

Satellite meeting for the European Congress on Obesity – Action on weight management in cancer - Meeting Report

27 April 2019, Dundee

SUMMARY

Today's meeting, hosted by The Centre for Research into Cancer Prevention and Screening, (CRiPS), University of Dundee and supported by The World Cancer Research Fund International, Association for the Study of Obesity Scotland Network and Scottish Cancer Prevention Network, was inspired by the NIHR Cancer and Nutrition Collaboration research on cancer prevention and screening, and reflects the many discussions the group has had on how best to explore the benefits of weight management in the cancer context.

The aim of the meeting was to discuss the three aspects of lifestyle that need to be considered: diet, physical activity and weight management. Each of these aspects can be explored within human weight loss trials -- at least in theory. We attempted to discuss and answer the following questions:

- Can these three aspects be explored in practice?
- Can people living normal everyday lives really change behaviour to meet study protocols?
- Can we learn from diabetes prevention trials?
- How important is trial level evidence for the public, patients and clinicians?
- What are the convincing end points for cancer occurrence and reoccurrence and do they take decades and billions of pounds to discover?

Representatives of the Cancer and Nutrition NIHR infrastructure collaboration gave twenty-minute presentations on key issues to consider. The themes cover experimental work, patient and public views, preventions, survivorship and tools for measuring the impact of the research being undertaken. The talks centred on nutrition in a cancer context and focused on cancer prevention, public health screening (epidemiology), and cancer survivorship. They also included two components combining nutrition with physical activity. The presentations gave a snapshot of where we are now and the issues that need to be considered to move forward. Delegates were invited to share their thoughts and ideas on answering these important questions during the discussion sections. Summary points of each talk are noted as well as key discussion points.

INTRODUCTION

The workshop opened with a welcome from the Chair of the meeting, Bob Steele. Dr Simon Williams gave a brief overview of the [Association of the Study of Obesity](#) which he chairs. Professor Annie S Anderson, co-director of the [Scottish Cancer Prevention Network](#) gave an overview of the day. Dr Kate Allen gave an introduction to the morning sessions from the [World Cancer Research Fund International](#) perspective.

Scientific evidence and policy implications for obesity and cancer prevention: the WCRF perspective: *Dr Kate Allen*

Key Points:

- New cases of cancer expected to hit approx 30 million globally by 2040, largely fuelled by an increase in overweight/obesity
- Strong evidence linking overweight/obesity to 12 cancer types – various mechanisms involved that impact hallmarks of cancer through modification of specific metabolic pathways.
- Research gaps include mechanisms, life course, impact of weight reduction
- Whole of government, whole of society approach needed to tackle overweight/obesity – policy frameworks helpful to organise evidence
- Coming from WCRF – CO CREATE, new grant call (late July), cancer survivors

Why is body fatness important in cancer prevention? Lessons from Mendelian Randomisation

Prof Richard Martin

Key Points:

- MR studies confirm causality of adiposity in oesophageal, gastric, pancreatic, renal, colorectal, endometrial, lung & ovarian cancers
- Observational studies underestimate its effect on risk
- Per SD higher insulin: 50-75% increase in kidney, pancreatic & lung cancers
- MR will identify additional causal pathways
- Adiposity influences smoking behaviour with implications for interventions
- Increased physical activity lowers risk of CR, breast & prostate cancer
- Statins protective in OC– potential use in high-risk women?
- Rapidly increasing genetic data will allow development of more powerful / specific instruments to better understand the role of adiposity
- Per SD increase in BMI (4.6kg/m²):
 - 58% risk increase of kidney cancer (95%CI: 1.35-1.85) & 34% risk increase of pancreatic cancer (95%CI: 1.09-1.65)
 - Double the risk observed in traditional studies
- Per SD increase in fasting insulin (44.4 pmol/L):
 - 50-75% risk increase of kidney, pancreatic and lung cancer
 - also observed for endometrial cancer. (Nead et al. 2015)
 - potential risk factor for cancer overall

Is change in body fatness important in cancer prevention? Lessons from weight loss interventions

Prof Annie Anderson

Key Points:

- There are significant observational data that indicate that intentional weight loss in adulthood is associated with cancer risk reduction
- The strongest data is for female cancers notably post-menopausal breast cancer
- There is an absence of trial data available to support clinical guidelines and public advice

Weight loss interventions for trials? Lessons from the behavioural intervention world

Prof Falko Sniehotta

Key Points:

- The importance of thorough intervention development
- Negative associations with both weight management and cancer might lead to disengagement
- Offering a positive evidence-based approach to regain control over weight and health might be welcome
- Implementation features in DiRECT
 - Strong embedding in primary care services
 - Integrated evidenced based intervention package
 - Food reintroduction, weight loss maintenance support
- The option of refreshers

Are intervention trials so challenging?

Prof Shaun Treweek

Key Points:

- Trials have a key role in healthcare evaluation.
- It's easy to do poor intervention trials.
- Avoiding this is often not rocket science.
- Much of the challenge of a good intervention trial is in conduct. In the UK there's help available for this.

Discussion and debate – how important is trial evidence and why?

Prof Elio Riboli

Questions/Comments that arose from the morning session:

- Regarding the talk on Mendelian Randomisation, a query arose re the assumptions of causality. When the proportions are very small, it's difficult to see how two facts can be related. The response noted that Mendelian Randomisation assumes a linear relationship with a large sample size.
- There was a comment from Prof Martin's talk re his slide on young people. The slide shows an increase in cancer driven by obesity, but this is only a partial explanation due to the complexity of the issue. The importance of bringing evidence from different areas to provide an overall picture, ie triangulation is key in interpretation.
- A question arose re Mendelian Randomisation on prostate and physical activity and what to do when triangulation doesn't work. It was explained that Mendelian Randomisation is a useful tool in prioritisation to ensure best use of research funds. It's also useful for de-prioritisation. For example, if a study doesn't find a relationship, the result is still meaningful as Mendelian Randomisation can be used to predict and demonstrate that trials are needed for x not y, providing powerful underpinning for larger, more informed trials.
- There was a comment expressed about the disadvantages of seeing individuals as individuals rather than in family groups when considering weight loss and weight management

programmes/interventions, as eating behaviours are intensely social activities. It's important to bring the social and cultural aspects into play to ensure these programmes/interventions can be maintained.

In response, an example was given regarding reducing smoking. What made the difference was not guilt, but the price of cigarettes and the image of smoking. Lessons could be learned from this as there will never be enough funding to tackle the issue at an individual level.

In looking at the importance of trial evidence, Prof Riboli discussed colorectal cancer data rates from a US study, then EPIC data and made these points.

- The data showed BMI was not helpful for predicting colorectal cancer in women.
- The data showed anomalies with diabetes/breast cancer and obesity. While a conclusion was reached that the obesity and cancer relationship is not clear, it supports the need for a research agenda to try and understand what we don't understand.

Lessons from the BWEL study – a weight management programme for breast cancer survivors

Prof Jennifer Ligibel

Key Points:

- Patient interest in weight loss interventions after breast cancer diagnosis is high
- Significant weight loss is feasible in breast cancer survivors
- Lifestyle intervention research is challenging in breast cancer survivors (as in other populations), with outcomes potentially limited by attrition and poor intervention adherence
- Large-scale trials provide important opportunity to study mechanisms through which weight loss/related factors could impact breast cancer risk and outcomes

Pragmatic exercise and dietary interventions in overweight cancer survivors: impact on body weight and other health outcomes

Prof John Saxton

Key Points:

- Structured exercise and/or physical activity brings health benefits to cancer survivors that go beyond weight loss.
- Studies show that exercise can enhance the effects of dietary interventions on body composition and cancer-relevant blood-borne biomarkers in cancer survivors.
- The provision of comprehensive dietary support is also needed for clinically-important body fat reduction in overweight/obese cancer survivors

What are the important core outcomes measures in cancer survivorship?

Dr Amanda Cross

Key Points:

- Need to decide Who, What, When and How
- Input from all stakeholders
- Consider sources of heterogeneity
- Use existing initiatives such as COMET to ensure robust, standardised outcomes

Do no harm – risks and potential benefits

Dr Chloe Grimmer

Key Points

- We need evidence but we risk excluding a significant proportion of people affected by cancer in our trials
- Interventions need to be achievable
- Clearly report intervention components and characteristics
- Debate best time to intervene
- Look beyond RCTs

Discussion – the way forward

Professor Andrew Renehan

Summary of key points from morning sessions:

- Martin: causality
- Anderson: change/ best 'fat' surrogate
- Sniehotta: The 'right' intervention
- Treweek: The 'right' trial design
- Riboli: The 'right' evidence
- Ligibel: Evidence from cancer survivorship
- Saxton: Combined interventions – max. value for money
- Cross: The 'right' outcome measure
- Grimmett: Are there any harms?

The collaborative is preparing a viewpoint manuscript to submit for publication in a major journal that suggests the time is right for a major intervention trial of weight management plus or minus physical activity for cancer prevention. In order to convince a funder to move forward, the following questions would need to be addressed, particularly if limited to securing a UK funder.

Key message for convincing a major trial funder

- The Setting: primary versus secondary? Primary will have the bigger impact
- Causal association incl. reversibility – There's a need to convince there is causal association, to show without doubt that obesity is linked with cancer. Experts in animal work and biological plausibility could be included to strengthen the causality case that triangulation makes. There is also a need to convince the funder the association is reversible.
- The 'target population' – Should the focus be high risk groups, age groups, ethnic groups or ?
- 'The right' intervention -- How do we find that?
- 'The right' timing (and for how long?) -- At what point does the intervention occur? Is it tagged on to bowel cancer screening, for example? When is the right opportunity to start a study?
- The optimum 'fat' mediator/ biomarker – Are there new technologies that could be used?

Using the points above as prompts, the following points were made:

- The funding needed would be similar to the level of the UK BioBank, meaning only a very few funders are available at this level – perhaps only one or two.
- There was a suggestion to crowd fund the needed amount.
- The importance of picking the population carefully, choosing high-risk (risk stratification)
- The Nutrition community could work closer with the oncology community to find cost-effective opportunities
- Start with the budget and determine what intervention could be done for that amount. Strip it down so it's not flabby. (highly targeted)

- Successful intervention tends to happen during ‘teachable moments’ -- when someone discovers they have cancer, then they’re susceptible to behaviour change. Otherwise the message can get lost.
- Focused interventions could be developed for people who are not yet patients, offering them some gain.
- It’s important to consider intermediate points. Then studies could be smaller and for shorter periods. (cheaper) Currently, minimum numbers for results are 20,000 - 30,000 cases to give an answer in 7 to 8 years.
- There is an urgent need to find biomarker endpoints sufficient enough to convince clinical guideline committees that we should be doing these interventions. Currently, they don’t exist. With high-risk groups and follow-ups it would be possible to discover some.
- Web material is more readily available and accessible, making it a more cost-effective method.
- A successful bid will require a top multi-disciplinary team. Luckily, we have one!