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Title Page

The Nutrition Society Member-led Meeting was held at the University of Sheffield, UK on 11 July 2019.

Meeting report: "1st Annual Nutrition and Cancer Networking"

Title

Nutrition and Cancer: Evidence Gaps and Opportunities for Improving Knowledge

Short Title

Nutrition and Cancer Meeting

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Abstract

The Nutrition Society's 1st Annual Nutrition and Cancer Networking Conference brought together scientists from the fields of Nutrition, Epidemiology, Public Health, Medical Oncology and Surgery with representatives of the public, cancer survivors and cancer charities. Speakers representing these different groups presented the challenges to collaboration, how the needs of patients and the public can be met, and the most promising routes for future research. The conference programme promoted debate on these issues to highlight current gaps in understanding and barriers to generating and implementing evidence-based nutrition advice. The main conclusions were that the fundamental biology of how nutrition influences the complex cancer risk profiles of diverse populations needs to be better understood. Individual and population level genetics interact with the environment over a lifespan to dictate cancer risk. Large charities and government have a role to play in diminishing our current potently obesogenic environment and exploiting nutrition to reduce cancer deaths. Understanding how best to communicate, advise, and support individuals wishing to make dietary and lifestyle changes, can reduce cancer risk, enhance recovery, and improve the lives of those living with and beyond cancer.

Introduction

The link between nutrition and cancer is now unequivocal. Around 10-15% of all cancers are considered preventable by nutritional parameters, and correct nutrition can improve both recovery from treatment and survival[1, 2]. The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR)[2], the American Cancer Society[3], and the World Health Organisation[4] have provided evidence-based nutrition and physical activity public health guidelines to reduce cancer risk. Overwhelming consensus exists for advising people to: maintain a healthy weight (typically considered a BMI of 18.5-24.9 with WCRF suggesting to be at the lower end of this range); engage in regular physical activity; consume a diet rich in vegetables, fruits, whole grains and plant-based protein sources such as legumes, nuts and seeds legumes; limit consumption of highly processed or 'fast foods' that are high in saturated fat, sugar, salt and refined carbohydrates; limit consumption of red and processed meats, sugar-sweetened beverages and alcohol. Adherence to these guidelines has repeatedly been shown to reduce risk of cancer incidence in multiple populations at multiple sites including colorectal[5-8], head and neck[9], pancreas[10], and breast[11-13].

Sex and ethnicity modify cancer risk, as do multiple genetic variants that mediate risk for body fatness and/or cancer. The molecular explanations for site-, sex-, and ethnicity-specific risk profiles remain as gaps in current understanding and represent a significant barrier to enacting stratified (if not yet personalised) prevention strategies. Other critical unanswered questions include: how best to communicate existing advice that is based on robust and convincing evidence to the public; should advice differ following diagnosis or following treatment and what are the most pressing nutrition research areas to reduce cancer rates and improve survival and quality of life? The aim of the 1st Annual Nutrition and Cancer Networking Conference, held in Sheffield in July 2019, was to bring together nutritional scientists, clinicians, funding agencies, patients and their representatives to discuss these outstanding issues.

Nutrition across the course of cancer treatment

Malnutrition is a frequent complication of cancer therapy and impairs patient survival and recovery. Speaker Dr Alessandro Laviano (University of Sapienza) contributed to The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for cancer patients, which are aimed at identifying early warning signs of malnutrition and provide methods for multi-disciplinary teams to prevent the deterioration of metabolic health of cancer patients[14]. Patients at risk of cachexia and sarcopenia, or who may have their therapy dose capped due to excessive BMI may benefit most from prehabilitation. Studies of dose capping in obese individuals suggest better outcomes when doses are

not capped despite toxicity concerns[15]. As described by Ms Mary Pegington (University of Manchester) at the meeting, assessing lean body mass may be more informative for deciding chemotherapy dose than BMI. A meta-analysis of 22 studies found prehabilitation typically mitigates the damage caused by major surgery, radio- and chemo-therapy, resulting in a more rapid return to pre-surgical capabilities quicker[16]. Delegates discussed that there may be cases where prehabilitation should be balanced with the concern that delaying treatment may increase relapse rates in some cancer types. Of note is a recent report highlighted by Dr Wootton conducted by Macmillan, the National Institute for Health Research (NIHR) Nutrition and Cancer Collaboration, and the Royal College of Anaesthetists. This report summarised the benefits of prehabilitation and provided guidance for its use in the management and care of people with cancer[17]. Patient wellbeing should also be considered, as empowerment for some patients may be perceived as shouldering the burden for others[18].

In general, cancer site specific nutrition advice for survivors is lacking. Although breast cancer survivors do have tailored advice and guidelines (e.g. the WCRF document "Survivors of breast and other cancers"), advice for survivors of all other cancers is underdeveloped, in part due to a weak or absent evidence-base of protective benefit. Maintaining a healthy weight seems to be effective for prevention of breast, colorectal, and bladder cancer recurrence, but the evidence that this advice would be effective in prevention of other cancers is lacking (explored further below). Furthermore, there are multiple changes associated with obesity that may be linked to cancer recurrence and it is still unclear exactly what the physiological mechanisms are that drive relapse. Obesity is also associated with other co-morbidities such as dyslipidaemia and insulin resistance (metabolic syndrome) that may also play a role in the development of some cancers. How poor nutrition and body composition both of which independently raise primary risk, are linked to development of metastatic disease is also unknown at this time, indeed if there is any role at all. These gaps were considered at the meeting as critical to address if cancer recurrence rates or disease-free survival times are to be ameliorated.

Translating nutrition knowledge into behaviour change

Communicating complex risk profiles to the general population who have idiosyncratic risk profiles for many cancers is problematic in itself. Communication barriers are further compounded and contradicted by the obesogenic environment individuals who attempt to act on advice are faced with[19]. Scientific understanding of behaviour change and communication methods is still evolving[20-22] and there are likely to be improvements in how advice is presented as these fields develop[23]. An important consideration raised during the course of the meeting was how should researchers communicate the robust and evidenced-based advice for cancer prevention with the

people who need it and translate research findings into bona fide behaviour change? Dr Rebecca Beeken (University of Leeds) explained that there are a variety of reasons why people generally struggle to adhere to guidelines. Often decisions about meals and physical activity are taken by family units together rather than individuals indicating that the entire family needs to change their habits to allow successful adherence to the advice being provided. Supportive structured advice such as the "10 top tips" to facilitate individuals in their attempts to reduce their cancer risk through changes in diet and physical activity[20, 24] have been used to overcome such barriers. Self-monitoring (e.g. physical activity trackers, dietary recording tools) combined with individually tailored goal planning techniques are twice as likely to succeed as other interventions[25].

Encouragingly, there are now a variety of reports indicating that there are distinct teachable moments open to clinical staff where patients are highly receptive to advice. However, if these moments are not seized upon, the information vacuum is worryingly filled by the wealth of information available via the internet. This advice is frequently unsubstantiated, lacks peer-review, and may be posted or published for private financial incentives. Therefore, providing simple, coherent, easy to adopt, and robust advice at key teachable moments is paramount to aid in appropriate behaviour change.

Individual nutrients

The role of individual nutrients in cancer prevention or therapy has been more challenging to validate and implement into clinic than modifying dietary patterns but is gaining traction. Researchers involved in the UK Therapeutic Cancer Prevention Network, and the NIHR Cancer and Nutrition Collaboration are coordinating clinical trials to understand how compounds such as resveratrol[26], omega-3 fatty acids[27], and plant sterols[28, 29], may improve therapy, support metabolic health, slow cancer initiation or growth and improve relapse free survival. Aspirin and omega-3 fatty acids (at nutraceutical doses of 2-4g/day) have shown promising results in reducing adenoma size in a colorectal cancer prevention trial[30]. Ms Samantha Hutchinson (University of Leeds) explained that plant sterols that are already indicated for management of cardio-vascular disease as an alternative or adjunct to statins, are now emerging as potential anti-cancer agents[31, 32], potentially through suppression of intra-tumour cholesterol metabolism[29]. On the other hand, although the molecular evidence that Vitamin D should act in a cancer chemoprevention manner[33], clinical and epidemiolocal studies remain inconclusive[33-38]. In all these trials, lessons are being learnt. For example, attempting to deliver the maximum tolerated dose of a nutritive compound, as typical in pharmacological trials, does not always appear to be beneficial[26]. Hypotheses that link nutrients with cancer prevention typically arise from chronic long-term low-dose exposure in free-living individuals. Such epidemiological attempts to identify causal links between individual nutrients and

cancer can be hampered by recall bias, unavoidable confounders, and the observational nature inherent in nutrition research, especially over the time scales required to observe differences in cancer incidences. This has led to some expensive mistakes.

An example of such a mistake was explored by Dr Sarah Lewis (University of Bristol) who described how low selenium levels had been reported to be associated with increase prostate cancer risk[39], but the $114m SELECT trial into selenium supplementation was halted early as selenium actually led to increased risk of prostate cancer and type 2 diabetes[40]. Mendelian randomisation (MR) studies that exploit the plethora of genome wide association studies now available have the ability to link nutrition, metabolic and genetic profiles of individuals with cancer risk, examining life-time exposure to nutrient profiles dictated by genetic variants. As reported by Dr Sarah Lewis, MR studies remove many of the biases and confounding effects of observational cohort studies that are hampered by inaccuracies in recall of participants. Indeed, after the SELECT trial was abandoned, an MR study conducted by Dr Lewis and colleagues corroborated the adverse influence of selenium on prostate cancer and type 2 diabetes[41]. Designing clinical trials with individual nutrients should be preceded with comprehensive MR where instruments covering sufficient trait variance as are available. A further development for the MR field, as survival data becomes more complete, will be to consider how individual nutrients and genetic predictors of their circulating concentrations associate with hard clinical endpoints such as progression free survival.

Patient's perspectives

Individuals living with and beyond cancer are perhaps the most neglected group in terms of validated robust nutritional advice. Financial and other constraints often mean nutrition advice is rarely provided at the point of care[42] despite several agencies including ESPEN[14], ACS[43], WCRF[44] having published guidelines for cancer patients and survivors. Whereas the evidence behind advice to the general public about nutrition and cancer risk is robust but the uptake is poor; at the peri-diagnosis period the evidence underpinning advice is weaker but uptake is greater. A critical point made by Dr Steve Wootton (University of Southampton) is that while eight in ten cancer patients receive some kind of nutrition advice[45], only eight in ten of the clinicians providing this advice are aware of the clinical nutrition guidelines for cancer patients[46]. Advice therefore falls short of the best possible, and typically relapses to the standard advice of a balanced diet and regular physical activity[45]. As researchers and clinicians are reluctant to provide advice without a stringently robust evidence base, an information vacuum has been opportunistically filled by low quality information derived from unregulated internet sites. This presents a serious challenge as highlighted by the patient and public representatives at the meeting with Jacqui Gath (Independent Cancer Patients' Voice)

commenting "patients can't wait ten years to find out the results of your trial". A paucity of nutritional training throughout the medical education system exacerbates the problem as clinicians are not supported in giving the best advice possible for their patients[47]. Attendees fully agreed with Dr Alessandro Laviano who raised the point that integration of nutrition in clinical training is highly likely to provide long term benefit to patients with cancer and a wide range of other diseases.

Notably, attempts to understand whether interventions can improve the mental wellbeing of patients have also been equivocal. As highlighted by Ms Mary Pegington during the meeting, although there is evidence to suggest that vitality scores are increased by weight management interventions in cancer patients shortly after treatment, worryingly, there is a slightly increased susceptibility to depression in the longer term, which is perhaps consistent with a failure to maintain the weight loss. Maintaining weight loss is not a problem restricted to cancer patients. If temporary weight loss peri-therapeutically was found to improve longer term outcomes, then a more effective approach may be to exploit the teachable moment to encourage patients to undergo more dramatic changes to diet and lifestyle but adherence would be improved as the temporary nature of the intervention 'seems more achievable'.

Societal and political barriers

Perhaps the greatest barrier to improving nutrition linked cancer rates and survival are widespread health inequalities. In England, between 2015 to 2017 the gap in healthy life expectancy between the least and most deprived areas was 19.1 years for males and 18.8 years for females; the gap in life expectancy was 9.4 and 7.4 years respectively[48]. A recent Lancet report established that contemporary increases in unemployment and austerity measures have been associated with increases in cancer mortality rates[49]. Austerity measures are both regressive, disproportionally impacting low socio-economic groups who already suffer the highest cancer and obesity rates, and are bad for health[50]. Reassuringly, PHE now indicate that a healthy diet and a healthy weight are one of their top most priorities for the 2020-2025 period[51]; a critical question is how might this to be achieved? A combination of legislative, financial, and public advisory methods may provide an effective solution. For example, economic modelling suggests that price increases[52, 53] and reformulation[54] of energy dense foods and could rapidly drive obesity rates down resulting in a lagged reduction in cancer rates. Driving down obesity rates will not just improve cancer incidence, and recurrence and mortality rates, but also reduce incidence of other non-communicable diseases such as non-alcoholic fatty liver disease, cardio-vascular disease, and type 2 diabetes.

Controversial campaigns by major charitable organisations aimed at increasing the awareness of the link between obesity and cancer have been perceived as stigmatising[55], with weight stigma

negatively affecting well-being[56], health correlates and behaviours[57]. Dr Malcolm Clark (Cancer Research UK; CRUK) presented the CRUK's "Ob_s__y" campaign along with the concept and justification. Excess body fatness is the leading cause of diet-preventable cancers, with estimates suggesting it accounts for 6.3% of all cancers in the UK[1]. At the molecular level, obesity activates an array of signalling pathways involved in cancer pathogenesis. Altered adipokine, cytokine and hormone production drive inflammation and proliferation; whist disruption of insulin and cholesterol signalling leads to deregulation of cellular energy homeostasis and metabolism[58]. Epidemiological evidence indicates that BMI is associated with many cancers across a J-shaped curve, where low (<20) and high (>25) BMIs are associated with a general elevated risk, with risk continuing to increase as adiposity does[59]. Excess body weight increases risk of recurrence and reduced survival from breast[60] and other cancers such as colorectal[61] and bladder[62] . However, this is not true for all cancers; risk of lung, pre-menopausal breast, prostate, and oral cavities cancers actually reduces with increasing BMI[59, 63]. For some cancers, such as pre-menopausal breast cancer, overweight in early adulthood appears to protect against cancer in later years[59]. Adherence to advice by the general public remains incomplete, at least in part due to a lack of acceptable and potentially inefficacious delivery methods[23]. Yet, we know that obesity causes cancer so the time to act is already upon us[64]. Society, government and charities must act coherently and cooperate to provide a single clear message and provide tangible support to aid those wishing to maintain and regain a healthy BMI.

Future Directions

Advances in research methods such as applying MR to dietary exposures, and highly accurate yet inexpensive dietary recording methods, should provide far more robust hypothesis testing in clinical trials than has been possible before, especially where individual nutrients are concerned. Understanding how best to communicate, advise, and support individuals wishing to make changes, combined with advances in legislative changes to ameliorate the potently obesogenic environment we all face, will generate the greatest levels of success in exploiting nutrition to reduce cancer deaths. Organisations such as the Nutrition Society, NIHR Cancer and Nutrition Collaboration, and ESPEN, recognize the importance of robust research into how nutrition can reduce cancer risk, enhance recovery, and improve the lives of those living with and beyond cancer. The open nature of these organisations, and their attempts to link key stakeholders will be crucial in shaping nutrition and cancer research partnerships in the coming years.

Future meetings should develop a better understanding of the barriers still in place. Aims of future meetings should be to describe and understand the fundamental biology linking nutrition with cancer, how individual and population level genetics alter these links, the role of the environment in the context of biological mechanisms and in commercial and government decision making, public advice,

taxation and incentivization. To achieve this in the coming years, all stake holders including patients and public representatives, the food industry, cancer prevention charities, government policy makers, scientists and clinicians need representation. An established interaction between these stake holders under the guidance of learned societies and structured collaborations and networks will occur as subsequent meetings are held. The authors welcome any interested members of the scientific community, the public, patients, government or industry representatives to contact us directly, or via our roles in the Nutrition Society and NIHR Nutrition and Cancer Collaboration.

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Conflict of Interest

None

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