Outline

• How do we know whether/how diet is related to cancer?
• What more do we need to know?
• Why is multidimensionality important, and what are the key questions?
• Why is dynamism important, and what are the key questions?
• Wrap-up
How do we know whether/how diet is related to cancer?
Hierarchy of evidence

- Systematic reviews
- Randomized control trials
- Cohort studies
- Case-control studies
- Cross-sectional surveys
- Case reports
- Expert opinion
Systematic evidence review criteria

Is the review based on a focused question that is adequately formulated and described?

Were eligibility criteria for included and excluded studies predefined and specified?

Did the literature search strategy use a comprehensive, systematic approach?

Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?

Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?

Were the included studies listed along with important characteristics and results of each study?

Was publication bias assessed?

Was heterogeneity assessed?
WCRF/AICR follows established criteria

http://www.aicr.org/reduce-your-cancer-risk/
WCRF/AICR cancer prevention recommendations

http://www.aicr.org/reduce-your-cancer-risk/
WCRF/AICR cancer prevention recommendations
|-----------------------------------------|--------------------|----------------------|------------------------|------------------------|--------------------------|------------------------|--------------------------|-------------------|-------------------|-----------------|----------------------|---------------------| |
| Processed meat                          |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Canteen-style boiled fish                |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Diets high in calcium                   |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Foods preserved by salting              |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Glycemic load                           |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Arsenic in drinking water               |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Salt                                     |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Alcoholic drinks                         |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Coffee                                  |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Beta-carotene                           |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Physical activity                       |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Body fatness                            |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Adult attained height                   |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Greater birth weight                    |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |
| Lactation                               |                    |                      |                        |                        |                          |                        |                          |                   |                   |                 |                      |                     | |

In partnership with
- American Institute for Cancer Research
- World Cancer Research Fund
- World Cancer Research Fund
- World Cancer Research Fund
- World Cancer Research Fund
| Foods containing dietary fibre | Allulose | Non-starchy vegetables | Allium vegetables | Garlic | Fruits | Red meat | Processed meat | Chinese-style salted fish | Diets high in calcium | Foods preserved by salting | Glycemic load | Arsenic in drinking water | NAM | Alcoholic drinks | Coffee | Beta-carotene | Physical activity | Body fatness | Adult attained height | Greater birth weight | Lactation |
|--------------------------------|---------|------------------------|-------------------|--------|--------|---------|-------------|--------------------------|---------------------|-------------------------|----------------|----------------------------|--------------|-------------------------|------|--------------|-------|-------------|----------------|-------------|-------------------|-------------------|---------|

In partnership with

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In partnership with
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What more do we need to know?
“…even a small insect is much more complicated than a star, and… everything about humans is very complicated…”

Considering the confusion about diet, “It’s not that the people working in those fields are less competent, it’s that anything to do with humans and their behavior … is far more complicated than the cosmos…”

Lord Martin Rees, Cosmologist and Astrophysicist, On Being, November 21, 2013
Definition of “dietary patterns”

“... the quantities, proportions, variety, or combination of different foods, drinks, and nutrients (when available) in diets, and the frequency with which they are habitually consumed”
Further extend this definition to include:

**Multidimensionality**
- Diet is a complex exposure: it is multilayered and multidimensional

**Dynamism**
- Diet is a dynamic exposure: it varies over time, at both shorter and longer intervals
Why is multidimensionality important?
Diet is multidimensional

Macro-nutrients

Fat

Diet

Protein

Carbohydrate
Diet is multidimensional

Vitamins and minerals

- Vitamin D
- Folate
- Zinc
- Selenium
- Vitamin C
Diet is multidimensional

- Blueberries
- Green tea
- Broccoli
- Garlic

Foods
Diet is multidimensional
Diet is multidimensional

- Pizza
- Tacos
- Burgers
- French fries
- Milk-shakes
- Fruit juice

Foods as eaten
Diet is multidimensional

- Temporal
- Social context
- Specific constituents

Diet components:
- Resveratrol
- Genistein
- Quercetin
- Curcumin
- Isoflavones
- Catechins
Multiple dimensions compound complexity

SYNERGY

INTERACTIONS
What are the key questions regarding multidimensionality?
Selective Diets
(e.g., Vegetarian)

Who are the vegetarians?

I am!

Exclude
- Meat
- Fish
- Poultry
- (Eggs)
- (Milk)

Include
- Fruits?
- Vegetables?
- Whole grains?
- Refined grains?
- Added sugars?
- Solid fats?
Indexes/Scores

How close is the population to meeting a set of dietary recommendations?

Overall Diet Quality: Total score = 58/100
Cluster Analysis

Are there groups of people with distinct eating patterns?

Groups **people** according to their dietary patterns
Factor Analysis

What are the dietary patterns in this population?

Identifies elements of the diet that track together

Factor 1
- Red meat
- Potatoes
- Soft drinks

Factor 2
- Salads
- Yogurt
- Nuts and seeds

Factor 3
- Cereal
- Milk
- Fruit

What elements of the diet track together in explaining variation in diets?

Identifies elements of the diet that track together
Hypothesis Testing

- **Selective Diets**: People who meet/don’t meet criteria
- **Indexes/Scores**: Individuals’ scores on quality and its components
- **Cluster Analysis**: Groups of individuals and their diet patterns
- **Factor Analysis**: Factors explaining variation in individuals’ scores

**Regression Model**

**How do dietary patterns relate to health outcome?**
Findings This systematic review included 21 articles from prospective cohort studies and one article from an RCT published since 2000 that examined the relationship between dietary patterns and risk of colorectal cancer.

The articles used diverse methodology to assess dietary patterns. Nine articles used indices and scores to assess dietary patterns, 10 articles used data-driven methods and three used other approaches.

The dietary patterns examined in this systematic review were defined in various ways, making comparisons between articles difficult. However, despite general heterogeneity in this body of evidence, some protective dietary patterns emerged, particularly in articles where patterns were defined by index or score; articles using data-driven methods were less consistent.

- Patterns emphasizing vegetables, fruits, fish and seafood, legumes, low-fat dairy, and whole grains were generally associated with reduced risk of colorectal cancer.
- Patterns higher in red and processed meats; potatoes and French fries; and sodas, sweets, added sugars were generally associated with increased risk of colorectal cancer.

The relationship between dietary patterns and colorectal cancer risk often varied by sex and tumor location. Results based on analysis by sex were mixed, while analysis in tumor subgroups seemed to indicate that dietary patterns may be more strongly associated with tumor development in distal regions of the colon and rectum.
Dietary Patterns Methods Project

a systematic comparison of diet quality indices with mortality
Adjusted for age, race/ethnicity, education, marital status, physical activity, smoking, energy, BMI, diabetes, alcohol (HEI & DASH), HRT (women only).
Perfect HEI score
Average HEI-2010 component scores, by quintile of total score

Data Source: AARP study, FFQ, total scores = 52, 63, 69, 74 and 80
Average HEI-2010 component scores, by quintile of total score

Data Source: AARP study, FFQ, total scores = 52 and 80
10 randomly selected females within quintile 1 of total HEI-2010 score

Data Source: AARP study, FFQ, range of total scores = 37-58
10 randomly selected females within quintile 5 of total HEI-2010 score

Data Source: AARP study, FFQ, range of total scores = 76-89
Are different patterns of overall high quality equally protective?
Indexes, modifications and hypothesis testing

Are all components of pattern necessary or is a subset sufficient?

Necessary?  Sufficient?
Sorting of population, indexes, and hypothesis testing

Is recommended pattern of eating optimal/necessary/sufficient for everyone?

Ideal for some?

Ideal for others?
Why is dynamism important?
Cancer has a long latency

- DNA damage to cells
- Abnormal cell growth
- Lesion
- Metastasis
- Diagnosis
- Treatment
Cellular processes are influenced by diurnal variations

**WAKE/FEEDING**
- Liver: Glycogen, cholesterol, bile acid synthesis, insulin secretion
- Pancreas: Lipogenesis, adiponectin production
- Fat: Fatty acid synthesis, glycolytic metabolism
- Muscle: Oxidative metabolism

**SLEEP/FASTING**
- Liver: Gluconeogenesis, glycogenolysis, mitochondrial biogenesis
- Pancreas: Glucagon secretion
- Fat: Lipid catabolism, leptin secretion
- Muscle: Oxidative metabolism

What are the key questions regarding dynamism?
Long-term

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<th>Infancy and Childhood</th>
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Do specific time periods represent heightened risk?
Life transitions and diet change

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<tr>
<td>Reflects maternal diet</td>
<td>Breast/formula fed?</td>
<td>Food intake independent of parents</td>
<td>Partner, children influence food choices</td>
<td>Dietary change explored or necessary</td>
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<td>Food preferences established</td>
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“Overall, the IOM finds that major advances have been made in understanding breast cancer and its risk factors, but more needs to be learned about its causes and how to prevent it. The report urges a life-course approach to studying breast cancer because new information suggests that women and girls might be more susceptible to some risk factors during certain life stages.”
Atomic bomb radiation and breast cancer

Estrogen levels throughout life

Most breast cancer studies

Kushi, Workshop: Extending Methods in Dietary Patterns Research, 2016
Risk of early puberty by infant feeding practice*


*BCERP studies
Does risk or benefit accumulate over time?

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Development of Cancer

Infancy and Childhood
- Breast Feeding
- Infections/PEM
- Micronutrients
- Contaminants (air, food, water)
- Growth rate
- Stature
- Behaviours
- Physical Activity
- Food choice
- Obesity

Adolescence

Adult Life
- Smoking
- Contaminants (air, food, water)
- Timing of puberty
- Obesity
- Physical activity
- Inactivity (exercise and sedentarism)

Older ages
- Pregnancy and Lactation
- Established adult risky behaviours
- Diet and Physical activity
- Tobacco, Alcohol

Exposure to Carcinogens

Accumulated risk

Genetic susceptibility to Cancer

Age

Uauy and Solomons, J Nutr., 2005
Does a change in diet alter the course of the risk profile?

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Healthy diet

Unhealthy diet
Short-term

What are the patterns of eating frequency?

- 6 am
- Noon
- 6 pm
Examples of eating frequency patterns

A. 3 meals and snacks
B. 3 meals consumed during the day
C. 2 meals no breakfast
D. 3 small meals
E. Complete fast

Common Diet

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Mattson et al., *P. Natl. Acad. Sci. USA*, 2014
Short-term

If we alter eating frequency, does it modify the biology?
Short-term metabolic effects

**Wake/Feeding**
- Liver: Glycogen, cholesterol, bile acid synthesis
- Pancreas: Insulin secretion
- Fat: Lipogenesis, adiponectin production
- Muscle: Fatty acid synthesis, glycolytic metabolism

**Sleep/Fasting**
- Liver: Gluconeogenesis, glycojenolysis, mitochondrial biogenesis
- Pancreas: Glucagon secretion
- Fat: Lipid catabolism, leptin secretion
- Muscle: Oxidative metabolism

Circadian Coordination of Metabolism and Energetics

- Rise in blood pressure
- Highest probability of death
- Lowest body temperature
- Deepest sleep
- Melatonin secretion starts
- Menopausal hot flashes at worst
- Cholesterol synthesis elevated
- Highest body temperature
- Highest blood pressure
- Greatest cardiovascular & muscle strength
- Best coordination
- Noon 12:00
- WAKE/FEEDING
- Midnight 00:00
- SLEEP/FASTING
Downstream effects on health

Putting it all together...
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Key takeaways

Evidence-based reviews that follow strict criteria represent the pinnacle of research quality.

The WCRF/AICR recommendations are based on reviews which follow such criteria.

Diet is extraordinarily complex, involving both multidimensionality and dynamism.

Diets are multi-dimensional on a number of layers and dynamic in both the short-term and long-term

Patterns of multidimensionality and long- and short-term dynamism may be critical to cancer control

Further research into patterns of multidimensionality and dynamism may help elucidate better understanding of relationship between diet and cancer risk.
# Acknowledgements

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