

Obesity: is it responsible for cancer? Data and possible mechanisms

Maria Kyrgiou

Senior Lecturer – Consultant Gynaecologic Oncologist



Obesity Cancers



Endometrial Cancer

Ovarian Cancer

Cervical Cancer

Vaginal Cancer

Vulval Cancer

Breast Cancer

Colorectal Cancer etc.



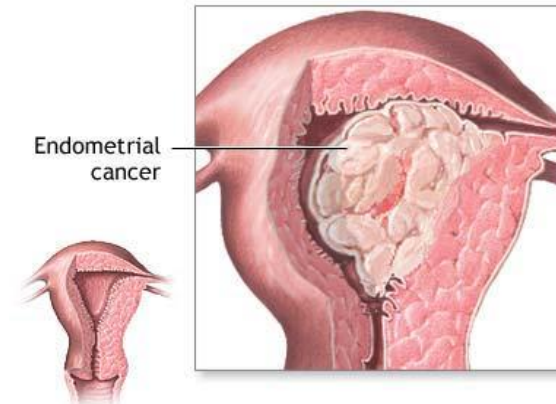
Challenges of Obesity & Cancer...

➔ Understanding the magnitude of the problem...
Epidemiological research

Manage medical and surgical challenges
Surgical trials, new technologies

Answer scientific gaps... Explore mechanisms
Lab-based research

Improve prevention
Education, better detection, chemoprevention

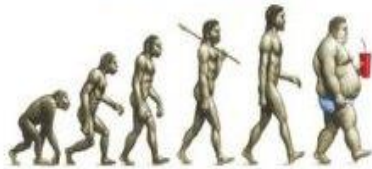


Obesity: a Global Epidemic...



FAT

THE FADS, TRENDS, POLICIES, AND
PRODUCTS THAT ARE FATTENING
THE HUMAN RACE



Barry Popkin

- Obesity rates are rising worldwide
- 2008: 1.5 billion <20y are obese
- **UK:** 25% of adults are obese
50% of women will be obese by 2050
[The Government commissioned Foresight report 2007]
- **USA:** one-third of adults (33.8%) obese

Obesity: Preventing and managing the global epidemic. Geneva : WHO , 2000.

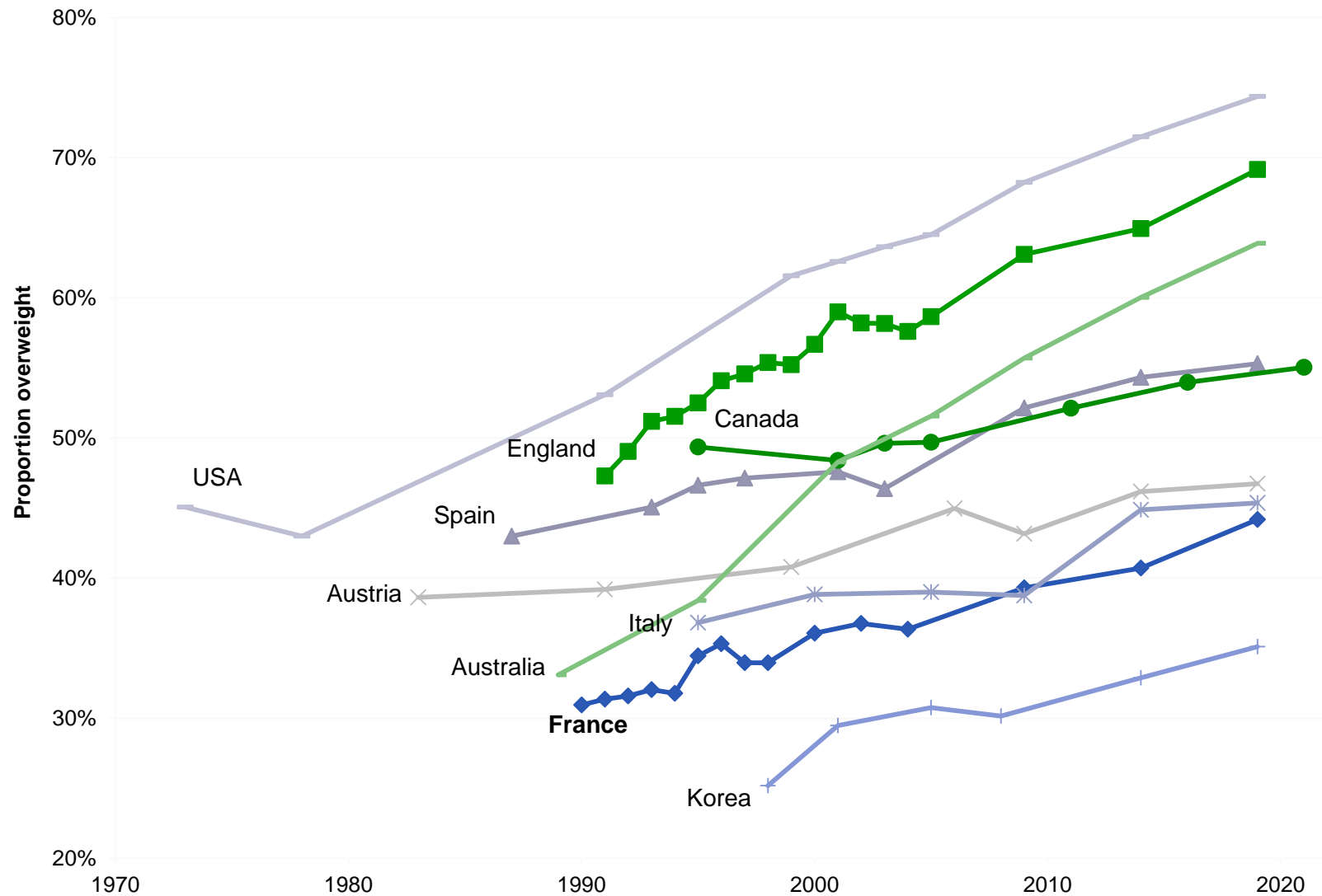
National Health & Nutrition Examination Survey (NHANES) 2007 -2008

Statistics on Obesity, physical activity & diet :England 2010 in NHS information centre for life style statistics 2010.

Barry Popkin



Trends in Overweight and Obesity

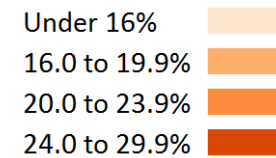




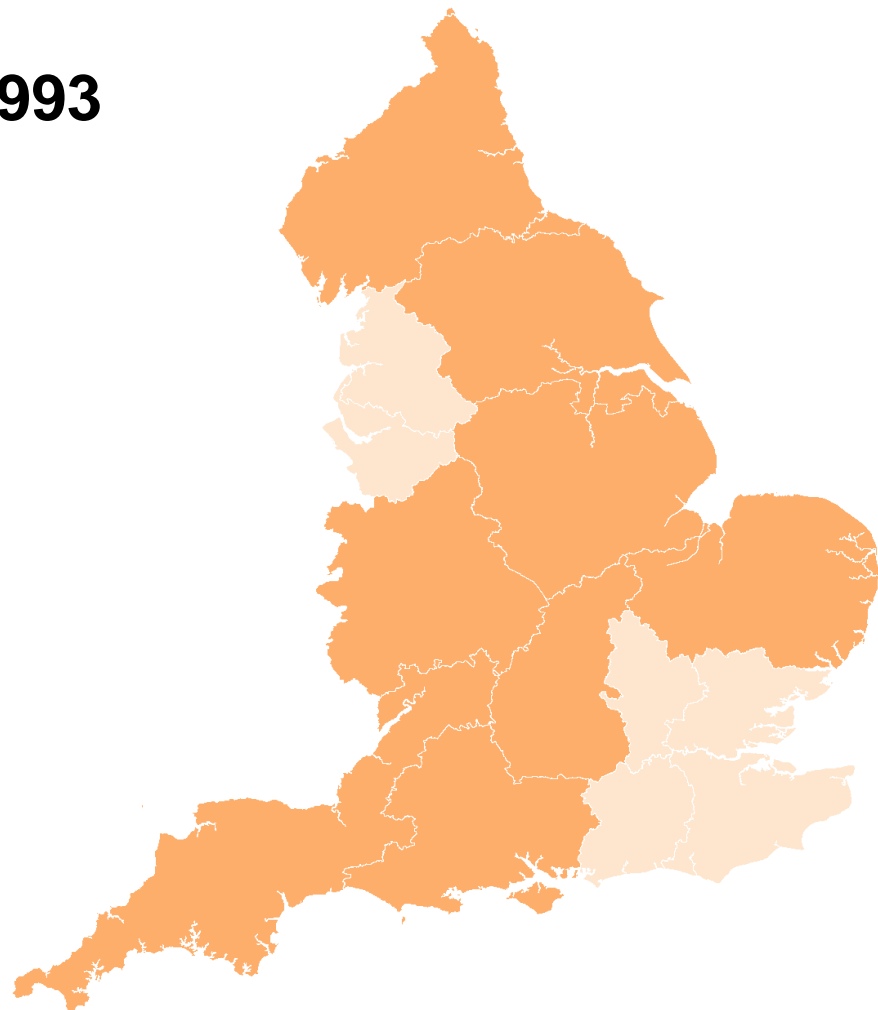
Public Health
England

Prevalence of obesity in adults (aged 16+)

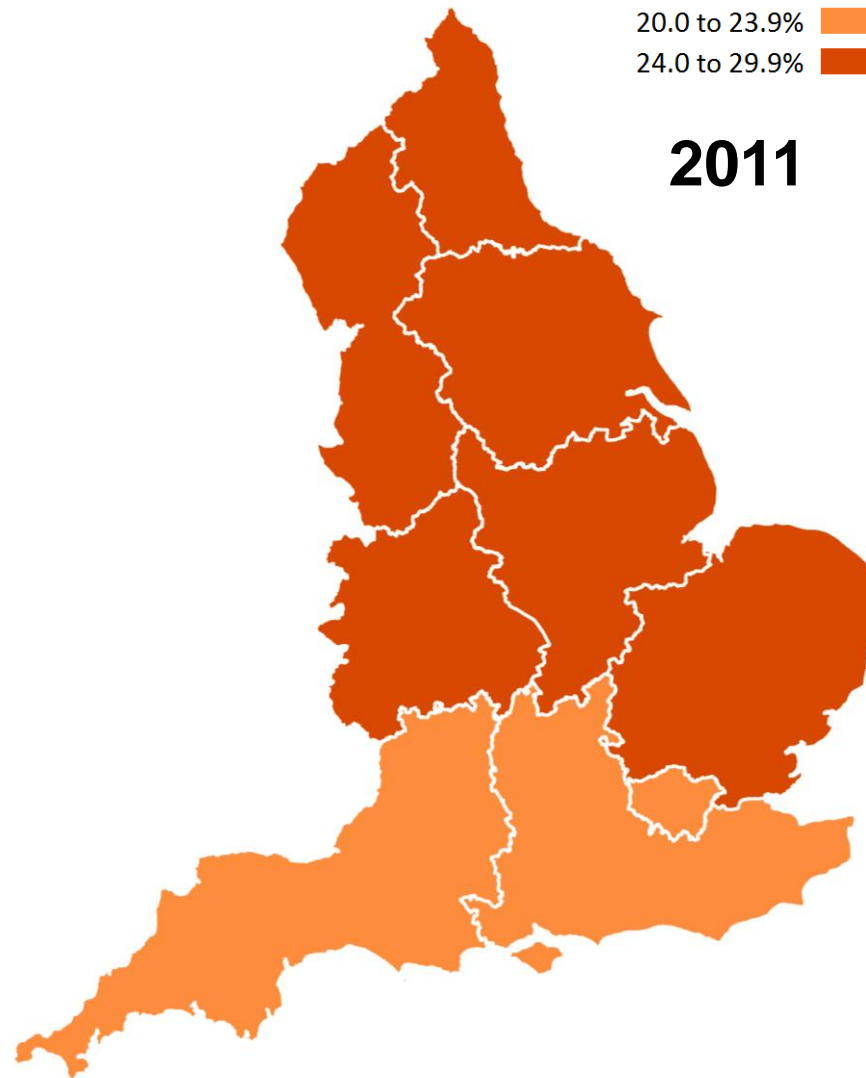
Source: Health Survey for England



1993



2011



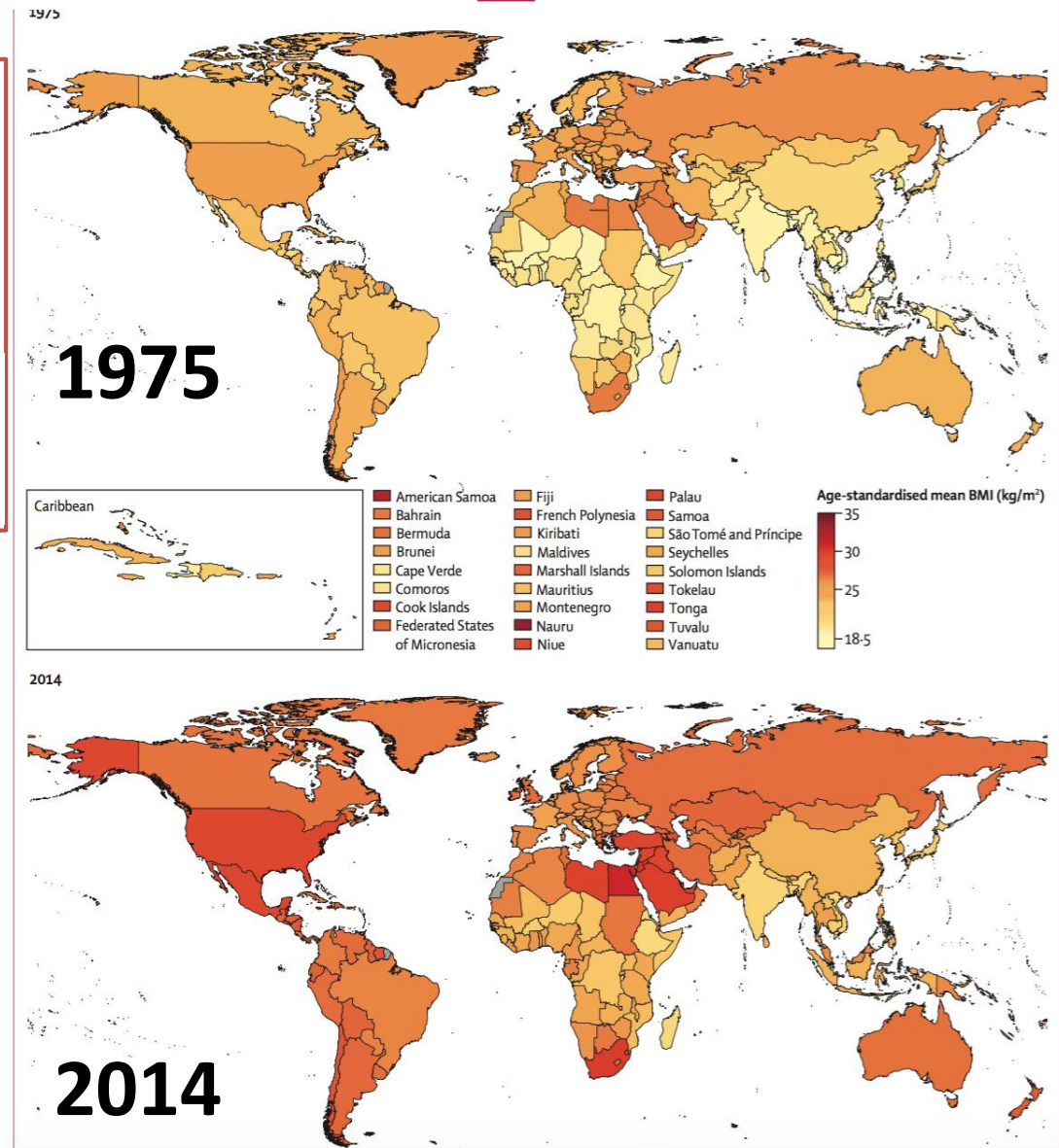
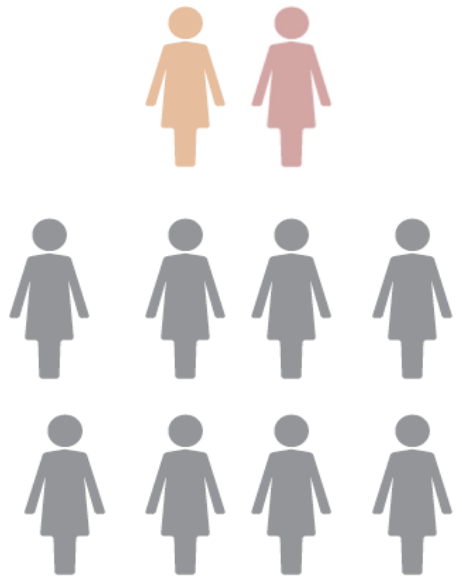
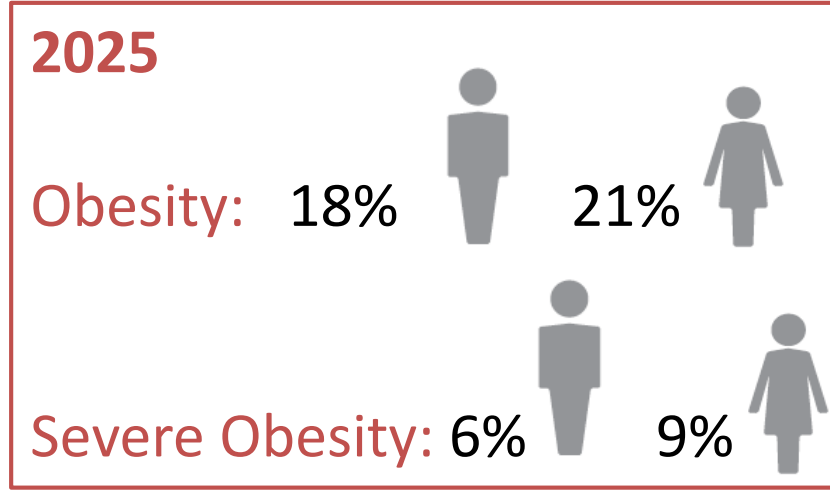
Females

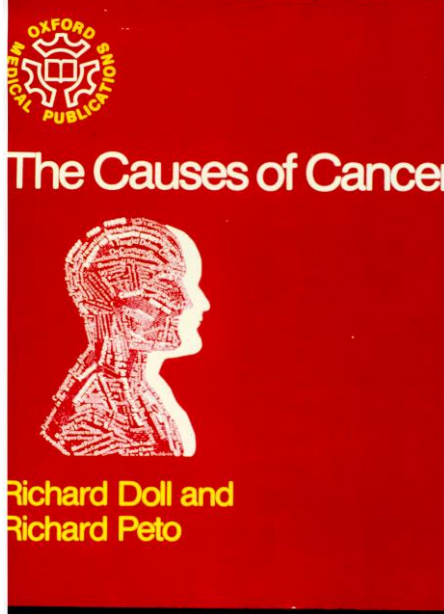
Adult obesity: BMI \geq 30kg/m²

Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants



NCD Risk Factor Collaboration (NCD-RisC)*





Population Attributable Risks(%):

| | |
|-----------------------|-------|
| Smoking | 29-31 |
| Diet | 20-50 |
| Alcohol | 4-6 |
| Infection | 10-20 |
| Occupation | 2-4 |
| Reproductive hormones | 10-20 |

J Natl Cancer Inst.

1981 Jun;66(6):1191-308.

WHO: overweight and obesity are the most important known avoidable cause of cancer after tobacco...

No.1

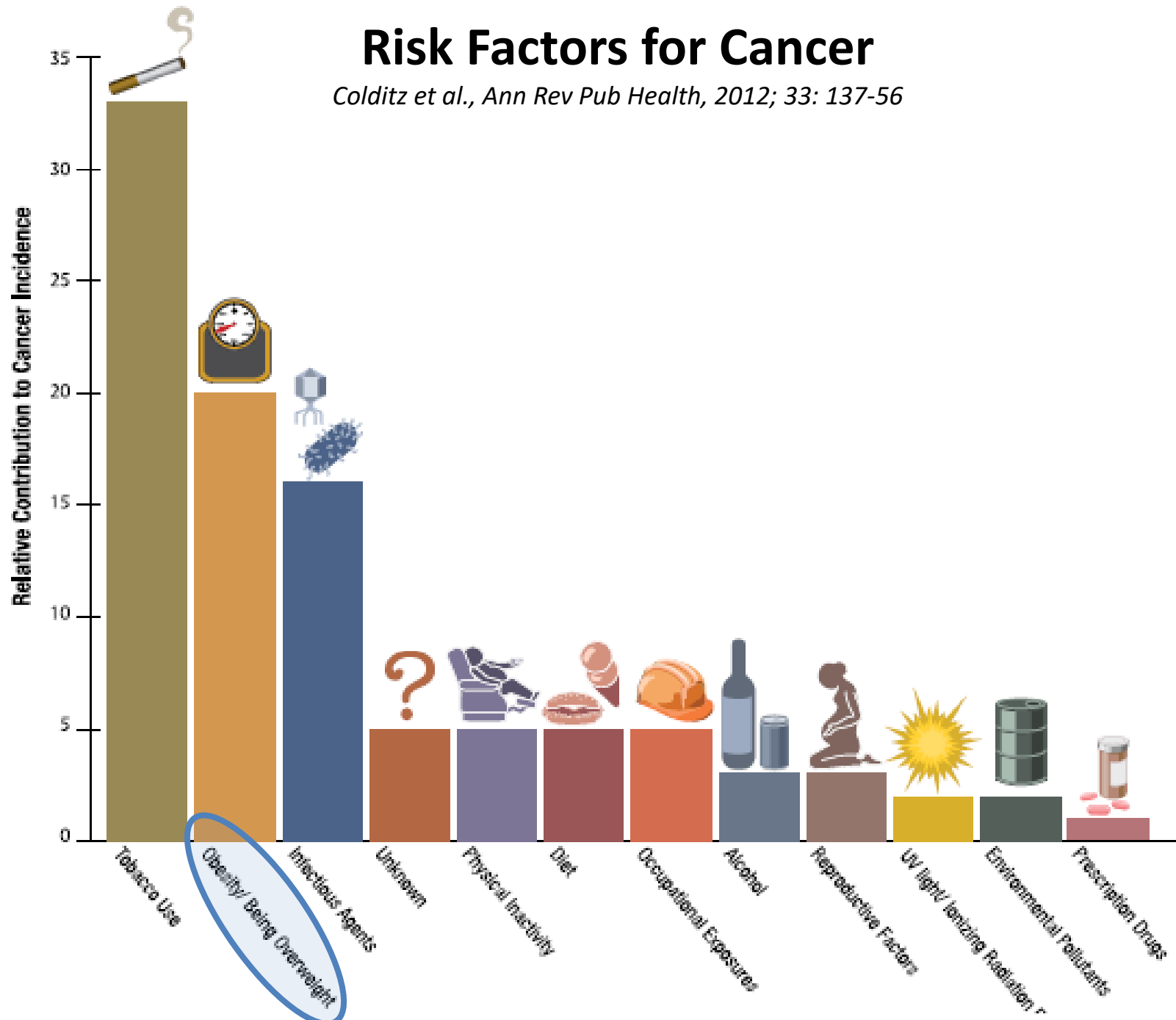


No.2



Risk Factors for Cancer

Colditz et al., *Ann Rev Pub Health*, 2012; 33: 137-56



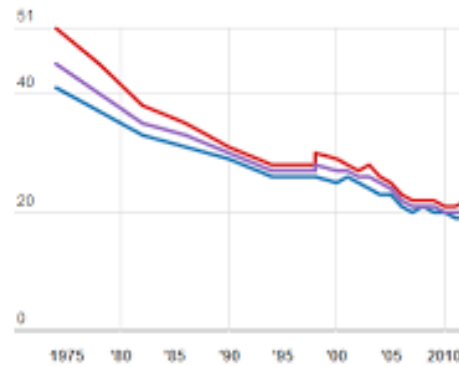


dreamstime.com

Smoking rates

% of individuals aged 16+

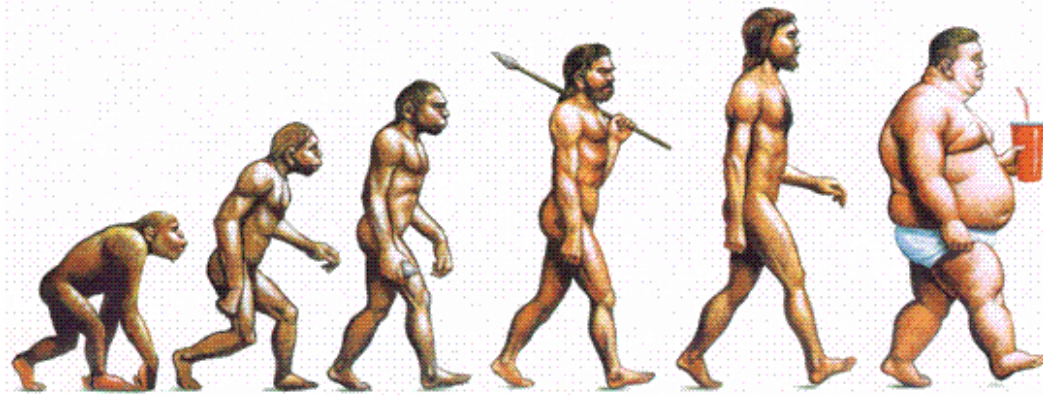
■ Men ■ UK Average ■ Women



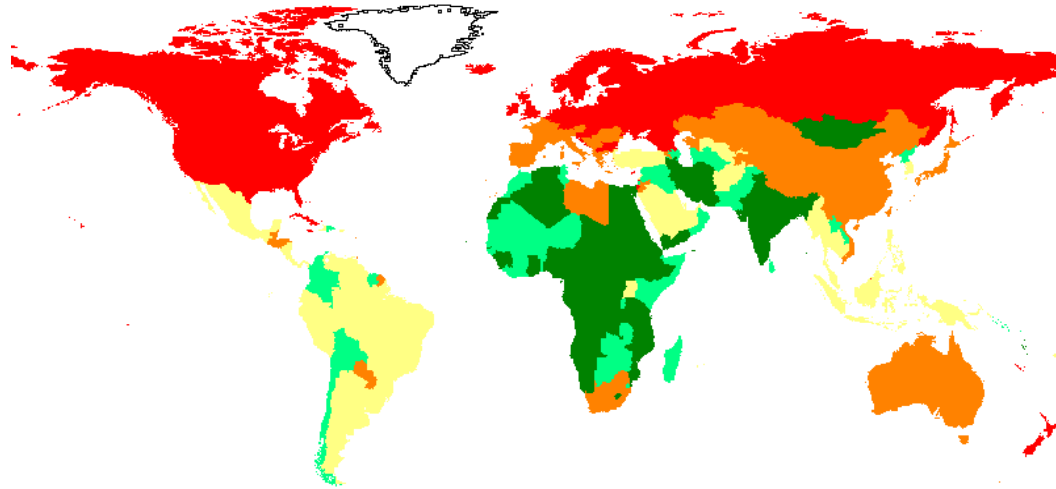
Created with [Datawrapper](#)

Source: [ONS](#) [Get the data](#)

The shape of things to come



The Economist, Dec 13-19, 2003



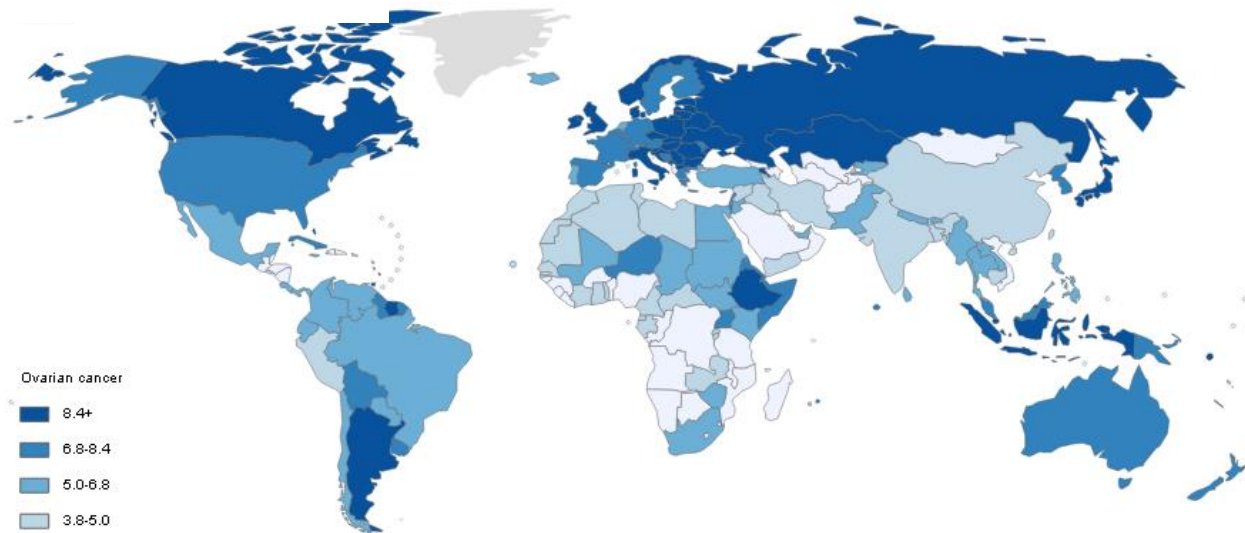
■ < 2.1 ■ < 3.7 ■ < 6.1 ■ < 11.3 ■ < 18.7

GLOBOCAN 2008 (IARC) - 22.2.2011

Age-Standardized Endometrial Cancer Incidence Rates, 2012

Globocan

Age-Standardized Ovarian Cancer Incidence Rates, 2012



Ovarian cancer

■ 8.4+
■ 6.8-8.4
■ 5.0-6.8
■ 3.8-5.0
■ <3.8
■ No Data



| | Incidence | Mortality |
|--------------------|-----------|-----------|
| Breast cancer | 795,000 | 313,000 |
| Cervical cancer | 450,000 | 300,000 |
| Ovarian cancer | 165,000 | 101,000 |
| Endometrial cancer | 142,000 | 42,000 |



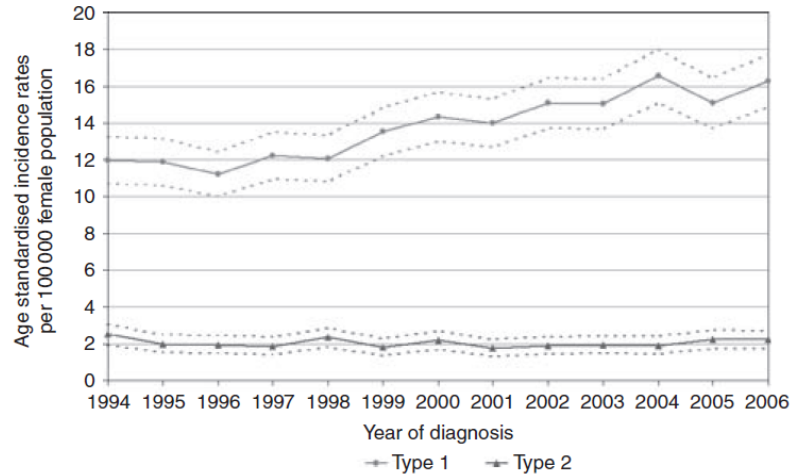
Western societies:

Better prevention of some cancers like Cx Ca
 BUT also
 Obesity pandemic and diabetes...

| Site | Incidence | | Mortality | |
|--------|-----------------|---|------------------|---|
| | Number of cases | European age-standardised rate per 100,000 (95% CI) | Number of deaths | European age-standardised rate per 100,000 (95% CI) |
| Ovary | 6,537 | 16.2 (19.9-16.6) | 4,373 | 9.7 (9.4-10.0) |
| Uterus | 7,703 | 19.4 (18.9-19.8) | 1,741 | 3.6 (3.4-3.8) |
| Cervix | 2,938 | 8.7 (8.4-9.0) | 957 | 2.4 (2.2-2.5) |
| Vulva | 1,157 | 2.5 (2.4-2.7) | 400 | 0.7 (0.6-0.7) |
| Vagina | 258 | 0.6 (0.4-0.7) | 77 | 0.1 (0.1-0.2) |

Endometrial Cancer: Incidence & Deaths

England & Wales (1997)



40%

USA

New Cases: 47,130 - Deaths: 8,010

Most common Gynae Ca

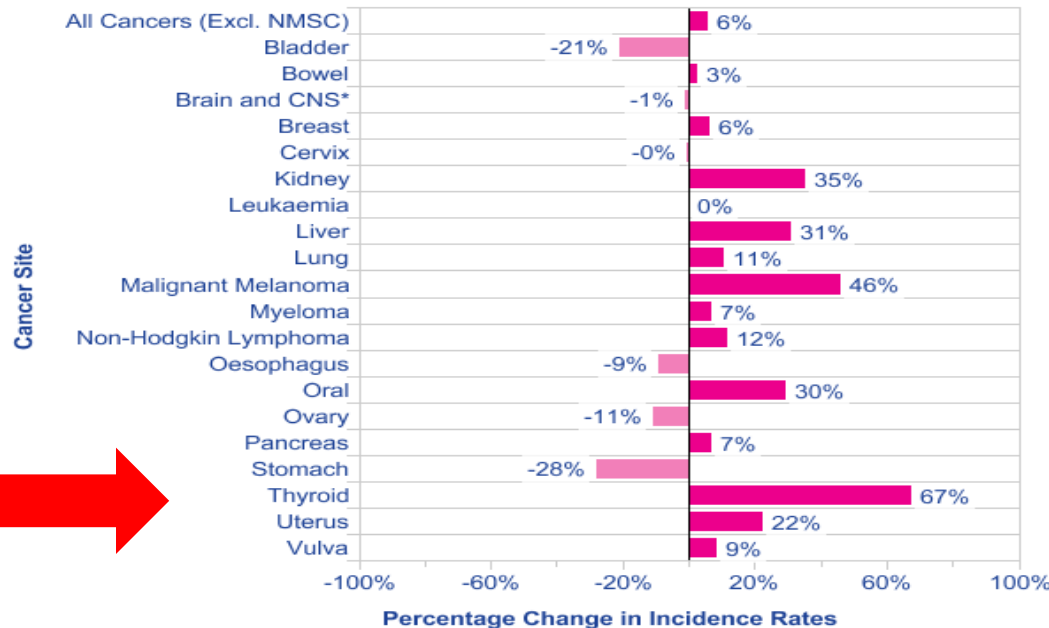
6% of all cancer in women

UK: similar

4000/year in E&W

25-30% of all Gynae Ca

Figure 1 Differential trends in endometrial cancer incidence across the two types. Age standardised incidence rates and confidence intervals are shown.

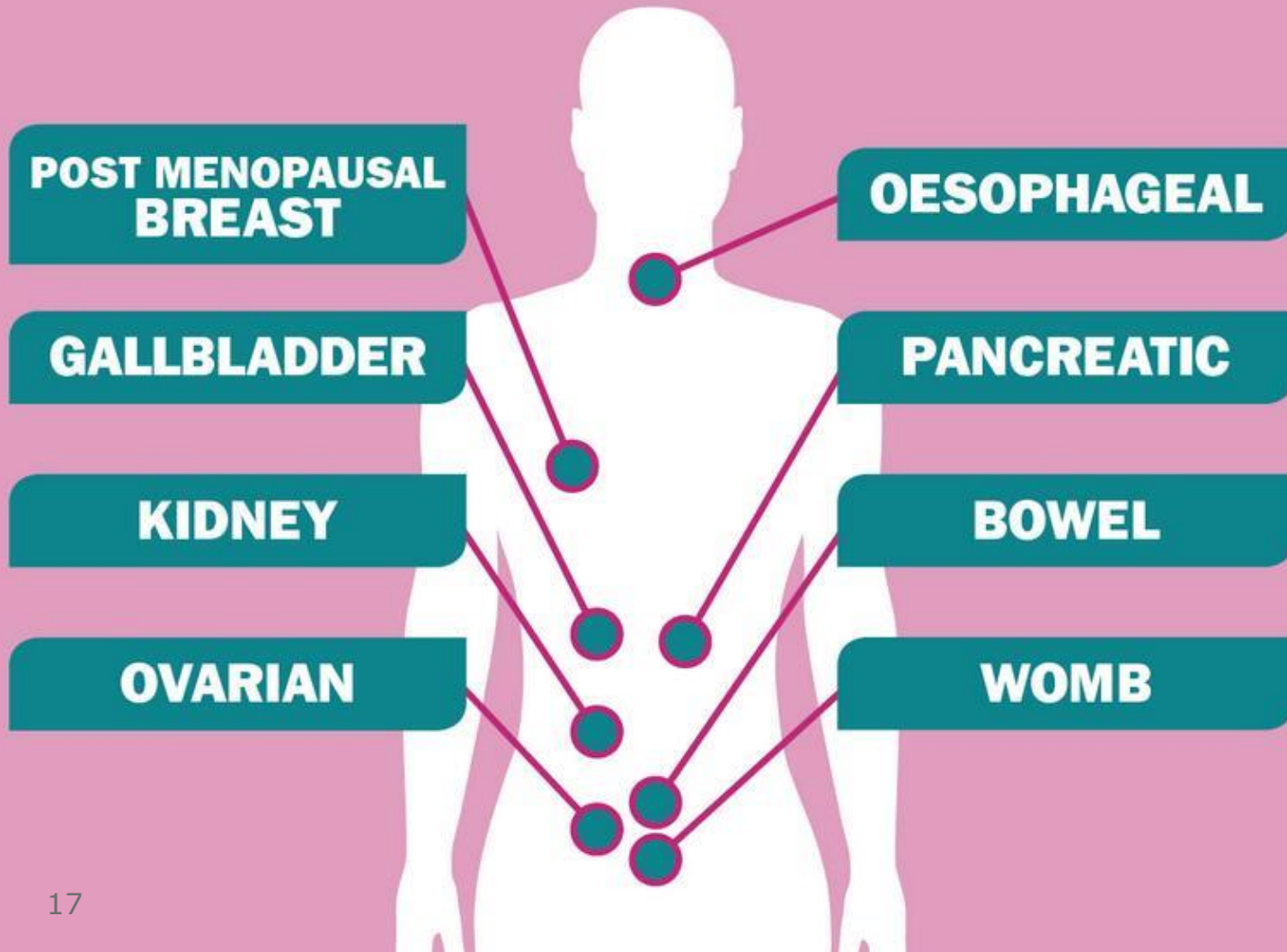


Type 1 EC accounts for incidence increase

The 20 Most Commonly Diagnosed Cancers: 1999-2001 and 2008-2010
 Percentage Change in European Age-Standardised Incidence Rates per 100,000 Population, Females, UK



8 CANCERS ARE NOW LINKED TO BEING **OVERWEIGHT**





SPECIAL REPORT

Body Fatness and Cancer — Viewpoint of the IARC Working Group

August 2016

Béatrice Lauby-Secretan, Ph.D., Chiara Scocciati, Ph.D., Dana Loomis, Ph.D.,
Yann Grosse, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D.,
for the International Agency for Research on Cancer Handbook Working Group

Table 2. Strength of the Evidence for a Cancer-Preventive Effect of the Absence of Excess Body Fatness, According to Cancer Site or Type.*

| 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) |

Adiposity and cancer at major anatomical sites: umbrella review of the literature



Maria Kyrgiou,^{1,2} Ilkka Kalliala,¹ Georgios Markozannes,³ Marc J Gunter,⁴ Evangelos Paraskevaïdis,⁵ Hani Gabra,^{1,2} Pierre Martin-Hirsch,^{6,7} Konstantinos K Tsilidis^{3,8}

2017

204 meta-analyses – incidence & mortality from 36 cancers

| Table 1 Summary of evidence grading for meta-analyses associating continuous measures of obesity and risk of cancer—cohort studies only. Risk refers to cancer incidence unless otherwise stated | | | |
|--|--|--|---|
| Evidence | Criteria used | Decreased risk | Increased risk |
| Strong (n=12) | P<10 ⁻⁶ *; >1000 cases; P<0.05 of largest study in meta-analysis; I ² <50%; no small study effect†; prediction interval excludes null value; no excess significance bias‡; survive 10% credibility ceiling | None | Oesophageal adenocarcinoma (BMI); colon cancer, men (BMI); rectal cancer, men (BMI); biliary tract system cancer§ (BMI); pancreatic cancer (BMI); postmenopausal breast cancer, never HRT use (WG); endometrial cancer (WHR); premenopausal endometrial cancer (BMI); kidney cancer, men and women (BMI); multiple myeloma, overall and women (BMI) |
| Highly suggestive (n=17) | P<10 ⁻⁶ *; >1000 cases; P<0.05 of largest study in meta-analysis | Oesophageal squamous cell carcinoma, overall and women (BMI); lung cancer, overall and men (BMI) | Colon cancer (BMI and waist circumference per 10 cm); liver cancer (BMI); postmenopausal breast cancer (BMI); endometrial cancer (BMI, BMI in young adulthood, weight per 5 kg, WG); postmenopausal endometrial cancer (BMI); endometrial cancer, type I (BMI); endometrial cancer, type II (BMI); kidney cancer (BMI) |
| Suggestive (n=23) | P <10 ⁻³ *; >1000 cases | Oesophageal squamous cell carcinoma, men (BMI); lung cancer, smokers (BMI); premenopausal breast cancer (BMI); localised prostate cancer (BMI) | Colon cancer, women (BMI); colon cancer, men and overall (WG); colon cancer (WHR and WC); colorectal cancer (WG per 1kg); rectal cancer (BMI); pancreatic cancer (WHR and WC); ovarian cancer (BMI and BMI in young adulthood); prostate cancer mortality (BMI); thyroid cancer, overall and women (BMI); non-Hodgkin's lymphoma (BMI); multiple myeloma, men (BMI); leukaemia (BMI) |
| Weak (n=19) | P<0.05* | Lung cancer, women (BMI); melanoma, women (BMI) | Oesophageal adenocarcinoma in men and women (BMI); melanoma, men (BMI); endometrial cancer (HC per 10 cm); postmenopausal endometrial cancer, never HRT use (BMI and WG); postmenopausal endometrial cancer, ever HRT use (BMI and WG); endometrial cancer mortality (BMI); ovarian cancer (weight per 5 kg); postmenopausal ovarian cancer, never HRT use (WG); prostate cancer, advanced (BMI); prostate cancer, countries with high screening rate for prostate specific antigen (WG); thyroid cancer, men (BMI); non-Hodgkin's lymphoma mortality (BMI); leukaemia, men and women (BMI) |

OBESITY INCREASES THE RISK OF THESE 11 CANCERS



Adiposity and cancer at major anatomical sites: umbrella review of the literature



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2017

204 meta-analyses – incidence & mortality from 36 cancers

-Risk increase ranged from 9% for **rectal cancer among men** to 56% for **biliary tract system cancer** for every 5 kg/m² BMI

-Risk of **postmenopausal breast cancer among women** who have never used HRT increased by 11% for each 5 kg of weight gain

-Risk of **endometrial cancer** increased by 21% for each 0.1 increase in waist to hip ratio.

Challenges of Obesity & Gynae Cancer...

Understanding the magnitude of the problem...

Epidemiological research



Manage medical and surgical challenges

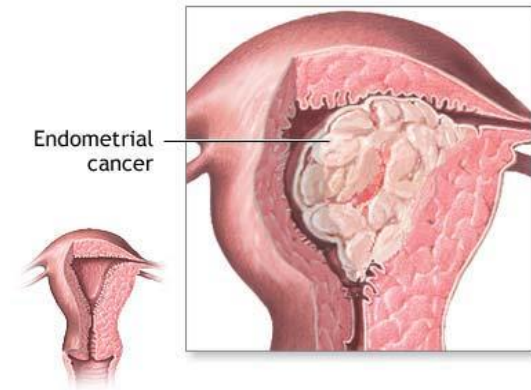
Surgical trials, new technologies

Answer scientific gaps... Explore mechanisms

Lab-based research

Improve prevention, survival..

Education, better detection, chemoprevention



Debates - Controversies....

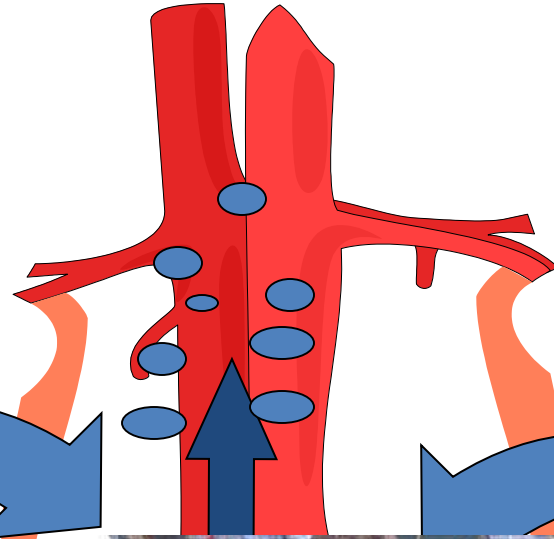
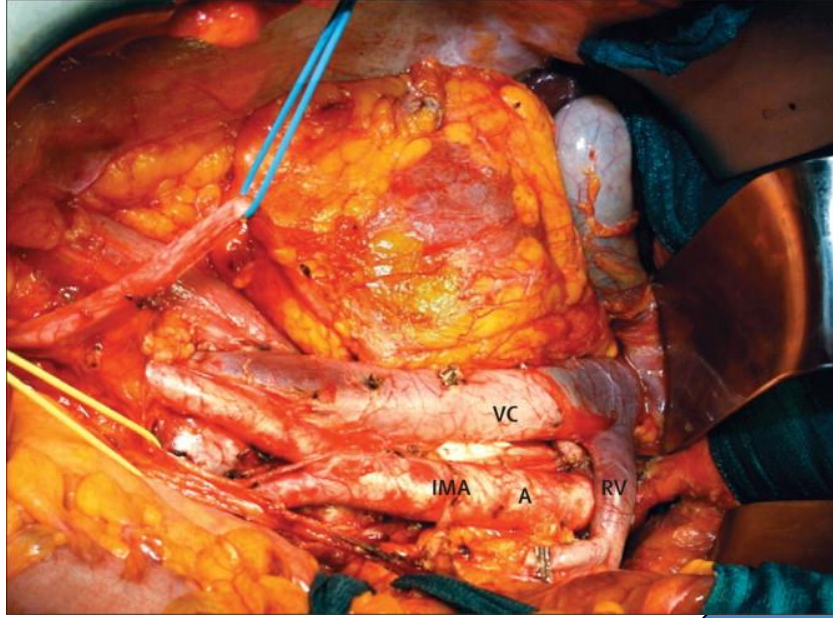
- *Is surgical staging – LND required in **Endometrial Cancer**?...*
- *Primary or Interval debulking in **Ovarian Cancer**?....*
- *How about **Laparoscopic** staging?....*

Tailored approach....

BMI major factor that often affects our surgical approach & decision making...



Lymphadenectomy.....



Challenges....

Pre-Operative Issues

- Diagnostic challenges: difficult to examine, perform endometrial biopsy, hysteroscopy, TVS
- Imaging challenges: MR scanners have weight limit, Unable to radiologically stage, ? Use equine scanner
- Nursing challenges: Moving, wound dressing, mobilising
- Equipment challenges: Weight limit of bed, operating table, buy specialist equipment

Anaesthetic Issues

- Co-morbidities
- IV access
- Ventilation: poor lung compliance, high pressures
- Intubation difficulties

Surgical Challenges

- Difficult moving patient to correct position
- Difficult access
- Limited head down for laparoscopic surgery
- Anatomical landmarks not relevant due to abdominal pannus
- Intra-abdominal fat

Post-Surgical Risks

- Higher rate of conversion of lap procedures to open
- Wound infections, dehiscence , hernias
- PE , DVTs
- Cardiac events: arrhythmias, Mis
- Chest Infections
- Sleep Apnoea



Laparoscopic surgery: as safe, less morbid...

Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial

Marian J E Mourits, Claudia B Bijen, Henriëtte J Arts, Henk G ter Brugge, Rob van der Sijde, Lasse Paulsen, Jacobus Wijma, Marlies Y Bongers, Wendy J Post, Ate G van der Zee, Geertruida H de Bock



Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial

Monika Janda, Val Gebski, Alison Brand, Russell Hogg, Thomas W Jobling, Russell Land, Tom Manolitsas, Anthony McCartney, Marcelo Nascimento, Debarah Neesham, James L Nicklin, Martin K Oehler, Geoff Ott on, Lewis Perrin, Stuart Salfinger, Ian Hammond, Yee Leung, Tom Walsh, Peter Sykes, Hextan Ngan, Andrea Garrett, Michael Laney, Tong Yow Ng, Karfai Tam, Karen Chan, C David H Wrede, Selvan Pather, Bryony Simcock, Rhonda Farrell, Andreas Obermair

JOURNAL OF CLINICAL ONCOLOGY

Recurrence and Survival After Random Assignment to Laparoscopy Versus Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group LAP2 Study

Joan L. Walker, Marion R. Piedmonte, Nick M. Spirtos, Scott M. Eisenkop, John B. Schlaerth, Robert S. Mannel, Richard Barakat, Michael L. Pearl, and Sudarshan K. Sharma

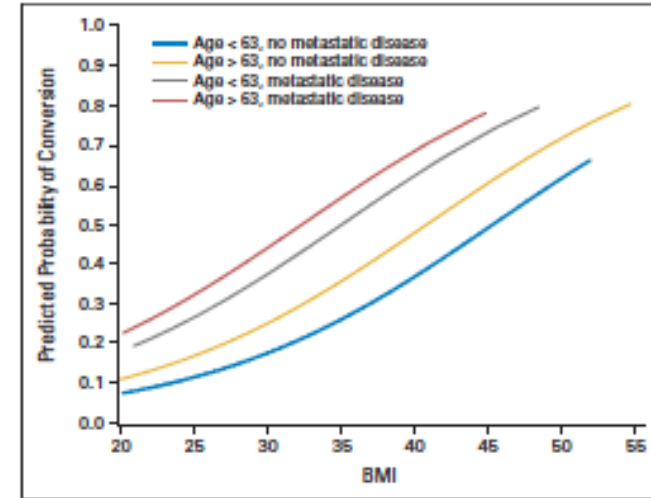
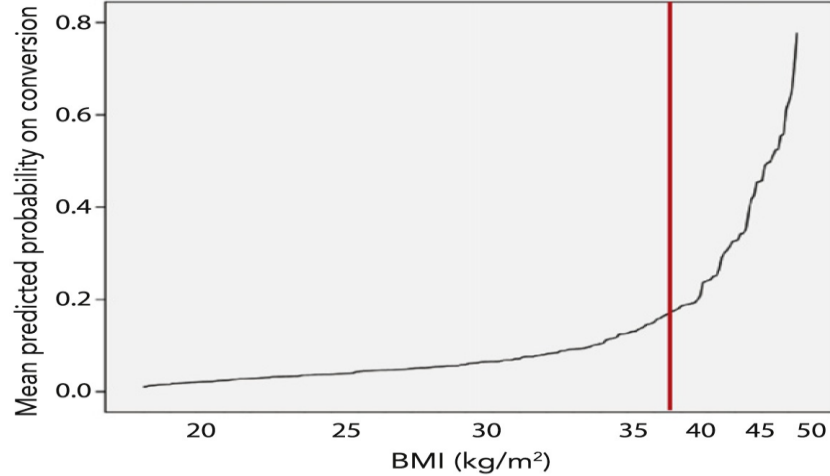
A Comparison of Outcomes Following Laparoscopic and Open Hysterectomy With or Without Lymphadenectomy for Presumed Early-Stage Endometrial Cancer

Results From the Medical Research Council ASTEC Trial



Maria Kyrgiou, MD, PhD,*† Anne-Marie Swart, PhD,‡ Wendi Qian, PhD,§ and Jane Warwick, PhD||

Obesity & Conversion rates



Conversion rate: 10.8% - **increases with BMI**
Not cost-effective BMI>35 depends on
surgeon's experience

Conversion rate: 26%
(**obese** – aged)



Farthing et al. 2010

201 pts with 62% BMI>30

Conversion rate: 1%

Need to centralise cases

Challenges of Obesity & Gynae Cancer...

Understanding the magnitude of the problem...

Epidemiological research

Manage surgical and post-operative challenges

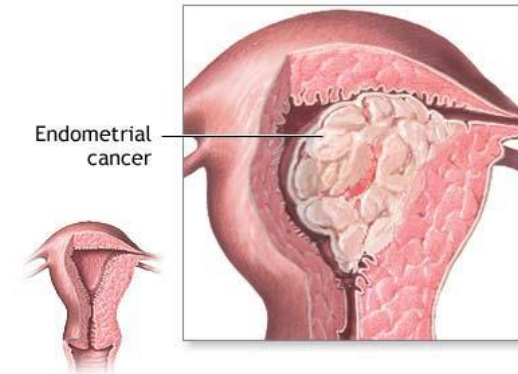
Surgical trials, new technologies

➔ Answer scientific gaps... Explore mechanisms

Lab-based research

➔ Improve prevention, survival..

Education, better detection, chemoprevention



Potential mechanisms

Being overweight/obese it causes lots of disruption of **hormonal and metabolic** pathways...

Excess fat has been linked to higher ***oestrogen*** levels...

higher ***insulin*** levels ...

and increased ***inflammation***...

all of which can affect **cell division**



Risk factors for Endometrial Cancer

-
- Obesity
 - Early Menarche
 - Late Menopause
 - PCOS
 - Type 2 Diabetes
 - Hypertension
 - An-ovulatory Infertility
 - HNPCC (hereditary non-polyposis colon Ca)
 - Tamoxifen
 - HRT
 - Ethnicity (white north americans)
 - Pelvic RDT

- COC
- E+P
- Mirena IUS?
- Smoking??
(weight related)
- Caffeine?

Risk factors & Endometrial Cancer: umbrella review

Raglan, Kalliala I, Markozannes G, Gunter M, Paraskevaidis E, Gabra H, Martin-Hirsch P, Tsilidis K, Kyrgiou M



2017 (under review)

Obesity and Cancer: Mechanisms

Exposures

Diet ↔

Obesity

↔

Physical activity

Mechanisms

Growth factors

Insulin resistance

Adipokines, Inflammation

Steroid hormones

Genetic variation



Biomarkers

IGF-1

Insulin

Leptin

Oestrogen

IGFBP-3

C-Peptide

CRP

Progesterone

Free IGF-I

HbA1c

TNF- α

SHBG

Endpoint

Cancer

Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies

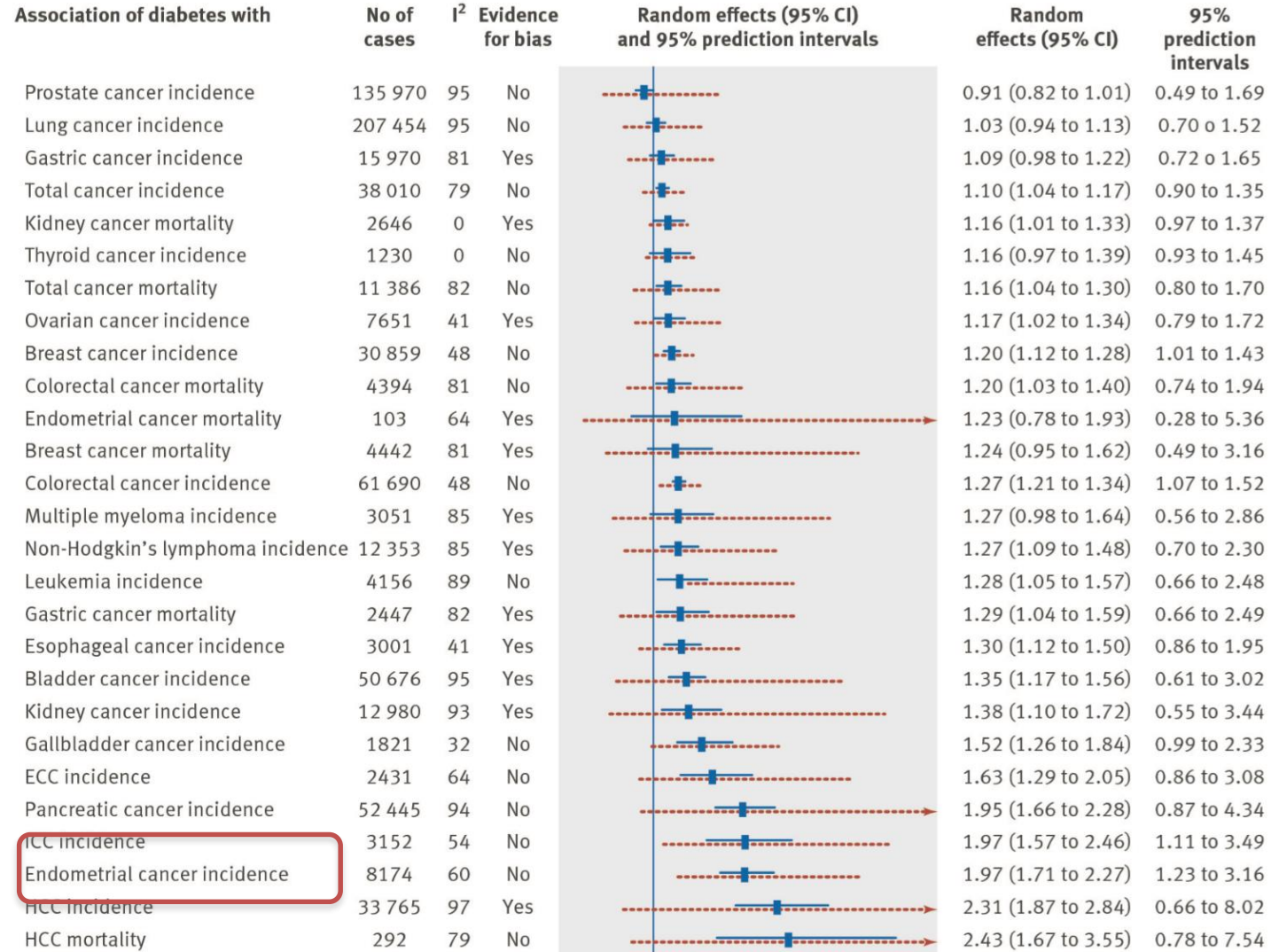


OPEN ACCESS

Konstantinos K Tsilidis *assistant professor*^{1,2}, John C Kasimis *PhD student*¹, David S Lopez *assistant professor*³, Evangelia E Ntzani *assistant professor*¹, John P A Ioannidis *professor*⁴

20 cancer sites

EC incidence strongest association



0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0

A Prospective Evaluation of Insulin and Insulin-like Growth Factor-I as Risk Factors for Endometrial Cancer

Cancer Epid Cancer Prev
2008

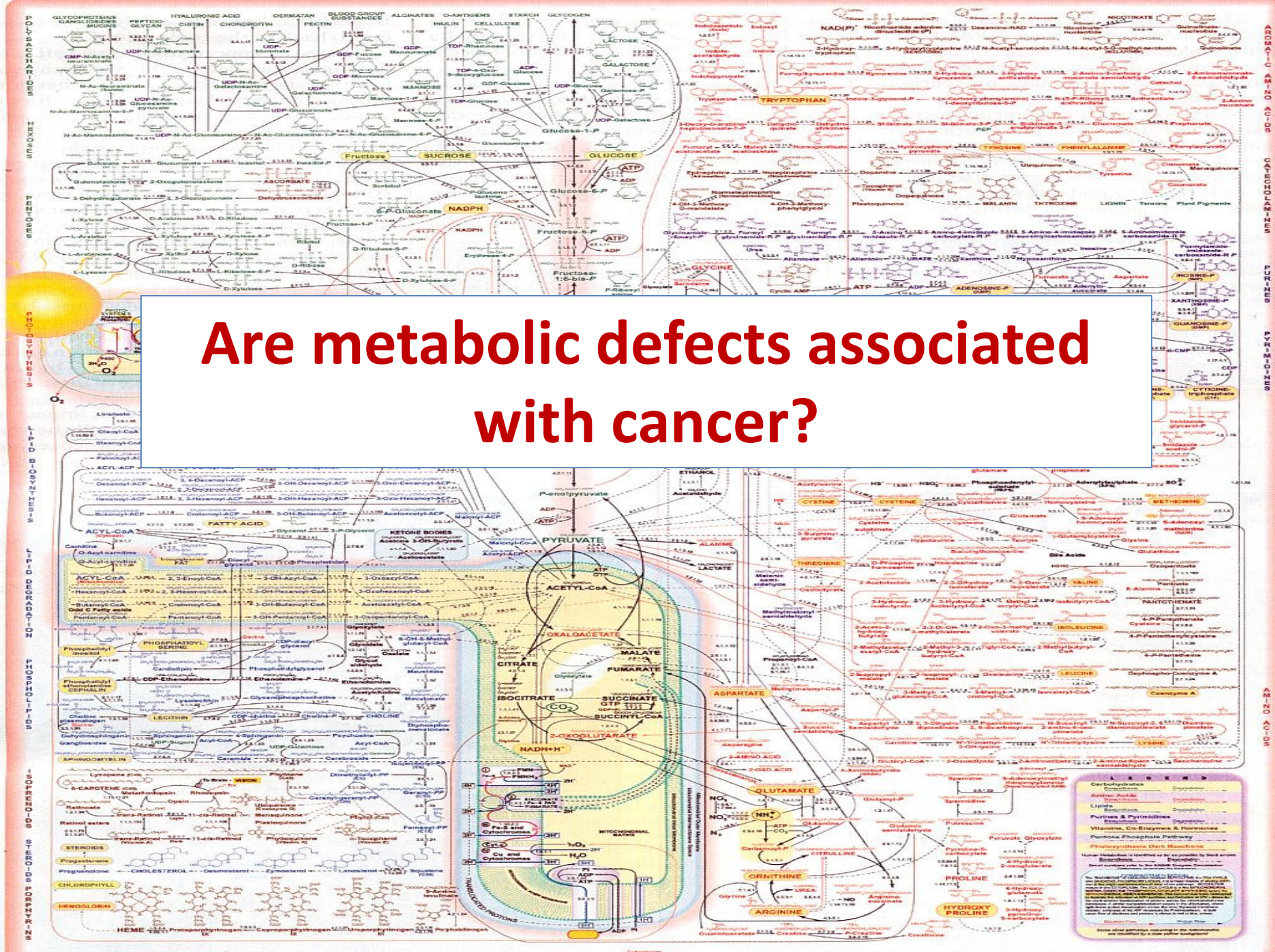
Marc J. Gunter,¹ Donald R. Hoover,³ Herbert Yu,⁴ Sylvia Wassertheil-Smoller,¹
JoAnn E. Manson,⁵ Jixin Li,³ Tiffany G. Harris,¹ Thomas E. Rohan,¹ XiaoNan Xue,¹
Gloria Y.F. Ho,¹ Mark H. Einstein,² Robert C. Kaplan,¹ Robert D. Burk,¹ Judith Wylie-Rosett,¹
Michael N. Pollak,⁶ Garnet Anderson,⁷ Barbara V. Howard,⁸ and Howard D. Strickler¹

- case-cohort study
- Women's Health Initiative Observational Study
- 250 cases and 465 controls

- Insulin positively associated with EC [HR_{q4-q1}: 2.33, 1.13-4.82] after adjustment for age and estradiol
- Free IGF-I inversely associated with EC [HR_{q4-q4}: 0.53, 0.31-0.90] after adjustment for age, HRT, and estradiol

- Both associations stronger among overweight/obese, especially the association between insulin and EC (HR_{q4-q1}, 4.30, 1.62-11.43)

Hyperinsulinemia may represent a risk factor independent of estradiol



Are metabolic defects associated with cancer?

| Category | Examples |
|---|--|
| Carbohydrates | Glucose, Fructose, Sucrose, Galactose, Lactose, Maltose, Dextrin, Glycogen |
| Amino Acids | Alanine, Aspartate, Glutamate, Glutamine, Glycine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine |
| Lipids | Acetyl-CoA, Fatty Acids, Glycerol, Phospholipids, Steroids, Cholesterol, Triglycerides |
| Purines & Pyrimidines | Adenine, Guanine, Cytosine, Uracil, Thymine, Adenine, Guanine, Cytosine, Uracil, Thymine |
| Vitamins, Co-Enzymes & Hormones | Vitamin B1, Vitamin B2, Vitamin B3, Vitamin B5, Vitamin B6, Vitamin B7, Vitamin B9, Vitamin C, Vitamin D, Vitamin E, Vitamin K, Hormones |
| Pentose Phosphate Pathway | Glucose-6-phosphate, 6-Phosphogluconate, 2-Ketogluconate, Sedoheptulose-7-phosphate, Ribulose-5-phosphate, Ribose-5-phosphate, Xylulose-5-phosphate, Glyceraldehyde-3-phosphate, Dihydroxyacetone phosphate, Phosphoenolpyruvate, Pyruvate, Acetyl-CoA |
| Phosphotransferase Dark Reactions | Phosphoenolpyruvate, 2-Carboxy-3-oxobutanoate, Malate, Oxaloacetate, Citrate, Isocitrate, alpha-Ketoglutarate, Succinyl-CoA, Succinate, Fumarate, Malate, Oxaloacetate |
| Home Metabolism is modified to be responsive to local stress conditions | Glucose, Fatty Acids, Amino Acids, Vitamins, Hormones |
| Home Metabolism is modified to be responsive to local stress conditions | Glucose, Fatty Acids, Amino Acids, Vitamins, Hormones |

THE RISING TIDE OF DIABETES – THE CHALLENGE FOR ENGLAND

Diabetes is big, and it's growing

Every three minutes someone in the UK learns that they have diabetes¹¹. Right now there are 2.5 million people in England living with the condition, and estimates suggest a further 850,000 people in the UK have diabetes but are either unaware, or have no confirmed diagnosis¹².

Another 7 million people could be at high risk of developing diabetes, and the numbers are rising dramatically every year. If current trends continue by 2025, it is estimated that, **5 million** people in the UK will have diabetes.

10 per cent of people have Type 1 diabetes, and 90 per cent have Type 2 diabetes¹³.

Type 1 diabetes develops if the body cannot produce any insulin. It usually appears before the age of 40, especially in childhood. It is the less common of the two types of diabetes. It cannot be prevented and it is not known why exactly it develops. Type 1 diabetes is treated by daily insulin doses by injections or via an insulin pump

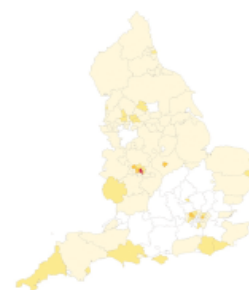
Type 2 diabetes develops when the body can still make some insulin, but not enough, or when the insulin that is produced does not work properly (known as insulin resistance). Type 2 diabetes is treated with a healthy diet and increased physical activity. In addition, tablets and/or insulin can be required.

Increasing prevalence in England

Prevalence of diabetes expected to increase significantly

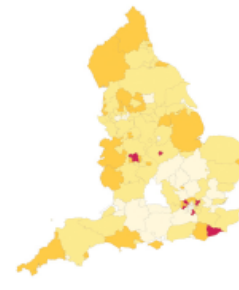
2010

Map 1: Diabetes Prevalence by PCT, 2010



8 Years

Map 2: Diabetes Prevalence by PCT, 2020



18 Years

Map 3: Diabetes Prevalence by PCT, 2030



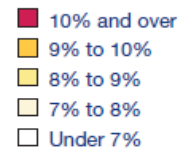
Produced by YHPHO June 2010

Source: Office of National Statistics

Crown Copyright material is reproduced with the permission of the Office of Public Sector Information (OPSI).

Contains Ordnance Survey data ©

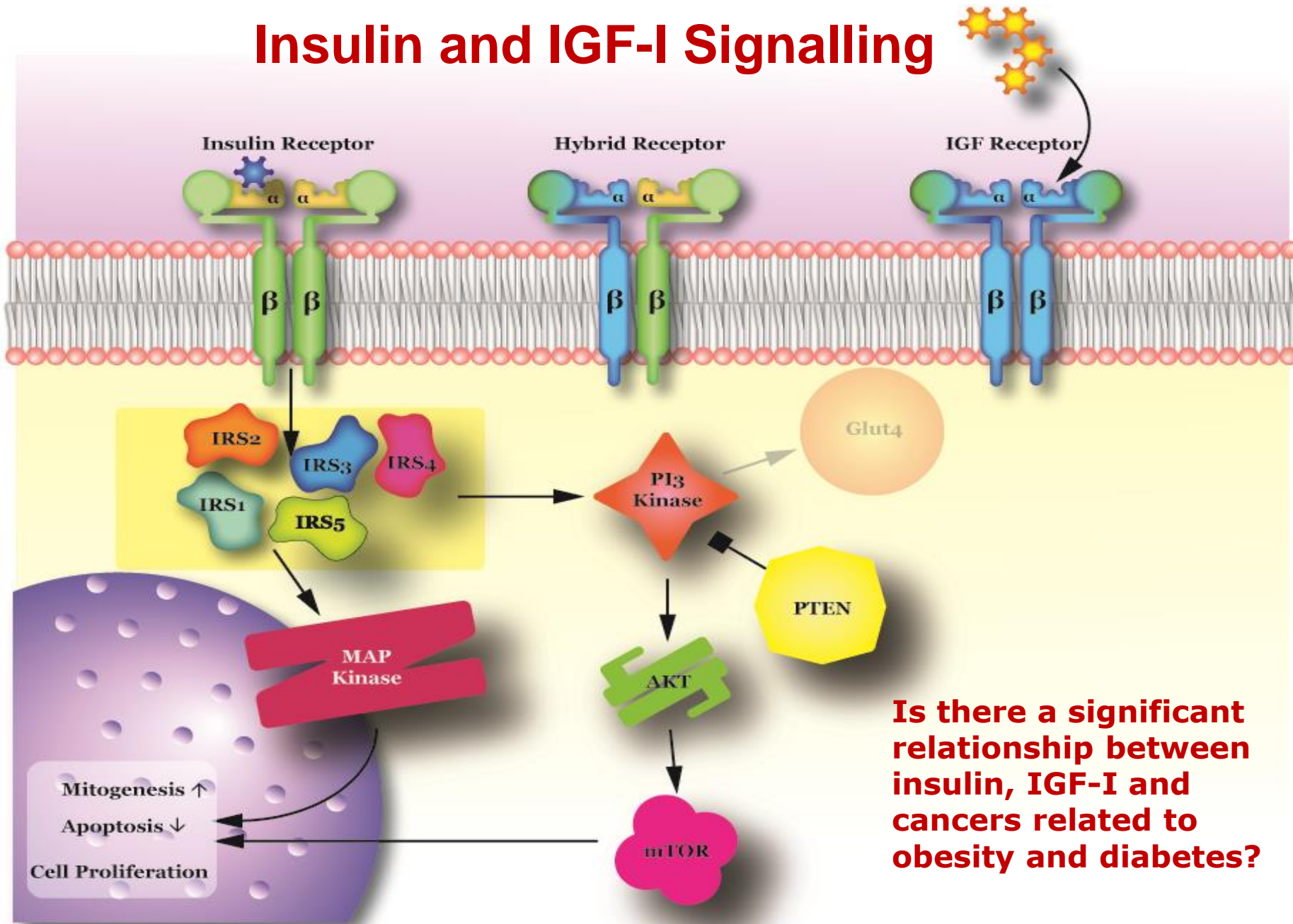
Crown copyright and database right 2010



Diabetes is expensive

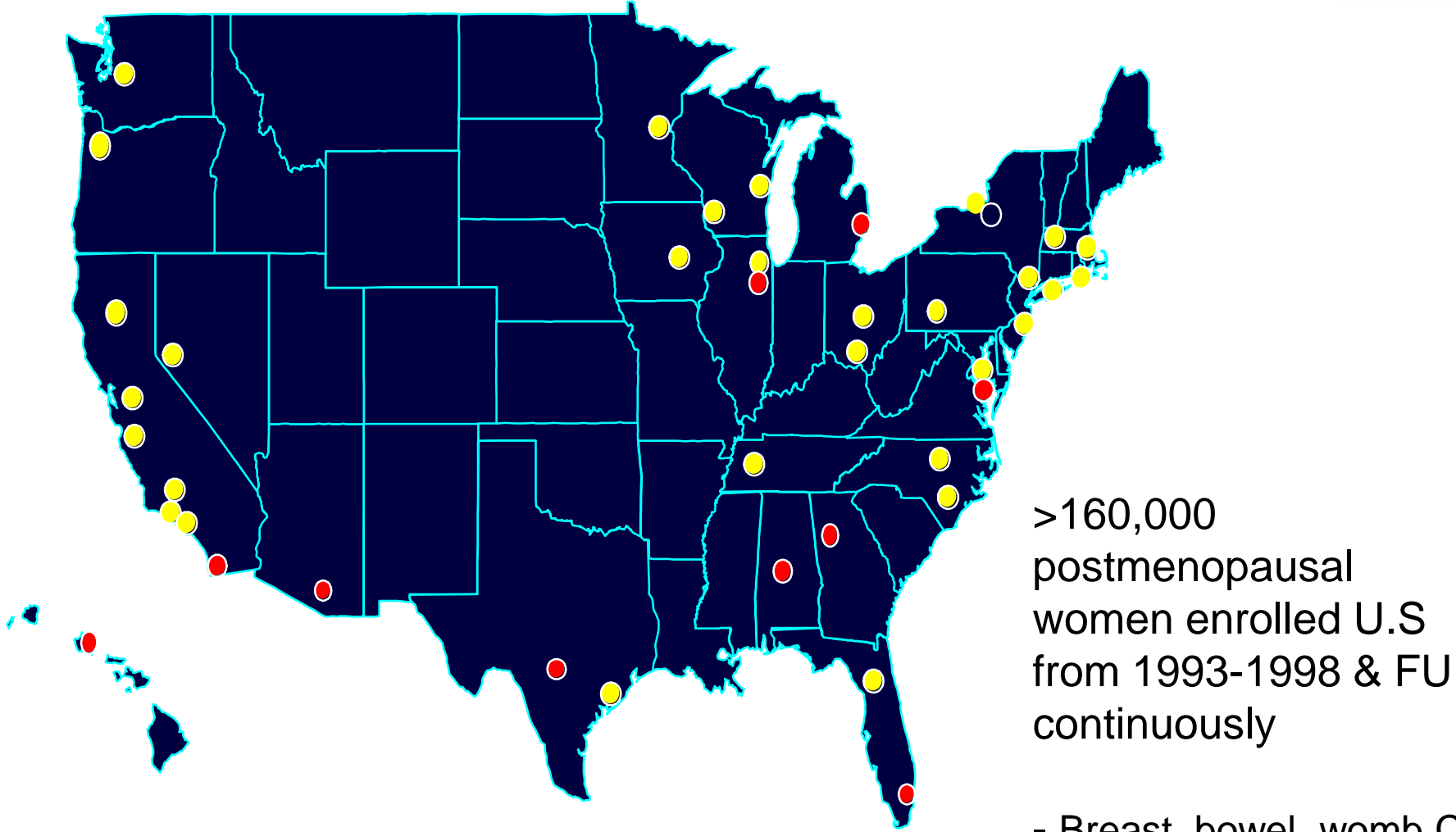
The rapidly growing scale of the condition is alarming, as are the associated care and treatment costs. NHS spending on diabetes was almost £10 billion in 2011, or £1 million per hour, which is 10 per cent of the NHS budget. 80 per cent of NHS spending on diabetes goes into managing avoidable complications. People with diabetes account for around 19 per cent of hospital inpatients at any one time, and have a three day longer stay on average than people without diabetes. Most of Type 2 diabetes costs are due to hospitalisation¹⁴.

Insulin and IGF-I Signalling

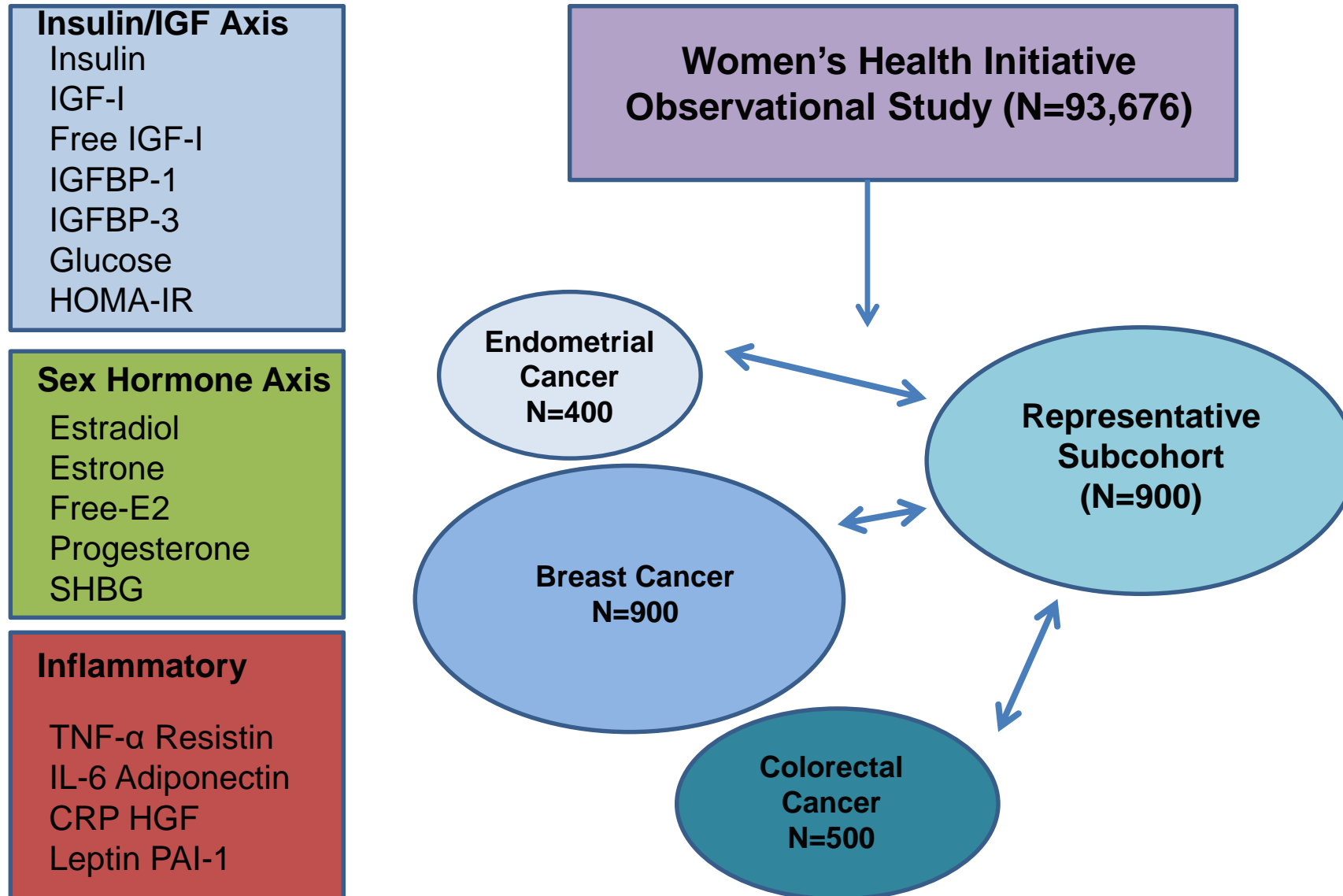


Is there a significant relationship between insulin, IGF-I and cancers related to obesity and diabetes?

The Women's Health Initiative



Obesity Pathways & Cancers in Postmenopausal Women



Metabolic Subtypes in Obesity

Metabolically Healthy Obese

vs

Metabolically Abnormal Obese



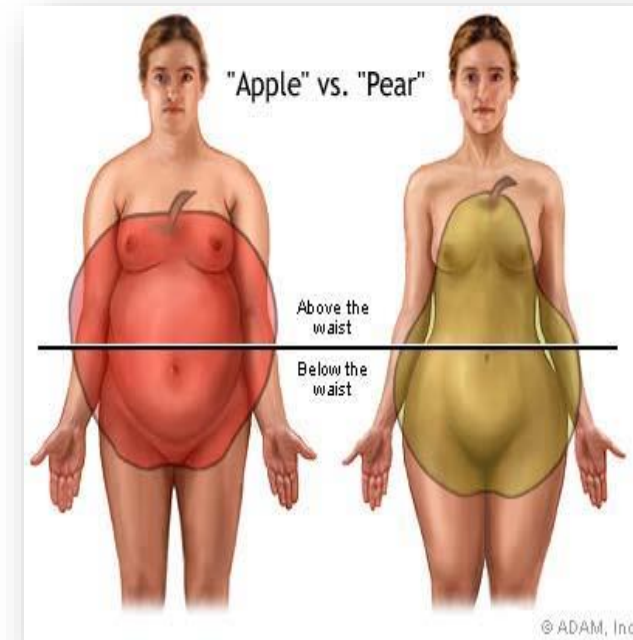
Adipose-tissue metabolism?

Muscle characteristics?

Gene expression?

High fat mass
High insulin sensitivity
Low ectopic fat
Low triglycerides
Low inflammation
High HDL-cholesterol
Low intima-media thickness
High adiponectin
Low ApoB

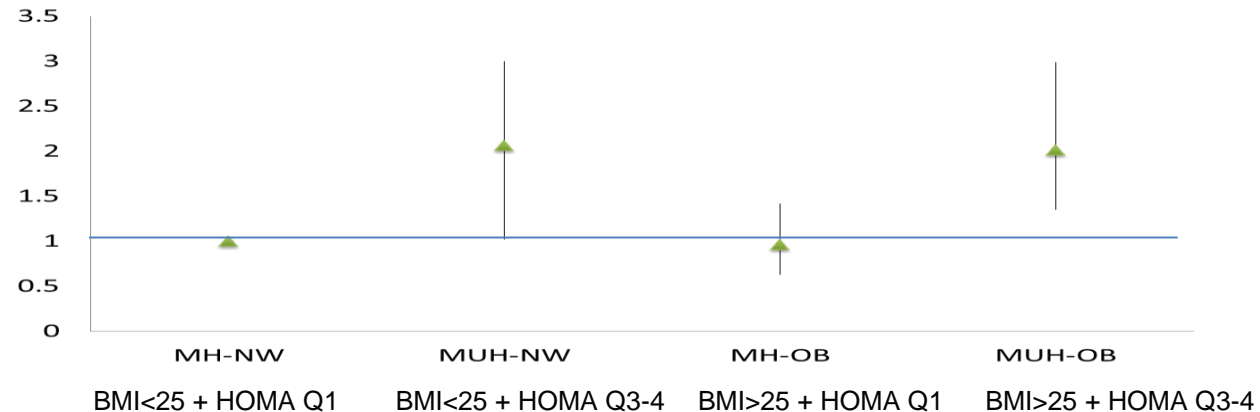
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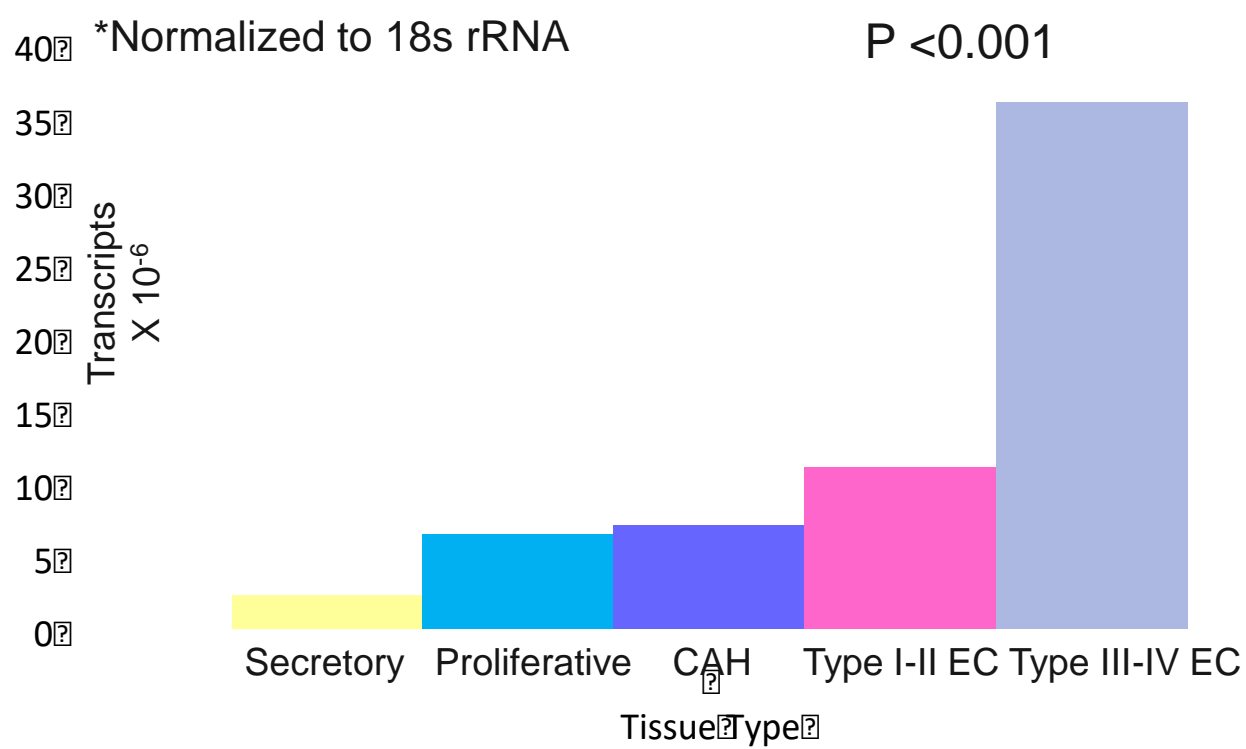


Not all obesity is the same - is this relevant for cancer?

Women's Health Initiative (500 cases, 2,380 controls)

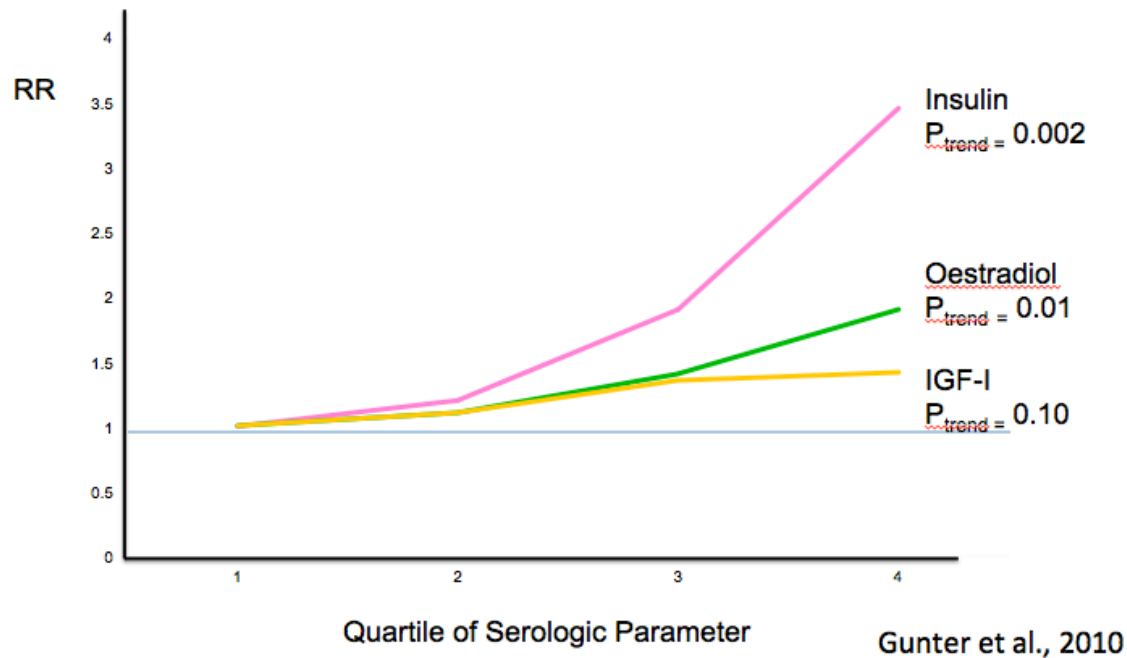
Metabolically-defined
Obesity Subtypes &
Breast Cancer Risk





Insulin Receptor
Expression in
Endometrial Tissues

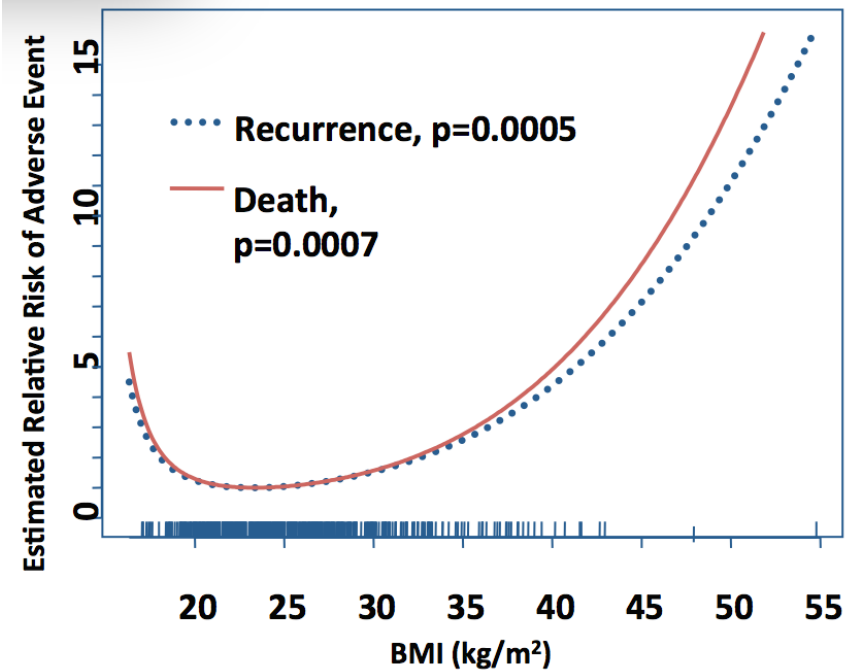
Similar in colorectal
& breast...



Insulin, IGF-I,
Oestradiol &
Endometrial Cancer
Risk in the Women's
Health Initiative

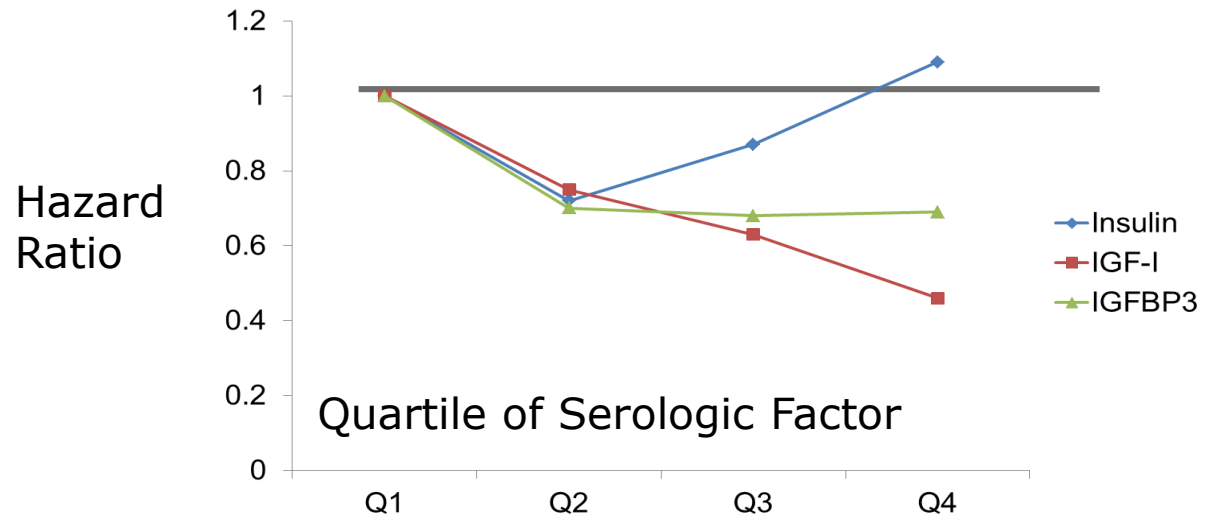
Obesity Risk of recurrence & survival

Gunter et al., 2014



Insulin, IGF-I, IGFBP-3 & Progression Free Survival in GOG-0210 (n = 800 patients, n = 310 recurrences to date)

Multivariate model
includes age, stage,
grade, BMI



Important Unanswered Questions

What are the precise metabolic and biochemical pathways **that increase risk** of developing endometrial and ovarian cancer?

- Enhance understanding of aetiology and biological mechanism
- Identify biomarkers of susceptibility in healthy women
 - Risk Prediction
 - Risk Stratification, surveillance
 - Interventions?

Do metabolic factors play a role in **recurrence** of endometrial & ovarian cancer and can they be used as **prognostic tools**?

Biobank

EPIC

Bariatric Sx

Cross-sectional...

Longitudinal...

Intervention...

Serum markers

mRNA

RPPA

Metabonomics ...

Biochemical entities
known *a priori*
(targeted)

Unknown
(untargeted)



ovarian
cancer **action**

THE UNIVERSITY OF TEXAS

MD Anderson
Cancer Center

Making Cancer History®

EPIC study

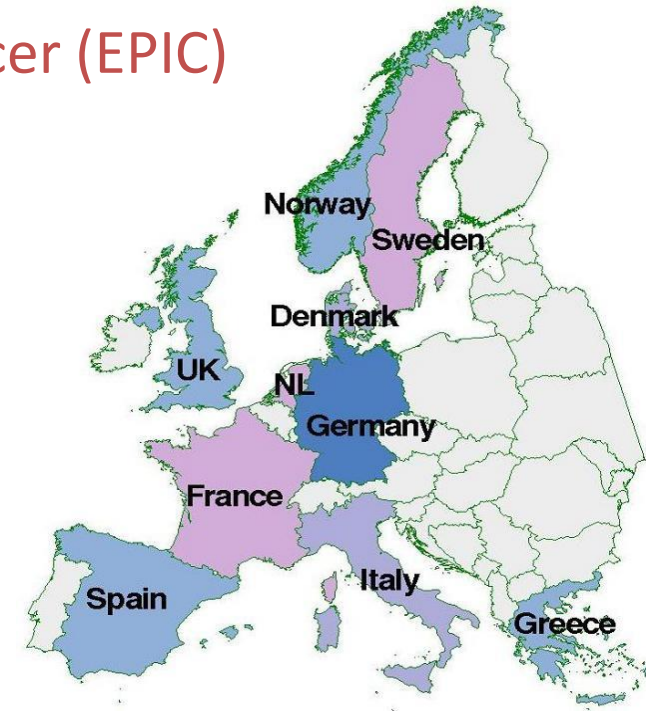
ENITEC

European Network Individualized Treatment in Endometrial Cancer

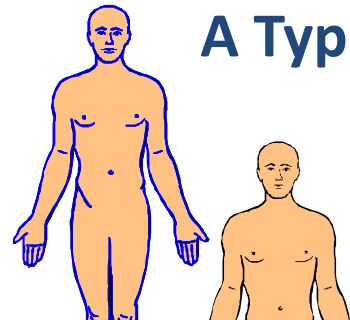
genesis
research
trust
helping life begin

European Prospective Investigation into Cancer (EPIC)

- N = ~520,000 recruited across 23 centres
- On-going follow-up since 1992
- ~ 30,000 cancer cases & ~20,000 deaths
- High quality anthropometric, medical & lifestyle data
- Serum, tissue blocks



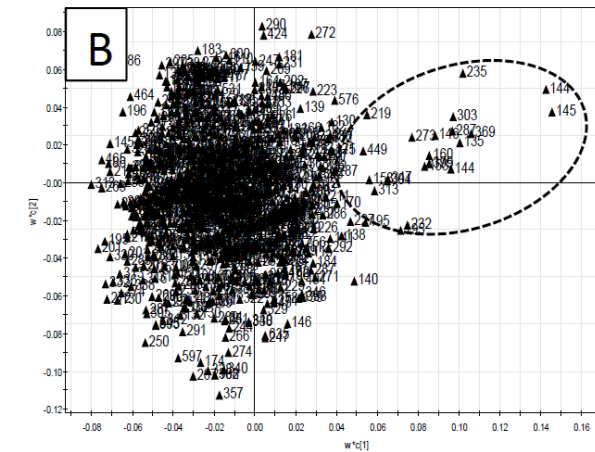
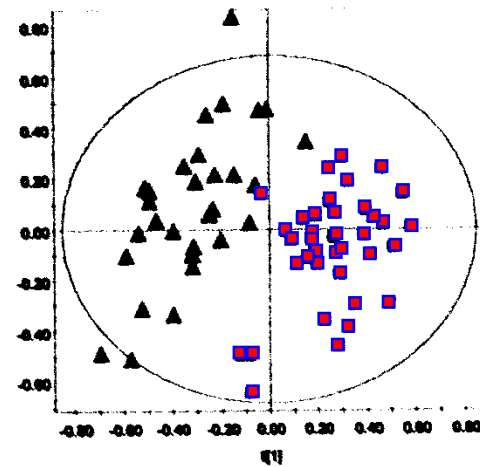
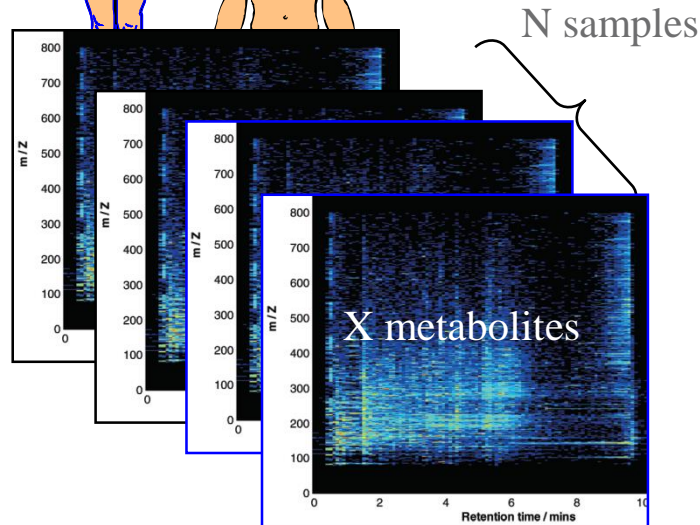
A Typical Metabolomic Experiment



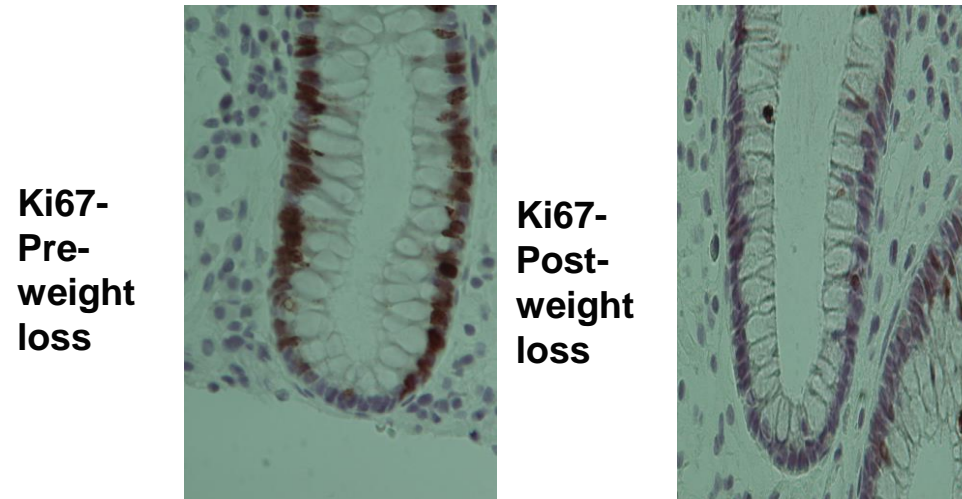
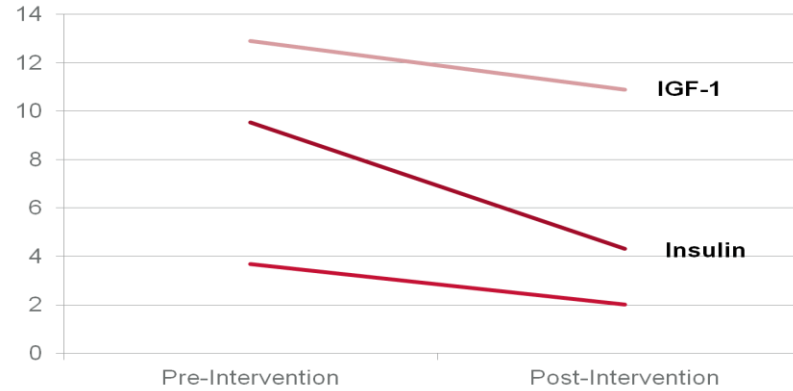
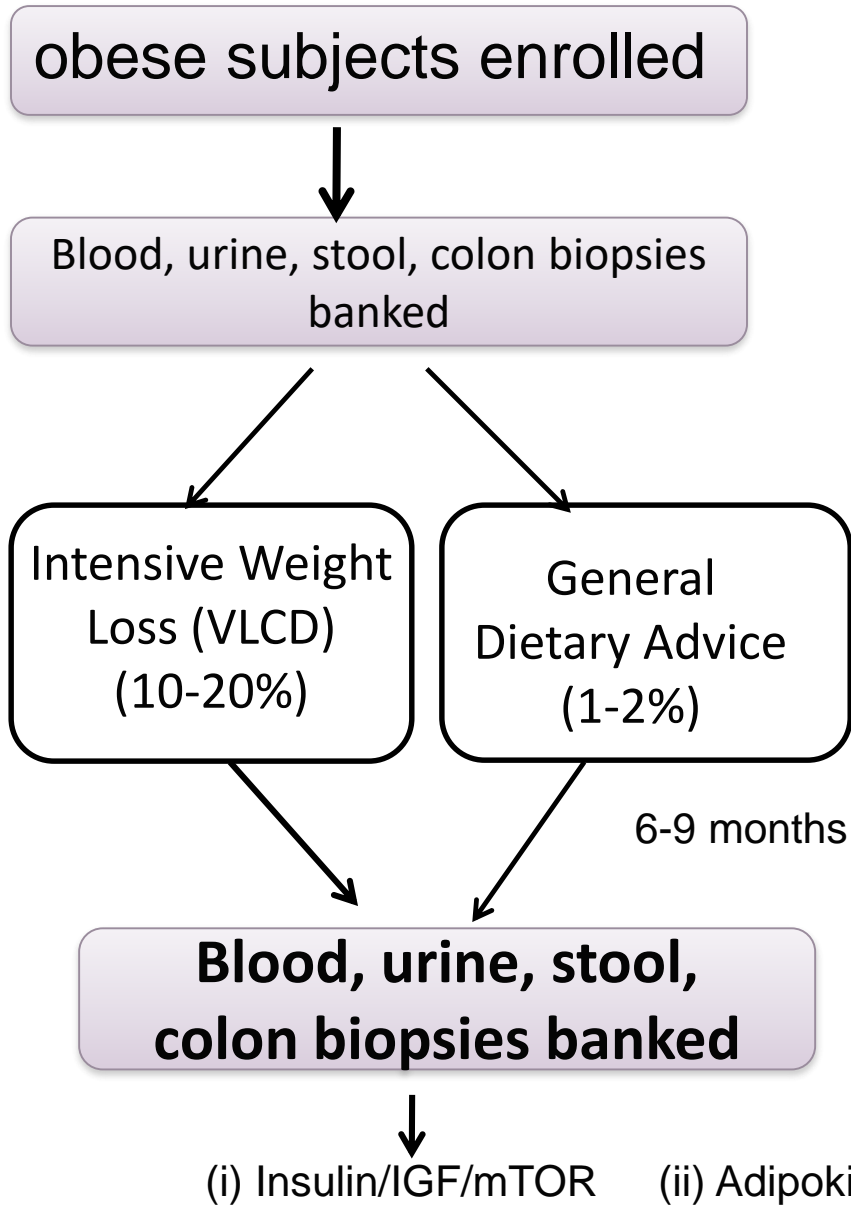
Data acquisition

Multivariate statistics

Biomarker identification

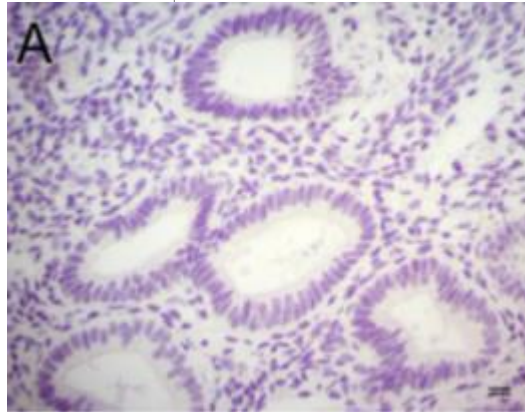
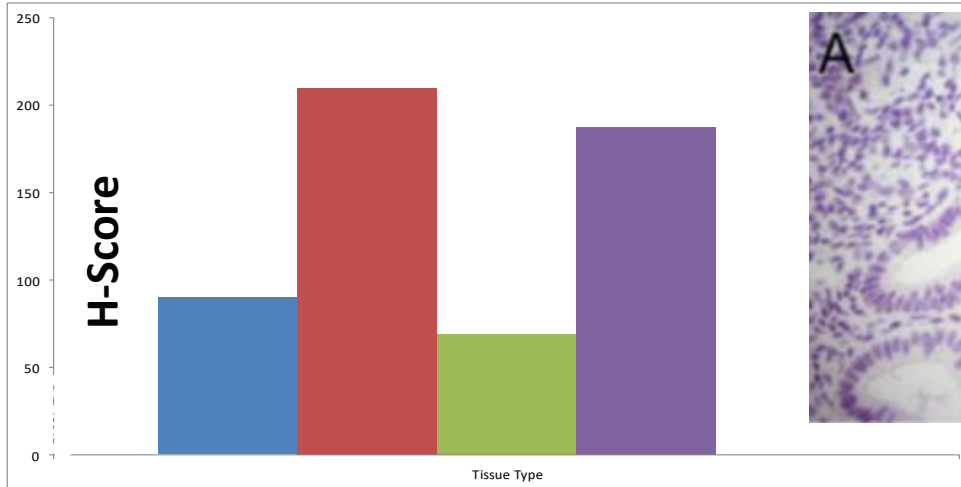


Weight Loss & Colorectal Ca: *INTERCEPT*

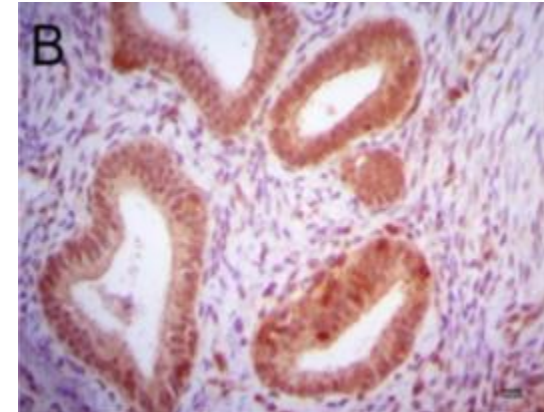


OBITEC: Bariatric surgery & Endometrial Ca

Phosphorylated Insulin/IGF Receptor Expression in Postmenopausal Endometrium



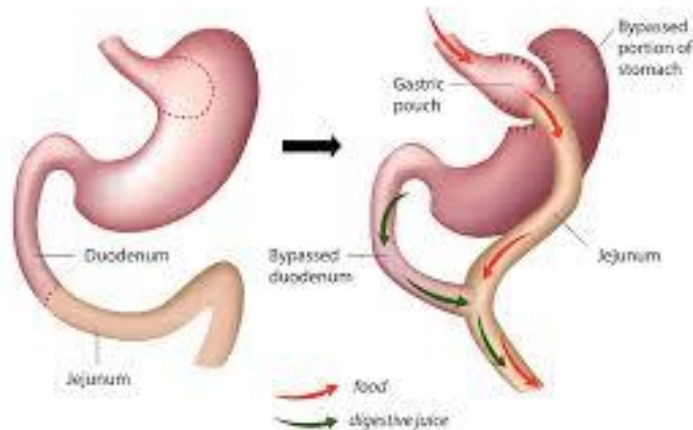
Non-diabetic



Diabetic

Normoglycaemic T2D Normal Insulin Hyperinsulinemia

Roux-en-Y Gastric Bypass (RNY)



**Diabetes remission at 2 years:
95% in biliopancreatic-diversion group**

Mingrone NEJM 2012

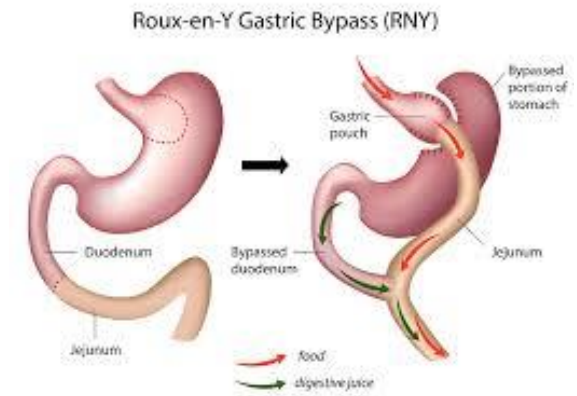
Population screening & Preventive Measures

Screening

- No certain method for screening population at risk
- Outpatient endometrial sampling & TVS: may be used in combination, but invasive ?value
- Tumours usually present early with symptoms...

Preventative measures

- Weight loss: Life Style changes(diet & exercise)
 - Pharmaco-therapy
 - Bariatric surgeries
- Chemo-prophylaxis : *COCP
 - *Oral progesterone
 - *Injectable progesterone
 - *Mirena IUS (FEMME trial – no update)
 - *Metformin – mTOR inhibitors



Schmidt 2015:

Meta-analysis of 33 studies on **physical activity**

RR=0.80, 0.75–0.85

Bandera 2007:

Meta-analysis of 17 studies high vs. low categories of **vegetable intake** reported

RR=0.71, 0.55–0.91

Mulholland 2008:

Meta-analysis of 5 studies of **high GL consumers**

RR=1.20, 1.06 – 1.37)

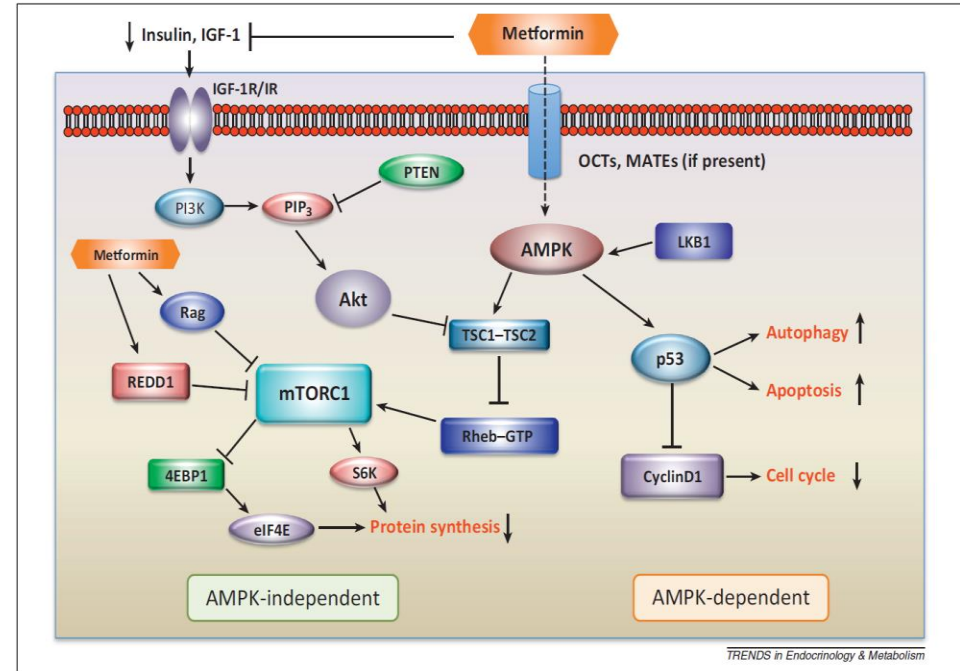
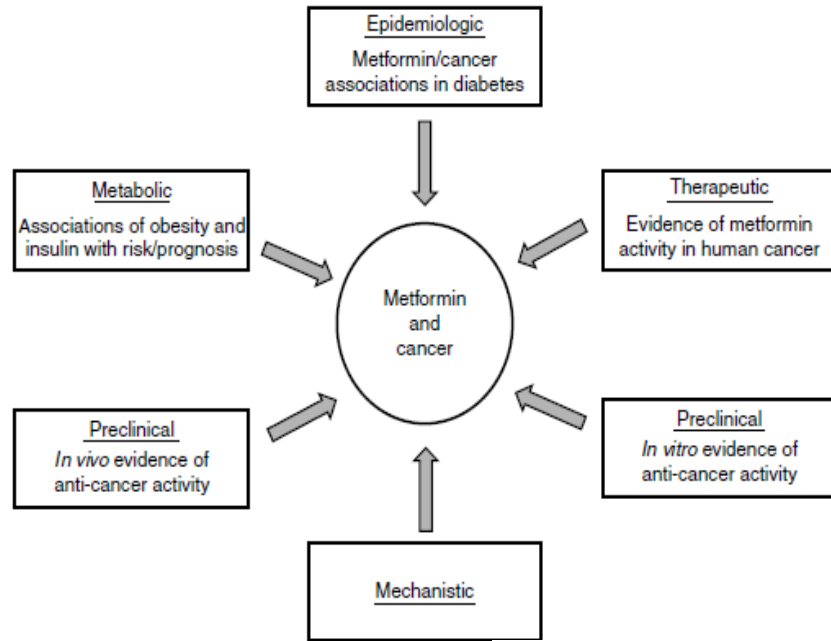
Upala 2015:

meta-analysis of 6 studies on the effect of **bariatric surgery**

RR=0.40 (0.20-0.79)

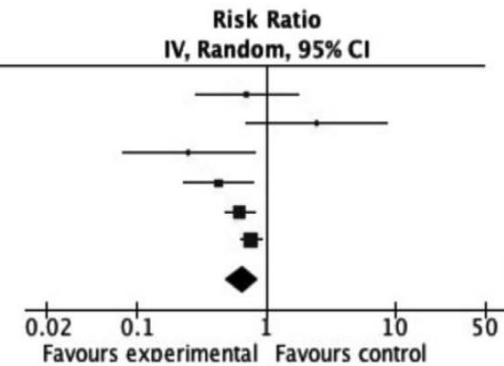


Metformin...against cancer



Mortality

| Study | Weight | Risk Ratio IV, Random, 95% CI |
|---|---------------|----------------------------------|
| UKPDS34 (met), 1998* | 8.4% | |
| UKPDS34 (SU-based), 1998* | 4.8% | |
| Mellbin et al, 2011 | 5.5% | |
| Landman et al, 2010 | 14.4% | |
| Libby et al, 2009 | 31.6% | |
| Bowker et al, 2006 | 35.3% | |
| Total (95% CI) | 100.0% | 0.66 [0.49, 0.88] |
| Heterogeneity: Tau ² = 0.05; Chi ² = 10.83, df = 5 (P = 0.05); I ² = 54% | | |
| Test for overall effect: Z = 2.81 (P = 0.005) | | |



Rizos, Eur J Pharmacology 2013

Noto et al, PLoS One, 2012

Dowling et al, Journal of Molecular Endocrinology (2012)

Summary

Probing Further into the Obesity-Cancer Relation...

- **Obesity & diabetes** are significant, positive risk factor for a number of cancers (e.g. bowel, **womb**, kidney, postmenopausal breast, liver, oesophageal) many of which are becoming increasingly more common
 - Many **unanswered questions** around causality, mechanism and heterogeneity across cancer subtypes
- Growing evidence to implicate **hyperinsulinemia, oestrogens and inflammatory factors** in the biological mechanism underlying the association between obesity and some malignancies
- Future and current studies
 - applying **new molecular technique & more advanced 'omics'** technologies to understand the obesity cancer relationship
 - Metabolomics – Epigenetics - Genomics (GxE; Mendelian Randomization)
 - **Intervention studies with molecular outcomes**
 - Weight loss trial and effects on endometrial tissue biology
- Impact of obesity & metabolic pathways on **prognosis & survival** among cancer patients?
 - Insulin signaling pathway and high stage endometrial cancer recurrence
- **Anti-diabetes drugs and cancer** (e.g. Metformin)-intensely studied area at present



Thank you...

A Tailored Approach

Eligibility:

- *Complex Endometrial Hyperplasia with atypia*
OR
- *Grade 1 EAC –*
- *avoid enrolling patients with advanced disease who need expedited surgery*
- Patients at **high surgical risks** or **wish to retain fertility**
- BMI > 30 kg/m²
- CT scan: absence of extrauterine disease
- Myometrial invasion <50% (MRI)
- Serum CA125 ≤30 U/mL



AIMS

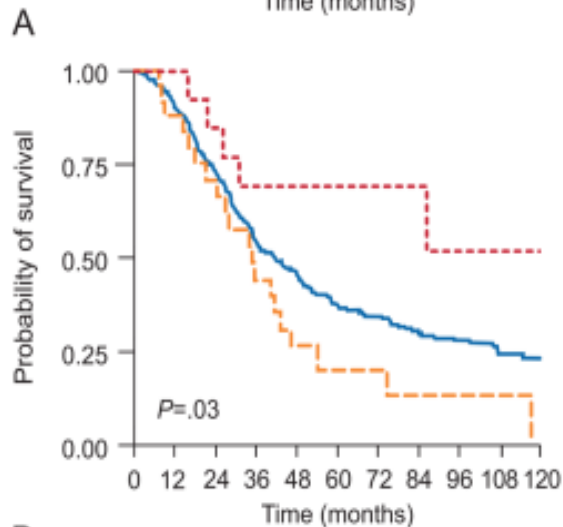
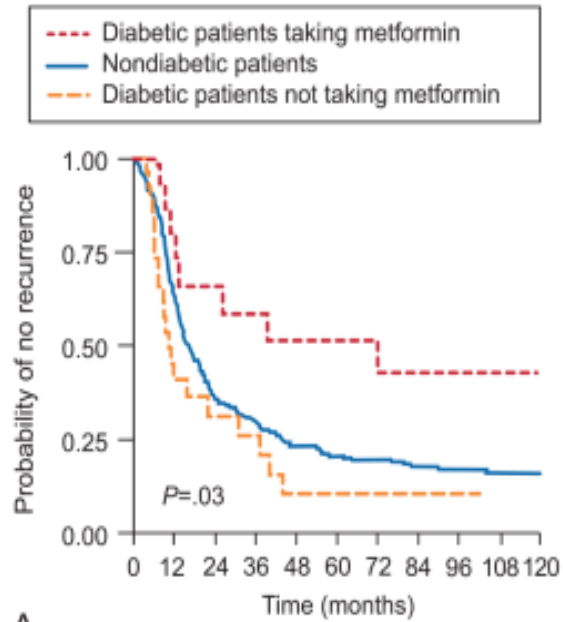
- **Primary aim:** Efficacy of Mirena \pm metformin/weight loss to achieve a pathological complete response at 6 months from randomisation
 - Hypothesis: will improve response rate from 45% to 60%
- **Secondary aims:** Predict the response to Mirena \pm metformin/weight loss through blood and tissue molecular biomarkers

UNANSWERED QUESTIONS

- HOW LONG IS SAFE?
- WHICH IS BEST PROGESTERONE?
- WHAT IS THE BEST DOSE?
- WHAT IS OPTIMAL SURVEILLANCE

- My answers!

Metformin and Ovarian cancer



Lengyel, Obstet Gynecol. 2012

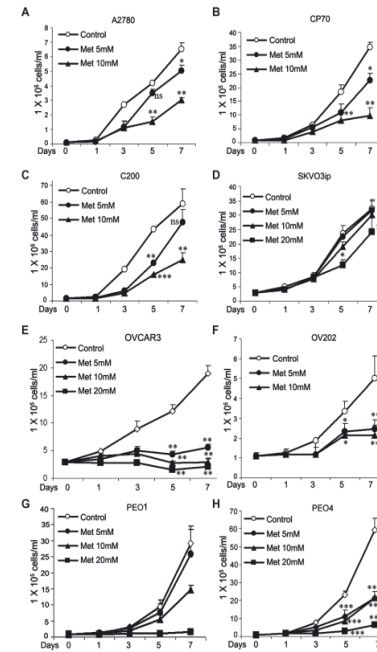
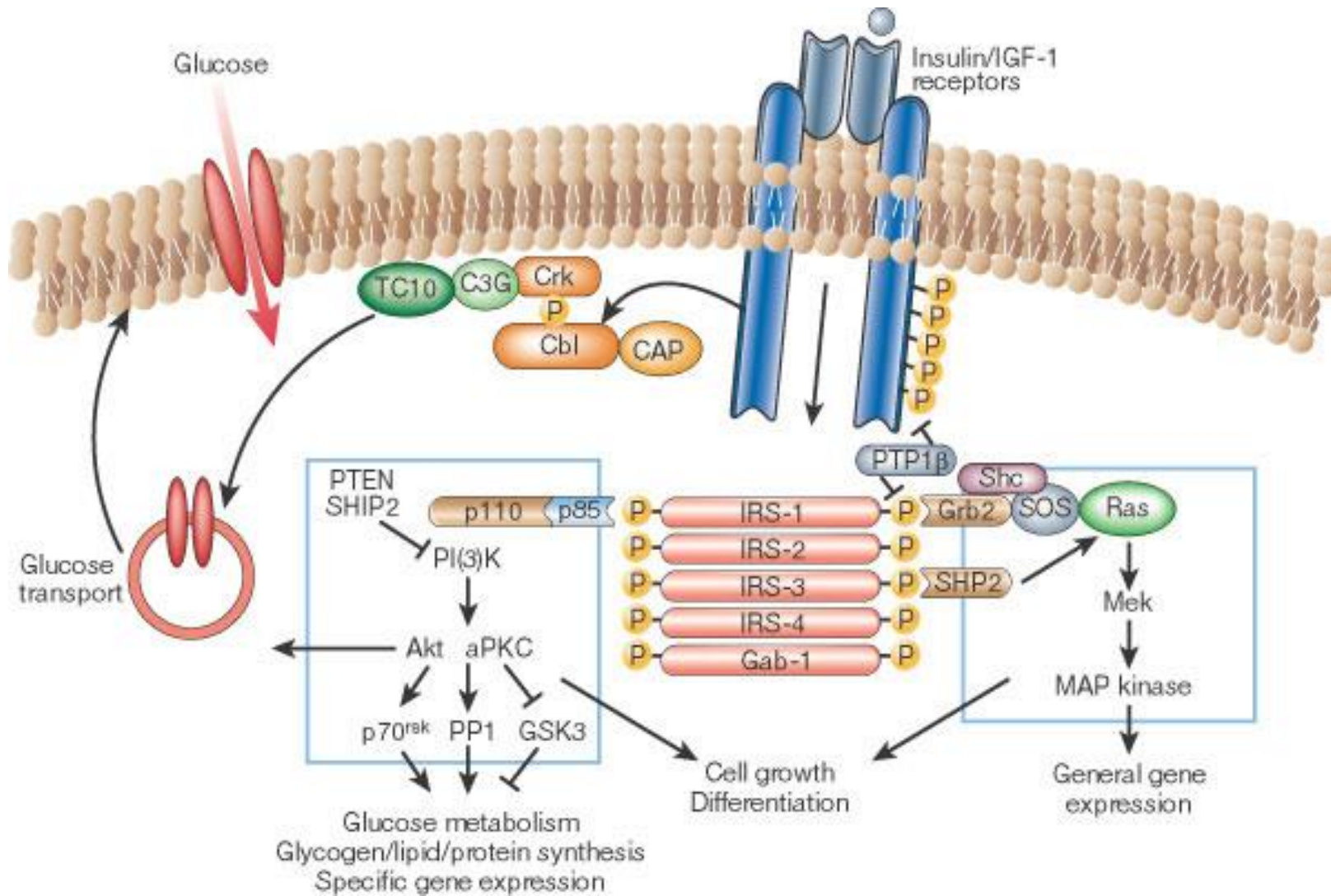


Fig. 1 Metformin inhibits proliferation of ovarian cancer cell lines. Various ovarian cell lines (A2780, CP70, C200, OV202, SKOV3ip, OVCAR3, PEO1 and PEO4) were treated with metformin with indicated doses. Cells were counted from days 0 to 7, on alternate days by trypan blue staining. The data represent three separate experiments done in triplicates. ** $P < 0.01$; *** $P < 0.001$; NS, not significant, compared to untreated cells at respective time-point.

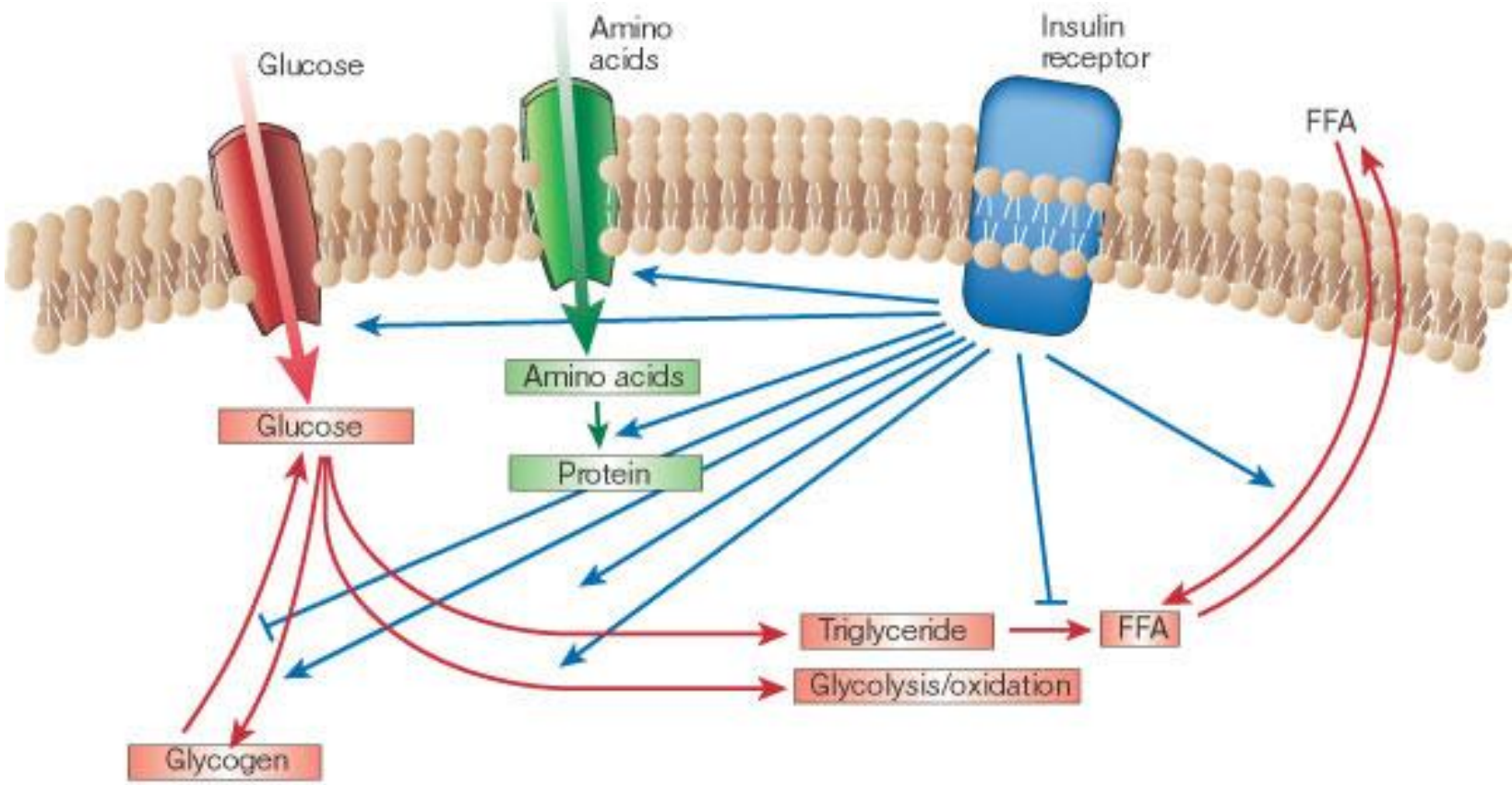
Rattan et al, J Cell Mol Med 2009

Metformin suppresses metastasis in xenograft models (Sridhar/Buckanovitch)

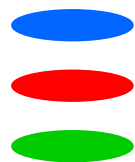
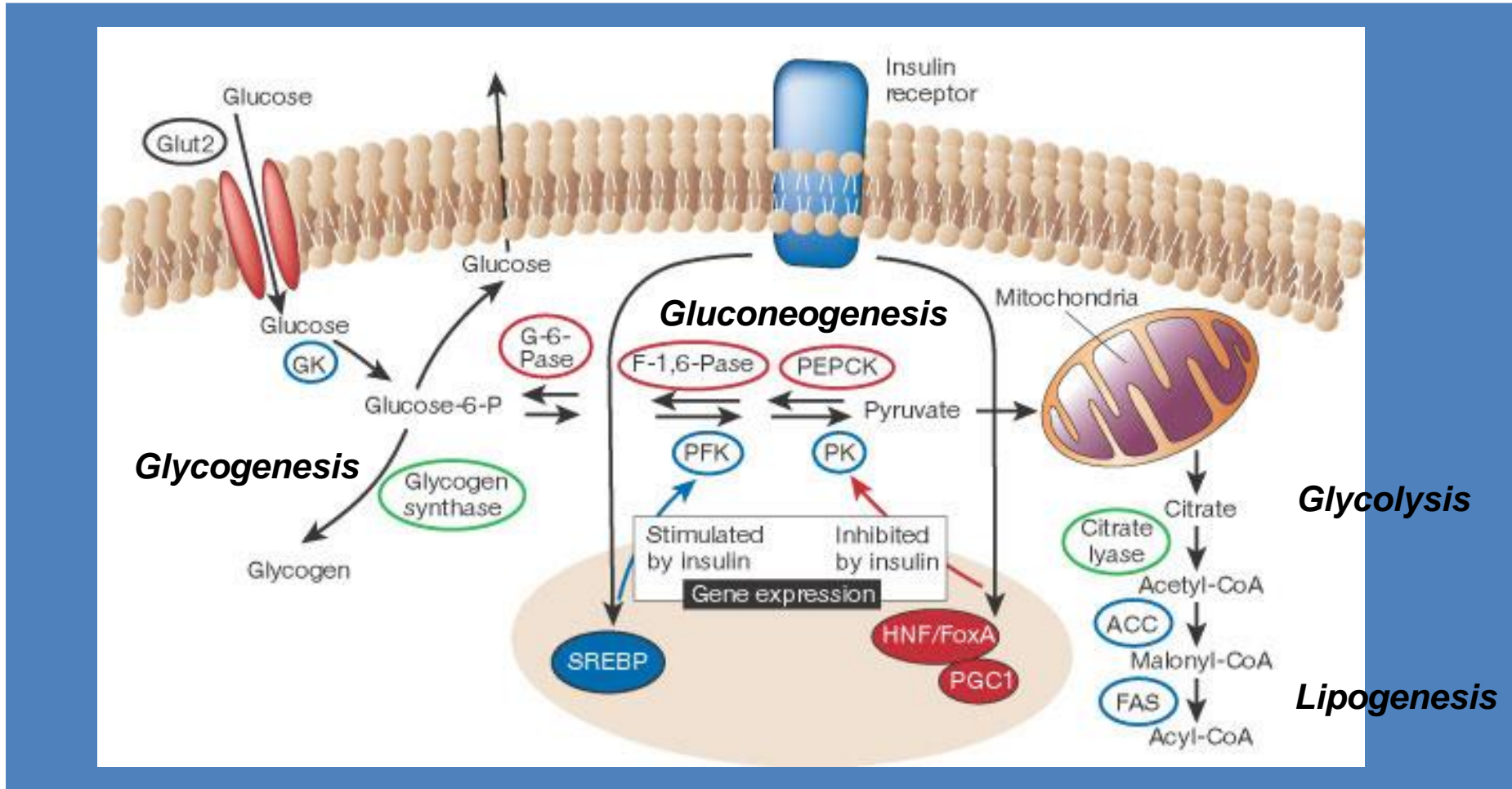
Insulin signalling



The metabolic effects of insulin



Regulation of metabolism by insulin



+ve regulation

-ve regulation

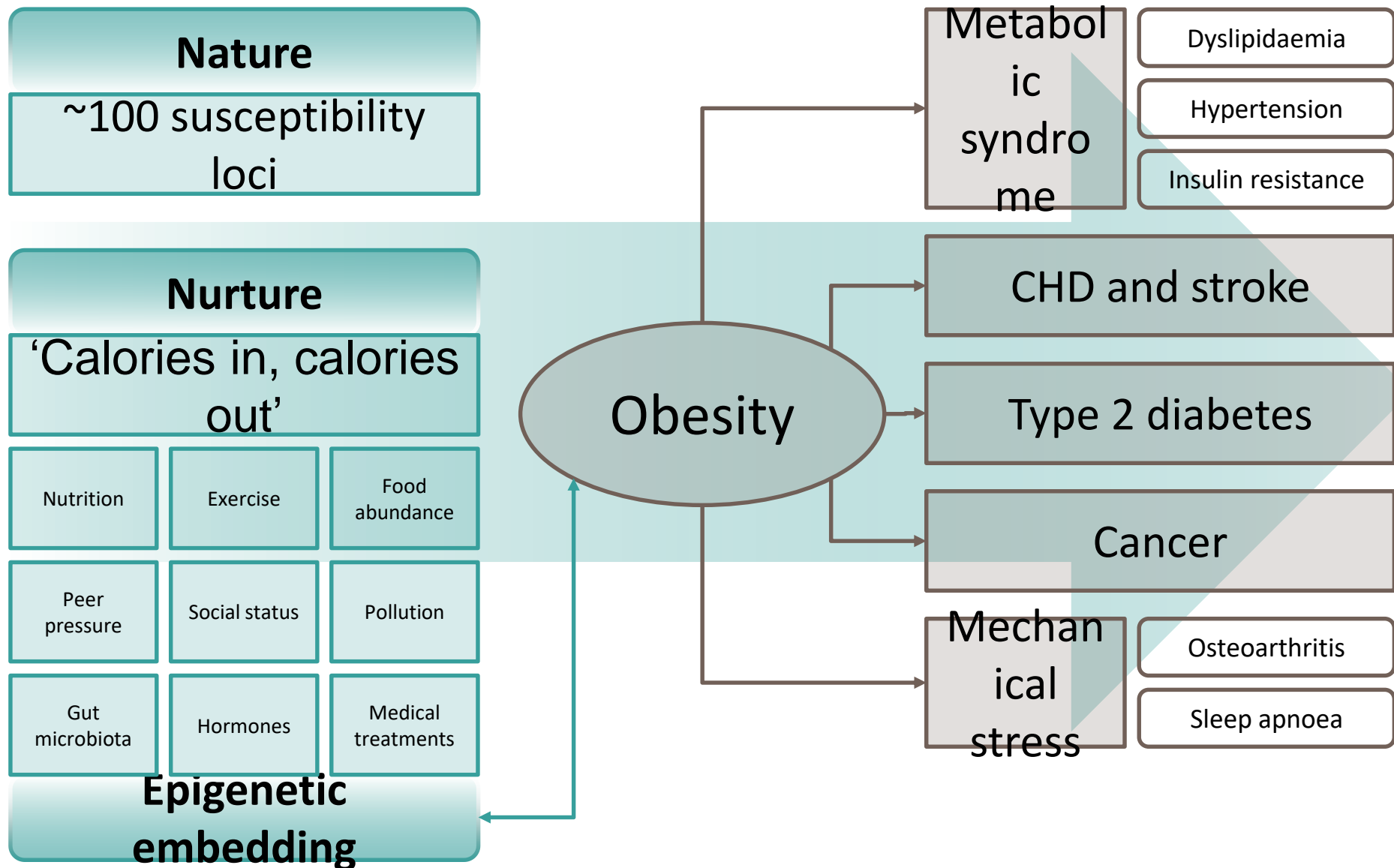
+ve regulation by phosphorylation

Study Design

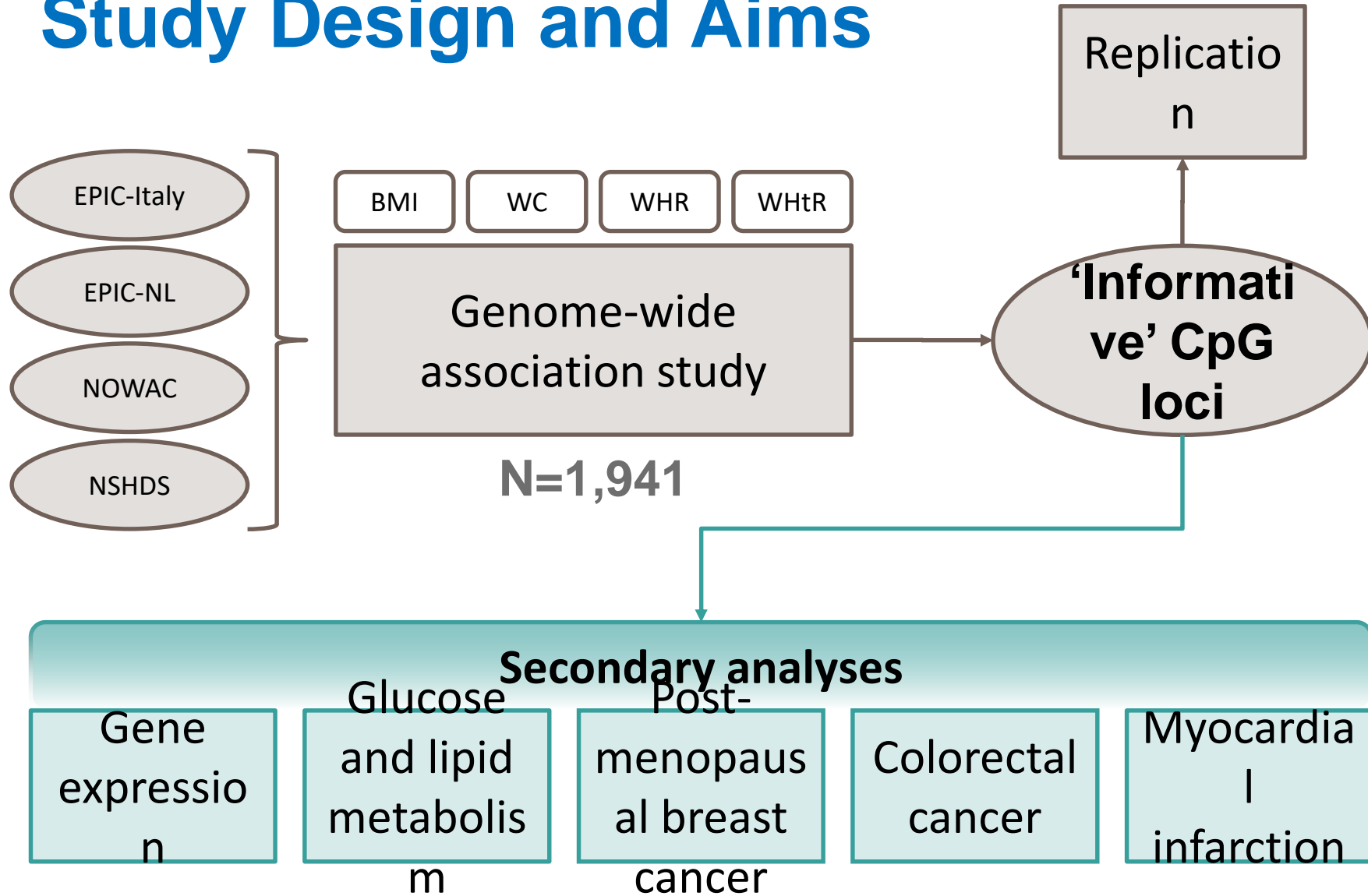
- Blood Samples
 - Serum
 - Plasma
 - DNA
- Diet
- Questionnaire

- Well-characterised case-control set
 - Genomics
 - Hyperinsulin

Epigenetic studies of Obesity and Cancer

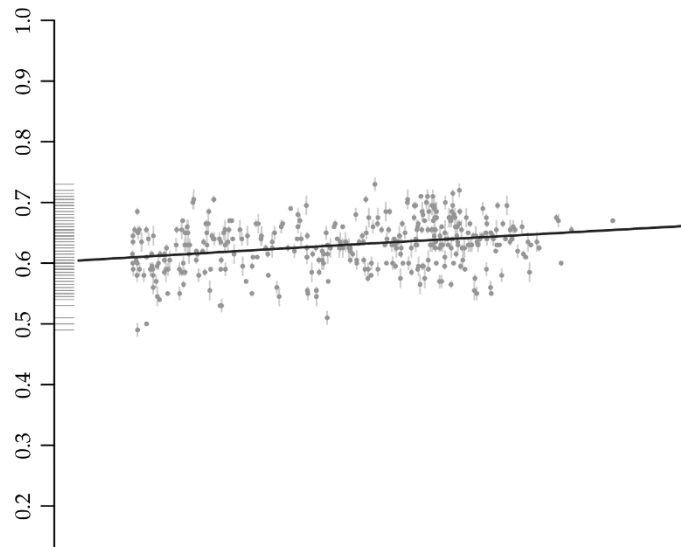
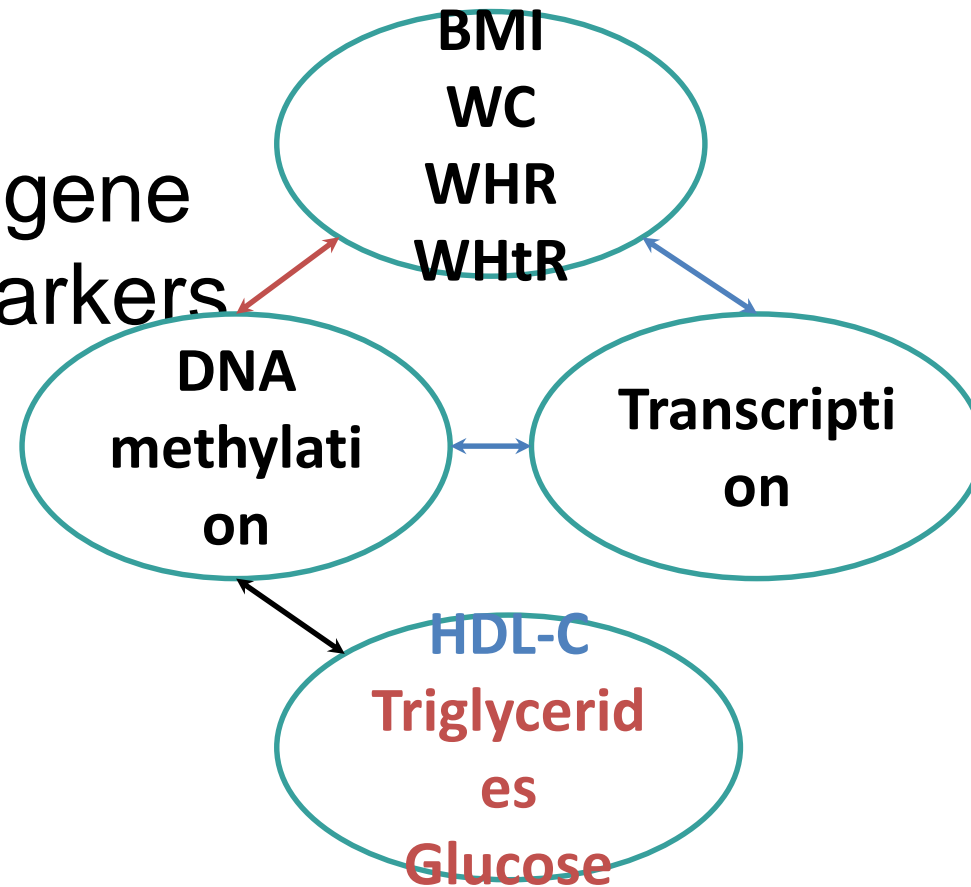


Study Design and Aims



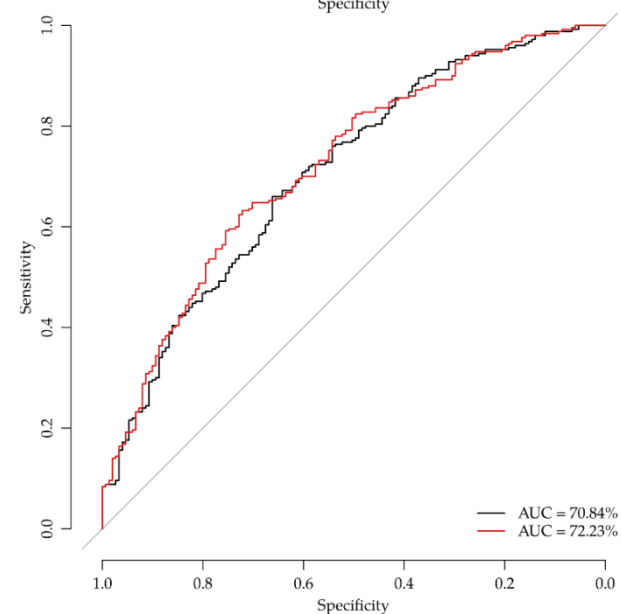
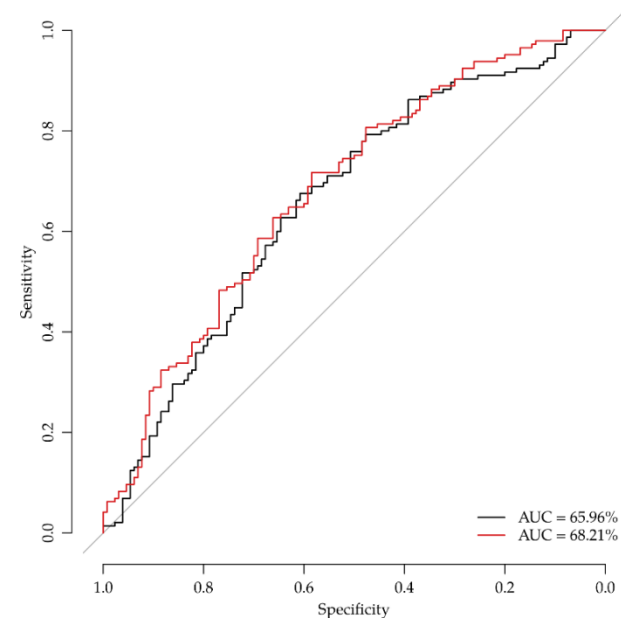
Results

- 40 'informative' CpG loci
- **ABCG1** associated with all four measures
- Also associated with gene expression and biomarkers of glucose and lipid metabolism



Results

- **40 ‘informative’ CpG loci**
- ***ABCG1*** associated with all four measures
- Also associated with gene expression and biomarkers of glucose and lipid metabolism
- Three CpGs associated with disease endpoints
 - Two with incident CRC (IL2RB, FGF18), one with incident BC (KIFC3)
 - ~2% increase in AUC beyond traditional risk factors



Pre-malignant conditions

- Endometrial hyperplasia +/- cellular atypia architecturally may be simple or complex
- Risk factors for these similar to EC
- Risk of progressing to endometrial cancer:
Simple 1% With atypia 8%
Complex 3% With atypia 30%
Risk even higher if patient is postmenopausal
- Management
- depends on age of patient & histological pattern of the hyperplasia
- Treat with progestogens & FU endometrial sampling
- Older or postmenopausal patients treat with hysterectomy specially if histology is high risk