Lifestyle Factors and Breast Cancer Risk

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Evolution … Lifestyle …

Michelangelo's "David"
1501-1504

Michelangelo's "McDavid"
2012

Body Size and Breast Cancer Risk

	Adverse	No Effect	Protective
Current BMI	Postmenopausal E+ P+ HR 1.7 *(Suzuki 2009)* Premenopausal E- P- H- HR 1.43 *(Pierobon 2013)*	Postmenopausal E- P- HR 0.90 *(Suzuki 2009)* Postmenopausal E- P- H- HR 0.99 *(Pierobon 2013)* Premenopausal E- P- HR 1.03 *(Suzuki 2009)*	Premenopausal E+ P+ HR 0.80 *(Suzuki 2009)*
Adult Weight Gain	E+P+ HR 2.03 E-P- HR 1.34 *(Vrieling 2010)*		
Birth Size	E+ P+ HR 1.16 *(Hurley 2011)*	E- P- HR 1.03 *(Hurley 2011)*	

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)		

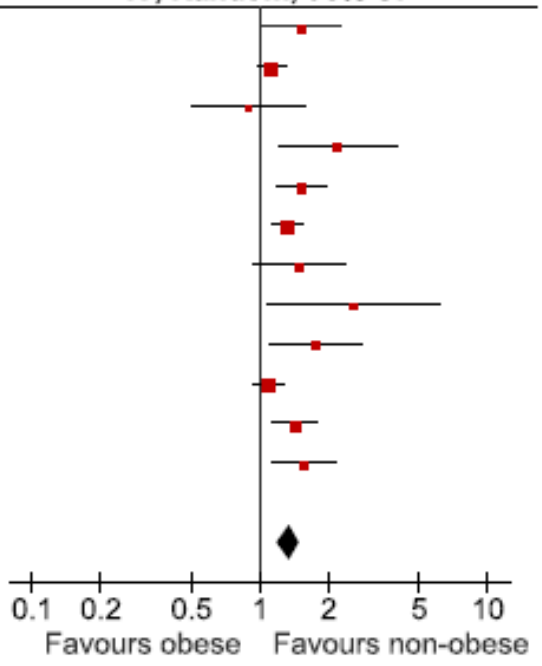
Protani M et al. BCRT 2010: 123:627-635

Effect of Obesity on Overall Survival in ER/PgR Positive Breast Cancer

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Azambuja 2010	0.41210965	0.20016032	6.1%	1.51 [1.02, 2.24]
Berclaz 2004 (1)	0.11332869	0.07336252	15.9%	1.12 [0.97, 1.29]
Chen 2010	-0.11653382	0.2941959	3.4%	0.89 [0.50, 1.58]
Daling 2001	0.77932488	0.30459913	3.2%	2.18 [1.20, 3.96]
davidson 2005	0.41871033	0.12724721	10.6%	1.52 [1.18, 1.95]
Dignam 2003	0.27002714	0.07994966	15.2%	1.31 [1.12, 1.53]
Enger 2004	0.39204209	0.23705169	4.8%	1.48 [0.93, 2.36]
Goodwin 2002	0.9439059	0.44232693	1.6%	2.57 [1.08, 6.12]
Keegan 2010	0.57097955	0.23807556	4.7%	1.77 [1.11, 2.82]
Majed 2008	0.0861777	0.08099556	15.1%	1.09 [0.93, 1.28]
Sparano 2010	0.35065687	0.11815628	11.4%	1.42 [1.13, 1.79]
Vitolins 2008	0.43825493	0.16578174	7.9%	1.55 [1.12, 2.15]
Total (95% CI)			**100.0%**	**1.35 [1.20, 1.51]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 21.22$, df = 11 (P = 0.03); $I^2 = 48\%$

Test for overall effect: Z = 5.08 (P < 0.00001)



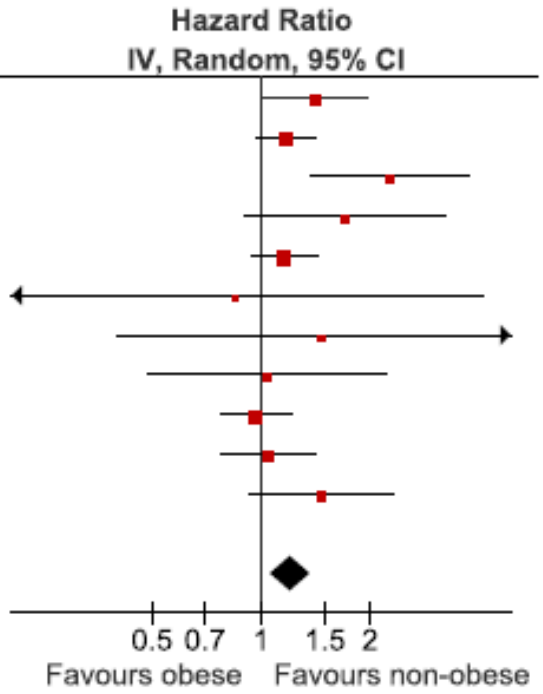
Niraula S and Goodwin PJ 2011

Effect of Obesity on Overall Survival in ER/PgR Negative Breast Cancer

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Azambuja 2010	0.3435897	0.1702273	10.6%	1.41 [1.01, 1.97]
Berclaz 2004	0.15700375	0.09564612	21.2%	1.17 [0.97, 1.41]
Chen 2010	0.81536481	0.25538942	5.5%	2.26 [1.37, 3.73]
Daling 2001	0.53062825	0.32449003	3.6%	1.70 [0.90, 3.21]
Dignam 2006	0.14842001	0.10729555	19.0%	1.16 [0.94, 1.43]
Fetting 1998	-0.16251893	0.80497364	0.6%	0.85 [0.18, 4.12]
Goodwin 2002	0.3852624	0.66406992	0.9%	1.47 [0.40, 5.40]
Keegan 2010	0.03922071	0.38397165	2.7%	1.04 [0.49, 2.21]
Majed 2008	-0.03045921	0.11781112	17.1%	0.97 [0.77, 1.22]
Sparano 2010	0.04879016	0.15312033	12.3%	1.05 [0.78, 1.42]
Vitolins 2008 (1)	0.3852624	0.23359261	6.4%	1.47 [0.93, 2.32]
Total (95% CI)			**100.0%**	**1.21 [1.07, 1.37]**

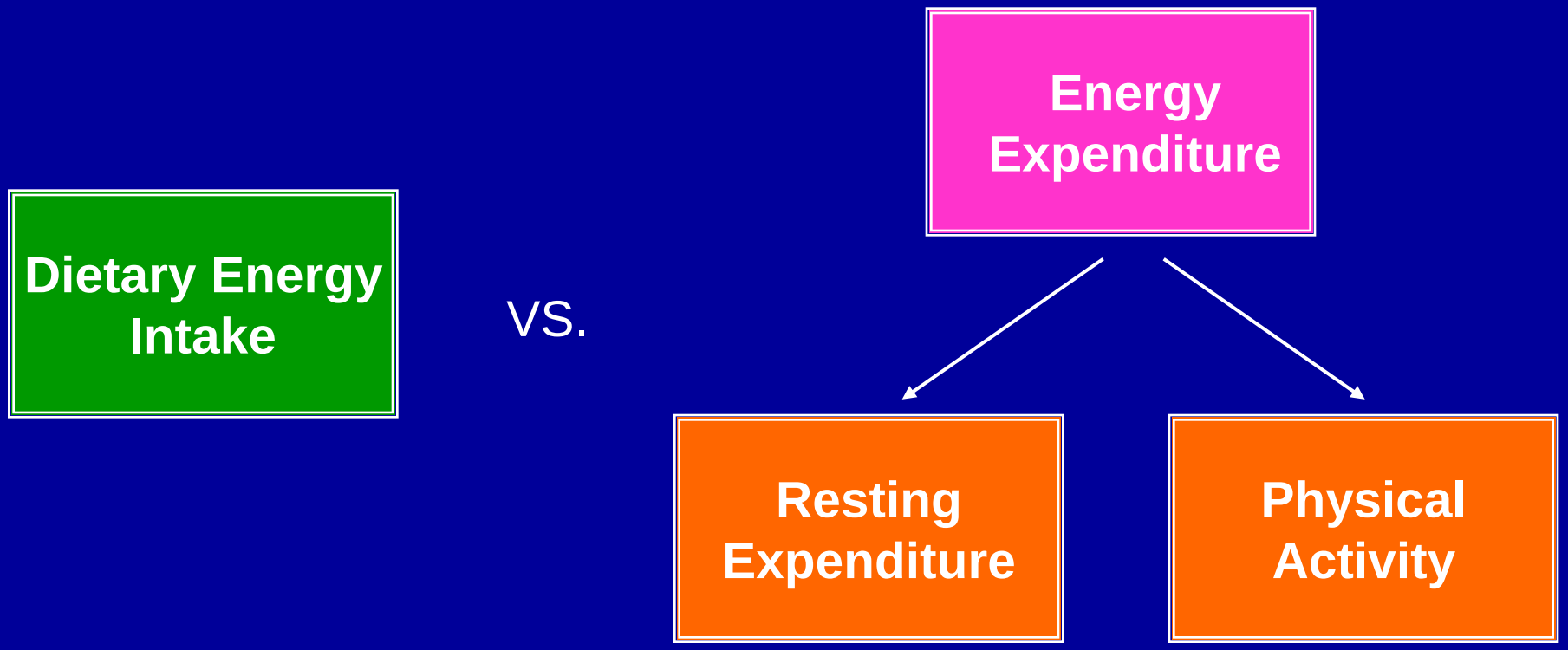
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.48$, df = 10 (P = 0.20); $I^2 = 26\%$

Test for overall effect: Z = 2.95 (P = 0.003)

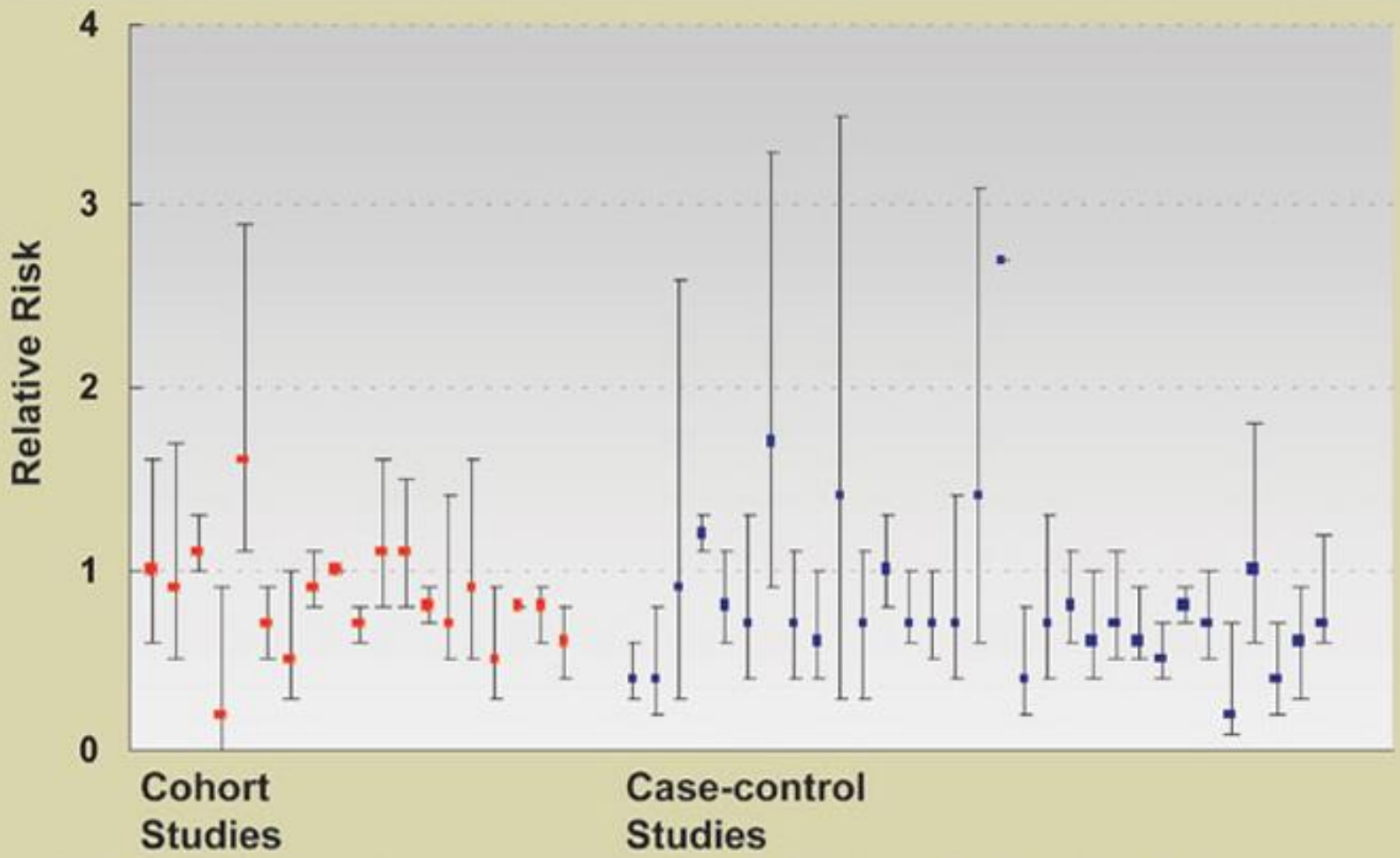


Niraula S and Goodwin PJ 2011

Obesity Reflects Energy Imbalance



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.

ASCO

Physical Activity and Breast Cancer Risk

- >20 cohort, >30 case-control studies
- Modest reduction in breast cancer risk with increased lifetime recreational physical activity
  - Nurses' Health Study
    RR 0.82 (0.70 – 0.97) 7 hrs/wk vs < 1hr/wk
  - ACS Cancer Prevention Study II (Postmenopausal)
    RR 0.71 (0.49-1.02) > 40 MET hr/wk vs. 0-7 MET hrs/wk
- Moderate to vigorous physical activity for > 3 hours per week associated with 30-40% reduced breast cancer risk
- Protective effect may be stronger after the menopause

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)**

BC Risk: Women's Health Initiative (WHI) – Low Fat Diet RCT

Population: 48,835 postmenopausal women 50-79 $\bar{x}$ = 62.3 years
No prior breast cancer; 8.1 year average follow-up
Gail model risk ≥1.7% / 5 years

Intervention:

	Goal	Intervention vs. Control
Fat	20% cals	10.7% year 1, 8.1% yr 6
Fruits/Vegetables	≥ 5/day	1 serving
Grains	≥ 6/day	transient difference

Results:

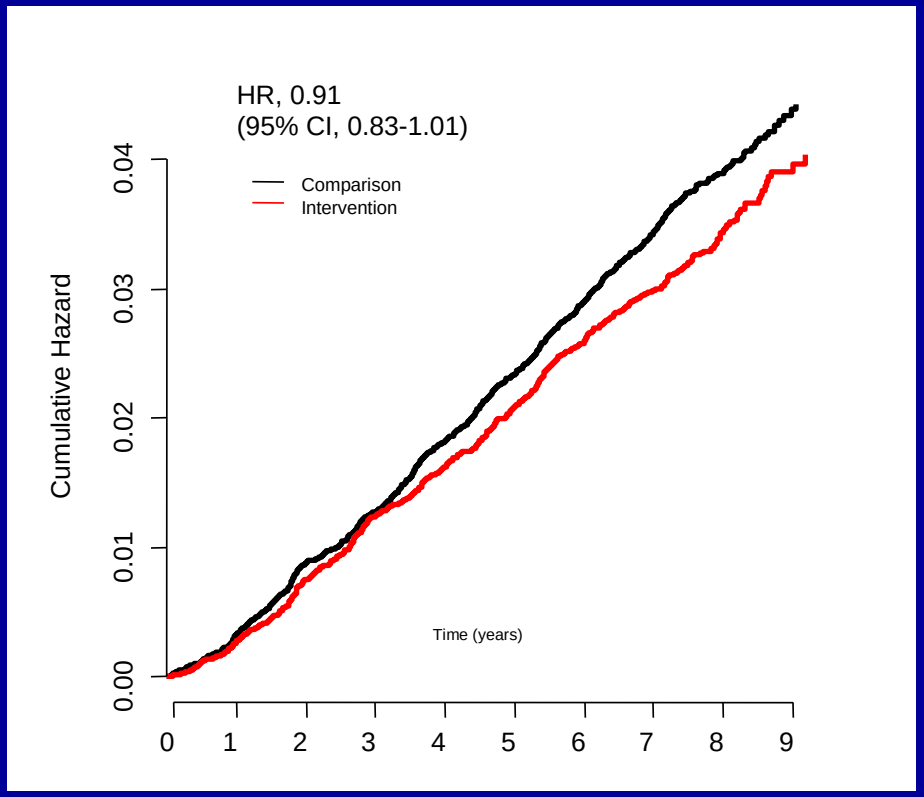
Invasive Breast Cancer HR 0.91 (0.83-1.01)
(0.42% vs. 0.45% annualized)

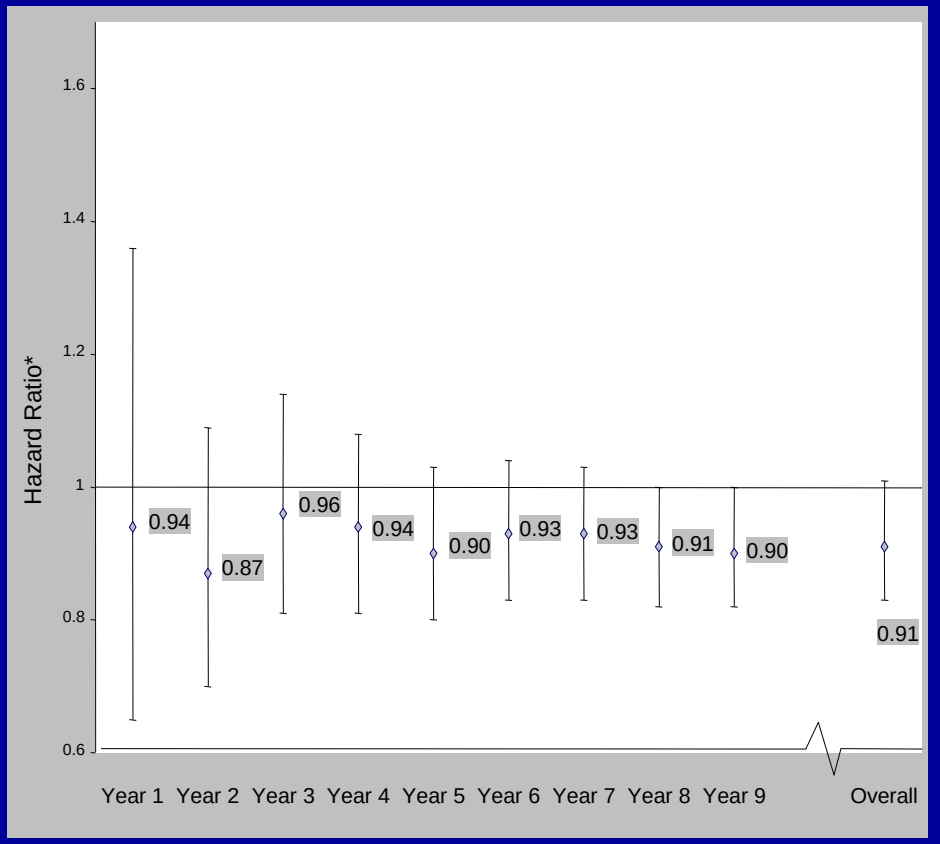
Greatest Effect

1) More adherent women
   HR 0.85 (0.71-1.02)
2) Higher fat intake at baseline
   HR 0.78 (0.64-0.95) Q4 p (trend) 0.04
3) ER/PgR discordant cancer
   HR 0.64 (0.49-0.84) ER+ PgR-
   HR 0.67 (0.29-1.54) ER- PgR+

Prentice RL et al JAMA 2006; 295:629

WHI Dietary Fat Reduction Trial
Breast Cancer Cumulative Hazard Ratios





BC Outcomes: Women's Intervention Nutrition Study (WINS)

- RCT of dietary fat reduction in postmenopausal women with 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 vs. WHEL

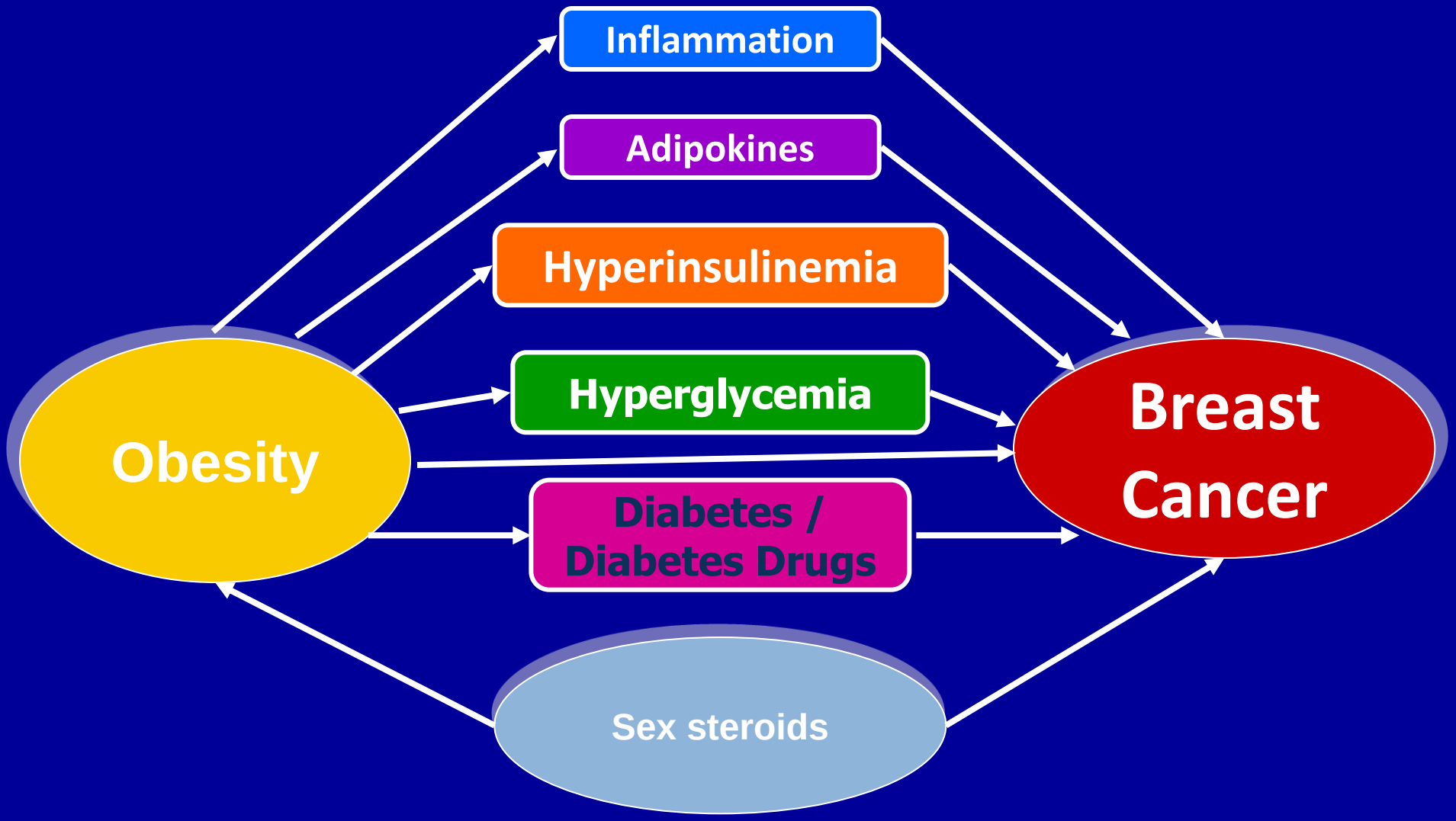
	WINS	WHEL
Population		
Number	2437	3088
Time Post Diagnosis	Up to 1 year	Up to 4 years
Menopausal Status	Post	Pre and Post
Age	48-79	18-70
Intervention Group		
Fat Intake	Reduction maintained	Transient reduction
Weight Change	2.3 kg. relative loss	Modest weight gain
DFS	HR 0.76 (0.60-0.98)	HR 0.96 (0.80-1.14)

Obesity and Breast Cancer

Summary

	Risk	Prognosis
Obesity	Adverse - Postmenopausal E+P+, Premenopausal TN Protective - Premenopausal E+P+	Adverse
Physical Inactivity	Adverse	Adverse
High Dietary Fat	Possibly Adverse (WHI)	Possibly Adverse (WINS/WHEL)

Obesity and Breast Cancer
Potential Mechanisms



Serum Sex Hormones in Postmenopausal Women n=176

	Estrone (pg/ml)	Estradiol (pg/ml)
BMI		
≤ 27.0	27.5	3.4
27.1-30.0	33.6	5.2
≥ 30.1	38.9	6.3
p	< 0.001	< 0.001
Correlation with BMI	r=0.38, p<0.001	r=0.41, p<0.001

Cauley JA et al AM J Epidemiol 1989

Interaction Between BMI / HRT and Breast Cancer

BMI	Absolute Increase in Breast Cancer Risk per 5 Years of HRT Use	
	Estrogen Alone	Estrogen + Progesterone
20 kg/m^2	+ 30%	+ 50%
30 kg/m^2	+ 8%	+ 26%

Potential Interpretation: There is a ceiling for estrogen effect on BC risk – because estradiol levels are higher in obese women, added effects of HRT are less.

Pike MC et al. Ernst Schering Foundation Symposium Proceedings 2007

Mediating Effects of Estrogen and Insulin in the Relation Between Obesity and Breast Cancer Risk

Population:

- case-cohort ancillary study nested in WHI
- fasting insulin, estradiol, BMI, BC risk factors
- not on hormone therapy at baseline

Analysis:

- 414 BC cases (126 ER^-); 486 controls
- mediator analysis → total, direct, indirect effects (expanded analyses of alcohol, estradiol alone)

Results:

(Estradiol was more strongly linked to ER^+ than ER^- BC)

Conclusions:

- Insulin may be a more important mediator than estradiol of the association of BMI with postmenopausal BC risk

Hvidtfeldt UA et al. CEBP 2012; 21:1202-1212

Prospective Study of the Role of Glucose Metabolism in Breast Cancer Occurrence

Population

- prospective ORDET cohort (1987-1992) n=10,663
- 356 breast cancers (median follow-up 13.5 years)
- up to 4 controls / case (age, menopausal status, length of storage

Results

	Breast Cancer Risk (Quartile 4 vs. 1)	
	HR (95% CI)	p (trend)
Glucose	1.63 (1.14-2.32)	0.003*
Insulin	1.33 (0.96-1.86)	0.069**
HOMA – IR	1.44 (1.03-2.02)	0.029**
SHBG	0.72 (0.51-1.02)	0.07

* significance persisted in pre/post menopausal subgroups

** also significant in subgroups < 55 years at diagnosis

Conclusions

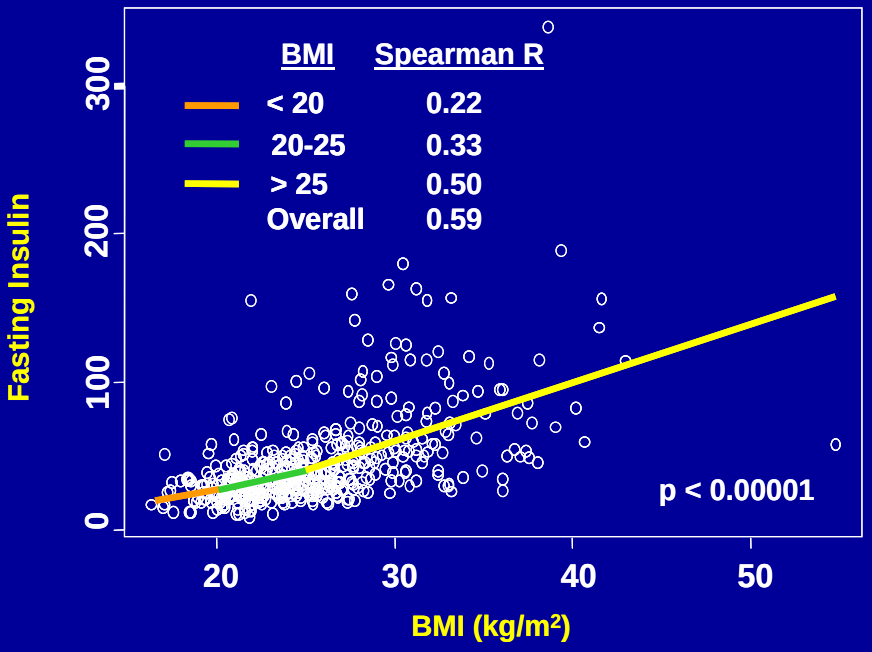
Hyperglycemia and insulin resistance are associated with increased breast cancer risk

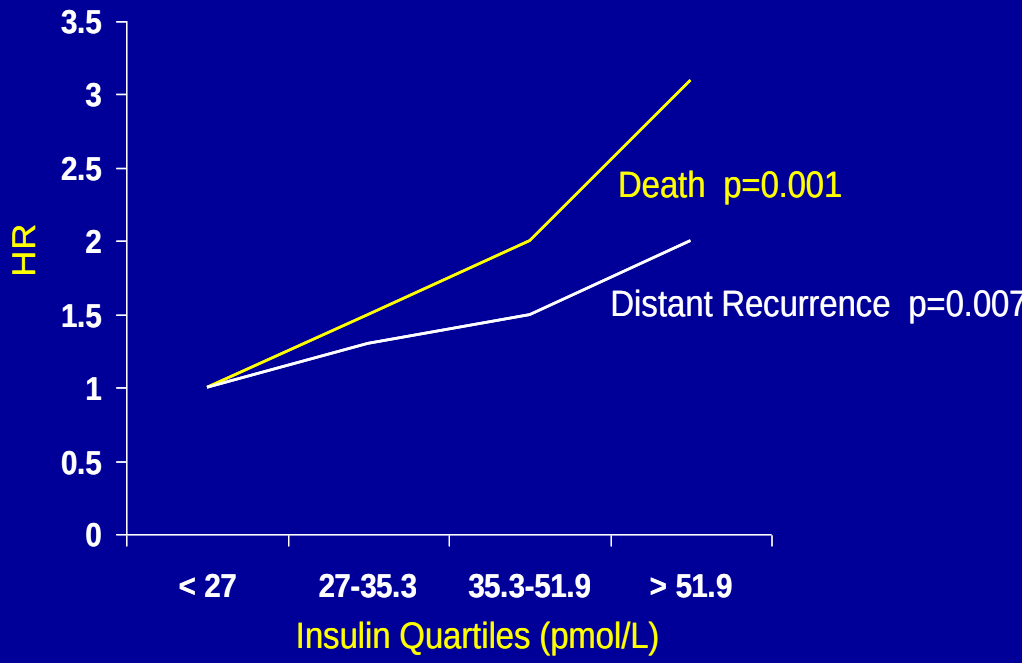
Sieri S et al. Int J Cancer 2011

Insulin is Associated with Poor Breast Cancer Outcomes

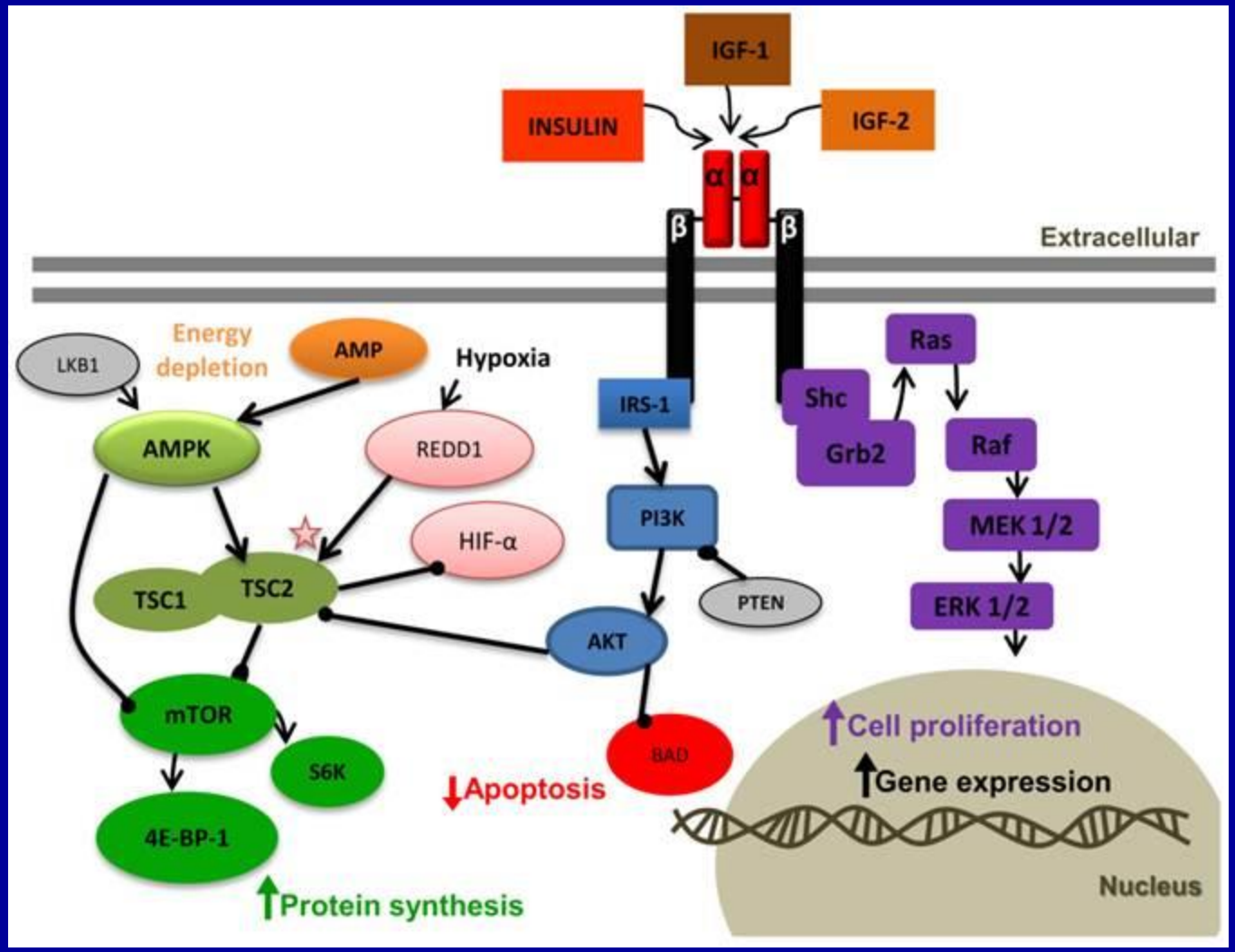
Goodwin PJ ASCO 1999, JCO 2002

Pasanisi 2006, Irwin 2010, Duggan 2010, Emaus 2010, Pritchard 2011





IGF-1R Signaling Pathway



Braun S et al. Int J Biol Sci 2011; 7:1003-1015

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* significance persisted in pre/post menopausal subgroups

** also significant in subgroups < 55 years at diagnosis

Conclusions

Hyperglycemia and insulin resistance are associated with increased breast cancer risk

Sieri S et al. Int J Cancer 2011

Fasting Glucose and Breast Cancer Outcomes

Population:

- 512 early stage breast cancer
- no known diabetes

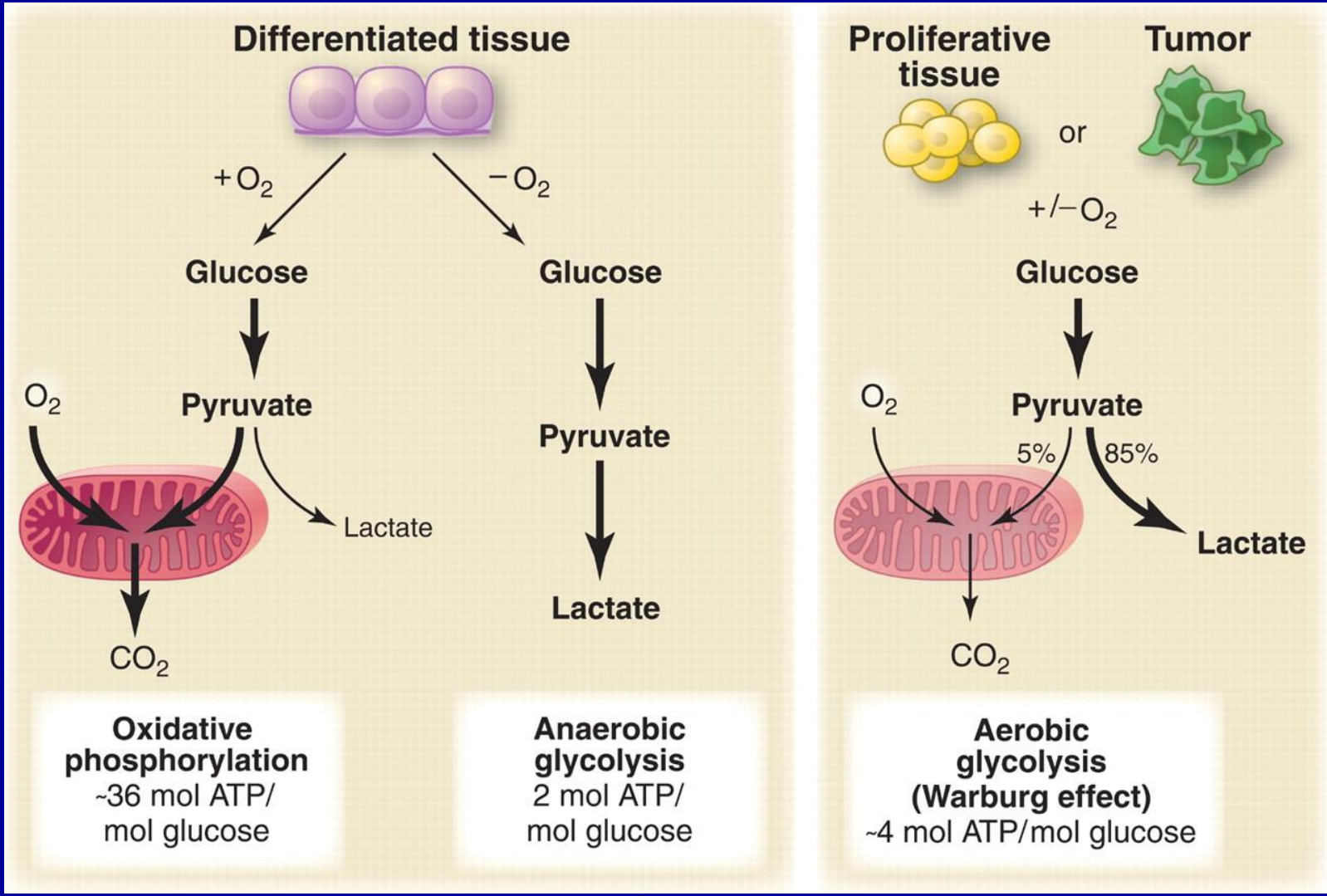
Results:

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=0.034 adjusted		p=0.036 unadjusted p=0.014 adjusted	

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

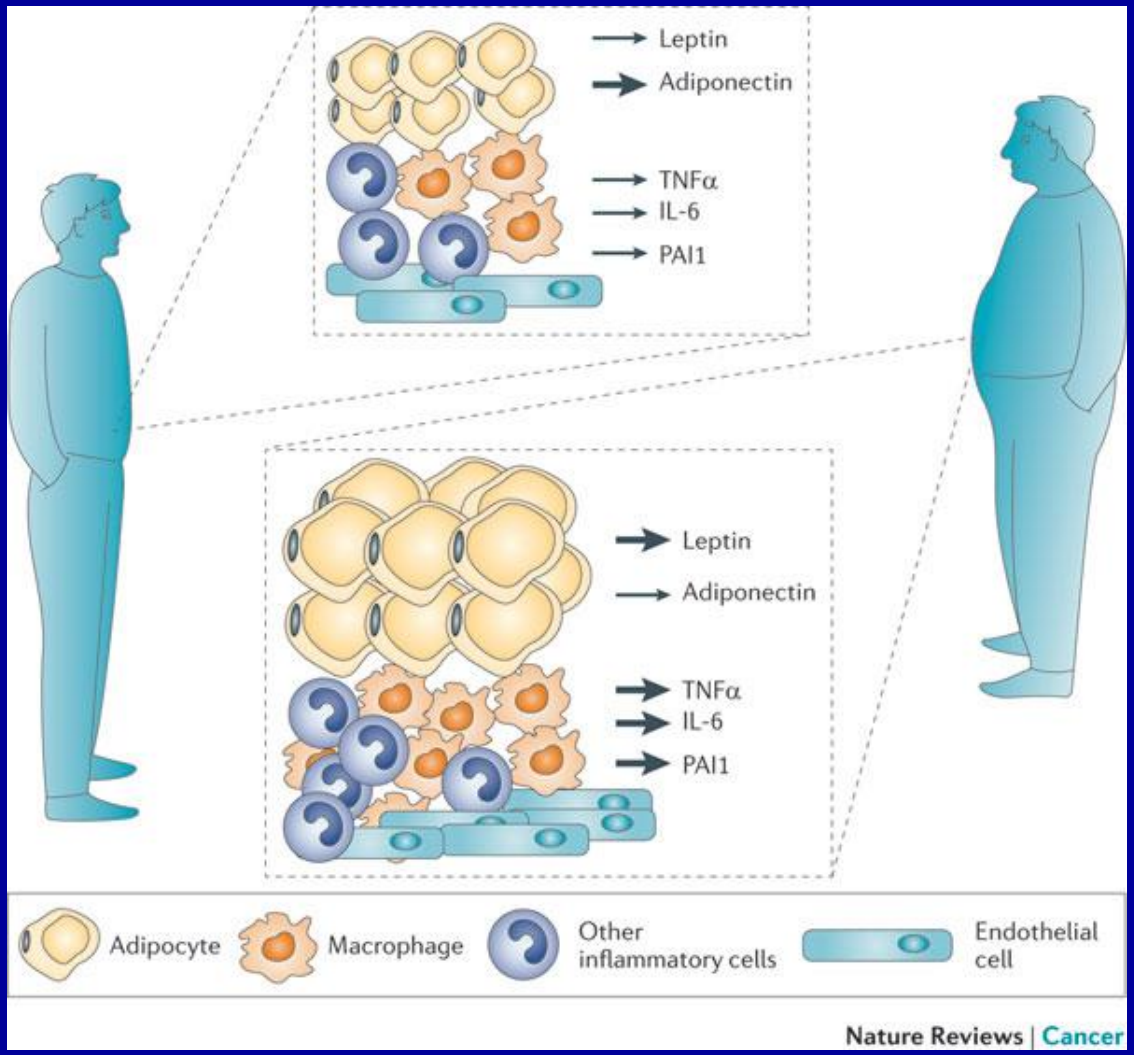
Goodwin PJ et al. J Clin Oncol 2012

Rapidly Proliferating Tissue Metabolizes Glucose "Inefficiently"



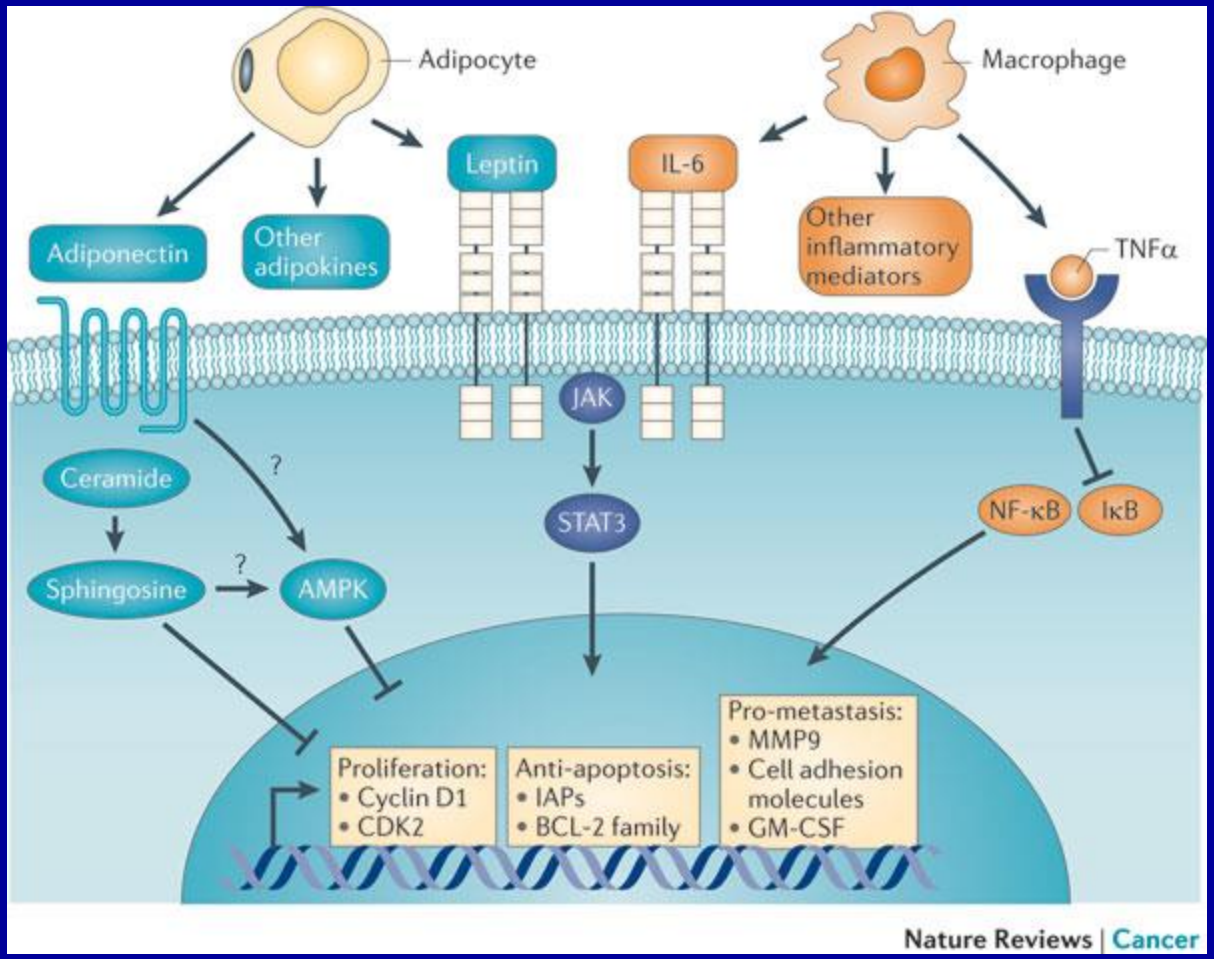
Vander Heiden MG et al. Science 2009; 324:1029-1033

Changes in Adipose Tissue in Obesity



Khandekar MJ et al. Nat Rev Cancer 2011; 11:886-895

Adipokine and Inflammatory Signalling in Obesity

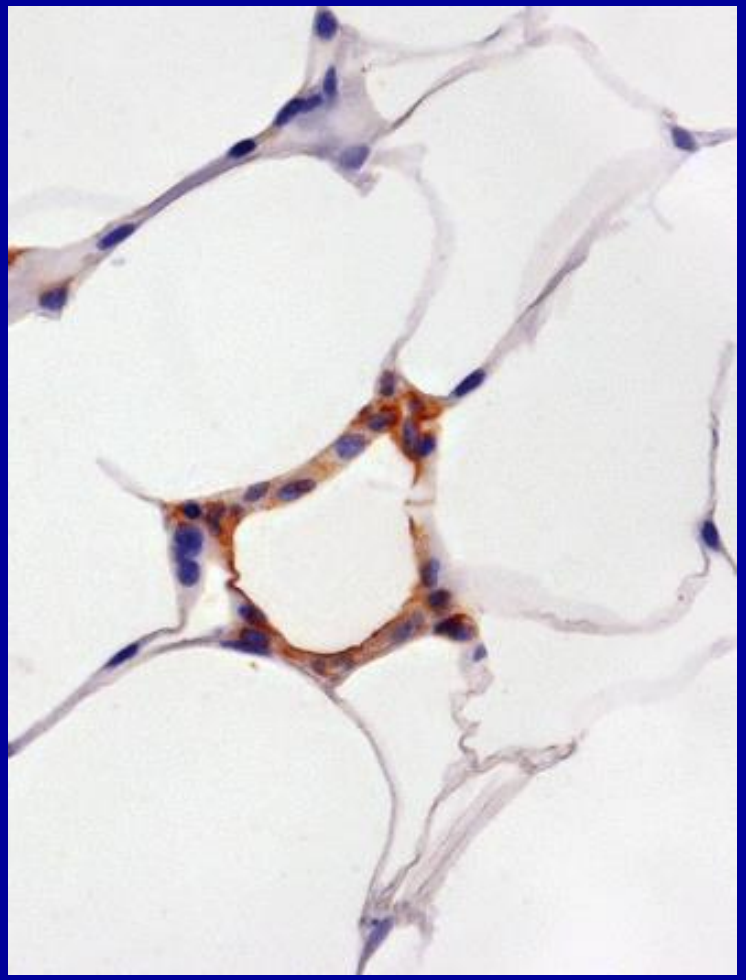


Khandekar MJ et al. Nat Rev Cancer 2011; 11:886-895

Local Inflammation: Crown-Like Structures

Necrotic adipocytes surrounded by macrophages

(Subbaramaiah K et al. Cancer Prevention Research 2011)



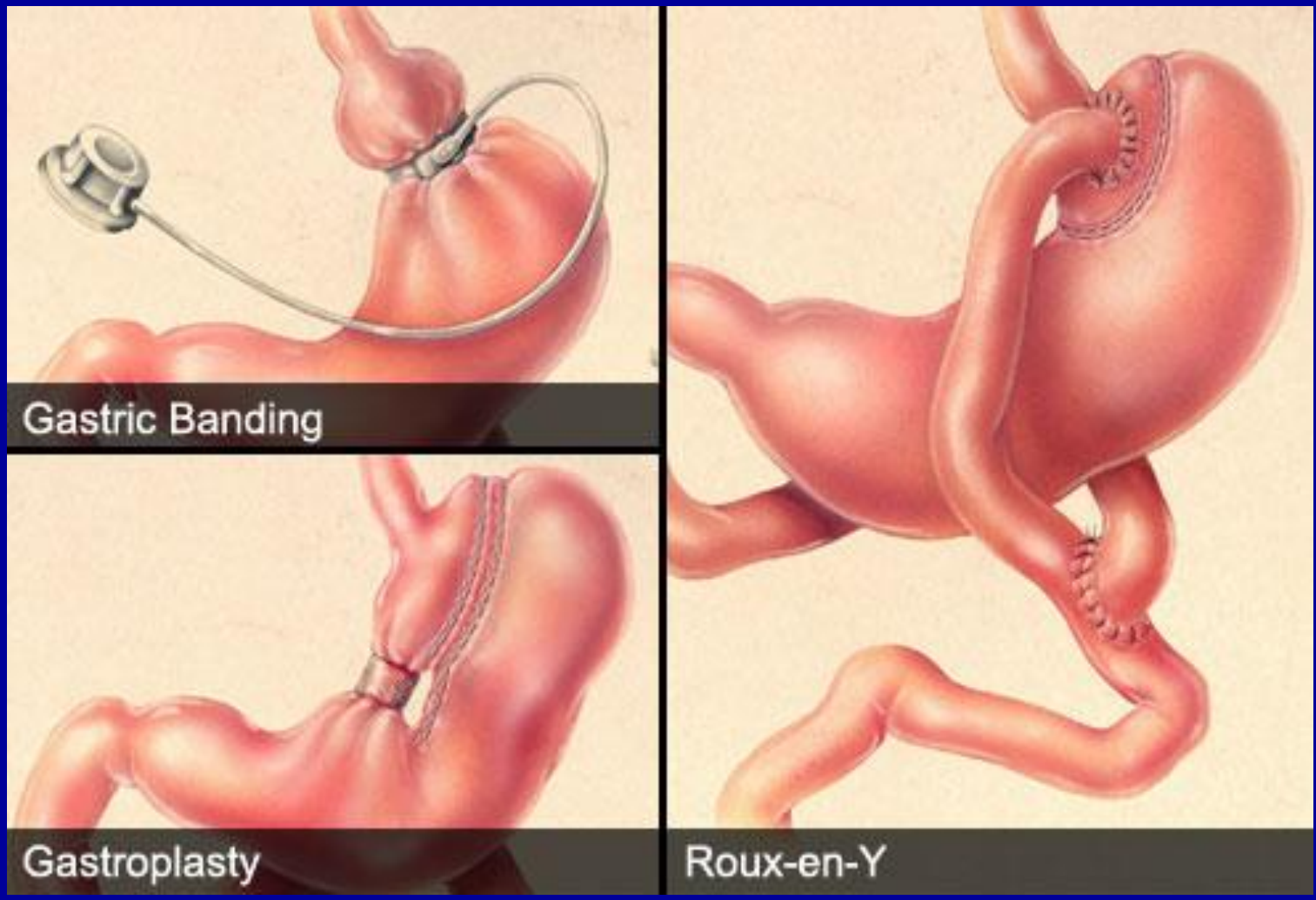
LISA Study – RCT of a Telephone Based Weight Loss Intervention vs. Education

- 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
6 months	-4.7 (5.7%)	-0.2 (0.2%)
12 months	-5.5 (6.6%)	-0.7 (0.8%)
18 months	-3.8 (4.6%)	-0.3 (0.4%)

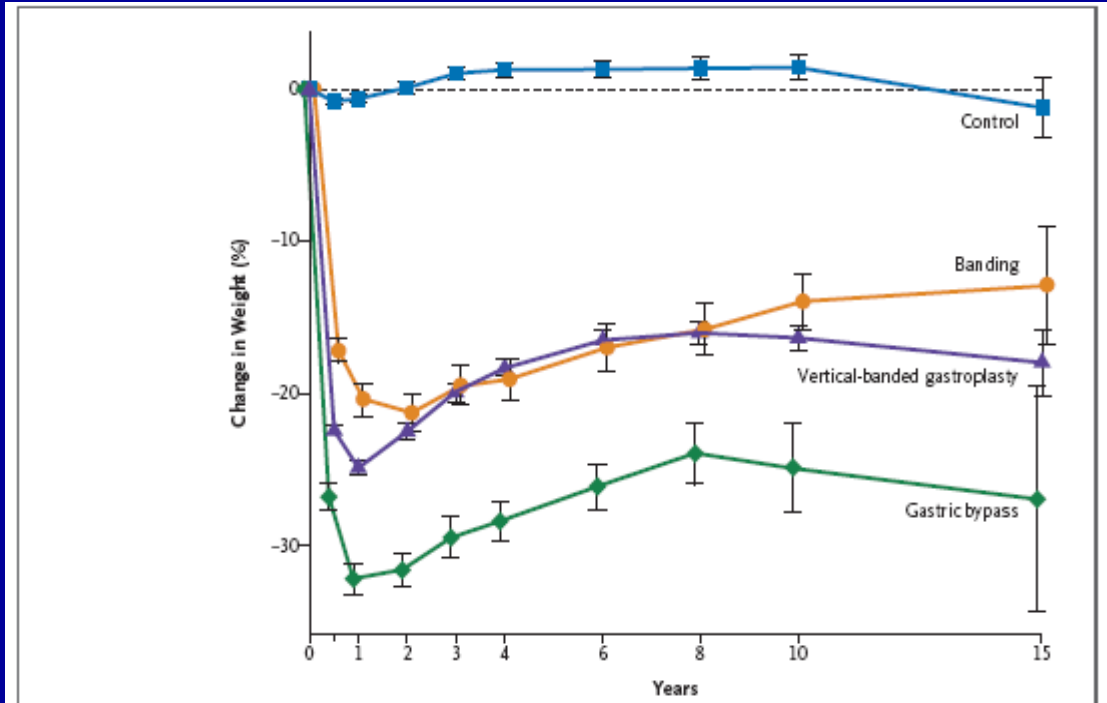
* Effect similar in women with BMI ≤ 30 kg/m^2 or > 30 kg/m^2

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


Gastric Banding
Gastroplasty
Roux-en-Y

Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects

Mean Percent Weight Change in the Control Group and the Surgery Group According to the Method of Bariatric Surgery



No. Examined									
Control	2037	1768	1660	1553	1490	1281	982	886	190
Banding	376	363	357	328	333	298	267	237	52
Vertical-banded gastroplasty	1369	1298	1244	1121	1086	1004	899	746	108
Gastric bypass	265	245	245	211	209	166	92	58	10

I bars denote 95% confidence intervals.

Sjöström L et al. NEJM 2007;357:741-752

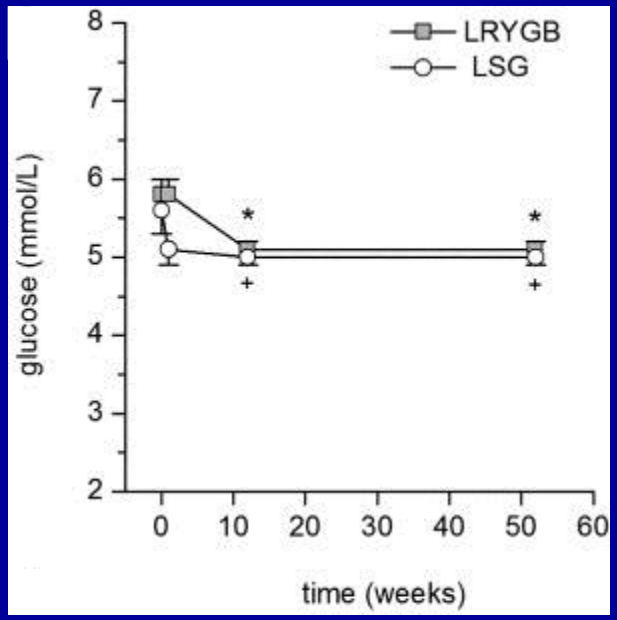
Intentional Weight Loss and Breast Cancer Risk

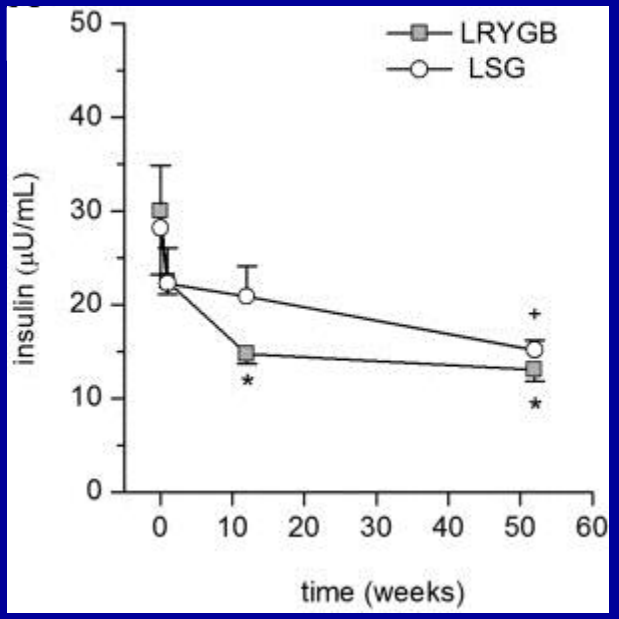
Cohort Studies			Weight Loss	Breast Cancer Risk
Eliassen	2006		≥ 14.5%	↓ 57%
Harvie	2005		≥ 5%	↓64%
Parker	2003		> 20 pounds	↓19%
Bariatric Surgery Studies			**Weight Loss**	**All Cancer Risk**
Sjöström	2009	(women)	31.9%	↓ 42%
Adams	2009	(women)	31.0%	↓ 27% (BC 9%)
Christou	2008	(both)	31.9%	↓ 78% (BC 83%)

Change in Physiologic Mediators	
Decrease	**Increase**
Estradiol (3X)	SHBG
Insulin (3X)	± IGFBPs
CRP (3X)	± IGF-I
TNF-α	
IL-6	
± IGFBPs, IGF-1	

Byers T et al. Diab Obes Met 2011

Insulin and Glucose Improve Post Bariatric Surgery BEFORE Major Weight Loss



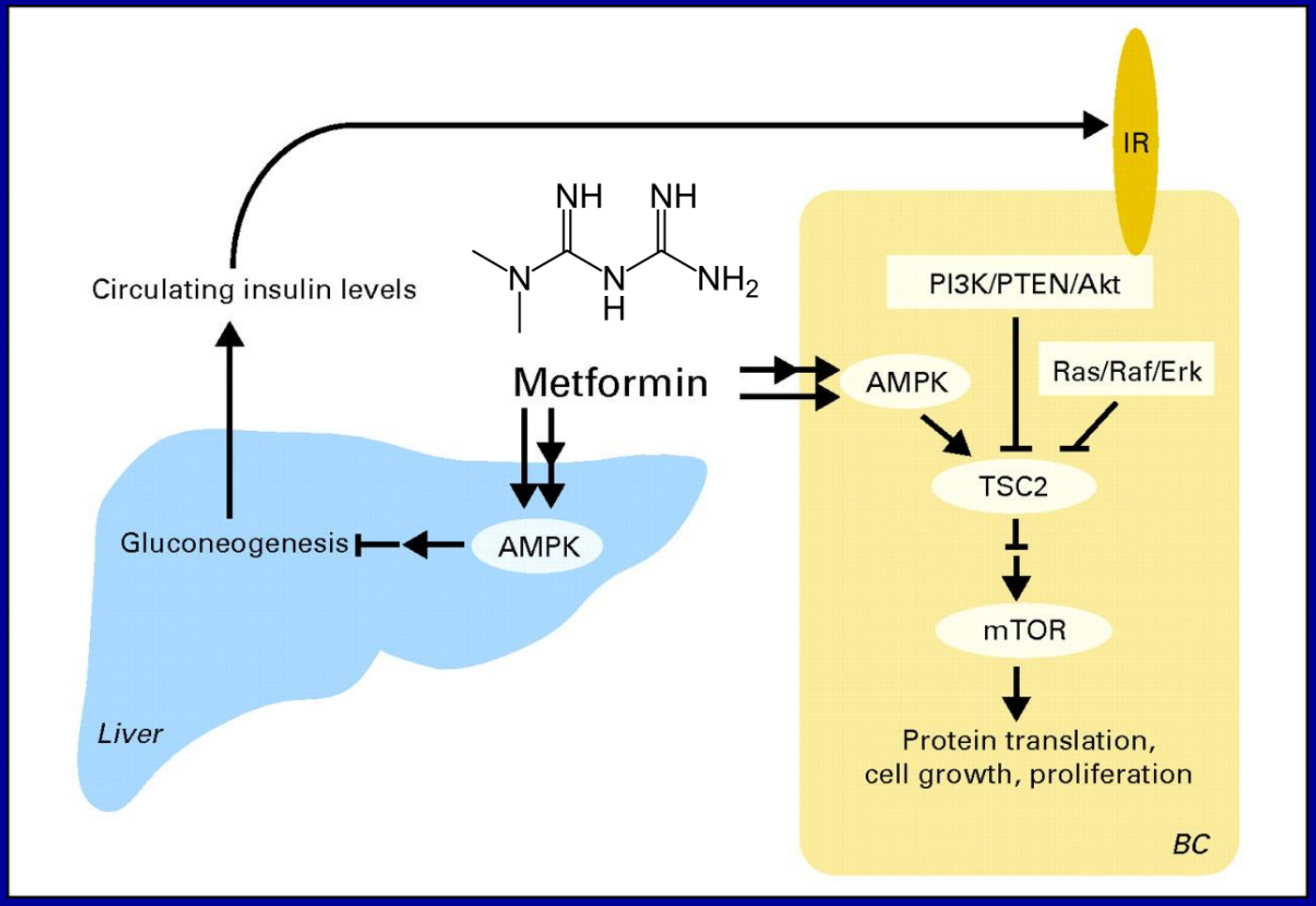


LRYGB = laparoscopic Roux-en-Y gastric bypass

LSG = laparascopic sleeve gastrectomy

Woelnerhanssen B et al. Surg Obes Relat Dis 2011; 7:561-568

Mechanism of Metformin Action in the Clinical Setting



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

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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), CCSRI, BCRF, Apotex Canada, CBCF, OICR

MA.32 Metabolic Substudy

Change from Baseline at 6 Months

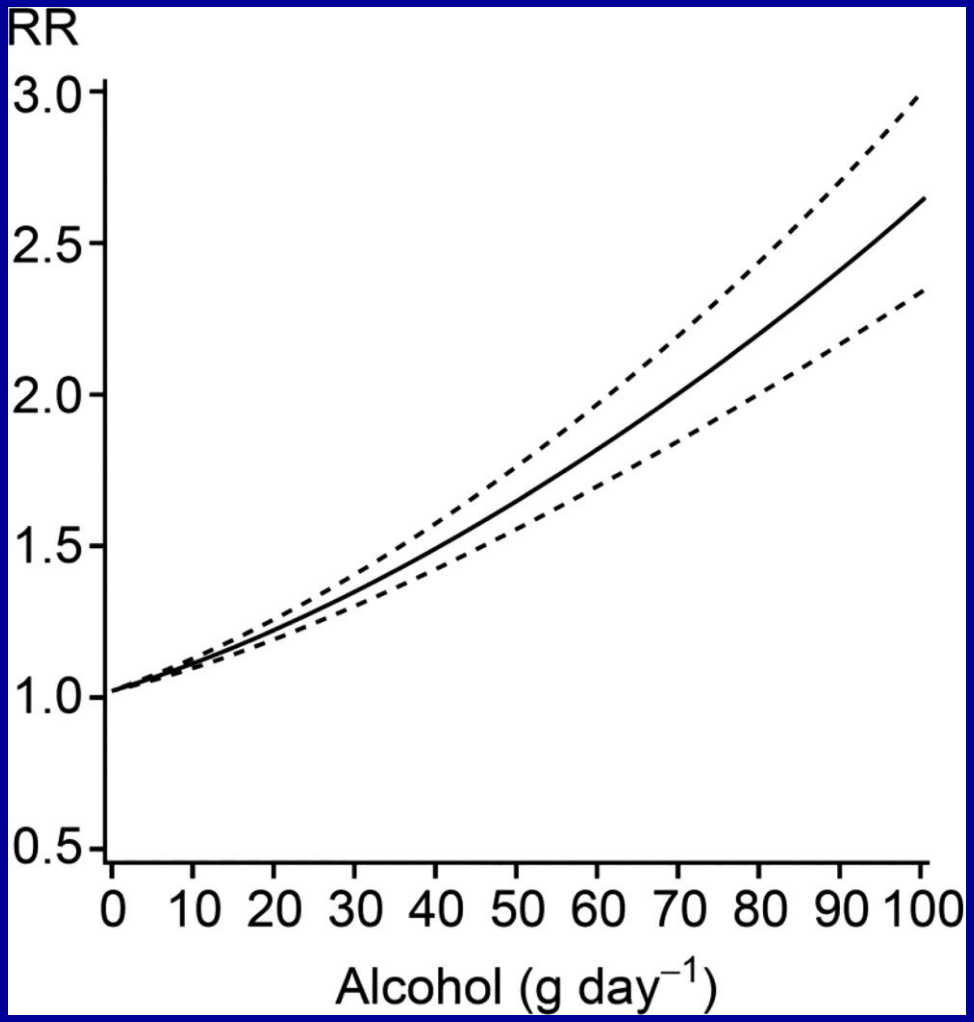
	Metformin n=237		Placebo n=255		Change		
	Change	%	Change	%	p(2-tail) (Wilcoxon)	Interaction with Baseline BMI	Interaction with Baseline Insulin
Weight (kg)	-1.96	- 2.6	+0.40	+ 0.5	<0.0001	0.32	0.17
BMI (kg/m^2)	-0.74	- 2.6	+0.15	+ 0.5	<0.0001	0.27	0.19
Glucose (mmol/L)	-0.1	- 1.9	+0.04	+ 0.8	<0.001	0.97	0.17
Insulin (pmol/L)	-7.88	-11.5	-1.78	- 2.5	0.027	0.79	0.84
HOMA* (n=331)	-0.08	- 4.0	+0.06	+ 2.6	0.014	0.56	0.89
Leptin (ng/ml)	-1.53	- 9.7	+1.42	+ 9.0	<0.0001	0.20	0.27
hs-CRP (µg/L)	-0.2	- 7.3	+0.84	+31.3	0.005	0.67	0.59

* *calculated from glucose and insulin in the 331 with blood draws for both on the same date*

ALCOHOL
SMOKING

Dose-Risk Function Between Alcohol Consumption and Breast Cancer

(extracted from Bagnardi et al. Br J Cancer 2001; 85:1700-1705)



Seitz HK et al. Alcohol Alcohol 2012; 47:204-212

Summary of Meta-Analysis and Pooled Analysis of Smoking Pack-Years, NAT2 Acetylators Status, Menopausal Status and Breast Cancer Risk

Type of analysis	Pack-years*	*NAT2* slow acetylators		*NAT2* rapid acetylators	
		Premenopausal RR (95% CI)	Postmenopausal RR (95% CI)	Premenopausal RR (95% CI)	Postmenopausal RR (95% CI)
Meta-analysis	Never active	1.00	1.00	1.00	1.00
	<20	1.21 (1.00 to 1.45)	**1.28 (1.08 to 1.50)**	1.00 (0.80 to 1.24)	1.12 (0.93 to 1.36)
	≥20	**1.47 (1.08 to 2.01)**	**1.41 (1.15 to 1.72)**	1.34 (0.94 to 1.89)	0.98 (0.77 to 1.26)
Pooled analysis	Never active	1.00	1.00	1.00	1.00
	<20	1.05 (0.86 to 1.28)	**1.23 (1.03 to 1.46)**	0.91 (0.72 to 1.16)	1.10 (0.89 to 1.35)
	≥20	**1.49 (1.08 to 2.04)**	**1.42 (1.16 to 1.74)**	1.29 (0.89 to 1.86)	0.88 (0.69 to 1.13)

Bold type indicates statistically significant increases in summary risk.
Source: Ambrosone *et al.*[14]
*Pack-years as a categorical variable were available from the following eight studies for meta-analysis: Ambrosone *et al.*, 1996; Morabia *et al.*, 2000; Chang-Claude *et al.*, 2002; Egan *et al.*, 2003; van der Hel *et al.*, 2003; Alberg *et al.*, 2004; Sillanpaa *et al.*, 2005; Lissowska *et al.*, 2006. Pack-years as a categorical variable were available from the following six studies for the pooled analysis: Ambrosone *et al.*, 1996; Morabia *et al.*, 2000; Chang-Claude *et al.*, 2002; Egan *et al.*, 2003; van der Hel *et al.*, 2003; Lissowska *et al.*, 2006.

Johnson KC et al. Tobacco Control 2011; 20:e2

Lifestyle and Breast Cancer Conclusions I

- Obesity rates are increasing in the US and around the world
- Obesity has been associated with increased postmenopausal breast cancer risk and adverse cancer outcomes
- Physical inactivity has been associated with increased breast cancer risk and poor outcomes
- Several potential biologic mediators of lifestyle effects have been identified, a multifactorial biologic basis is likely

Lifestyle and Breast Cancer Conclusions II

- Modest weight loss is difficult, but feasible
- Maintenance of weight loss is even harder
- Interventions may include lifestyle change, bariatric surgery and targeted agents
- The obesity-cancer link is a testable hypothesis
- In the prevention setting, the need for large sample sizes improvement in non-cancer outcomes before cancer outcomes are reached may limit the feasibility of RCTs

Collaborators

Clinical

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FUNDERS:

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CCSRI

CBCF

BCRF

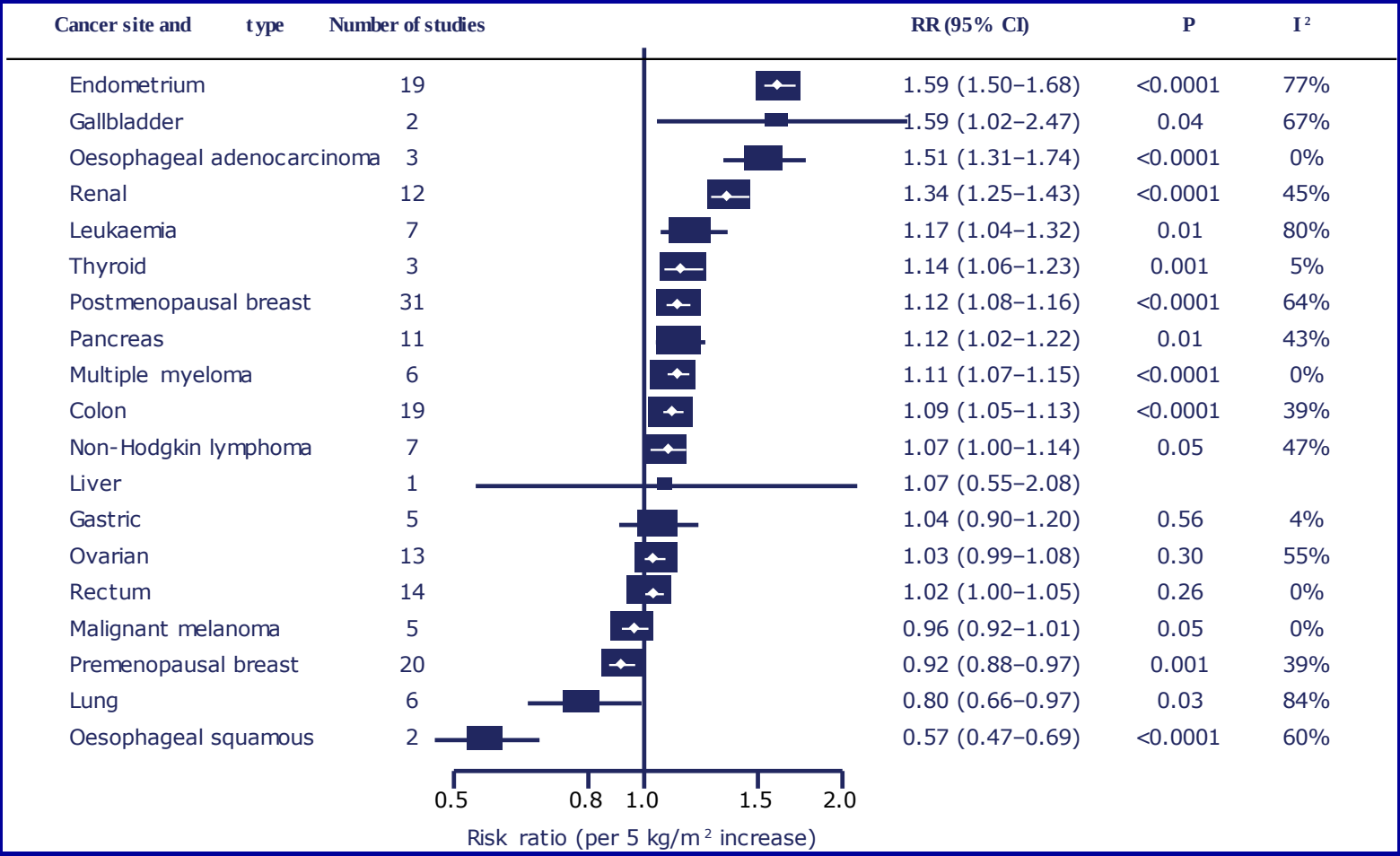
Komen

NCI (US)

Thousands of patients who have participated in our studies

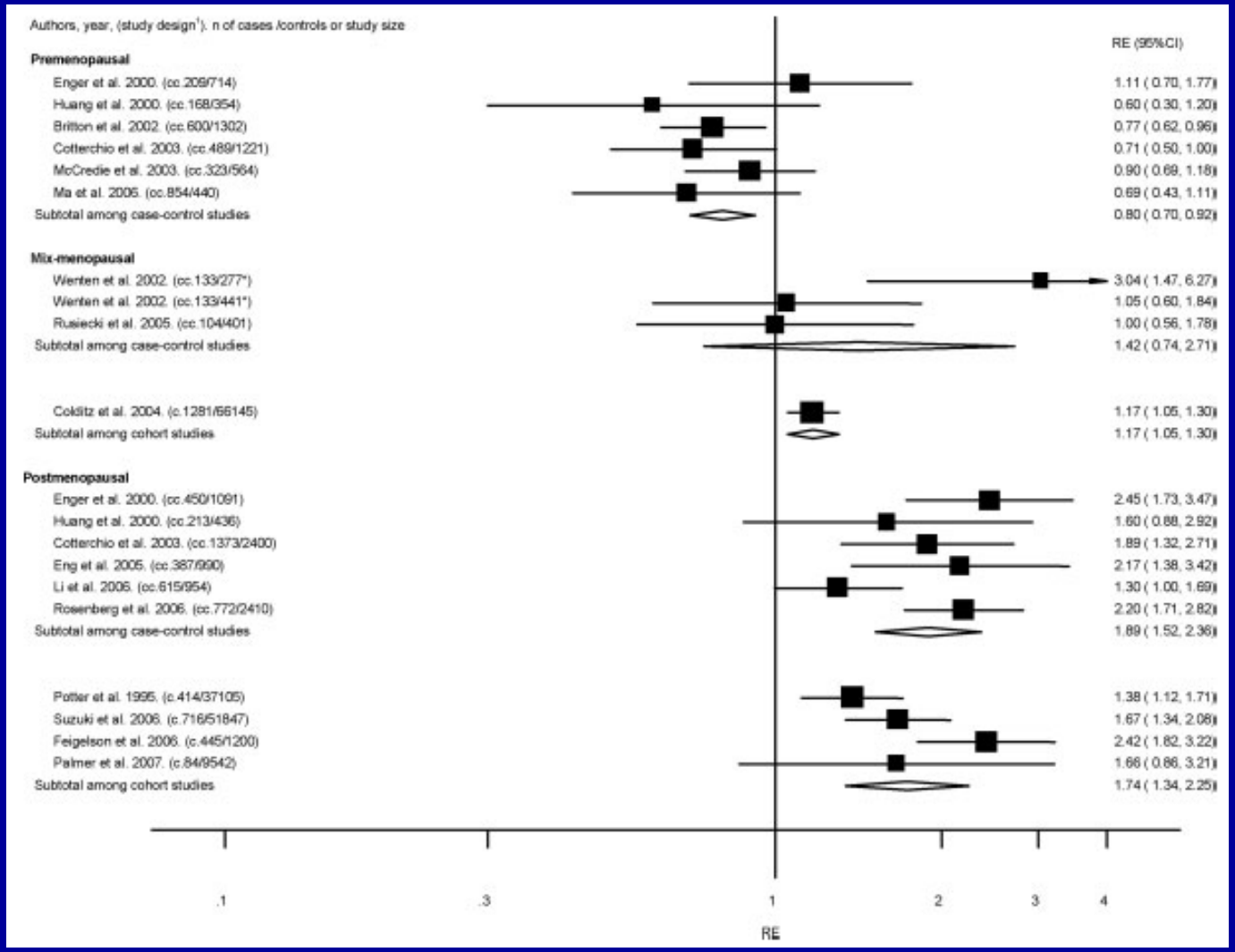
Sir Frederick Banting

BMI and CANCER RISK: WOMEN



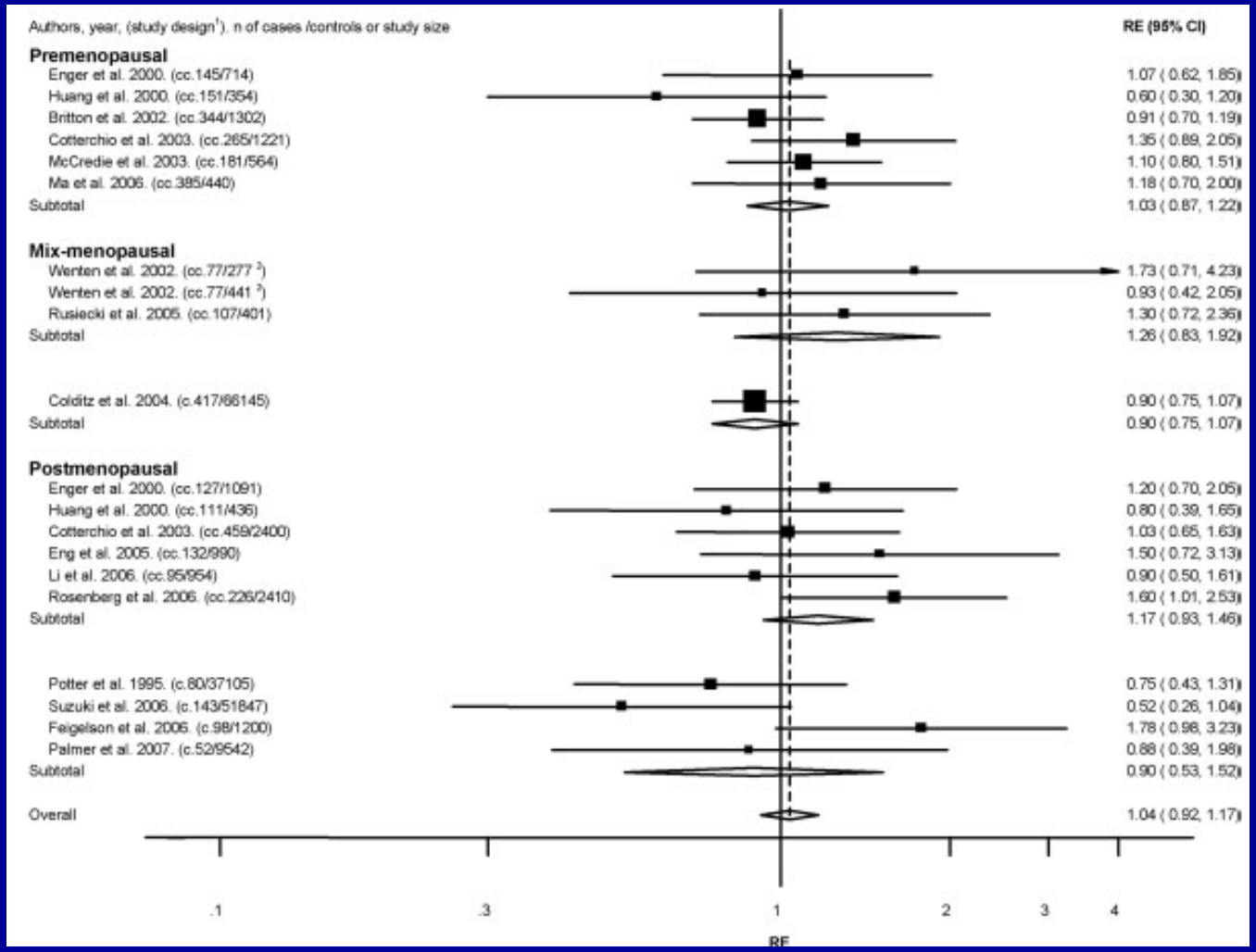
Renehan et al. Lancet 2008;371:569–578

Risk Estimates from Epidemiological Studies Estimating Association Between Body Weight and the Risk of $\underline{ER^+ PR^+}$ Breast Cancer



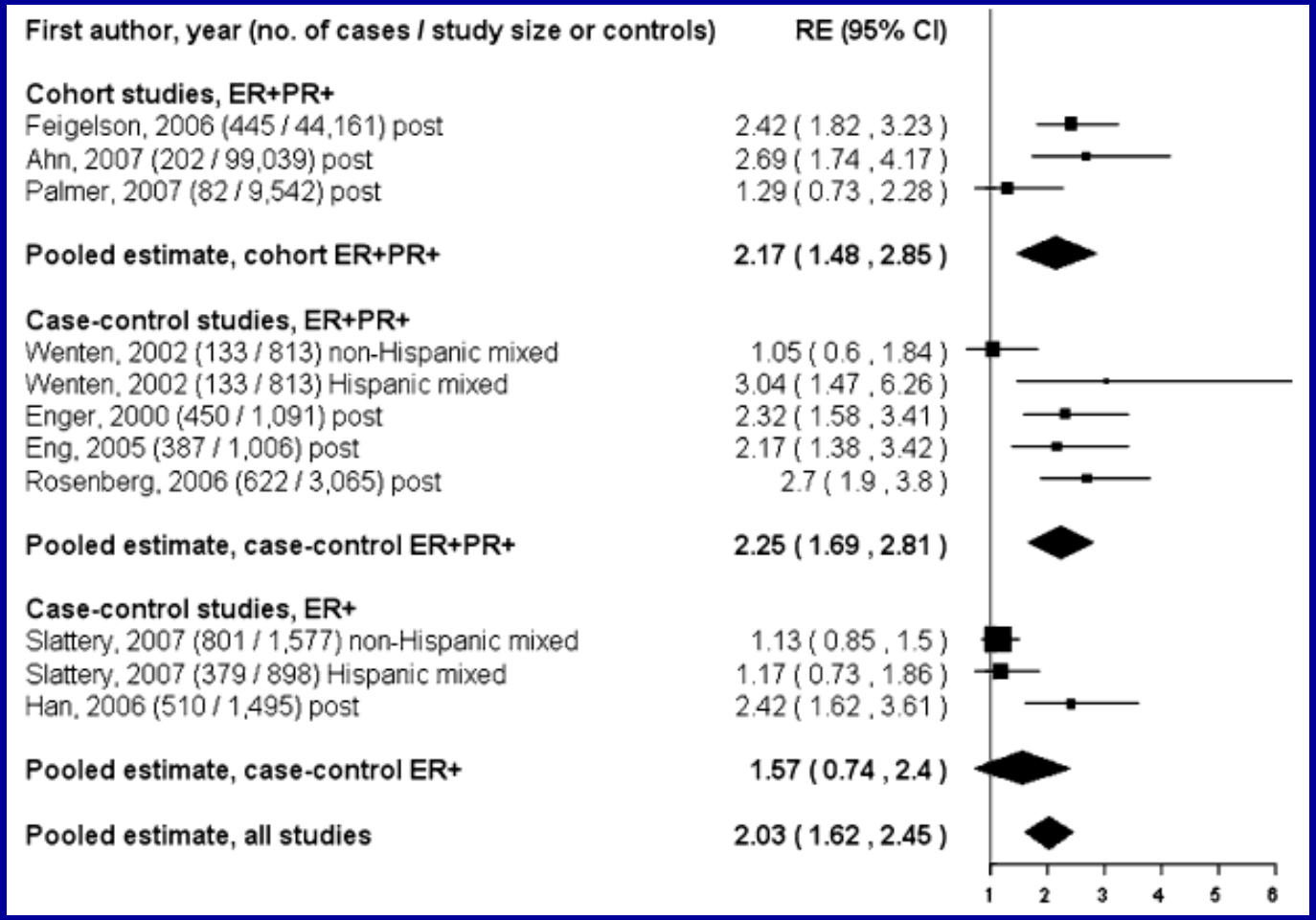
Suzuki R et al. Int J Cancer 2009; 124:698-712

Risk Estimates from Epidemiological Studies Estimating Association Between Body Weight and the Risk of ER$^-$ PR$^-$ Breast Cancer



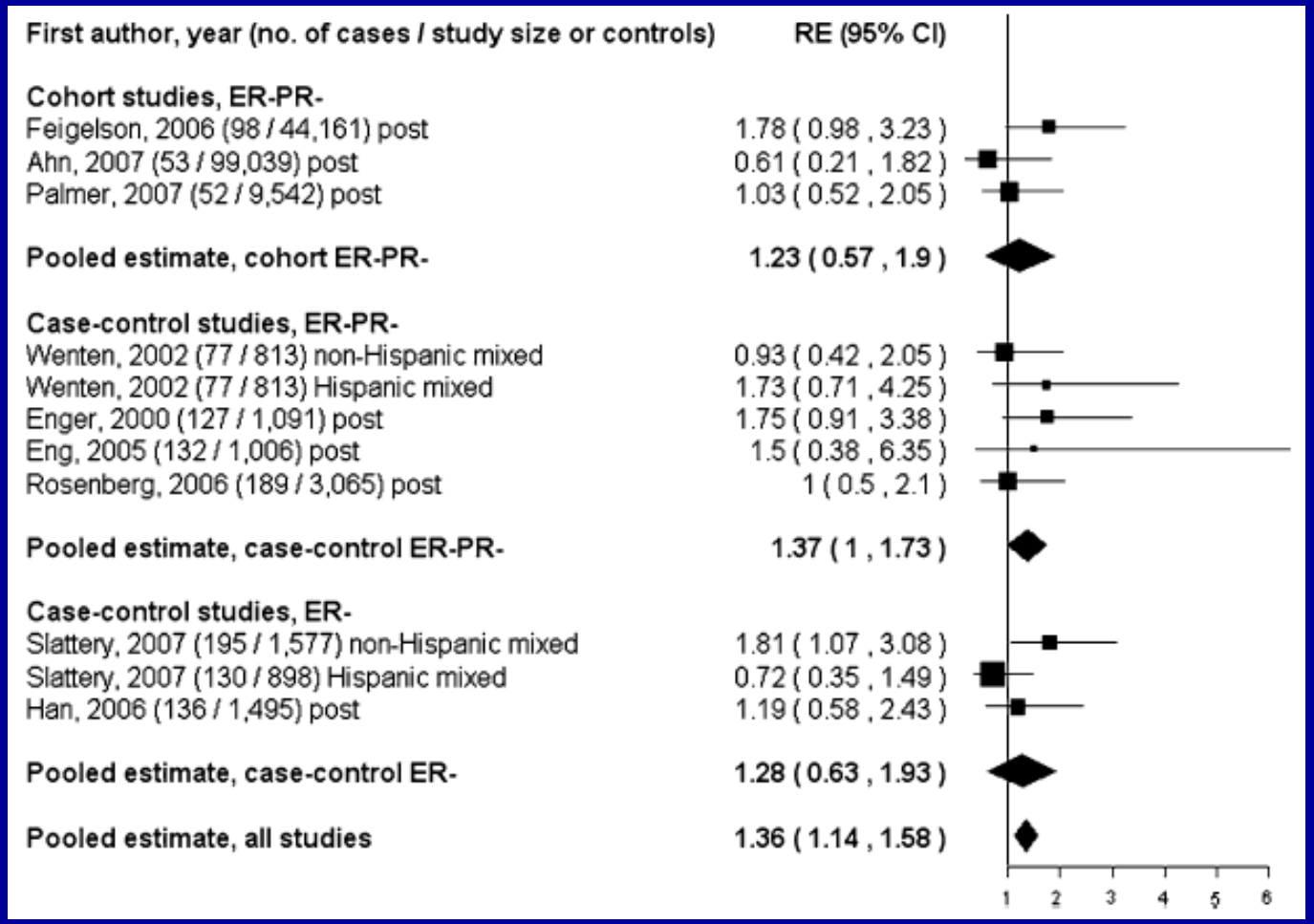
Suzuki R et al. Int J Cancer 2009; 124:698-712

Association Between Adult Weight Gain and ER+ PR+ Breast Cancer Risk



Vrieling A et al. Breast Cancer Res Treat 2010; 123:641-649

Association Between Adult Weight Gain and ER$^-$ PR$^-$ Breast Cancer Risk



Vrieling A et al. Breast Cancer Res Treat 2010; 123:641-649

Adjusted ORs and 95% CIs for Invasive Breast Cancer Associated with Birth Weight and Birth Length, by Tumor Hormone Receptor Status

	# Cases	OR	95% CI	# Cases	OR	95% CI	*p* (Interaction)**
	Estrogen receptor positive			Estrogen receptor negative			
Birth weight (g)	1,810			1,139			
<2,500	94	1.00	–	68	1.00	–	
2,500–2,999	347	1.02	0.78, 1.32	226	0.95	0.70, 1.28	
3,000–3,499	767	1.12	0.87, 1.43	479	1.00	0.75, 1.33	
3,500–3,999	488	1.26	0.98, 1.63	295	1.09	0.81, 1.46	
≥4,000	114	1.16	0.85, 1.58	71	1.03	0.71, 1.49	0.21
Trend *p*-value		0.01			0.27		
Birth length (inches)	1,791			1,129			
≤19	527	1.00	–	360	1.00	–	
>19–20	687	1.13	1.00, 1.28	429	1.03	0.89, 1.20	
>20	577	1.25	1.09, 1.43	340	1.06	0.90, 1.25	0.09
Trend *p*-value		<0.01			0.47		
	Progesterone receptor positive			Progesterone receptor negative			
Birth weight (g)	1,613			1,255			
<2,500	80	1.00	–	79	1.00	–	
2,500–2,999	308	1.04	0.79, 1.38	249	0.90	0.68, 1.20	
3,000–3,499	696	1.17	0.90, 1.52	515	0.94	0.72, 1.23	
3,500–3,999	422	1.24	0.95, 1.63	342	1.10	0.83, 1.46	
≥4,000	107	1.23	0.89, 1.71	70	0.90	0.63, 1.29	0.15
Trend *p*-value		0.02			0.23		
Birth length (inches)	1,595			1,242			
15–19	458	1.00	–	403	1.00	–	
>19–20	610	1.15	1.00, 1.31	471	1.02	0.88, 1.18	
>20	527	1.30	1.13, 1.49	368	1.04	0.89, 1.22	0.11
Trend *p*-value		<0.01			0.61		

Models adjusted for race, birth year, gestational age, birth order, maternal age, and paternal age

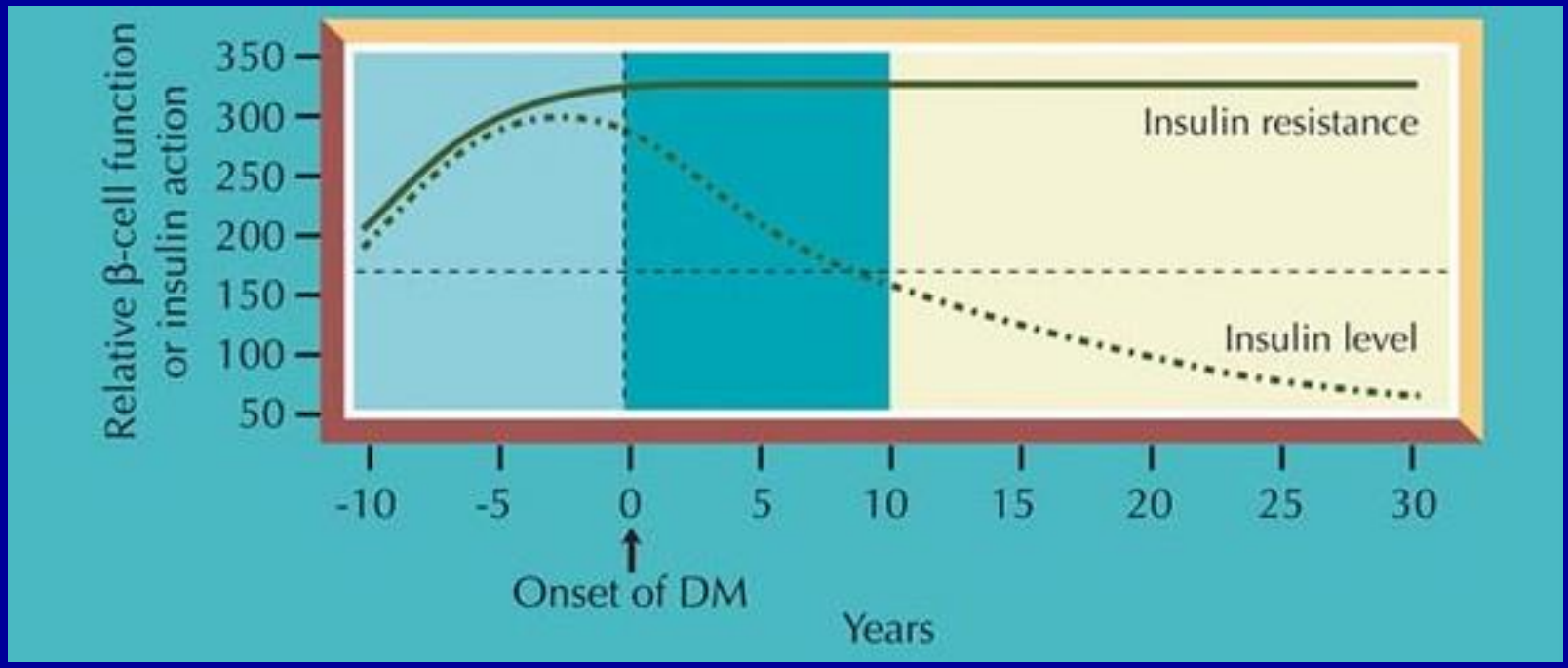
Numbers do not always add to total due to missing values

Cases with unknown hormone receptor status were excluded from the analyses

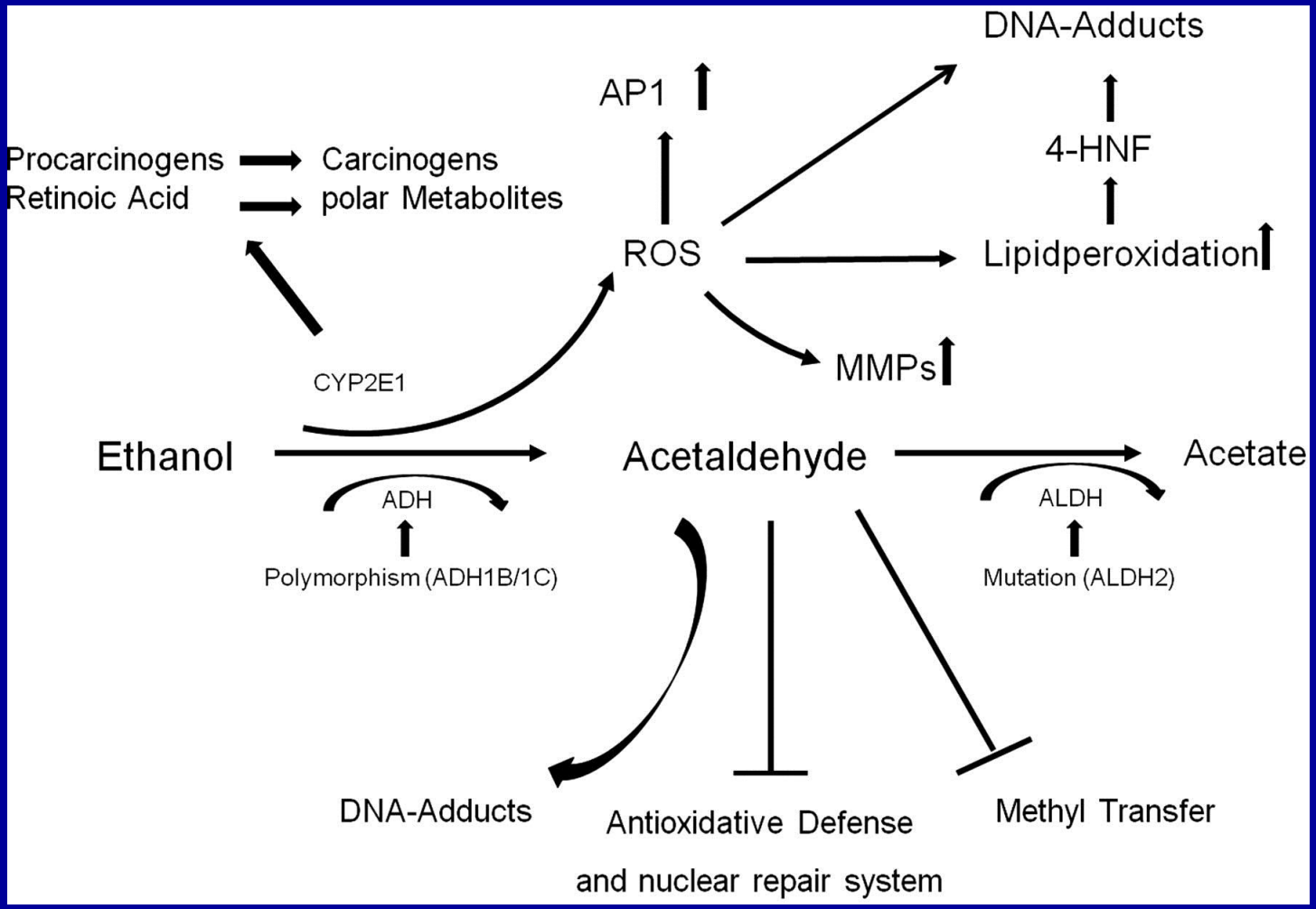
** *p*-Value for interaction computed from likelihood ratio tests from polytomous logistic regression models comparing fit of model with a common slope for all breast cancer outcomes to one that allows for different slopes for tumors with different hormone receptor status

Hurley S et al. Cancer Causes Control 2011; 22:1461-1470

Insulin Resistance is Present Prior to Clinical Diabetes



Ethanol Metabolism and Its Possible Role in Breast Carcinogenesis



Seitz HK et al. Alcohol Alcohol 2012; 47:204-212

Summary Risk Estimates for Breast Cancer Risk Associated with Ever Regular Secondhand Smoke Exposure in the Reports from the California EpA and US Surgeon General

	California EPA report[4]		US Surgeon General's report[5]	
Exposure	N	RR (95% CI)	N	RR (95% CI)
All studies	19	1.25 (1.08 to 1.44)	21	1.20 (1.08 to 1.35)
Premenopausal or women <50 (California EPA)/premenopausal (Surgeon General)	14	1.68 (1.31 to 2.15)	11	1.64 (1.25 to 2.14)
Premenopausal: studies with lifetime exposure assessment	5	2.20 (1.69 to 2.87)	6	1.85 (1.19 to 2.87)
Postmenopausal	9	*	10	1.00 (0.88 to 1.12)

*The California EPA did not report a summary risk estimate for postmenopausal women but concluded that risk estimates from the nine studies with data on postmenopausal women 'cluster around a null association'.

Johnson KC et al. Tobacco Control 2011; 20:e2

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

MA.32 Metabolic Substudy

Baseline (Fasting)

	Metformin n=237	Placebo n=255	p(2-tail) (Wilcoxon)
Weight (kg)	75.6 ± 15.5	75.9 ± 16.7	0.82
BMI (kg/m^2)	28.2 ± 5.4	28.4 ± 6.0	0.83
Glucose (mmol/L)	5.3 ± 0.5	5.2 ± 0.6	0.31
Insulin (pmol/L)	68.4 ± 51.8	70.6 ± 63.4	0.69
HOMA*	2.02 ± 1.25	2.27 ± 2.24	0.95
Leptin (ng/ml)	15.8 ± 13.3	15.8 ± 12.6	0.90
hs-CRP (µg/L)	2.75 ± 3.93	2.68 ± 3.72	0.74

** calculated from glucose and insulin, n=331 with blood draws for both on same date*

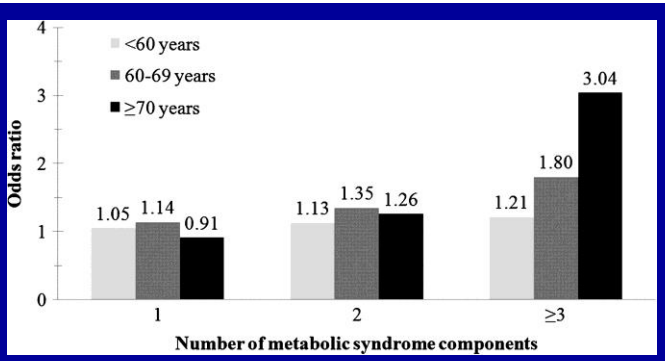
Metabolic Syndrome and the Risk of Breast Cancer in Postmenopausal Women

Population - 3,869 breast cancer patients / 4,082 controls
(2 hospital-based case control studies)

Results

	First study (1983–1994)		Second study (1991–2007)		All
	Cases : controls	OR (95% CI)[a,b]	Cases : controls	OR (95% CI)[a,c]	OR (95% CI)[a,c]
No. of MetS components					
None	1160 : 1148	1[d]	624 : 782	1[d]	1[d]
1	594 : 564	1.04 (0.90–1.21)	711 : 867	1.13 (0.97–1.32)	1.07 (0.96–1.18)
2	196 : 135	1.46 (1.14–1.85)	393 : 444	1.25 (1.04–1.50)	1.24 (1.08–1.43)
≥3	38 : 23	1.76 (1.03–3.02)	153 : 119	1.87 (1.42–2.47)	1.75 (1.37–2.22)
P for trend		0.0021		<0.0001	<0.0001

[a]Estimates from logistic regression models adjusted for age, study center, study period, education, alcohol consumption, age at menarche, age at first birth, age at menopause, hormone replacement therapy use, and family history of breast cancer.
[b]MetS was defined as diabetes, hypertension, hyperlipidemia, and body mass index ≥30 kg/m^2.
[c]MetS was defined as diabetes, hypertension, hyperlipidemia, and waist circumference ≥88 cm or body mass index ≥30 kg/m^2 for women with missing information for waist circumference.
[d]Reference category.



Conclusions The metabolic syndrome is significantly associated with postmenopausal breast cancer risk

Rosato V et al Ann Oncol 2011

Effects of Calorie Reduced Diet and Physical Activity in Healthy Postmenopausal Women

	Change at 12 Months		
	Insulin	**Glucose**	**HOMA-IR**
Diet*	**-22.3%**	**-2.4%**	**-24.3%**
Physical Activity**	-7.8%	-0.9%	-8.6%
Diet and Physical Activity	**-24.0%**	**-2.8%**	**-26.4%**
Control	-1.9%	+0.2%	-1.8%

* group based reduced calories with 10% weight loss goal

** 45 minute/day 5 days/week moderate to intense aerobic

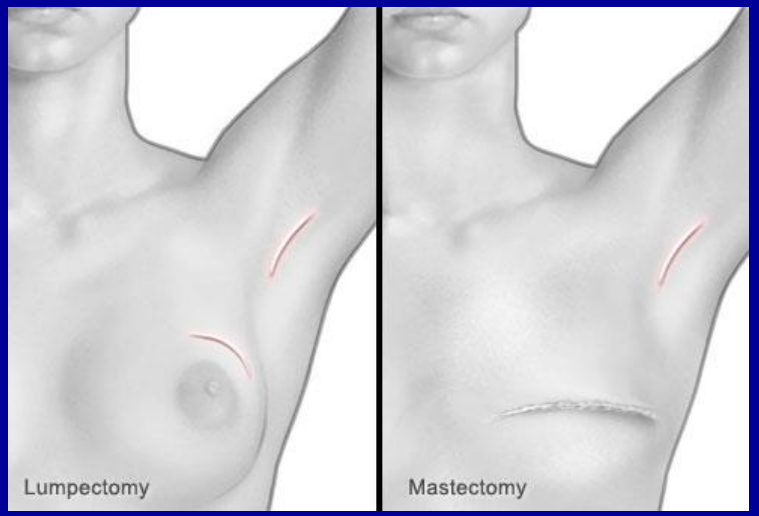
Bolded values p ≤ 0.008

Mason C et al. Am J Prev Med 2011

Metformin Favorably Impacts Breast Cancer Biology

METFORMIN

2-3 weeks

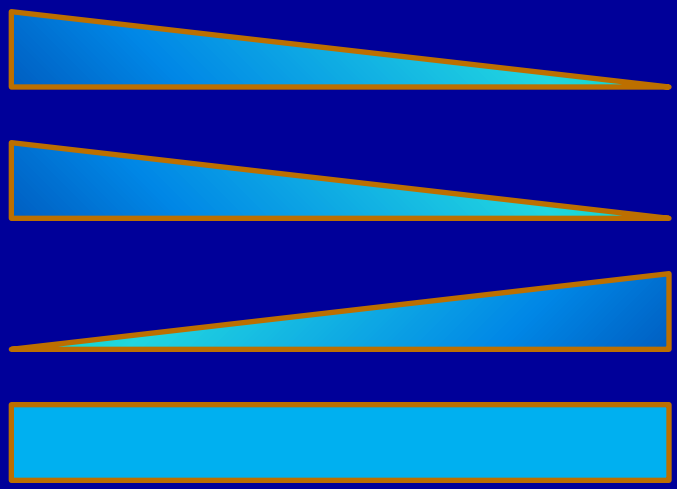


Insulin

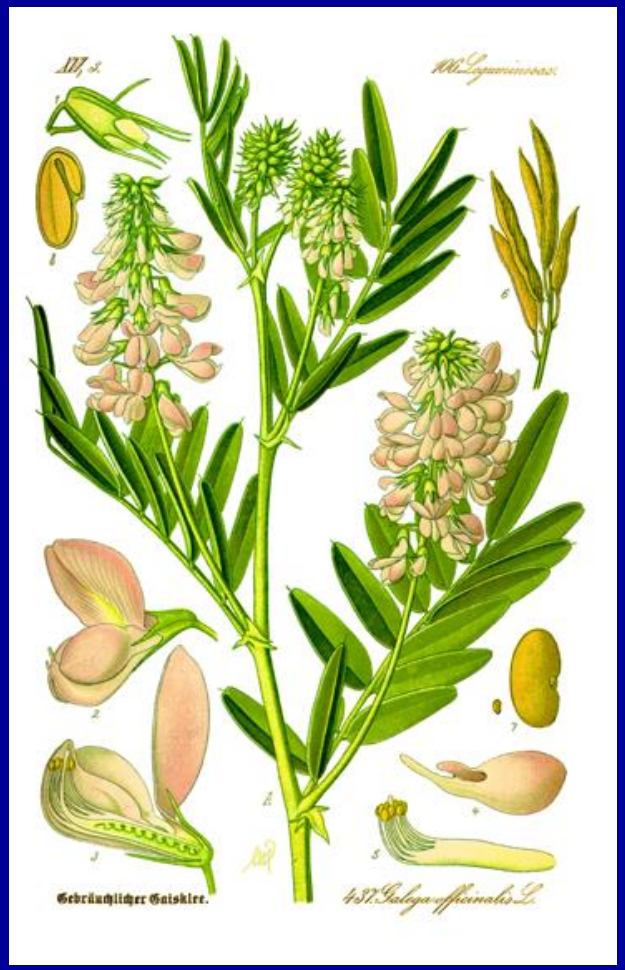
Cancer Proliferation

Cancer Cell Death

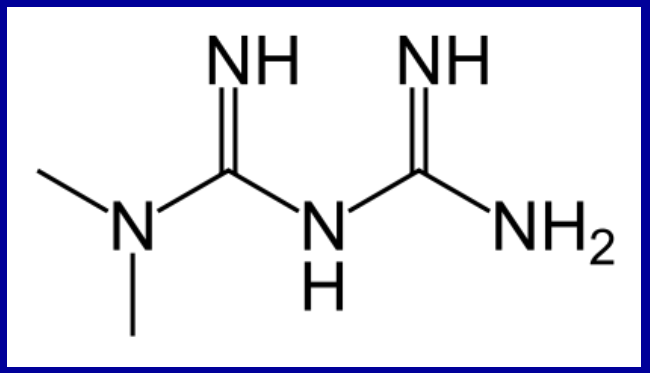
Quality of Life



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