## Disclosures for: [Ailsa Welch]

<table>
<thead>
<tr>
<th>AFFILIATION/FINANCIAL INTERESTS</th>
<th>CORPORATE ORGANIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grants/Research Support:</td>
<td>None</td>
</tr>
<tr>
<td>Scientific Advisory Board/Consultant:</td>
<td>None</td>
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<tr>
<td>Speakers Bureau:</td>
<td>None</td>
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<tr>
<td>Stock Shareholder:</td>
<td>None</td>
</tr>
<tr>
<td>Other Financial or Material Support/Honorarium:</td>
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</table>
DIET AND BREAST CANCER: NEW APPROACHES ARE NECESSARY

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28/4/14
Overview

- Aims and challenges for the IBCN
- Dietary assessment
  - Methodological challenges
  - Measurement error
- Biomarkers of nutritional intake
- Experiences of measuring nutrition in the European Prospective Investigations into Cancer and Nutrition Study (EPIC-Europe, EPIC-UK, EPIC-Norfolk)
- New methods for the IBCN
Diversity of Diet

- Wide exposure of dietary intakes
- Extreme differences in dietary patterns
- Expectation: this will lead to better understanding of relationships between diet and breast cancer mechanisms
Purpose of new approaches for IBCN

- Overall aim: to capture diet more accurately than previously possible, at same time as obtaining breast cancer tissue samples

- Aim to collect
  - Dietary intakes
  - Diet composites
  - Biomarkers/nutrient status measurements (indicators of nutritional exposure)

- Aim to relate dietary composition to epigenetics in breast cancer tissue samples
Challenges

- Diverse populations
- Capturing diet by self report complex
  - Some challenges with measurement error in dietary assessment
- Biomarkers
  - Some challenges with measurement and interpretation
- Some problems to be faced:
  - Literacy
  - Computer availability
  - Trust of researchers
Overview

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Assessment of dietary intake

- Self-reported or interviewed reports of intake
  - Current or retrospective
- Dietary composites — direct analysis of composition of foods
- Biological markers (biomarkers) of nutritional status
Examples of dietary methods: Open ended versus fixed structure (used in EPIC-Norfolk cohort)

**Record/Diary**
- 7-day diary
- Detailed text information
- Requires interpretation
- Labour intensive

**Frequency/FFQ**
- FFQ (Food Frequency Questionnaire)
- Epidemiology
  - Simpler, limited food list. Fixed structure
  - Intakes many nutrients
  - Measurement error

Welch AA, PHN, 2001
Welch AA, J Hum Nut Diet, 2005
Methods – principles of obtaining dietary data for analyses in studies

Collect intake data from individuals

Convert into data for analysis

Examples of challenges with databases

Recorded data
Frequency X amount food

Database of nutrients, bioactive phyto-chemicals

Total intake nutrients, bioactive phyto-chemicals
Food nutrient databases: challenges

- Limited food coverage
- Infrequently updated
- Limited coverage nutrients/bioactives
- Nutrient variability: carotenoids
- Different analytical techniques e.g. fibre, AOAC, Englyst
- Not all databases are consistently comparable across countries (potential bias)
Measurement error in dietary assessment

- Definition: difference between the measured exposure and the true exposure for diet

- Potential contributory causes for IBCN
  - Questionnaires – omitted foods
  - Length of period of recording
  - Respondent/social desirability bias
  - Interviewer bias
  - Data entry and issues with supporting databases
Example of importance of differences between diet methods
Effects of methodological differences in estimates of consumption on population monitoring (same subjects within same cohort) – fruits and vegetables

FFQ > estimates fruit & vegetables than ‘real time/record’ methods

Compared with 5-a-day recommendations

Challenges for policy

Methods ranked similarly against plasma vitamin C

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Nutritional biomarkers are indicators of nutritional exposure:
- Nutrients
- Bioactives
- More recently: other metabolites
Examples of biomarkers for estimating intake of nutrients/bioactive compounds

**Quantitative recovery**
Absolute value over period of time (integrates over time), 24-hr urine
- N, Na, K, sucrose, fructose, thiamin
- Energy – Doubly Labelled Water (DLW)
- Fruit & vegetables: hippuric acid (Krupp D, 2012)
- Whole-grain: Total alkylreoscinol, DHBA (3, 5-Dihydroxybenzoic acid), DHPPA (3-(3,5-Dihydroxyphenyl)-Propanoic acid) (Hedrick V, 2012)

**Concentration**
Relative ranking blood/skin
- **Nutrients**: vitamins C, E, D, B12, folate, fatty acids, carotenoids (recent skin – Mayne S, 2013)
- **Bioactives**: flavonoids, isoflavones

**Adipose tissue**
- Fatty acids, fat soluble vitamins
Biomarkers of nutritional intake

Utility for direct measurement of diet influenced by:

- Genetics
- Gender
- Homeostatic influences – integrated effects of metabolism
- Physiological effects (plasma vitamin C lower with higher waist:hip ratio)
- Behavioural influences (smoking & plasma vitamin C)
- Non-linear associations (vitamin C plateaus)
- Measurement error in lab
- Limited number available, though number expanding (metabolomic approaches)
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European Prospective Investigation into Cancer and Nutrition

- EPIC-Europe multi-center cohort study of diet and cancer
- 10 countries – started 1993
- 450,000 participants
- EPIC-Norfolk cohort 25,000 people 45-74 Y
- Extended to other chronic diseases eg CVD, diabetes, osteoporosis
- Diverse dietary patterns
- Different dietary assessment methods – literacy challenges
- Different food composition databases
Solutions within EPIC

**Databases - standardisation**
- Developed European Nutrient Database (ENDB)
- Standardisation project for EPIC – Europe, to reduce potential bias between countries
- 550-1550 foods/country
- National compilers, food chemists, EPIC nutritionists (Slimani et al, EJCN 2007)

**Biomarker validation**
- Biomarkers in subsets of the populations for validation of dietary methods. Used urine N, K & blood carotenoids (Bingham SA et al IJE, 2008)

**Dietary calibration**
- Development of standardised computer program for 24-hour interviews: EPIC SOFT
- Standardised: photographs for portions, conversion factors for food wastage, cooking changes, collection of descriptors for foods
- Interviews in subset of each cohort
- Data used to ‘calibrate’ main study analyses relating diet to cancer incidence (Bingham SA, Lancet 2003)

Highly labour intensive
Example of solution to measurement error: using calibration of dietary intake with a biomarker in relation to disease outcome

- **Protein intake & frailty** (Beasley JM, J Am Ger Soc, 2010). Debate on protein recommendations for frailty prevention.

- Calibrated using DLW & N excretion in subsample

- Calibrated values of FFQ used to estimate incident frailty (covariates: BMI, age, race, education, income, smoking & physical activity)

- OR of incident frailty in women 65-79Y

- > association with calibrated % protein intake (per 20% increase in protein versus uncalibrated protein intake)
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Proof of principle study

Aim to test feasibility of international sample collections

Phase 1 – diet composites

- Design 1 or 2 dietary patterns that represent common eating patterns in your region. Ideally from nationally representative data. To reflect appropriate energy intake for a woman 18-45 year old

Phase 2 – 24 H diet record, diet composite, fasting blood & urine

- Collect samples from generally healthy subjects consuming diets representative of the region.
- Record all eaten and drink
- Collect duplicate composite
- Following day – collect fasting blood and urine sample
Summary of participation in the IBCN project: Phase 1

<table>
<thead>
<tr>
<th>Country</th>
<th>Diet Pattern</th>
<th>Basis for Diet Pattern</th>
<th>Diet Homogenate</th>
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<tbody>
<tr>
<td>Lebanon</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>France</td>
<td>X</td>
<td>X</td>
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<tr>
<td>USA</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>China</td>
<td>X</td>
<td></td>
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<tr>
<td>England</td>
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<tr>
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<tr>
<td>Ghana</td>
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## Results: Dietary diversity, number of food items

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of foods</th>
<th>Beverages</th>
<th>Condiments, etc.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>6</td>
<td>0</td>
<td></td>
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<tr>
<td>UK</td>
<td>17</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>USA</td>
<td>10</td>
<td>5</td>
<td>4</td>
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<tr>
<td>Lebanon</td>
<td>11</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Uruguay</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>France</td>
<td>13</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

*Includes butter, jam, salt, oil, sugar, salad dressing, cream*
Results: mineral intakes in 4 countries (Ca, Mg, Na, K)
Results: mineral intakes in 6 countries (Ca, Mg, Na, K)
Results: mineral intakes in 4 countries (Cu, Fe, Zn)

<table>
<thead>
<tr>
<th>Mineral</th>
<th>United Kingdom</th>
<th>USA</th>
<th>Lebanon</th>
<th>Uruguay</th>
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<tbody>
<tr>
<td>Cu</td>
<td>18.0</td>
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<td>Fe</td>
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<td>31</td>
<td>31</td>
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<tr>
<td>Zn</td>
<td>18.0</td>
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US DRI – 31-50 Y
## Summary of progress on phase 2

<table>
<thead>
<tr>
<th>Country</th>
<th>Ethics Approval</th>
<th>Number Enrolled</th>
<th>Diet Homogenate Received</th>
<th>Menu &amp; preparation Data</th>
<th>Blood samples Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebanon</td>
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<td>France</td>
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<td>Uruguay</td>
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<tr>
<td>Ghana</td>
<td>X</td>
<td>2</td>
<td>X</td>
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</table>

** Close to having approval
Learning points & experiences

1. Some countries required special letters from Purdue indicating the contents and reason for shipping the diet homogenates.
2. Shipping generally completed in 4-9 days
3. Requirements for ethics approval vary greatly. Requests from various countries:
   - A proposal for the entire project
   - Record of human subjects training approval (CITI) for Dr. Weaver
   - A literature review on the topic
   - Many countries have not completed the ethics approval as the process is slow and complicated depending on the institutional infrastructure.
   - Memorandum of Agreement with Purdue University required (1 country)
4. US cannot ship supplies for Part 2 until a copy of the ethics approval has been obtained from the country institution.
Further learning points

- There was variation in the type of information received with the diet shipments (weights, menus) so the documents and instructions need to be improved.
- Emphasizes the problems working across cultures & disciplines.
- Setting up a protocol is not enough when working across countries.
  - Solution is potential training.
Conclusion

- Extensive progress
- Completion of first stages demonstrate the project is possible

- THANK YOU FOR LISTENING