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Meeting: 2nd Nutrition and Cancer Networking Meeting was an in-person event held at the University of Newcastle on 11 May 2022

The Second Nutrition and Cancer Networking Meeting Nutrition and Breast Cancer: Translating Evidence into Practice

James L Thorne[1]*, Ingunn Holen[2] and Bernard M Corfe[3]
[1]*School of Food Science and Nutrition, University of Leeds, Leeds, LS2 9JT, UK*
[2]*Department of Oncology and Metabolism, University of Sheffield, Sheffield, S10 2RX, UK*
[3]*Human Nutrition and Exercise Research Centre, Population and Health Sciences Institute, Newcastle University, Newcastle, NE2 4HH, UK*

The 2nd Nutrition and Cancer Networking Meeting '*Nutrition and Breast Cancer: Translating Evidence into Practice*' was held at Newcastle University in May 2022, with support from the Nutrition Society and British Association for Cancer Research. The first meeting in this series was held in Sheffield in 2019. The aim of this joint meeting was to bring together researchers with an interest in nutrition and breast cancer, with the programme spanning topics from risk and prevention to nutrition during treatment and beyond. Several key themes emerged, including the importance of engaging patients in the development of interventions and trials, making trials more accessible to diverse communities; training of clinical staff in nutrition and latest evidence; wider range of compounds should be considered in food composition tables; and alternative trial designs can be considered for prevention research to reduce financial burden and increase power.

Key words: Clinical trial: Nutrients: Breast neoplasms: Patients

There is increasing interest in nutrition amongst breast cancer patients, survivors and those at high risk of developing breast cancer, indicating a need for clear, evidence-based guidance for these groups. This is particularly important as many people currently obtain information online, which is often anecdotal, sometimes contradictory and frequently lacking a solid evidence-base. Cancer charities provide some general dietary advice for patients, but much of the advice aimed at breast cancer patients is focused on avoiding weight gain associated with endocrine therapy, or on maximising energy intake for patients with advanced disease. It is therefore paramount that the research community comes together to agree a strategy as to how we can generate the evidence-base for nutritional advice for breast cancer patients and provide this in an accessible format. This report summarises the key themes that emerged from the meeting.

There is considerable interest in the impact of diet in the cancer prevention space, an area where clinical trials are notoriously difficult to plan, fund and execute at adequate scale and where timeframes for obtaining results can be extensive. Professor Karen Brown (University of Leicester) set the scene by sharing her experience of testing dietary compounds (resveratrol) in colorectal cancer prevention. She described how around 20 years of preclinical work has been required in order for a clinical trial to be agreed and funded, involving a large team of scientists and clinicians. Colorectal cancer is ideal for prevention studies as it involves a pre-cancerous stage (polyps) that are detected as part of a screening programme, from which samples can be collected from a large number of patients. A similar approach is not feasible in breast cancer, as there is no real pre-cancerous stage that is monitored over time to allow assessment of interventions (ductal carcinoma

***Corresponding author:** James L Thorne, email j.l.thorne@leeds.ac.uk

in situ is most often surgically removed and not all cases progress to invasive disease). It is clear that with the resources required for prevention studies, large-scale trials of breast cancer prevention in the general population are unlikely to be realistic and would depend on the discovery of a surrogate marker of response.

Several themes emerged through the day, including exemplars on which new research can be based, or highlighted existing challenges to progress in the field. An over-arching aim within the community is to enable evidence-based decisions and patient guidance; but this can only occur from sufficiently robust studies. Trials need to be flexible and inclusive, to ensure recruitment, adherence and completion rates are sufficient for powered conclusions to be drawn. These are a particular challenge in breast cancer, where survival rates are high and surrogate markers of disease progression are lacking. Emerging/novel trial designs can add statistical power to studies, but funding bodies remain reluctant to adopt these new strategies. Major information gaps were identified, specifically a lack of knowledge regarding the nutritional content profile of foods, meaning that diet–drug interactions can't be effectively studied. A standardised method for scoring of cancer-protective diets does seem to be emerging based on the World Cancer Research Fund cancer prevention recommendations[1,2,3], a core strength that will help refine national guidelines in the coming years.

Flexibility and inclusivity from trialists and clinicians is needed

Our invited patient speaker, Dr Chatterjee, discussed patterns of information-seeking by patients, around advice and traditional approaches to prevent cancer relapse. Several delegates highlighted that these traditional approaches bore striking resemblance to interventions being trialled currently, including dietary restriction by fasting and anti-inflammatory diets[4,5]. Dr Chatterjee advocated strongly from a patient point of view for food-based, rather than pharmacological-based approaches to secondary prevention. An important benefit to food-based prevention strategies is empowerment, making adherence more likely. However, generating robust evidence of benefit of food-based interventions would be challenging, due to variability of food constituents, adherence and appropriate control groups.

Several speakers commented on reasons why adherence to various clinical trial regimens was below optimal, why trial participants dropped out, or proposed reasons why recruitment rates were lower than expected. The patient population is diverse in multiple ways. Collectively, the breast cancer population represent diverse ethnic groups but some remain under-supported during screening, diagnosis, treatment, follow-up[6] and non-White women are under-represented in cancer clinical trials[7]. To compound this, race is not always recorded even in studies where the breast cancer subtype is disproportionately affecting a non-White subgroup (triple negative breast cancer for example). Patients from socially deprived communities will face additional challenges with regards to eating healthily and following nutritional advice[8].

Successful implementation of lifestyle or dietary interventions also requires diverse approaches to be considered; the whole patient cohort can't be supported with a one-size-fits-all randomisation protocol. Professor John Saxton (University of Hull) described how the NEWDAY-ABC intervention (ISRCTN15088551), a bespoke weight management and behaviour change intervention for women treated for early-stage oestrogen receptor-positive breast cancer, was co-designed with patients to ensure that it addresses key physical and psychological challenges to physical activity and dietary behaviour change. An important feature of this intervention is the small group peer-support sessions and promising weight loss evidence has been gleaned from an external pilot study. In the WeSureCan trial (ISRCTN12000313), a total diet replacement is provided to breast cancer patients to reduce daily intake to 810 kcal for 3 months followed by a slow return to normal energy levels. Importantly, the participants attempting to adapt to this dramatic dietary change are supported by trained advisors. Work presented by Dr Michelle Harvie (University of Manchester) demonstrated how community-based outreach interventions can actively and effectively support patients to bring their BMI towards a healthy range following treatment, which consequently improves both functional and mental health[9]. Having patient support processes inbuilt as part of trial design, and co-designing trials with patient representatives, should optimise adherence and retention rates.

Using an intention-to-treat statistical model is particularly important to consider when asking trial participants to make nutritional and lifestyle changes[10]. Gathering intention-to-treat outcome data would allow separation of the intervention's efficacy from the support required to stably implement the protocol in the patient population. Allocating participants to different types of support and assessing adherence is a crucial component of trial design that can be developed in collaboration with patient–public involvement groups such as the Independent Cancer Patients' Voice[11].

Clinicians need training in nutrition

As with patients, there is variability in knowledge, engagement and skill sets amongst the clinicians who are best placed to provide nutrition-related guidance to cancer patients[12,13]. Dr Ellen Copson (University Hospital Southampton) raised the point that perhaps the greatest challenge is that even when a clinician is knowledgeable and is convinced there would be a benefit to their patient losing weight, gaining muscle mass or altering their diet or physical activity levels, systemic barriers prevent these conversations from happening. Pathways to refer patients to dieticians are blocked because of chronic underfunding, meaning referrals mainly occur for the most cachectic patients; leading to the worrying question raised for UK patients 'why

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would the clinical team spend valuable NHS time with their patients discussing nutrition options when there is no pathway of support once they've left the appointment?'. Oncologists do not typically receive training in how to discuss lifestyle interventions with patients, nor specific training regarding what constitutes best practice for lifestyle intervention. Finally, there is ongoing scepticism from clinical colleagues regarding the level of evidence linking nutrition or body composition with breast cancer outcomes. Further evidence is therefore clearly needed, but the significant research costs are likely to remain prohibitive for development and running the appropriate trials to provide this.

More evidence is needed and lower cost trial methodologies are emerging

The pharmaceutical industry has a clear financial model that allows the generation of new and profitable drugs. More than half of new cancer drugs approved by the European Medicines Agency between 2009 and 2013 did not improve survival in a real-world setting[14] and of the others, incremental improvements were made. Fully exploiting the fields of nutrition and lifestyle interventions in the cancer setting offers an opportunity for a step-change in improvements in survival outcomes that utilise a different biological path than the clinical fields of oncology and surgery. Researchers who intend to run nutrition and cancer trials need significant financial investment, as these generally require recruiting large numbers of patients that need to be followed for prolonged periods of time. Such investment is unlikely to come from the pharmaceutical industry and charities, although supportive, do not generally have the resources to fund larger clinical trials. It could be argued that the benefit of nutritional interventions in cancer patients will be on health economic grounds, rather than corporate profit, as the National Health Service is the ultimate financial beneficiary of nutrition and cancer research. Within the UK, the National Institute for Health and Care Research offers funding for research that ultimately benefits the National Health Service, but further investment from a wider range of organisations would yield greater benefits.

Several talks explored the World Cancer Research Fund cancer prevention recommendations[3] in the context of breast cancer prevention, treatment efficacy and survivorship. These recommendations are to be a healthy weight, be physically active for more than 150 min weekly, eat a wide variety of plant-based foods, avoid high-energy foods, limit consumption of red and processed meat, limit consumption of sugar-sweetened beverages and to avoid alcohol. A clear and standardised protocol for assessing World Cancer Research Fund adherence in a points-based system has been developed in the last few years, which will facilitate future studies and meta-analyses to make studies more comparable[15,16]. Dr Fiona Malcomson (Newcastle University) advocated that the use of a single method for data collection in this context should be more widely adopted to allow improved links with resources such as UK Biobank and European Prospective Investigation into Cancer, thus adding value for money to these resources.

New approaches for designing more efficient trials will secure the evidence needed for public health recommendations to help cancer survivors. The benefits of factorial experimental designs, as discussed by Dr Sam Smith (University of Leeds), including full factorial, fractional factorial and sequential multiple assignment randomised trials for optimising lifestyle interventions prior to definitive evaluation have the potential to catalyse scientific progress and produce more effective, affordable, scalable and efficient interventions. The multiphase optimisation strategy can be used as a guiding framework for designing, optimising and evaluating intervention packages for cancer survivors[17].

Too few non-nutrient compounds are included in food nutrition tables

Dr Alan Richardson (Keele University) suggested that The McCance and Widdowson nutrient content tables, used to support several nutrition–cancer studies[18,19], should be expanded to provide more information on the array of compounds present in food. For example, isoprenoid and geranylgeraniol levels are thought to impair the effect of statins on cancer cells via bypassing the effect of statins on oncogenic small GTPases[20], thus there is the potential for confounding or weakening hazard/risk ratios reported[21] if these compounds can't be accurately measured. Data regarding the content in foods of other compounds emerging as potential cancer prevention agents, such as resveratrol[22,23], phytosterols[24,25], polyacetylenes[26,27] and others, would enable a wider analysis of large datasets linking food intake to cancer risk.

Summary

By bringing together researchers focussing on the areas of nutrition and the breast cancer journey, this meeting highlighted several areas meriting future research. Key topics include improved understanding of patient diet and its link to recurrence, greater patient–clinician interaction to support optimal diet and lifestyle choices, how to overcome the cost and complexity issues surrounding cancer prevention in the primary setting, and how to improve engagement from diverse ethnic and social groups. Compared to other cancer sites, women with and at high risk of developing breast cancer are a highly engaged group, with a strong active interest in making changes to their lifestyle to prevent cancer initiation, progression and recurrence. An era of research that is designed with patient needs as a foremost consideration is urgently needed to provide a strong evidence-base that supports and guides lifestyle and nutritional choices. The breast cancer and nutrition research community combined with our engaged patient population could

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lead the way in generating the evidence-base needed for this change to occur.

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Conflict of Interest

None.

Authorship

The authors had sole responsibility for all aspects of preparation of this paper.

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