Evidence for the Role of Obesity in Breast Cancer Progression

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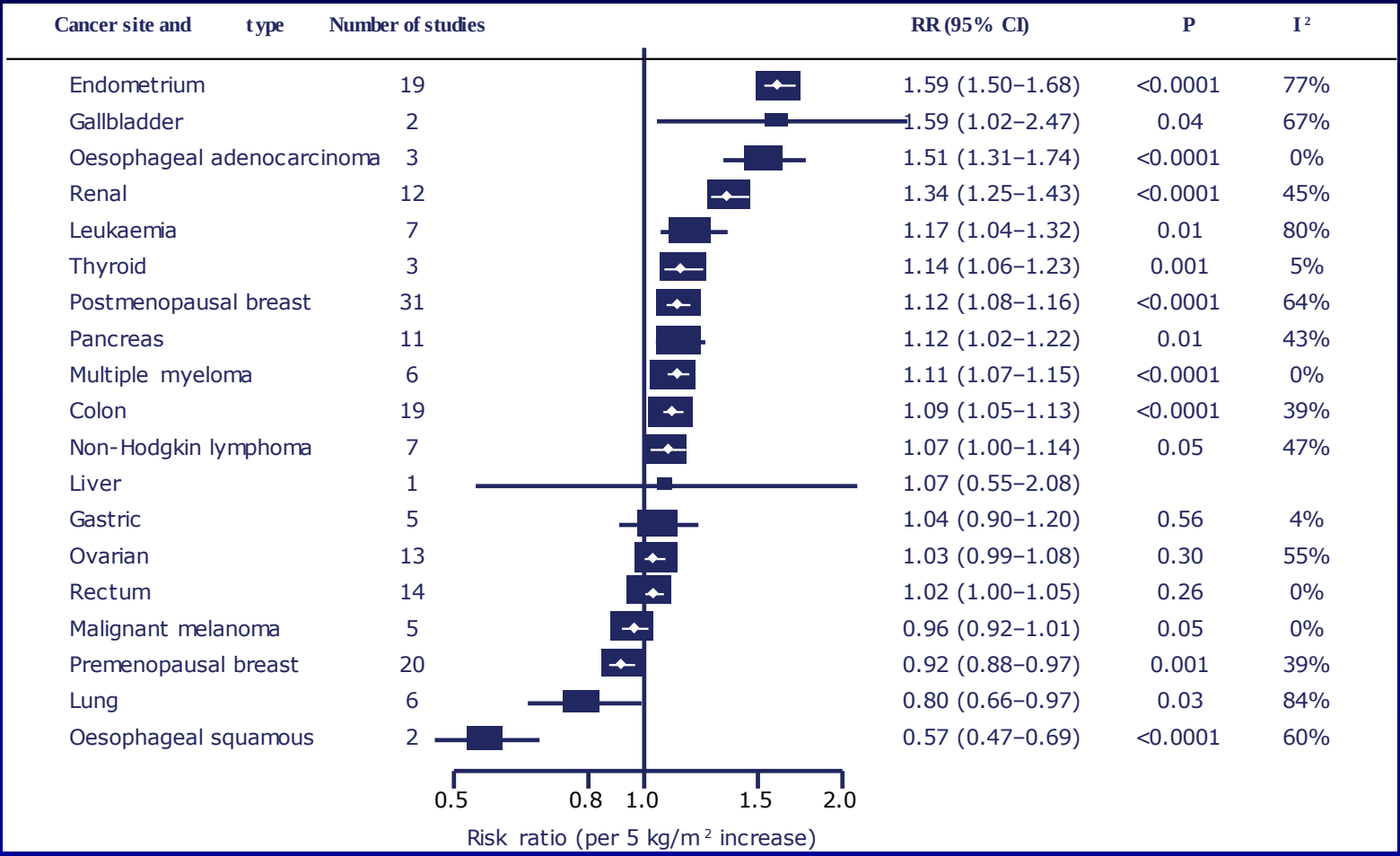
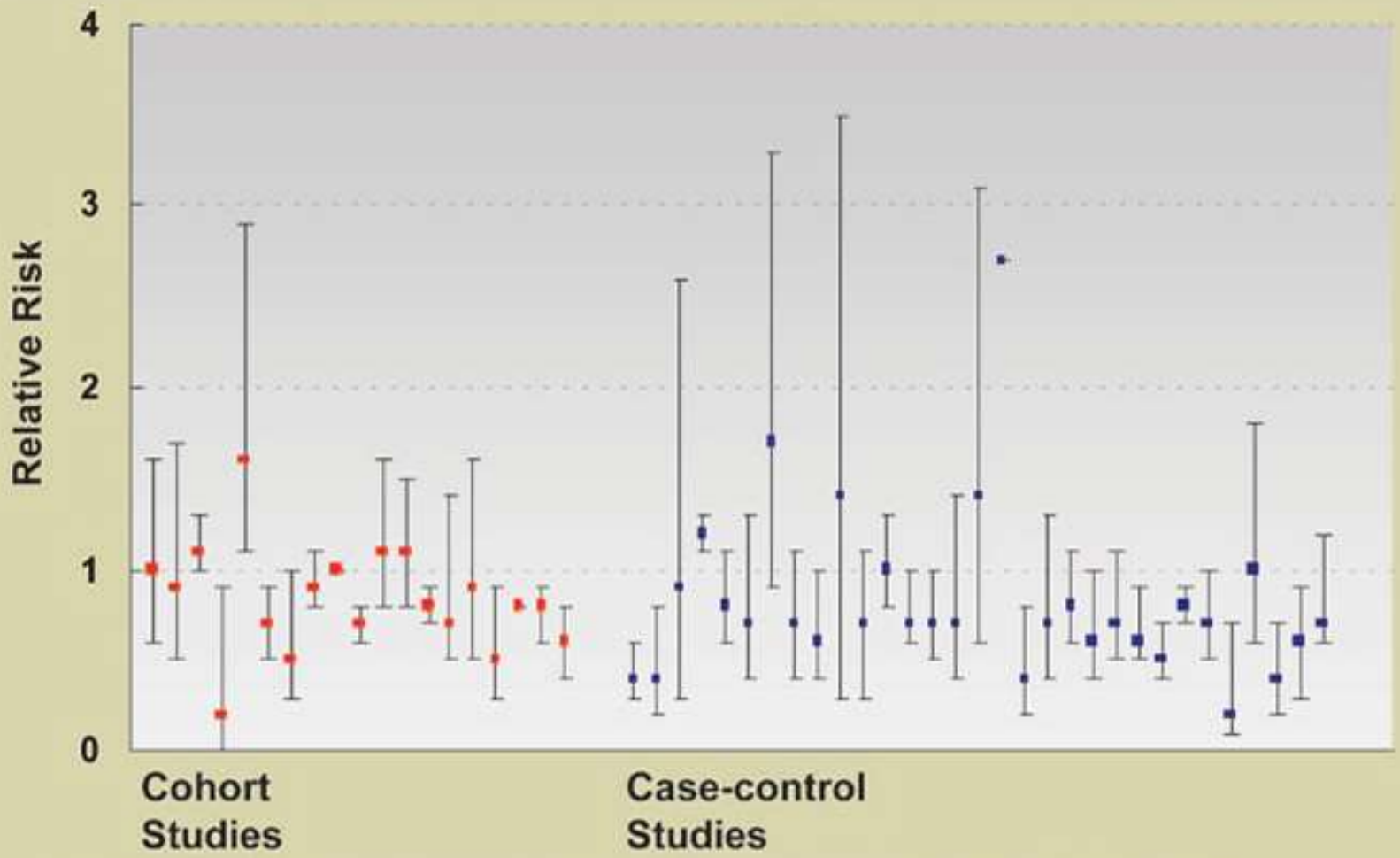
BMI and CANCER RISK: WOMEN



Renehan et al. Lancet 2008;371:569–578

Research Summary: Physical Activity and Breast Cancer Risk



Lee IM. Physical activity and cancer prevention—data from epidemiologic studies. *Med Sci Sports Exerc.* 2003;35:1823–1827. Reprinted with permission from Medscape.

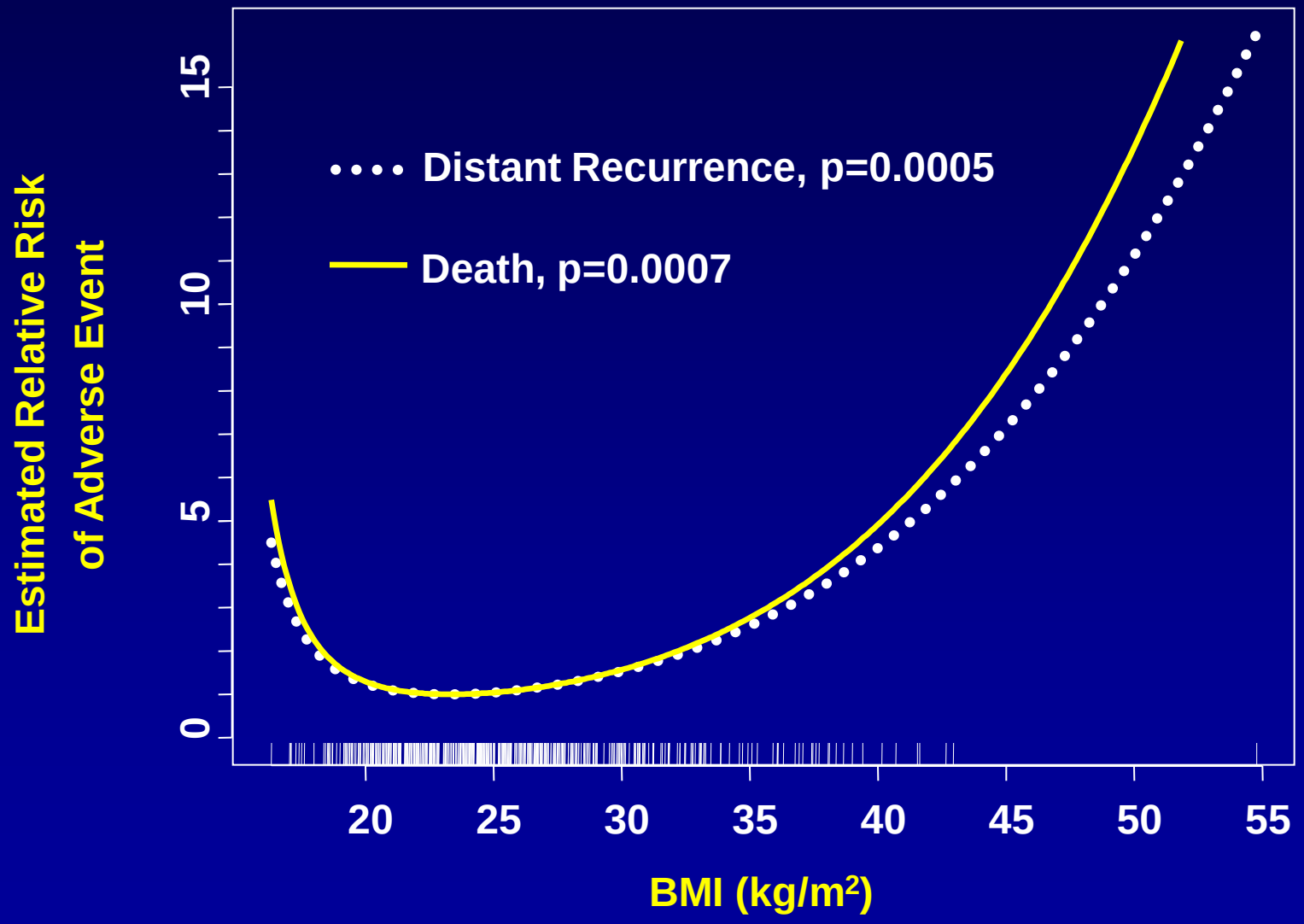
Influence of Lifestyle on Breast Cancer Risk

The risk of developing breast cancer may be influenced by lifestyle patterns associated with energy balance:

- low levels of physical activity
- obesity, weight gain (postmenopausal)

As a result, women who are diagnosed with breast cancer may have energy balance issues that differ from those of women in the general population.

Prognostic Effect of Body Size in Operable Breast Cancer



Obesity and Survival in Breast Cancer

Meta-Analysis

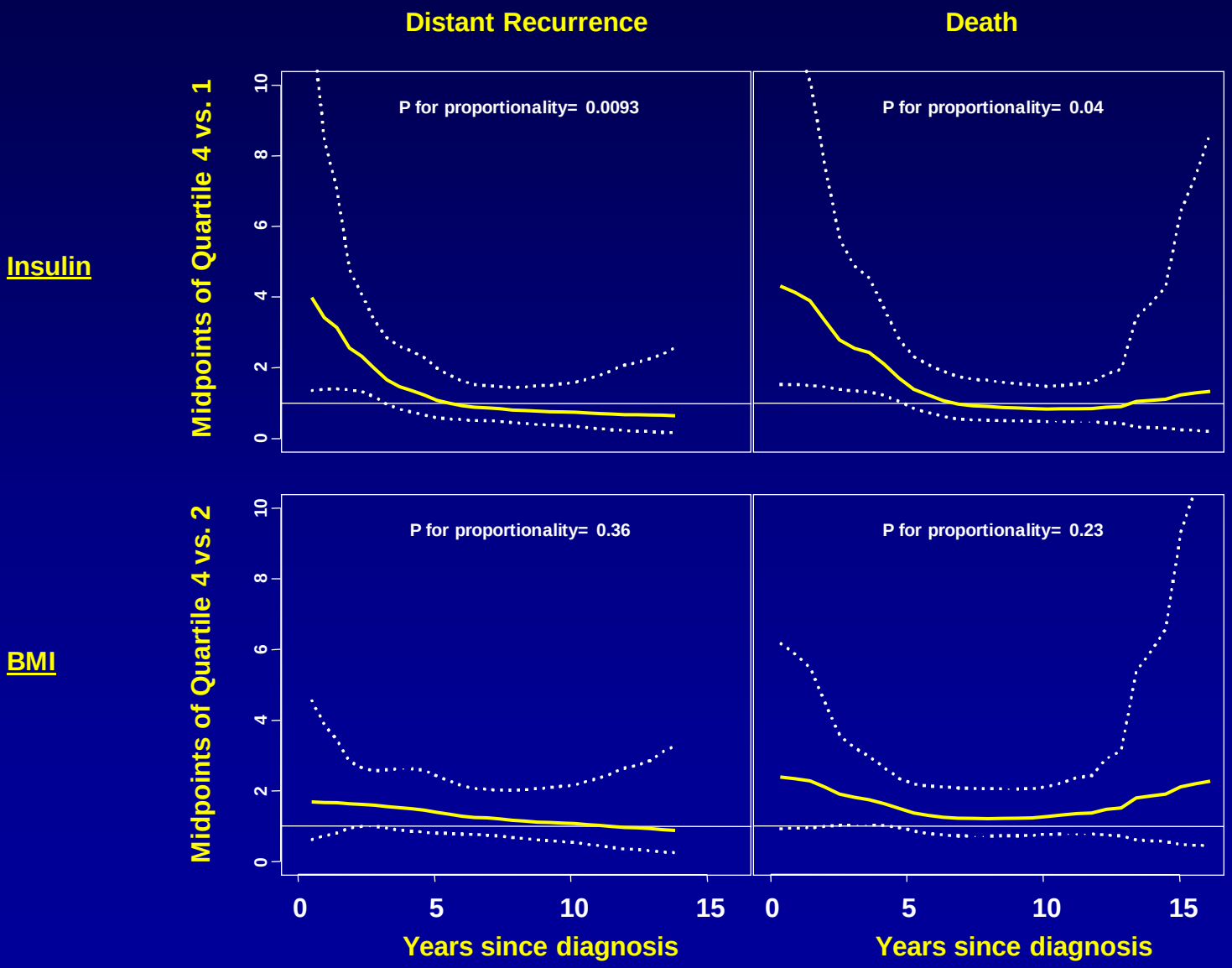
43 studies published 1963-2005 • comparison of obese vs. non-obese subjects

Subgroup	No. of estimates	Pooled HR (95% CI)		P-value
Survival measure				
All-cause	36	1.33 (1.21-1.47)		0.91
Breast cancer specific	19	1.33 (1.19-1.50)		
Obesity measure				
BMI	55	1.33 (1.23-1.44)		0.95
WHR	6	1.31 (1.14-1.50)		
Study design				
Observational cohort	48	1.36 (1.23-1.49)		0.53
Treatment cohort	7	1.22 (1.14-1.31)		
Menopausal status				
Pre-menopausal	16	1.47 (1.19-1.83)		0.25
Post-menopausal	12	1.22 (0.95-1.57)		
Both	36	1.33 (1.23-1.43)		
Year of diagnosis				
Pre-1995	30	1.31 (1.16-1.46)		0.17
Post-1995	11	1.49 (1.31-1.68)		

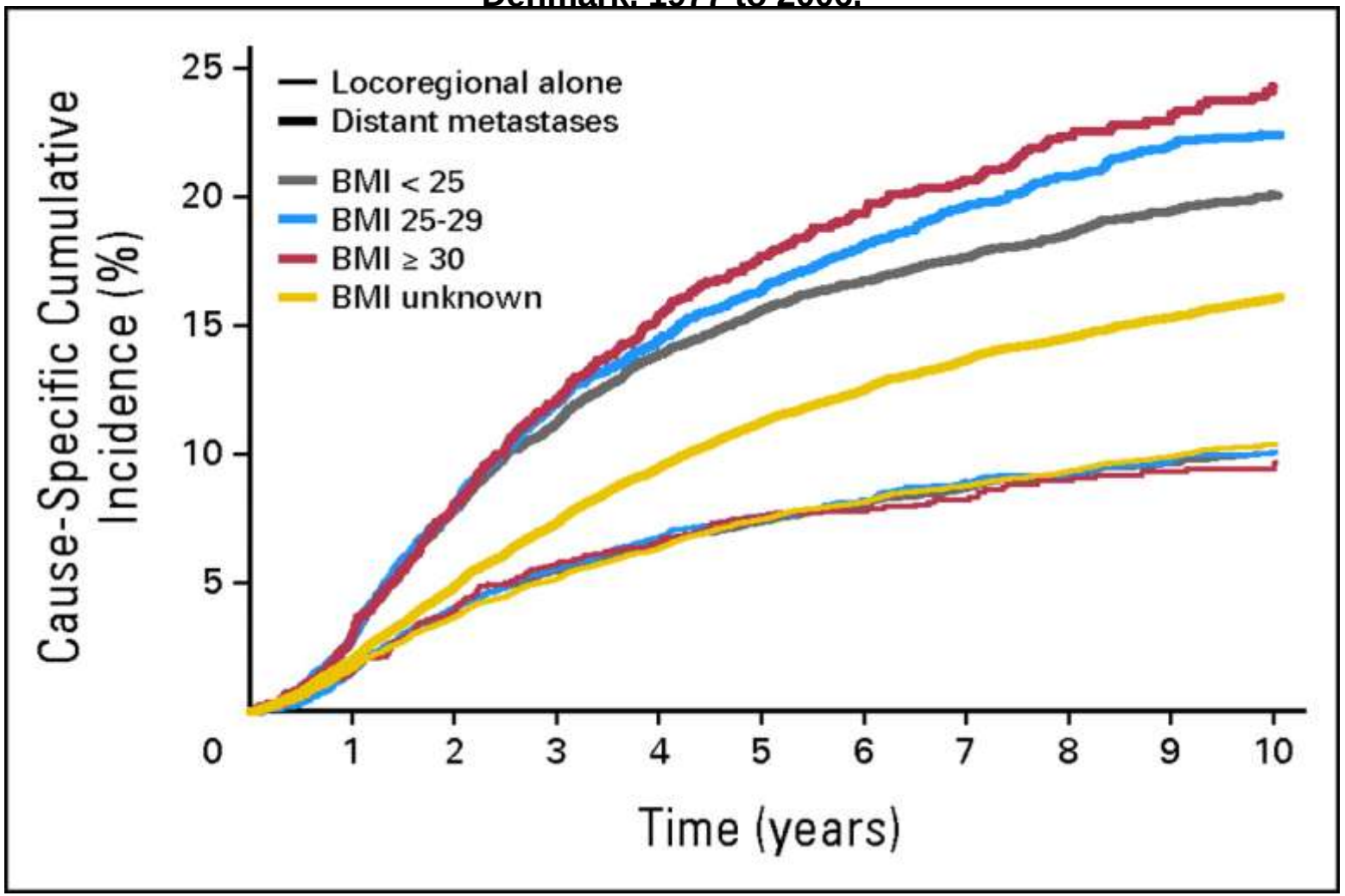
Protani M et al. BCRT 2010: 123:627-635

Temporal Pattern of Hazard Ratios for Fasting Insulin and BMI

Toronto Breast Cancer Obesity Study (JCO 2011 in press)



Cumulative incidence of first events (locoregional recurrences and distant metastases) in relation to body mass index (BMI) among 53,816 patients with early-stage breast cancer in Denmark, 1977 to 2006.



Ewertz M et al. JCO 2011;29:25-31

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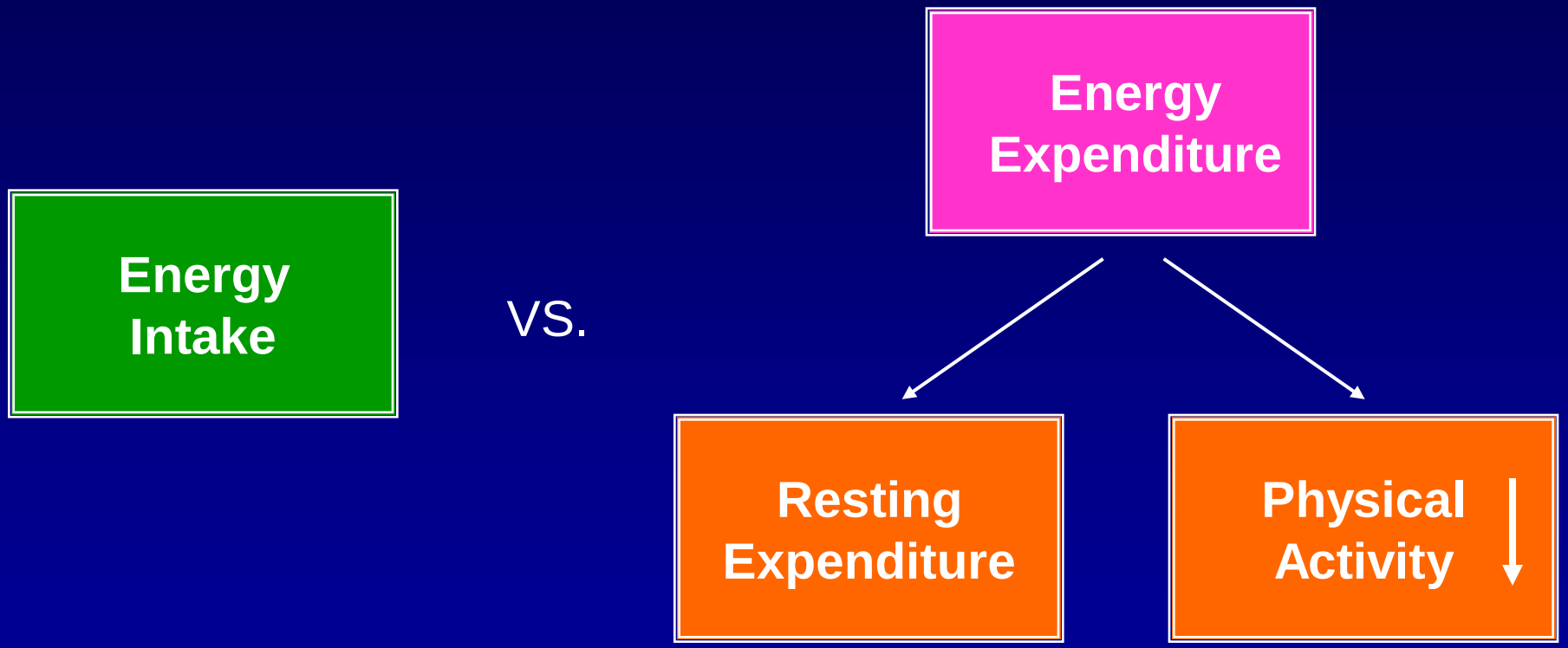
Obesity Reflects Energy Imbalance



Women's Intervention Nutrition Study (WINS)

- RCT of dietary fat reduction in postmenopausal breast cancer
- n=2437 age 48-79

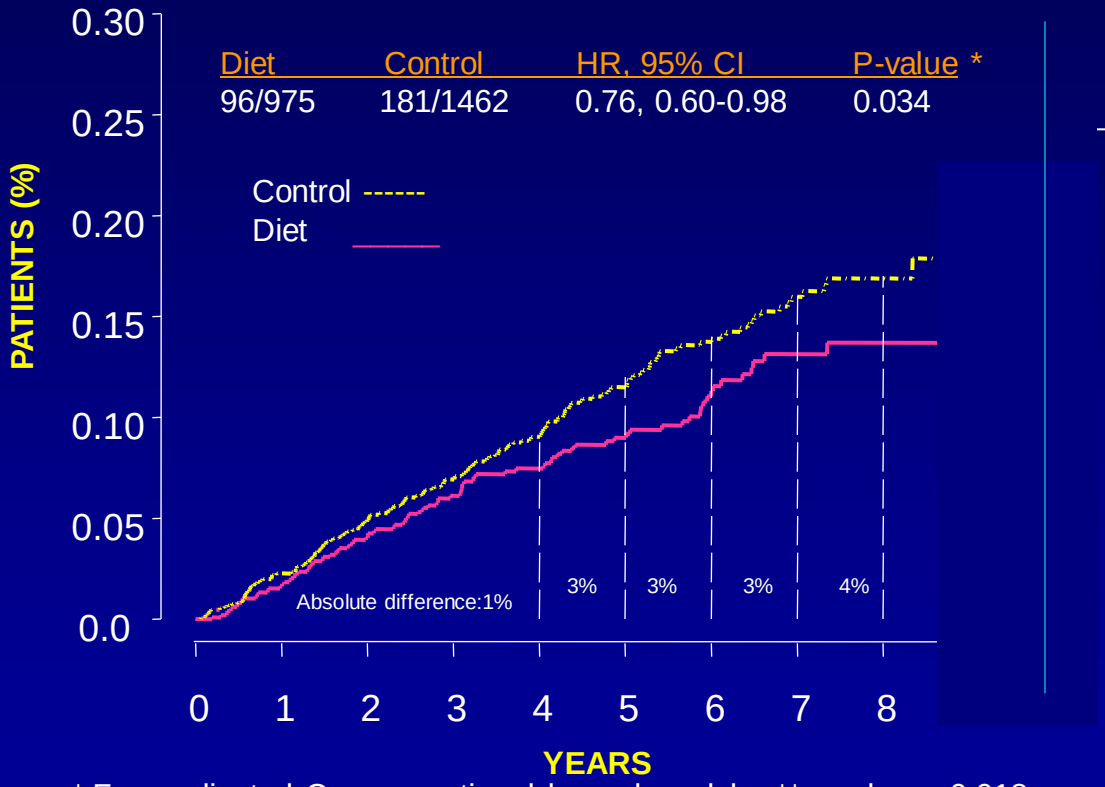
		12 MONTHS	
		Fat gram / day	Weight Change
Intervention		33.3 16.7	-2.1 kg
Control		51.3 24.4	+0.2 kg
	pvalue	<0.001	<0.05

	Relapse Free Survival (60 months)			
	Diet	Control	HR	p(2 tail)
All	96/975	181/1462	0.76 (0.60-0.98)	0.034
ER+	68/770	122/1189	0.85 (0.63-1.14)	0.277
ER-	28/205	59/273	0.58 (0.37-0.91)	0.018

Chlebowski R et al. JNCI 2006

WINS: RELAPSE-FREE SURVIVAL

ALL PATIENTS



* From adjusted Cox proportional hazard model; ** p value = 0.018

SUBGROUPS

	HR, 95% CI
ER+	0.85, 0.63-1.14
ER-	0.58, 0.37-0.91**
(interaction p=0.15)	
BMI	
< 25	0.83, 0.54-1.27
25-30	0.77, 0.51-1.18
≥ 30	0.66, 0.42-1.04

Chlebowski, Blackburn, Elashoff, et al. JNCI 2006

Women's Healthy Eating and Living Study (WHEL)

- RCT of telephone-based diet intervention in pre and postmenopausal women with breast cancer
- n=3088 age 18-70

	12 months		72 months	
	Intervention	Control	Intervention	Control
Vegetable (servings/day)	7.8	3.9	5.8	3.6
Fruit (servings/day)	4.2	3.4	3.4	2.6
Fiber (gm/day)	29.0	21.0	24.2	18.9
% fat calories	22.7	28.4	28.9	32.4
Weight (kg)	73.0	73.8	74.1	73.7

	DFS (events @ 5 yrs.)	OS (events @ 5 yrs.)
Intervention	27/1301	29/1410
Control	26/1319	26/1428
HR (95% CI)	0.96 (0.80-1.14)	0.91 (0.72-1.15)
P	0.63	0.43

Pierce JP et al JAMA 2007

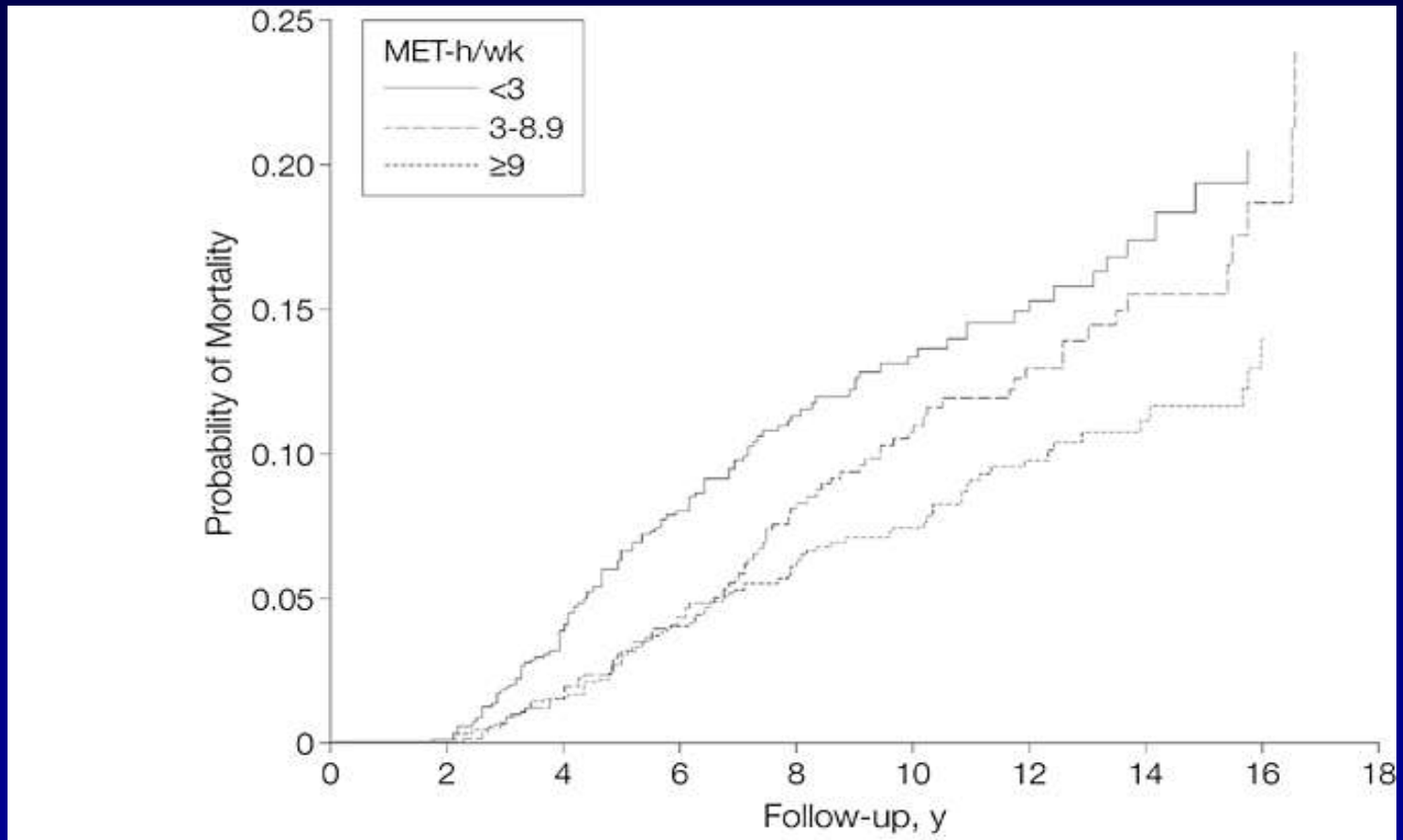
WINS vs. WHEL

	WINS	WHEL
Population		
Number	2437	3088
Time Post Diagnosis	Up to 1 year	Up to 4 years
Menopausal Status	Post	Pre and Post
Age	48-79	18-70
Intervention Group		
Fat Intake	Reduction maintained	Transient reduction
Weight Change	2.3 kg. relative loss	Modest weight gain
DFS	HR 0.76 (0.60-0.98)	HR 0.96 (0.80-1.14)

Physical Activity and Breast Cancer Outcomes

Holmes JAMA 2005	NHS n=2987	• Recreational physical activity 2 years post-diagnosis; ≥ 9 met hours per week (vs. < 3) Death — HR 0.59 p=0.03 (trend) BC Death — HR 0.50 p=0.004 (trend) Recurrence — HR 0.57 p=0.05 (trend)
Abrahamson Cancer 2006	n=1264	• Recreational physical activity 1 year pre-diagnosis Mortality Q4 vs. Q1 All Subjects — HR=0.78 (0.56-1.08) BMI* ≥ 25 — HR=0.70 (0.49-0.99) < 25 — HR=1.08 (0.77-1.52) * Interaction p=0.05
Holick CEBP 2008	n=4482 CWLS	• Recreational physical activity 5-6 years post-diagnosis; 8-20.9 met hours per week (vs. < 2.8) BC death (26%) — HR=0.53 p=0.01 (trend) Non BC death (74%) — HR=0.52 p<0.001 (trend)
Irwin JCO 2008	HEAL n=933	• Total physical activity 9 met hours vs. inactive Year Pre-diagnosis — HR 0.69 p=0.045 2 Years Post-diagnosis — HR 0.33 p=0.046
Sternfeld CEBP 2009	LACE n=1970	• Total physical activity up to 3+ years post-diagnosis Q4 vs. Q1 Death — HR 0.76 p=0.20 (trend) BC Death — HR 0.87 p=0.41 (trend) Recurrence — HR 0.91 p=0.78 (trend)
Chen 2011	Shanghai n=1826	• Recreational physical activity 36 months post-diagnosis (8.3 met hours per week (vs. 0) BC recurrence and/or death — HR 0.59 (0.45-0.76) Death (any cause) — HR 0.65 (0.05-0.84)

Mortality According to Physical Activity Level in Breast Cancer



No. at Risk

Physical Activity, MET-h/wk									
<3	959	957	809	573	407	286	222	83	43
3-8.9	862	862	767	569	489	372	184	84	31
≥9	1166	1166	1066	773	692	449	290	164	86

Holmes MD et al JAMA 2005;293:2479-2486

Obesity – Breast Cancer Prognosis
Direct or Indirect Effect?

INDIRECT:

- later diagnosis / higher stage at diagnosis
- suboptimal CXT dosing (BSA caps)
- reduced treatment efficacy (e.g. with AIs)
- higher co-morbidity/competing COD death

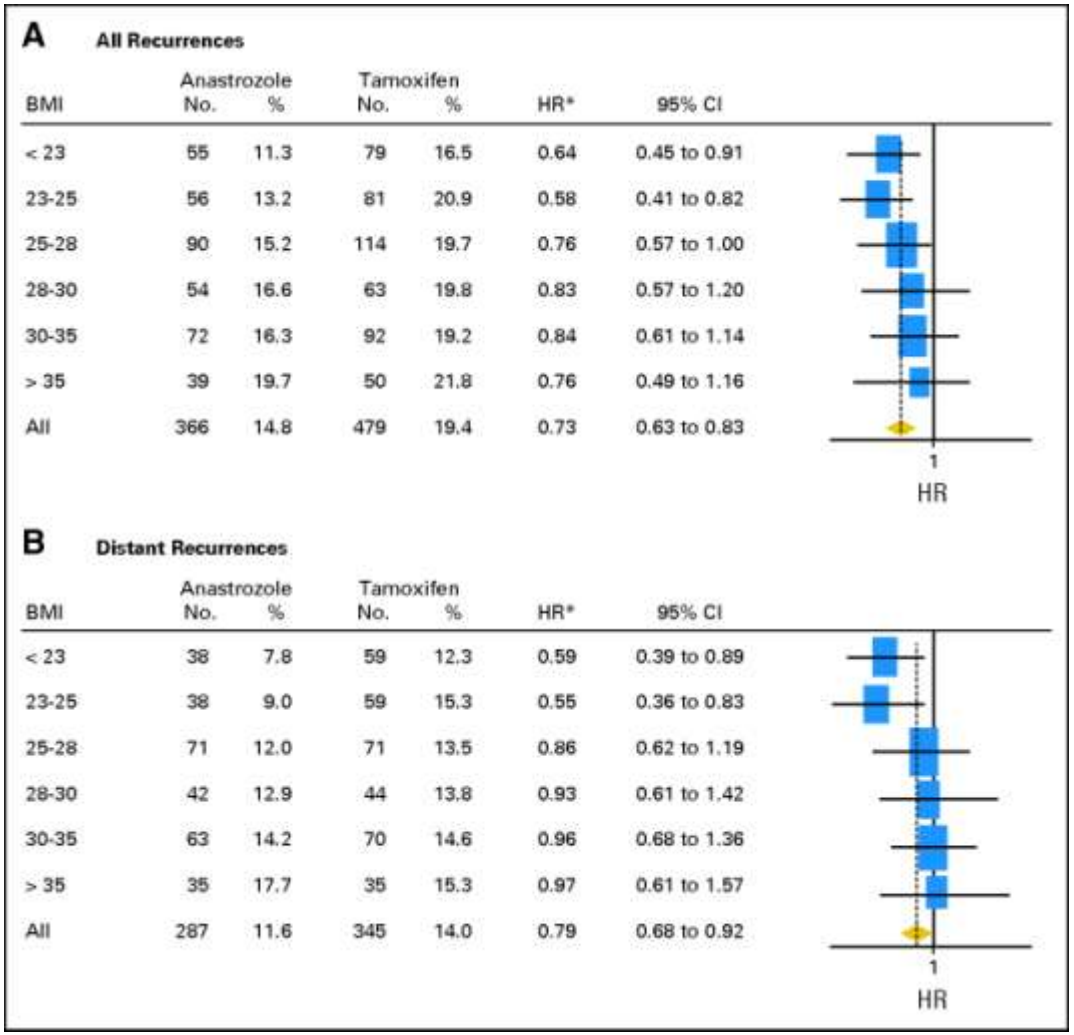
DIRECT:

- growth stimulating effects of physiologic attributes of obesity

Chemotherapy Dosing in Obese Breast Cancer Patients

- Capping of chemotherapy doses common in the past, for example, at BSA = 2 (e.g. Madarnas Y BCRT 2001)
- Can lead to reduced treatment efficacy, potentially greatest effect in ER- BC (e.g. Colleoni M Lancet 2005)
- When actual body size is used to calculate doses, toxicity is not increased (Jenkins P Eur J Cancer 2007)
- Current recommendations are to use actual body size to calculate dose; recent RCT protocols reflect this approach (e.g. Greenman C Cancer 2007)

ATAC Trial: Hazard plots for anastrozole versus tamoxifen by body mass index (BMI) group for all recurrences and distant recurrences (Interaction p < 0.05).



A All Recurrences

BMI	Anastrozole No.	Anastrozole %	Tamoxifen No.	Tamoxifen %	HR*	95% CI
< 23	55	11.3	79	16.5	0.64	0.45 to 0.91
23-25	56	13.2	81	20.9	0.58	0.41 to 0.82
25-28	90	15.2	114	19.7	0.76	0.57 to 1.00
28-30	54	16.6	63	19.8	0.83	0.57 to 1.20
30-35	72	16.3	92	19.2	0.84	0.61 to 1.14
> 35	39	19.7	50	21.8	0.76	0.49 to 1.16
All	366	14.8	479	19.4	0.73	0.63 to 0.83

B Distant Recurrences

BMI	Anastrozole No.	Anastrozole %	Tamoxifen No.	Tamoxifen %	HR*	95% CI
< 23	38	7.8	59	12.3	0.59	0.39 to 0.89
23-25	38	9.0	59	15.3	0.55	0.36 to 0.83
25-28	71	12.0	71	13.5	0.86	0.62 to 1.19
28-30	42	12.9	44	13.8	0.93	0.61 to 1.42
30-35	63	14.2	70	14.6	0.96	0.68 to 1.36
> 35	35	17.7	35	15.3	0.97	0.61 to 1.57
All	287	11.6	345	14.0	0.79	0.68 to 0.92

Sestak I et al. JCO 2010;28:3411-3415

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ABCSG-12 BMI Effects

	HR Overweight / Obese vs. Normal Weight	
	DFS	OS
All Subjects (⅓ obese)	1.24 (0.92-1.68)	1.49 (1.00-2.68)
Tamoxifen	0.94 (0.60-1.64)	0.83 (0.35-1.93)
Anastrozole	1.53 (1.01-2.31)	1.93 (1.04-3.58)

	Anastrazole vs. Tamoxifen	
	DFS	OS
Normal Weight	0.87 (0.59-1.27)	1.21 (0.63-2.33)
Overweight / Obese*	1.47 (0.90-2.40)*	3.23 (1.39-7.53)**

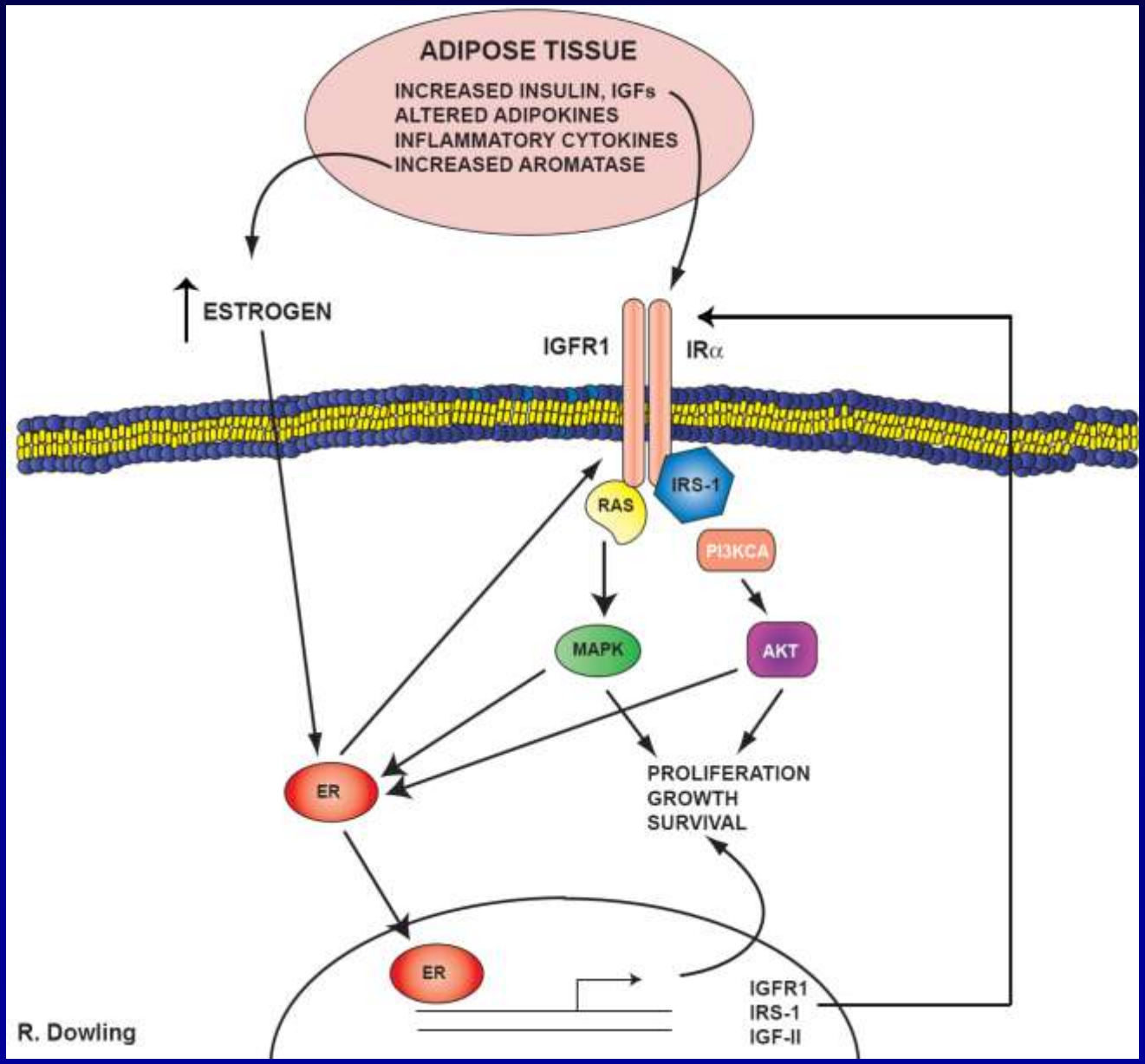
* 30 events TAM, 42 events ANA

** 8 events TAM, 22 events ANA

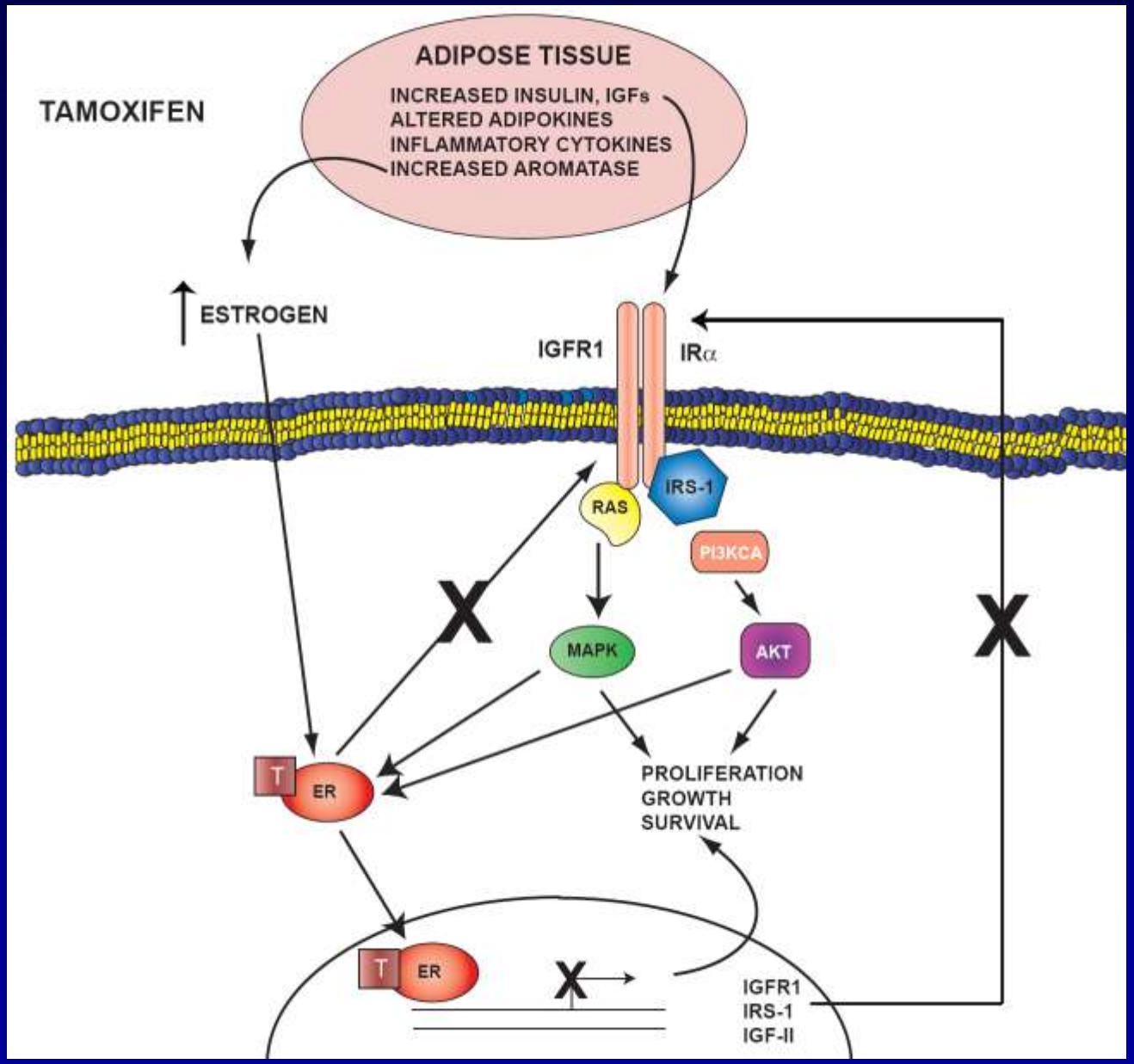
Conclusion: **Anastrazole significantly less effective than tamoxifen in overweight or obese women**

Pfeiler et al JCO 2011

ER – IGF – Cross-talk



ER – IGF – Cross-talk



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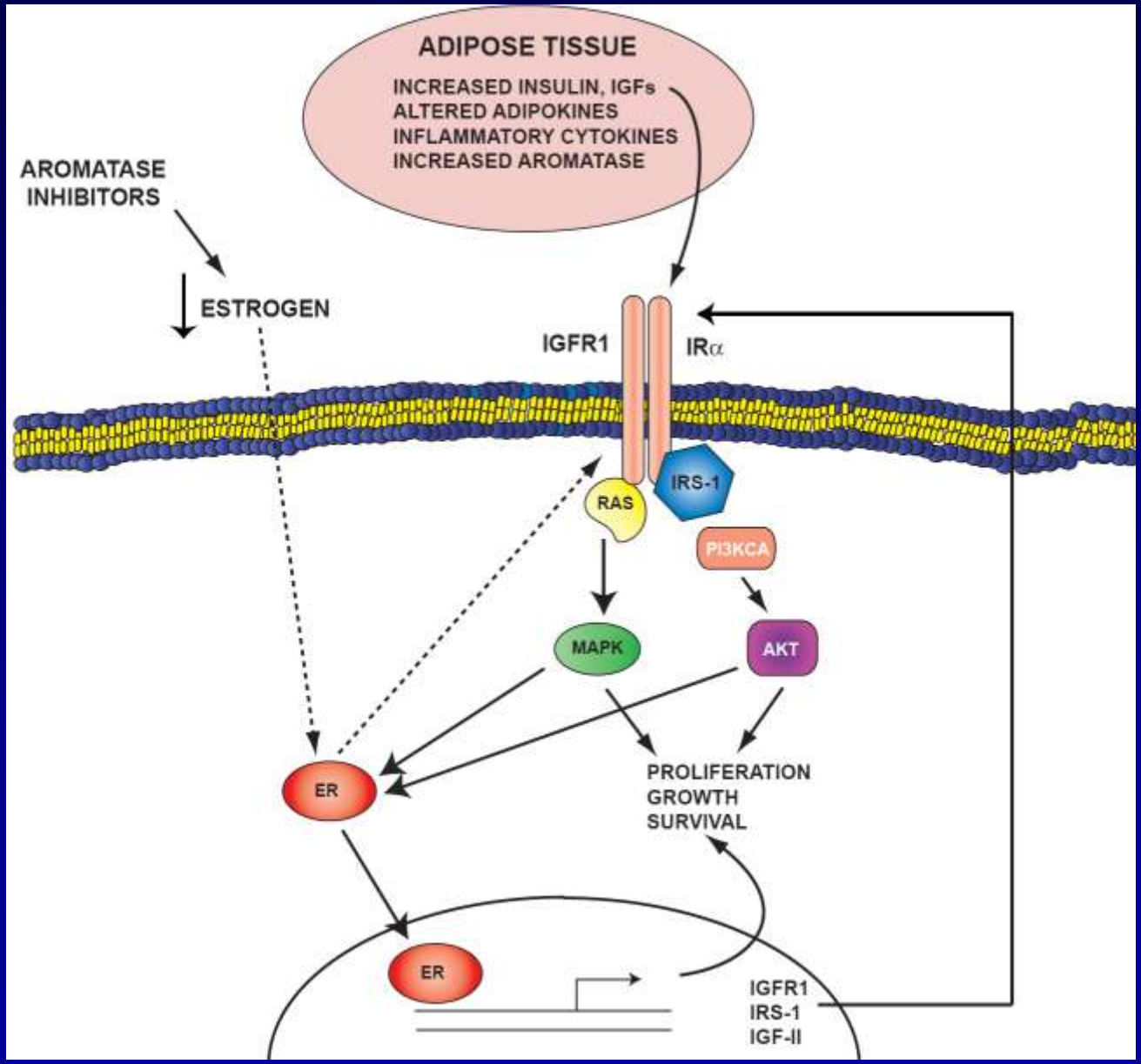
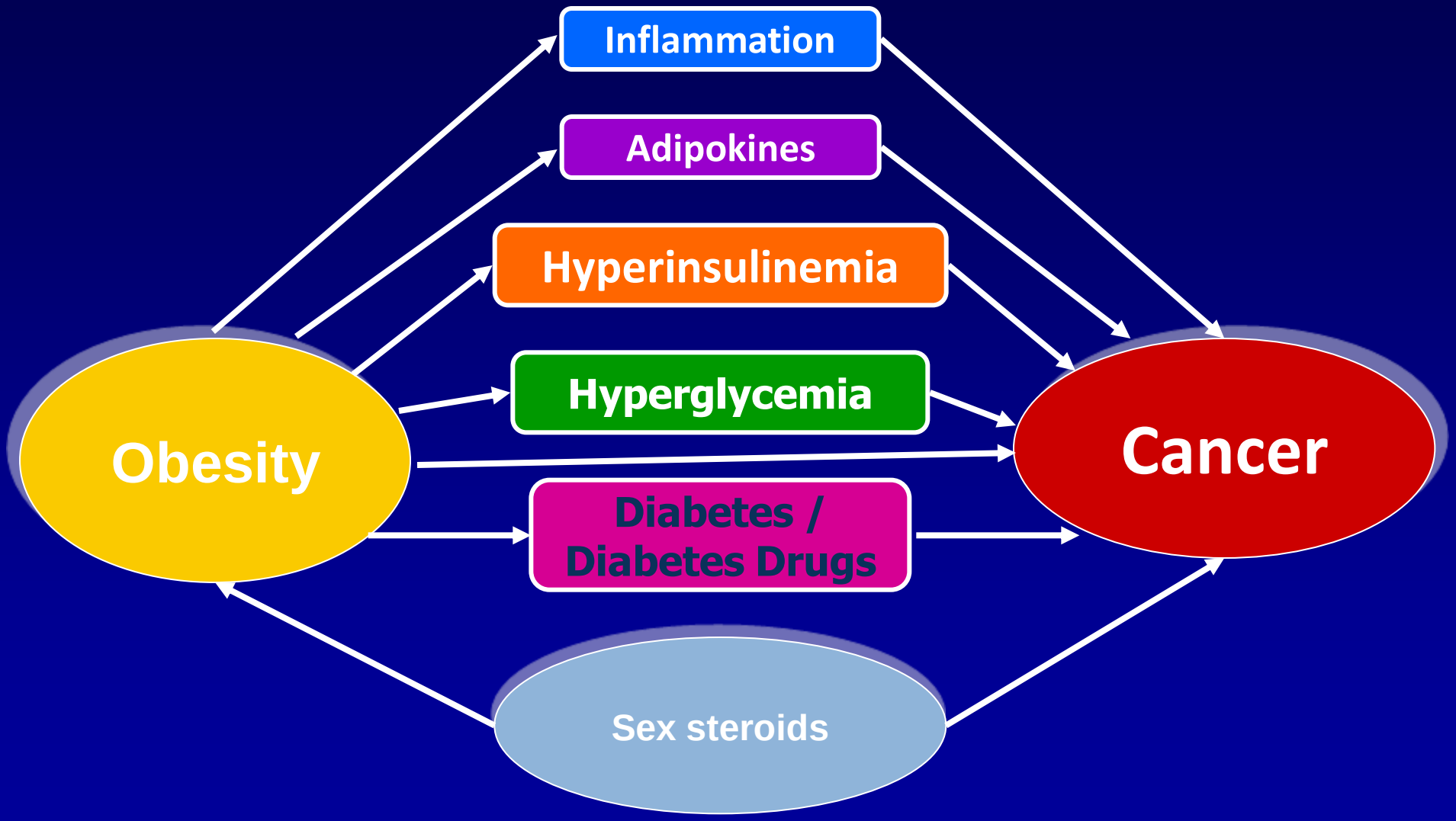


Obesity, Insulin Resistance and Cancer
Potential Mechanisms



Reproductive Hormones and Breast Cancer Survival

- nested case-control study within WHEL Study
- cases: 153 BC recurrence
- controls: 153 BC no recurrence

Results:

	HR for Recurrence (per unit increase in log hormone concentration)		
Estradiol	1.41	(1.01-1.97)	p=0.04
Bioavailable estradiol	1.26	(1.03-1.53)	p=0.02
Free estradiol	1.31	(1.03-1.65)	p=0.03

No significant difference: testosterone (total, bioavailable, free), SHBG

Rock CL et al. CEBP 2008;17:614

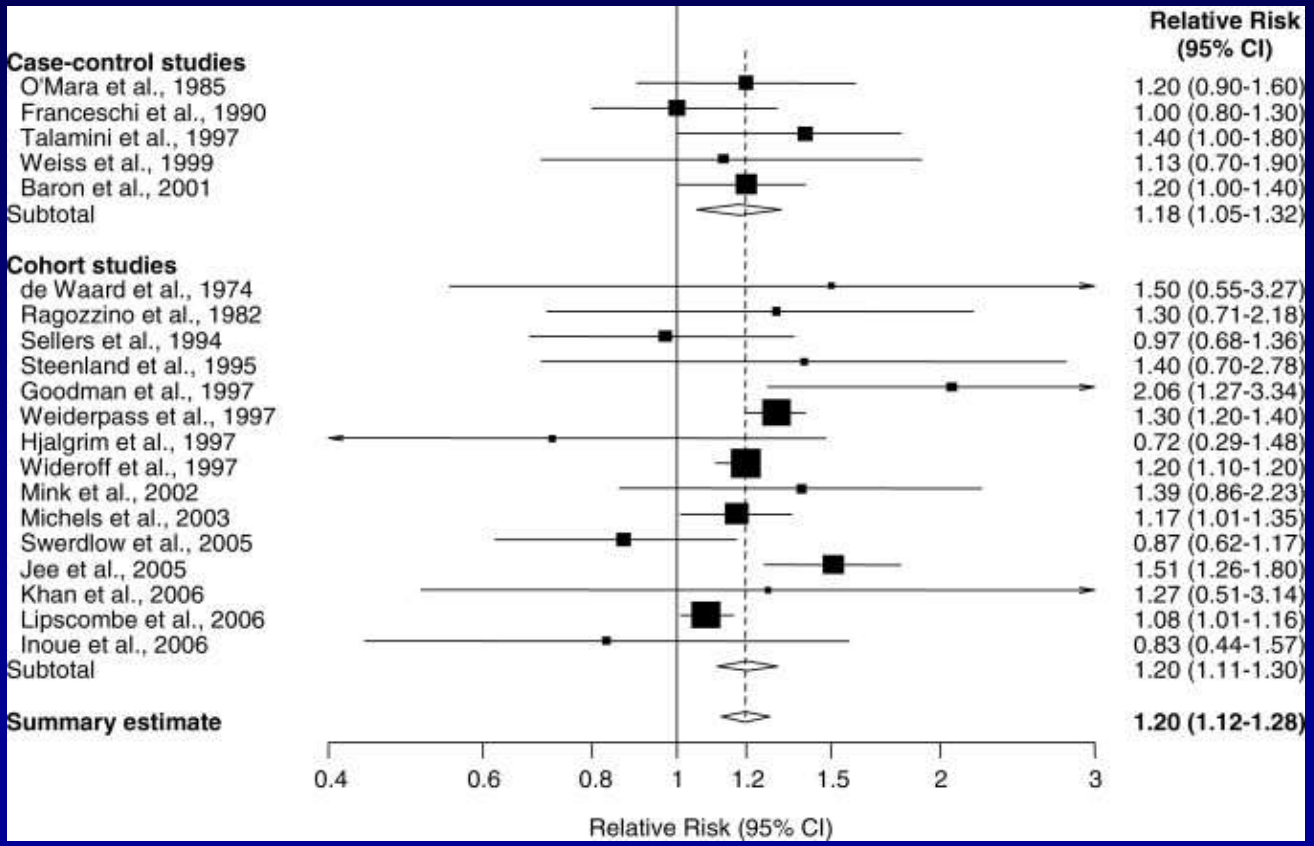
Obesity and the Insulin Resistance Syndrome
(Metabolic Syndrome)

- A **CLINICAL** syndrome associated with obesity that predicts risk of **DIABETES** and CV disease

- **Physiologic alterations** include: insulin resistance, systemic inflammation, altered adipokine profile, prothrombotic state

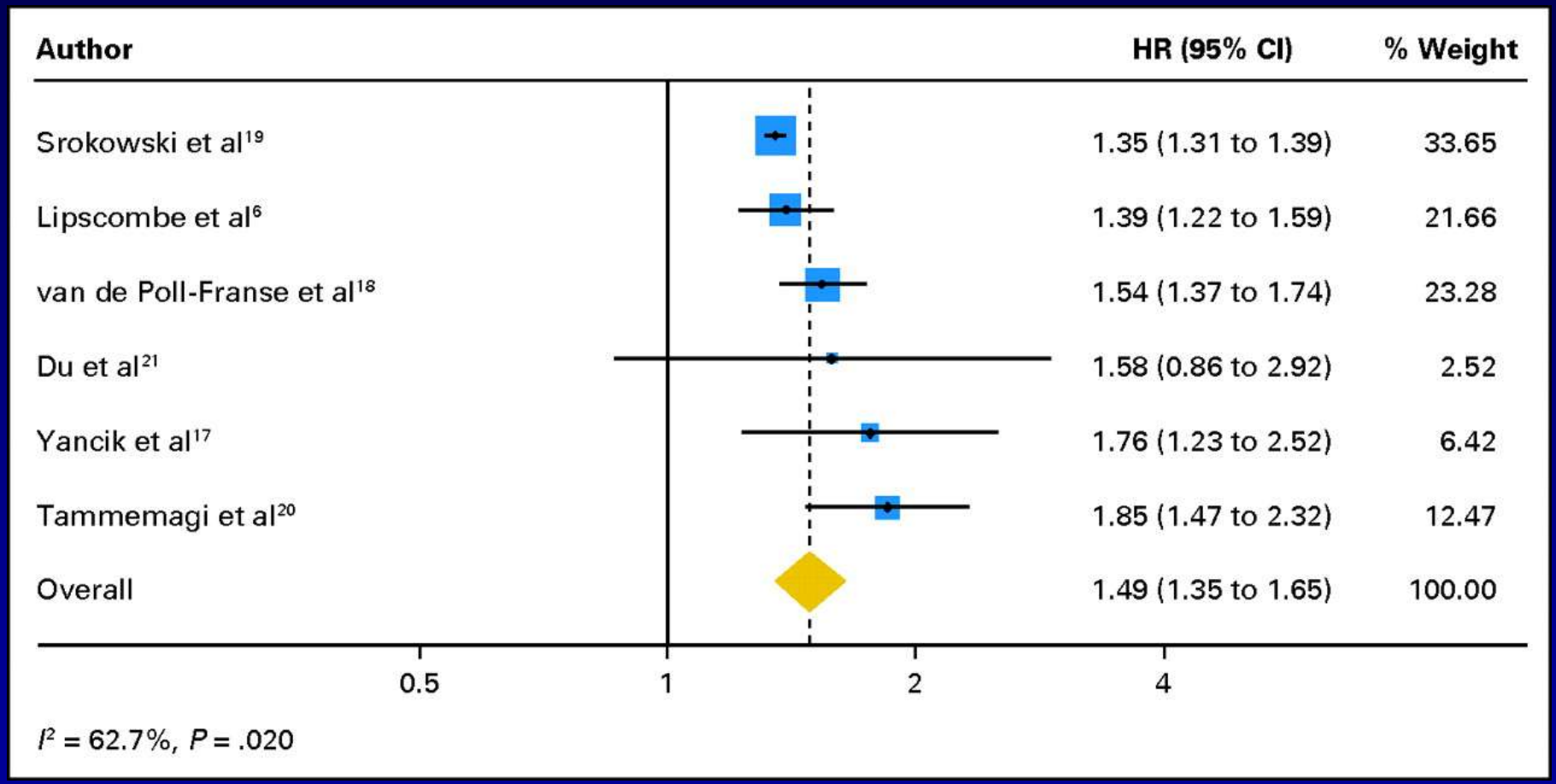
- Multiple **definitions**, all include:
  - **Obesity** (cut point varies with ethnicity)
  - Abnormal fasting **glucose**
  - Abnormal **lipid** profile (high TG / low HDL-C)
  - Elevated **blood pressure**

Diabetes and Breast Cancer Incidence: A Meta-Analysis



Larsson SC et al. Int J Cancer 2007; 121:856-62

Diabetes and All Cause Mortality in Breast Cancer



Peairs et al. J Clin Oncol 2010; 29:40-46

Fasting Glucose and Breast Cancer Outcomes

Population:
- 512 early stage breast cancer
- no known diabetes

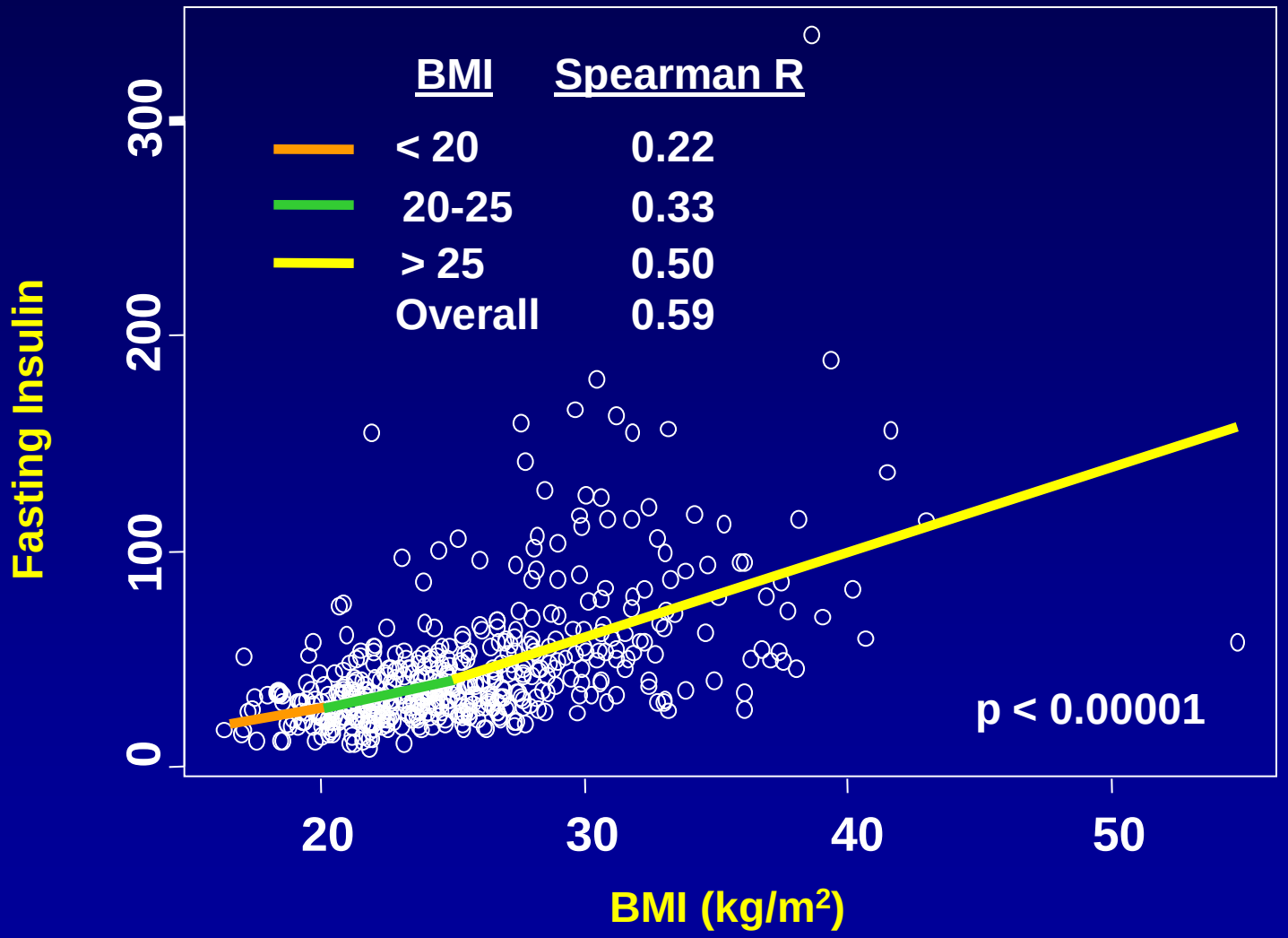
Results:

Quartile		DDFS		OS	
Mean	Range	HR (adjusted)*	(95% CI)	HR (adjusted)*	(95% CI)
4.5	3.5-4.7	1		1	
4.9	4.7-5.1	1.28	(1.02-1.60)	1.26	(0.93-1.70)
5.2	5.1-5.4	1.50	(1.04-2.17)	1.46	(0.89-2.40)
5.7	5.4-11.6	1.88	(1.06-3.35)	1.81	(0.83-3.93)
		p=0.027 unadjusted		p=0.036 unadjusted	
		p=0.034 adjusted		p=0.014 adjusted	

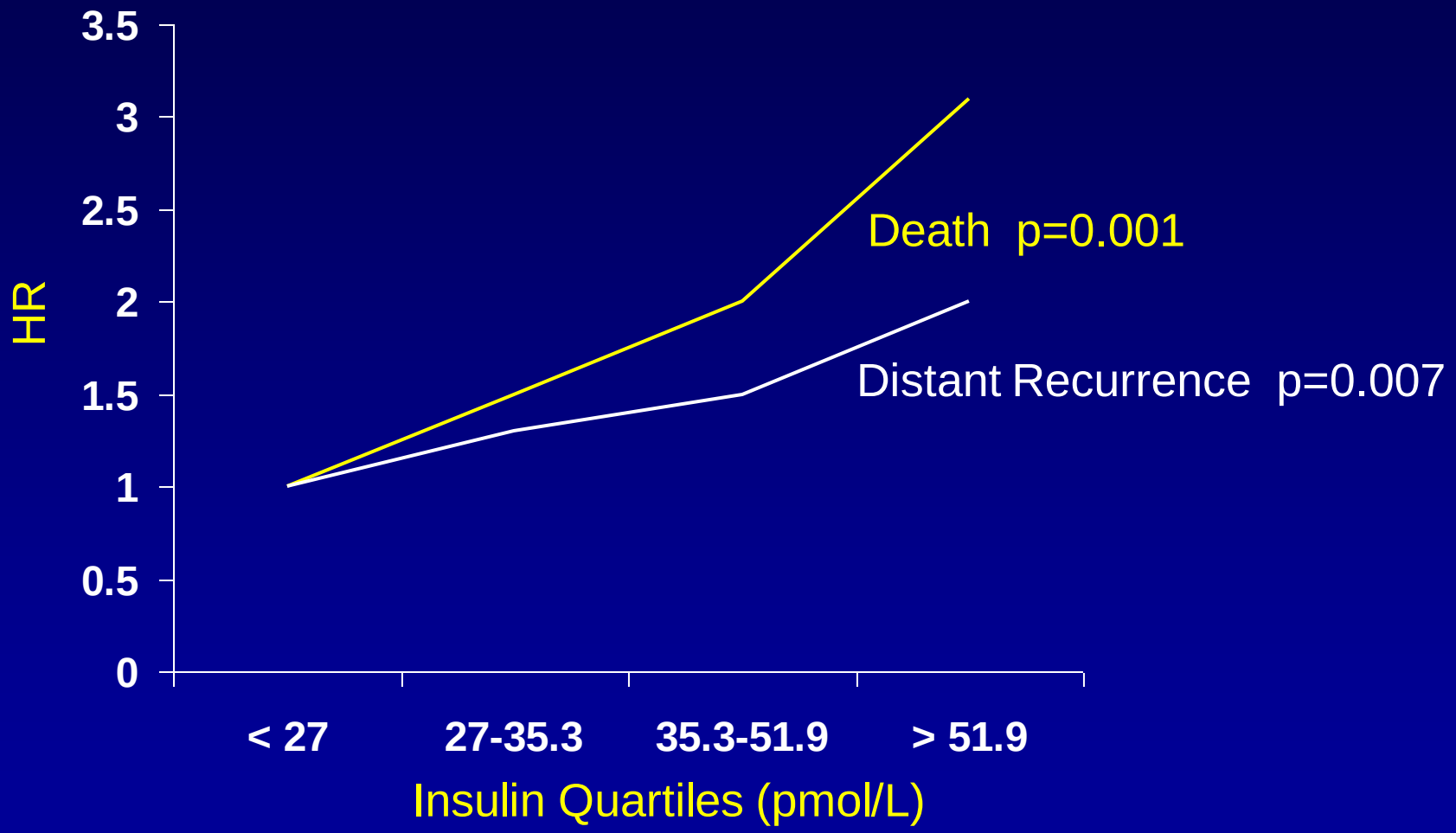
* adjusted for age, T, N, grade, hormone receptor, chemotherapy, hormone therapy

Goodwin PJ et al. J Clin Oncol 2011 (in press)

BMI and Fasting Insulin



Insulin and Breast Cancer Prognosis



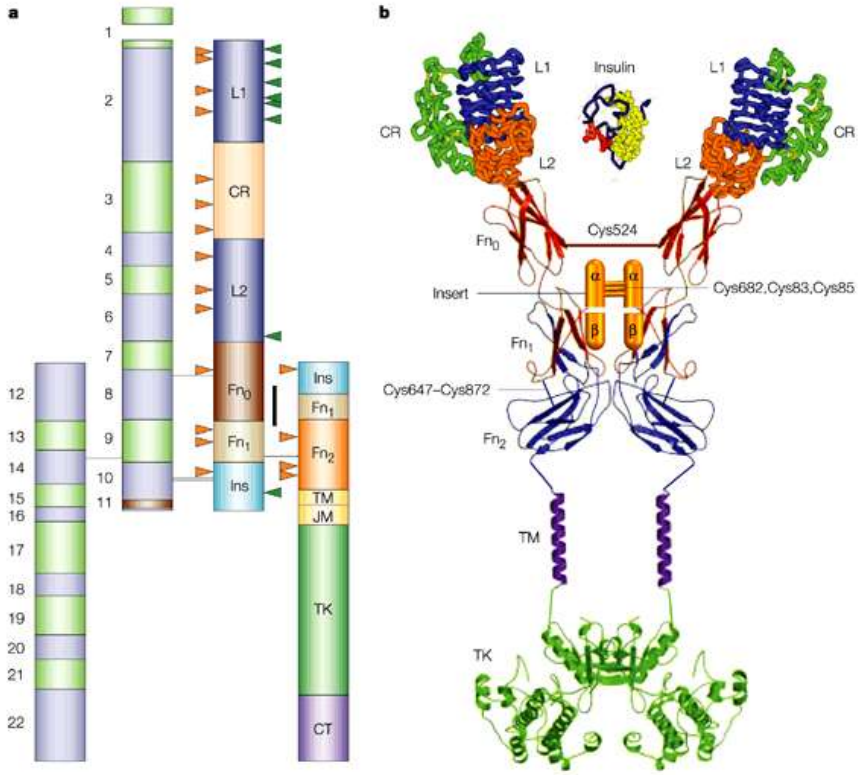
Goodwin PJ et al. J Clin Oncol 2002; 20:42-51

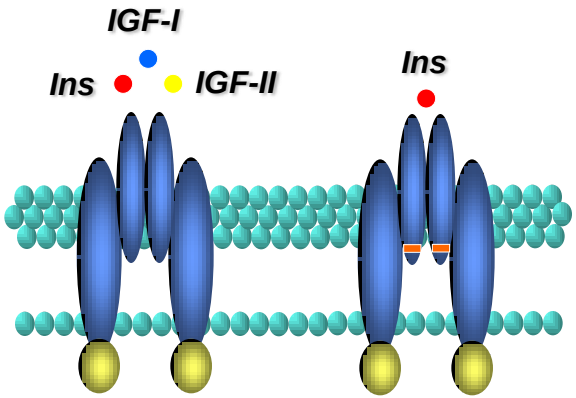
Prognostic Associations of Insulin in Breast Cancer

		n	Factor Measured	Recurrence	Death
Goodwin	2002	512	Fasting Insulin	HR=2.0	HR=3.1
Pasanisi	2006	110	Fasting Insulin IRS	HR=2.42 HR=3.0	
Pritchard	2011	667	Non-fasting C-peptide	p < 0.05*	
Irwin (HEAL)	2010	689	Fasting C-peptide		HR=3 (significant)
Duggan (HEAL)	2010	527	HOMA		HR=4.3 (BC death) HR=1.6 (all deaths)
Emaus	2010	1364	IRS Components: BMI, cholesterol, BP, exercise		HR 1.3-3.0 (significant)

* HR not provided

Insulin Receptor Isoforms





IR-A

Metabolic and Mitogenic Effects

IR-B

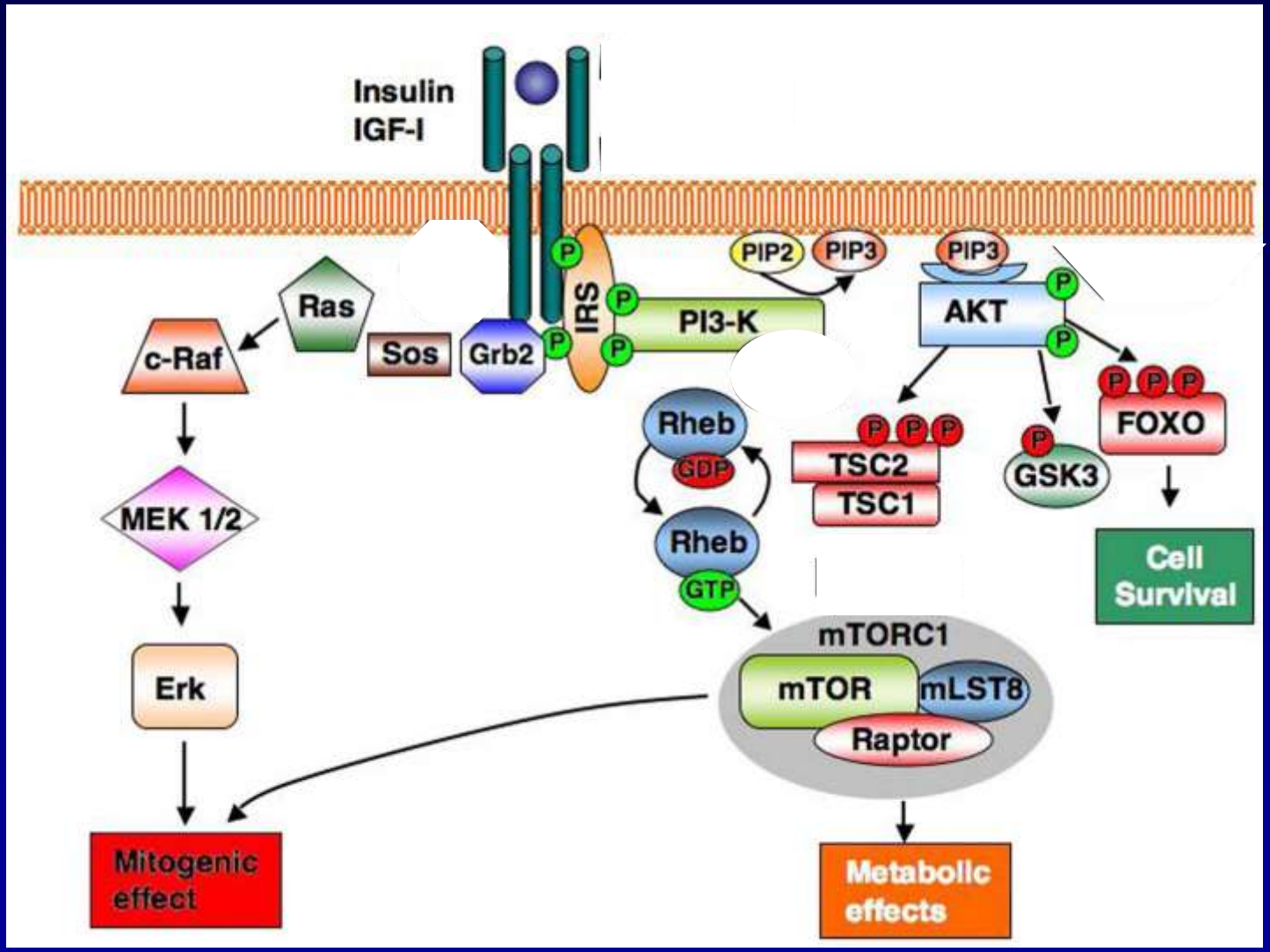
Metabolic Effects

High Levels of Expression in Fetal and Neoplastic Tissues

DeMeyts and Whittaker *Nat Rev Drug Discov* **2002; 1: 769-783**

Frasca et al. ***Mol Cell Biol*** **1999; 19: 3278-3288**

Molecular Action of Insulin



Adapted from Vigneri P et al., Endocr Relat Cancer 2009 Jul 20 (epub ahead of print)

IR, IGFIR in Human Breast Cancer

Population: 438 women with invasive BC

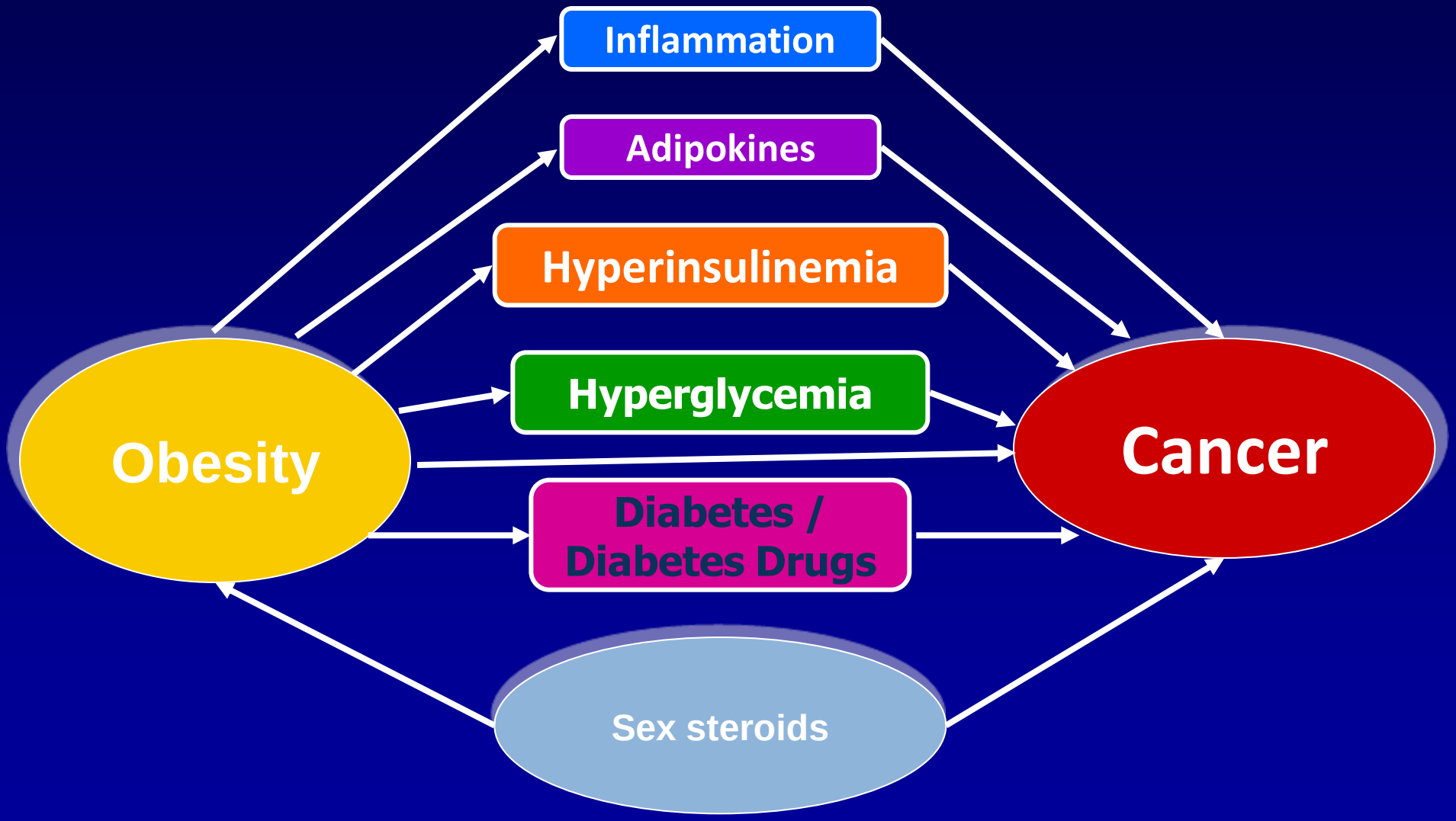
Prognostic Effects:

	% Positive	Survival	P Survival
Total IR*	59.0	Worse	0.009
Total IGFIR	37.5	Worse	0.30
Phosphorylated IGFIR/IR	55.3	Worse	0.046

* present vs. absent

Law JH et al. Cancer Res 2008

Obesity, Insulin Resistance and Cancer
Potential Mechanisms



Biomarkers of Inflammation and Breast Cancer Outcome

- HEAL Study n=734 breast cancer survivors
- measurements mean 31 months post-diagnosis
- 4.1 years follow-up (DFS), 6.9 years follow-up (OS)

Results:

	DDFS		OS	
	HR	(95% CI)	HR	(95% CI)
C-Reactive Protein (mg/L)				
≤ 1.2	1		1	
1.3-3.8	1.58	(0.88-2.83)	0.94	(0.50-1.76)
≥ 3.9	1.91	(1.04-3.51)	2.05	(1.14-3.69)
	p=0.04		p=0.01	
Serum Amyloid A (mg/L)				
≤ 4.2	1		1	
4.3-8.0	1.00	(0.56-1.79)	0.97	(0.49-1.89)
≥ 8.0	1.62	(0.94-2.80)	2.91	(1.61-5.26)
	p=0.07		p=0.0001	

(adjusted for age, stage, race / site, BMI, HR, cardiovascular events)

Pierce BL et al. JCO 2009;27:3437

Systemic Inflammatory Response and Breast Cancer Survival

- n=300
- 46 month follow-up
- pre-operative measurement

Results:

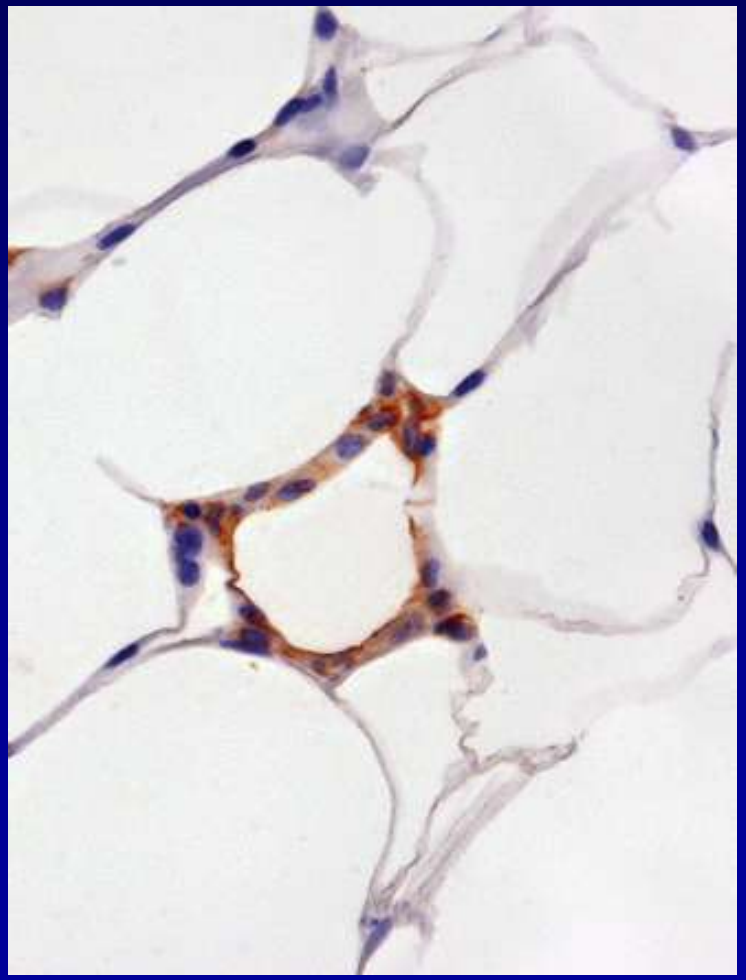
	RFS		Survival			
			BC Specific		Overall	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
C-reactive Protein (ng/L) ≤ 10 vs. > 10	0.40	(0.10-1.68)	0.62	(0.15-2.65)	0.60	(0.19-1.95)
	p=0.21		p=0.52		p=0.40	
Albumin (gm/L) ≤ 43 vs. > 43	3.39	(1.61-7.12)	5.01	(1.85-13.57)	3.23	(1.58-6.59)
	p=0.001		p=0.002		p=0.001	

Murri AM et al. Br J Cancer 2007; 96:891

Local Inflammation: Crown-Like Structures

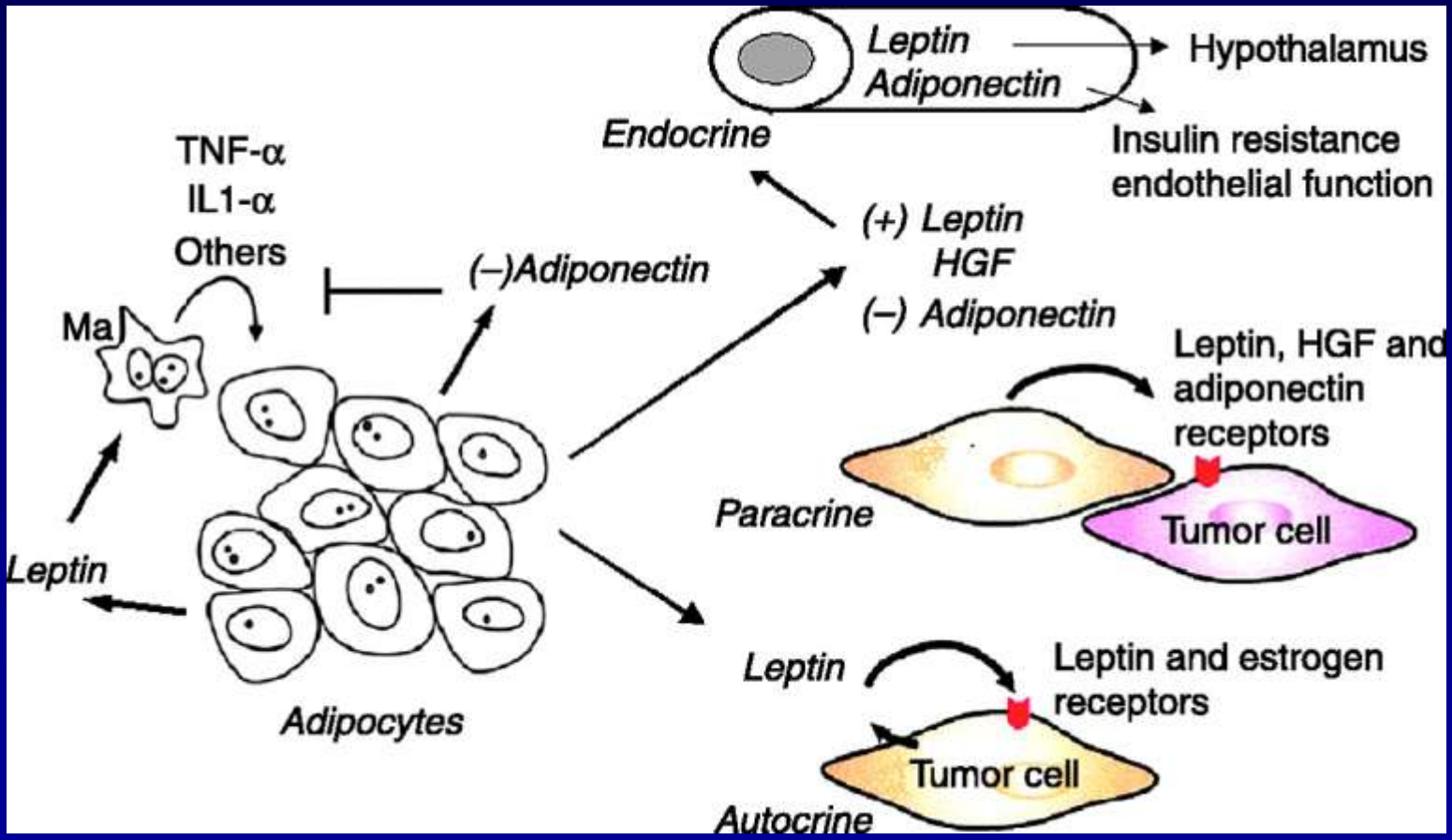
Necrotic adipocytes surrounded by macrophages

(Subbaramaiah K et al. Cancer Prevention Research 2011)



Adipokines in Cancer Risk and Progression

Adipokines as paracrine factors: ligand and receptor



Vona-Davis and Rose *Endocr Relat Cancer 2007;14:189-206*

Leptin and Breast Cancer Prognosis

Toronto Breast Cancer Cohort Study

Population:

- n=512 women with newly diagnosed breast cancer 1989-1996
- fasting blood draw 6 weeks post-op, before systemic therapy
- mean BMI=25.5 kg/m^2

Results: Leptin : BMI - Pearson r = 0.80

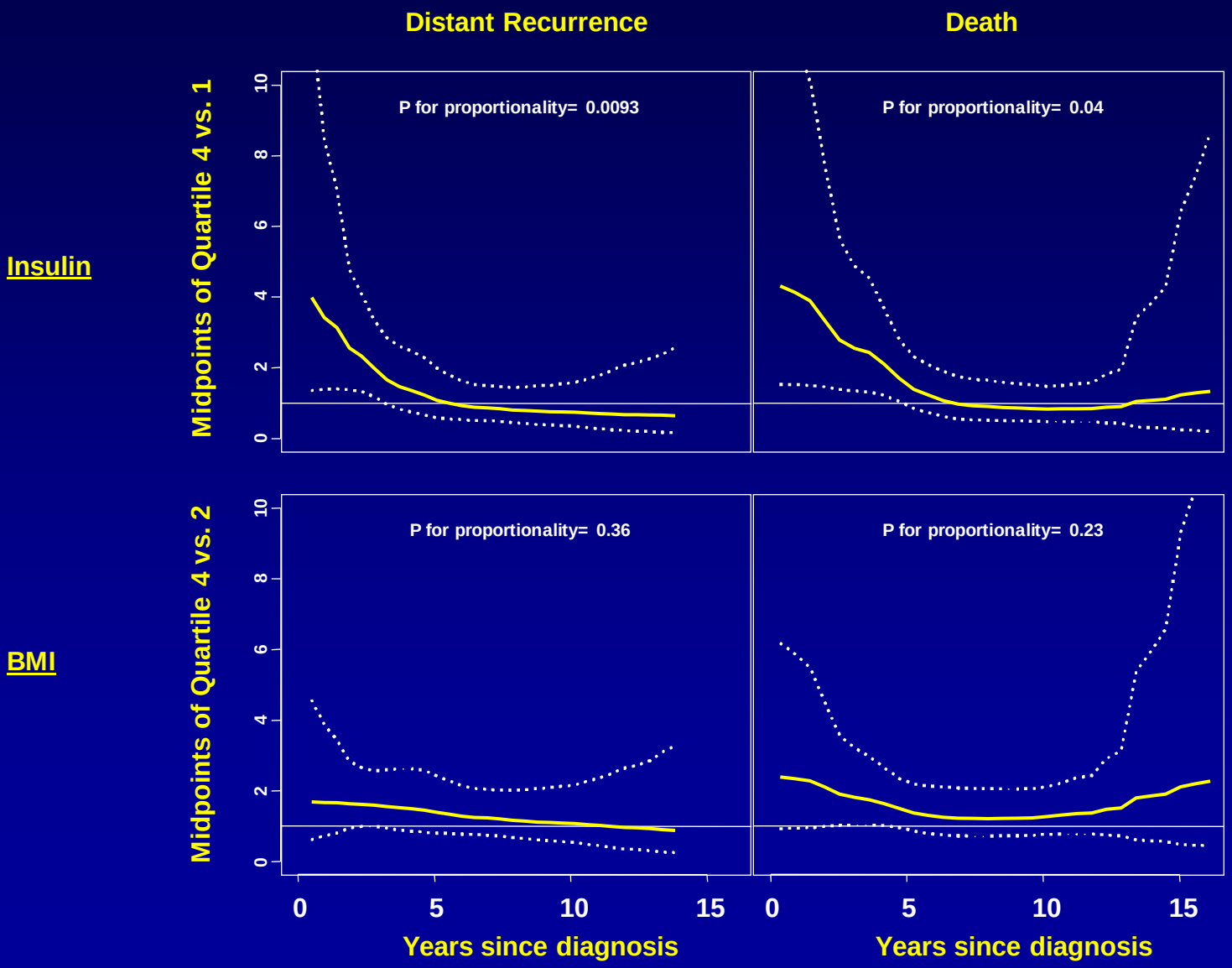
	Leptin (ng/ml) (mean)	DDFS HR		OS HR	
		Univariate	Adjusted*	Univariate	Adjusted*
Q1	4.97	1.16	1.0	1.23	1.15
Q2	10.2	1	1	1	1
Q3	16.2	1.09	1.12	1.10	1.09
Q4	27.4	1.58	1.52	1.71	1.56
		p=0.005	p=0.0055	p<0.001	p=0.011

* adjusted for age, T, N, grade, ER, pgR, adjuvant chemotherapy and hormone therapy

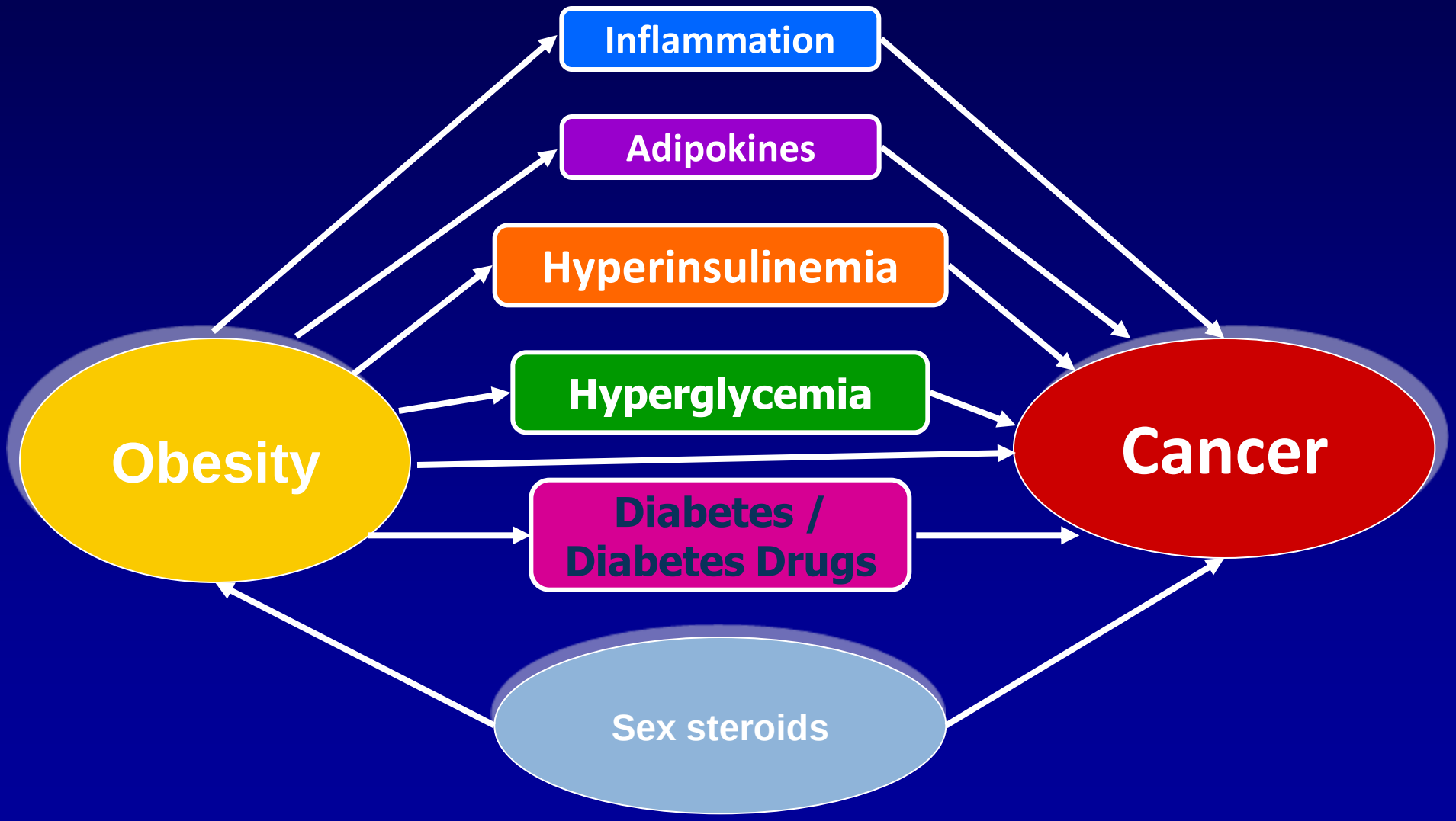
Goodwin PJ et al. J Clin Oncol 2011 (in press)

Temporal Pattern of Hazard Ratios for Fasting Insulin and BMI

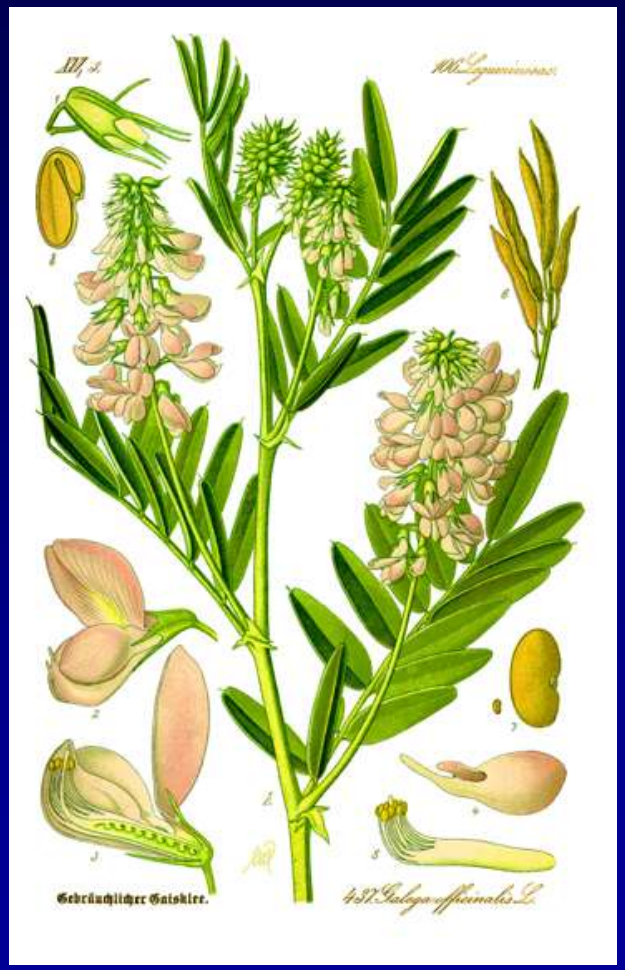
Toronto Breast Cancer Obesity Study (JCO 2011 in press)



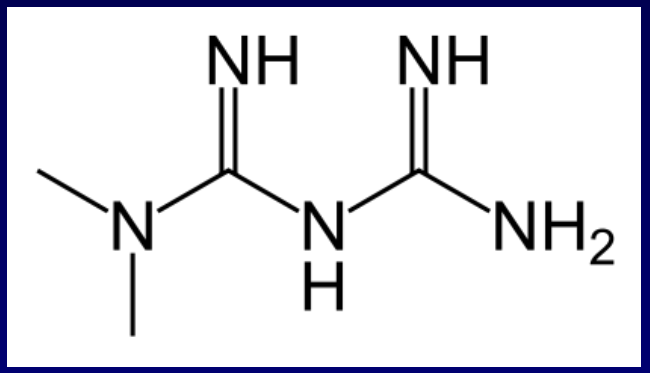
Obesity, Insulin Resistance and Cancer
Potential Mechanisms



Metformin (Glucophage–Aventis)



Galega officinalis (Goat's rue, French lilac)



- Widely used as treatment for type II diabetes
- Well tolerated, minor GI toxicity
- Lactic acidosis, severe but rare
- Lowers blood glucose and insulin levels without causing weight gain
- AMPK activator, but mechanism uncharacterized

Observational Studies of Metformin and Breast Cancer Risk

Year	Author	Study Type	HR (95% CI)	Comparison
2009	Libby	Cohort	0.60 (0.32-1.10)	Metformin users vs not
2009	Currie	Cohort	0.88 (0.48-1.63)	Metformin now vs insulin
2010	Bodmer	Nested case control	0.44 (0.24-0.82)	Metformin > 5 yrs vs not
2010	Bosco	Nested case control	0.81 (0.63-0.96)	Metformin > 1 yr vs not
2010	Decensi	Meta-analysis	0.70 (0.28-1.77) RR	Bosco published after meta-analysis

None have reported details of breast cancer characteristics

Libby G, Bonnelly LA, Donnan PT, et al. Diabetes Care 2009; 32:1620-5.

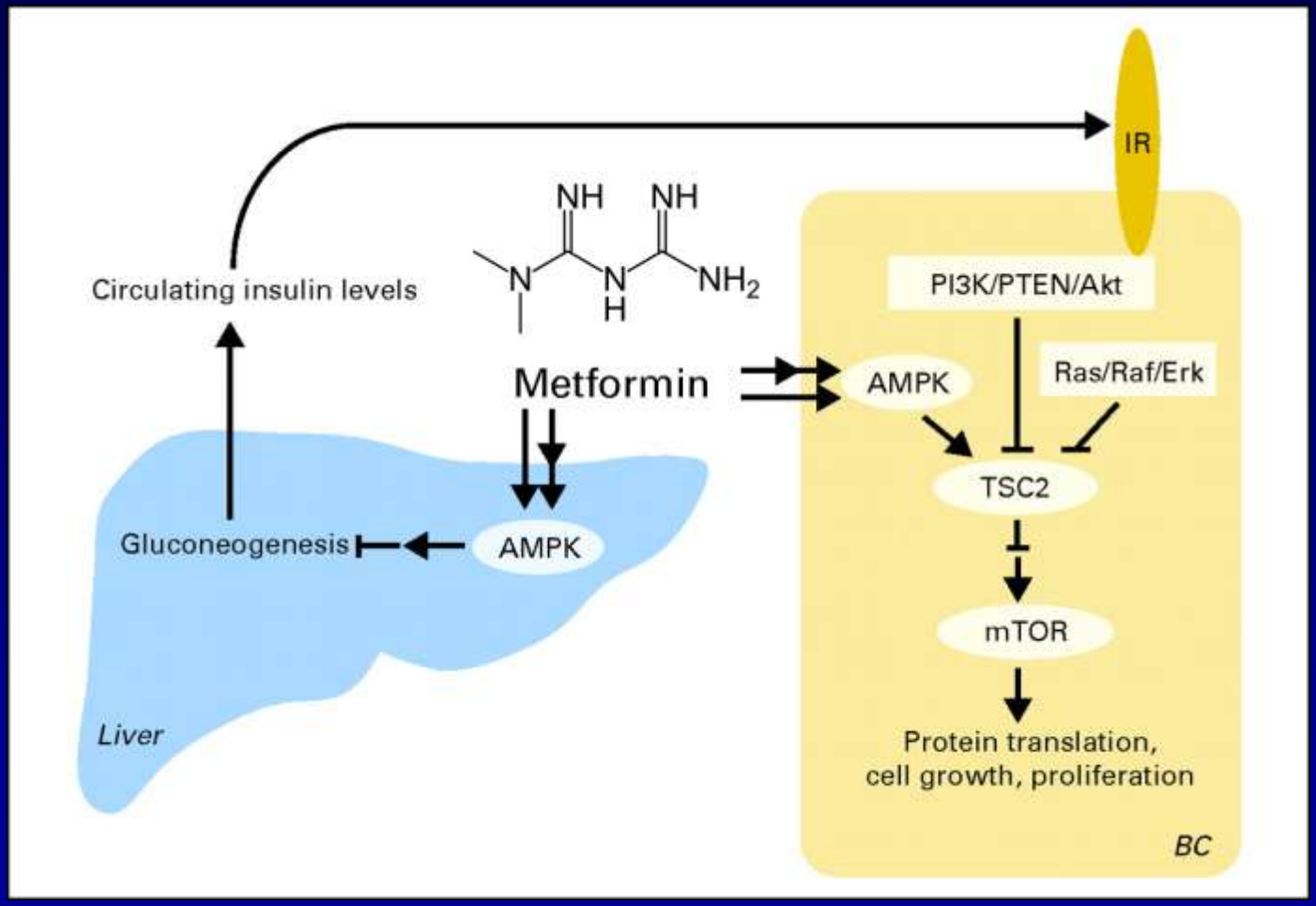
Currie CJ, Poole CD, Gale EA, et al. Diabetologia 2009;52: 1766-77.

Bodmer M, Meier C, Krahenbuhl S, et al. Diabetes Care 2010; 33:1304-8

Bosco JLF, Antonsen S, Sorensen HT, et al. Cancer Epidemiol Biomarkers Prev 2011; 20:101-111

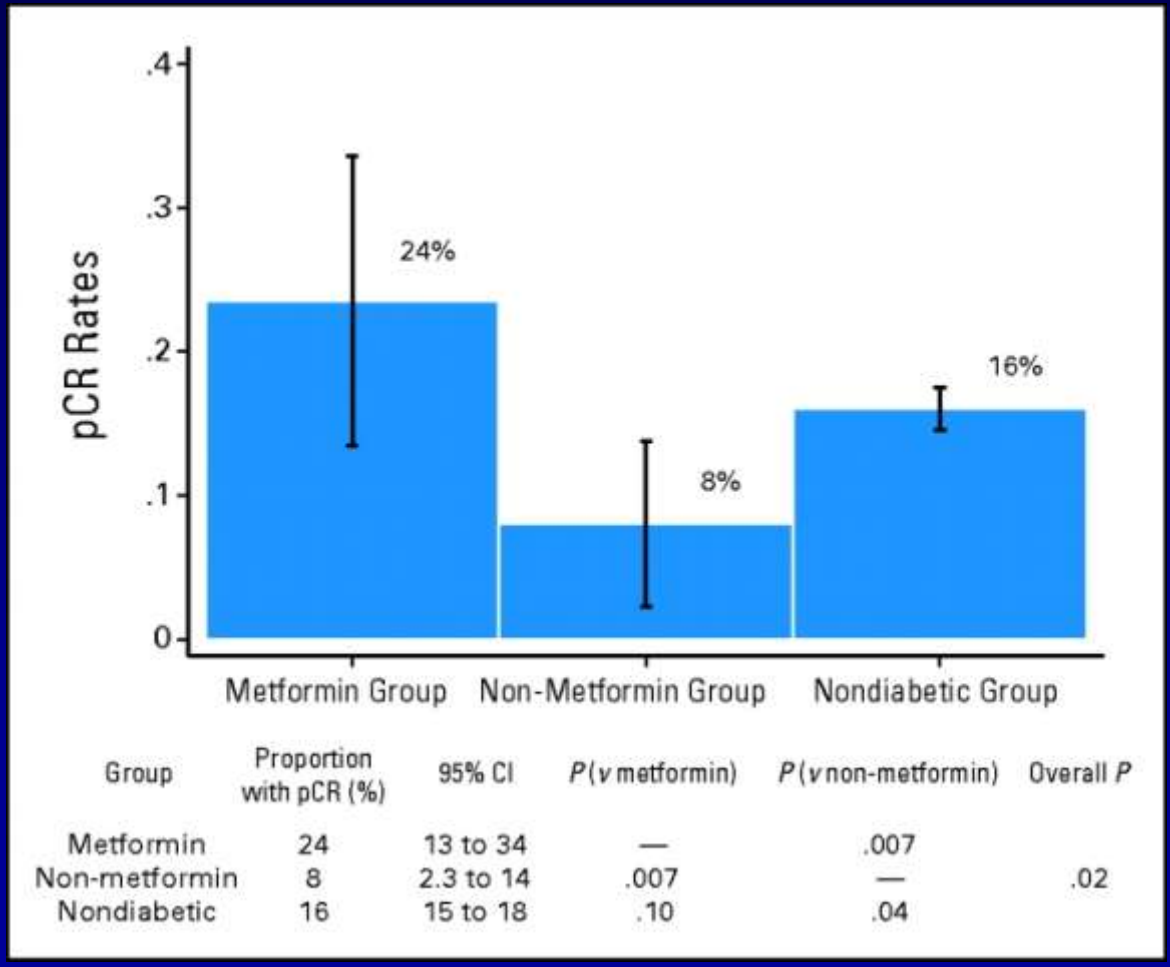
DeCensi A, Puntoni M, Goodwin P, et al. Cancer Prev Res 2010; 3:1451-1461

Mechanism of Metformin Action in the Clinical Setting



Adapted from Goodwin P J et al. J Clin Oncol 2009; 27:3271-3273

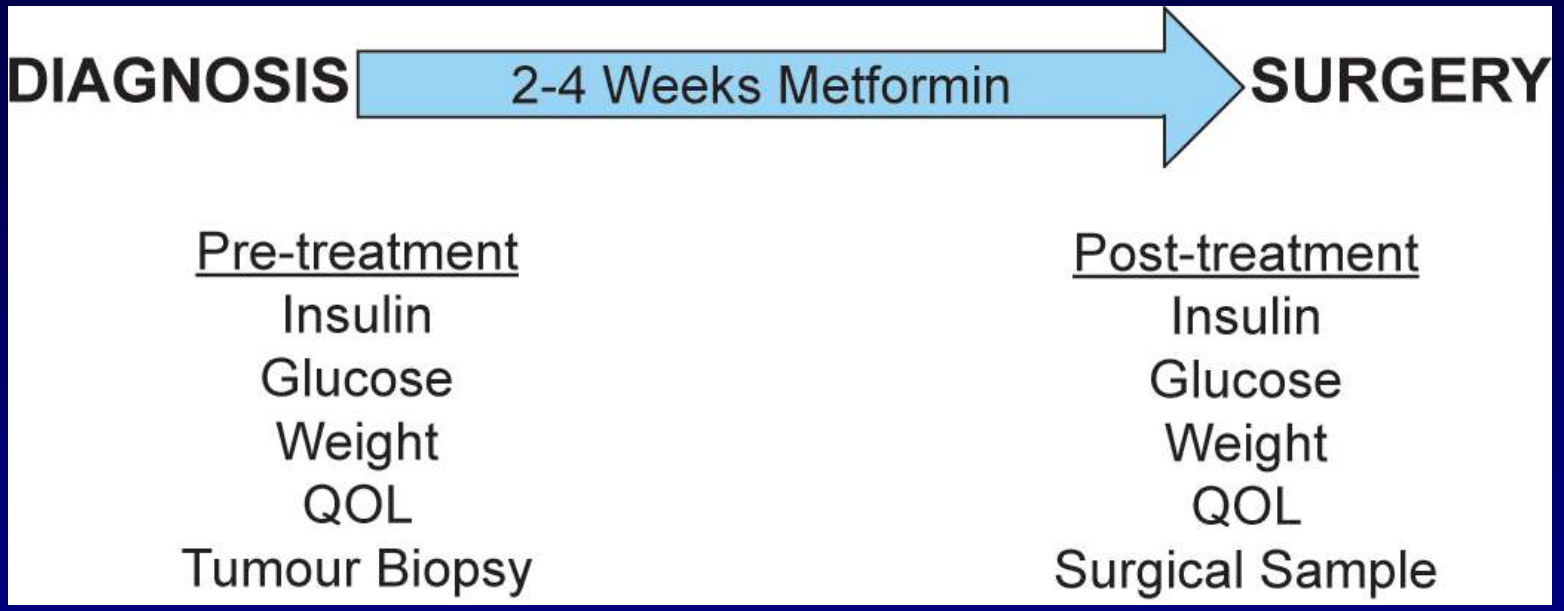
Pathologic Complete Response Between Study Groups (Metformin, No Metformin, Non-Diabetic)



Group	Proportion with pCR (%)	95% CI	*P* (*v* metformin)	*P* (*v* non-metformin)	Overall *P*
Metformin	24	13 to 34	—	.007	
Non-metformin	8	2.3 to 14	.007	—	.02
Nondiabetic	16	15 to 18	.10	.04	

Jiralersprong S et al. J Clin Oncol 2009; 20:3297-3302

Neoadjuvant “Window of Opportunity” Study



Physiology
Insulin
Glucose
Body mass index

Tumour Cell
Proliferation: Ki67
Apoptosis: TUNEL, cleaved caspase-3

Molecular Signalling
Phosphorylation: AKT(Ser473), AMPK(Thr172)

NCIC CTG MA.32 STUDY SCHEMA

T1–3*, N0-3,M0 invasive breast cancer diagnosed within 1 year
Any radiotherapy, chemotherapy**, endocrine therapy, trastuzumab, biologics, bisphosphonates

* If pT1C, ≥ 1 adverse prognostic factor

** CXT must be completed

RANDOMIZE

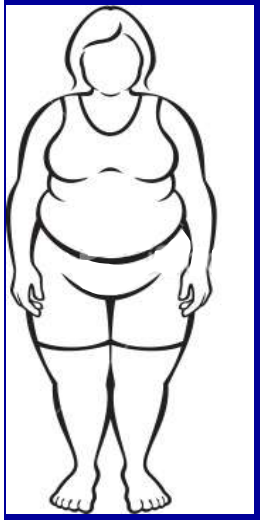
Metformin
850 mg po bid X 5 years
(includes 4-week ramp-up of 850mg po daily)

Identical Placebo
One caplet po bid X 5 years
(includes 4 week ramp-up of one caplet po daily)

Primary Outcome:	Invasive cancer free survival
Secondary Outcome:	Overall survival, Distant Disease-Free Survival, Breast Cancer Free Interval, Adverse Events, Hospitalization (CV, diabetes), QOL (888 subjects)
Embedded Correlative:	Weight, Fasting Insulin (baseline, 6 months, 5 years), Tumour Tissue
Sample Size:	3,582 (431 events) – 5 year IDFS 0.85 in placebo arm, HR =0.76, α=0.05 β=0.20 2 interim analyses (benefit, futility) at 144 and 288 events Planned subset analyses (α=0.10, 2 sided; β=0.80) in ER/PgR neg (HR 0.65) and Triple Neg (HR 0.55)

FUNDED BY: NCI (US), CCS, BCRF, Apotex Canada, CBCF, Komen

Potential Predictors of Metformin Benefit in Human Cancer

		Indirect Effect (Insulin-Mediated)	Direct Effect
Host 	↑ BMI	+	
	Physical Inactivity	+	
	↑ Fasting Insulin	+	
	Insulin Resistance	+	
	OCT1/2/3 (liver)	+	
	Germline gene expression	+	
Tumor 	Tumor gene expression	+	+
	IR/IGF-IR	+	
	↑ PI3K/mTOR	+	+
	OCT1/2/3		+
	LKB1		+

DOES WEIGHT CHANGE ALTER BREAST CANCER OUTCOMES?

Prognostic Effects of Weight Gain

		n	Weight Gain (kg)	Prognostic Effect
Bonomi	1984	67	8.2	Adverse
Heasman	1985	237	4.3	None
Chlebowski	1986	62	>10	Adverse
Chlebowski	1986	62	< 10	None
Goodwin	1988	637	1.21-5.55	None
Camoriano	1990	545	5.9 (premenopausal)	Adverse (premenopausal)
Levine	1991	32	4.2	None
Goodwin	2001	445	1.6	None
Kroenke	2005	"Healthy" subsets "Less Healthy" subsets	> 2kg vs. 0.5 kg loss > 2kg vs. 0.5 kg loss	Adverse None
Caan	2006	3215	5-10% >10%	None None

Weight Change and Survival After Breast Cancer Diagnosis

Population - Nurses' Health Study, 5204 non-metastatic breast cancer 1976-2000

Measurement - self-report weight before and ≥ 12 months post diagnosis

- self-report vs. actual weight r=0.99

Results

Breast Cancer Mortality (RR)

		BMI Change Post Diagnosis (kg/m²)				
		Loss >0.5	Maintain	Gain 0.5-2.0	Gain >2.0	p
Smoking	• Never	1.01	1.00	1.35	1.64	0.03
	• Ever	1.18	1.00	1.10	1.05	0.84
Baseline BMI	• <25	1.41	1.00	1.63	1.90	<0.01
	• ≥25	0.81	1.00	0.78	0.75	0.18
N Stage	• N0	1.10	1.00	1.22	1.74	0.007
	• N1	1.06	1.00	1.18	1.10	0.74
T Stage	• T1	1.04	1.00	0.97	1.78	0.003
	• T>1	0.87	1.00	1.07	0.99	0.89

Kroenke CM et al. JCO 2005;23:1370-1378

LISA Study – RCT of a Telephone Based Weight Loss Intervention vs. Education

- 19 phone calls over 2 years based on Diabetes Prevention Program
- Goals → up to 10% weight loss (to BMI ≥ 21 kg/m^2)
  → calorie deficit 500-1000 kcal per day
  → physical activity 150-200 minutes per week

	Effect on Weight (kg)*	
	Intervention n=165	Control n=158
Baseline	82.8	81.3
5 months	-4.7	-0.2
12 months	-5.5	-0.7
18 months	-3.8	-0.3

* Effect similar in women with BMI ≤ 30 kg/m^2 or > 30 kg/m^2

PJ Goodwin (PI) / R Segal (Call Center Lead) / OCOG
ASCO 2011

Intentional Weight Loss and Breast Cancer Risk

Cohort Studies		Weight Loss	Breast Cancer Risk
Eliassen	2006	≥ 14.5%	↓ 57%
Harvie	2005	≥ 5%	↓ 64%

Bariatric Surgery Studies			Weight Loss	Cancer Risk
Sjöström	2009	(women)	31.9%	↓ 42%
Adams	2009	(women)	31.0%	↓ 24%
Christou	2008	(both)	31.9%	↓ 78%

Change in Physiologic Mediators	
Decrease	**Increase**
Estradiol	SHBG
CRP	± IGFBPs
TNF-α	± IGF-I
IL-6	
Insulin	
± IGFBPs	
± IGF-I	

Byers T et al. Diab Obes Met 2011 (in press)

Effects of Exercise on Insulin in Breast Cancer

- exercise fairly consistently associated with reduced insulin levels in obese and diabetic individuals without breast cancer
- results inconsistent in breast cancer subjects

	Type of Exercise	Effect on Insulin	
Fairey, Courneya (2003)	Aerobic	No change	p=0.94
Schmitz, Yee (2005)	Weight training	No change	p=0.46
Ligibel (2008)	Mixed weight and aerobic	Reduction	p=0.07
Irwin (2009)	Aerobic	Reduction	p=0.09

Obesity and Breast Cancer Outcomes Conclusions

- Obesity has been associated with adverse breast cancer outcomes
- Several potential biologic mediators of obesity effects in cancer have been identified, some may lead to targeted interventions
- Lifestyle or surgical interventions leading to weight loss and/or enhanced physical activity could potentially reverse these effects

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NCI(US)

Thousands of patients who have participated in our studies