MARTEDÌ DELL'ORDINE

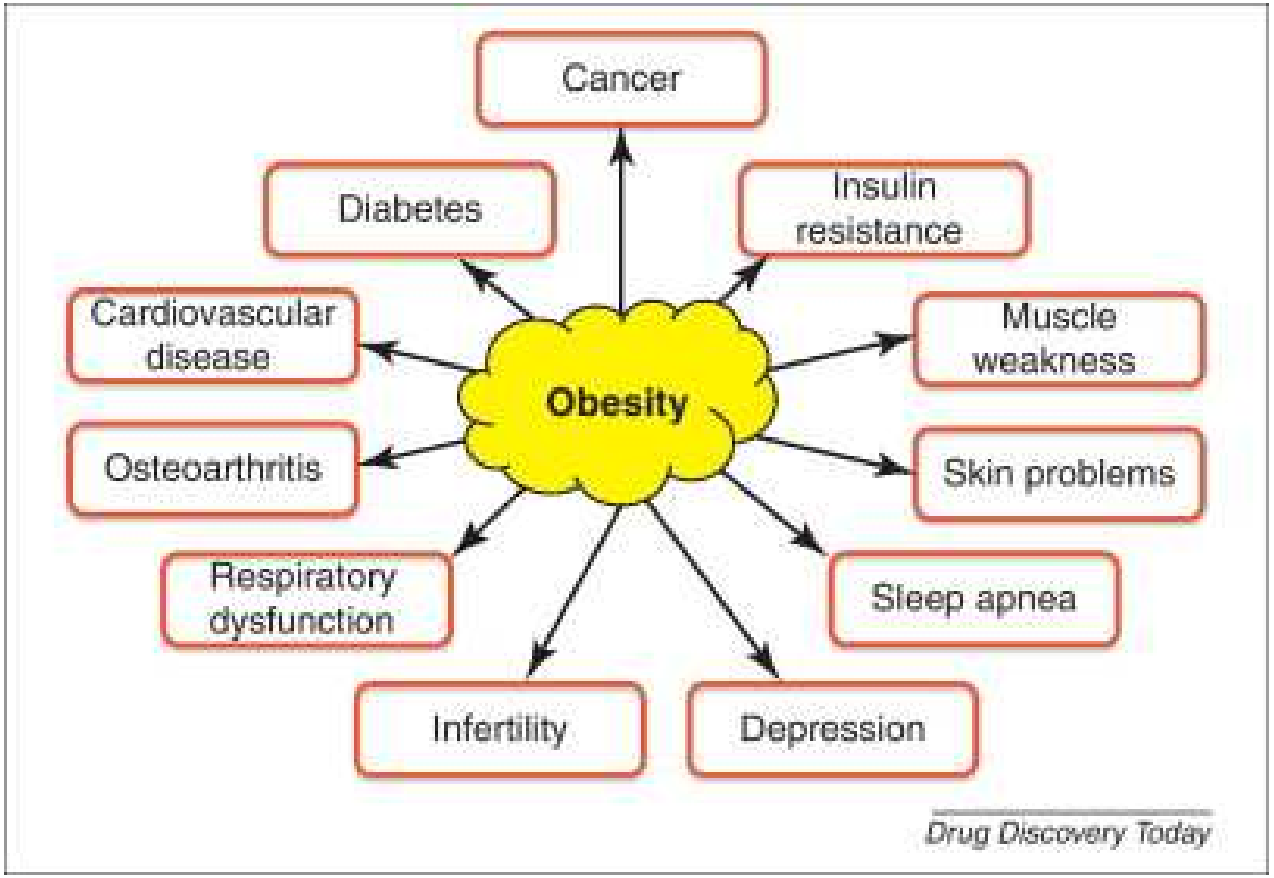
Obesità e tumori: quali legami ?

Elisabetta Dall'Aglio

Parma 6 ottobre 2015

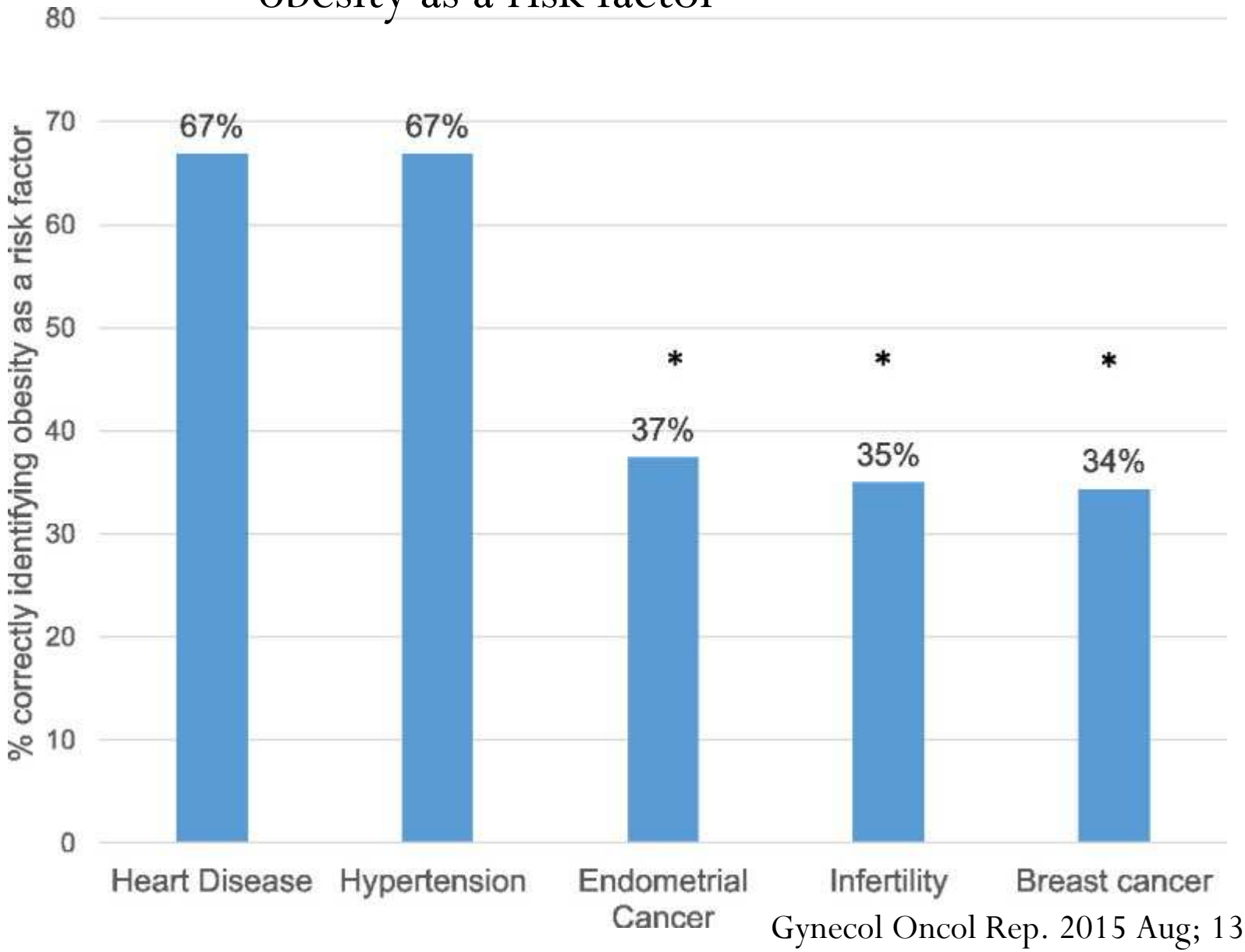
Role of obesity in disease pathogenesis.

Obesity is associated with a wide range of health conditions leading to a decrease in quality of life and/or life expectancy, some of which are indicated here.



Drug Discovery Today
Available online 21 May 2012

Percentage of women correctly identifying obesity as a risk factor



Gynecol Oncol Rep. 2015 Aug; 13: 71–75.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2003 VOL. 348 NO. 17

Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults

Eugenia E. Calle, Ph.D., Carmen Rodriguez, M.D., M.P.H., Kimberly Walker-Thurmond, B.A., and Michael J. Thun, M.D.

- 900,053 people
- Follow up for 16 years

Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults

Eugenia E. Calle, Ph.D., Carmen Rodriguez, M.D., M.P.H., Kimberly Walker-Thurmond, B.A., and Michael J. Thun, M.D.

Background The influence of excess body weight on the risk of death from cancer has not been fully characterized.

Methods In a prospectively studied population of more than 900,000 U.S. adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982, there were **57,145 deaths from cancer during 16 years of follow-up**

Results **The heaviest members of this cohort, those with a body-mass index [the weight in kilograms divided by the square of the height in meters] of at least 40, had death rates from all cancers combined that were 52 percent higher (for men) and 62 percent higher (for women) than the rates in men and women of normal weight.** In both men and women, body-mass index was also significantly associated with higher rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney; the same was true for death due to non-Hodgkin's lymphoma and multiple myeloma. Significant trends of increasing risk with higher body-mass-index values were observed for death from cancers of the stomach and prostate in men and for death from cancers of the breast, uterus, cervix, and ovary in women.

N Engl J Med 2003;348:1625-38

Summary of mortality from cancer according to BMI for US women in the Cancer Prevention Study II, 1982–1998.

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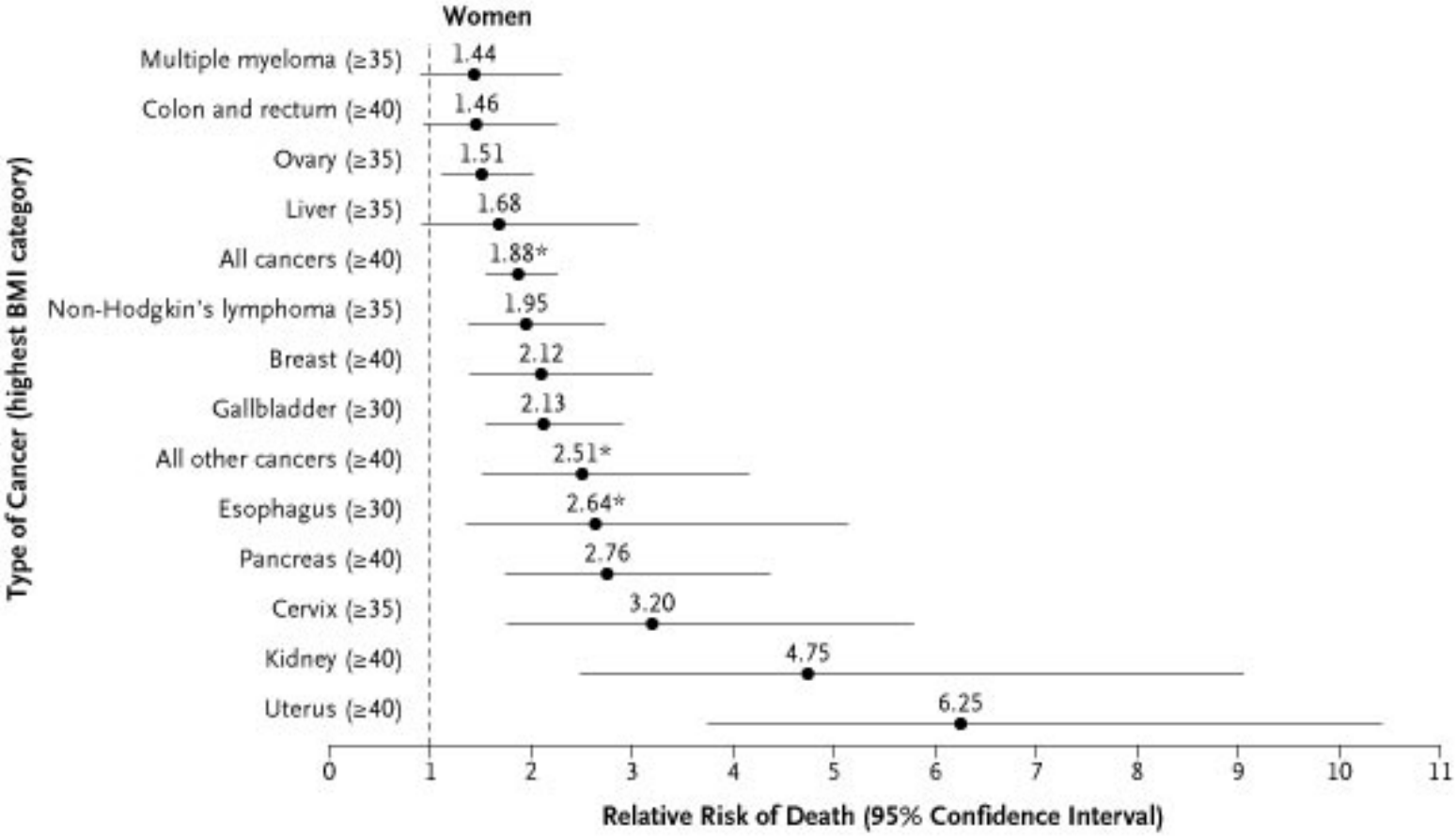

Calle EE et al. N Engl J Med 2003; 348: 1625–1638

Summary of mortality from cancer according to BMI for US men in the Cancer Prevention Study II, 1982–1998.

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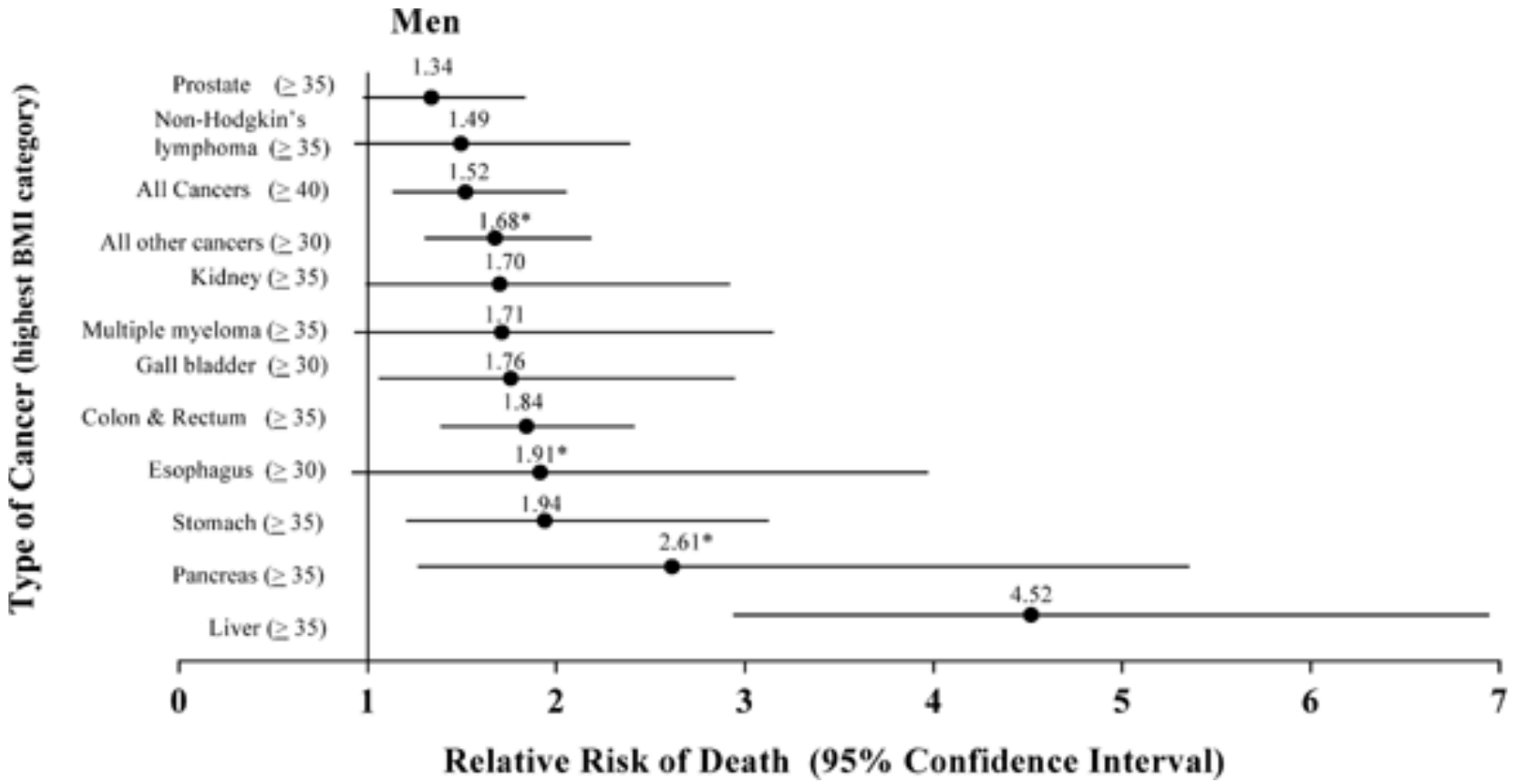


Calle EE et al. N Engl J Med 2003; 348: 1625–1638

Statistiche relative a obesità e rischio di cancro

In accordo con i dati esaminati dall'IARC Expert Report 2009, le percentuali di cancro che sono causate dall'obesità sono :

49% cancro dell'endometrio

35% cancro dell'esofago

28% cancro al pancreas

24% cancro del rene

21% cancro della colecisti

17% cancro della mammella post menopausa

9% cancro del colon-retto

Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies.

Renehan AG, Tyson M, Egger M, et al.

Systematic review and standardized meta-analysis of prospective observational studies (221 datasets in 20 cancer types) quantifying associations between a 5-kg/m^2 BMI increase and risk of incident cancer

It was demonstrated that associations

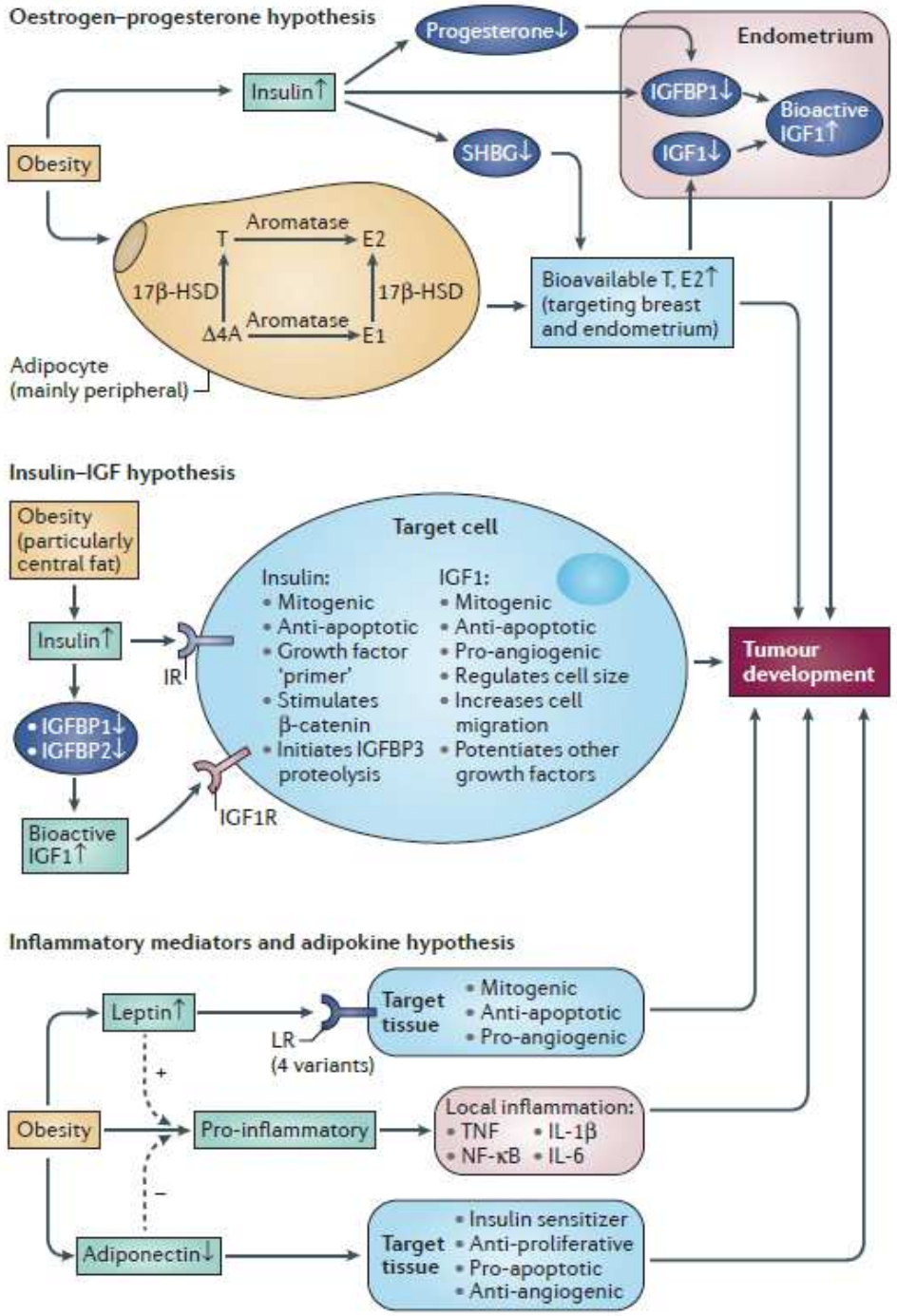
- (*a*) are sex-specific
- (*b*) exist for a wider range of malignancies than previously thought
- (*c*) are broadly consistent across geographic populations

Tali dati implicano la presenza di meccanismi biologici specifici per sesso e tipo di cancro sottesi a queste associazioni.

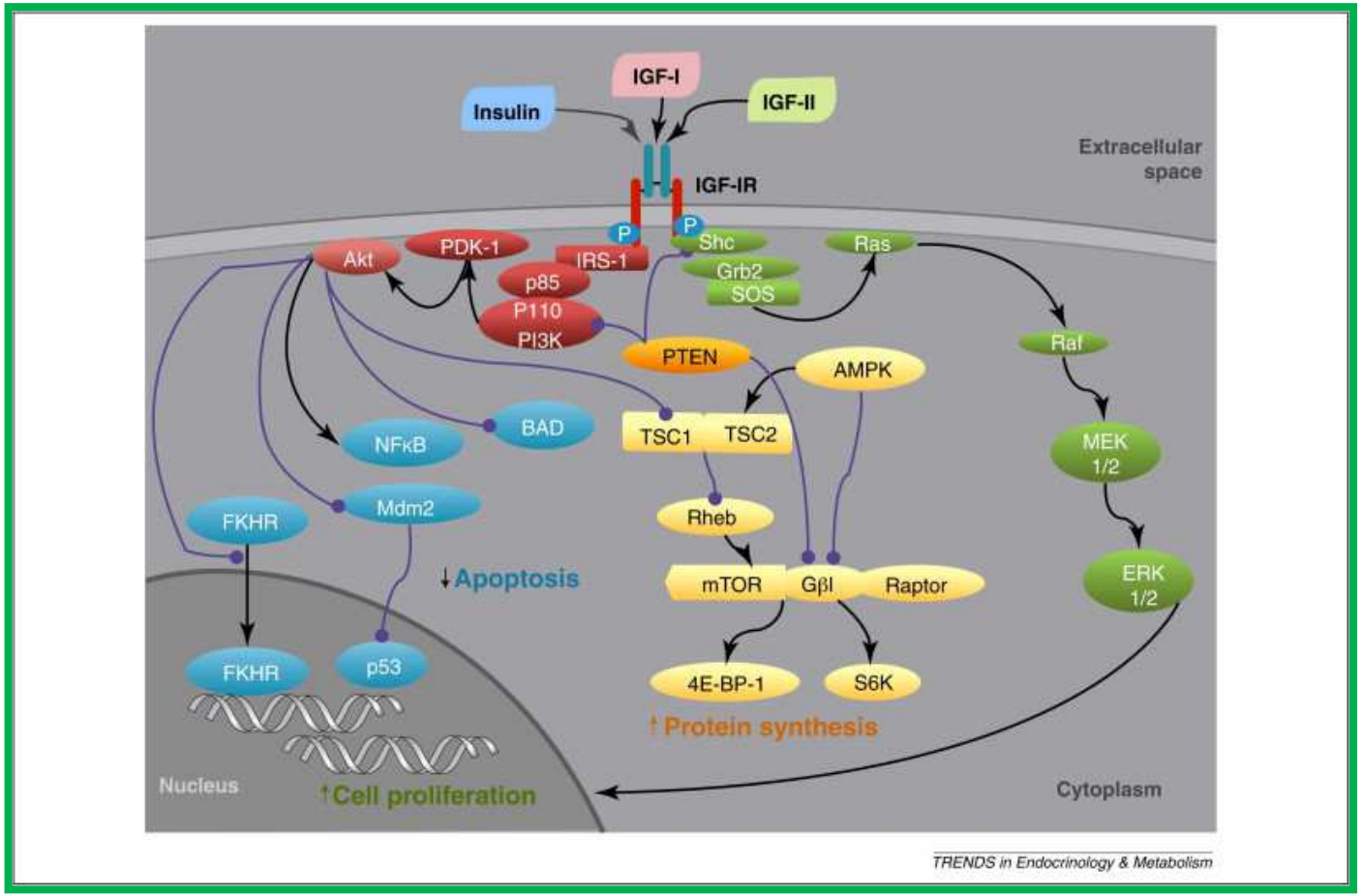
Lancet 2008 371:569-78

Meccanismi patogenetici che legano obesità e cancro NON uno solo

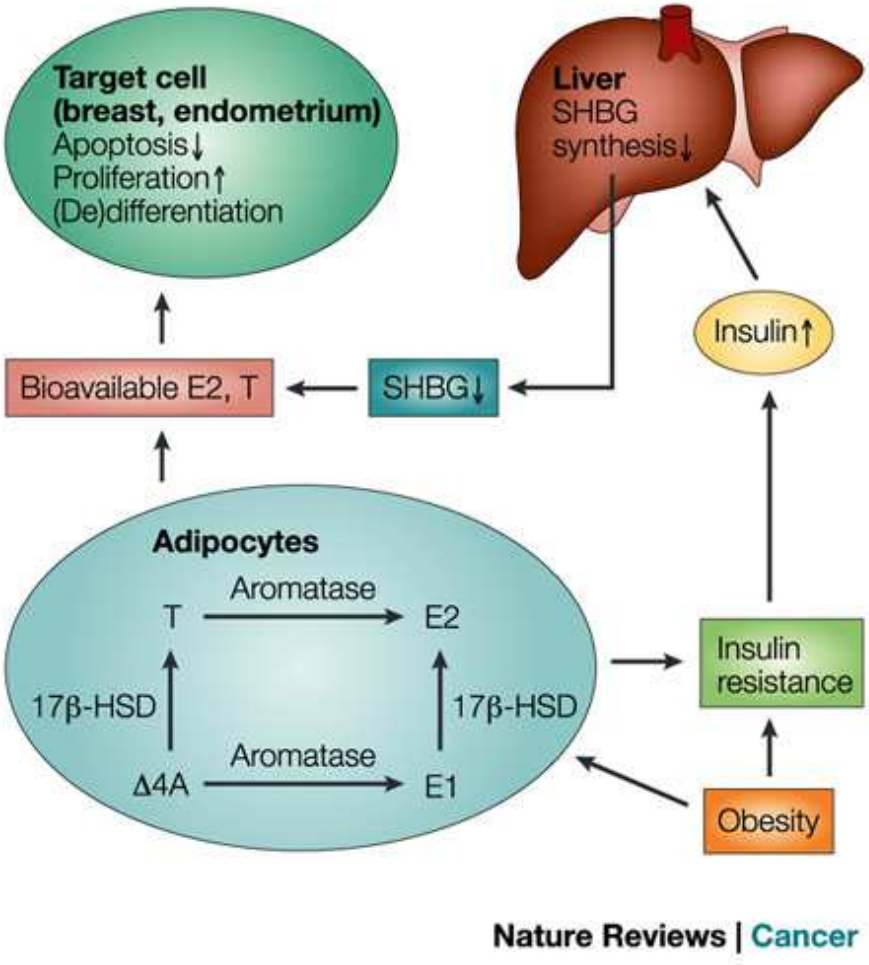
- Aumento del tessuto adiposo: modificazioni a carico del tessuto adiposo di “per se”
- Modificazioni sistemiche favorenti; secondarie all’obesità come la resistenza insulinica e il diabete tipo 2
- Modificazioni particolari in grado di spiegare cancri quali esofago, fegato, mammella, endometrio


Oestrogen–progesterone hypothesis
Progesterone↓
Endometrium
Insulin↑
IGFBP1↓
Bioactive IGF1↑
Obesity
SHBG↓
IGF1↓
Aromatase
T
E2
17β-HSD
17β-HSD
Δ4A
Aromatase
E1
Bioavailable T, E2↑ (targeting breast and endometrium)
Adipocyte (mainly peripheral)
Insulin–IGF hypothesis
Obesity (particularly central fat)
Target cell
Insulin:
• Mitogenic
• Anti-apoptotic
• Growth factor 'primer'
• Stimulates β-catenin
• Initiates IGFBP3 proteolysis
IGF1:
• Mitogenic
• Anti-apoptotic
• Pro-angiogenic
• Regulates cell size
• Increases cell migration
• Potentiates other growth factors
Insulin↑
IR
Tumour development
• IGFBP1↓
• IGFBP2↓
IGF1R
Bioactive IGF1↑
Inflammatory mediators and adipokine hypothesis
Leptin↑
LR
(4 variants)
Target tissue
• Mitogenic
• Anti-apoptotic
• Pro-angiogenic
+
Obesity
Pro-inflammatory
Local inflammation:
• TNF • IL-1β
• NF-κB • IL-6
–
Adiponectin↓
Target tissue
• Insulin sensitizer
• Anti-proliferative
• Pro-apoptotic
• Anti-angiogenic

Insulin, IGF-I and IGF-II signaling



Effects of obesity on hormone production.



Adipose tissue produces the enzymes aromotase and 17β-hydroxysteroid dehydrogenase (17β-HSD).

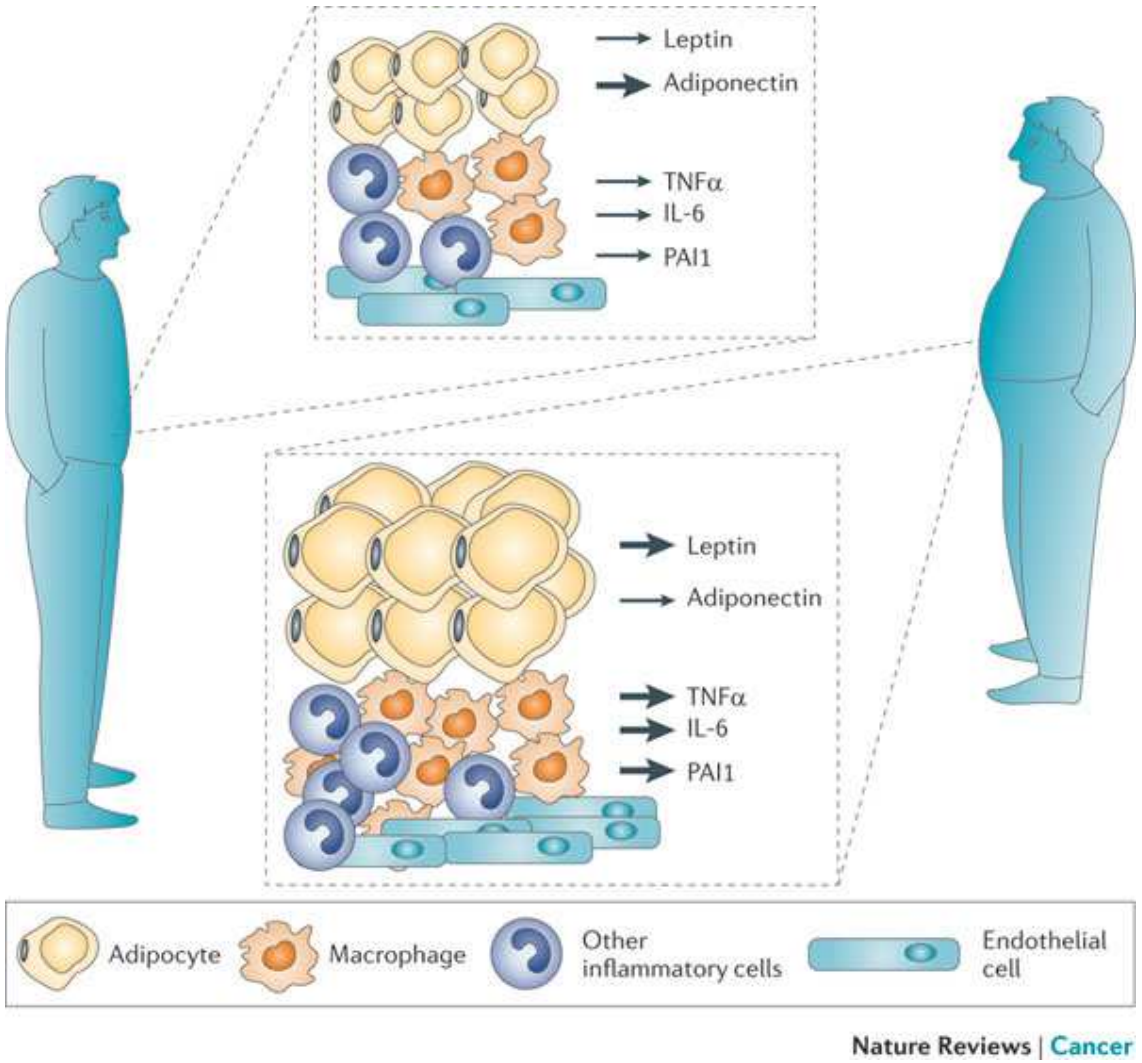
In obese individuals, there is typically an increased conversion of the androgens Δ4-androstenedione (Δ4A) and testosterone (T) into the oestrogens oestrone (E1) and oestradiol (E2).

In parallel, obesity leads to hyperinsulinaemia, which causes a reduction in the hepatic synthesis and circulating levels of sex-hormone-binding globulin (SHBG).

The combined effect of increased formation of oestrone and testosterone, along with reduced levels of SHBG, leads to an increase in the bioavailable fractions of E2 and T that can diffuse to target cells.

The effects of sex steroids binding their receptors can vary, depending on the tissue types.

Changes in adipose tissue in obesity



Vol 11; 886-895 December 2011

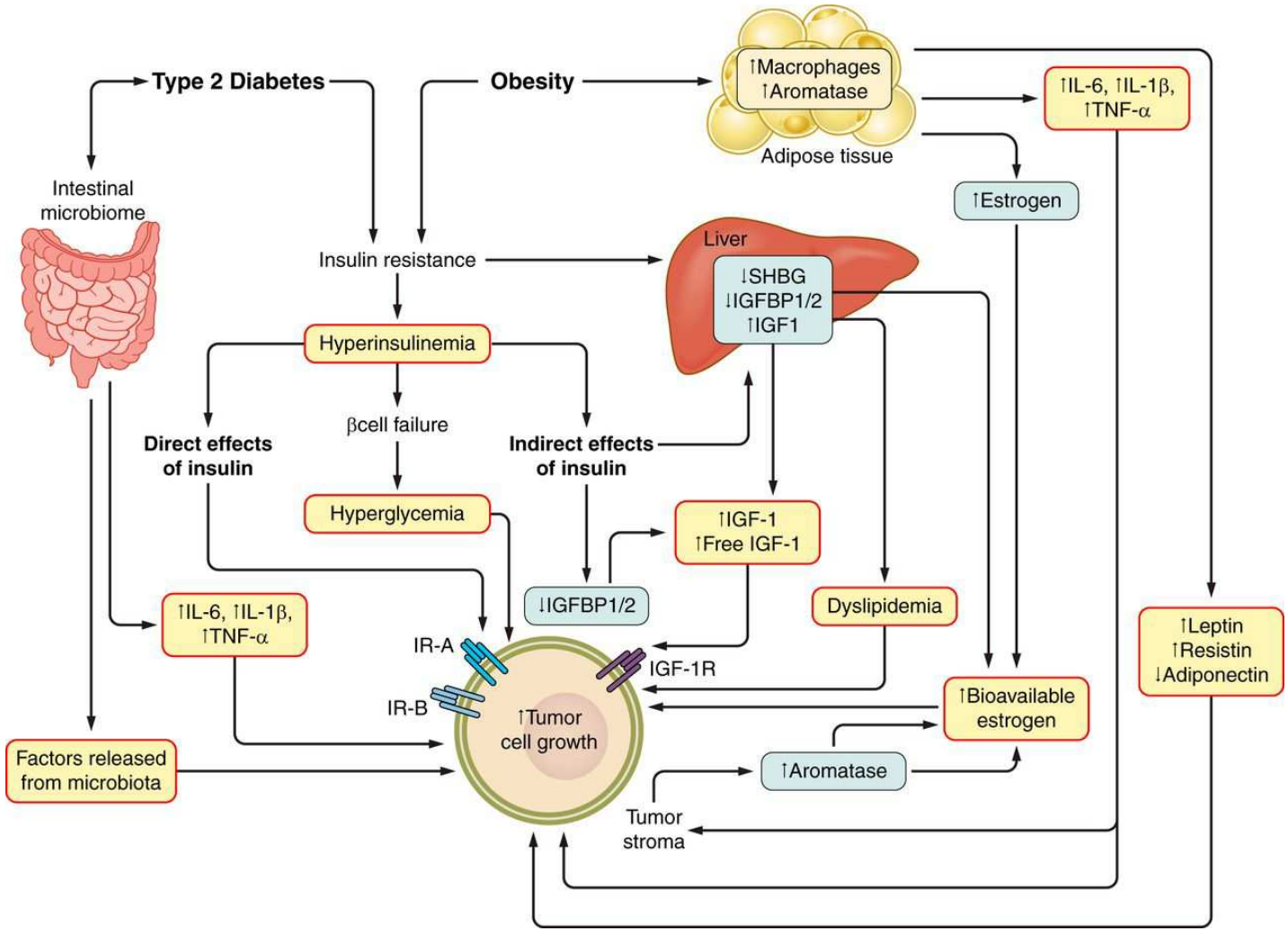
Effetto dell'aumento del tessuto adiposo di "per se"

- Infiammazione, adipokine TNFα, IL-6, PAI1, ipossia
- Leptina ↑
- Adiponectina ↓
- Proliferazione dei progenitori degli adipociti

Effetto delle conseguenze secondarie all'obesità

- Insulino resistenza, Iperinsulinemia, C-peptide
- IGF-1 ; IGFBP-1 e IGFBP-2
- Elevati livelli di lipidi e ac grassi
- Entità cliniche correlate: sindrome metabolica e diabete mellito tipo 2 (con effetti indipendenti da obesità)

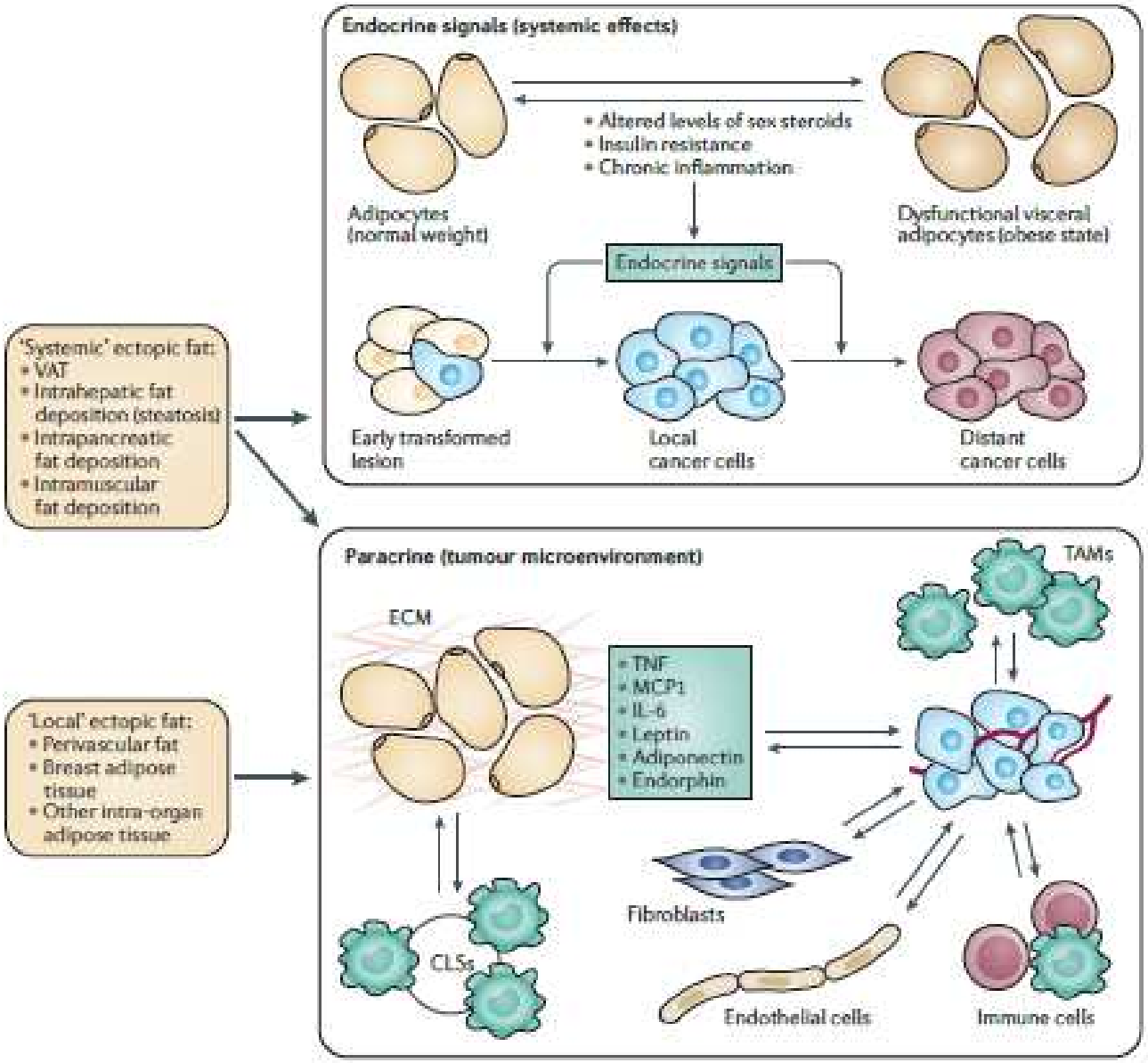
Mechanisms linking obesity, type 2 diabetes, and cancer.



Emily Jane Gallagher, and Derek LeRoith Physiol Rev 2015;95:727-748

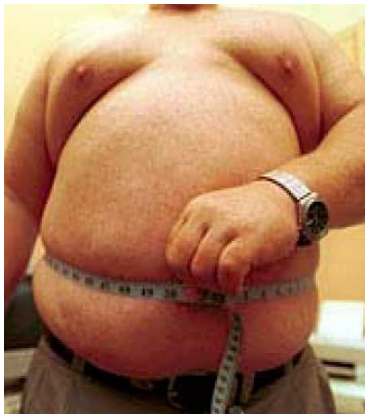
Physiological Reviews

Il ruolo del grasso ectopico



Adenocarcinoma esofageo

- Nel 41% dei casi è associato a sovrappeso e obesità
- Un aumento del BMI e soprattutto un aumento della circonferenza vita si associa a:
  - Aumento del grasso viscerale



  - Aumento della pressione intraddominale
  - Aumento della frequenza di reflusso gastroesofageo e di ernia iatale

Vaughan 2002

Se l'obesità costituisce un importante fattore di rischio per lo sviluppo del cancro

La perdita di peso comporta una riduzione nell'insorgenza del cancro?

Relative Risk of Postmenopausal Breast Cancer According to Weight Change Since Menopause.

Table 3. Relative Risk of Postmenopausal Breast Cancer According to Weight Change Since Menopause

Weight Change Since Menopause, kg	Simple Update* No. of Cases	Simple Update* Age-Adjusted RR	Simple Update* MV-Adjusted RR (95% CI)‡	Stable Change† No. of Cases§	Stable Change† MV-Adjusted RR (95% CI)‡
Overall					
Loss					
≥10.0	41	0.73	0.77 (0.56-1.08)	29	0.70 (0.47-1.04)
5.0-9.9	113	1.06	1.12 (0.91-1.37)	66	1.00 (0.76-1.30)
2.0-4.9	184	0.89	0.91 (0.77-1.08)	77	0.77 (0.60-0.99)
Loss or gain <2.0	642	1.00	1.00	348	1.00
Gain					
2.0-4.9	552	1.00	1.01 (0.90-1.14)	303	0.94 (0.80-1.10)
5.0-9.9	486	1.03	1.08 (0.96-1.22)	397	1.02 (0.88-1.18)
≥10.0	358	1.04	1.18 (1.03-1.35)	334	1.12 (0.96-1.32)
P for trend‖		.07	.002		.001
P for weight loss trend¶		.09	.38		.12
Ever used PMH#					
Loss					
≥10.0	18	0.66	0.81 (0.50-1.33)	15	0.81 (0.47-1.41)
5.0-9.9	64	1.13	1.25 (0.95-1.64)	36	1.02 (0.71-1.47)
2.0-4.9	106	0.93	0.98 (0.79-1.22)	43	0.78 (0.56-1.09)
Loss or gain <2.0	379	1.00	1.00	227	1.00
2.0-4.9	327	0.99	1.02 (0.87-1.18)	190	0.92 (0.75-1.12)
5.0-9.9	279	0.94	1.03 (0.88-1.21)	232	0.92 (0.76-1.11)
≥10.0	206	0.95	1.15 (0.96-1.38)	196	1.05 (0.86-1.29)
P for trend‖		.93	.22		.18
P for weight loss trend¶		.31	.85		.42
Never used PMH#					
Loss					
≥10.0	18	0.80	0.63 (0.38-1.05)	9	0.43 (0.21-0.86)
5.0-9.9	40	0.97	0.89 (0.63-1.26)	24	0.85 (0.54-1.33)
2.0-4.9	73	0.95	0.90 (0.69-1.18)	32	0.85 (0.57-1.27)
Loss or gain <2.0	238	1.00	1.00	111	1.00
Gain					
2.0-4.9	205	1.05	1.04 (0.86-1.26)	94	0.87 (0.66-1.16)
5.0-9.9	180	1.19	1.17 (0.95-1.43)	141	1.12 (0.87-1.45)
≥10.0	122	1.18	1.19 (0.94-1.50)	111	1.13 (0.86-1.50)
P for trend‖		.02	.002		.002
P for weight loss trend¶		.28	.04		.01

Abbreviations: CI, confidence interval; MV, multivariate; PMH, postmenopausal hormone; RR, relative risk.
*Simple update uses weight change as of current questionnaire cycle.
†Weight change defined as gain, no change, or loss for at least 2 consecutive questionnaire cycles.
‡Multivariate adjustments include all factors listed in the footnotes in Table 2 plus weight at menopause (continuous).
§Excludes women who switched between gain, no change, or loss categories since previous questionnaire cycle.
‖Calculated using medians of categories.
¶Calculated using medians of loss and loss or gain <2.0 kg categories.
#*P* = .13 for interaction PMH × weight change.

Prospective cohort study within the Nurses' Health Study. A total of 87,143 postmenopausal women were followed up for up to 26 years to assess weight change since age 18 years.
Weight change since menopause was assessed among 49,514 women who were followed up for up to 24 years. Overall, 4393 cases of invasive breast cancer were documented.

- Women who gained 25.0 kg or more since age 18 years were at an increased risk of breast cancer (relative risk [RR], 1.45; 95% confidence interval [CI], 1.27-1.66; P<.001 for trend), with a stronger association among women who have never taken postmenopausal hormones (RR,1.98; 95% CI, 1.55-2.53).
- Compared with weight maintenance, women who gained 10.0 kg or more since menopause were at an increased risk of breast cancer (RR, 1.18; 95% CI, 1.03-1.35; P = .002 for trend).
- Women who lost 10.0 kg or more since menopause, and kept the weight off were at a lower risk than those who maintained weight (RR, 0.43; 95% CI, 0.21-0.86; P = .01 for weight loss trend).

CONCLUSIONS:

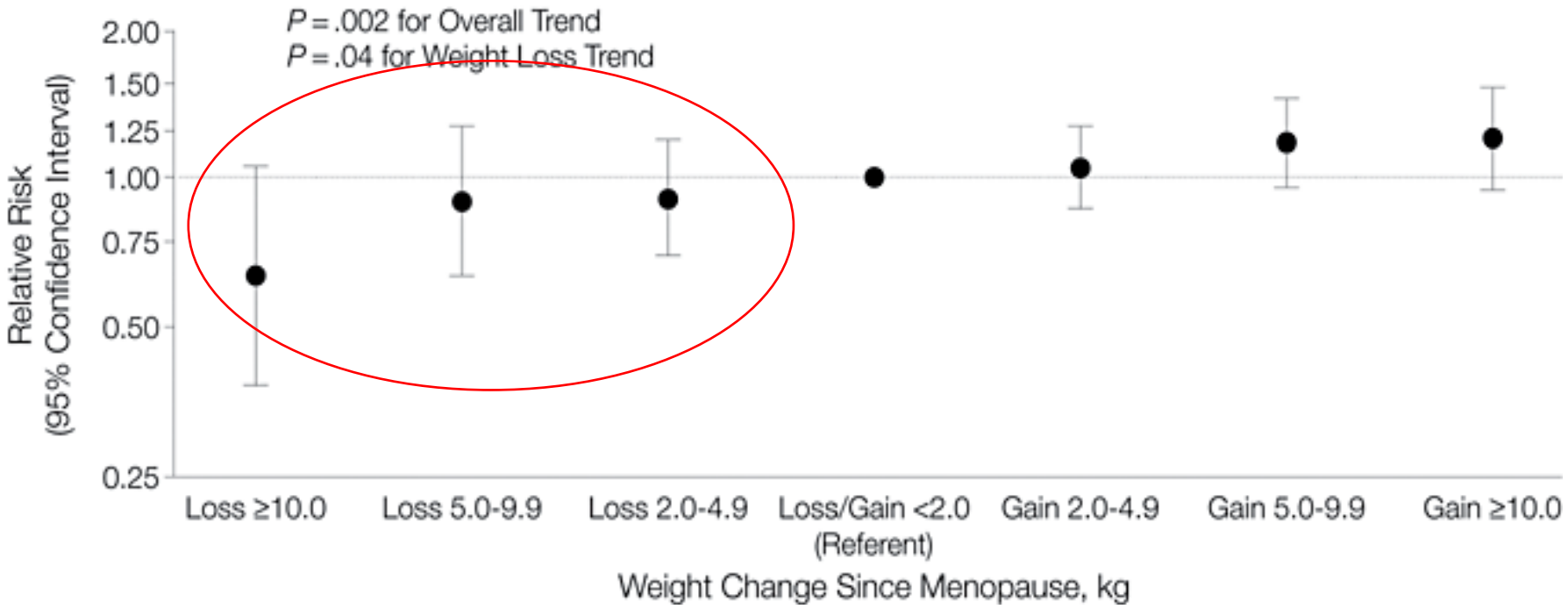
These data suggest that weight gain during adult life, specifically since menopause, increases the risk of breast cancer among postmenopausal women, whereas weight loss after menopause is associated with a decreased risk of breast cancer.

JAMA

Eliassen, A. H. et al. JAMA 2006;296:193-201

Relative Risk of Postmenopausal Breast Cancer Among Women Who Have Never Used Postmenopausal Hormones According to Weight Change Since Menopause.

Eliassen, A. H. et al. JAMA 2006;296:193-201



JAMA

Cancer incidence[a] and hazard ratios in the study groups (1984–2002) for common cancer sites, cancers by sex, obesity-related cancers, and nonobesity-related cancers

	Surgery $N = 6,596$		Control $N = 9,442$			
Cancer site[b]	Number of cases	Rates/1,000 person years	Number of cases	Rates/1,000 person years	Hazard ratio[c] (95% CI)	*P* value
All cancers	254	3.13	477	4.28	0.76 (0.65–0.89)	0.0006
All cancers, male	39	3.73	65	3.83	1.02 (0.69–1.52)	0.91
All cancers, female	215	3.04	412	4.36	0.73 (0.62–0.87)	0.0004
Obesity-related cancers[d]	104	1.28	253	2.27	0.62 (0.49–0.78)	<0.0001
Nonobesity-related cancers[e]	150	1.85	224	2.01	0.91 (0.73–1.12)	0.37

Obesity (Silver Spring). 2010 April 24

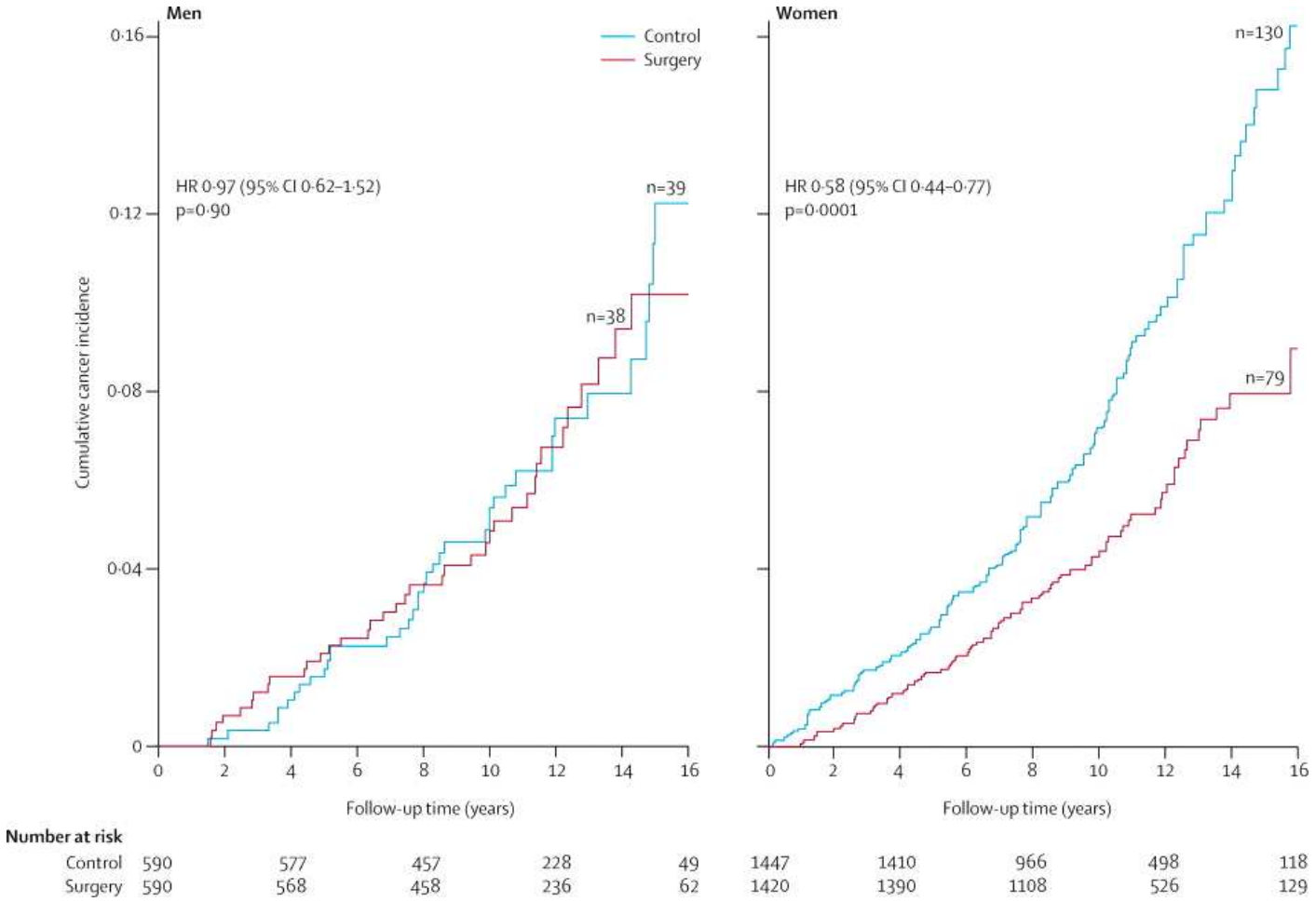
Vantaggi gender specifici dopo bariatrica

Il calo ponderale dopo chirurgia bariatrica riduce la morbilità e la mortalità correlata al cancro significativamente nelle donne

Tale effetto legato al calo ponderale, alla restrizione energetica ad altro?

The unadjusted cumulative fatal plus non-fatal cancer incidence from the start of the intervention by sex in surgically treated obese individuals and in obese control individuals

Lars Sjöström M et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (SOS Study): a prospective, controlled intervention trial. Lancet Oncology 10:653-662,2009



Does intentional weight loss reduce cancer risk?

Type of study/Author (ref)	Cancer site	Population studied	Body weight loss	Cancer risk reduction (%)
Cohort studies				
Parker [4]	All sites	Post-menopausal Iowa women	≥16.4%*	11
Eliassen [5]	Breast	US nurses	≥14.5%†, ‡	57
Harvie [6]	Breast	Post-menopausal Iowa women	≥5%	64§
Bariatric surgery studies				
Sjöström [7]	All sites	Women	31.9%	42
		Men	19.3%	3
Adams [8]	All sites	Women	31.1%	24
		Men		2
Christou [9]	All sites	Men and women	31.9%¶	78
Dietary RCTs				
Pierce [10]	Breast‖	Women	0.5% group difference	4
Prentice [11]	Breast	Women	1.0% group difference	9
Chlebowski [12]	Breast‖	Women	3.7% group difference	24

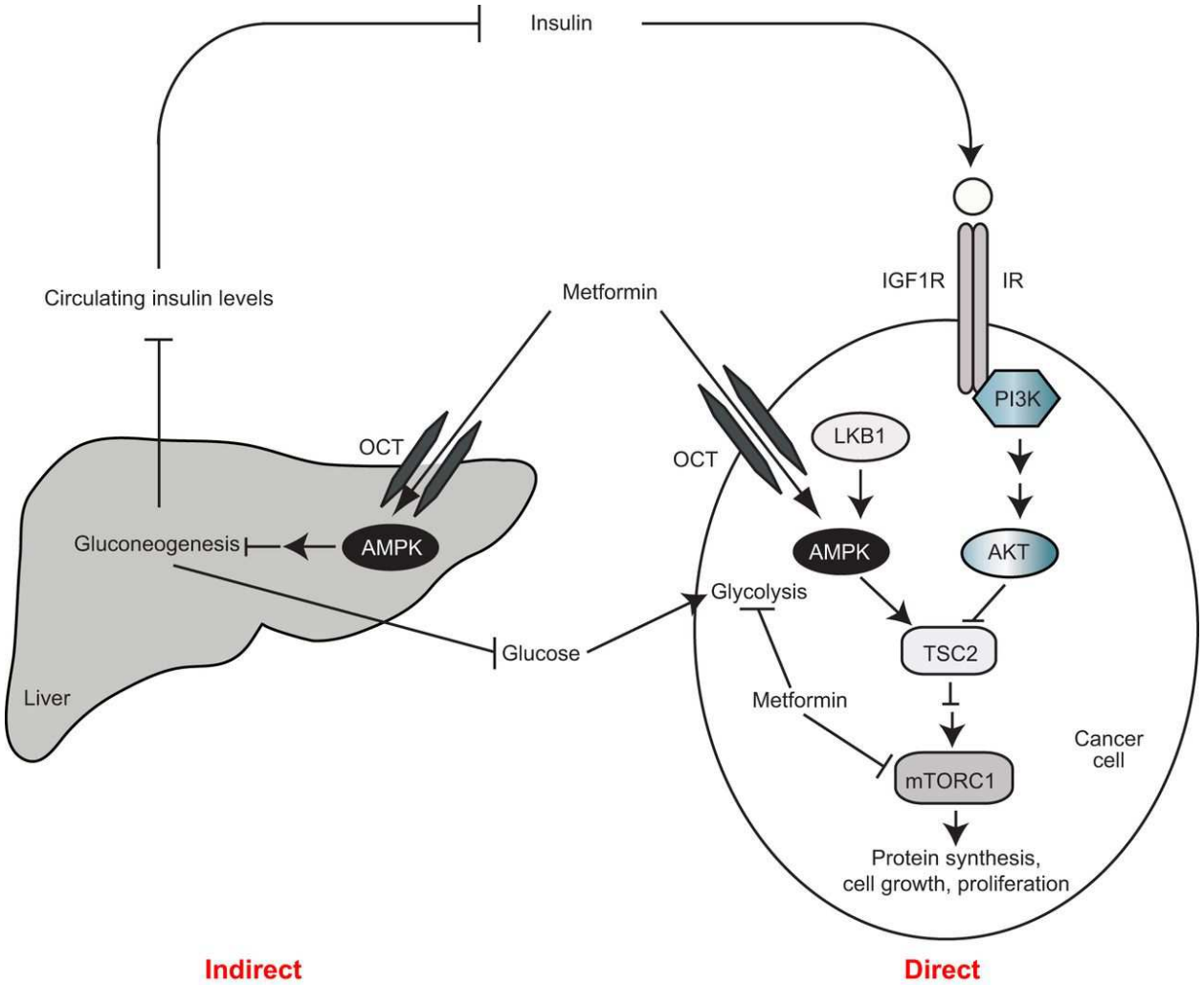
The relationship between intentional weight loss and cancer incidence, coming from observational cohort studies, trials of bariatric surgery, and
from dietary randomized controlled trials (RCTs) that examined weight loss as a secondary outcome.

Diabetes, Obesity and Metabolism 13: 1063–1072, 2011.

Metformina

- Pazienti DMT2 in trattamento con Metformina presentavano mortalità per cancro ridotta in confronto ai pazienti trattati con sulfaniluree ed insulina
- Azione sistemica, riduzione della resistenza insulinica, dei livelli di insulina e della glicemia
- Azione locale sulle cellule tumorali????
- Trials clinici in corso

The potential direct and indirect effects by which metformin may decrease cancer growth. [Adapted from Dowling et al.



Physiological Reviews

Emily Jane Gallagher, and Derek LeRoith Physiol Rev 2015;95:727-748

Recommendations for individual Choices

- Maintain a healthy weight throughout life
- Balance caloric intake with physical activity
- Avoid excessive weight gain throughout life
- Achieve and maintain a healthy weight

Obesity: single house for many evils

Grazie !

DIABETE TIPO 2, INSULINA ESOGENA, RISCHIO DI CANCRO

- DMT2 è associato, indipendentemente dall'obesità, al cancro della mammella, colon-retto, pancreas, rene, endometrio e vescica (un cancro non associato ad obesità), ma è inversamente correlato al Ca. prostatico
- Legami patogenetici con insulino resistenza, iperinsulinemia, IGF-1, infiammazione cronica, iperglicemia
- Evidenze che i pazienti diabetici che utilizzano insulina o analoghi, possono avere un aumento di rischio in confronto ai non trattati
- L'utilizzo della metformina può avere un ruolo protettivo

The supersized tumour microenvironment

The risk of certain types of breast cancer increases with obesity, and the density of the extracellular matrix (ECM) is also known to be a risk factor for breast cancer. Seo *et al.* found that obesity and ECM density are connected: they showed that the mammary fat pads of obese mice are enriched with myofibroblasts and ECM components that are associated with increased stiffness. In particular, adipose stromal cell characteristics were altered in obese mice such that they produced more myofibroblasts and generated dense and stiff ECMs. Caloric restriction reduced myofibroblast content in mice, indicating that obesity-associated fibrosis and the associated changes in tissue mechanics can be reversed.

ORIGINAL RESEARCH PAPER Seo, B. R. *et al.* Obesity-dependent changes in interstitial ECM mechanics promote breast tumorigenesis. *Sci. Transl Med.* **7**, 301ra130 (2015)

Obesità e Cancro

Menù

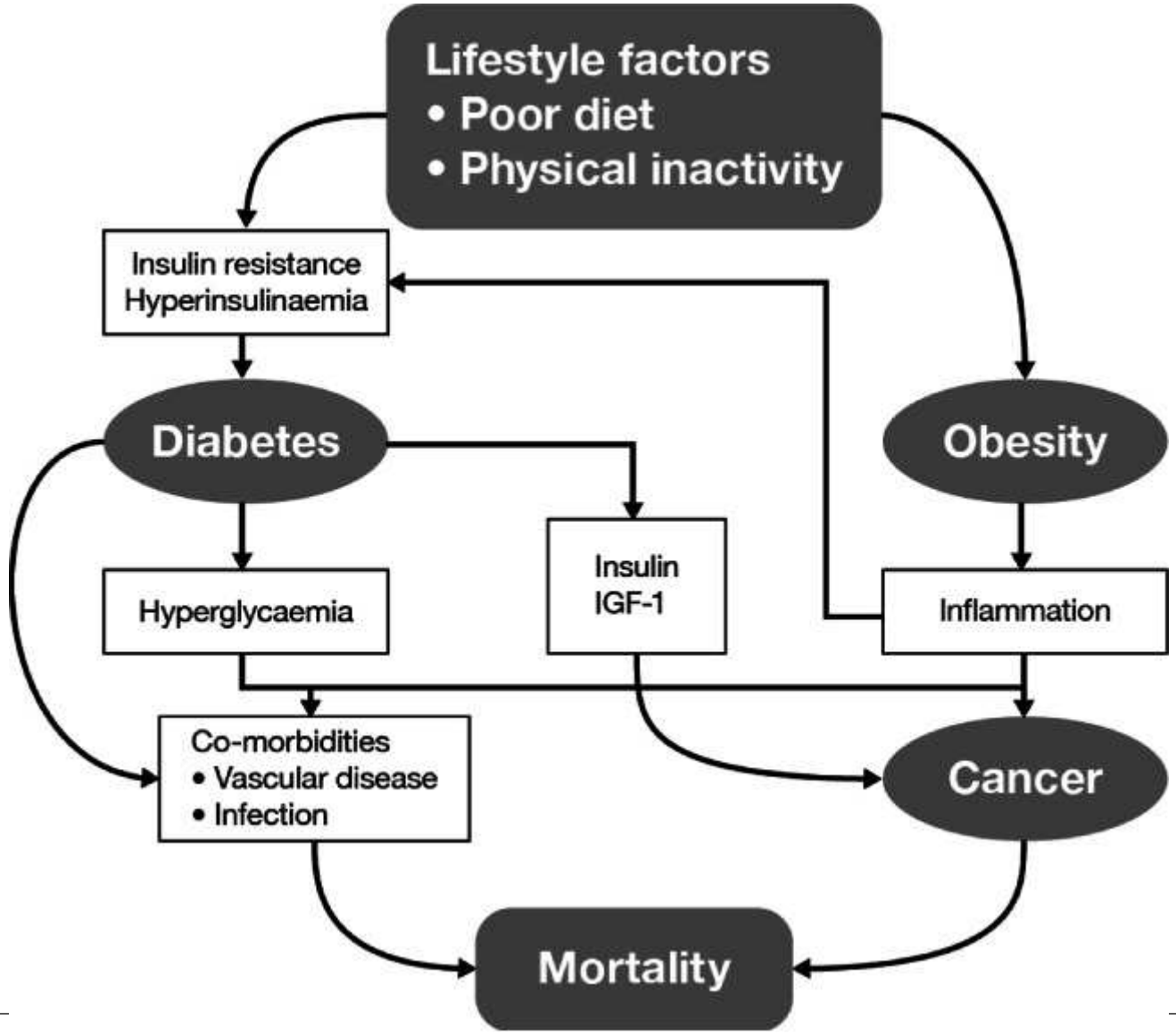
- Epidemiologia : associazione tra obesità e insorgenza di cancro
- Ipotesi patogenetiche che legano obesità e cancro
- Obesità e tumore alla mammella
- Possibilità di riduzione dell'insorgenza di cancro dopo calo ponderale
- Influenza dell' obesità sulla mortalità

American Society of Clinical Oncology position statement on obesity and cancer.

Ligibel JA[1], Alfano CM[2], Courneya KS[2], Demark-Wahnefried W[2], Burger RA[2], Chlebowski RT[2], Fabian CJ[2], Gucalp A[2], Hershman DL[2], Hudson MM[2], Jones LW[2], Kakarala M[2], Ness KK[2], Merrill JK[2], Wollins DS[2], Hudis CA[2]. J Clin Oncol. 2014 Nov 1;32(31):3568-74

Rates of obesity have increased significantly over the last three decades in the United States and globally. In addition to contributing to heart disease and diabetes, obesity is a major unrecognized risk factor for cancer. Obesity is associated with worsened prognosis after cancer diagnosis and also negatively affects the delivery of systemic therapy, contributes to morbidity of cancer treatment, and may raise the risk of second malignancies and comorbidities. Research shows that the time after a cancer diagnosis can serve as a teachable moment to motivate individuals to adopt risk-reducing behaviors. For this reason, the oncology care team--the providers with whom a patient has the closest relationships in the critical period after a cancer diagnosis--is in a unique position to help patients lose weight and make other healthy lifestyle changes. The American Society of Clinical Oncology is committed to reducing the impact of obesity on cancer and has established a multipronged initiative to accomplish this goal by 1) increasing education and awareness of the evidence linking obesity and cancer; 2) providing tools and resources to help oncology providers address obesity with their patients; 3) building and fostering a robust research agenda to better understand the pathophysiology of energy balance alterations, evaluate the impact of behavior change on cancer outcomes, and determine the best methods to help cancer survivors make effective and useful changes in lifestyle behaviors; and 4) advocating for policy and systems change to address societal factors contributing to obesity and improve access to weight management services for patients with cancer.

Interrelationship between pathological mechanisms and modifiable and non-modifiable risk factors involved in diabetes, obesity and cancer
Diabetes Obes Metab. 2014 Feb; 16(2): 97–110.



Risk ratio for cancer per 5 kg/m2 higher body mass index

Cancer type	Men (RR [95% CI])	Women (RR [95% CI])	Suggested causal mechanism
Oesophageal adenocarcinoma	1.52 (1.33–1.74)*	1.51 (1.31–1.74)*	Reflux oesophagitis and chronic irritation
Thyroid	1.33 (1.04–1.70)†	1.14 (1.06–1.23)‡	Unknown
Colon	1.24 (1.20–1.28)*	1.09 (1.05–1.13)*	Insulin
Renal	1.24 (1.15–1.34)*	1.34 (1.25–1.43)*	Hypertension is one factor
Liver	1.24 (0.95–1.62)	1.07 (0.55–2.08)	Fatty liver cirrhosis
Malignant melanoma	1.17 (1.05–1.30)‡	0.69 (0.92–1.01)	Unknown
Multiple myeloma	1.11 (1.05–1.18)*	1.11 (1.07–1.15)*	Inflammatory pathways—IL-6
Rectum	1.09 (1.06–1.12)*	1.02 (1.00–1.05)	Unknown
Gallbladder	1.09 (0.99–1.21)	1.59 (1.02–2.47)†	Chronic secretion—gallstones and irritation
Leukemia	1.08 (1.02–1.14)‡	1.17 (1.04–1.32)†	Unknown
Pancreas	1.07 (0.93–1.23)	1.12 (1.02–1.22)‡	Possibly insulin pathways
Non-Hodgkin's lymphoma	1.06 (1.03–1.09)*	1.07 (1.00–1.14)	Inflammatory pathways—IL-6
Prostate	1.03 (1.00–1.07)	—	Unknown
Lung	0.76 (0.70–0.83)*	0.80 (0.66–0.97) ‡	People who smoke are more likely to be lean leading to bias and this cancer is caused by smoking
Oesophageal squamous	0.71 (0.60–0.85)*	0.57 (0.47–0.69)*	People who smoke are more likely to be lean leading to bias and this cancer is caused by smoking
Endometrium	—	1.59 (1.50–1.68)*	Endogenous oestrogen
Breast (postmenopausal)	—	1.12 (1.08–1.16)‡	Endogenous oestrogen
Breast (premenopausal)	—	0.92 (0.88–0.97)†	Irregular menstrual cycles, hormones

RR, risk ratio; CI, confidence interval.

*$p < 0.0001$;

†$p < 0.01$;

‡$p < 0.05$.

*Biased to null because this includes predominantly low-grade lesions

Diabetes as a risk factor for cancer (summary of meta-analyses)

		Case–control studies		Prospective cohort studies	
Authors	**Tumour type**	**n**	**RR (95% CI)**	**n**	**RR (95% CI)**
Larsson et al. 23	Bladder	7	1.4 (1.0–1.8)	3	1.4 (1.2–1.7)
Larsson et al. 24	Breast	5	1.2 (1.1–1.3)	15	1.2 (1.1–1.3)
Wolf et al. 25	Breast	4	1.1 (1.0–1.3)	6	1.3 (1.2–1.3)
Larsson et al. 26	Colorectal	6	1.4 (1.2–1.5)	9	1.3 (1.2–1.4)
Friberg et al. 28	Endometrium	13	2.2 (1.8–2.7)	3	1.6 (1.2–2.2)
El-Serag et al. 29	HCC	13	2.5 (1.9–3.2)	12	2.5 (1.9–3.2)
Chao et al. 31	NHL	10	1.2 (1.0–1.4)	3	1.8 (1.3–2.5)
Mirri et al. 30	NHL	11	1.1 (0.9–1.3)	5	1.4 (1.1–1.9)
Everhart et al. 32	Pancreatic	11	1.8 (1.1–2.7)	9	2.6 (1.6–4.1)
Huxley et al. 33	Pancreatic	17	1.9 (1.5–2.5)	19	1.7 (1.6–1.9)
Bonovas et al. 34	Prostate	5	0.9 (0.7–1.2)	9	0.9 (0.9–1.0)
Kasper et al. 35	Prostate	7	0.9 (0.7–1.1)	12	0.8 (0.7–0.9)
Bansal et al. 38	Prostate	16	0.85 (0.74–0.96)	29	0.87 (0.80–0.94)

CI, confidence interval; HCC, hepatocellular carcinoma; NHL, non-Hodgkin lymphoma; RR, pooled relative risk.

Diabetes and cancer mortality in men

Cause of Death	Diabetes Risk Relative to No Diabetes (Men)	
	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)*
Oral cavity of pharynx	1.39 (1.04–1.87)	1.44 (1.07–1.94)
Colon	1.21 (1.08–1.35)	1.15 (1.03–1.29)
Liver or intrahepatic bile duct	2.40 (2.02–2.86)	2.26 (1.89–2.70)
Pancreas	1.42 (1.25–1.61)	1.40 (1.23–1.59)
Bladder	1.23 (1.02–1.48)	1.22 (1.01–1.47)
Breast	4.37 (2.32–8.24)	4.20 (2.20–8.04)
Prostate	0.89 (0.80–0.98)	0.88 (0.79–0.97)

↵* Adjusted for age, education, BMI, smoking, alcohol intake, vegetable intake, red meat intake, physical activity, and aspirin use. [Data from the Cancer Prevention II Study .]

No significant difference in RR was found for cancer of the esophagus, rectum or anus, gallbladder or extrahepatic bile duct, larynx, lung, bronchus or trachea, connective tissue, other skin, melanoma, kidney or other urinary organs, brain or nervous system, lymphoma, multiple myeloma, and leukemia.

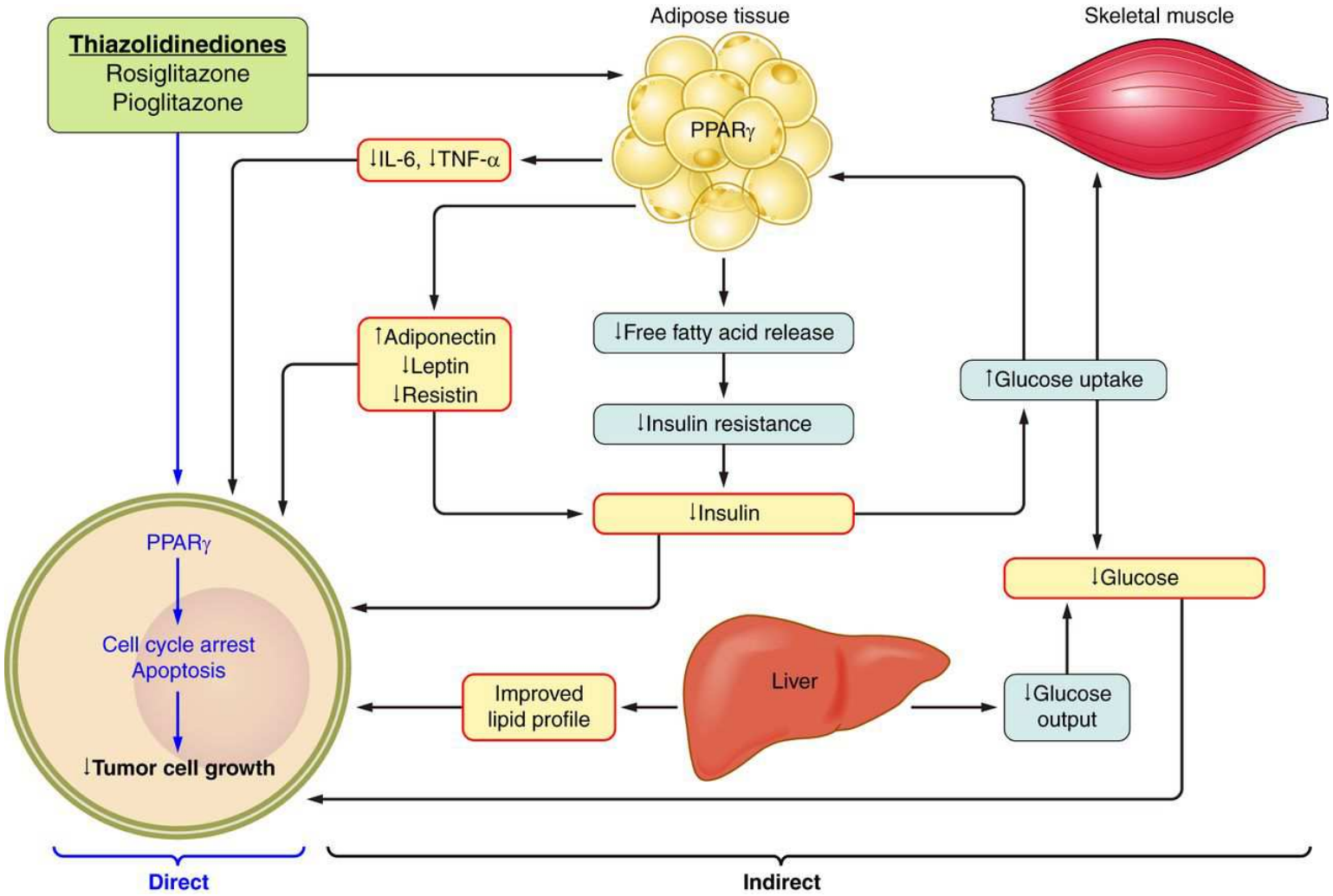
Diabetes and cancer mortality in women

Cause of Death	Diabetes Risk Relative to No Diabetes (Women)	
	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)*
Stomach	1.42 (1.08–1.85)	1.24 (0.95–1.63)
Colon	1.29 (1.15–1.45)	1.18 (1.04–1.33)
Liver or intrahepatic bile duct	1.65 (1.25–2.18)	1.40 (1.05–1.86)
Pancreas	1.37 (1.19–1.58)	1.31 (1.14–1.51)
Breast	1.24 (1.11–1.39)	1.16 (1.03–1.29)
Endometrial	1.72 (1.40–2.12)	1.33 (1.08–1.65)
Cervix	1.90 (1.19–3.03)	1.47 (0.91–2.37)
Kidney and other urinary organs	1.42 (1.09–1.87)	1.15 (0.88–1.52)

↵* Adjusted for age, education, BMI, smoking, alcohol intake, vegetable intake, red meat intake, physical activity, and aspirin use. [Data from the Cancer Prevention II Study (28).]

No significant difference in RR was found for cancer of the oral cavity or pharynx, esophagus, rectum or anus, gallbladder or extrahepatic bile duct, lung, bronchus or trachea, connective tissue, other skin, melanoma, brain or nervous system, lymphoma, multiple myeloma, and leukemia.

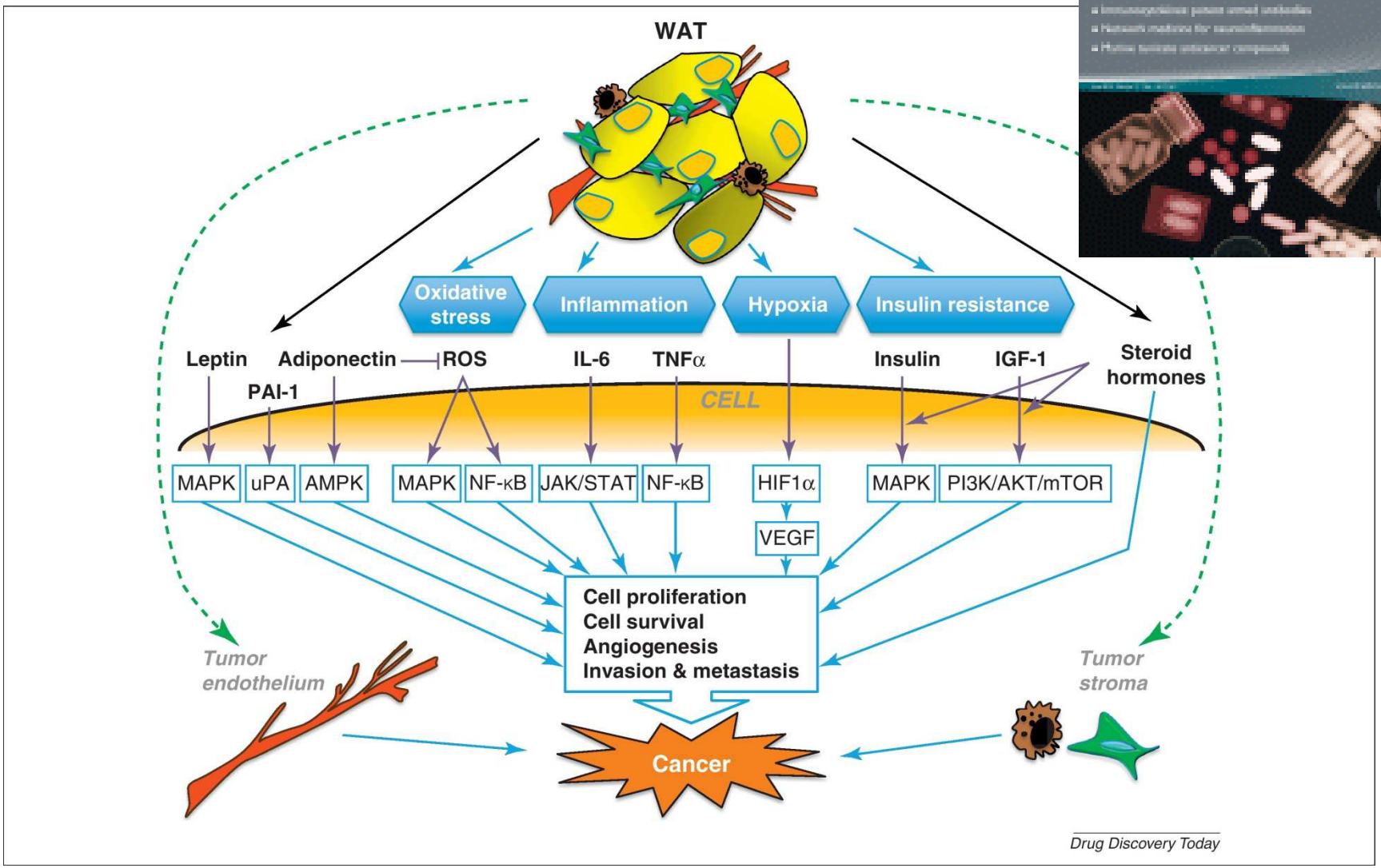
The potential mechanisms through which thiazolidinediones may improve metabolism and indirectly or directly reduce tumor growth and progression.



Emily Jane Gallagher, and Derek LeRoith Physiol Rev 2015;95:727-748

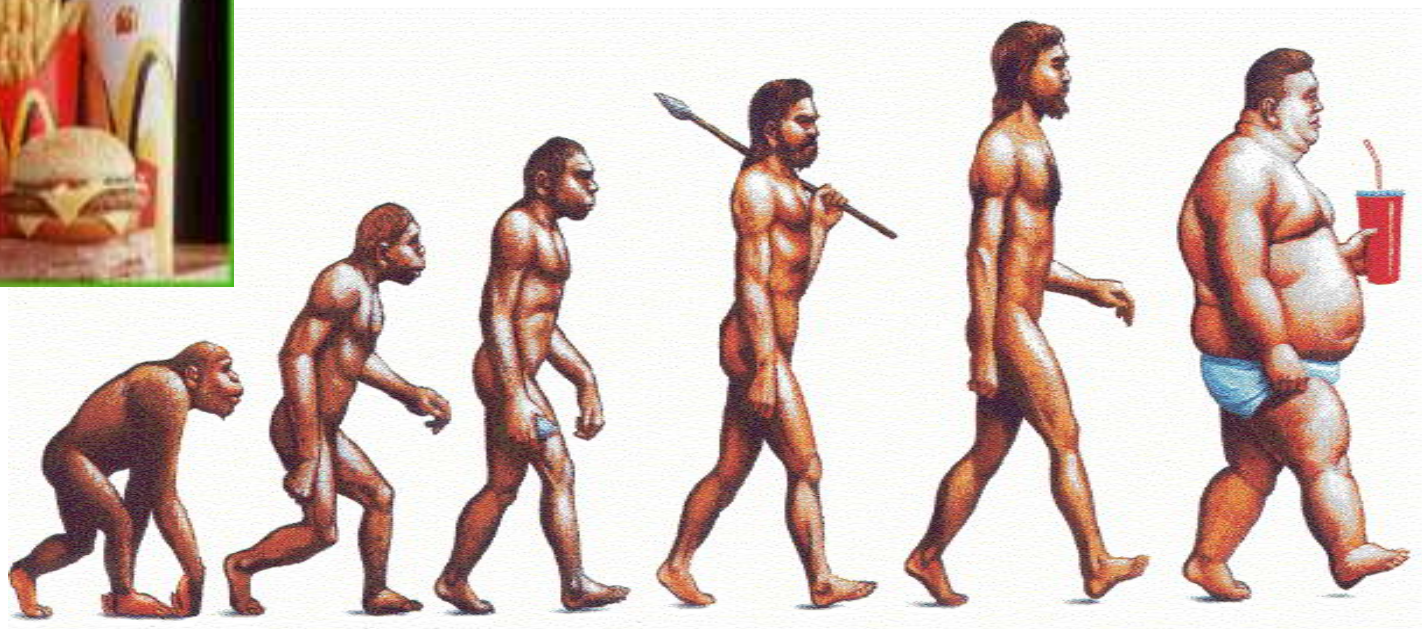
Physiological Reviews

Mechanisms through which WAT is proposed to pr
cancer.



Obesity, Physical Activity

WHO estimates 20% of cancers caused by obesity, lack of physical activity



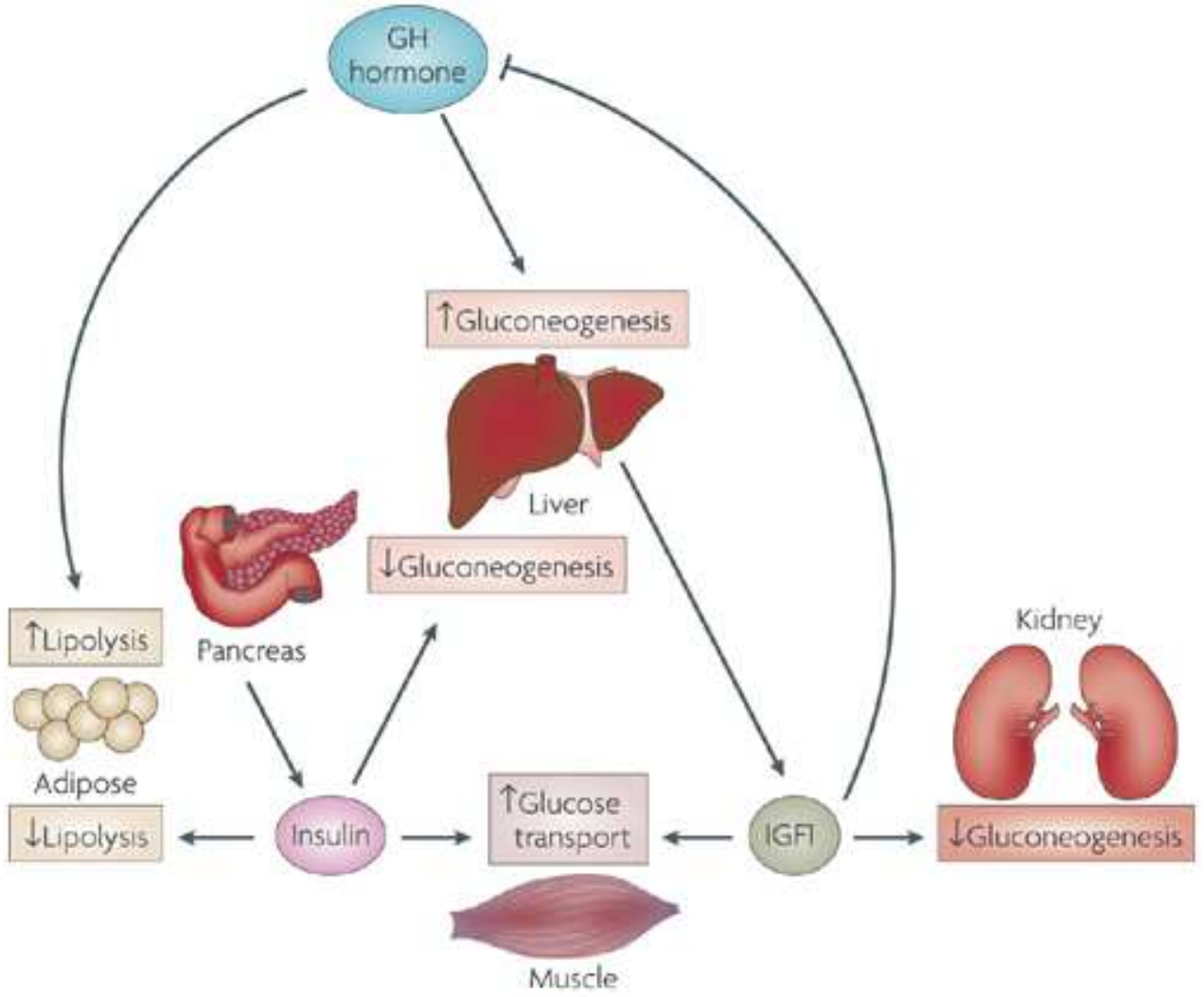
Summary

- The International Agency for Research on Cancer has determined that, based on results from epidemiological studies,people who are overweight or obese are at increased risk of developing several cancer types, including adenocarcinoma of the oesophagus, colon cancer, breast cancer (in postmenopausal women), endometrial cancer and kidney (renal-cell) cancer.
- Epidemiological evidence also indicates that cancers of the liver, gallbladder and pancreas are obesity related, and that obesity might also increase risk for haematopoietic cancers and for aggressive prostate cancer.No association is seen between obesity and lung cancer.Results for other cancers have been inconsistent.
- Insulin resistance develops as a metabolic adaptation to increased levels of circulating free fatty acids released from adipose tissue, especially intra-abdominal adipose. Insulin resistance is generally compensated by increased pancreatic insulin secretion. There is mounting epidemiological and experimental evidence to indicate that chronic hyperinsulinaemia increases risk of cancers of the colon and endometrium, and probably other tumours (for example, of the pancreas and kidney).

Summary 2

- Serum levels of insulin-like growth factor 1 (IGF1) are also associated with different forms of cancer.However, there is no simple,direct relationship between circulating levels of IGF1 and the degree of adiposity.
- Circulating levels of oestrogens are strongly related to adiposity. For cancers of the breast (in postmenopausal women) and endometrium, the effects of overweight and obesity on cancer risk are largely mediated by increased oestrogen levels.
- In 4–8% of premenopausal women, obesity and ensuing insulin resistance can either cause or aggravate syndromes of ovarian androgen excess (polycystic ovary syndrome) and chronic progesterone deficiency. There is strong evidence that such syndromes, along with reduced progesterone production, increase the risk of endometrial cancer.
- Successful intervention strategies for weight loss and maintenance at the individual and community level are needed to reduce cancer risk

Growth hormone and IGF1 actions on glucose homeostasis.



Nature Reviews | Drug Discovery

Table 1 | **Obesity-related cancers**

Type of cancer	Relative risk* with BMI of 25–30 kg/m^2	Relative risk* with BMI of ≥ 30 kg/m^2	PAF (%) for US population‡	PAF (%) for EU population§
Colorectal (men)	1.5	2.0	35.4	27.5
Colorectal (women)	1.2	1.5	20.8	14.2
Female breast (postmenonopausal)	1.3	1.5	22.6	16.7
Endometrial	2.0	3.5	56.8	45.2
Kidney (renal-cell)	1.5	2.5	42.5	31.1
Oesophageal (adenocarcinoma)	2.0	3.0	52.4	42.7
Pancreatic	1.3	1.7	26.9	19.3
Liver	ND	1.5–4.0	ND‖	ND‖
Gallbladder	1.5	2.0	35.5	27.1
Gastric cardia (adenocarcinoma)	1.5	2.0	35.5	27.1

Relative risks associated with overweight and obesity, and the percentage of cases attributable to overweight and obesity in the United States (US) and the European Union (EU). *Relative risk estimates are summarized from the literature cited in the main text. ‡Data on prevalence of overweight and obesity are from the National Health and Nutrition Examination Survey (1999–2000)[205] for men and women from the United States aged from 50–69 years. §Data on prevalence of overweight and obesity are from a range of sources[206] for adult men and women residing in 15 European countries in the 1980s and 1990s. ‖PAFs were not estimated because the magnitude of the relative risks across studies are not sufficiently consistent. BMI, body mass index; ND, not determined; PAF, population attributable fraction (BOX 3).

Effetto delle conseguenze secondarie all'obesità

- Iperinsulinemia, insulino resistenza
- IGF ; IGFBP-1 e IGFBP-2
- Elevati livelli di lipidi
- Entità cliniche correlate: sindrome metabolica e diabete mellito tipo 2 (con effetti indipendenti da obesità)

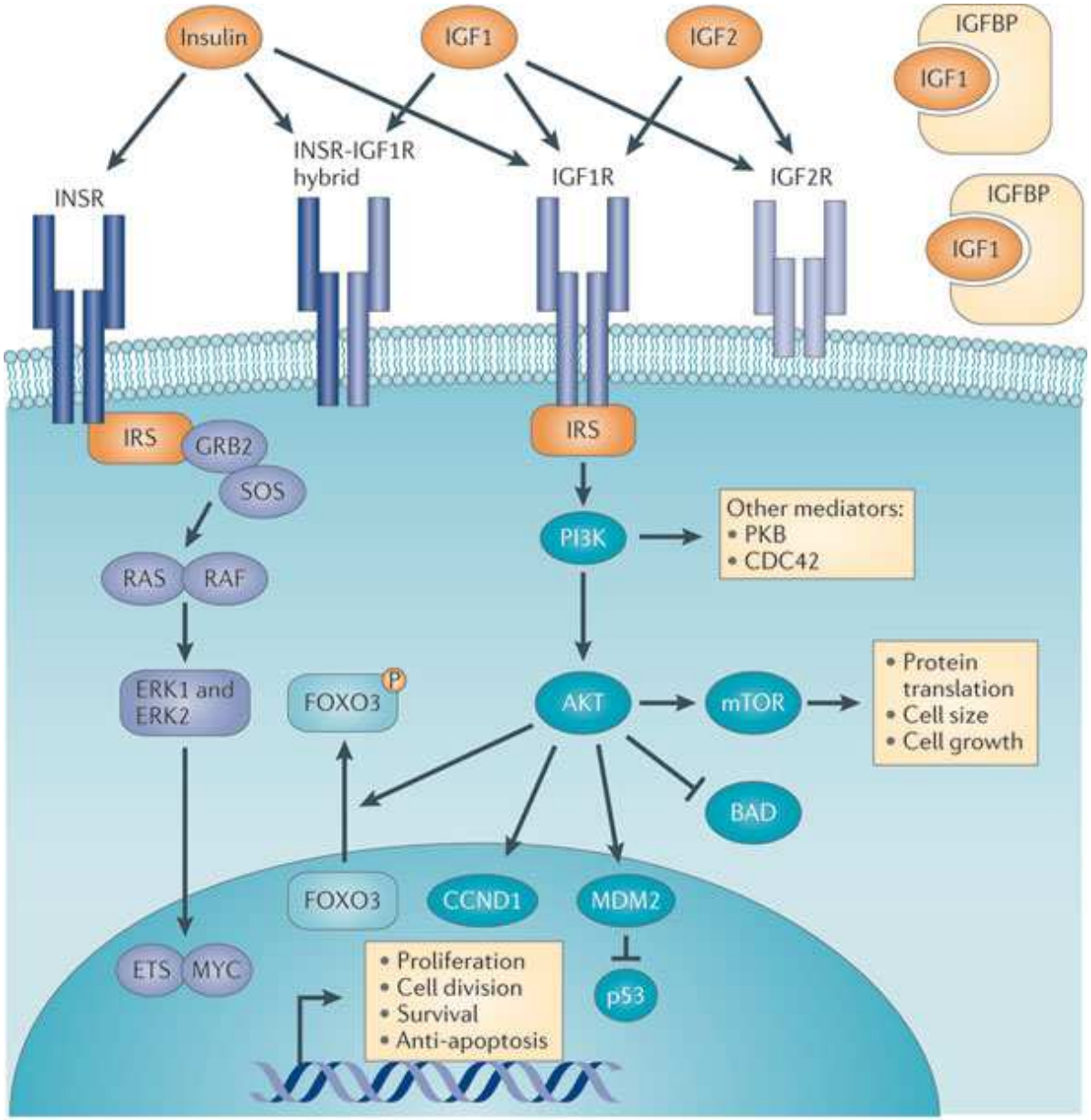
Cancer Deaths Preventable per year

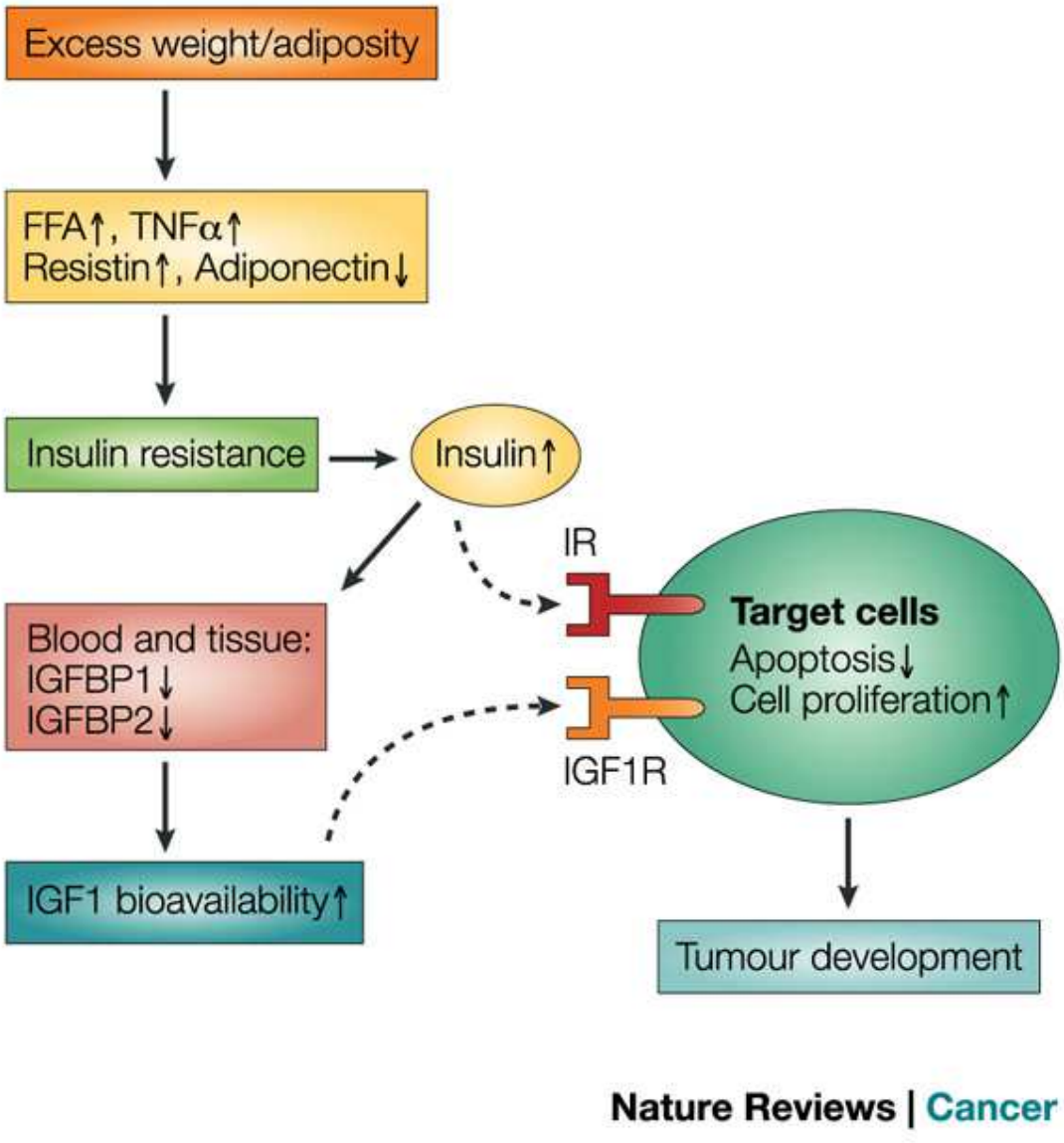
- 36,000 cancer cases could be avoided by halving the prevalence of overweight & obese people in Europe (Bergstrom et al, Int J Cancer, 2001)

- 90,000 cancer deaths could be avoided in USA if BMI kept below 25 kg/m2 (Calle et al, NEJM, 2003)

- 14% of all deaths from cancer in men and 20% of all deaths from cancer in women. (Calle et al, NEJM, 2003)

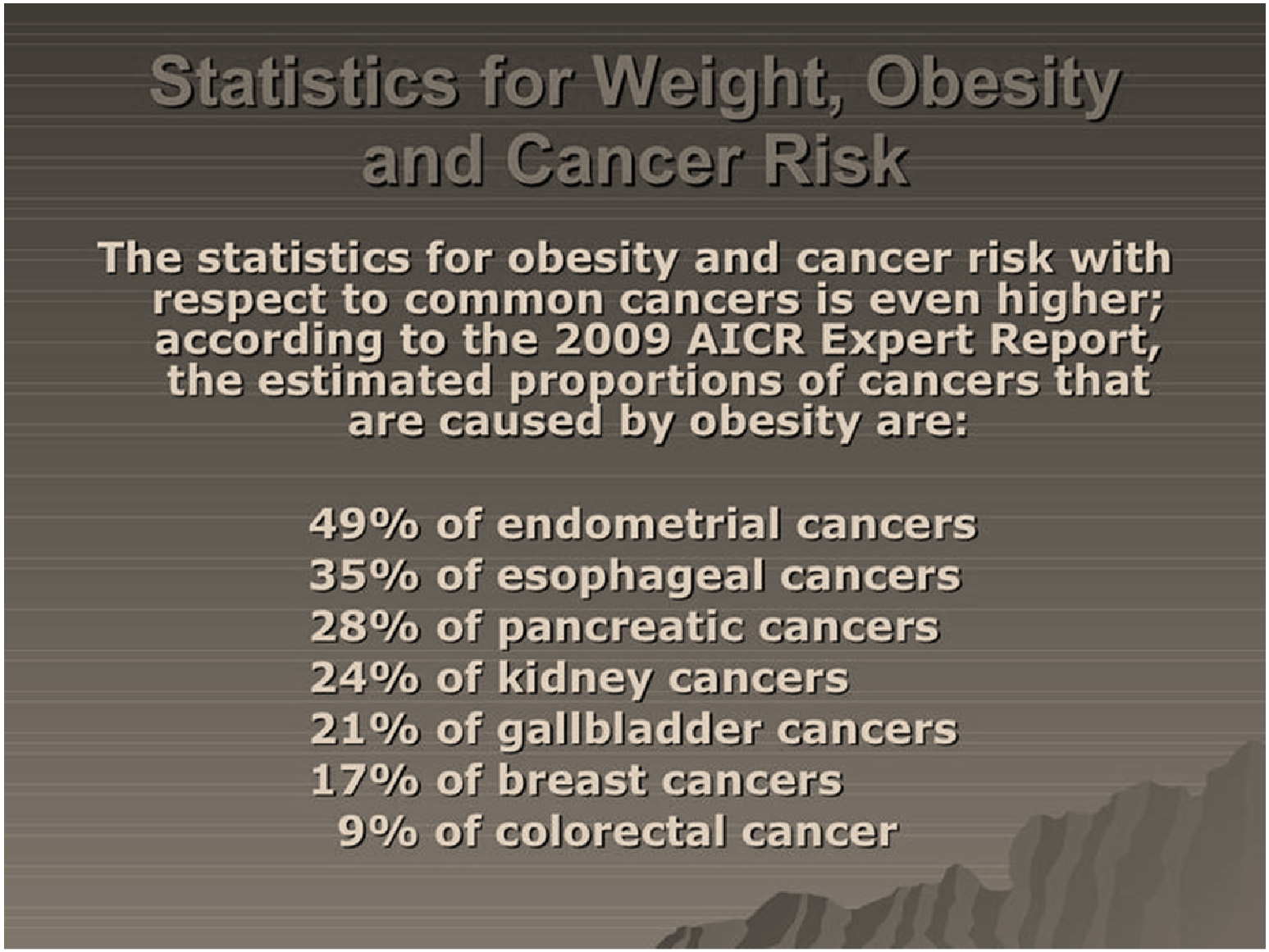
Insulin signalling in obesity.





Effects of obesity on growth-factor production

In obesity, increased release from adipose of FFA, TNF and resistin, and reduced release of adiponectin lead to the development of insulin resistance and compensatory, chronic hyperinsulinaemia.
Increased insulin levels, in turn, lead to reduced liver synthesis and blood levels of IGFBP1, and probably also reduce IGFBP1 synthesis locally in other tissues.
Increased fasting levels of insulin in the plasma are generally also associated with reduced levels of IGFBP2 in the blood.
This results in increased levels of bioavailable IGF1.
Insulin and IGF1 signal through the insulin receptors (IRs) and IGF1 Receptor (IGF1R), respectively, to promote cellular proliferation and inhibit apoptosis in many tissue types.
These effects might contribute to tumorigenesis.


Statistics for Weight, Obesity and Cancer Risk
The statistics for obesity and cancer risk with respect to common cancers is even higher; according to the 2009 AICR Expert Report, the estimated proportions of cancers that are caused by obesity are:
49% of endometrial cancers
35% of esophageal cancers
28% of pancreatic cancers
24% of kidney cancers
21% of gallbladder cancers
17% of breast cancers
9% of colorectal cancer

Gender-specific estimated risk ratios[a] by cancer types

	Men			Women		
	n[b]	Risk ratio (95% CIs)	I^2 (%)	*n*[b]	Risk ratio (95% CIs)	I^2 (%)
Colorectal cancer						
colon	22	1.24 (1.20, 1.28)	21%	19	1.09 (1.05, 1.13)	39%
rectum	18	1.09 (1.06, 1.12)	3%		NA	
Gallbladder cancer		NA[c]		2	1.59 (1.02, 2.47)	67%
Leukemia	7	1.08 (1.02, 1.14)	0%	7	1.17 (1.04, 1.32)	80%
Malignant melanoma	6	1.17 (1.05, 1.30)	44%		NA	
Multiple myeloma	7	1.11 (1.05, 1.18)	7%	6	1.11 (1.07, 1.15)	0%
Non-Hodgkin lymphoma	6	1.06 (1.03, 1.09)	0%	7	1.07 (1.00, 1.14)	47%
Esophageal adenocarcinoma	5	1.52 (1.33, 1.74)	24%	3	1.51 (1.31, 1.74)	0%
Pancreatic cancer		NA		11	1.12 (1.02, 1.22)	43%
Renal cancer	11	1.24 (1.15, 1.34)	21%	12	1.34 (1.25, 1.43)	45%
Thyroid cancer	4	1.33 (1.04, 1.70)	77%	3	1.14 (1.06, 1.23)	5%
Prostate cancer	27	1.03 (1.00, 1.09)	0%		NA	
Post-menopausal breast cancer		NA		31	1.12 (1.08, 1.16)	43%
Endometrial cancer						
below 27 kg/m^2		NA		19	1.221 (1.084, 1.376)	NA
above 27 kg/m^2		NA		19	1.729 (1.598, 1.872)	NA

a Risk estimates are per increase in 5 kg/m2 BMI (body mass index). All risk estimates are taken from meta-analyses of the previously published meta-analysis. Only risk estimates for cancer types with a significant positive association with BMI are shown.

b Number of studies.

The common cancers(in red) (as noted by the IARC and WRCF reports) are endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal cancer; **the less common malignancies** (in green) are leukemia, non-Hodgkin's lymphoma, multiple myeloma, malignant melanoma, and thyroid cancer.

The International Agency for Research on Cancer has determined that, based on results from epidemiological studiose,people who are overweight or obese are at increased risk of developing several cancer types, including adenocarcinoma of the oesophagus, colon cancer, breast cancer (in postmenopausal women), endometrial cancer and kidney (renal-cell) cancer.

Epidemiological evidence also indicates that cancers of the liver, gallbladder and pancreas are obesity related, and that obesity might also increase risk for haematopoietic cancers and for aggressive prostate cancer.

No association is seen between obesity and lung cancer. Results for other cancers have been inconsistent.

SObes Rev. 2012 Oct;13(10):868-91. doi: 10.1111/j.1467-789X.2012.01010.x. Epub 2012 Jun 4.

A systematic review of the impact of weight loss on cancer incidence and mortality.

Birks S[1], Peeters A, Backholer K, O'Brien P, Brown W.

Author information

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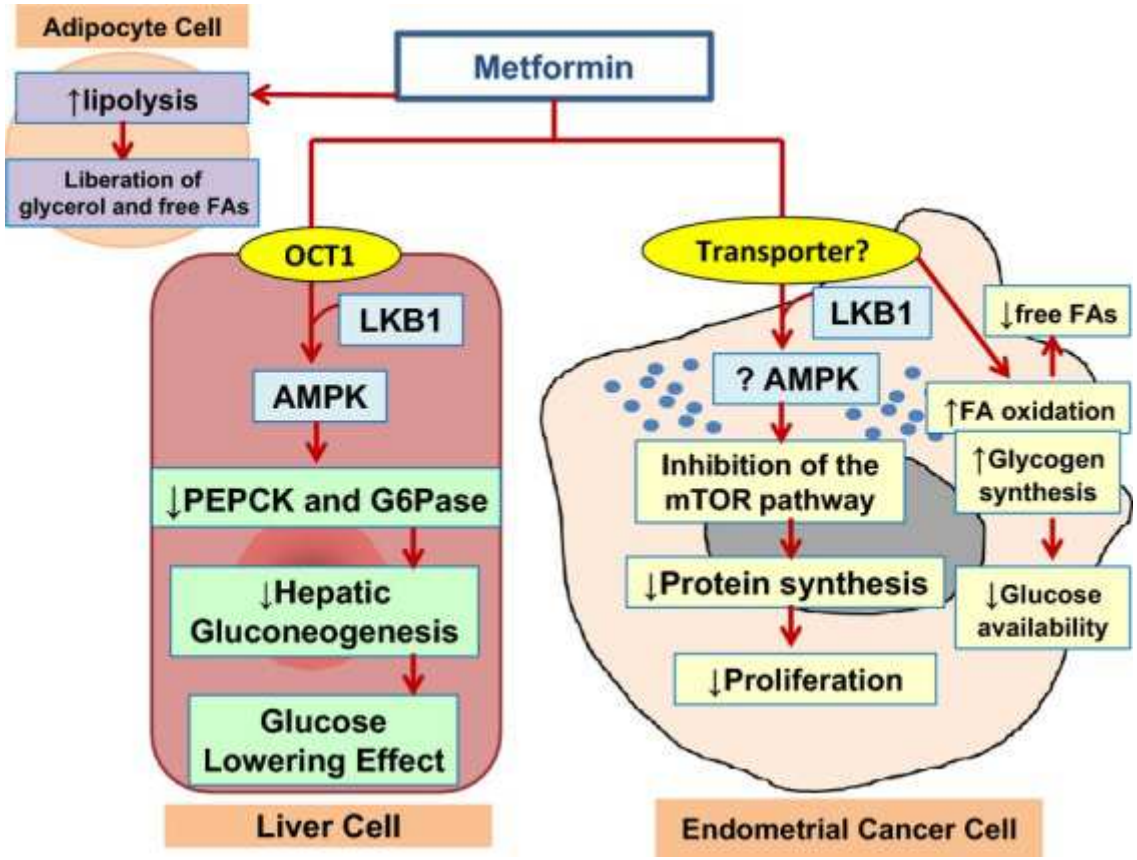
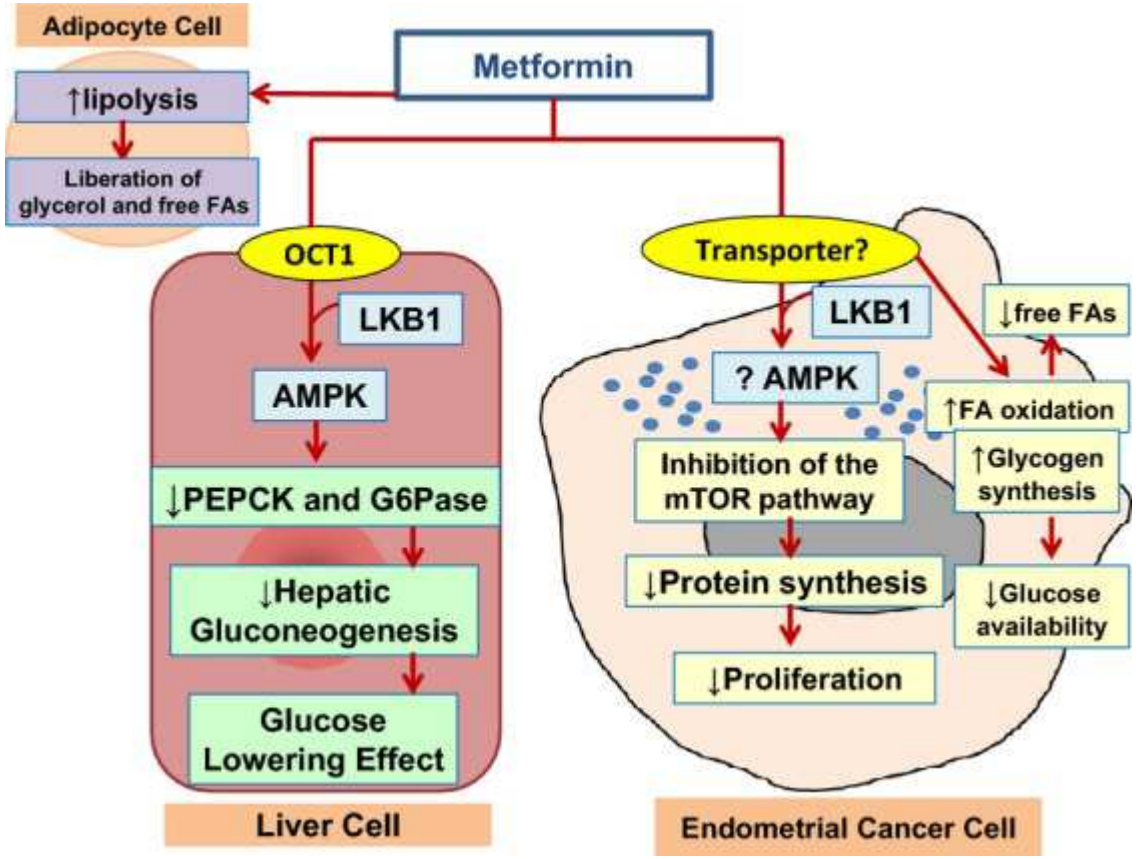
Abstract

Obesity is well recognized as a significant risk factor for certain cancers; however, a corresponding risk reduction with weight loss is not yet clearly defined. This review aims to examine the literature investigating the effect of all types of weight loss on cancer incidence and mortality, and to more clearly describe the relationship between these two factors. A literature search identified 34 publications reporting weight loss data in relation to cancer incidence or mortality. All except one were observational studies and the majority used self-reported weights and did not define intentionality of weight loss. 16/34 studies found a significant inverse association between weight loss and cancer incidence or mortality. The remainder returned null findings. The observed association was more consistently seen in studies that investigated the effect of intentional weight loss (5/6 studies) and the risk reduction was greatest for obesity-related cancers and in women. In conclusion, intentional weight loss does result in a decreased incidence of cancer, particularly female obesity-related cancers. However, there is a need for further evaluation of sustained intentional weight loss in the obese with less reliance on self-reported weight data and more focus on male populations.

Dati epidemiologici: associazione obesità e rischio di cancro

- International Agency for Research into Cancer (IARC) in 2001 International Agency for Research in Cancer. 2002. *Weight Control and Physical Activity. IARC Handbook of Cancer Prevention, Vol. 6*, ed. H Vainio, F Bianchini. Lyon: IARC Press
- World Cancer Research Fund (WCRF) World Cancer Research Fund. 2007. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: Am. Inst. Cancer Res.
- Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms Nature Review Cancer 2004; 4: 579-591
- Body –mass index and incidence of cancer: a systematic review and metanalysis of prospective observational studies Lancet 2008; 371, 569-578

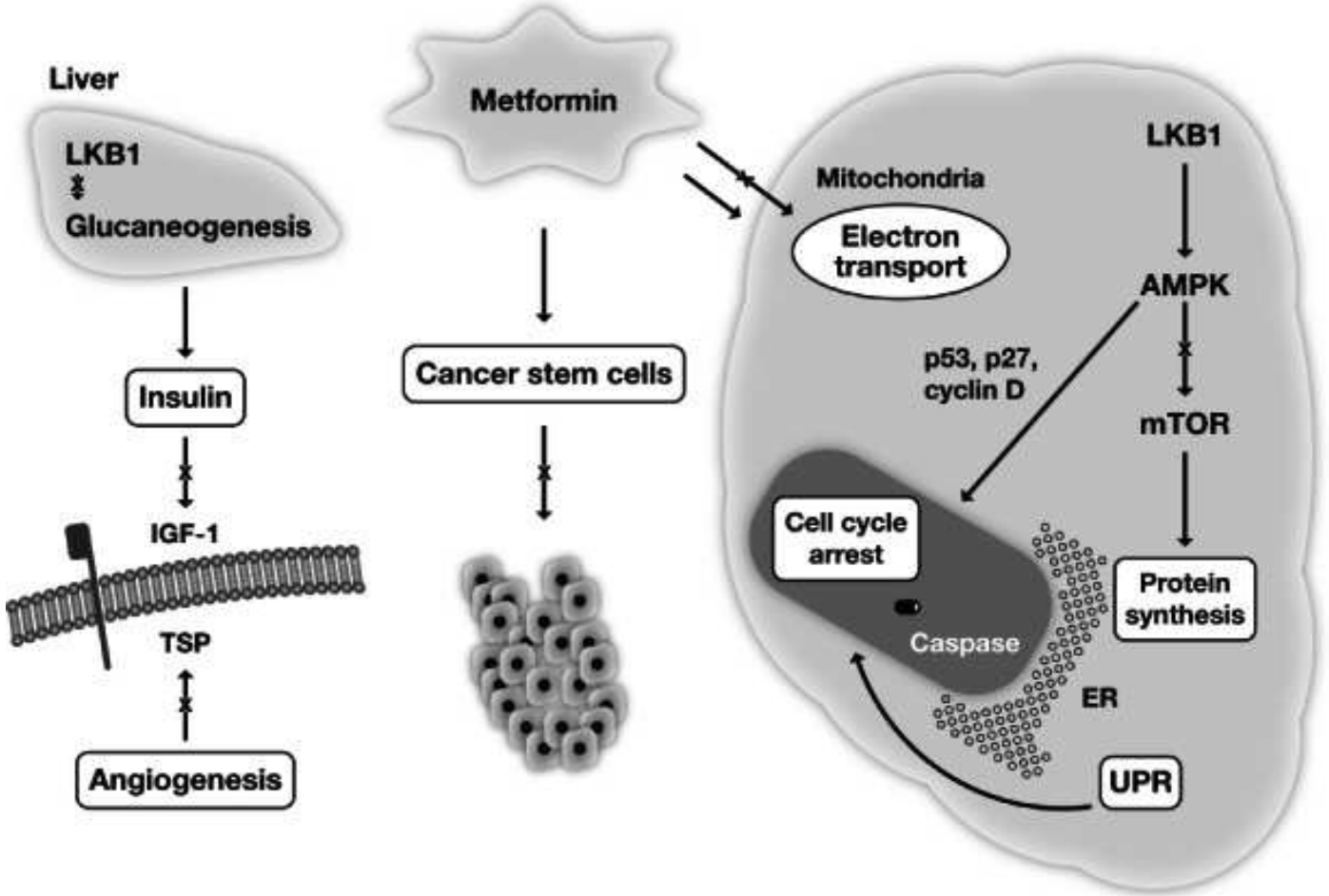

Adipocyte Cell
↑lipolysis
Liberation of glycerol and free FAs
Metformin
OCT1
LKB1
AMPK
↓PEPCK and G6Pase
↓Hepatic Gluconeogenesis
Glucose Lowering Effect
Liver Cell
Transporter?
LKB1
? AMPK
Inhibition of the mTOR pathway
↓Protein synthesis
↓Proliferation
↓free FAs
↑FA oxidation
↑Glycogen synthesis
↓Glucose availability
Endometrial Cancer Cell



Indirect and direct effects seen by meformin in a preoperative window study in obese endometrial cancer patients. Metformin treatment resulted in a systemic decrease in serum glucose and enhanced lipolysis coupled with inhibition of the mTOR pathway and increased fatty acid oxidation and glycogen synthesis in the endometrial tumor cells themselves. These effects were more pronounced in responders versus nonresponders to metformin treatment

Cancer Med. 2015 Feb; 4(2): 161–173

Possible mechanism by which metformin may be able to inhibit cancer cell growth



AMPK, adenosine monophosphate-activated protein kinase; ER, endoplasmic reticulum; IGF, insulin-like growth factor; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin;

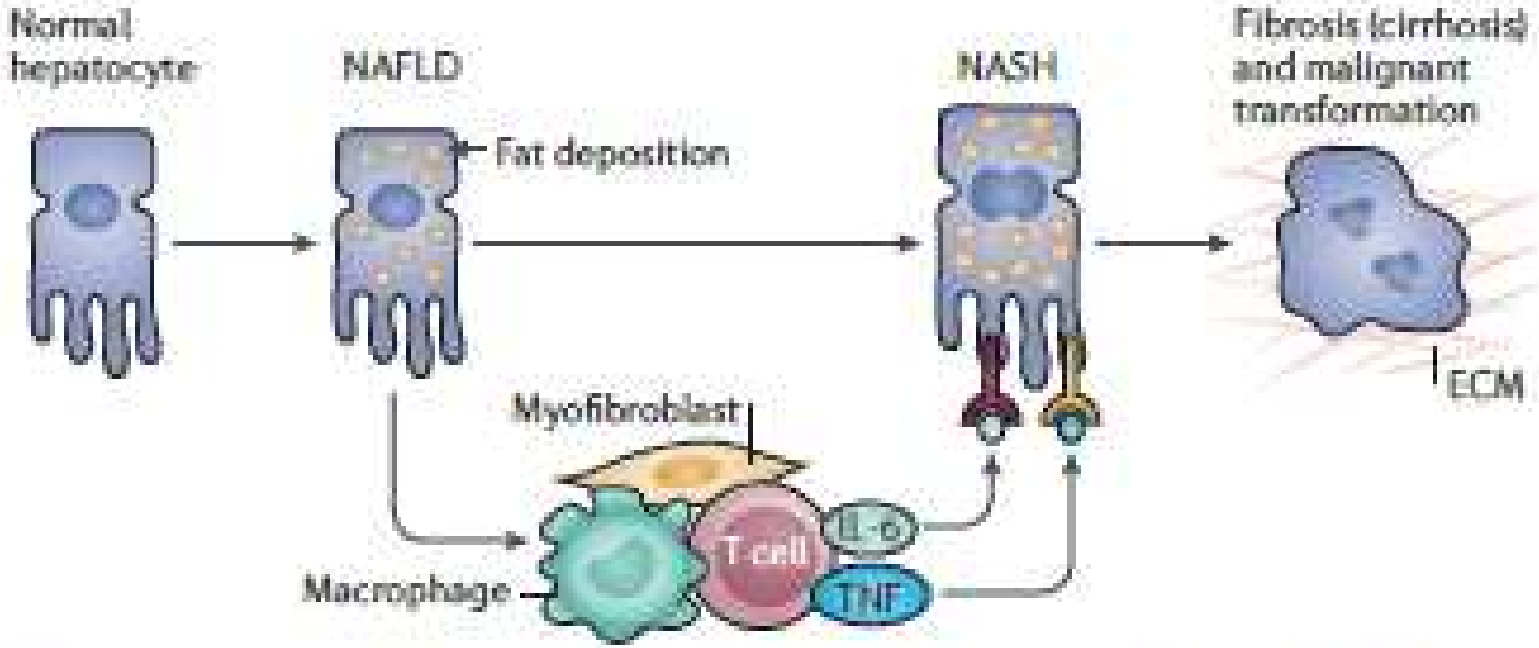
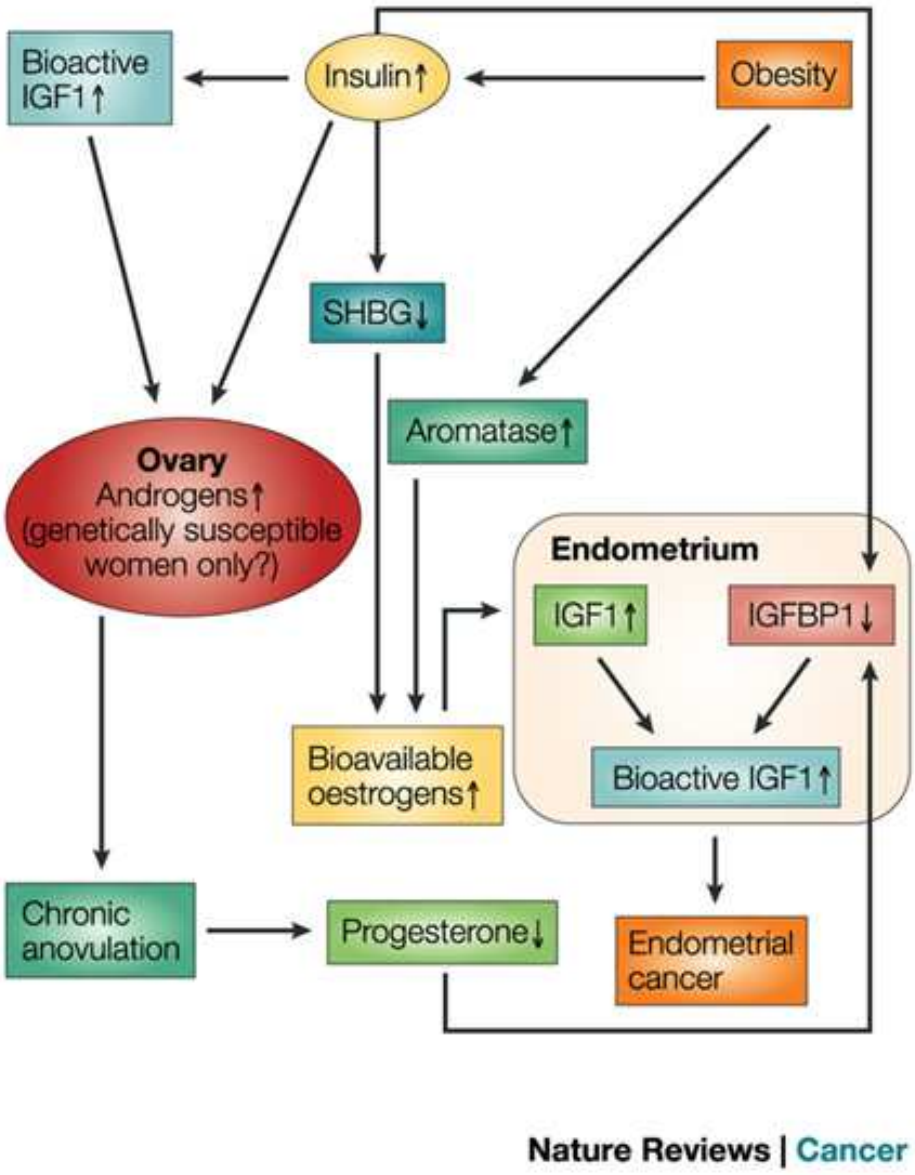


Figure 3 | **Hypothesized steatosis–hepatocellular carcinoma pathway.** In the absence of common hepatic insults, such as excess alcohol, accumulation of fat in the liver (nonalcoholic fatty liver disease (NAFLD)) is associated with chronic inflammation, known as nonalcoholic steatohepatitis (NASH). In some subpopulations, over time, 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.

Obesity, hormones and endometrial cancer



Obesity can increase risk of endometrial cancer through several parallel endocrine pathways.

Obesity is associated with increased insulin levels, increases in IGF1 activity and, in some individuals, an increased androgen production by the ovaries.

Increased adiposity also increases aromatase activity, leading to increased levels of bioavailable oestrogen levels in postmenopausal women.

Among premenopausal women, the lack of progesterone, because of ovarian androgen production and continuous anovulation,leads to reduced production of IGFBP1 by the endometrium.

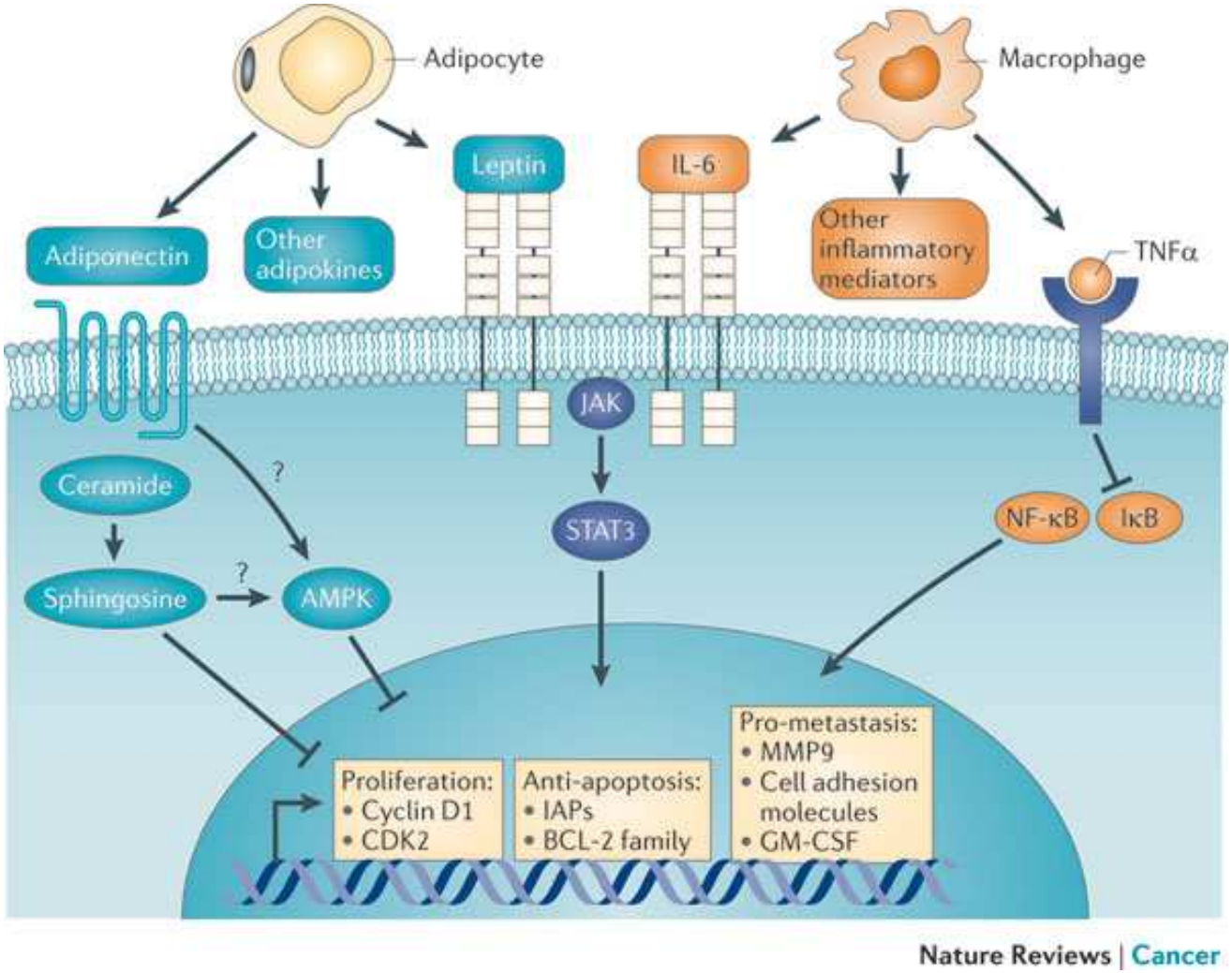
After menopause the more central risk factor seems to be obesity-related increases in bioavailable oestrogen levels.

Table 2 | **Associations of obesity with selected hormones and proteins**

Hormone or binding globulin	Obesity versus normal weight
Insulin	Increased levels with obesity
IGF1	Non-linear relation, with peak levels in people with BMIs of 24–27 kg/m^2
Free IGF1	Increased levels with obesity
IGFBP1	Decreased levels with obesity
IGFBP3	Increased levels with obesity or no observed effect
SHBG	Decreased levels with obesity
Total testosterone	Decreased levels with obesity (men); no observed effect (women); increased levels with obesity (premenopausal women with polycystic ovary syndrome)
Free testosterone	No observed effect or decreased levels with obesity (men); increased levels with obesity (women)
Total oestradiol	Increased levels with obesity (men and postmenopausal women); no observed effect (premenopausal women)
Free oestradiol	Increased levels with obesity (men and postmenopausal women); no observed effect (premenopausal women)
Progesterone	No observed effect or decreased levels with obesity in women with a susceptibility to develop ovarian hyperandrogenism (premenopausal women only)

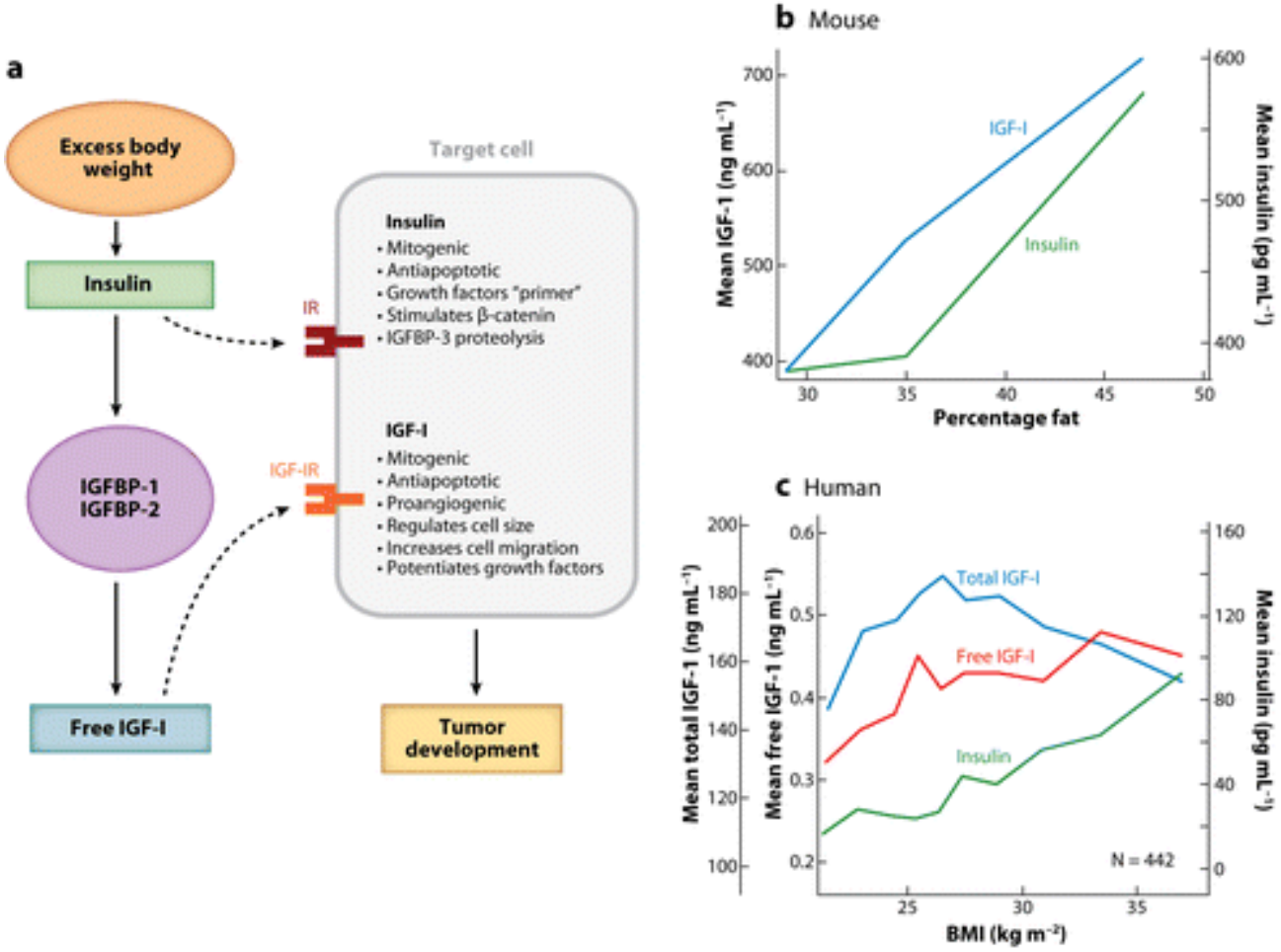
BMI, body mass index; IGF1, insulin-like growth factor 1; IGFBP, IGF-binding protein; SHBP, sex-hormone-binding globulin.

Adipokine and inflammatory signalling in obesity



Vol 11; 886-895 December 2011

The insulin-IGF hypothesis of obesity-related cancer



Roberts DL, et al. 2010.
Annu. Rev. Med. 61:301–16

La resistenza insulinica si sviluppa come adattamento metabolico ad un eccesso di FFA e di ormoni rilasciati dal tessuto adiposo specie viscerale ed è compensata da ipersecrezione insulinica.
Vari dati indicano che l'iperinsulinemia cronica aumenta il rischio di cancro del colon e dell'endometrio.
I livelli di insulin-like growth factor 1 (IGF1) sono associati con diversi tipi di cancro, anche se non c'è un relazione lineare tra i livelli circolanti di IGF1 ed il grado di obesità

I livelli circolanti di estrogeni sono correlati all'obesità.
Per il cancro della mammella in post menopausa e dell'endometrio, gli effetti dell'obesità sul rischio di cancro sono mediati dagli alti livelli di estrogeni, che sono 50-100 volte superiori nelle obese.
Nel 4–8% delle donne in premenopausa, l'obesità e la resistenza insulinica possono essere sia la causa, sia la causa aggravante della sindrome dell'ovaio policistico e delle deficienza cronica di progesterone.
Ci sono evidenze che PCOS aumenta il rischio del cancro dell'endometrio.