



University of
BRISTOL



World
Cancer
Research
Fund International

Novel method for reviewing mechanistic evidence on diet, nutrition (including body composition), physical activity and cancer

Sarah Lewis

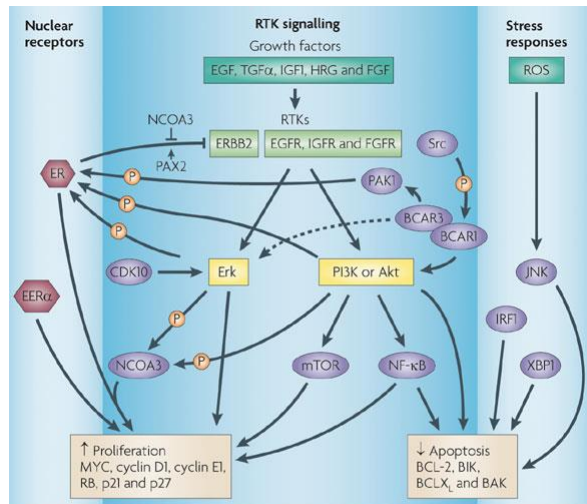


Conflict of interest: None

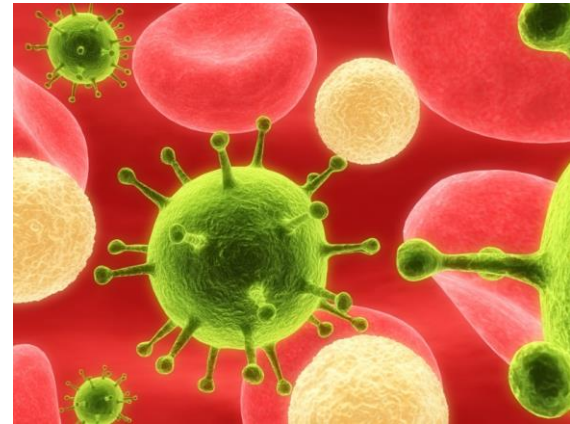


Aim

To develop and publish methodology for carrying out rigorous systematic reviews of mechanistic studies.



Nature Reviews | Cancer



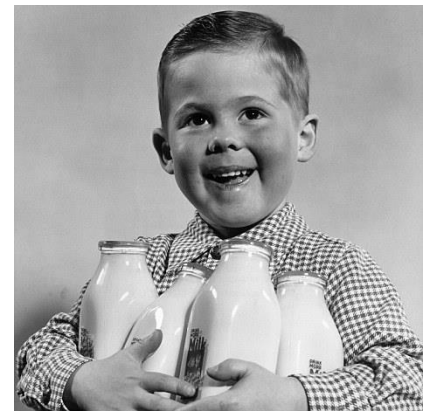
Why is this important?

- ▶ Wealth of data on potential mechanisms often not taken into account.
- ▶ Methods for combining information from human, animal and cell studies are lacking.
- ▶ Need to identify gaps in the research.



Milestones

- ▶ Develop a method for searching for relevant mechanisms
- ▶ Develop a method for systematically reviewing specific mechanisms
- ▶ Test the methodology above using a case study



Analytical approach

- ▶ Large multi-disciplinary group
- ▶ 5 workshops -mixture of presentations with discussion, small group exercises, round table discussions
- ▶ On going searches, and development of methods, feedback to members of the team
- ▶ Regular meetings between PIs and research associates



Stage 1- **Search for mechanisms**



Searching for studies

Incorporate an exhaustive list of mechanistic targets
(**intermediate phenotypes**-eg hallmarks of cancer,
hormones etc)

Three sets of searches:

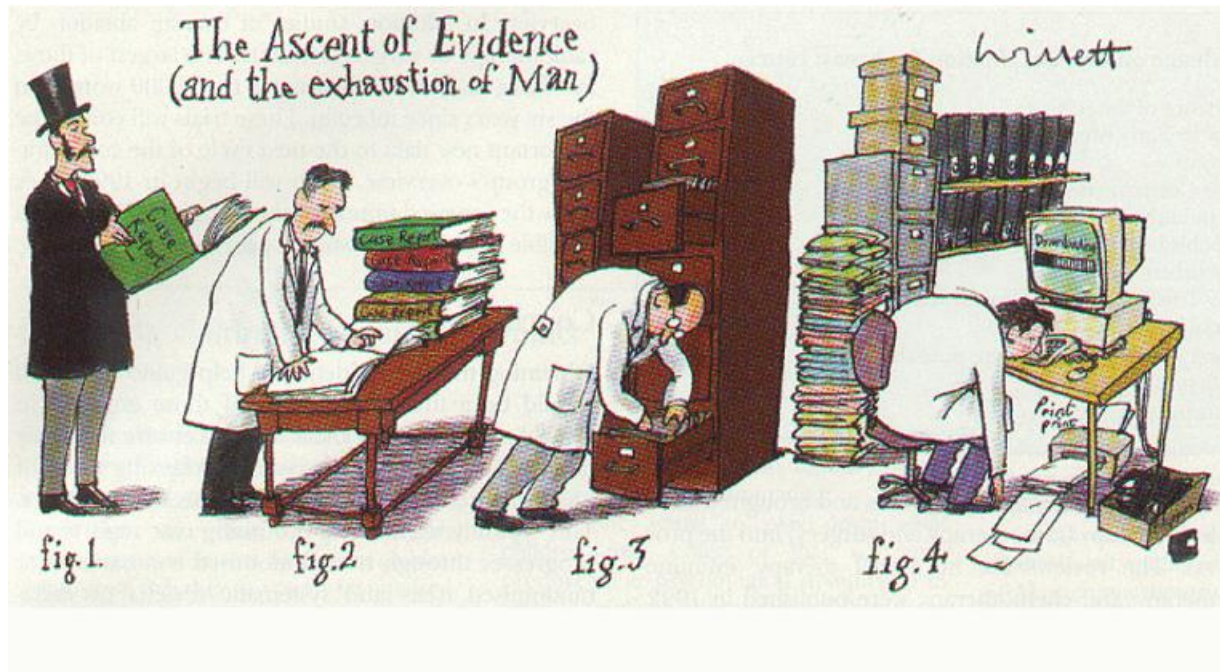
Exposure-Outcome ($E \rightarrow O$)

Exposure-Intermediate phenotype ($E \rightarrow IP$)

Intermediate phenotype and Outcome ($IP \rightarrow O$)



Why automate the search for mechanisms?

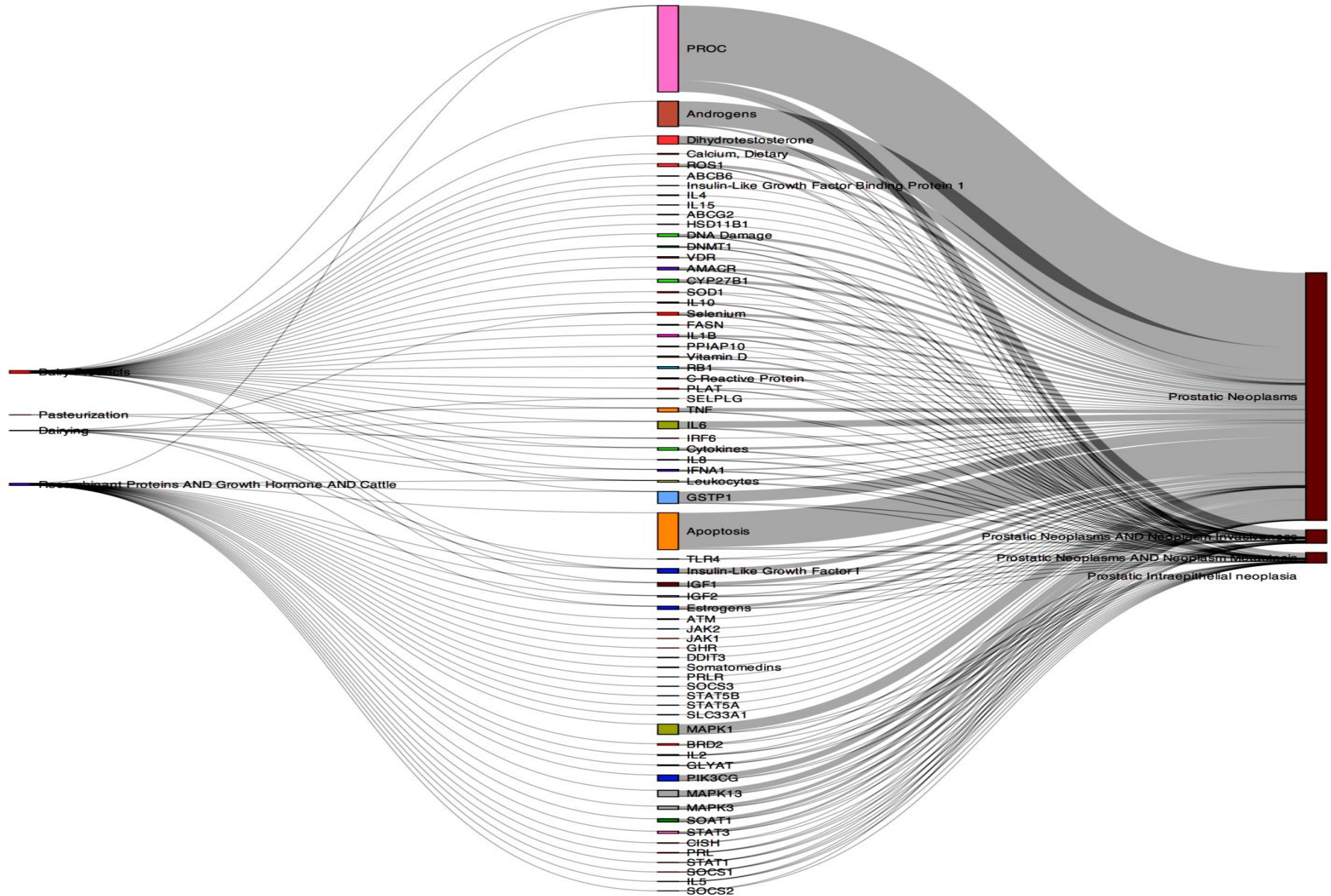


Introducing **TeMMPo: Text Mining for Mechanism Prioritisation** -Tom Gaunt

- ▶ Identifies co-occurrence of MESH headings in scientific publications to indicate papers that link an intermediate mechanism to either an exposure or an outcome.
- ▶ <https://www.temmpo.org.uk/>

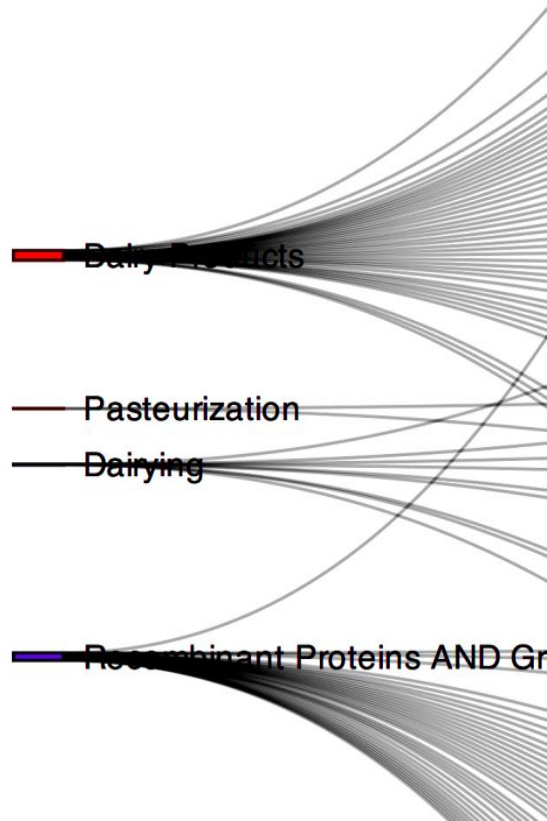


Sankey plot

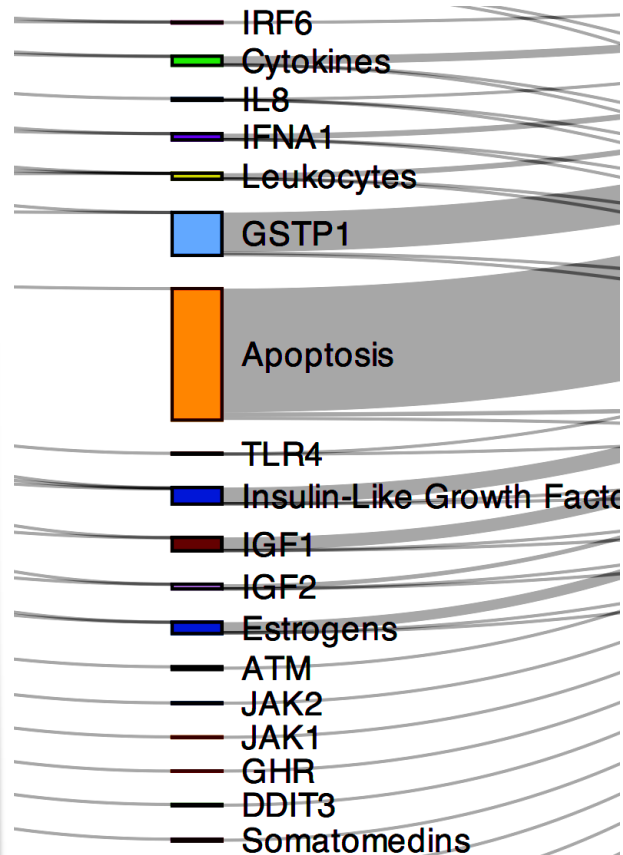


Automated mechanism quantification and display

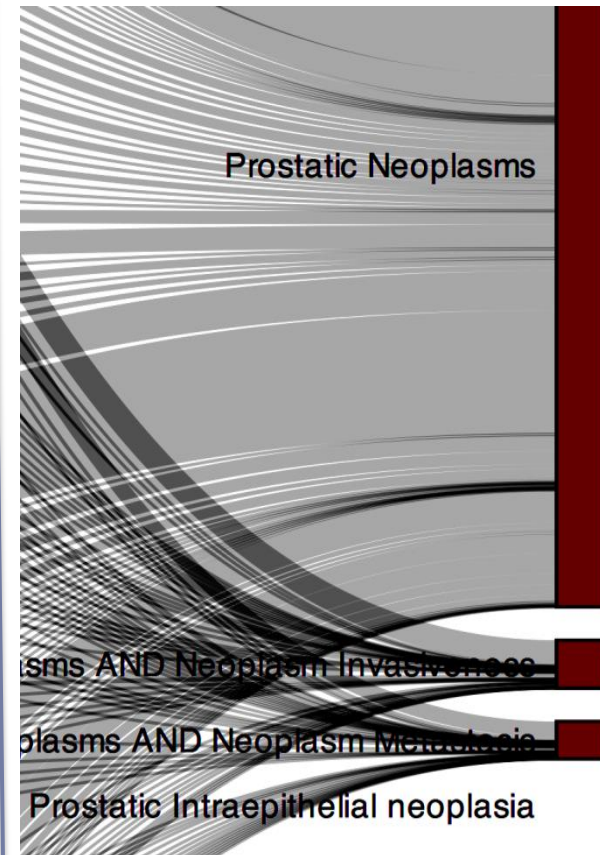
EXPOSURES



INTERMEDIATE MECHANISMS



OUTCOMES



Stage 2-Systematic review of a specific mechanism



Step 1: Specify research objectives

Step 2: Search for studies

Step 3: Apply inclusion/exclusion criteria, including an assessment of relevance

Step 4: Extract data

Step 5: Assess the quality of individual studies

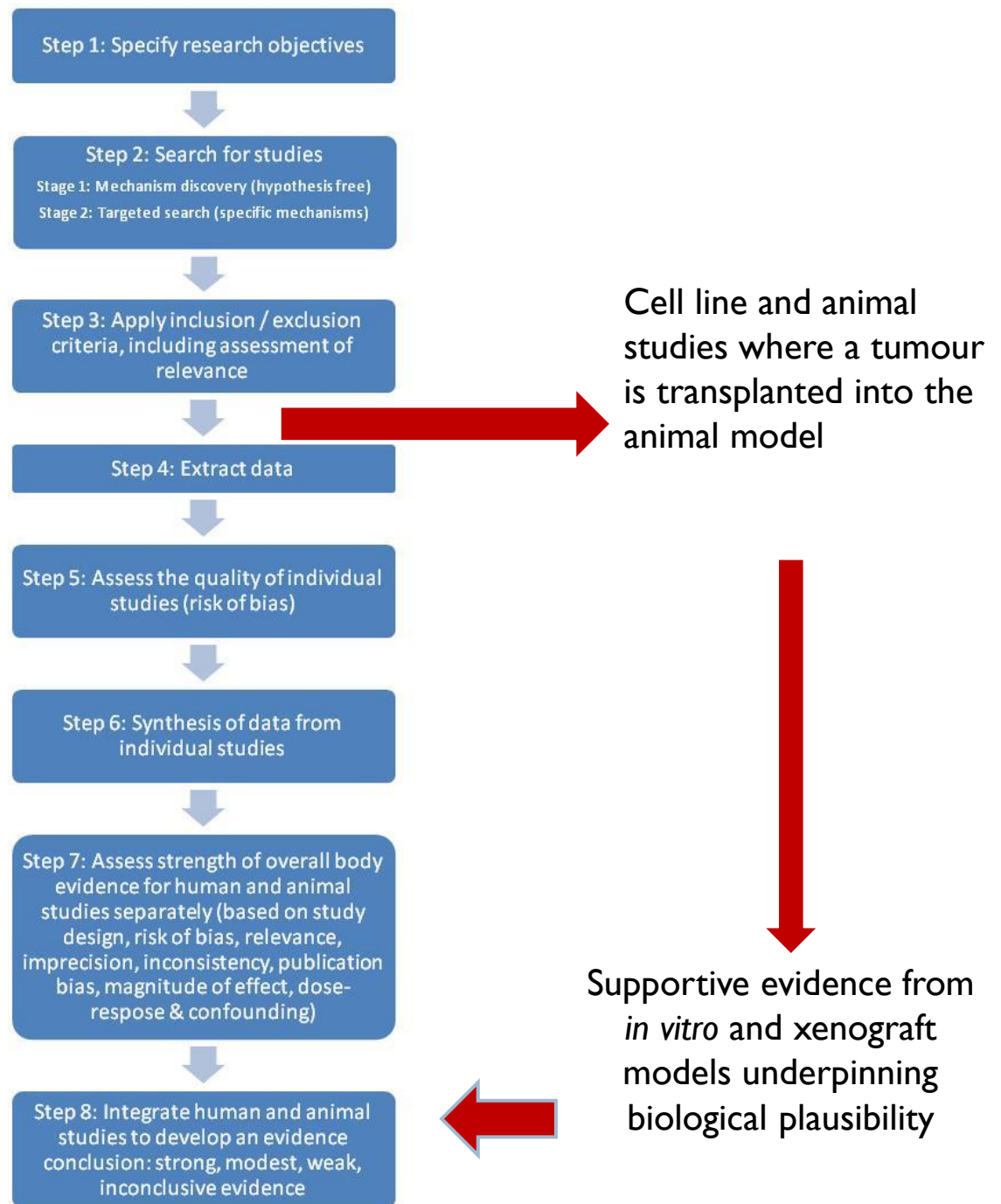
Step 6: Synthesis of data from individual studies

Step 7: Assess strength of overall body of evidence for human and animal studies separately

Step 8: Integrate human and animal studies to develop an evidence based conclusion

Step 9: Synthesis of supporting evidence from *in vitro* and xenograft models underpinning biological plausibility

Question 1 - Has the cancer arisen in the animal model rather than being transplanted into the animal?.



Wider potential impact

- ▶ Apply this to WCRF systematic review of diet, physical activity and cancer
- ▶ Apply this to other systematic reviews of cancer
- ▶ Apply this to research on other diseases



Strengths

- ▶ Allows identification of potential mechanisms
- ▶ Quantity and quality of data on specific mechanisms can be assessed
- ▶ Data from human and animal studies can be assessed together
- ▶ Will help to identify gaps in the research



Limitations

- ▶ Time consuming
- ▶ Requires a multi-disciplinary team
- ▶ Can only review one mechanism at a time



Current gaps / priorities

- ▶ Ability to identify pathways rather than single intermediates
- ▶ Ability to identify mechanisms using completely hypothesis free approaches
- ▶ Further automation to speed up process (eg using text mining for RoB)



Future research

- ▶ Incorporate changes recommended by validation studies

Marty Weijenberg -Gökhan Ertaylan and Eline van Roekel

Rudolf Kaaks- Renée T. Fortner, Audrey Jung, Charlotte Le Cornet

- ▶ WCRF funded project -Diet and prostate cancer – mechanistic reviews of BMI and Vit D and PC
- ▶ Integrative Cancer Epidemiology – ICEP funded by CRUK – ongoing mechanistic reviews and work on methodology – Julian Higgins



The Team

PI- **Dr Sarah Lewis** –Genetic epidemiology

Co-PI- **Prof Richard Martin** –Epidemiology

Dr Mona Jeffreys- Cancer Epidemiology

Dr Mike Gardner – Animal biology/systematic reviews

Prof Jeff Holly- Molecular biology – IGF and cancer

Dr Claire Perks – Molecular biology

Dr Tom Gaunt – Bioinformatics

Prof Jonathan Sterne- Systematic review methodology

Professor Julian Higgins –Evidence synthesis

Prof Steve Thomas –Head and neck cancer surgeon

Dr Pauline Emmett - Nutritional epidemiology

Dr Kate Northstone – Nutritional Epidemiology

Cath Borwick – Librarian/ Search strategies

Sean Harrison- PhD student

Rosie Lennon-PhD student

Vanessa Tan- PhD student

University of Cambridge

Dr Suzanne Turner-

Animal models

WCRF

Prof Martin Wiseman

Dr Pangiota Mitrou

Dr Rachel Thompson

IARC

Dr Sabina Rinaldi-

Hormones and cancer

