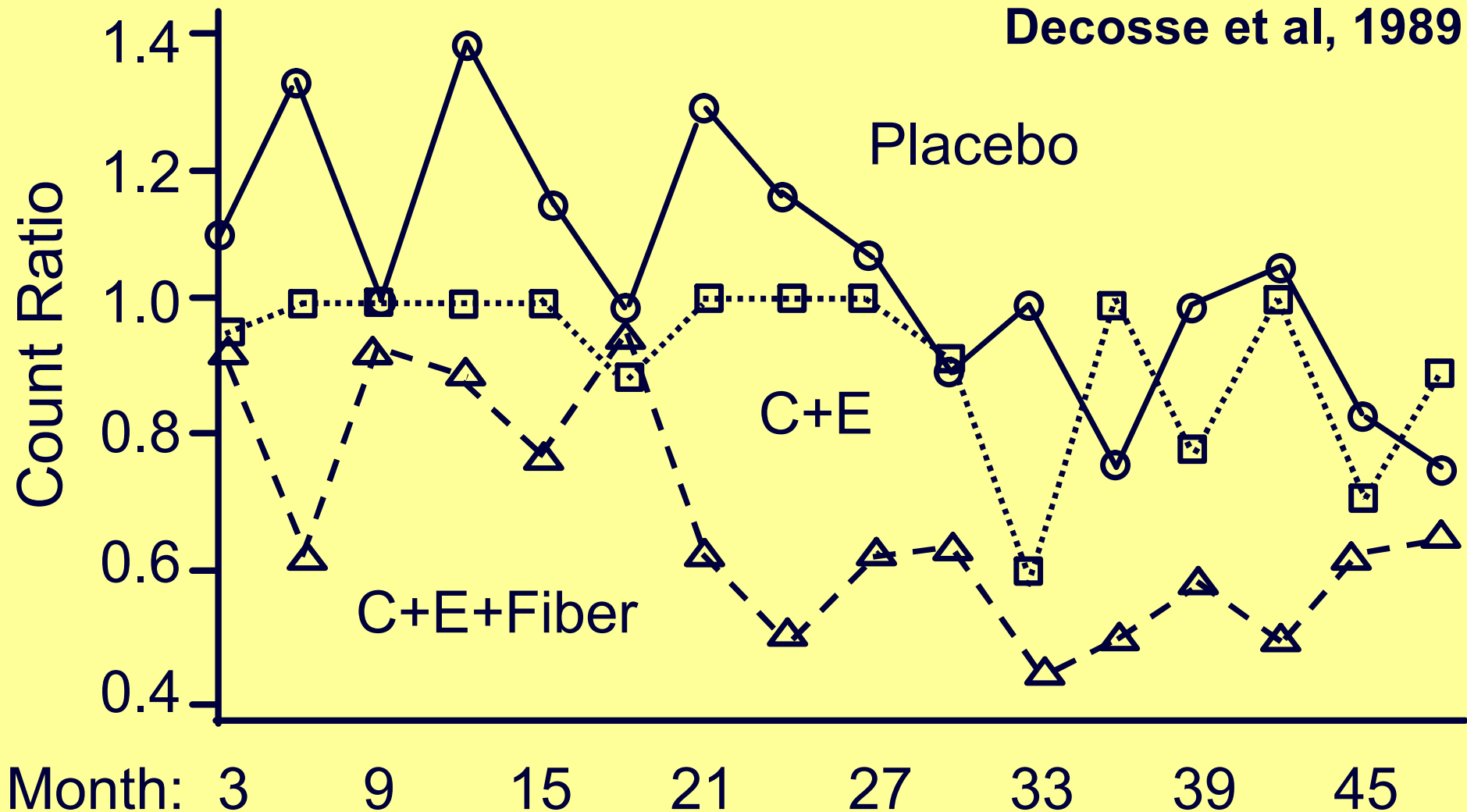
Fiber Chemoprevention

Polyp Prevention Studies

	Dose	N	Duration	RR
Cereal fiber				
MacLennan	25 g	411	4 yrs	1.5 (0.9 - 2.5)
Alberts	13.5 g	1303	3 yrs	0.9 (0.7 - 1.1)
Ispaghula husk (Psyllium)				
Bonithon-Kopp	3.5 g	665	3 yrs	1.6 (1.0 - 2.8)
Resistant starch (FAP)				
Burns	30 g	133	1+ yrs	no effect

FAP: Vit C+E, Cereal Fiber

58 patients, 4 years



Ursodeoxycholic Acid

New

	<u>N</u>	<u>Time</u>	<u>Result</u>
Larson	594	1 yr	no effect
Alberts	1285	4 yrs	no effect
Pardi	52	6+ yrs	74% ↓ p = 0.049

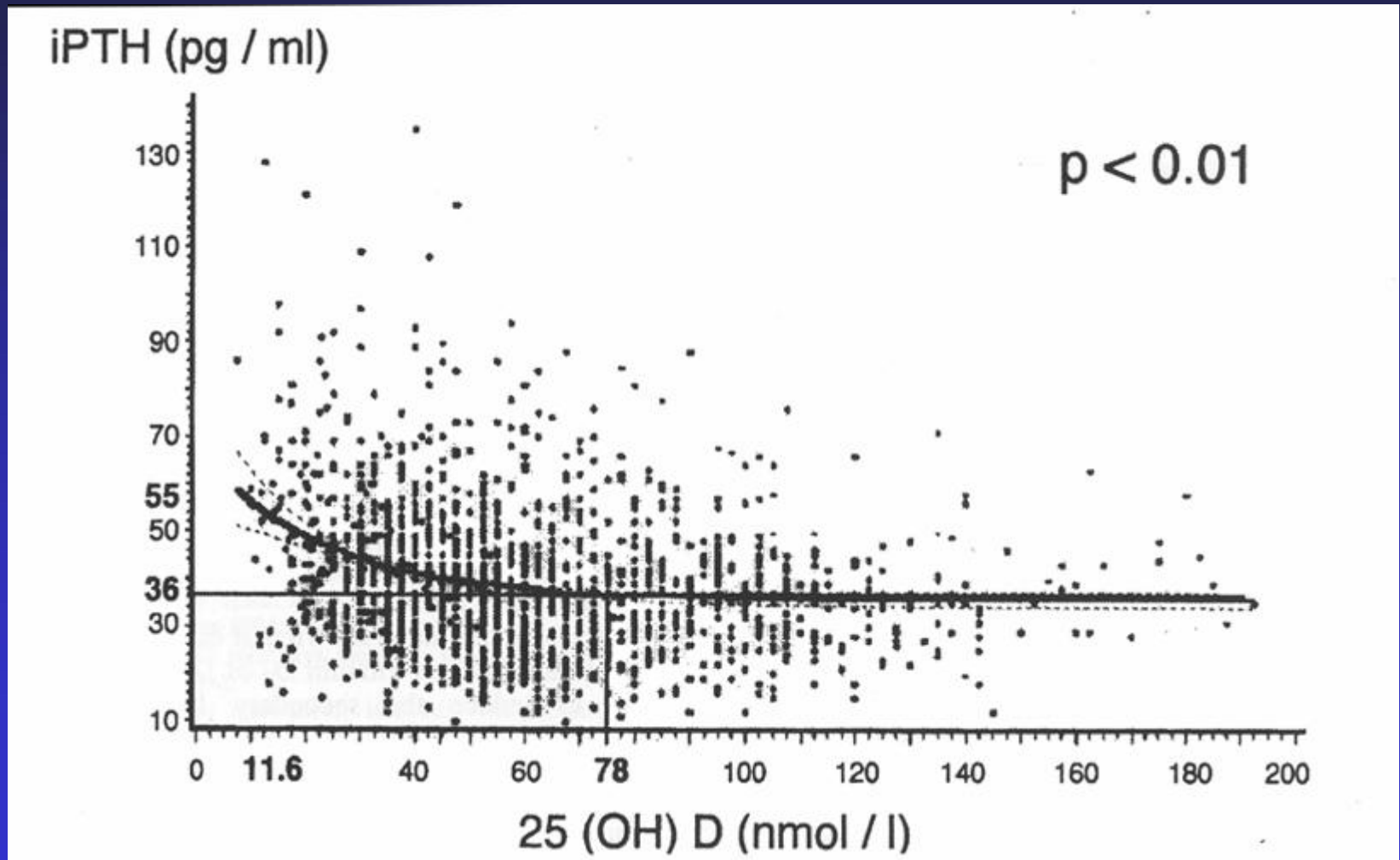
(ulcerative colitis + sclerosing cholangitis)

CAPP 3 Proposal

Calcium/Vit D \pm Statin

- Ca, Vit D: safe, “proven”
- Statins: sexy, new

Vitamin D & PTH Suppression

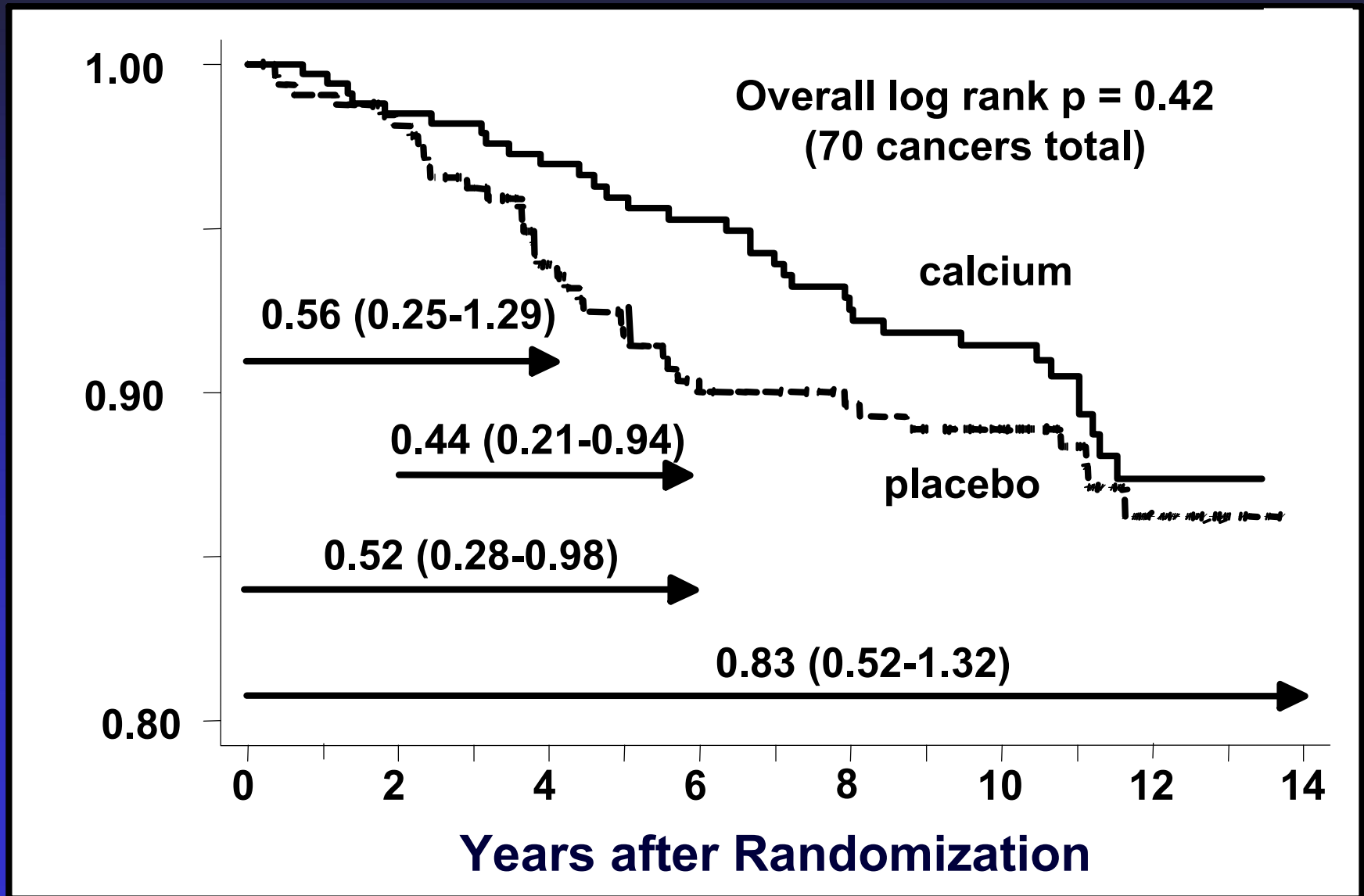


Vitamin D Supplementation

A sheep in wolf's clothing?



Calcium & Prostate Cancer



Antioxidants & Colorectal Neoplasia

Vitamins C/E Adenoma Trials

	<u>Dose</u>	<u>N</u>	<u>Duration</u>	<u>RR</u>
McK'n-Eyssen				
	400/400 mg	129	2 years	0.9 (0.5-1.8)
Greenberg				
	1000/400 mg	864	4 years	1.1 (0.9-1.3)

Antioxidants & Colorectal Neoplasia

Vitamins C/E Adenoma Trials (FAP)

	<u>Agent</u>	<u>N</u>	<u>Duration</u>	<u>Result</u>
Bussey	Vit C 3 gm	30	18 mos	hints of benefit
Decosse	Vit C 1 gm Vit E 0.4 gm	58	4 years	negative