Role of nutrition in improving cancer treatment outcomes:
evidence, challenges, and future directions

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Research on nutrition interventions across the cancer continuum

**Prevention**

Extensive research over the past 40 years, primarily from large prospective, observational epidemiology cohort studies

**Cancer diagnosis**

**Least studied area**

Few evidence-based practice guidelines available to guide clinical practice

**Treatment completed**

Many behavioral intervention studies aimed at reducing the risk of cancer recurrence, and the incidence and/or impact of long-term and late effects.
“The current evidence on breast cancer survivors, as reviewed by the CUP, has a number of limitations, including a lack of evidence from randomized controlled trials. In addition, the quality of most published studies is limited because they do not account for relevant factors such as cancer subtypes, type and intensity of treatment, and other illnesses. These limitations are also likely to apply to the evidence for survivors of other cancers.”
“Nutrition and physical activity recommendations established recently by the ACS for the primary prevention of cancer are broadly relevant to survivors undergoing and immediately after cancer treatment”.
Guidance to clinicians: Evidence-based practice guidelines

- Summarize best available evidence in the field
- If applied consistently, can standardize quality of care and improve outcomes
Levels of evidence

Randomized controlled trials (RCTs) are generally considered the highest level of evidence for individual studies.

RCTs are designed to minimize the possibility of selection and information bias, confounding, and chance findings.

"Hierarchy of Evidence Pyramid" adapted from EBP & the Medical Librarian training manual, Duke University 2019, and Online EBM Page Generator, Dartmouth College and Yale University 2019, under the license CC-BY-NC.

Graphic courtesy of: https://guides.library.unisa.edu.au/SystematicReviews/Protocols
Considerations with RCTs

- Randomization is not a “cure” for poor study design or small sample size.
- Study population usually very specifically defined to minimize confounding, thus results may not be generalizable beyond the population that was studied.
- RCTs are conducted in very controlled settings that may not reflect the true patient experience.
- For some questions, RCTs may not be possible or even the best study design.
- RCTs are often expensive to conduct, and may take 5 or more years to accrue sufficient numbers of participants.
Evidence for ... dietary and weight loss interventions during cancer treatment was very limited.
Diet-specific question: Does consuming a particular dietary pattern or food(s) during cancer treatment safely improve outcomes related to quality of life, treatment toxicity, or cancer control?

Methods:
• Only data from individual RCTs or systematic reviews of RCTs were considered.
• Patients with head and neck cancer were excluded from the diet systematic review “because of their unique nutritional challenges”.
• The guideline does not address dietary supplements, cancer cachexia, malnutrition, enteral or parenteral nutrition.
• Interventions considered included: dietary counseling, specific diets (e.g. ketogenic), fasting, functional foods/other changes to dietary composition, weight loss/avoidance of weight gain
• Literature search included studies published between January 1, 2000 – May 17, 2021.
Results: Only eight nutrition RCTs (11 publications) met the inclusion criteria.

“Overall, the quality of evidence was higher for exercise interventions than for dietary interventions in this population.”

“There is currently insufficient evidence to recommend for or against dietary interventions such as ketogenic or low-carbohydrate diets, low-fat diets, functional foods, or fasting to improve outcomes related to quality of life, treatment toxicity, or cancer control.”

“The heterogeneity of the RCTs that have been conducted and the limited number of rigorously designed studies with robust sample sizes make it difficult to develop recommendations.”
Discussion:

“The lack of guidance in these areas should not be interpreted as a statement that dietary change and weight management have no value in patients during or after cancer treatment.”

“Our goal was to . . . . underscore the need for more research in areas where evidence is currently insufficient to provide concrete recommendations, in hopes that future guidelines will provide a more comprehensive blueprint to improve short-term and long-term outcomes in patients undergoing cancer treatment.”
Pathways to Prevention (P2P) Program

Nutrition as Prevention for Improved Cancer Health Outcomes

July 2022

Systematic Literature Review
(AHRQ, University of Minnesota EPC)

P2P Workshop

Independent panel report

Key questions (KQ) for the systematic literature review:

• In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutrition interventions before (KQ1) or during (KQ2) cancer treatment in preventing negative treatment outcomes such as effects on dose tolerance, hospital use, adverse events, and survival?

• What is the effect of nutrition interventions before or during cancer treatment on associated symptoms such as fatigue, nausea, vomiting, appetite, physical and functional status and quality of life (KQ3)?

Parsons et al. JNCI Cancer Spectr 2023;7(3):pkad035. PMID: 37212631
Key questions (KQ) for the systematic literature review - continued:

- In adults diagnosed with cancer who are overweight or obese, what is the effect of nutrition interventions intended for weight loss before or during cancer treatment in preventing negative treatment outcomes such as effects on dose, hospital use, adverse events, and survival (KQ4)

Parsons et al. JNCI Cancer Spectr 2023;7(3):pkad035. PMID: 37212631
Methods for the systematic literature review:

- Literature search limited to:
  - Randomized controlled trials (RCTs)
  - Published in English
  - Randomly assigned at least 50 participants

- Literature search included studies published between January 1, 2000 – July 2022.

Parsons et al. *JNCI Cancer Spectr* 2023;7(3):pkad035. PMID: 37212631
Results of the systematic literature review:

• 206 RCTs described in 219 publications met the eligibility criteria
• Studies were predominantly conducted in populations with gastrointestinal and head and neck cancers
• Almost all studies were conducted outside of the US
• The reviewers were struck by the lack of adherence to basic reporting standards (e.g. Consolidated Standards of Reporting Trials (CONSORT) statement) of the included studies
• Nutrition interventions varied significantly, and outcome often poorly defined
• Literature broadly lacked a clear conceptual framework describing how each intervention would be expected to improve outcomes.
Results of the systematic literature review:

“Two decades of randomized trial evidence on nutrition interventions for adults prior and/or during cancer treatment provide only limited high-quality evidence to improve cancer treatment outcomes.”

Recommendations:

1. Standardizing definitions and taxonomies for populations, interventions, and outcomes
2. Improving rigor in the primary intent, design and reporting of studies
3. Coordinating efforts to develop detailed conceptual frameworks for mechanisms of nutrition interventions across patient nutrition risk categories, cancers and treatments.

Parsons et al. JNCI Cancer Spectr 2023;7(3):pkad035. PMID: 37212631
ESPEN practical guideline: Clinical Nutrition in cancer

43 recommendations on all aspects of oncology nutrition care (screening, assessment, interventions - not limited to parenteral/enteral nutrition support):

- Most with low/very low (31, 72%) or moderate (7, 16%) level of evidence
- 5 recommendations with high level of evidence:
  - Maintain or increase physical activity to support muscle mass, physical function, metabolism
  - Consider use of corticosteroids and progestins for appetite stimulation
  - Use of enhanced recovery after surgery (ERAS) protocols for patients scheduled for curative or palliative surgery
  - Use of oral/enteral immunonutrition (e.g. arginine, n-3 fatty acids) nutritional supplements for patients with upper GI cancers undergoing surgical resection

2021, PMID: 33946039
Site specific oncology nutrition practice guidelines – head and neck cancer

UK National Multidisciplinary Guidelines: Nutritional management of head and neck cancer (PMID: 27841109)

- R (evidence-based recommendation): 18 recommendations (64%)
- G (good practice point/clinical experience): 10 recommendations (36%)

American Society for Parenteral and Enteral Nutrition (ASPEN) Nutrition Guidelines for Adult Head and Neck Cancer are currently under development (https://www.nutritioncare.org/clinicalguidelines/)
Older oncology nutrition guidelines

- **Academy of Nutrition and Dietetics (AND)** - Oncology Nutrition Guidelines (2011-2013)

- **American Society for Parenteral and Enteral Nutrition (ASPEN)**: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation (2009, PMID: 19713551)

- **Clinical Oncology Society of Australia (COSA)** - Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer (2011)
Why the lack of evidence on the role of nutrition during cancer treatment?

Historical concerns with nutrition intervention studies:

- Patients being overwhelmed with their cancer diagnosis
- Competition with other oncology treatment trials
- Concern that nutrients may feed cancer growth and progression

More recently: solitary focus on RCTs

Challenges in oncology nutrition research

- More than 100 different types of cancer, each with different treatment regimens and different nutrition-related issues to be addressed
- Current dietary assessment tools can be burdensome to participants, and measurement errors are concerns
- Lack of common terminology (e.g. “malnutrition”)
- Lack of common data collection and reporting
- Limited research funding
Building a stronger base to support future oncology nutrition RCTs

Need:

- More basic science research to better understand mechanisms by which nutritional status/dietary factors alter treatment outcomes
- More clinical observational data to guide RCT development
  - Documenting the prevalence of nutrition issues
  - Hypothesis generation
  - Prioritization of issues
  - Clues for dose finding
Include clinical observational research in evidence-based practice guidelines

- Well designed clinical observational studies with rigorous data collection and reporting is better than poor quality RCTs and “expert consensus”

- May better represent “real world” patient experience than data from a tightly controlled RCT?

WCRF/AICR, American Cancer Society and Academy of Nutrition and Dietetics evidence analysis processes already include large, high-quality observational studies
Real World Data (RWD)  
Real World Evidence (RWE)

- Big data sets from a variety of sources, including electronic health records, medical claims data, registries, patient-reported data, wearables
- Can be used to conduct pragmatic studies, “target trial emulation” studies
- Accelerating the pace of oncology research exponentially

Need large data sets to be able to stratify on key demographics and clinical factors (e.g. cancer subtypes, treatment regimens)

**BUT**: Dietary intake and body composition are not currently captured in these data sets
RCTs vs. RWD studies

Ongoing changes in:

* scientific knowledge, clinical practice, data collection tools, etc.*
Overcoming the challenges: Collecting nutrition-related data

Improving accuracy and ease of dietary intake reporting:

• Electronic tools for dietary assessment  
  e.g. NCI’s ASA24 and DHQ, VioScreen, DietID

• Include these dietary assessment tools with patient intake surveys?
Overcoming the challenges: Collecting nutrition-related data

Routinely collect and report other nutrition-related variables, such as:

**Malnutrition:**
- Global Malnutrition Composite Score (GMCS) electronic Clinical Quality Measure (eCQM)

**Nutrition impact symptoms:**
- Patient Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE)

**Food security status:** Hunger Vital Sign
Need for routine oncology nutrition data collection and reporting

Example of the problem:
Current knowledge on the prevalence of malnutrition or food insecurity among people being treated for cancer comes from cobbling together data from individual studies or from large administrative datasets.

In 2017, AACR, ACS, ASCO and NCI called for routine collection of data on the social determinants of health, including food security status, followed by “meaningful action and continued monitoring to ensure that the action was successful”.

Robien et al. J Acad Nutr Diet 2023. PMID: 35840079
Need for routine oncology nutrition data collection and reporting

Need further discussion on which data elements should be routinely collected and reported

Work with electronic health record companies to develop structured data fields for nutrition-related data collection

What data collection/reporting can/should be:

- Patient-reported
- Automated (e.g. malnutrition scores, body composition estimates from routine imaging)
- Documented by the dietitian?
Rigor

Guidance on rigorous conduct and reporting of clinical observational research:

Observational study reporting should follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (PMID: 18313558)

FDA guidance on the Use of Electronic Health Record Data in Clinical Investigation

ENICTO Consortium

The Exercise and Nutrition Interventions to Improve Cancer Treatment-related Outcomes (ENICTO) Consortium is a collaborative research program funded by the National Cancer Institute.

Primary research question:
Does exercise during chemotherapy improve the patient’s ability to receive all scheduled chemotherapy?

Web: enicto.org
Twitter: @ENICTO_Study
Instagram: enicto_consortium
Facebook: Enicto Study
## ENICTO project teams

<table>
<thead>
<tr>
<th>study</th>
<th>cancer</th>
<th>intervention</th>
<th>delivery site</th>
<th>end point</th>
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<td>aerobic exercise</td>
<td>home with real-time monitoring</td>
<td>RDI</td>
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<td>Yale, University of Miami</td>
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<td>LSU, Dana Farber, Kaiser Permanente of Northern California</td>
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<td>270</td>
<td>Schmitz, Katie Ligibel, Jennifer Berger, Nathan</td>
<td>Pittsburgh, Dana Farber, Case Western</td>
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*Recent New Investigators. Abbreviations: RDI = relative dose intensity
Dietary interventions

The ovarian cancer project (TEAL study) is the only ENICTO group to include a full dietary intervention component

- 18 weekly (30 minute) sessions with an RD
- ≥ 5 servings of fruit and vegetables/day
- ≥ 25 g fiber/day
- 1.2 g protein/kg/day
- ≤ 30 g added sugar/day
- < 18 oz red meat/week
- ≥ 64 fl oz water/day
- Avoid alcohol

The breast cancer project (THRIVE 65) is encouraging adequate dietary protein intake (1.2 g/kg body weight) to maintain muscle.
Dietary data collection

ENICTO teams will collect the following data:

- 24-hour dietary recall data from participants at baseline and at the end of treatment/intervention
- Dietary supplement use
- Nutrition-impact symptoms at each chemotherapy cycle (PRO-CTCAE)
- Malnutrition (PG-SGA)
- Food security status

At the end of the funding period (~July 2027), a de-identified dataset will be made available to the broader research community through one of the controlled-access data repositories maintained by the NIH, such as dbGAP
Planned cross-consortium nutrition questions

Planned nutrition-related research questions:

- Documenting the clinical course of nutrition impact symptoms during cancer treatment
- Association between baseline diet quality and RDI
- Evaluating how diet quality changes from pre- to post-treatment
- Additional questions to be determined

Pilot projects underway:

- Feasibility of continuous glucose monitoring
- End of intervention participant survey on preferred sources of diet and physical activity information
What do evidence-based practice guidelines look like in the era of precision nutrition?

“What providing the right treatment at the right time to the right person taking into account patients’ health history, genes, environments, and lifestyles” - Precision Medicine Initiative

https://obamawhitehouse.archives.gov/the-press-office/2016/02/25/fact-sheet-obama-administration-announces-key-actions-accelerate

In the future, we will tailor nutrition interventions to the patient’s cancer type and planned treatment regimen AND their: comorbidities, social determinants of health, readiness for behavior change, chronobiology, genetics, metabolomics, microbiome . . . .

Large datasets will be needed!
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