Overview of the Evidence Relating Cancer Outcomes to Obesity and Body Weight

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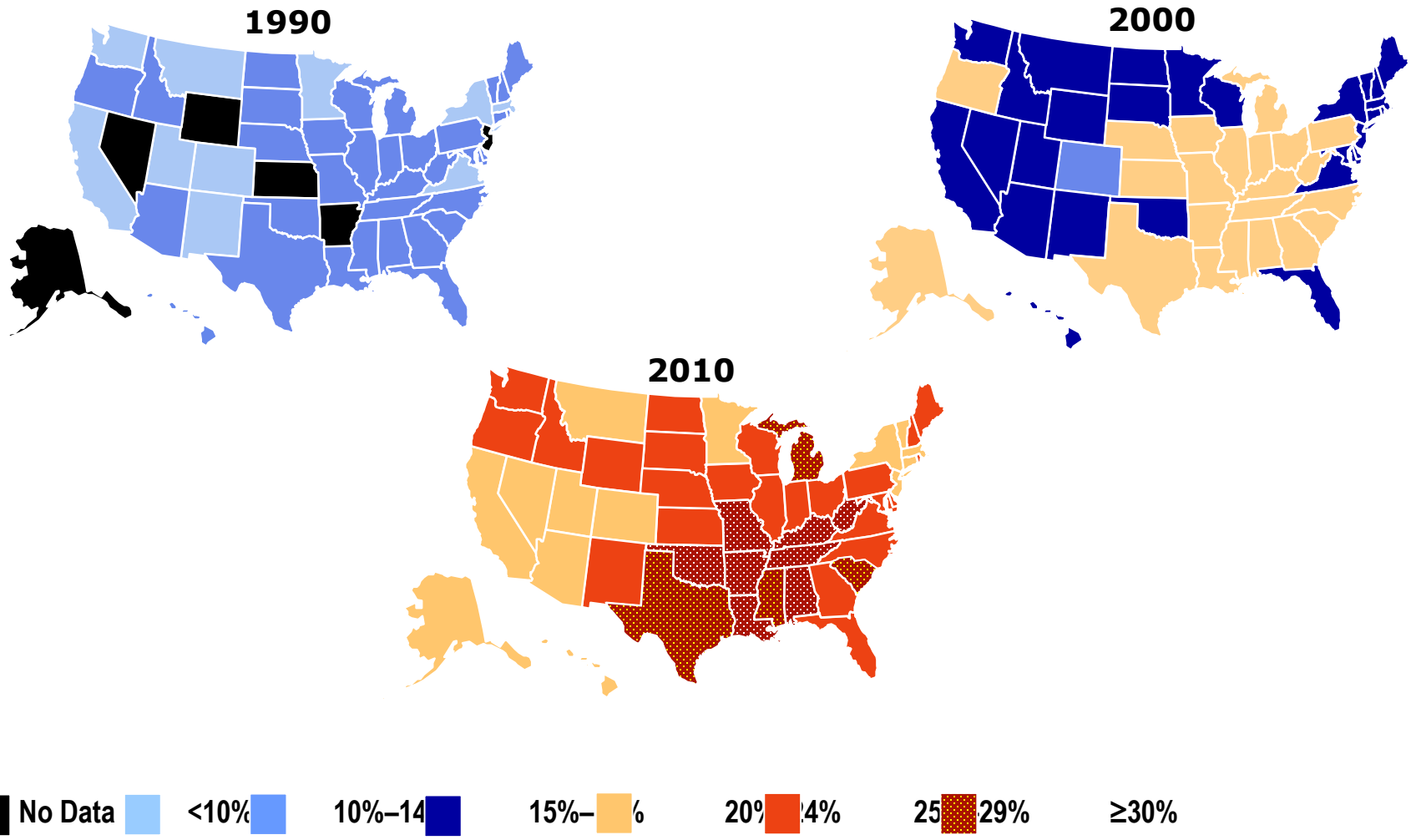
Obesity Trends* Among U.S. Adults

BRFSS, 1990, 2000, 2010

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



IARC Working Group 2016:
Evidence for a Cancer-Prevention Effect of the Absence of Excess Body Fatness

Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	Sufficient	1.3 (1.2–1.4)
Pancreas	Sufficient	1.5 (1.2–1.8)
Breast: postmenopausal	Sufficient	1.1 (1.1–1.2)§
Corpus uteri	Sufficient	7.1 (6.3–8.1)
Ovary	Sufficient	1.1 (1.1–1.2)
Kidney: renal-cell	Sufficient	1.8 (1.7–1.9)
Meningioma	Sufficient	1.5 (1.3–1.8)
Thyroid	Sufficient	1.1 (1.0–1.1)§
Multiple myeloma	Sufficient	1.5 (1.2–2.0)

Lauby-Secretan B et al. NEJM 2016; 375:794-798

Global Burden of Cancer Attributable to High BMI in 2012: A Population-Based Study

The population attributable fraction is:

- **Higher in developed than undeveloped countries**
- **Higher in females than males**

One-quarter of all high-BMI-related cancer cases in 2012 could be attributed to the increase in BMI between 1982 and 2002 – this number was 35.6% in North America

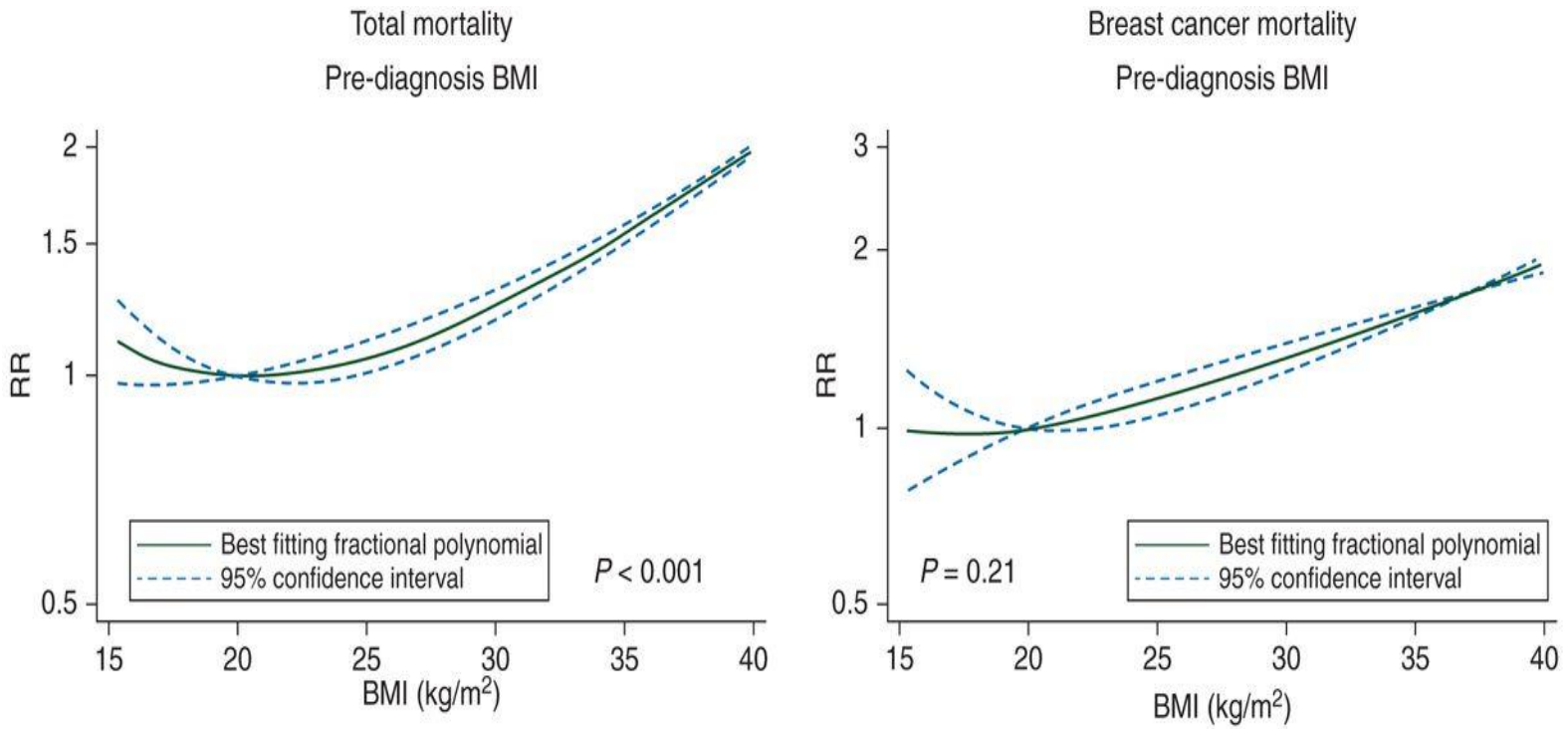
Arnold M et al. Lancet Oncol 2015; 16:36-46

Patients diagnosed with cancer are more commonly obese than the general population

This obesity has been associated with poor outcomes in many cancers

Obesity and Cancer Outcomes

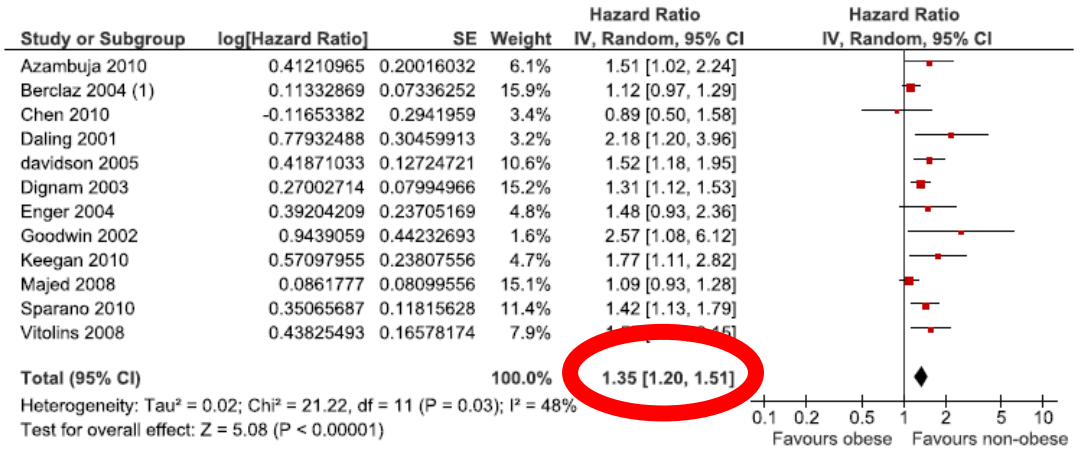
BMI and Mortality in Breast Cancer: A Meta-Analysis



Chan DSM et al Ann Oncol 2014

Effect of Obesity on Breast Cancer Survival By ER/PgR Status

ER/PgR Positive Breast Cancer

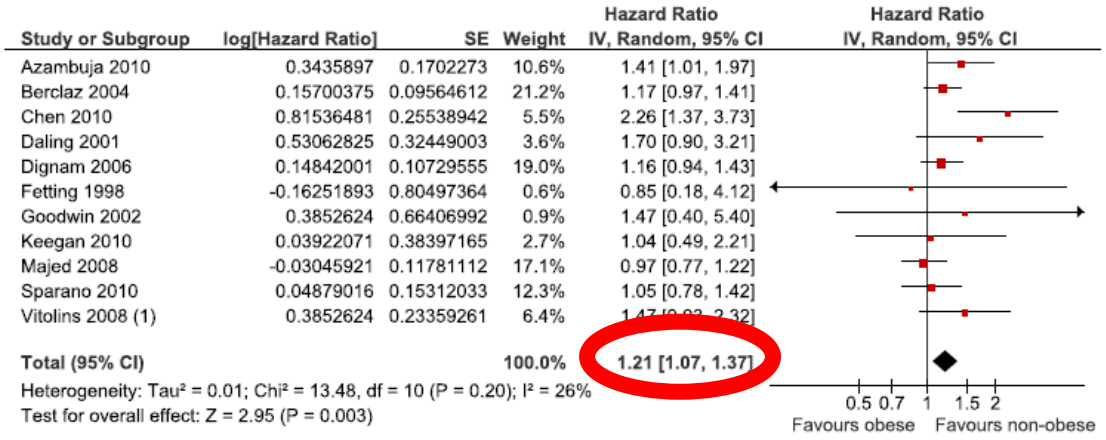


Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Azambuja 2010	0.41210965	0.20016032	6.1%	1.51 [1.02, 2.24]
Berclaz 2004 (1)	0.11332869	0.07336252	15.9%	1.12 [0.97, 1.29]
Chen 2010	-0.11653382	0.2941959	3.4%	0.89 [0.50, 1.58]
Daling 2001	0.77932488	0.30459913	3.2%	2.18 [1.20, 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%	[illegible]
Total (95% CI)			**100.0%**	**1.35 [1.20, 1.51]**

Heterogeneity: Tau² = 0.02; Chi² = 21.22, df = 11 (P = 0.03); I² = 48%
Test for overall effect: Z = 5.08 (P < 0.00001)

Hazard Ratio IV, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours obese Favours non-obese

ER/PgR Negative Breast Cancer



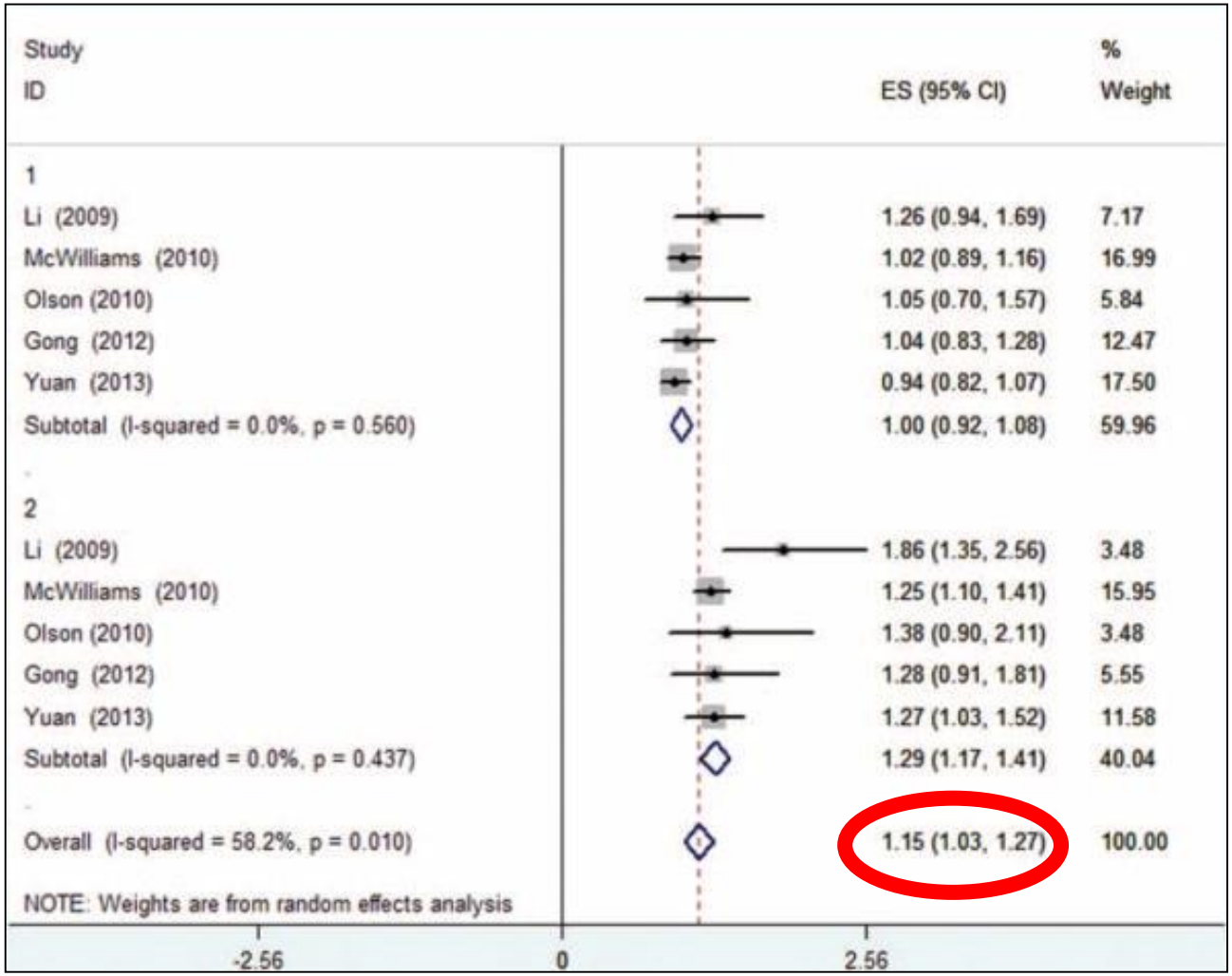
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Azambuja 2010	0.3435897	0.1702273	10.6%	1.41 [1.01, 1.97]
Berclaz 2004	0.15700375	0.09564612	21.2%	1.17 [0.97, 1.41]
Chen 2010	0.81536481	0.25538942	5.5%	2.26 [1.37, 3.73]
Daling 2001	0.53062825	0.32449003	3.6%	1.70 [0.90, 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%	[illegible]
Total (95% CI)			**100.0%**	**1.21 [1.07, 1.37]**

Heterogeneity: Tau² = 0.01; Chi² = 13.48, df = 10 (P = 0.20); I² = 26%
Test for overall effect: Z = 2.95 (P = 0.003)

Hazard Ratio IV, Random, 95% CI
0.5 0.7 1 1.5 2
Favours obese Favours non-obese

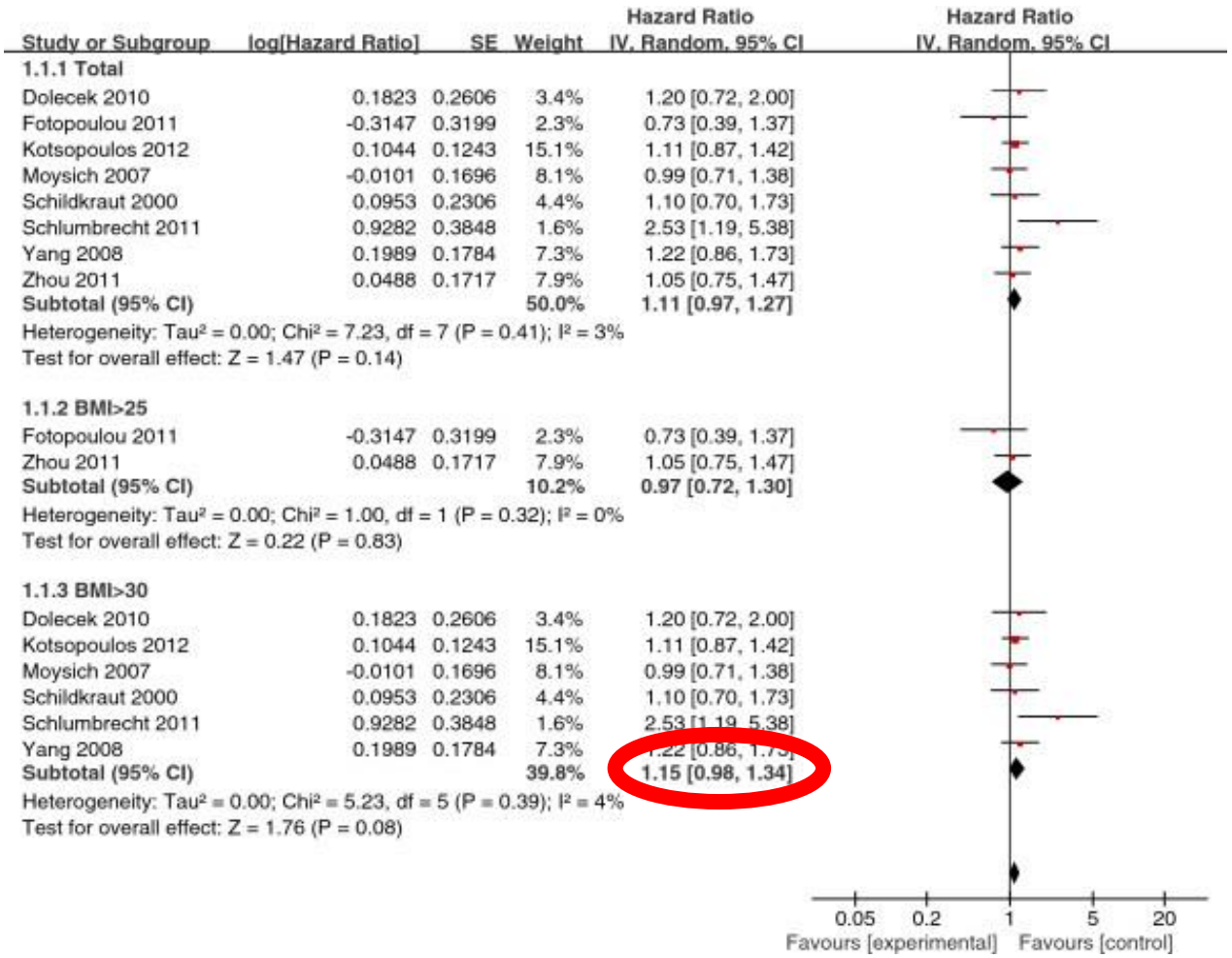
Niraula S and Goodwin PJ BCRT 2012

Obesity (Lower Panel) but not Overweight (Upper Panel) is Associated with Poor Survival in Pancreatic Cancer



Shi Y-Q et al. Medicine 2016;95(14):e3305

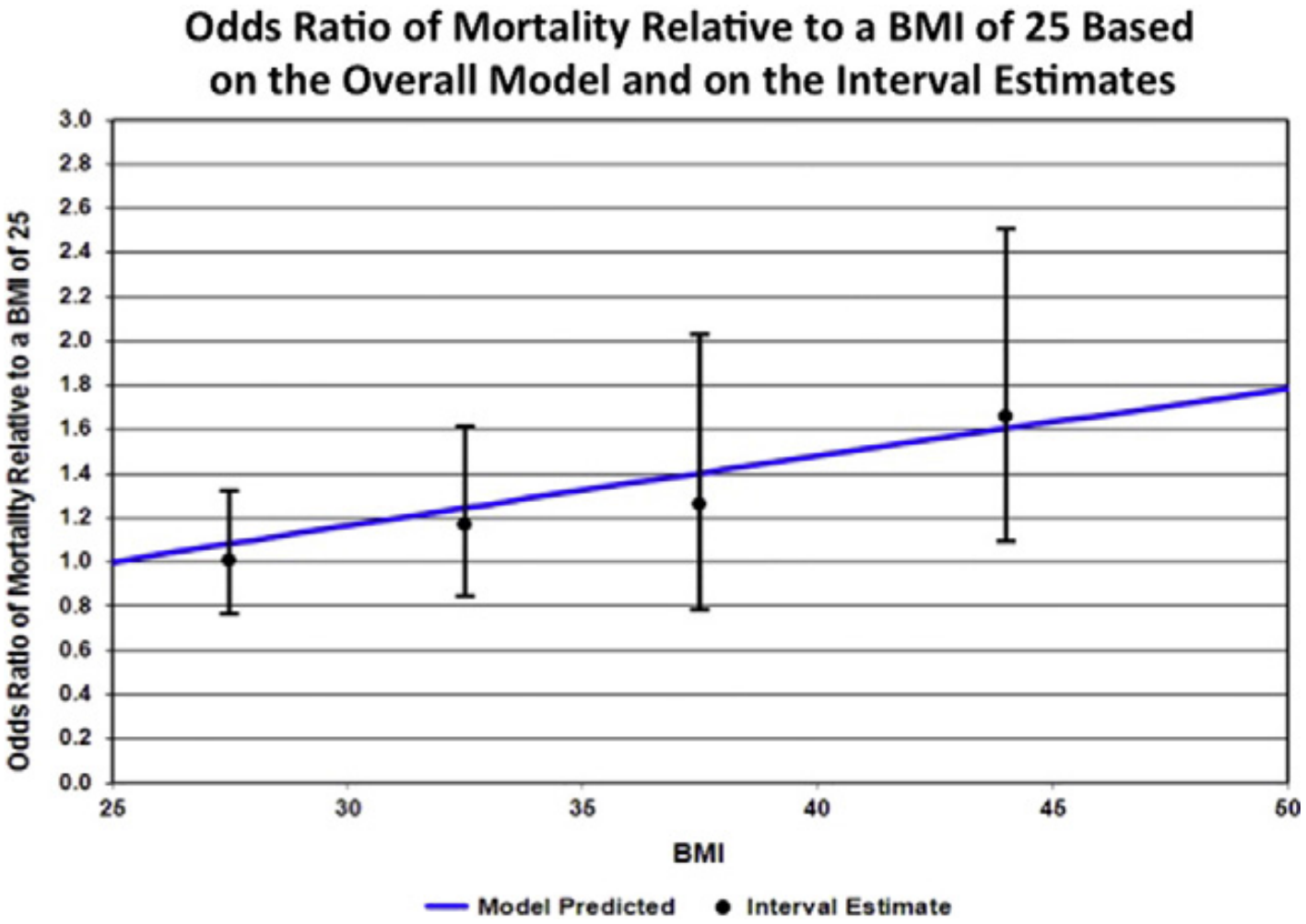
BMI > 30 kg/m^2 is Associated with Lower Survival in Epithelial Ovarian Cancer



Continuous BMI: OR 1.02 (1.01-1.04) per kg/m^2

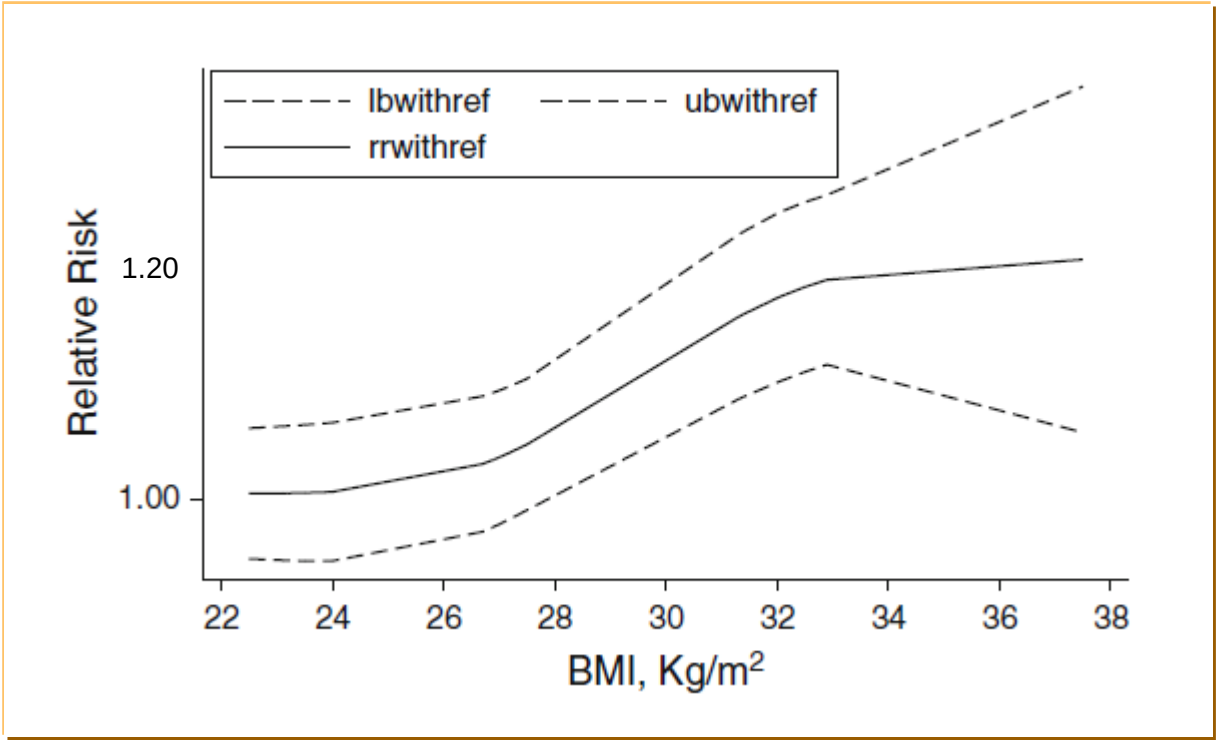
Bae HS et al. J Ovarian Res 2014; 7:41

Endometrial Cancer:
Meta-Analysis of the Association of BMI with Mortality



Alvarez Secord A et al. *Gynecol Oncol 2016;140:184-190*

Obesity is Associated with Biochemical Recurrence of Prostate Cancer (Meta-Analysis)



Adverse associations of obesity were seen overall, after radical prostatectomy; post-external beam XRT but not in those receiving brachytherapy.

Hu M-B et al. Med Oncol 2014; 31:829

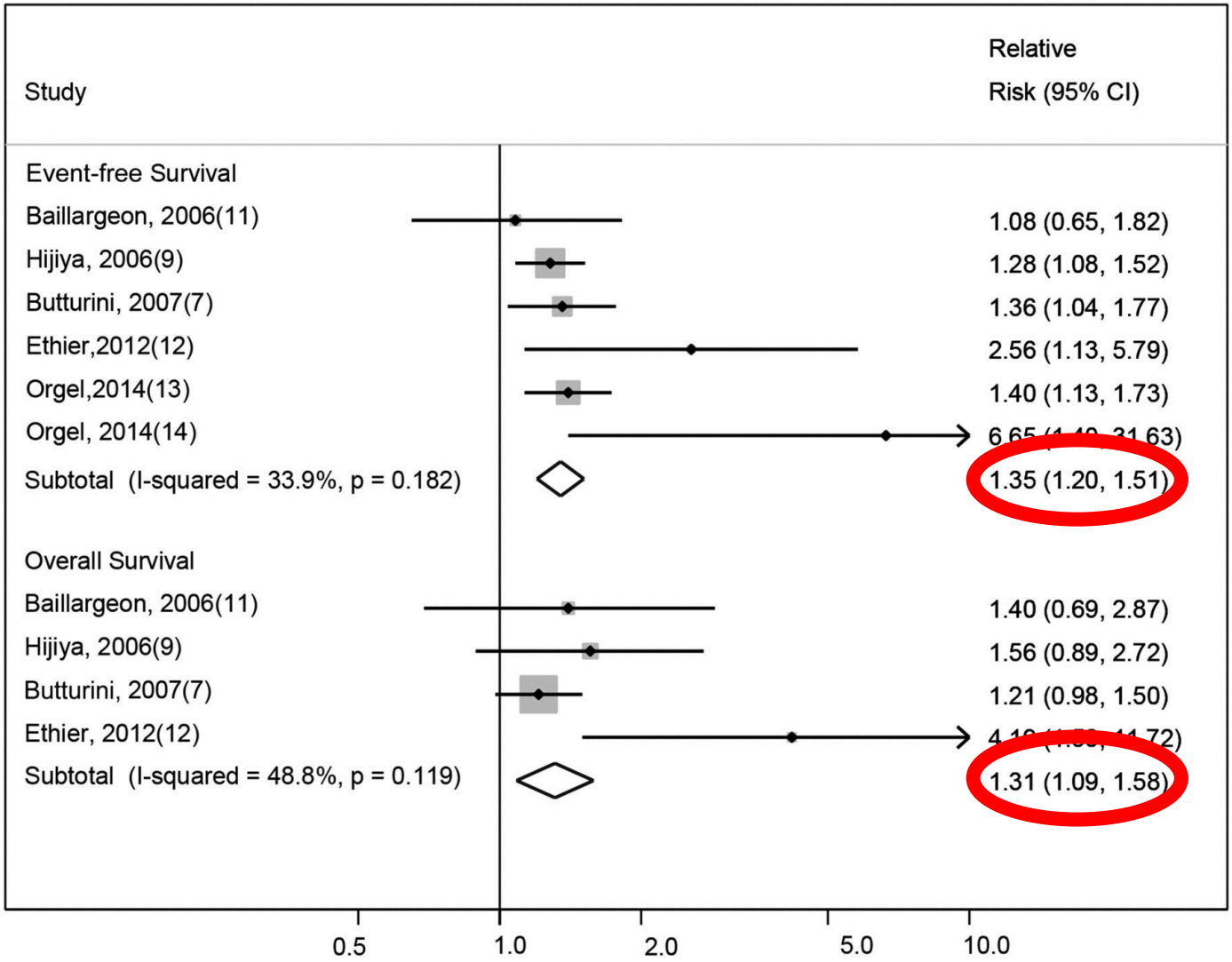
Colorectal Cancer: Meta-Analyses of BMI Associations by Gender and Cancer Location

	Men		Women		Colon cancer		Rectal cancer	
	N	HR (95 % CI)	*N*	HR (95 % CI)	*N*	HR (95 % CI)	*N*	HR (95 % CI)
All-cause mortality								
Overweight	7	0.96 (0.91, 1.02)	10	1.09 (1.00, 1.19)	11	1.00 (0.96, 1.04)	5	1.05 (0.89, 1.24)
Obesity	7	1.11 (1.00, 1.22)	10	1.21 (1.09, 1.35)	11	1.12 (1.07, 1.18)	5	1.31 (1.03, 1.68)
Underweight	5	1.40 (1.26, 1.57)	7	1.26 (1.09, 1.46)	7	1.33 (1.18, 1.49)	2	1.43 (1.09, 1.88)
Cancer-specific mortality								
Overweight	4	1.04 (0.89, 1.21)	7	1.12 (0.97, 1.29)	10	1.03 (0.91, 1.15)	6	1.05 (0.83, 1.32)
Obesity	4	1.28 (1.07, 1.54)	7	1.20 (1.03, 1.38)	10	1.18 (1.08, 1.29)	6	1.28 (0.94, 1.75)
Underweight	1	–	4	1.36 (0.99, 1.86)	6	1.46 (1.14, 1.87)	2	1.67 (0.55, 5.03)
Disease-free survival								
Overweight	2	0.93 (0.88, 0.99)	2	1.02 (0.95, 1.10)	4	0.96 (0.92, 1.00)	1	–
Obesity	2	1.09 (1.01, 1.17)	2	1.04 (0.96, 1.12)	4	1.07 (1.01, 1.13)	1	–
Underweight	2	1.33 (1.17, 1.51)	2	1.18 (0.96, 1.46)	3	1.31 (1.12, 1.54)	1	–
Recurrence								
Overweight	3	0.98 (0.92, 1.04)	3	1.04 (0.93, 1.17)	4	1.01 (0.96, 1.07)	2	0.98 (0.81, 1.19)
Obesity	3	1.09 (1.01, 1.18)	3	1.04 (0.88, 1.23)	4	1.07 (1.02, 1.13)	2	1.09 (0.88, 1.35)
Underweight	3	1.17 (0.97, 1.41)	3	1.06 (0.97, 1.16)	4	1.13 (1.04, 1.21)	2	1.00 (0.53, 1.89)

BMI body mass index, *HR* hazard ratio, *CI* confidence interval

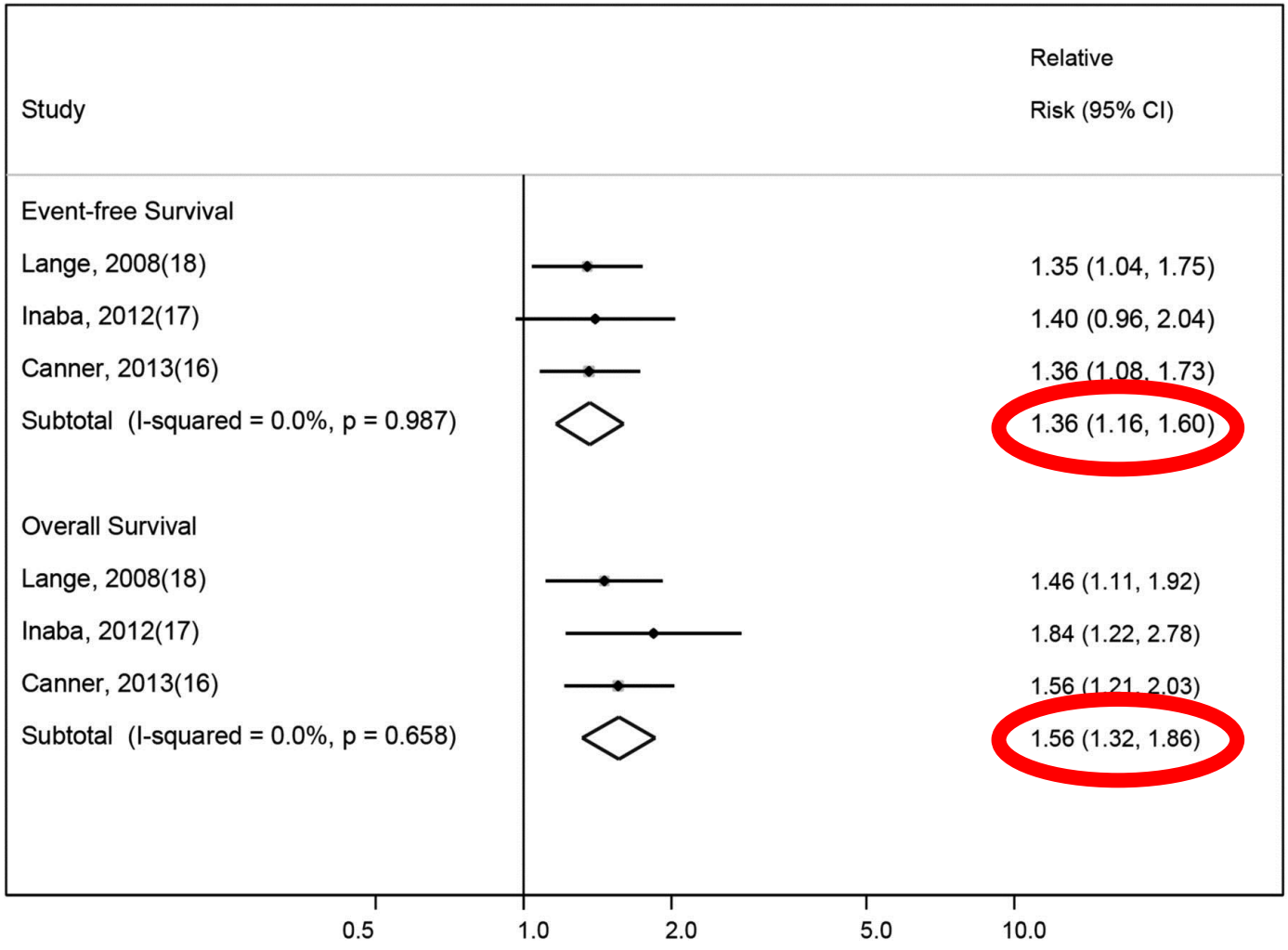
Doleman B et al. ***Tech Coloproctol 2016;20:517-535***

High BMI is Associated with Poor Event-Free and Overall Survival in Children with ALL



Orgel E et al. *Am J Clin Nutr 2016;103:808-817*

Higher BMI is Associated with Poor Event-Free and Overall Survival in Children with AML



Orgel E et al. *Am J Clin Nutr 2016;103:808-817*

BMI and Prognosis in Adult Hematologic Malignancies

Multiple Myeloma

- Lower BMI associated with poor prognosis

Beason TS et al. Oncologist 2013; 18:1074-1079
Jung S-H et al. Ann Hematol 2014; 93:835-840

Diffuse Large Cell Lymphoma

- Lower BMI associated with poor prognosis

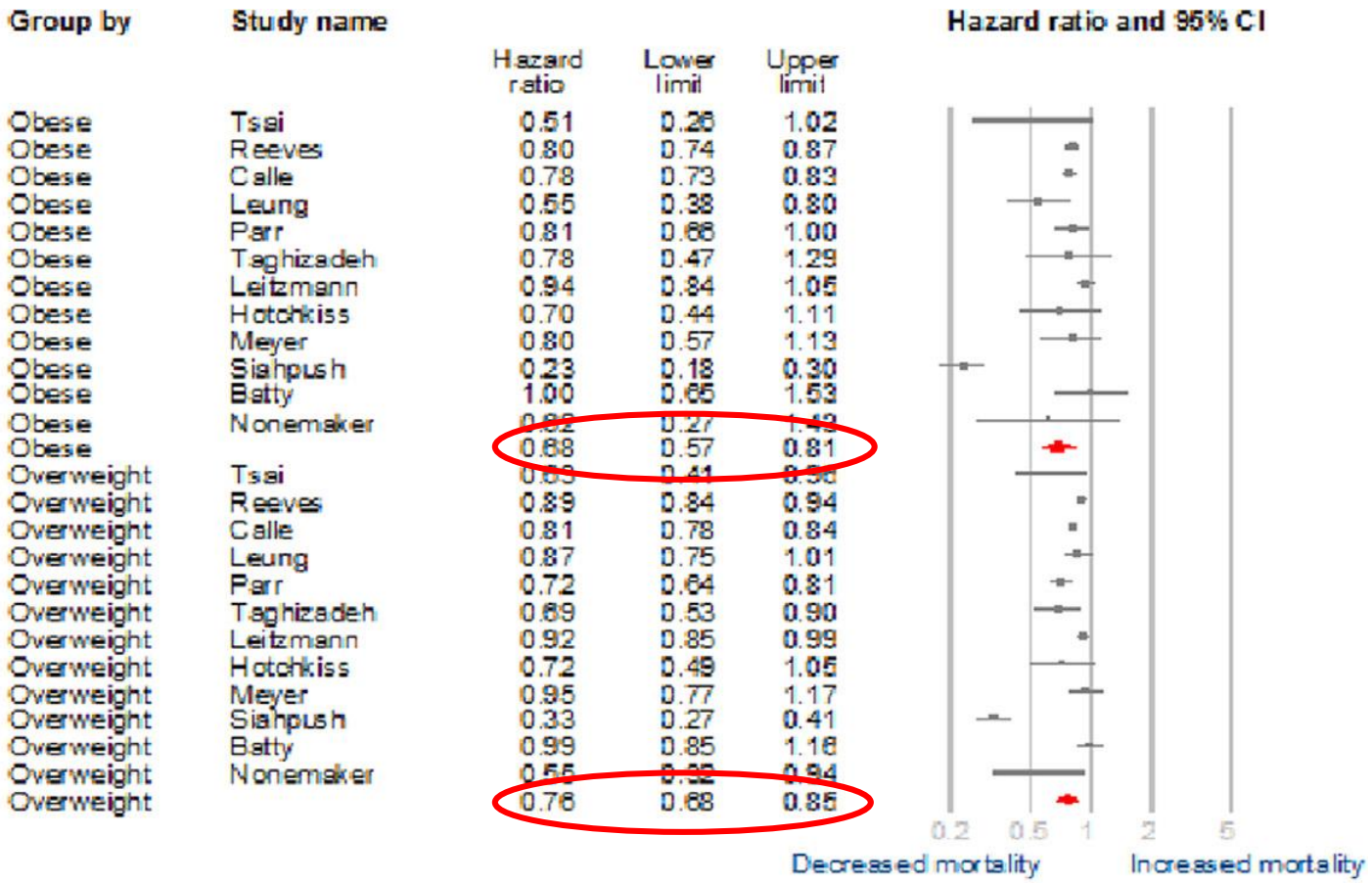
Carson KR et al. J Clin Oncol 2012; 30:3217-3222
Weiss L et al. Ann Oncol 2014; 25:171-176

- BMI not associated with prognosis

Hong F et al. Ann Oncol 2014; 25:669-674

"Disease-related weight loss may contribute to prognosis"

Lung Cancer Prognostic Association of Obesity and Overweight (vs normal weight)

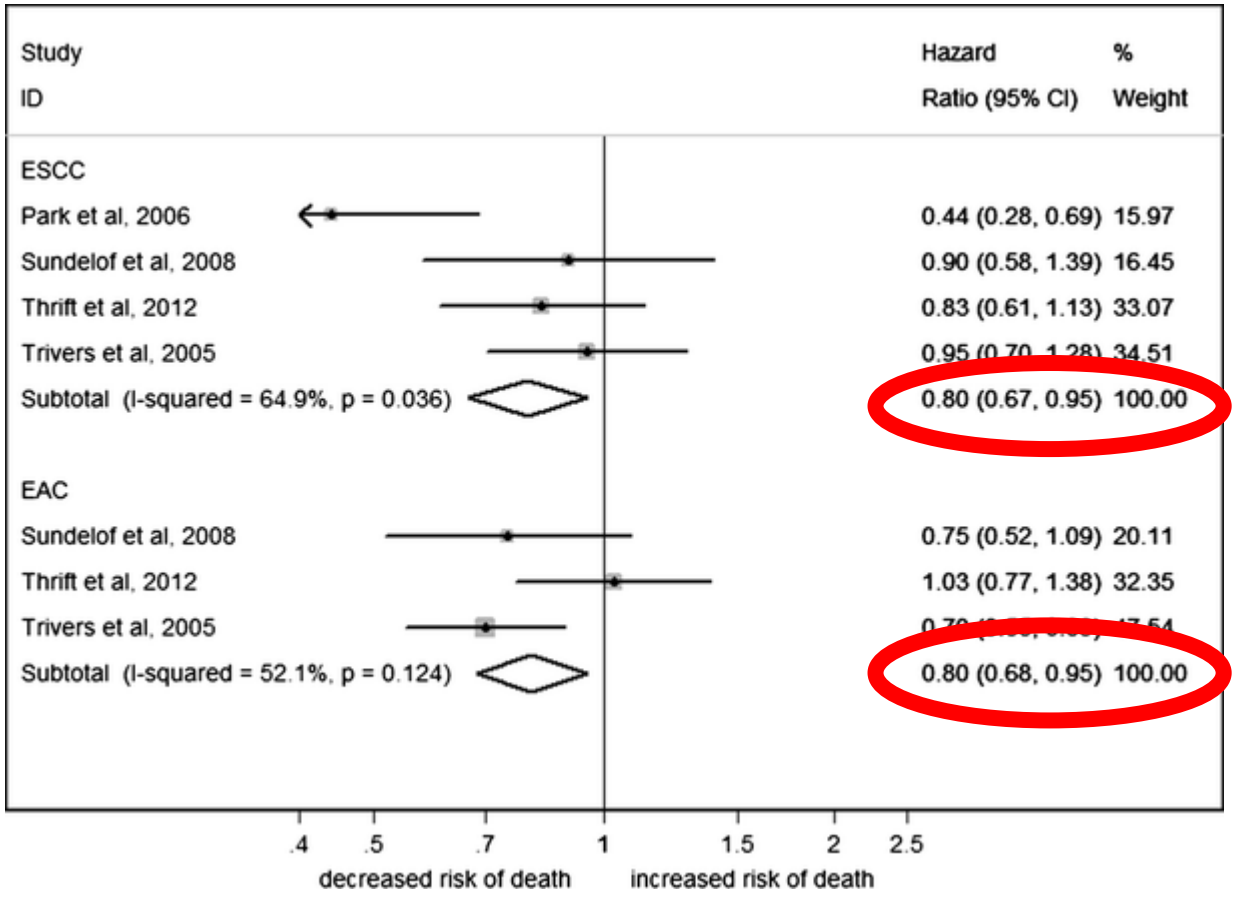


Gupta A et al. Lung Cancer 2016;102:49-59

Esophageal Cancer Prognosis
Overweight or Obese vs. Normal Weight

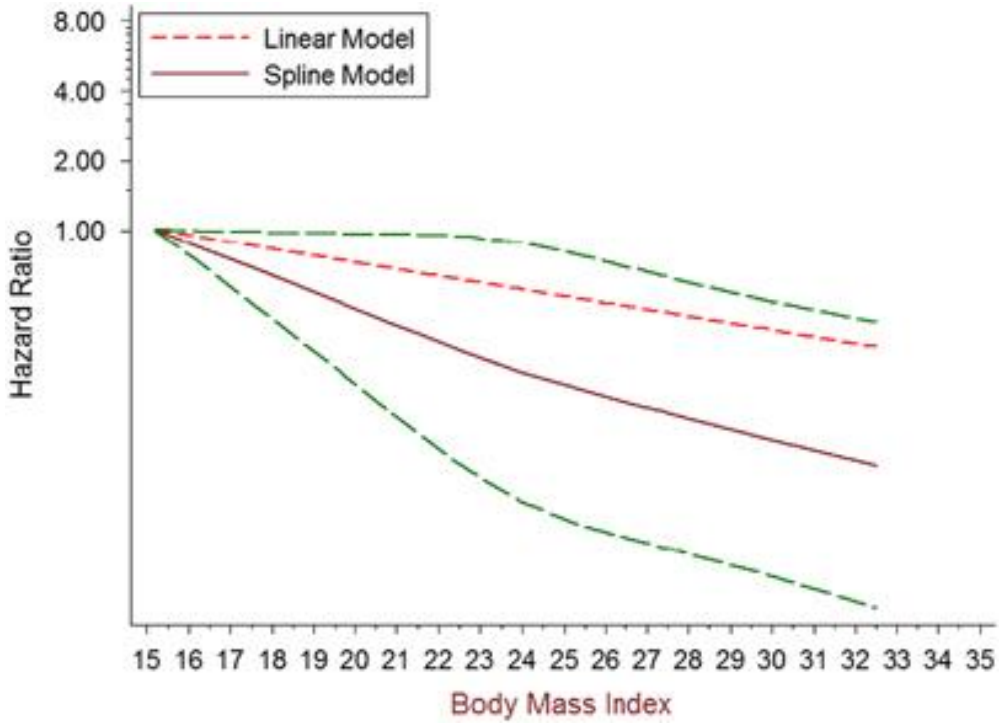
Squamous Cell Cancer

Adenocarcinoma



Fahey PP et al. Cancer Causes Control 2015;26:1365-1373

Renal Cell Cancer: Higher BMI Associated with Lower HR for Cancer Specific Mortality



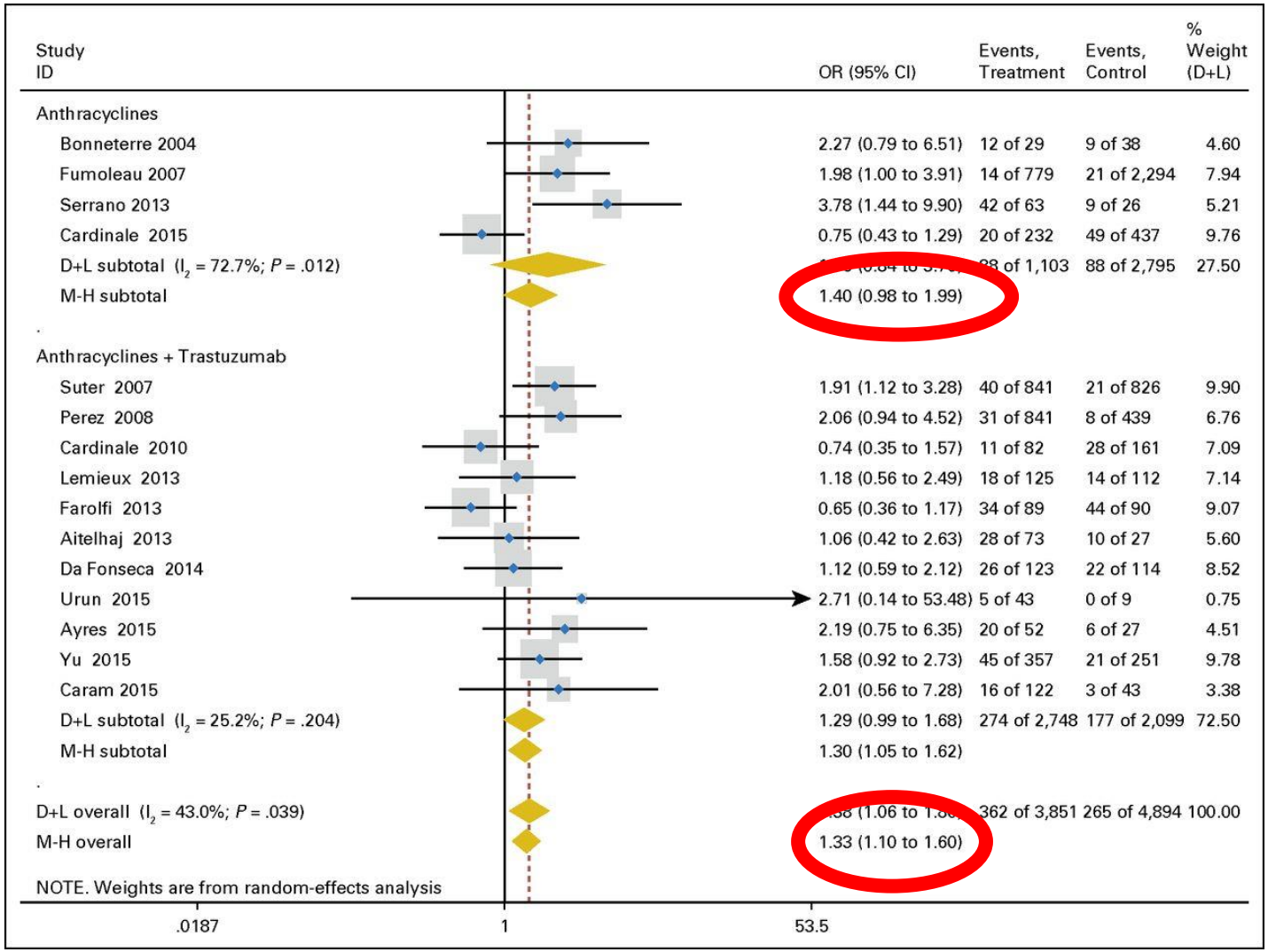
Bagheri M et al. Intl J Obes 2016;40:1817-1822

Obesity and Cancer Outcome

- Obesity is associated with modestly higher risk of recurrence and/or death in many common cancers (e.g.breast, CRC, ovarian, endometrial)

- Obesity is associated with modestly lower risk of recurrence or death in some cancers (e.g lung, esophageal, hematological) possibly reflecting cancer-associated weight loss

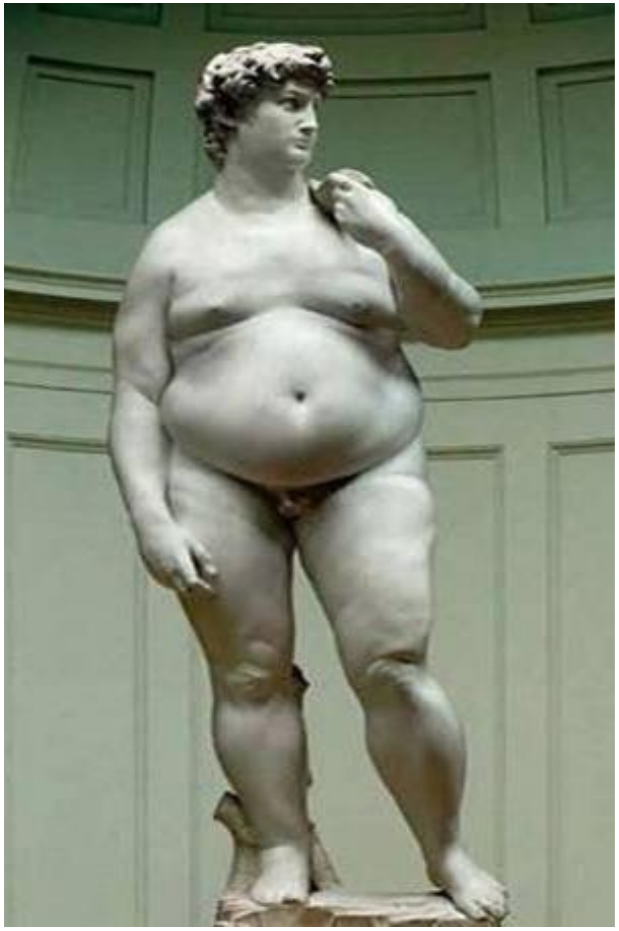
Effects of Overweight and Obesity on Cardiotoxicity of Anthracyclines (with or without trastuzumab) in Breast Cancer Patients



Guenancia C et al. J Clin Oncol 2016; 34:3157-3165

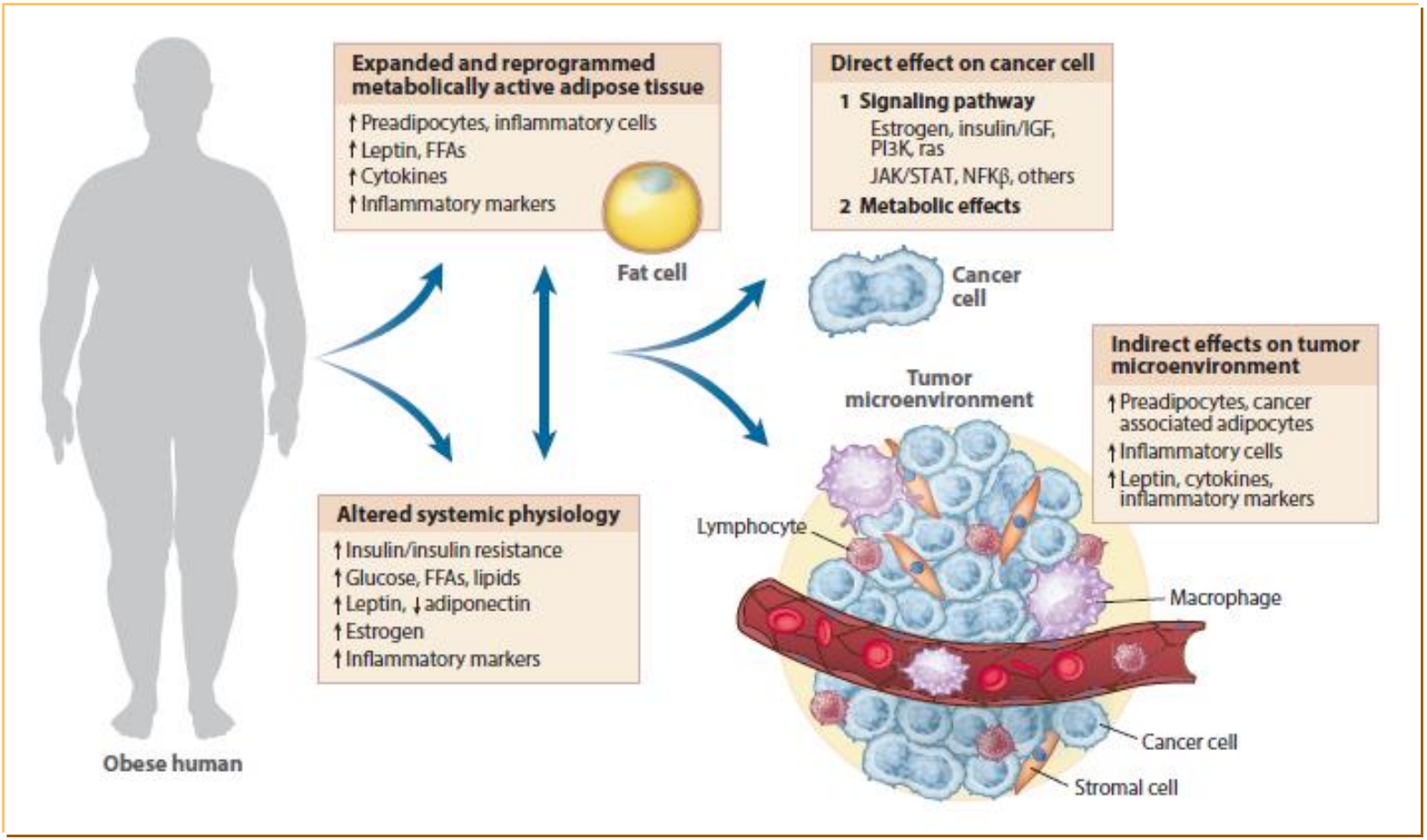
Our Hunter Gatherer Genes Have Not Evolved at the Same Pace as our Lifestyles …

Michelangelo's "David"
1501-1504



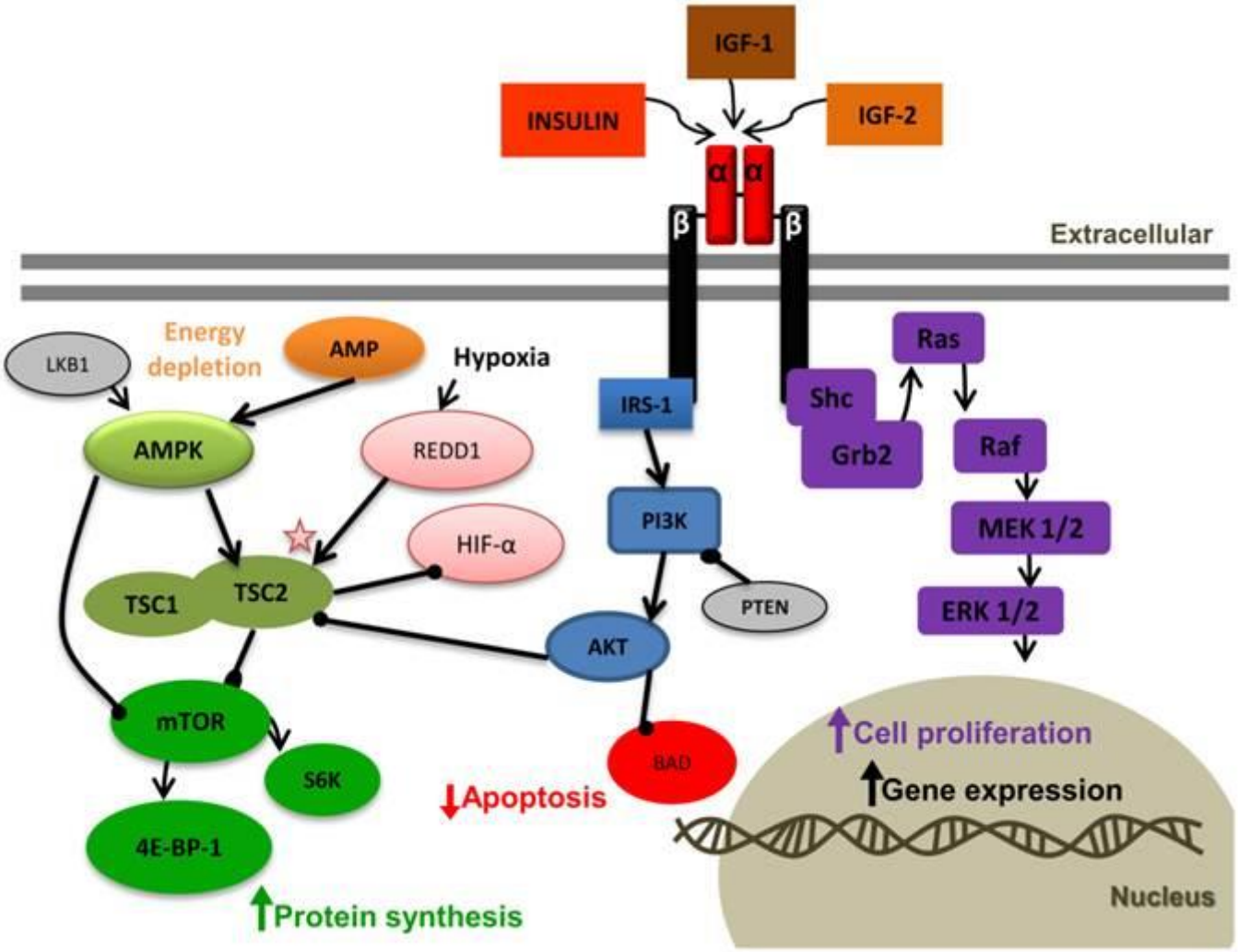
Michelangelo's "McDavid"
2012

The Complex Association of Obesity and Cancer



Goodwin PJ and Stambolic V Ann Rev Med 2015

IGF-1R Signaling Pathway

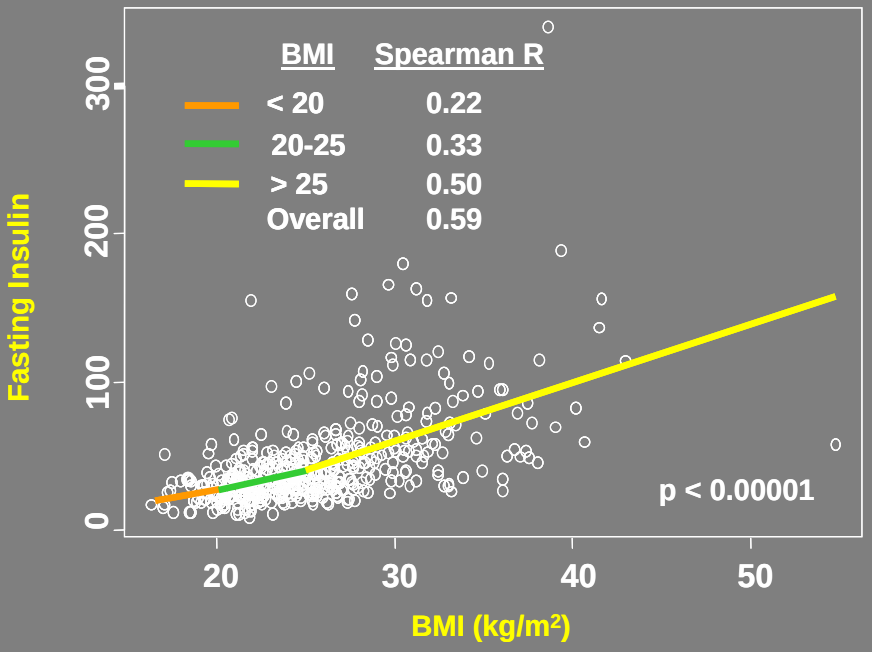


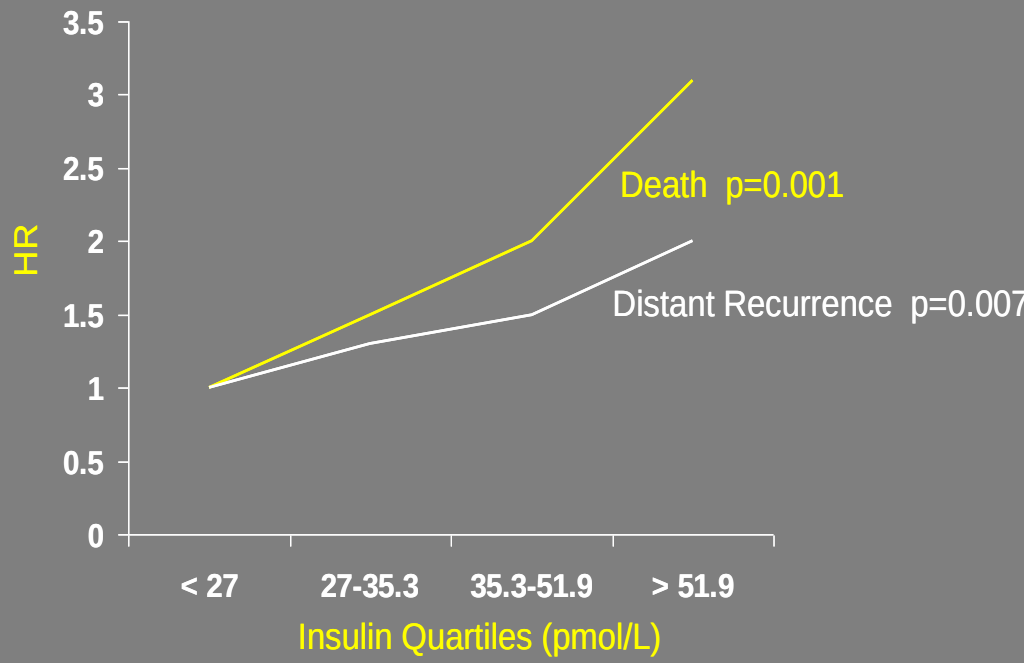
Braun S et al. Int J Biol Sci 2011; 7:1003-1015

Insulin is Associated with BMI and Poor Breast Cancer Outcomes

Goodwin PJ ASCO 1999, JCO 2002

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





Insulin Receptors in Early Stage Breast Cancer

n=178 women with invasive BC

		IR	IGFI-R
IHC*	• neg (0-2)	1.1%	25.3%
	• weak (3-5)	11.2%	63.5%
	• strong (6-8)	87.6%	11.2%

Spearman Correlations		IR	IGFI-R
IHC*	• IR	_	0.42
	• IGFI-R	0.42	_
Plasma*	• insulin	-0.02	-0.02
	• IGFI	-0.11	-0.10

*

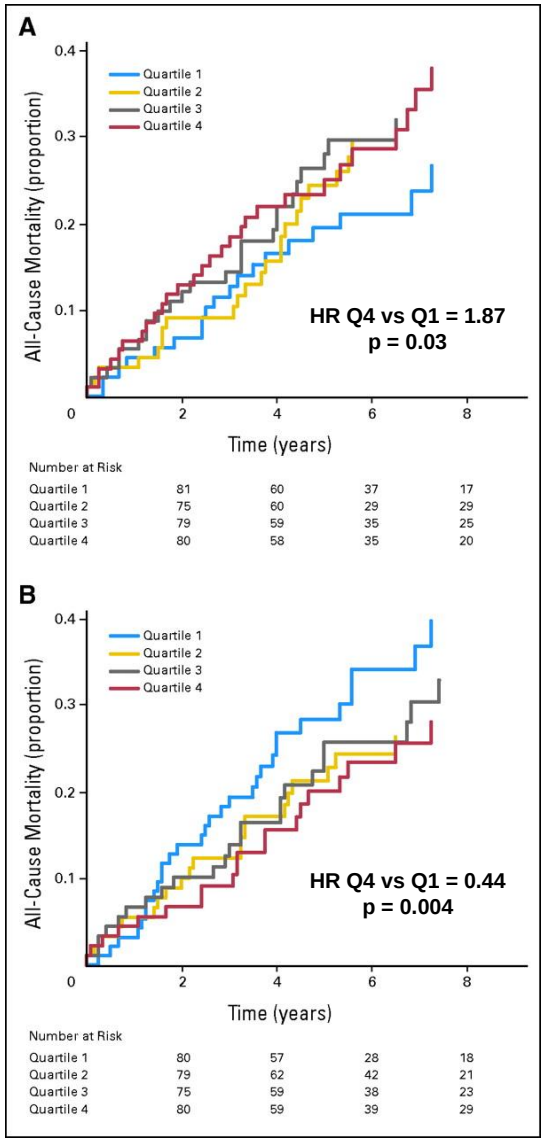
Mulligan AM, O'Malley F, Goodwin PJ BCRT 2007

n = 438 women with invasive BC

	% +ve	OS	P Survival
IR*	59.0	Worse	0.009
IGF-IR	37.5	Worse	0.30
pIGF-IR/IR	55.3	Worse	0.046

Law JH et al. Cancer Res 2008

Non-Metastatic Colorectal Cancer (n = 373)
Circulating C-peptide (top) and IGFBP-1 (bottom) and Overall Mortality

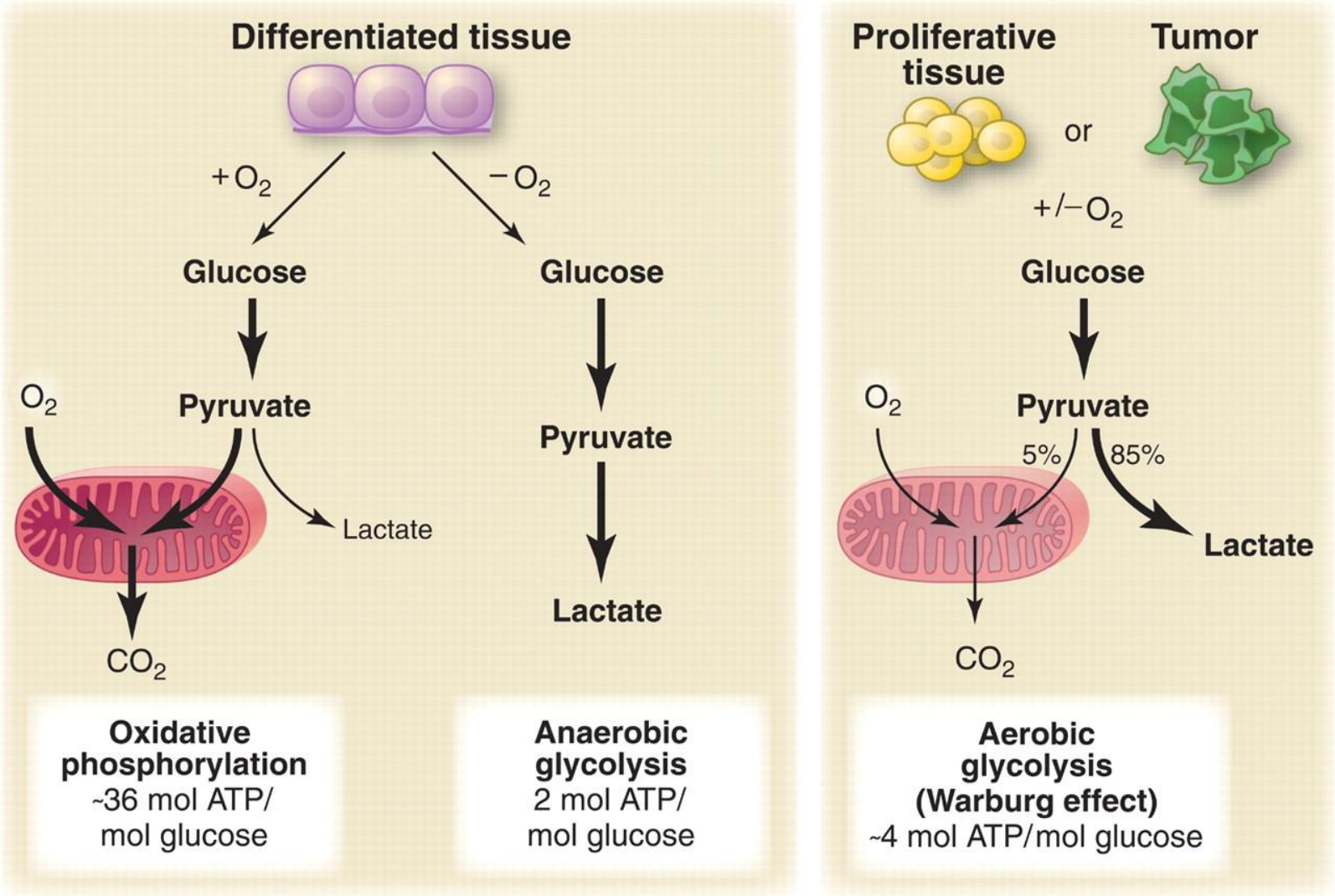


Higher C-peptide is associated with higher overall mortality

Higher IGFBP-1 (inversely related to insulin) is associated with lower overall mortality

Wolpin BM et al. J Clin Oncol 2009; 27:176-185

In Rapidly Proliferating Tissue Abundant Glucose May Lead to the Warburg Effect



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

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

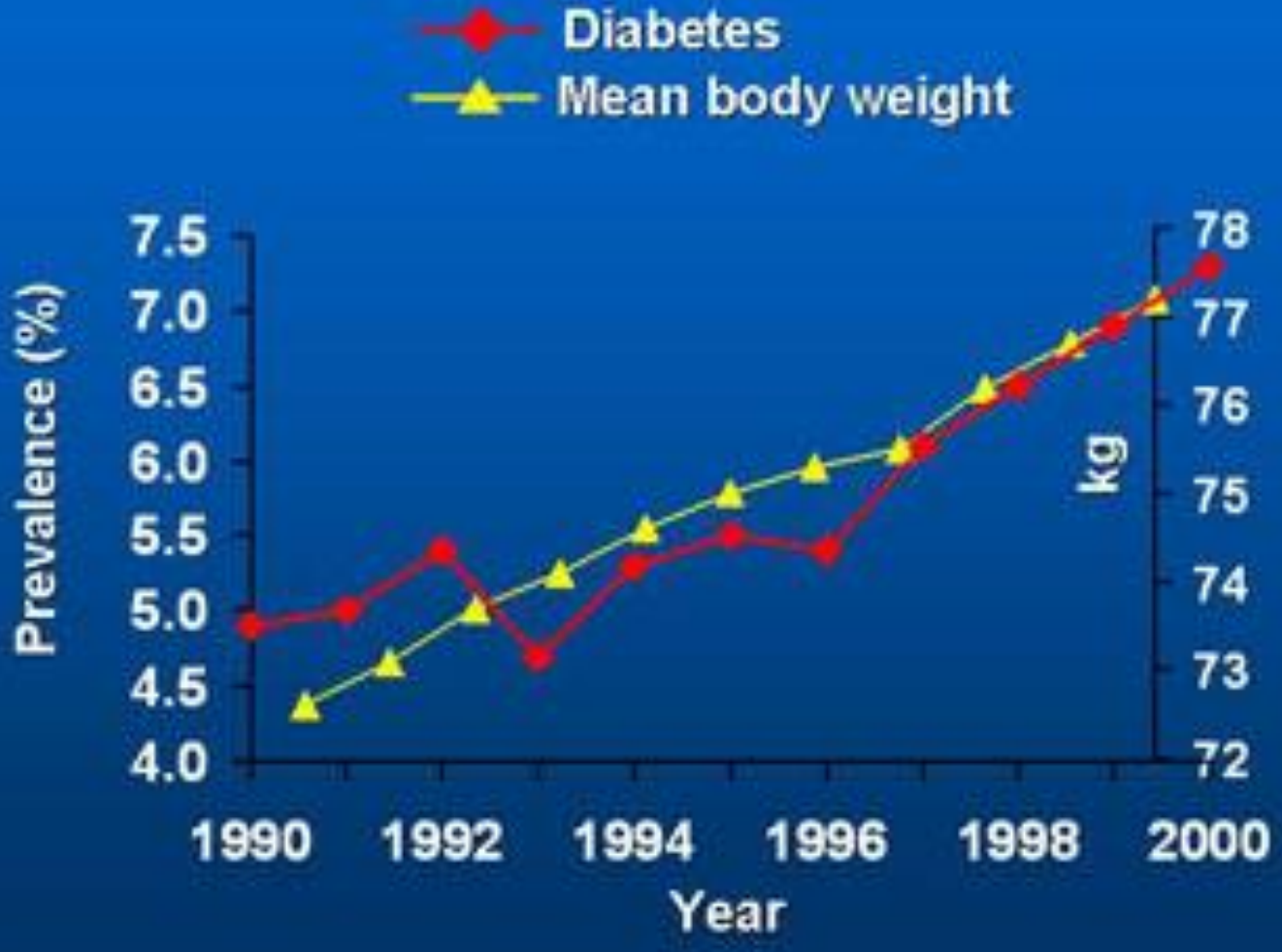
Higher Glucose Levels at Diagnosis are Associated with Increased Risk of Recurrence in Men with Localized Prostate Cancer Post-Prostatectomy

Quartile	*Range (mg/dl)*	N	*Events (%)*	*Overall HR (95% CI)*[a]
First	31–98	464	61 (13)	1.00 (referent)
Second	99–111	416	68 (16)	1.35 (0.95–1.92)
Third	112–137	414	76 (18)	1.57 (1.10–2.24)
Fourth	138–1015	438	76 (17)	1.44 (0.97–2.14)

[a]HR adjusted for age, race, body mass index, diagnosis of diabetes, treatment year, treatment, clinical stage, diagnostic PSA and Gleason Sum.

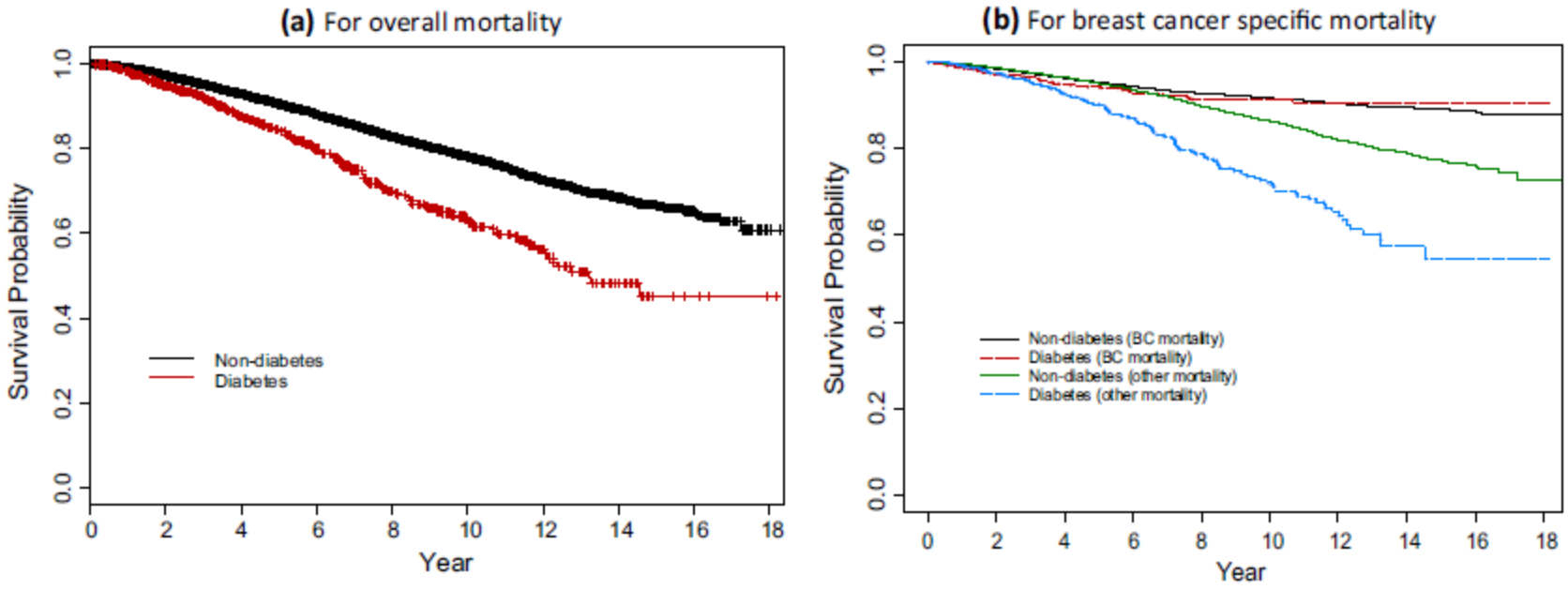
Wright JL et al. Prostate Cancer Prostatic Dis 2013; 16:204-208

Diabetes and Obesity: The Continuing Epidemic



Mokdad AH et al. *Diabetes Care*. 2000;23:1278-83.
Mokdad AH et al. *JAMA*. 1999;282:1519-22.
Mokdad AH et al. *JAMA*. 2001;286:1195-200.

Diabetes is Associated with Increased Overall Mortality (But Not Cancer Specific Mortality) in Breast Cancer (WHI)



Luo J et al. Breast Cancer Res Treat 2014; 148:153-162

Obesity vs. Metabolic Health

Systemic Review and Meta-Analysis

BMI	< 25	Normal
	≥ 25-30	Overweight
	≥ 30	Obese

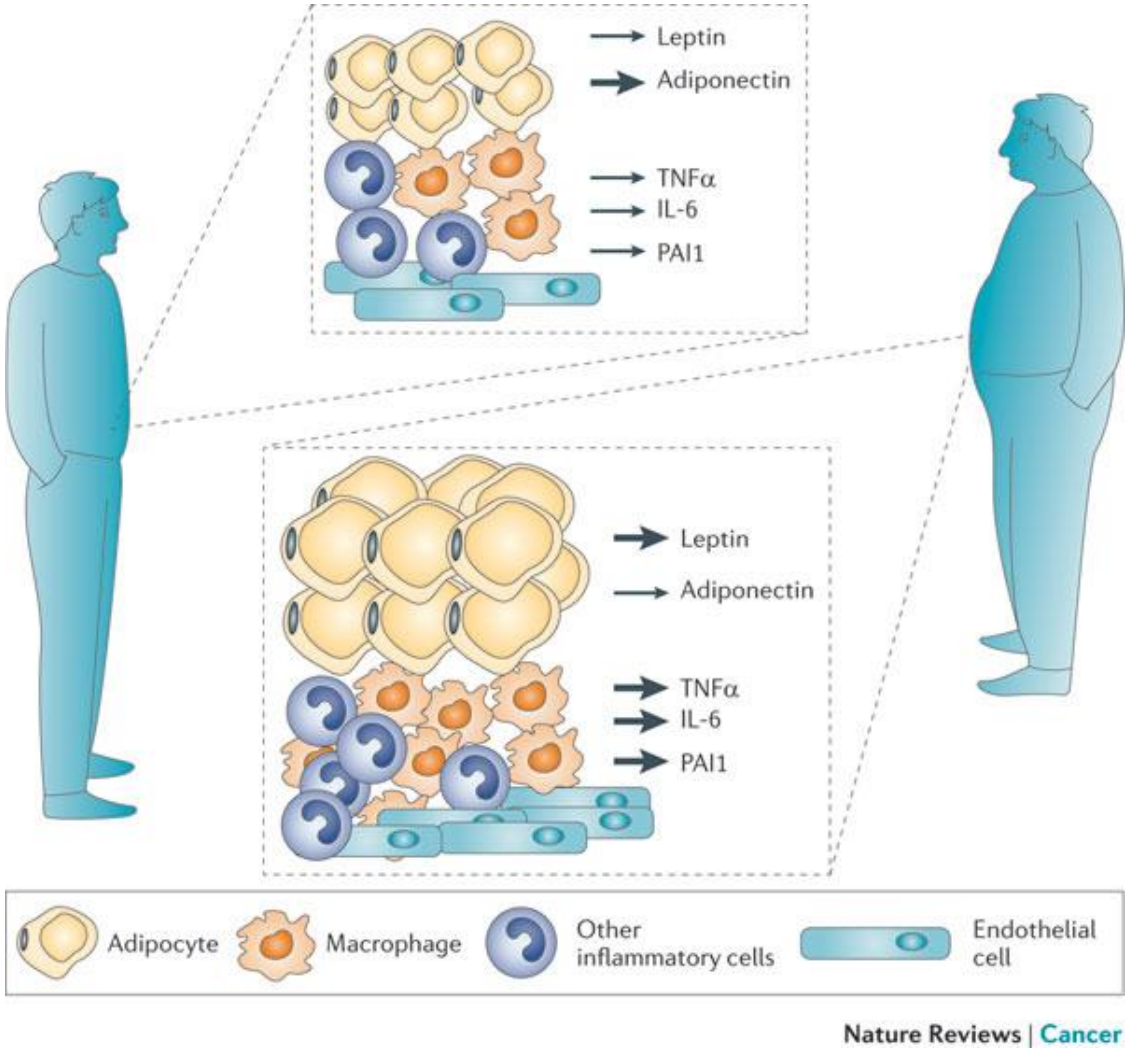
Metabolic Healthly: No components of IRS
Metabolic Unhealthy: ≥ 1 IRS component

BMI	RR (95% CI) All Cause Mortality or CV Event	
	Metabolically Healthy	Metabolically Unhealthy
N	Reference	3.14 (2.36-3.93)
OW	1.10 (0.90-1.24)	2.70 (2.08-3.30)
OB	1.19 (0.98-1.38)*	2.65 (2.18-3.12)

* 1.24 (1.02-1.55) with > 10 years follow-up

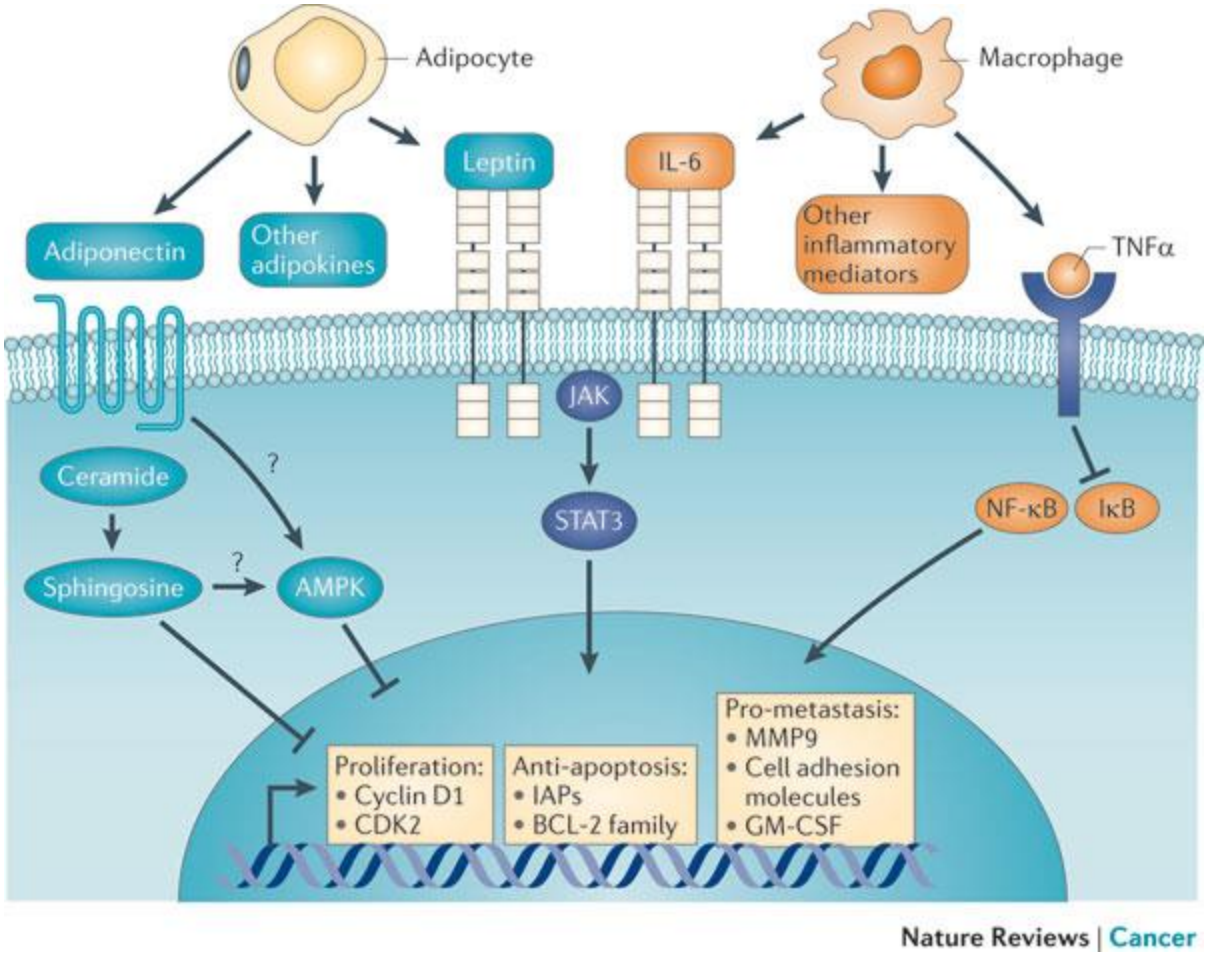
Kramer CK et al. Ann Intern Med 2013; 159:758-769

Adipose Tissue Associated Factors



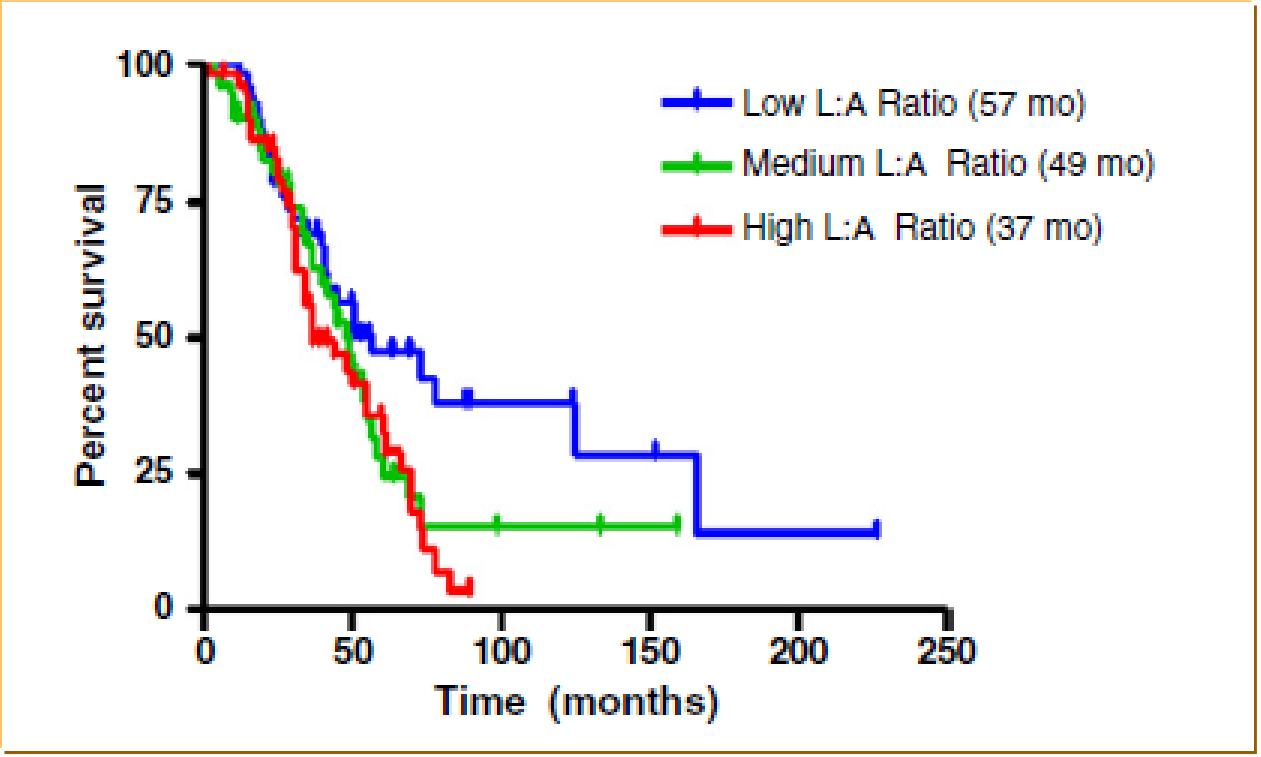
Khandekar MJ et al. Nat Rev Cancer 2011; 11:886-895

Adipokine and Inflammatory Signalling in Obesity



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

High Leptin : Adiponectin Ratio is Associated with Poor Survival in Stage III, IV Epithelial Ovarian Cancer

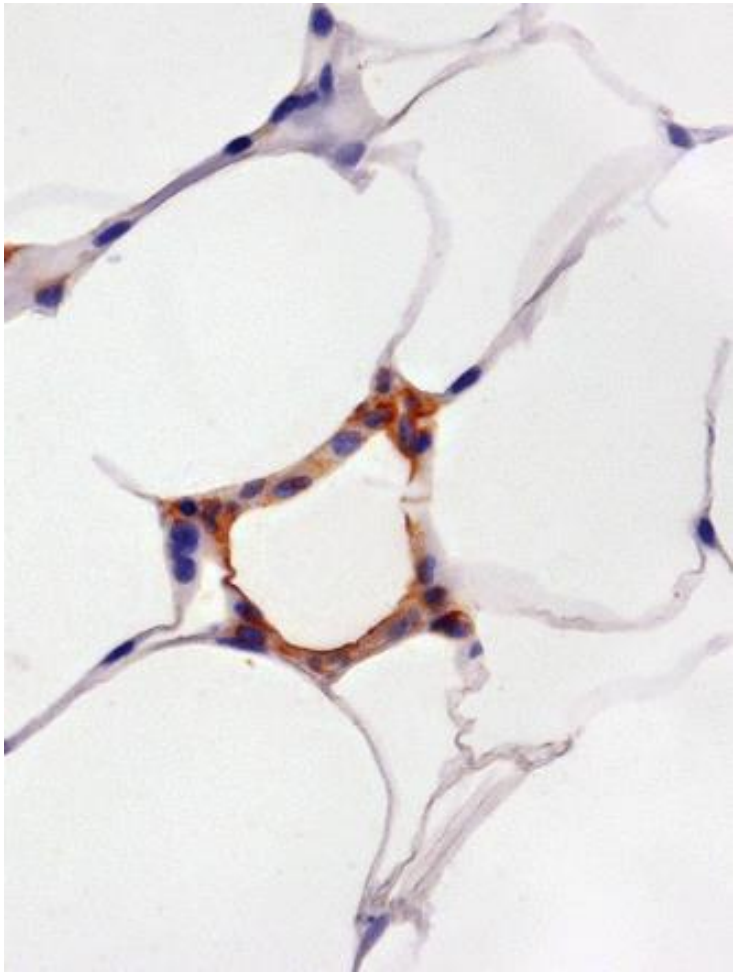


Diaz ES et al. Gynecol Oncol 2013; 129:353-357

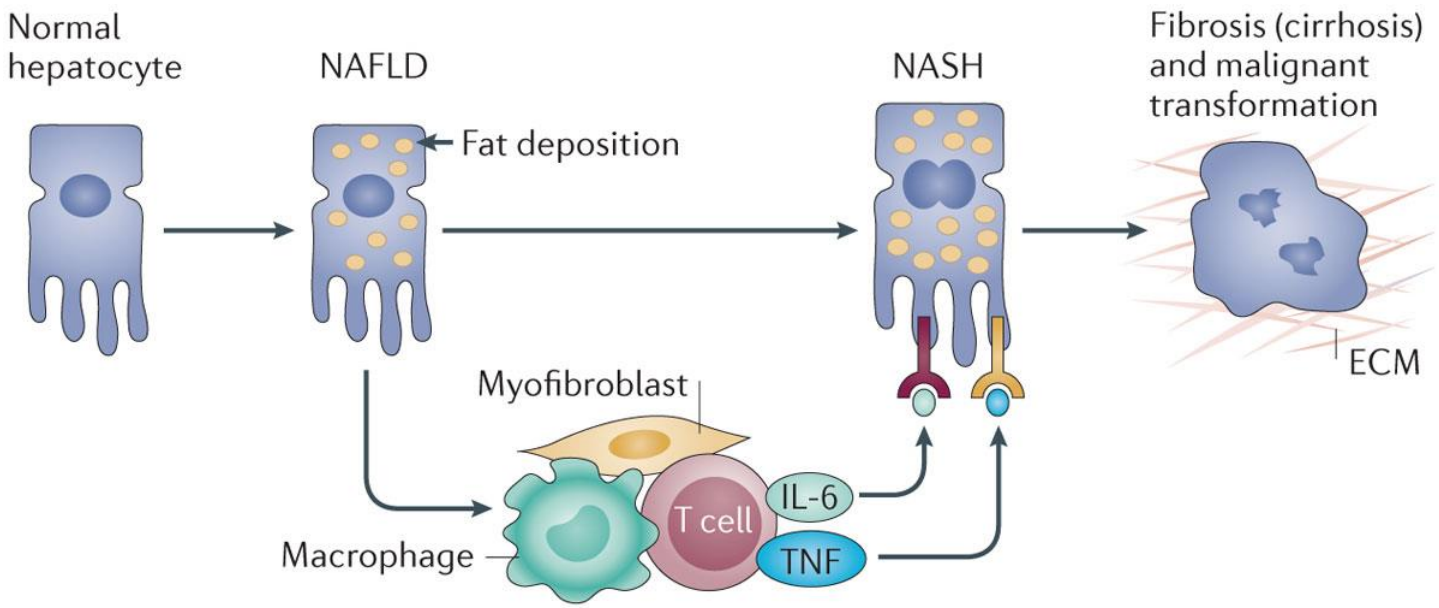
Local Inflammation: Crown-Like Structures

Necrotic adipocytes surrounded by macrophages

(Subbaramaiah K et al. Cancer Prevention Research 2011)



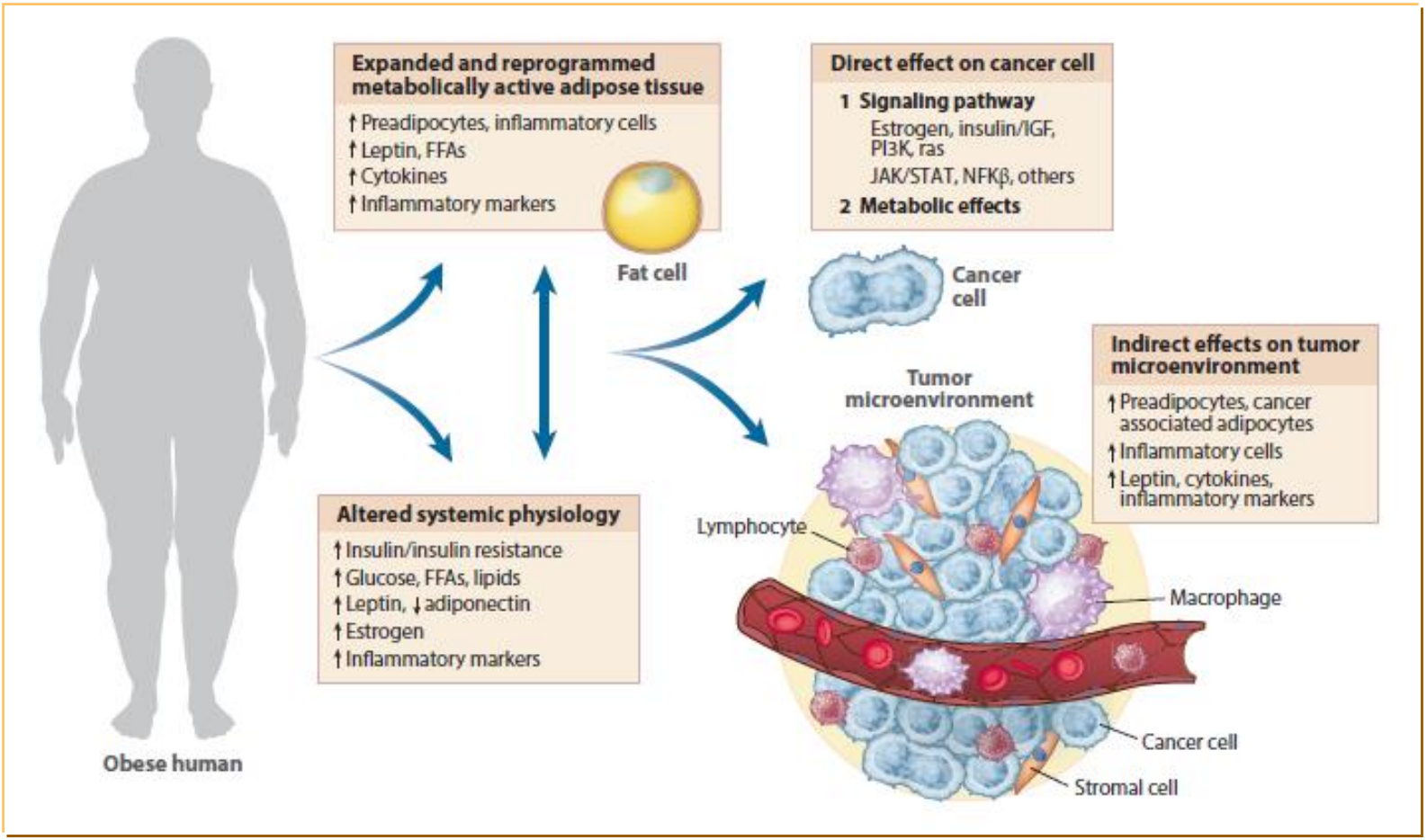
Hypothesized Steatosis-Hepatocellular Carcinoma Pathway



Accumulation of fat in the liver (nonalcoholic fatty liver disease (NAFLD)) is associated with chronic inflammation, known as nonalcoholic steatohepatitis (NASH). NASD may progress either directly to hepatocellular carcinoma or indirectly through a cirrhosis state. ECM, extracellular matrix; IL-6, interleukin-6; TNF, tumour necrosis factor.

Renehan AG et al. Nat Rev Cancer 2015; 15:484-498

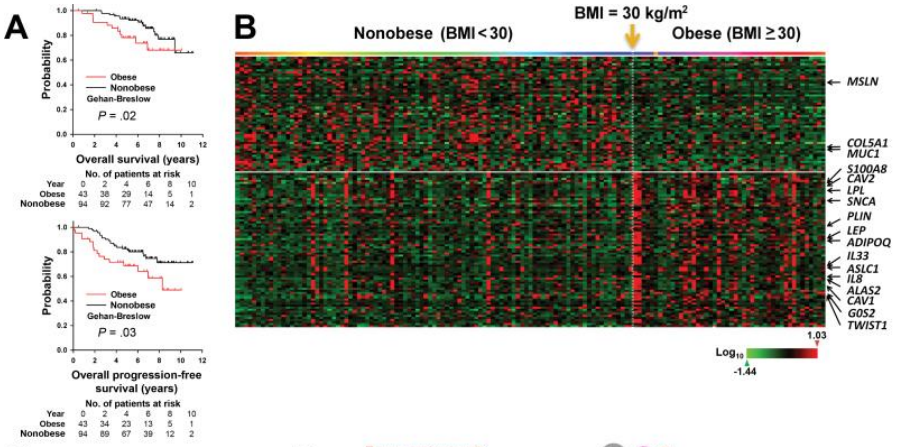
The Complex Association of Obesity and Cancer



Goodwin PJ and Stambolic V Ann Rev Med 2015

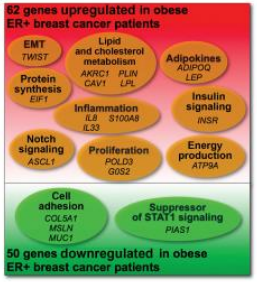
Transcriptomic Changes Associated with Obesity in 137 ER+ Breast Cancers

A. Obesity associated with poor prognosis

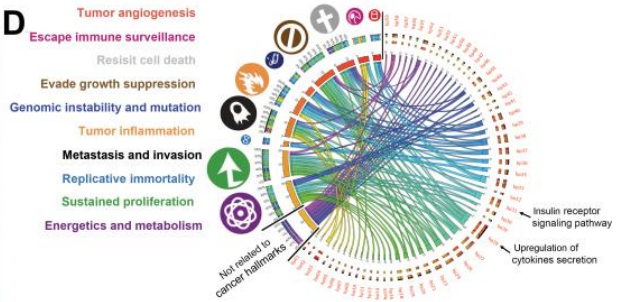


B. Gene expression significantly different in tumors occurring in obese vs non-obese patients

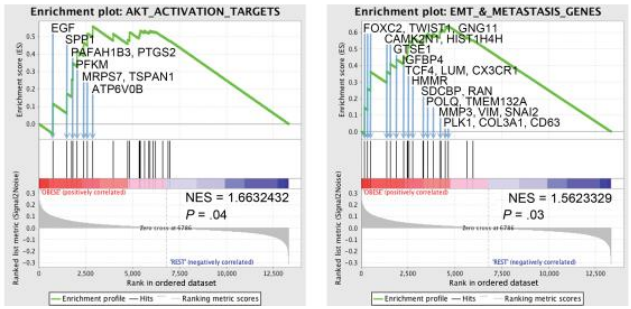
C. Genes upregulated in tumors in obese (vs non-obese) patients are linked to obesity-associated pathways



D. Circos plot linking biologic changes in obesity associated cancers to the Hallmarks of Cancer



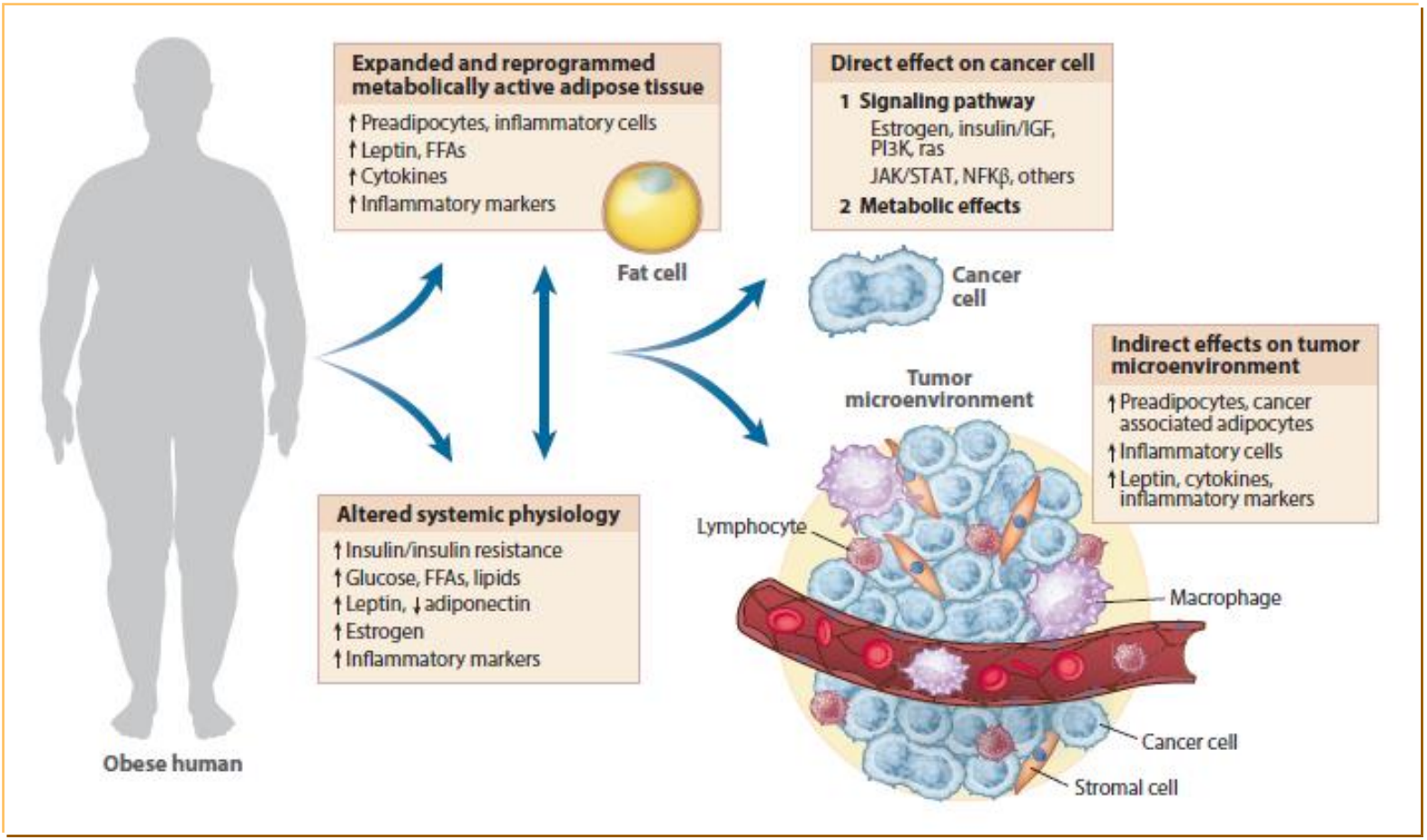
E. Gene enrichment analyses – AKT (left), EMT and metastasis (right)



Conclusions: Multiple processes, including AKT/mTOR activation, adipokine secretion, insulin and estrogen signaling and inflammation, play a role in obesity-associated aggressiveness.

Fuentes-Mattei E et al. JNCI 2014;106(7). pii: dju158. doi: 10.1093/jnci/dju158

The Complex Association of Obesity and Cancer



Goodwin PJ and Stambolic V Ann Rev Med 2015

Do We Have Enough Evidence to Recommend Lifestyle Change to Improve Cancer Outcomes?

Association vs Causation

A **non-causal** association could reflect:

- bias/confounding
- under-treatment of obese
- more advanced stage in obese

If **causal**, lifestyle change may not improve BC outcome:

- Inherent biologic aggressiveness of obesity associated cancer
- Magnitude of feasible change insufficient

RCTs with cancer outcomes will be essential.

In the meantime, clarity regarding the purpose (general health benefits, reduction in toxicity, etc) of any weight loss recommendation is recommended.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