Cancer survival: what is the role of body composition pre- and post-diagnosis?

Dr Ellen Copson
Associate Professor in Medical Oncology, University of Southampton
I have no conflicts of interest
Research on food, nutrition, physical activity, and cancer survival is at an early stage.

The available evidence on cancer survivors has a number of limitations: it is of variable quality; it is difficult to interpret; and it has not yet produced any impressive results.

Definite general judgements are made more problematic because of differences in the health of cancer survivors at various stages; between cancers of various sites; and between the effects of the many types of conventional and other therapies used.”
BODY FATNESS*

Pre-diagnosis

<12 months from Dx

>12 months from Dx

Diet, nutrition, physical activity and breast cancer survivors

* BMI or anthropometric measures
Obesity and survival of early breast cancer patients

Chan et al. 2014:
Meta-analysis of 82 studies, 213075 breast cancer survivors

Pre-diagnosis:

BMI >30 : RR total mortality = 1.41
BMI 25-30 : RR = 1.07

For each additional 5kg/m2

pre, <12 months >12 months from diagnosis
17% 11% 8% increase in total mortality
18% 14% 29% increase in breast cancer mortality
Post-menopausal vs Premenopausal breast cancer

Pre-diagnosis:

Pre-menopausal  BMI > 30: RR total mortality = 1.75
Post-menopausal  BMI >30: RR total mortality = 1.34

Even though obesity is not a risk factor for developing pre-menopausal breast cancer

Chan et al, 2015
## WCRF CUP 2013: Breast Cancer Survivors

<table>
<thead>
<tr>
<th>Timing of exposure assessment</th>
<th>Before Diagnosis</th>
<th>Less than 12 Months after Diagnosis</th>
<th>12 Months or More after Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DECREASES RISK</td>
<td>INCREASES RISK</td>
<td>DECREASES RISK</td>
</tr>
<tr>
<td></td>
<td>Exposure</td>
<td>Outcome</td>
<td>Exposure</td>
</tr>
<tr>
<td>Strong Evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convincing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited-suggestive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foods containing fibre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fatness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fatness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited-no conclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits, vegetables, foods containing folate, foods containing soy, carbohydrate, glycaemic index, glycaemic load, protein, dietary supplements, alcoholic drinks, dietary patterns, underweight, body fatness (premenopause), adult attained height, energy intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foods containing fibre, carbohydrate, protein, total fat, saturated fatty acids, alcoholic drinks, physical activity, underweight, body fatness (premenopause), adult attained height, energy intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits, vegetables, foods containing folate, foods containing soy, carbohydrate, glycaemic index, glycaemic load, protein, total fat, saturated fatty acids, alcoholic drinks, dietary patterns, physical activity, body fatness, underweight, height, energy intake</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RCTs: patient selection**  
**Cohort: confounders poorly reported**
Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH)

- Prospective multicentre cohort study of young breast cancer patients

- Primary aim:
  - Determine whether underlying BRCA1/2 mutation influences prognosis and clinical course of breast cancer

- Secondary aims:
  - To determine whether inherited genetic variants influence tumour biology
  - Determine influence of other host factors on pathology and outcome of breast cancer in pre-menopausal patients
    - BMI
    - Ethnicity
POSH cohort in brief

- 3025 cases < 41 years at diagnosis or known gene carriers aged 41-50

- Diagnosed between 1\textsuperscript{st} January 2000 – 31\textsuperscript{st} December 2007

- Eligibility: Invasive breast cancer

- 127 UK recruiting centres
POSH: Patients and methods

- Treated as per local protocols
- Blood sample stored for genetic analysis
- Family history by questionnaire
- Height and weight measured by research nurse
- Pathology, treatment and clinical course obtained from records
- Central pathology review and tissue microarray analysis ongoing
- Annual follow-up
- Flagging of deaths
POSH: Southampton based multicentre cohort study

2956 Patients age <41 years at first diagnosis of breast cancer

2843 BMI data

1526 BMI < 25

784 25 ≥ BMI <30

533 BMI ≥ 30

Overall survival

Distant disease free survival

## Pathological features

<table>
<thead>
<tr>
<th>Pathological Feature</th>
<th>Underweight or Healthy weight n=1526</th>
<th>Overweight n=784 (27.6%)</th>
<th>Obese n=533 (18.8%)</th>
<th>U/H vs. Ov: p&lt;0.0001</th>
<th>U/H vs. Ob: p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean tumour size/ mm</td>
<td>20 (0-170)</td>
<td>24 (0-199)</td>
<td>26 (0-130)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>12 (30.6%)</td>
<td>220 (30.4%)</td>
<td>130 (27.2%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>879 (59.0%)</td>
<td>485 (63.6%)</td>
<td>331 (63.9%)</td>
<td>U/H vs. Ob: p =0.04</td>
<td></td>
</tr>
<tr>
<td>Node positive</td>
<td>736 (49.0%)</td>
<td>419 (54.2%)</td>
<td>284 (54.6%)</td>
<td>U/H vs. Ov: p=0.019</td>
<td>U/H vs. Ob: p=0.027</td>
</tr>
<tr>
<td>ER negative</td>
<td>483 (31.7%)</td>
<td>273 (34.9%)</td>
<td>213 (40.1%)</td>
<td>U/H vs Ob: p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HER 2 positive</td>
<td>381 (28.2%)</td>
<td>180 (26.4%)</td>
<td>129 (27.3%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>ER/ PR/ HER 2 negative</td>
<td>305 (20.8%)</td>
<td>176 (23.4%)</td>
<td>136 (26.8%)</td>
<td>U/H vs. Ob: p=0.005</td>
<td></td>
</tr>
</tbody>
</table>

Tumour biology and microenvironment

- Insulin like growth factor/ adipocytokines
- Pro-inflammatory tumour environment
Multivariate analysis: adjusted for tumour size, grade, nodal status and HER 2 status

Oestrogen receptor (ER) positive patients:

- Obesity: HR for recurrence 1.37 (p=0.015)
- Obesity: HR for overall survival 1.46 (p=0.007)

Oestrogen receptor (ER) negative patients:

- Obesity not a significant independent influence on DDFS or OS

Why is obesity an adverse prognostic factor?

- Delayed presentation
- Co-morbidities
- Tumour biology microenvironment
- Health behaviour
- Ethnicity
- Treatment Issues
Overall survival

Copson et al. *BJC* 2014; 110 (1): 230-241
Why is obesity an adverse prognostic factor?
Treatment Issues

- Increased surgical/ radiotherapy complications

- Hormonal therapy- efficacy/ tolerance/ adherence

- Chemotherapy- dosing/ tolerance
  - Most cytoxics prescribed by body surface area
  - Body surface area not designed for extremes
  - Dose capping traditionally common

  - Griggs et al. 2012: “40% patients underdosed”
Investigation of local adjuvant chemotherapy dosing (n=80)

- No initial dose reductions
- Significant difference in dose delays: 33.3% vs. 5.9%, p=0.0068

- Toxicities
- Access issues
- AWOL
What is “risky” about obesity?

- Excess adipose tissue?
- Alcohol?
- Lack of lean muscle?
- Diet/nutrients?
- Lack of exercise?
- Health Behaviour?

BMI and anthropometric measures cannot distinguish between lean mass and fat mass.
Challenges of assessing body composition

- Gold standard body composition:
  - 4 compartment model:
    - Deuterium dilution
    - Under water weighing
    - Plethysmography
    - DEXA
  - Not suitable for routine clinical practice

- Clinical studies:
  - Anthropometric studies
  - Computerised tomography
  - DEXA
Body composition beyond BMI following a diagnosis of breast cancer

- James et al 2015 EJC

- 4 studies of body fatness and outcome; n=8543
  - Anthropometric measures
  - 2 studies no association WMR and outcome
  - 1 positive association WHR and poorer outcome
  - 1 positive association only with high BMI

- 2 studies of lean mass and outcome; 548 patients
  - 1 CT, 1 DEXA
  - 1: increased mortality with sarcopaenia
  - 1: increased response to neo-adjuvant chemo with sarcopaenia
CANDO-2 Feasibility Study

- Demonstrate feasibility of using sBIS to obtain detailed body composition measurements in EBC patients at routine chemo clinic appmts
- Validate Sliceomatic software against sBIS
- Obtain preliminary data: chemo toxicity & body composition patterns
- Biobank serial plasma/ serum samples
BMI vs Percentage fat
Changes in Fat Mass

- Mean increase in fat mass of 1.1 kg
- Correlation between BMI and gain of fat mass
Relationship between chemotherapy toxicity and body composition

- Red dots = patients with Grade 3+ toxicity
- Blue Dots = patients with no record of Grade 3+ toxicity

- High fat
- Low lean
- High fat
- High lean
- Low fat
- Low lean
- High fat
- High lean
Comparison of body composition data from sBIS and CT
Summary:

- Obesity is associated with reduced breast cancer specific and overall survival.
- Cohort studies indicate that obesity is associated with a number of known poor prognostic factors in early breast cancer; it is possibly an independent risk factor for poorer survival.
- However, much work is needed to fully investigate body composition patterns and other nutritional/metabolic markers in order to fully define the true nature of this risk factor in early breast cancer patients.
Acknowledgements:

- Tom Maishman
- Bryony Eccles
- Louise Dent
- Ramsey Cutress
- Sue Gerty
- Lorraine Durcan
- Diana Eccles
- The POSH patients
- NIHR Southampton BRC - Nutrition

Work supported by:
- Cancer Research UK
- Wessex Cancer Fund
- Breast Cancer Campaign
- National Cancer Research Network
Thank you