Dietary phytochemicals for breast cancer prevention and therapy

Maria O’Connell
School of Pharmacy

University of East Anglia
Inflammation

Cancer

Homeostasis

Natural products

Phytochemicals

Marine products
Inflammation

- Kinases
  - Nrf2
  - NFκB
  - Egr-1

- Pro-inflammatory mediators
  - Cytoprotective proteins

Cancer

- Kinases
  - Nrf2
  - NFκB
  - p53
  - Mcl-1

- Proliferation
  - Resistance

Homeostasis

Resolution
Inflammation → Cancer

Kinases

NFκB

Pro-inflammatory mediators
TNF, IL-1, IL6, chemokines, VCAM-1

Phytochemicals

Proliferation
Anti-apoptotic pathways

Homeostasis
Inflammation

Homeostasis

Cancer

Kinases

Nrf2

Phytochemicals

Cytoprotective proteins

Resistance
Chronic inflammation is associated with breast cancer.
Chronic Inflammation and Breast Cancer

- Higher levels of inflammatory markers in breast cancer
  - CRP, IL6, TNF α —correlate with cancer stage, prognosis, recurrence and survival
  - Tumor associated macrophages correlate with shorter survival
- Obesity/overweight is a chronic inflammatory condition and a risk factor for breast cancer
- Breast cancer treatments all induce local and systemic inflammation
- Breast cancer survivors have higher levels of pro-inflammatory cytokines longterm than healthy controls
Inflammation

Phytochemicals

Homeostasis

Inflammation → Cancer

Flavonoids
Organosulphur compounds
Carotenoids
Vitamins C and E
Alpha lipoic acid
Vitamin D
Bioactive peptides
Are dietary phytochemicals beneficial in breast cancer?
Dietary patterns and breast cancer

• Higher pro-inflammatory diet is associated with increased risk
  – Red meat, high fat

\[\text{VS}\]

• Mediterranean diet associated with lower risk

• Vegetable and/or grain intake is associated with decreased risk
  – Pre and post menopausal
  – Mainly ER negative breast cancer
  – Fruit
  – Conflicting data from different studies
Epidemiological evidence for the role of diet in breast cancer

- Prospective cohorts
- Case-control studies

- Several limitations
  - Normal confounders for breast cancer
  - Dietary assessment methods
  - Different populations
  - Longterm, large numbers, compliance
  - Single nutrients – type, dose and form of supplement
Plant foods linked to reducing risk or recurrence of breast cancer

- **Vegetables**
  - *Reduction*

- **Legumes**
  - *Mixed effects*

- **Fruit**
  - *Weak reduction*

- **Wholegrain**
  - *Reduction*

- **Spices**
  - *Weak*
What phytochemicals could be responsible?

<table>
<thead>
<tr>
<th>Compound</th>
<th>Effect on risk</th>
<th>Type</th>
<th>Pre/post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibre (from veg)</td>
<td>Decrease</td>
<td>ER-, PR-</td>
<td>Pre + post</td>
</tr>
<tr>
<td>Folate</td>
<td>None, Decrease</td>
<td>ER-, PR-</td>
<td>Post/pre</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Decrease</td>
<td>ER, PR</td>
<td>Pre</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Decrease</td>
<td>ER, PR</td>
<td>Pre</td>
</tr>
<tr>
<td>Vitamin C, E, α, β carotene</td>
<td>None, Decrease</td>
<td>ER-, ER-</td>
<td>Pre + post</td>
</tr>
<tr>
<td>Other carotenoids</td>
<td>None, Decrease</td>
<td>ER-</td>
<td>Pre/post</td>
</tr>
<tr>
<td>Isoflavonoids</td>
<td>None/Increase (West)</td>
<td>R- (pre), R+</td>
<td>Pre + post</td>
</tr>
<tr>
<td>Other flavonoids (phenolic acids etc)</td>
<td>Decrease (Asia)</td>
<td>(pre/post)</td>
<td>Pre</td>
</tr>
<tr>
<td>Lignans</td>
<td>None, Decrease</td>
<td>R+/R-</td>
<td>Pre/post</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Decrease/None</td>
<td>ER-, PR- trend</td>
<td>Post</td>
</tr>
<tr>
<td>Organosulfur compounds</td>
<td>Decrease/None</td>
<td>R+/R-</td>
<td>Pre + post</td>
</tr>
</tbody>
</table>
Phytochemicals reduce tumor burden in ER+ animal models

- Organosulfur compounds
- Caffeine
- Flaxseed
- Stilbenes – resveratrol
- Vitamin E
- Carotenoids
  - Lycopene
- Flavonoids
  - Berries, pomegranate, phenolic acids, curcumin, isoflavonoids, xanthohumol, quercetin etc etc

Bak et al 2016
Mechanisms of action of phytochemicals in inhibiting breast cancer

Phytochemicals

- ER binding or expression
- Proliferation
- Metastasis
- Epigenetic changes
- Glucose uptake and metabolism
- Apoptosis
- Angiogenesis
- Inflammation
- Cell cycle
- Sensitisation to radiation and chemotherapy
Effects of isoflavones on breast cancer cells

Isoflavones (Genistein/Daidzein/Equol)

- ERα and β binding +/- effects
- Proliferation: Decrease/Increase (ER+/ER-)
- Metastasis
- Oxidative stress: Decrease/Increase

Sensitisation and resistance to chemotherapy

- DNA methylation
- NFκB, MMP2

Apoptosis (ER+/ER-)

- Cell cycle (ER+/low ERα:β)
- Inflammation
- NFκB, MMP2, Casp
- CYP1B1, PP2A

Glucose and lactate uptake and metabolism

Tumor suppressor expression

- pAkt, Bcl2/Bax, XIAP

Chemotherapy sensitisation and resistance
Mechanisms of action of flavonoid inhibition of breast cancer

Li et al Nutrients 2017
Keating & Martel, Front Nutr 2018
Dandewate et al 2016

Flavonoids

- Proliferation (ER+/-)
  Ellagitannins, Citrus, Naringin, Hesperidin, Apple, Mango, Ellagic acid, Ursolic acid, EGCG, Quercetin

- Metastasis
  Ellagitannins, Citrus, Apple, Grape, Quercetin

- Oxidative stress
  Mango, Berries, Quercetin

- Glucose uptake and metabolism
  Naringenin, hesperitin, quercetin, EGCG, myricetin, kaempferol etc

- Inflammation
  Apple, Grape, EGCG, Quercetin

- Apoptosis
  Ellagitannins, Xanthones, Citrus, Naringin, Apple, Mango, Ellagic acid, Ursolic acid, EGCG, Quercetin

- Cell cycle
  Ellagitannins, Naringin, Apple, Grape, Quercetin

- Angiogenesis
  Citrus
Anti-inflammatory effects of flavonoid metabolites

Inhibited:
- TNF secretion in monocytes
- VCAM-1 expression in endothelial cells

Metabolites > Parents
Combinations – synergistic effects

Bohn et al 2012
Di Gesso et al 2015 Mol Nutr and Food Res
Warner et al 2016 J Nutr
Warner et al 2017 Mol Nutr Food Res
Cruciferous Vegetables

- **Glucosinolates ➔ Isothiocyanates**
  - Benzyl isothiocyanate (BITC)
  - Phenethyl isothiocyanate (PEITC)
  - Sulforaphane (SFN)

- **Indole-3-carbinol ➔ 3,3’-diindolylmethane**
  (I3C) (DIM)
Mechanisms of action of phytochemicals in inhibiting breast cancer

Cruciferous vegetables

ER expression
SFN, I3C

Proliferation
BITC, PEITC, SFN, I3C, DIM

Metastasis
BITC, PEITC, I3C, DIM

Autophagy
BITC

Epigenetic changes
SFN

Sensitisation to chemotherapy
DIM

Cell cycle
I3C, DIM

Apoptosis
BITC, PEITC, SFN, I3C, DIM

Angiogenesis
BITC, PEITC

Inflammation
SFN

Stem cell formation and EMT
I3C

Li et al Nutrients 2017
## Spices

<table>
<thead>
<tr>
<th>Spice</th>
<th>Active compound</th>
<th>Risk</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginger</td>
<td>Gingerols, Shogaols</td>
<td>Only improved nausea</td>
<td>Inhibits growth and metastasis, induces autophagy, apoptosis and cell cycle arrest</td>
</tr>
<tr>
<td>Garlic</td>
<td>Diallyl sulfides, S-allyl mercaptocysteine, Allicin</td>
<td>Decrease/None</td>
<td>Inhibits growth and metastasis, ERα, inflammation, induces apoptosis and cell cycle arrest</td>
</tr>
<tr>
<td>Black cumin</td>
<td>Thymoquinone</td>
<td>Increase risk??</td>
<td>Inhibits/promotes growth, induces apoptosis/cell cycle arrest</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Curcumin</td>
<td>Reduced severity of radiation</td>
<td>Inhibits growth, angiogenesis, metastasis, tumor inflammation, cancer stem cells, induces apoptosis, cell cycle arrest, CTL, senescence</td>
</tr>
<tr>
<td>Red chili pepper</td>
<td>Capsaicin</td>
<td></td>
<td>Inhibits growth and metastasis, induces apoptosis</td>
</tr>
<tr>
<td>Black pepper</td>
<td>Piperine</td>
<td></td>
<td>Inhibits growth and metastasis, induces apoptosis</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>Cinnemaldehydes</td>
<td></td>
<td>Inhibits proliferation/angiogenesis, induces apoptosis/cell cycle arrest</td>
</tr>
</tbody>
</table>
Diallyl sulfides in garlic activate the Nrf2 pathway in monocytes – potency related to number of sulfurs

Garlic oils induce Nrf2 and HO-1, NQO1 and ferritin

Jonathan Cowan
# Selective activation of Nrf2 by dietary compounds

<table>
<thead>
<tr>
<th>Activators</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Catechins</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Sulforaphane</td>
<td>Resveratrol</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Triterpenoids</td>
</tr>
<tr>
<td>Alpha lipoic acid</td>
<td>Flavonoid metabolites</td>
</tr>
<tr>
<td>Diallyl sulfides</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
</tr>
</tbody>
</table>

*Rushworth et al, 2006; Ogborne et al, 2005; Ogborne et al 2008; L Wherry, R Norton*
Obesity

Inflammation  Breast Cancer
In addition to an anti-inflammatory diet...........

- Combinations of phytochemicals
- Phytochemicals in combination with cytotoxics
- Novel formulations eg nanoparticles
- Biosynthesis in plants
Acknowledgements

O’Connell Group
Nursabah Atli
Saurabh Prabhu
James Reed
Jenna Bradley
Jonathan Cowan
Jess Di Gesso
Lydia Wherry
Rosemary Norton
Stuart Rushworth
Richard Ogborne
Marco Cominetti

Collaborators
Pharmacy and UEA
Mark Searcey
Chris Hamilton
Rob Stockman

NCSU
Colin Kay

John Innes
Anne Osbourn

Jena
Otto Witte
Christiane Frahm

Taiwan NCDC
Ann Chen
Maria Ka

Funding  BBSRC, MRC, CEC, UEA