Epigenetics, abdominal obesity and early life events—the relationship between cancer and obesity.

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GREETINGS FROM CAPE TOWN

Cancer affects us all...
The Big Picture

- Carcinogens
- Epicarcinogens
- BPA and Omega-6
- Early life
- Obesity-Cancer link

Cancer affects us all...
Important concept No. 1

- 90% of all cancers are caused by environmental factors called carcinogens
Cancer Prevention: Liver cancer

Hepatitis virus

Vaccination
Important concept No. 2

- 90% of all obesity is caused by environmental factors of which calorie overload and insufficient exercise are most important. This has got little to do with mutational changes in DNA sequence.
Important concept No.3

- Gene expression can be reversibly and transgenerationally altered by nutrition and other environmental stimuli acting through epigenetic mechanisms during prenatal and postnatal development and increase susceptibility for chronic diseases such as obesity and cancer.
Important concept No.4

- Epicarcinogens are molecules that can increase the risk of cancer in specific tissues by altering the expression of critical genes through epigenetic mechanisms, especially during pre- and post-natal life.
Important concept No. 5

• Many man-made molecules, especially hormone disruptors, may be epicarcinogens involved especially with breast cancer.

• Example: Bisphenol A
Important concept 6

- Some nutrients used inappropriately in food, may be epicarcinogens increasing the risk for obesity and/or cancers.

- Example: Omega-6 fatty acid
Aim of this talk

BPA

Epi

n-6

OBESITY

CANCER

Cancer affects us all...
BPA and the Baby bottle story

Bisphenol A (BPA) used to make polycarbonate has estrogen-like activity

Cancer affects us all...
Effect of a low dose of BPA on breast tissue

Control milk duct in mouse breast tissue

Mice treated with 25 ng BPA/kg body weight per day

25 ng is 1000-times lower than the FDA safety limit of 25 ug.

Cancer affects us all...
BPA could be acting as an anti-hormone at the in vivo concentration that hormones work.
Increase in Omega-6
Omega-6 story

Arachadonic → Inflammation → Cancer acid
Decision made by CANSA to have all margarines analysed for fatty acid contents

Forty different margarine products bought from three different commercial outlets.

4th July 2008
Margarines delivered to CSIR - 4th July 2008
RESULTS: Ratio of omega-6 to omega-3 fatty acids

• The omega-6/omega-3 ratio differs widely (up to 20-fold) when the different margarines were compared. The lowest was 2.21 and the highest was 44.30.

• There is growing consensus that this ratio should be low, in the order of 2 to 1, to be beneficial and to reduce the risk of cancer by counteracting inflammation.

• Analysis of the data showed that there were two margarine products with ratios of 2.21 and 2.31 (see red arrows).

• These two products were Blossom Canola Margarine and Blossom Canola Light Margarine.
OMEGA-6/OMEGA-3 = 2/1
What has BPA and Omega-6 got to do with obesity and cancer?
## BPA, Omega-6 and cancer

<table>
<thead>
<tr>
<th>Bisphenol A</th>
<th>Omega-6 fatty acid</th>
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### CANCER

- **BPA may be influencing the susceptibility of the mammary gland to cancer transformation**

- Canola oil (21% n-6) fed to pregnant mice had significantly fewer mammary glands with tumours than mice fed corn oil (57% n-6).

### Reference

- Munoz-de-Toro M et al., Endocrinology 2005, 146, 4138
- Ion et al., BMC Cancer 2010, 10, 81
## BPA, Omega-6 and obesity

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>OBESITY</td>
<td>Inhibits adeponectin production (1) and release (2) at nM doses.</td>
</tr>
<tr>
<td></td>
<td>Promote adipogenesis (1) Pro-inflammatory effects (2)</td>
</tr>
</tbody>
</table>

**Reference**

(1) Kidani et al., J Atheroscler Thromb, 2010, May 13
(2) Hugo et al., Environ Health Perspect 2008, **116**, 1642

Massiera et al., J Lipid Res. 2003, **44**, 271
Ailhaud et al., Br J Nutr. 2008, **100**, 461
Schmitz & Ecker, Prog Lipid Res, 2008, **47**, 147
**Epigenetic effect of BPA and n-6**

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<tr>
<th>Bisphenol A</th>
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<tbody>
<tr>
<td>Causes hypomethylation of metastable loci in murine epigenome,</td>
<td>Corn oil induces fatty acid synthase (Fas) while Canola oil represses this gene 7 to 8 fold even after 109 days off the Canola oil diet. This suggests differential PUFA-induced gene expression during pregnancy and beyond. Could be epigenetic.</td>
</tr>
<tr>
<td>Dolinoy et al., -nas, 2007, 104, 13056</td>
<td>Ion et al., BMC Cancer 2010, 10, 81</td>
</tr>
</tbody>
</table>
Time line of experiment

Canola oil
20% Omega-6
2/1

Canola oil
PREGNANCY
14

Corn oil

Epigenetic effects

FAS
5

109

30

Corn oil
57% Omega-6
57/1

mRNA results suggest that Canola diet also reduced NFκB

Ion et al., BMC Cancer 2010, 10:81

Cancer affects us all...
## Comparison of Dietary Fats

<table>
<thead>
<tr>
<th>Dietsary Fat</th>
<th>Fatty Acid Content Normalized to 100 per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canola oil</td>
<td>7% 21% 11% 61%</td>
</tr>
<tr>
<td>Safflower oil</td>
<td>10% 76% Trace 14%</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>12% 71% 1% 16%</td>
</tr>
<tr>
<td>Corn oil</td>
<td>13% 57% 1% 29%</td>
</tr>
<tr>
<td>Olive oil</td>
<td>15% 9% 1% 75%</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>15% 54% 8% 23%</td>
</tr>
<tr>
<td>Peanut oil</td>
<td>19% 33% Trace 48%</td>
</tr>
<tr>
<td>Cottonseed oil</td>
<td>27% 33% 54% Trace 19%</td>
</tr>
<tr>
<td>Lard*</td>
<td>43% 9% 1% 47%</td>
</tr>
<tr>
<td>Beef tallow*</td>
<td>48% 2% Trace 49%</td>
</tr>
<tr>
<td>Palm oil</td>
<td>51% 10% Trace 39%</td>
</tr>
<tr>
<td>Butterfat*</td>
<td>68% 3% 1% 28%</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>91% 2% 7%</td>
</tr>
</tbody>
</table>

*Cholesterol Content (mg/Tbsp): Lard 12; Beef tallow 14; Butterfat 33. No cholesterol in any vegetable-based oil.
Source: POS Pilot Plant Corporation, Saskatoon, Saskatchewan, Canada, June 1994

- **SATURATED FAT**
- **MONOUNSATURATED FAT**
- **POLYUNSATURATED FAT**
  - Linoleic Acid
  - Alpha-linolenic Acid (An Omega-3 Fatty Acid)
Important concept No.7

• Too much omega-6 and too little omega-3 in the diet before, during and after pregnancy could have a long-term epigenetic effect on gene expression relevant to cancer in mammary tissue.

• “Substituting canola oil for corn oil is an easy dietary change to make; such a change to the maternal diet may decrease risk for breast cancer in the daughter”

Ion et al., BMC Cancer 2010, 10, 81
Important concept No.8

• If NFkB is controlled epigenetically this could be a common master switch activating inflammation in adipose tissue and in cancer cells.
Important concept No. 9

• Are the carcinogenic and epicarcinogenetic factors involved in breast cancer causation coming into sight for the first time?
• Estrogen
• Estrogen-like man-made molecules (e.g. BPA)
• Pro-inflammatory, lipid, e.g. Omega-6
HYPOTHESIS

ADIPOCYTE

Adiponectin

Adipogenesis

Cancer affects us all...
HYPOTHESIS

ADIPOCYTE

Adiponectin

Adipogenesis

Cancer affects us all...
Link between Obesity and Cancer

Low grade INFLAMMATION
NF kappa B

Breeding ground

n-6

X, Y, Z

Obesity

Cancer

Cancer affects us all...
Important concept No.10

• Composition of dietary fat may contribute to adipose tissue development.
• The role of excess dietary linoleate (omega-6) has been ignored due to historical overestimation of linoleate requirements and enthusiasm for higher intake of “essential fatty acids”.
• More research is needed to address whether disequilibrium of dietary PUFA intake contributes to the risk of obesity in humans.
Important concept No. 10

1. Does unbalanced omega-6 act epigenetically in humans promoting obesity and cancer?

2. Is BPA at nanogram concentrations in blood involved in human cancer and obesity?

3. Can BPA and n-6 act synergistically to facilitate obesity and cancer?
Thank You