Obesity & Endometrial Cancer

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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


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

Trends in Overweight and Obesity

Proportion overweight

Year

USA
England
Spain
Austria
France
Canada
Australia
Korea

WHO, 2012
Prevalence of obesity in adults (aged 16+)
Source: Health Survey for England

Adult obesity: BMI ≥ 30 kg/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.

2025

Obesity: 18% 21%

Severe Obesity: 6% 9%

1975

2014
WHO: overweight and obesity are the most important known avoidable cause of cancer after tobacco...
Risk Factors for Cancer
The shape of things to come
Age-Standardized Endometrial Cancer Incidence Rates, 2012

Globocan

Age-Standardized Ovarian Cancer Incidence Rates, 2012

Source: GLOBOCAN 2012 (IARC)
Incidence & Mortality

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>795,000</td>
<td>313,000</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>450,000</td>
<td>300,000</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>165,000</td>
<td>101,000</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>142,000</td>
<td>42,000</td>
</tr>
</tbody>
</table>

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

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

England & Wales (1997)

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

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

Figure 1 Differential trends in endometrial cancer incidence across the two types. Age standardised incidence rates and confidence intervals are shown.
8 Cancers are now linked to being overweight

Post Menopausal Breast

Oesophageal

Gallbladder

Pancreatic

Kidney

Bowel

Ovarian

Womb
# Special Report

## Body Fatness and Cancer — Viewpoint of the IARC Working Group

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

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

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


2016 (under review)

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


#### EC
- WHR: per 0.1 unit increase (2447) 0 Strong
- BMI: per 5kg/m² increase (5981) 20 Strong
- Coffee consumption: yes vs. no (3144) 0 Strong
- Smoking: ever vs. never (2687) 0 Strong
- Weight: per 5kg increase (1778) 62 Highly suggestive
- WC: per 10cm increase (1524) 70 Highly suggestive
- BMI lya: per 5kg/m² increase (4345) 75 Highly suggestive
- BMI: per 5kg/m² increase (22320) 81 Highly suggestive
- BMI: 30+ vs. < 25 (4327) 66 Highly suggestive

#### EC, PreMP
- BMI: per 5kg/m² increase (10075) 89 Highly suggestive

#### EC, Type I
- BMI: per 5kg/m² increase (7125) 82 Highly suggestive

#### EC, Type II
- BMI: per 5kg/m² increase (1059) 76 Highly suggestive

#### EC
- Weight gain: per 5kg increase (2806) 47 Highly suggestive
- Diabetes, Type 1&2 (HR) (5310) 66 Highly suggestive
- Diabetes, Type 1&2 (IRR) (9070) 0 Highly suggestive
- Diabetes, Type 1&2 (SIR) (1041) 80 Highly suggestive
- Diabetes, Type 2 (SIR) (1030) 56 Highly suggestive

2016 (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
- IGFBP-3
- Free IGF-I
- Insulin
- C-Peptide
- Leptin
- CRP
- TNF-α
- Oestrogen
- Progesterone
- 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.

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

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

Metabolically-defined Obesity Subtypes & Breast Cancer Risk

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

Metabonomics...

Bariatric Sx

ovarian cancer action

EPIC study

ENITEC

Europe

MD Anderson Cancer Center

genesis research trust

The University of Texas
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
Diet low calorie intake
Vegetable and fruit consumption
Physical activity
Bariatric surgery
Mirena IUS
Metformin
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)