Does intermittent energy restriction have a role in the prevention & treatment of cancer?

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Outline

• Weight & cancer

• Rationale for using intermittent energy restriction

• Our 5:2 diet research:
  - In high risk women
  - In breast cancer patients

• What we know & what we need to know
Weight & Cancer Risk

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

Andrew G Renehan, Margaret Tyro, Matthias Egger, Richard Hoffer, Marcel Zwahlen

13 cancers:
1.07 – 1.60 RR per 5 kg / m² (13 - 16 kg)
Oesophageal, thyroid, colon, renal, endometrial, gallbladder, malignant melanoma, rectum postmenopausal breast, pancreatic, leukaemia, multiple myeloma, non-Hodgkin lymphoma

Renehan et al Lancet 2008; 371: 569–78

Weight & Cancer Outcome

Breast Cancer Mortality
1.17 – 1.29 RR per 5 kg / m² (13 kg)

Prostate Cancer Recurrence
1.16 RR per 5 kg / m² (13 kg)
Hu et al Med Oncology 2014 ;31(2):829
Energy Restriction Is Difficult To Achieve & Maintain In Humans!

- 25-30% adherence to daily low energy diets at 12 months
- 20-40% achieve > 5% weight loss with daily diets at 1 year
- Only 20% of women at high risk of breast cancer maintain > 5% weight loss at 5 years with daily diets
- Some metabolic benefits of weight loss attenuate once dieters reach a stable weight & no longer in energy deficit

Intermittent Energy Restriction (IER)
Animal Studies 1946-

- IER equivalent or superior to isocaloric continuous energy restriction (CER) to reduce:
  Breast, prostate, pancreatic tumours, sarcoma, lymphoma, CVD & dementia

**Variety of regimens studied**
- Alternate day fasting
- 3 weeks 50% restriction & 3 weeks ad lib
- Alternate weeks of 50% restriction & ad lib

**IER includes spells of >50% energy restriction which may:**
- Mobilise ectopic /visceral fat
- Reduce oxidative stress & cell proliferation

Harvie et al Proc Nutr Soc. 2012;71(2):263-75
Two Main Rationale For Intermittent Energy Restriction in Humans

1. May be easier to follow than daily diets?

2. May have more beneficial metabolic effects?
Human Studies

Normal weight

2005 Alternate day fasting 3 weeks (n = 16)

Weight loss research

5:2 diet
Harvie M et al 2010
Harvie M et al 2013

Alternate Day Fasting
Johnson JB 2007
Varady K et al 2009

Eat, Fast and Live longer (Horizon Mosley) Aug 2012

Harvie M et al Int J Obes 35:714-727, 2010

Study 1: RCT of Intermittent vs. Continuous Energy Restriction (2006-2009)

1. Is intermittent energy restriction (IER) acceptable & easier to follow than continuous restriction (CER)?

2. Does IER have better effects on risk markers for breast cancer, diabetes, CVD compared to CER?
Intermittent Energy Restriction

Our 5:2 diet

Overall 25% energy restriction

- Continuous energy restriction: 25% restriction 7 days/week
- Intermittent energy restriction: 70% restriction 2 days/week
Study 1: High Risk Women

**Intermittent (n = 52)**
- 2 days
- ~650 kcal/day:
  - 2 pints semi-skimmed milk
  - 1 fruit & 4 x 80g vegetable portions
  - 2 pints low-calorie drinks
- 5 days
- ~1900 kcal/day
  - Mediterranean diet

**Continuous (n = 52)**
- 7 days
- ~1500 kcal / day
  - Mediterranean diet

- 6 Months
  - Weight, body fat & waist
  - Markers of disease risk: Insulin, leptin, adiponectin, testosterone, IGF-1, inflammation, oxidative stress
Study 1: Main Findings

- Loss of fat Mean (SD) IER 6.0 (4.4) kg vs. CER 4.9kg (3.9)  P = 0.24

- Simple “milk and veg” intermittent diet was not much easier to follow than a daily diet

- Greater reduction in insulin with IER vs. CER during restricted & unrestricted days of the diet:
  Reductions in insulin on “non diet” days of IER & with CER :
  -30 vs. -17%
  Additional 25% reduction in insulin on diet days of IER

Study 2: High Risk Women
IER vs. CER

115 Overweight high risk women randomised to 3 groups

3 months weight loss
- 25% restriction
  - 2 day low carb
  - 650 kcal
  - & 5 days Med diet

1 month weight loss maintenance
- 1 day low carb
  - 650 kcal
  - & 6 days Med diet

- 25% restriction
  - Continuous restriction
  - Med diet

- 2 day Ad lib
  - low carb
  - & 5 days Med diet

- Maintenance
  - Med diet

- 1 day ad lib
  - low carb
  - & 6 days Med diet
Study 2 - Diets

**Intermittent low carb**
Energy restricted

- 2 days / week
- \( \sim 650 \) kcal
- 50g carbohydrate
- \( \sim 300 \)g protein foods
- 3 portions dairy
- 5 veg & 1 fruit
- 5 days / week
- Ad lib
- Mediterranean diet

**25% Continuous restriction Mediterranean diet**

- 7 days / week
- \( \sim 1500 \) kcal / day
- Mediterranean diet:
  - 30% fat : 15% MUFA, 7% PUFA, 7% saturated
  - 45% low GI carbs
  - 25% protein

**Intermittent Ad lib low carb**

- 2 days / week
- \( \sim 1000 \) kcal
- 50g carbohydrate
- Unlimited protein (meat, fish, eggs, tofu)
- MUFA & PUFA fats.
- 3 portions dairy
- 5 veg & 1 fruit
- 5 days / week
- Ad lib
- Mediterranean diet
Study 2 - Change in weight & body fat (kg) including drop outs (N = 115)

Drop outs
IER = 4
ICR = 10
CER = 13

Study 2 - Weight & insulin at 3 months (LOCF N = 115)

<table>
<thead>
<tr>
<th></th>
<th>2 DAY energy &amp; CHO restricted (n=37)</th>
<th>2 day Ad lib low CHO (n= 38)</th>
<th>Continuous energy restricted diet (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losing &gt; 5% weight</td>
<td>65%</td>
<td>60%</td>
<td>37%</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Waist reduction (cm)</td>
<td>-5.2 (-7.1 to -3.9)</td>
<td>-4.7 (-6.0 to -3.4)</td>
<td>-3.7 (-4.7 to -1.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Insulin % change</td>
<td>-22 (-35 to -11)%</td>
<td>-14 (-27 to -5%)</td>
<td>-4 (-16 to 9)%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Mean (95% confidence interval)

## Study 2 - Adherence

| Adherence to prescribed diet | 76% of potential 2 days | 74% of potential 2 days | 39% of days when achieve 25% restriction |

| Intake on non-diet days-kcal | 1360 (1241 to 1400) | 1533 (1400 to 1667) | 1459 (1327 to 1590) |

*Mean (95% confidence interval)*

IER: Intermittent Metabolic Changes

IER = 15     DER =9

Intermittent Diet Studies 2 & 3

Summary

• IER superior to CER for reducing body fat & insulin

• 2 day ad lib low carb is equivalent to 2 days energy restricted diet

• 1 day of restriction per week maintains weight loss in the short term

• Intermittent metabolic changes occur with IER
Can IER Help Breast Cancer Patients?
IER May Reduce Treatment Toxicity

- IER (2 day fast) leads to differential sensitization of tumour to chemo or radiotherapy in a number of xenograft models
- IER may reduce host oxidative stress & upregulate host stress response mechanisms.
- Ongoing trials of fasting & chemotherapy toxicity (3 USA, 2 Netherlands, 1 Germany and 1 UK) and radiotherapy toxicity (1 USA)

Safdie et al AgiAng (Albany NY) 2009 1:988-1007
Lee et al Sci Transl Med 2012 7;4 (124)
http://Clinicaltrials.gov
IER vs. CER During Chemotherapy
B-AHEAD-2 Study

Outcomes 3 weeks post final chemotherapy

- Weight, body fat (DXA), waist, hips
- Chemotherapy toxicity: self report & blood markers (Cytokeratin 18 & FMS Like Tyrosine Kinase 3 ligand markers).
- Breast cancer prognosis marker – insulin
- Oxidative stress markers
- CVD risk parameters: lipids, blood pressure
- Fitness, Quality of life, Dietary intake, Physical activity

n = 170  BMI>19
Scheduled to receive adjuvant or neoadjuvant chemotherapy

Group 1: n = 85
2 day / week IER (& exercise)
Individual advice and telephone support

Group 2: n = 85
Daily energy restricted diet (& exercise)
Individual advice and telephone support

4½ - 6 months of chemotherapy
IER in Advanced Cancer Patients
B-AHEAD 3 Study

n = 134  BMI > 25
Scheduled to receive chemotherapy for advanced breast cancer

Group 1: n = 67
2 day / week IER (& resistance exercise)
Individual advice and telephone support

Group 2: n = 67
Resistance exercise only
Individual advice and telephone support

Primary outcome
Time to disease progression

Secondary outcomes
Weight, lean body mass, body fat (CT scan), waist, hips
Breast cancer prognosis markers: insulin & proteomics (SWATH)
Muscle strength in upper (hand grip) and lower limbs (sit to stand)
Chemotherapy toxicity: self report
Quality of life & HADS
Self reported dietary intake & physical activity
The Intermittent Fasting Phenomena

130 books on 5:2 & ADF books & increasing!
## Intermittent Diet Summary

<table>
<thead>
<tr>
<th></th>
<th>5:2 diets</th>
<th>Alternate day fasting</th>
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</thead>
<tbody>
<tr>
<td>Total subjects studied</td>
<td>129 +110 in ongoing trials</td>
<td>119 + 25 unpublished</td>
</tr>
<tr>
<td>Gender</td>
<td>129 female</td>
<td>100 female 18 male</td>
</tr>
<tr>
<td>Recruitment</td>
<td>Family history clinic/hospital</td>
<td>Answered advert</td>
</tr>
<tr>
<td>Support</td>
<td>Self selected food Monthly face to face &amp; biweekly phone review dietitian</td>
<td>Diet days meals provided Weekly review with dietitian</td>
</tr>
<tr>
<td>RCT vs. daily diet</td>
<td>Study 1 =IER=CER Study 2 IER &gt; CER</td>
<td>Study 1 ADF= CER</td>
</tr>
<tr>
<td>Intake on unrestricted</td>
<td>-25%</td>
<td>+ 15%</td>
</tr>
<tr>
<td>days</td>
<td>Overall energy restriction</td>
<td>30 – 36%</td>
</tr>
<tr>
<td>Duration of studies</td>
<td>4 &amp; 6 months</td>
<td>2-3 months</td>
</tr>
<tr>
<td>Maintenance regimen</td>
<td>1 day</td>
<td>Not studied</td>
</tr>
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What We Know.......... 

• Intermittent diets are a potential alternative to daily diets for weight loss

• No evidence that intermittent leads to disordered eating or unhealthy diets.

• Appear to have beneficial effects on metabolism i.e. insulin resistance
What we need to know..........

- Need randomised trials to assess the long term success & safety of IER.
- Are intermittent metabolic changes (i.e. insulin) beneficial or harmful?
- 2 days of IER & ADF have been tested but what is the ideal IER for health? How low in calories? How long? How often?
- What is the optimum macronutrient intake on fasting & other days?
- Do intermittent diets target loss of fat & ectopic fat, preserve muscle mass & maintain REE? (our BRRIDE study)
- Are there any benefits of IER in healthy weight people? i.e. can one day week of IER prevent weight gain & disease?
- Application in cancer patients during treatment.
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