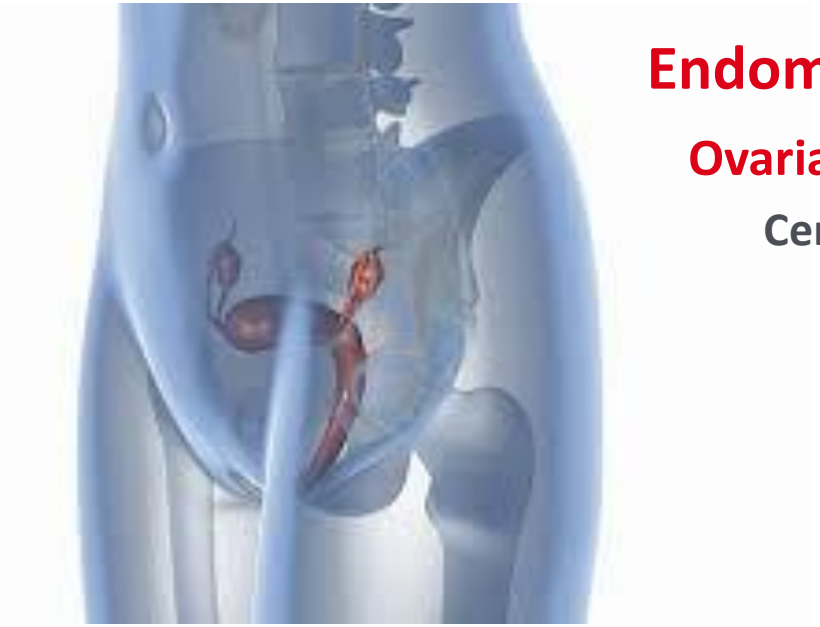
Imperial College London

Obesity & Endometrial Cancer

Maria Kyrgiou

Senior Lecturer – Consultant Gynaecologic Oncologist

Gynaecological Cancers



Endometrial Cancer

Ovarian Cancer

Cervical Cancer

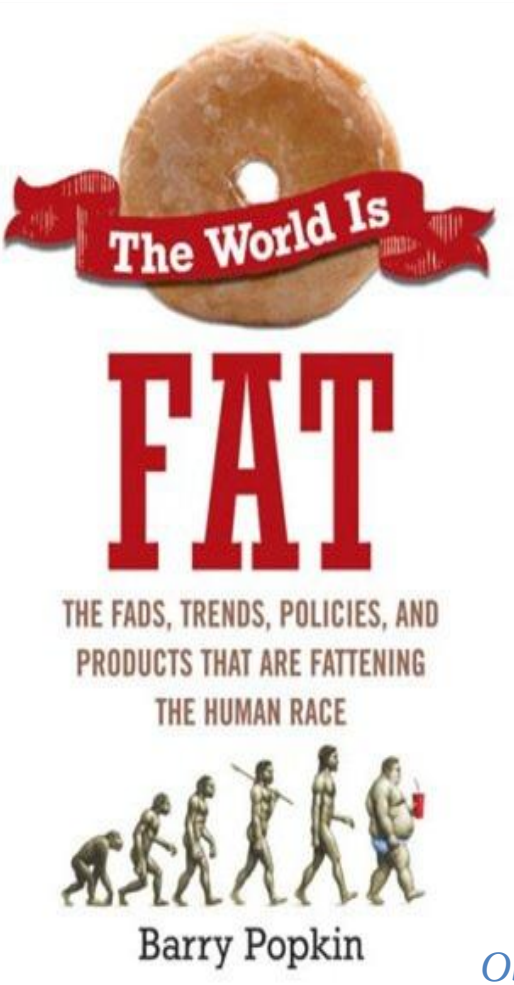
Vaginal Cancer

Vulval Cancer

Breast Cancer

Colorectal Cancer etc.

Obesity: a Global Epidemic…



- 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]

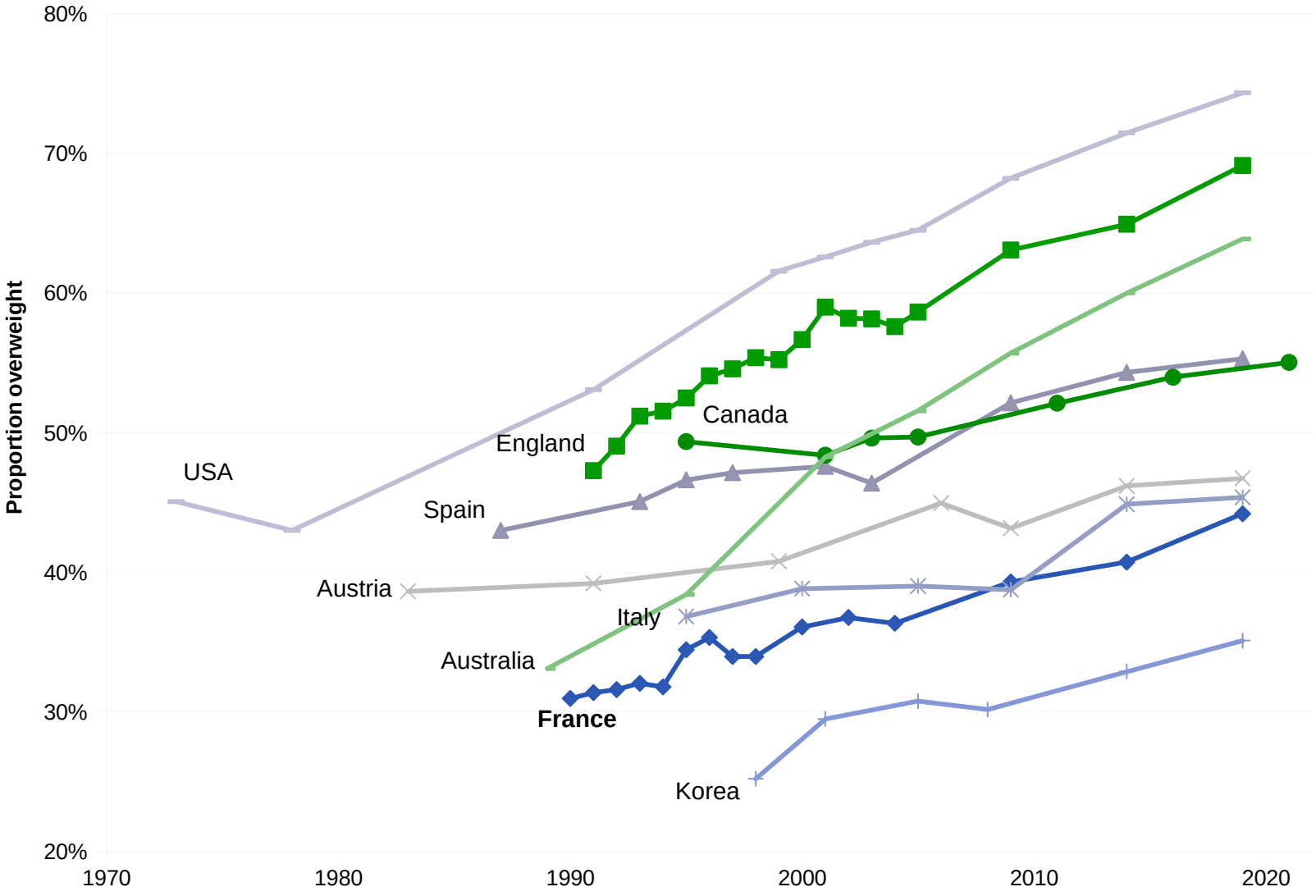
- USA: one-third of adults (33.8%) obese

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.

Trends in Overweight and Obesity



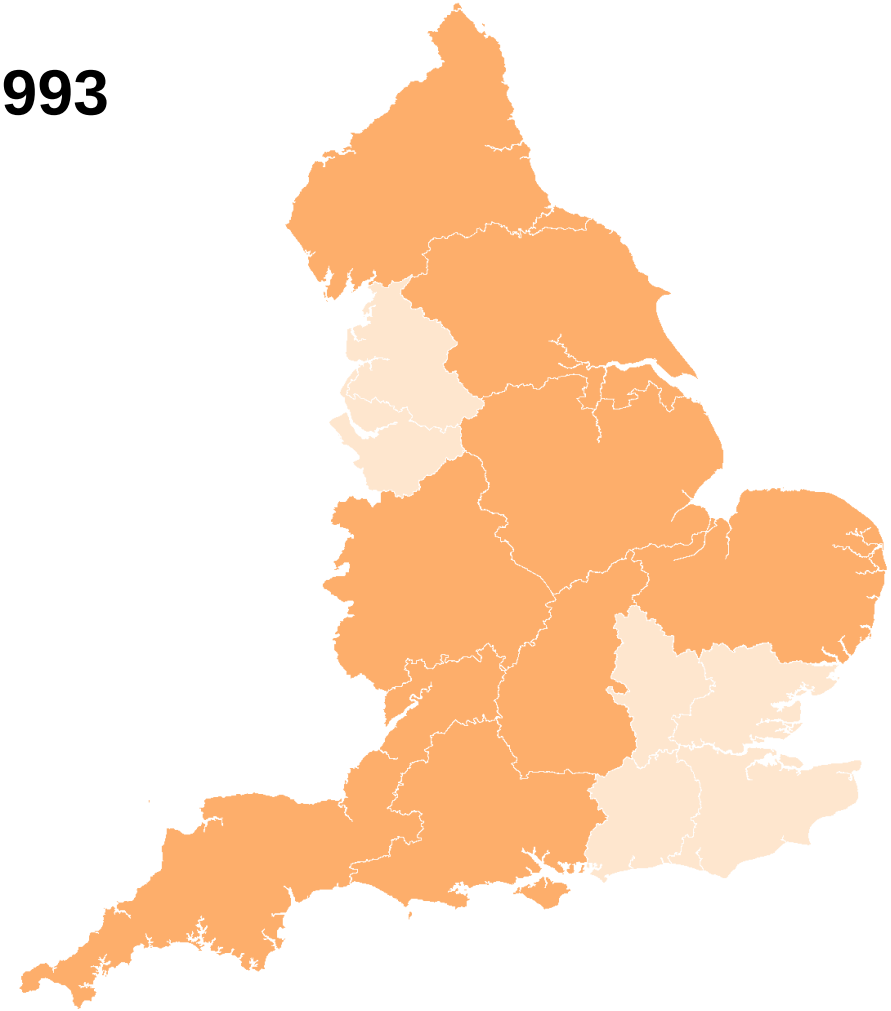
WHO, 2012

Public Health England

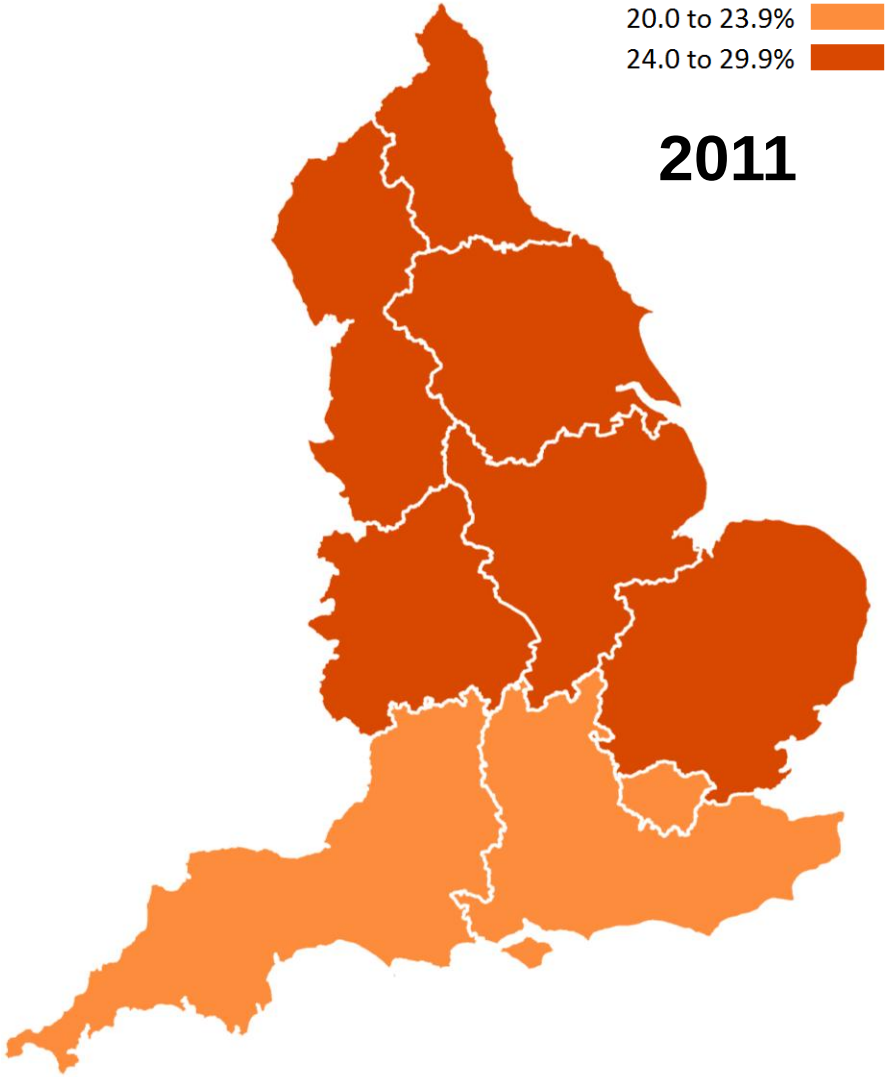
Prevalence of obesity in adults (aged 16+)
Source: Health Survey for England

Under 16%
16.0 to 19.9%
20.0 to 23.9%
24.0 to 29.9%

1993



2011



Females

Adult obesity: BMI ≥ 30kg/m^2

© Crown copyright and database rights 2013 Ordnance Survey 100016969

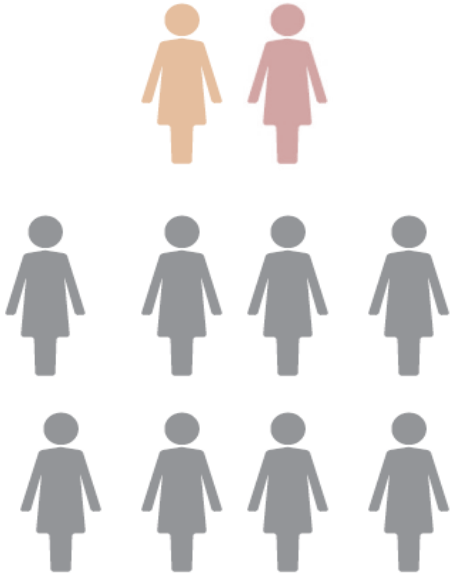
Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants

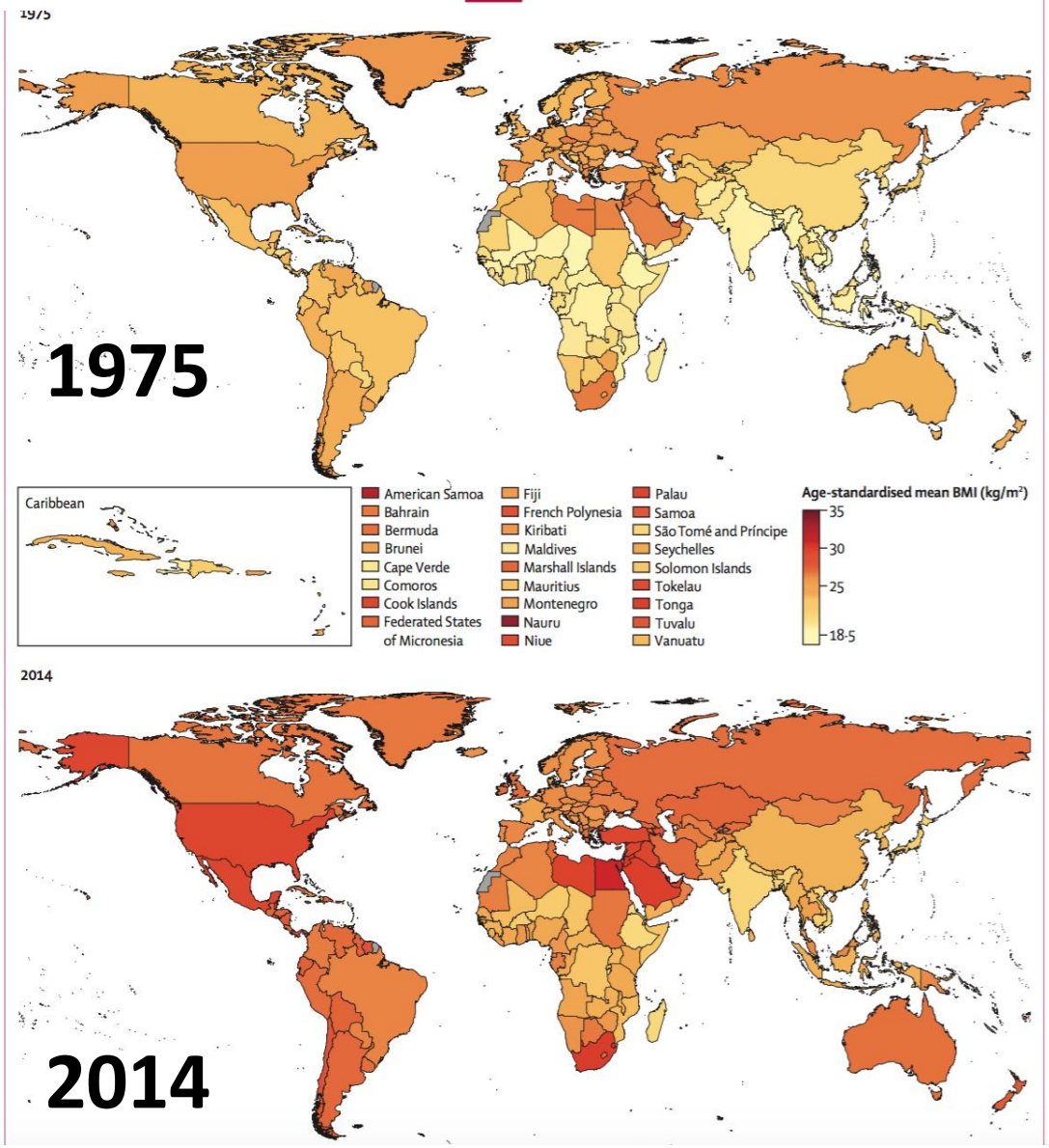
NCD Risk Factor Collaboration (NCD-RisC)*

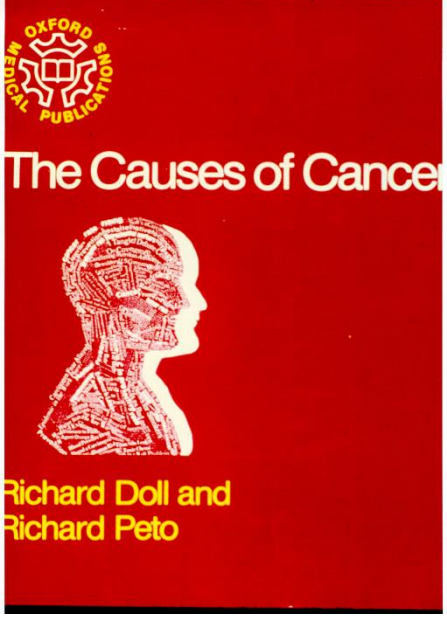
2025

Obesity: 18% 21%

Severe Obesity: 6% 9%







Population Attributable Risks(%):

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

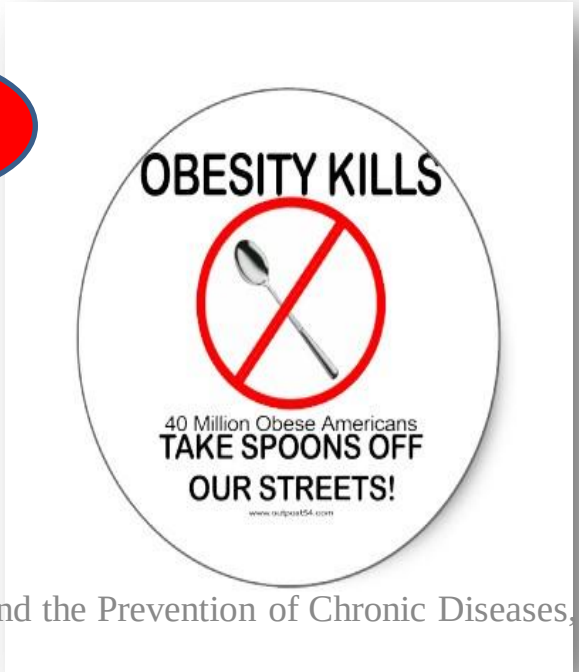
J Natl Cancer Inst.

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

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

No.1

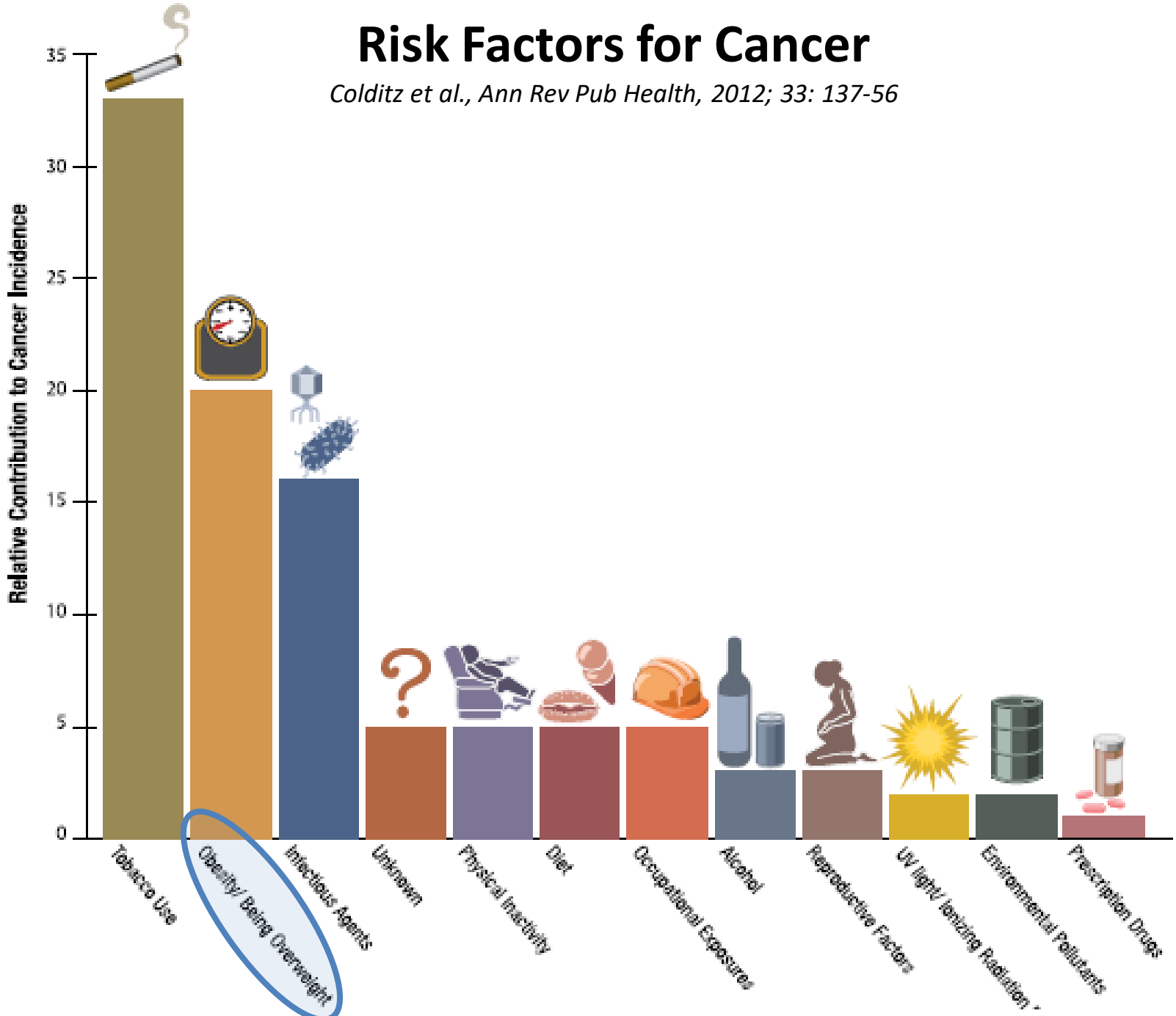
No.2



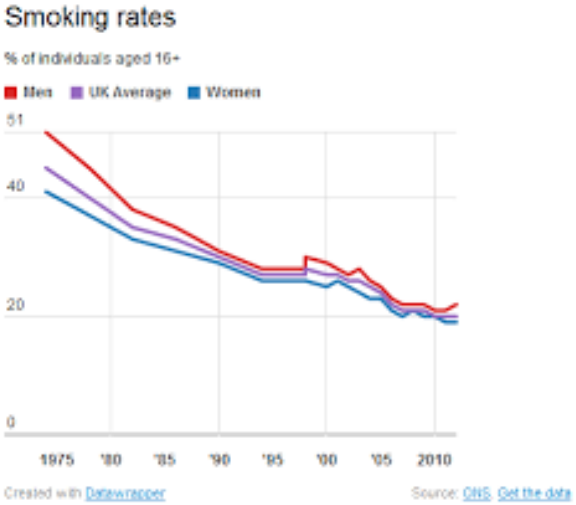
WHO/FAO, Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases, in WHO Technical Report Series. 2003, WHO: Geneva

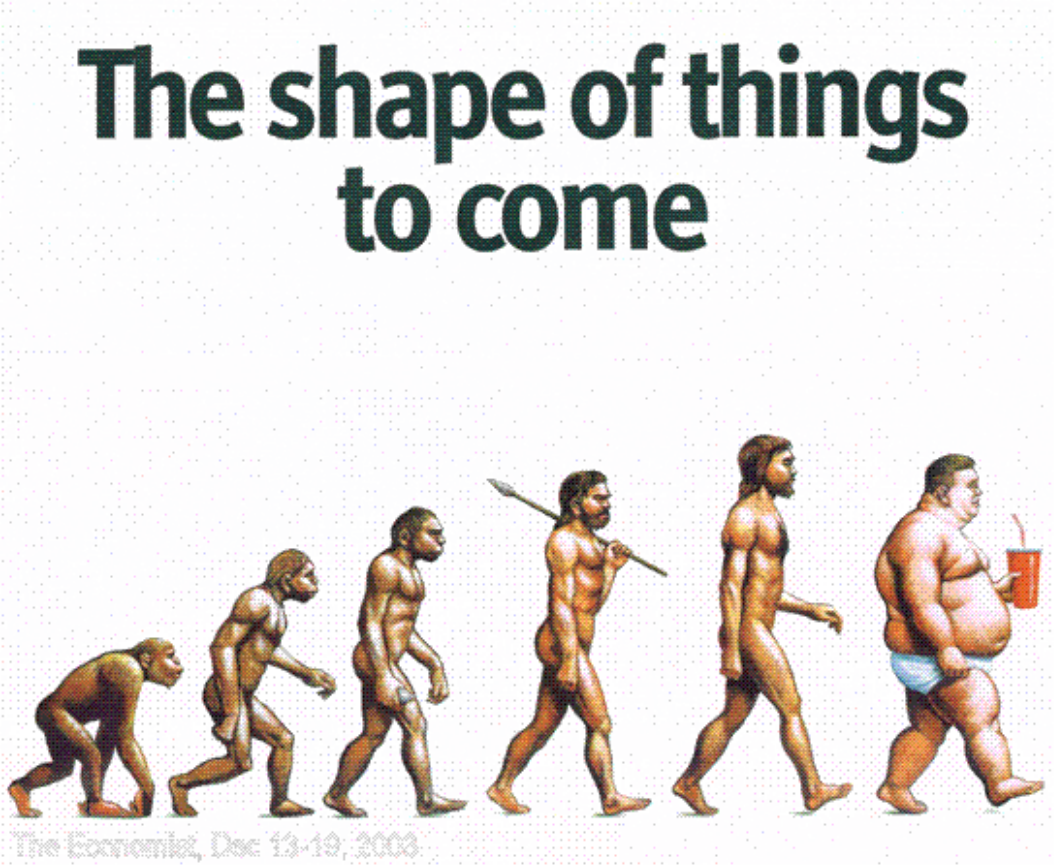
Risk Factors for Cancer

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

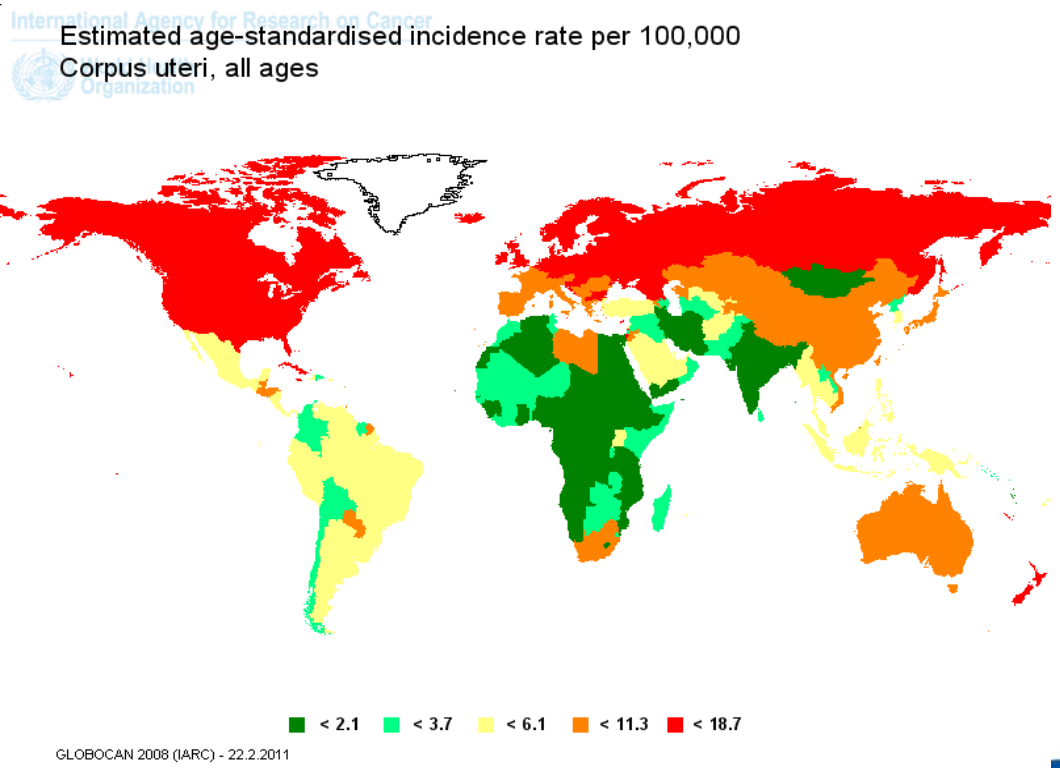


dreamstime.com


Smoking rates
% of individuals aged 16+
Men
UK Average
Women
51
40
20
0
1975
'80
'85
'90
'95
'00
'05
2010
Created with Datawrapper
Source: ONS. Get the data

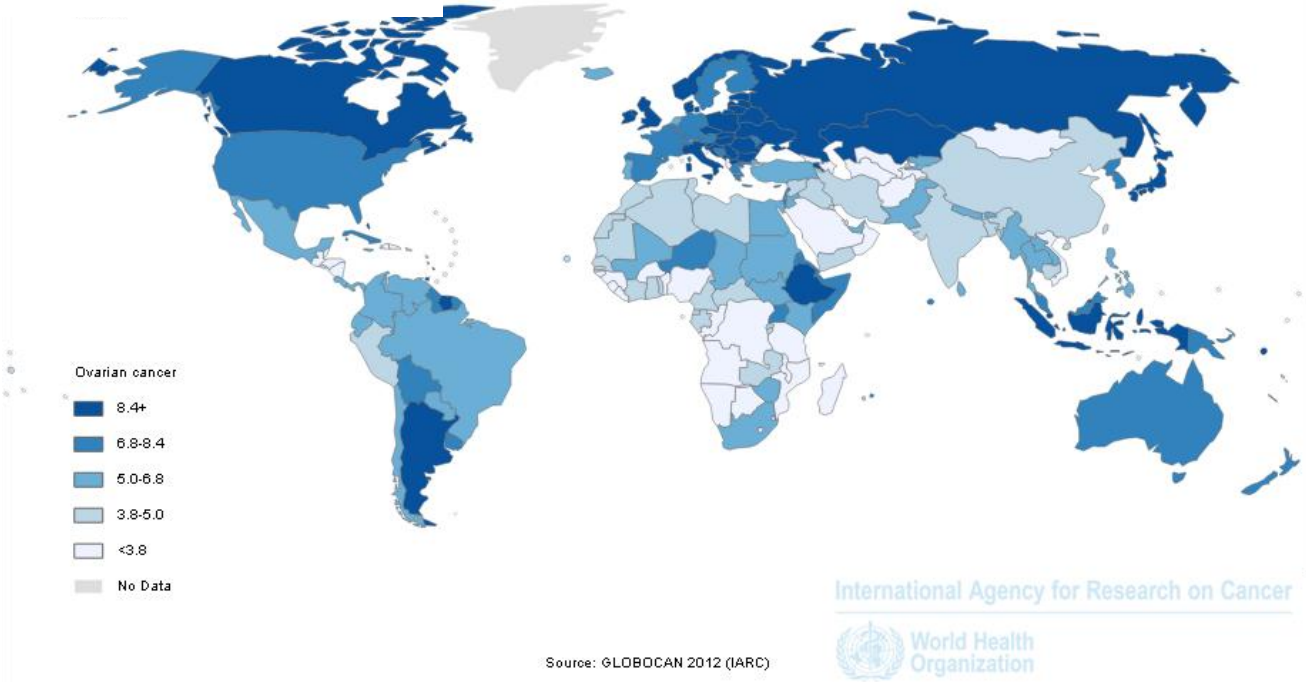

The shape of things to come
The Economist, Dec 13-19, 2003

Age-Standardized Endometrial Cancer Incidence Rates, 2012



Globocan

Age-Standardized Ovarian Cancer Incidence Rates, 2012



	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: Number of cases	Incidence: European age-standardised rate per 100,000 (95% CI)	Mortality: Number of deaths	Mortality: 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)

Cancer Research UK (2011) CancerStats: Ovarian Cancer

Endometrial Cancer: Incidence & Deaths

England & Wales (1997)

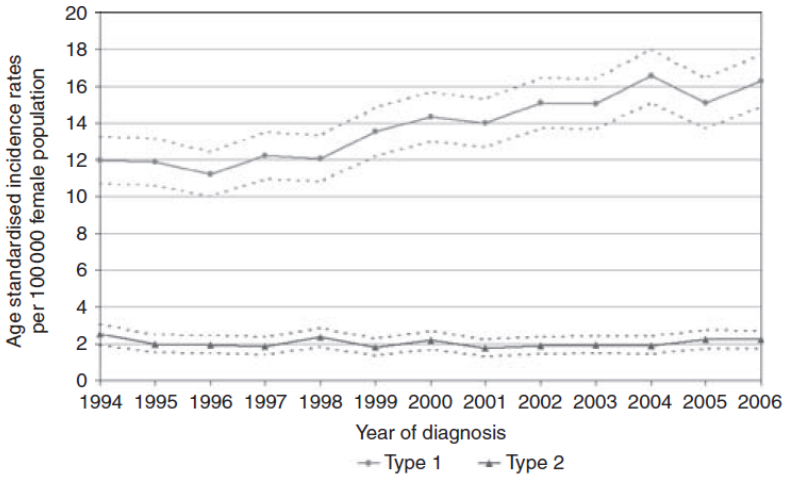


Figure 1 Differential trends in endometrial cancer incidence across the two types. Age standardised incidence rates and confidence intervals are shown.

40%

USA

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

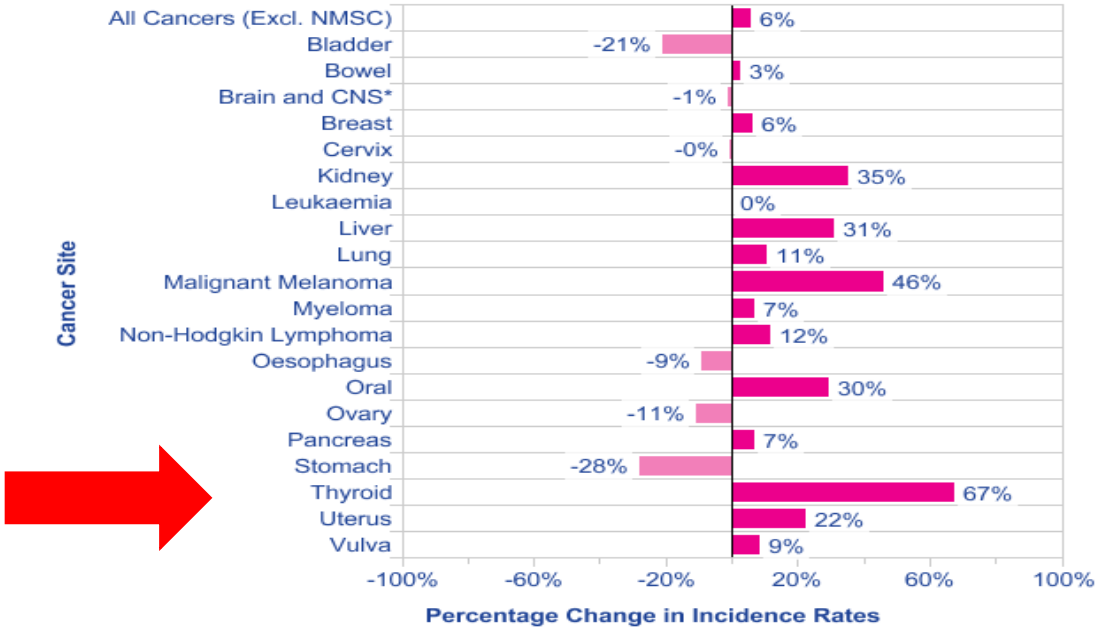
Most common Gynae Ca

6% of all cancer in women

UK: similar ….

4000/year in E&W

25-30% of all Gynae Ca



Type 1 EC accounts for incidence increase

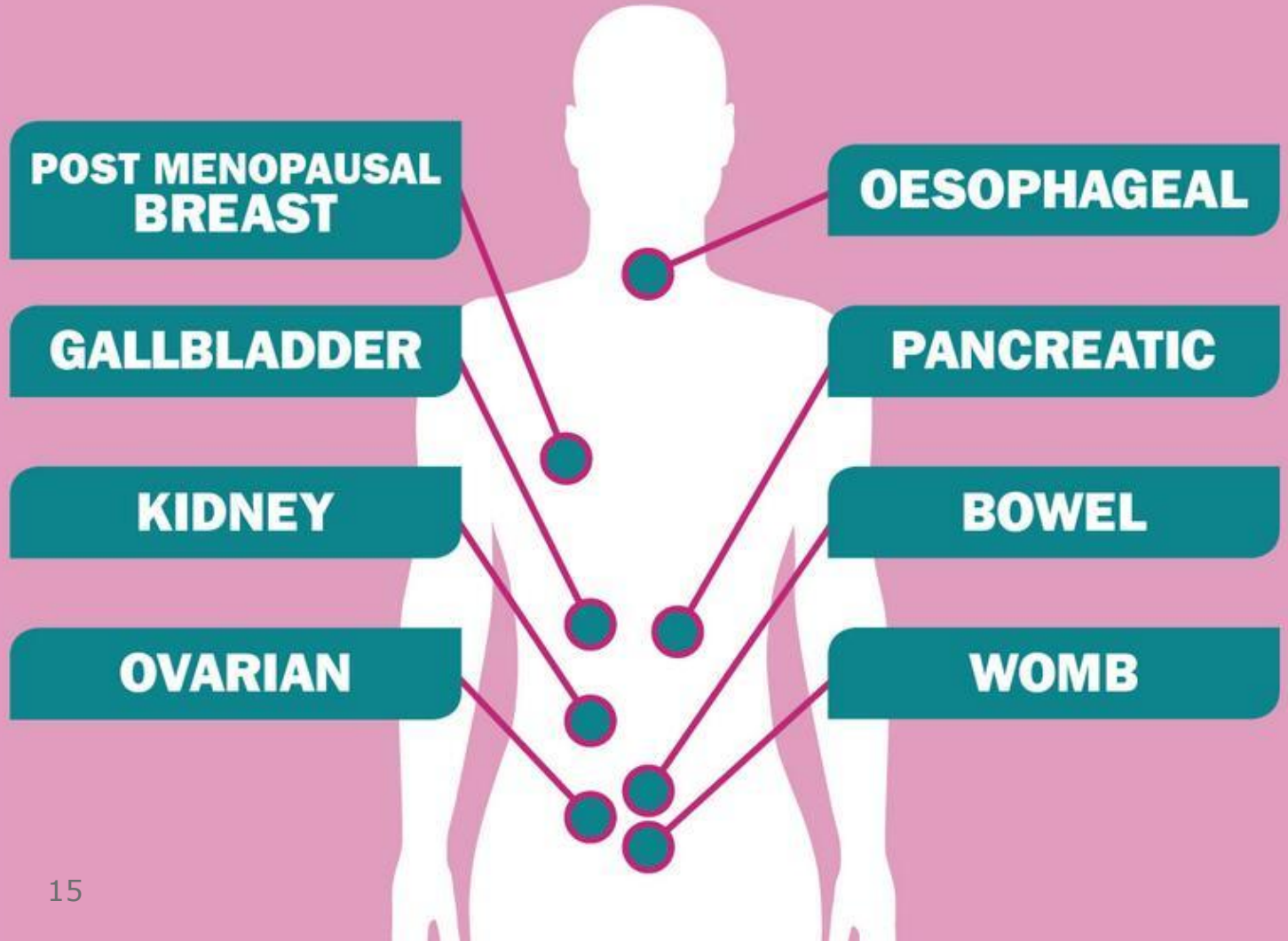
The 20 Most Commonly Diagnosed Cancers: 1999-2001 and 2008-2010

Percentage Change in European Age-Standardised Incidence Rates per 100,000 Population, Females, UK

World Cancer Research Fund International

www.wcrf.org

8 CANCERS ARE NOW LINKED TO BEING OVERWEIGHT



Continuous Update Project CUP

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Body Fatness and Cancer — Viewpoint of the IARC Working Group

August 2016

Béatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, 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.*

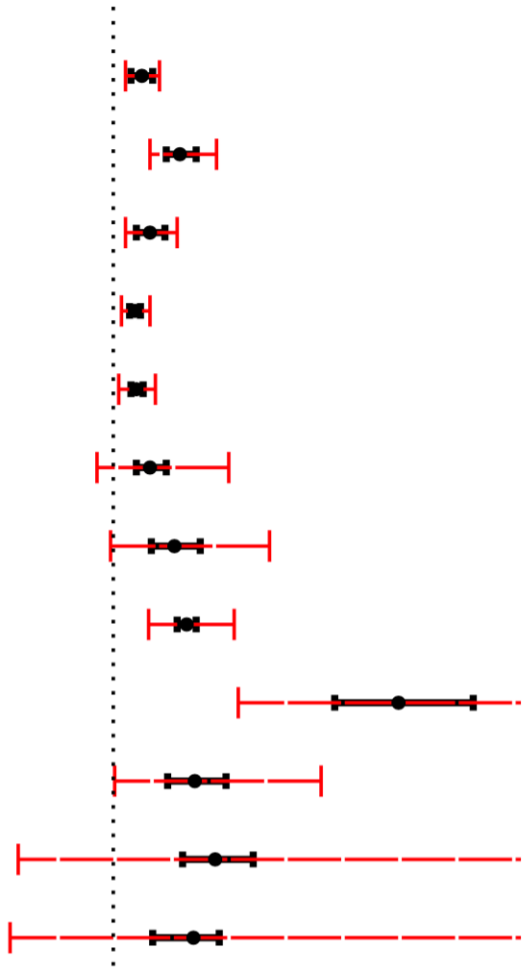
Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	Sufficient	4.8 (3.0–7.7)
Gastric cardia	Sufficient	1.8 (1.3–2.5)
Colon and rectum	Sufficient	1.3 (1.3–1.4)
Liver	Sufficient	1.8 (1.6–2.1)
Gallbladder	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)

Obesity & Cancer: umbrella review

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

2016 (under review)

Association of obesity with	Exposure	N of cases	I^2	Grade
Endometrial cancer incidence	WHR: per 0.1 unit increase	2447	0	Strong
Endometrial cancer incidence, PreMP	BMI: per 5kgm2 increase	5981	20	Strong
Ovarian cancer incidence	BMI: 30+ vs. < 25	6947	12	Strong
Endometrial cancer incidence	WG: per 5kg increase	2806	47	Highly suggestive
Endometrial cancer incidence	Weight: per 5kg increase	1778	62	Highly suggestive
Endometrial cancer incidence	WC: per 10cm increase	1524	70	Highly suggestive
Endometrial cancer incidence	BMI iya: per 5kgm2 increase	4345	75	Highly suggestive
Endometrial cancer incidence	BMI: per 5kgm2 increase	22320	81	Highly suggestive
Endometrial cancer incidence	BMI: 30+ vs. < 25	4327	66	Highly suggestive
Endometrial cancer incidence, PostMP	BMI: per 5kgm2 increase	10075	89	Highly suggestive
Endometrial cancer incidence, Type I	BMI: per 5kgm2 increase	7125	82	Highly suggestive
Endometrial cancer incidence, Type II	BMI: per 5kgm2 increase	1059	76	Highly suggestive



Clinical 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

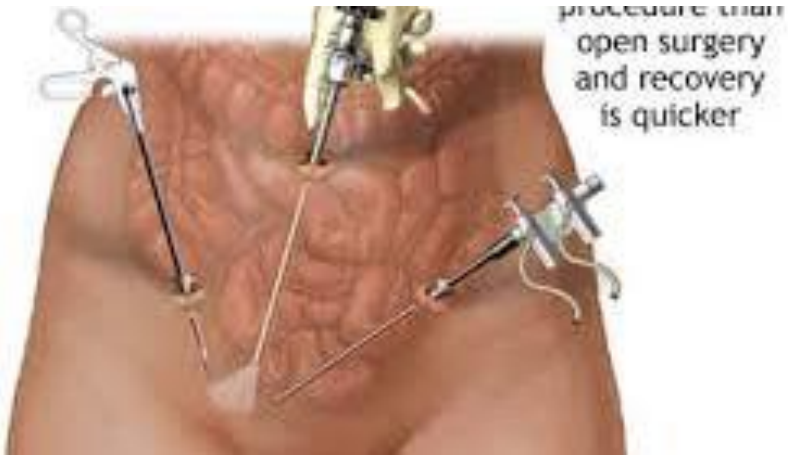
Surgical Challenges

- Difficult moving patient to correct postion
- 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 & Robotic Surgery



Skilled surgeons
as safe, less morbid, better recovery…

GOG LAP2 – LACE trial

Farthing 2010; Kyrgiou 2014; Janda 2010; Mourits 2010

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

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

2016 (under review)

EC	WHR: per 0.1 unit increase	2447	0	Strong
EC, PreMP	BMI: per 5kgm2 increase	5981	20	Strong
EC	Coffe consumption: yes vs. no	3144	0	Strong
EC	Smoking: ever vs. never	2687	0	Strong
EC	Weight: per 5kg increase	1778	62	Highly suggestive
EC	WC: per 10cm increase	1524	70	Highly suggestive
EC	BMI iya: per 5kgm2 increase	4345	75	Highly suggestive
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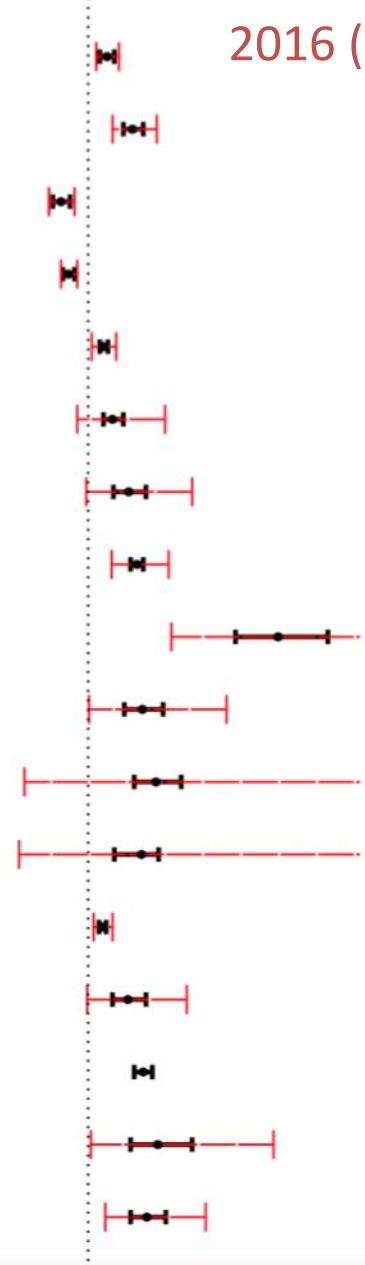
EC, Type I	BMI: per 5kgm2 increase	7125	82	Highly suggestive
EC, Type II	BMI: per 5kgm2 increase	1059	76	Highly suggestive
EC	Weight gain: per 5kg increase	2806	47	Highly suggestive
EC	Diabetes, Type 1&2 (HR)	5310	66	Highly suggestive
EC	Diabetes, Type 1&2 (IRR)	9070	0	Highly suggestive
EC	Diabetes, Type 1&2 (SIR)	1041	80	Highly suggestive
EC	Diabetes, Type 2 (SIR)	1030	56	Highly suggestive



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

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 diabetes[11]. 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 diagnosis[12].

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.

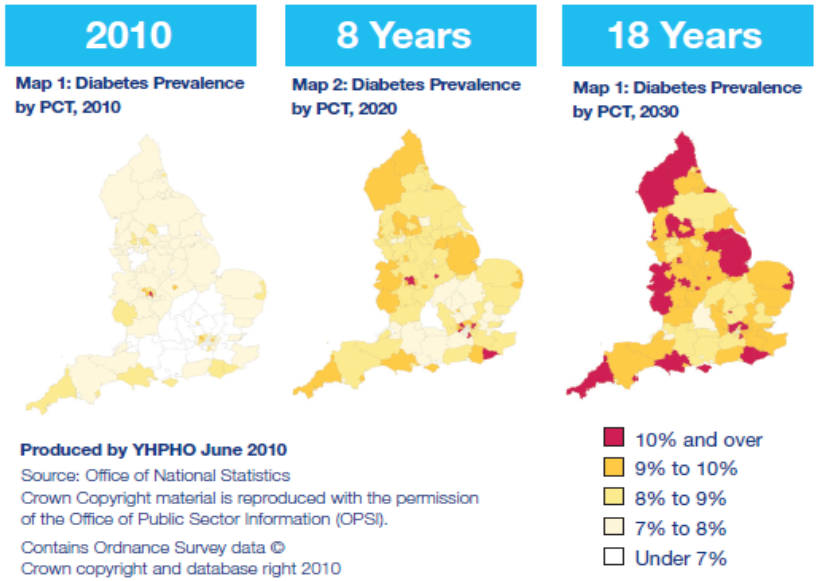
10 per cent of people have Type 1 diabetes, and 90 per cent have Type 2 diabetes[13].

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

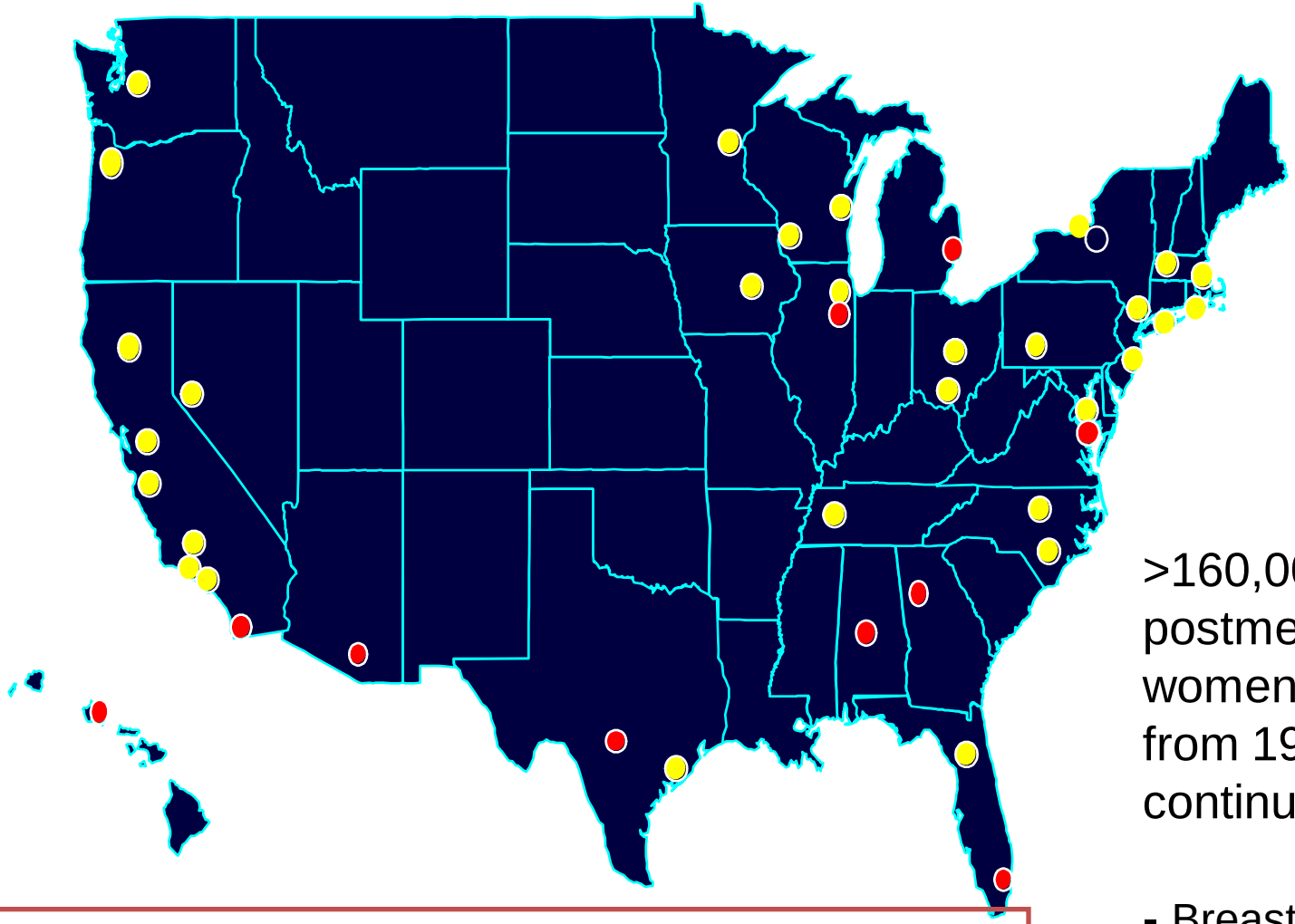
Prevalence of diabetes expected to increase significantly



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 hospitalisation[14].

The Women's Health Initiative



>160,000 postmenopausal women enrolled U.S from 1993-1998 & FU continuously

- Breast, bowel, womb Ca
- Heart Disease/Stroke
- Osteoporosis/fracture

Hyperinsulinemia may represent a risk factor independent of estradiol

Metabolic Subtypes in Obesity

Metabolically Healthy Obese vs **Metabolically Abnormal Obese**

Adipose-tissue metabolism?

Muscle characteristics?

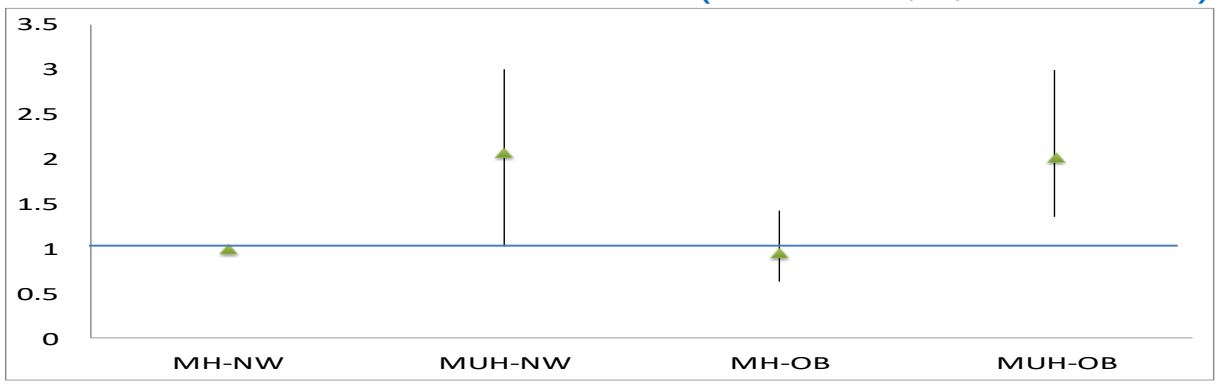
Gene expression?

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

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

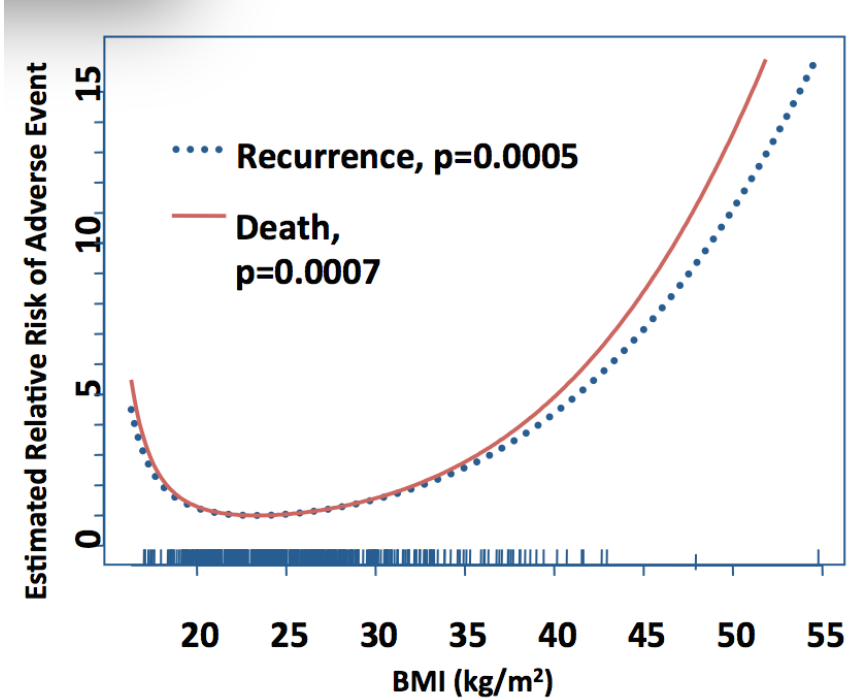


BMI<25 + HOMA Q1 | BMI<25 + HOMA Q3-4 | BMI>25 + HOMA Q1 | BMI>25 + HOMA Q3-4

Gunter et al., 2015; Cancer Research; 75: 270

Obesity
Risk of recurrence & survival

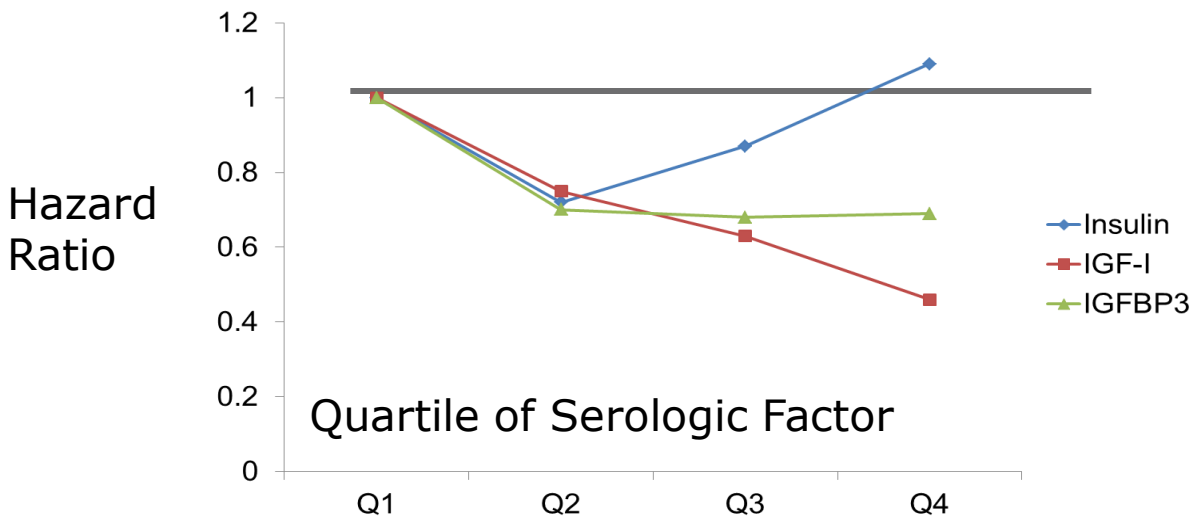
Gunter et al., 2014



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**?

Gunter et al., 2014

Imperial College London

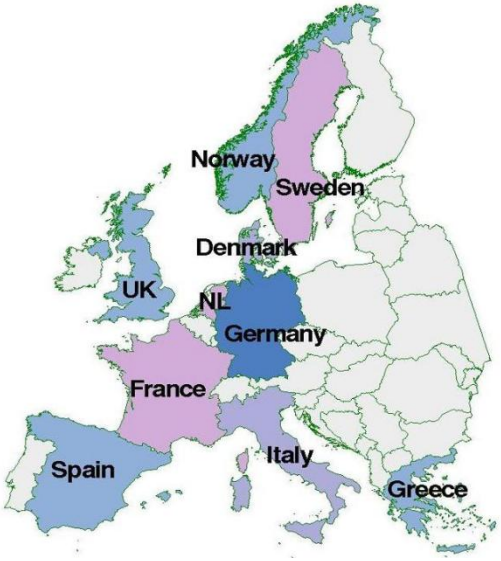
Program of research

Biobank → Cross-sectional… Longitudinal… Intervention…

EPIC → Serum markers, mRNA, RPPA

Bariatric Sx → Metabonomics …

EPIC study



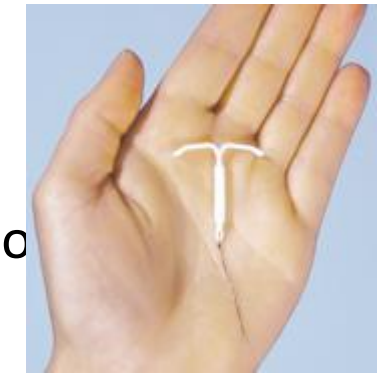
ovarian cancer action

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

ENITEC
European Network Indvidualized Treatment in Endometrial Cancer

genesis research trust
helping life begin

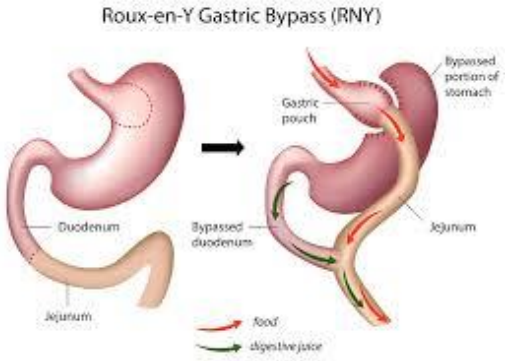
Population screening & Preventive Measures



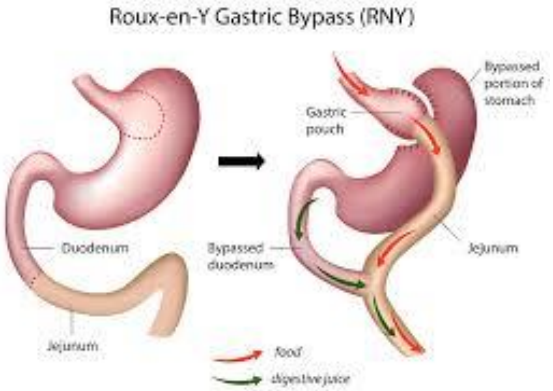
Screening

- No certain method for screening population at risk
- Outpatient endometrial sampling & TVS: may be used in co
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



Diet low calorie intake

Vegetable and fruit consumprion

Physical activity

Bariatric surgery

Mirena IUS

Metformin

Take home messages…

EC is increasing

Obesity & diabetes increase the risk of womb cancer

Increased awareness: present early with symptoms

Reduction of obesity: diet, exercise, education…

Reduced BMI: reduced incidence – better prognosis in cancer

Research to improve prevention (high-risk groups, chemoprevention)