

Nutrition as Prevention for Improved Cancer Health Outcomes

Executive Summary



Main Points

- Two decades of randomized trial evidence from 206 studies of nutrition interventions in adults prior to and/or during cancer treatment focused on use of dietary supplements (not including vitamins and minerals), nutrition support (including oral nutrition supplements), and the route or timing of nutrition interventions. Studies were predominately conducted in individuals with gastrointestinal and head and neck cancers, with few studies conducted within the U.S. setting.
- Studies focused on evaluating changes in body weight/composition, adverse events, length of hospital stay, and quality of life.
- Among studies with a high volume of literature (n=114), which predominately examined dietary supplements and nutrition support in gastrointestinal and head and neck cancers, 11 percent (n=12) were rated as low risk of bias (higher quality), 40 percent (n=46) medium risk of bias and 49 percent (n=56) as high risk of bias (lower quality).
- Low- and medium-risk-of-bias studies reported mixed results on the effect of nutrition interventions across outcomes for cancer and cancer treatment (detailed in the evidence summary results below).
- Among studies included in our Key Questions, few (4%, n=8) studies reported a formal evaluation of the value of the nutrition interventions (e.g., cost-effectiveness, cost-benefit) or provided costs detailed by intervention component; generally, these studies reported only overall costs from inpatient non-U.S. settings. In our grey literature search, we found few studies that conducted cost-effectiveness or cost-benefit analyses, and, among those, we found mixed results on the value of nutrition interventions in non-U.S. health systems.

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- Future research would benefit from studies focused on priorities and interventions most relevant to specific stakeholders (e.g., oncologists, patients, dietitians, researchers, policymakers). Future studies could then be specifically designed to evaluate the main outcomes of interest relevant for clinical practice.
- Future research would also benefit from a creation of standardized taxonomies for interventions and outcomes as well as more rigorous design and reporting of nutrition interventions.



Background and Purpose

Among adults with cancer, malnutrition is associated with decreased treatment completion, more use of healthcare, and worse survival.¹⁻⁴ Prevalence of malnutrition is high among adults with cancer,⁵⁻⁷ but only 30 to 50 percent of cancer patients at risk for malnutrition receive nutrition support or intervention.^{8,9} No high-quality guidelines exist with recommendations for preventing or treating malnutrition in adults with cancer, potentially due to several factors, including: (1) the broad range of criteria that define malnutrition, (2) variability of nutrition interventions (from medical nutrition therapy to optimize body weight or muscle mass to dietary supplements intended to replace specific micronutrient deficiencies), and (3) the lack of cohesive evidence-based approaches to malnutrition in this population.

This systematic review sought to examine the current evidence for the effectiveness of providing nutrition interventions before or during cancer therapy to improve outcomes for cancer and cancer treatment, with the goal of informing stakeholders about relevant research gaps and challenges. Findings from the review informed discussions among experts and stakeholders at the National Institutes of Health (NIH) Pathways to Prevention (P2P) workshop, *Nutrition as Prevention for Improved Cancer Health Outcomes*, which took place July 26-28, 2022. In addition, our review aims to contribute to the development of a research agenda for evaluating nutrition interventions in inpatient and outpatient cancer care. Results may help inform clinical guidelines on prevention and treatment of malnutrition in cancer care by providing a summary and synthesis of the available evidence for clinical and policy stakeholders to use in the development of such guidelines.



Methods

The methods for this systematic review follow the Agency for Healthcare Research and Quality Methods Guide for Effectiveness and Comparative Effectiveness Reviews and the PRISMA reporting guidelines.¹⁰ See the review protocol (<https://effectivehealthcare.ahrq.gov/products/improved-cancer-outcomes/protocol>) and the methods appendix for additional details. The review was guided by a set of Key Questions, which were established by the NIH planning committee for the *Nutrition as*

Prevention for Improved Cancer Health Outcomes workshop. Briefly, we searched Ovid Medline®, Ovid Embase®, and the Cochrane Central Register of Controlled Trials to identify randomized controlled trials published and indexed in bibliographic databases from 2000 through July 2022. We also conducted grey literature searches to identify additional resources relevant to cost-effectiveness.



Results

We identified 9798 unique references, with 206 studies from 219 publications reporting findings from randomized controlled trials (RCTs) of nutrition interventions to improve negative outcomes from cancer treatment. Overall, we found two decades of randomized trial evidence on nutrition interventions for adults prior to and/or during cancer treatment. This evidence focused on use of dietary supplements, nutrition support (including oral nutrition supplements), and the route or timing of nutrition interventions. Studies were predominately conducted in populations with gastrointestinal and head and neck cancers, and included both inpatient surgical and outpatient settings. Most of the studies were conducted outside of the United States. Studies focused on evaluating changes in body weight/composition, adverse events, length of hospital stay, and quality of life. Few studies were conducted within the U.S. setting. Among studies with a high volume of literature, which predominately included studies in dietary supplements and nutrition support in gastrointestinal and head and neck cancers, 11 percent (n=12) were rated as low risk of bias (higher quality), 40 percent (n=46) medium risk of bias and 49 percent (n=56) high risk of bias (lower quality).

Low- and medium-risk-of-bias studies, reported mixed results on the effect of nutrition interventions outcomes for cancer and cancer treatment. Among eight low- or medium-risk-of-bias studies in nutrition support prior to cancer treatment, studies reported mixed results on development of complications, improvements in weight loss, and length of hospital stay.¹¹⁻¹⁸

Among studies initiated prior to and continuing through cancer treatment, four medium-risk-of-bias studies across five publications showed mixed results for the effect of dietary supplements on weight changes, readmissions, length of hospital stay, development of complications, and survival.¹⁹⁻²³ Two low- and four medium-risk-of-bias study of nutrition support reported mixed results, with some studies reporting a benefit and some reporting no difference in reducing adverse events, readmissions, length of hospital stay, and survival.²⁴⁻³⁰

Among four low- and 14 medium-risk-of-bias studies of dietary supplements conducted during cancer treatment, results were mixed, with most studies reporting no benefit of added dietary supplements on body weight, adverse events, length of hospital stay, or survival.³¹⁻⁴⁵ Two low-risk-of-bias studies reported fewer adverse events and decreased length of hospital stay with soybean and fish oil.^{34, 45} One medium-risk-of-bias study of glutamine reported improved body weight, reduction in adverse events, and improved treatment tolerance,³⁸ while another medium-risk-of-bias study reported fewer adverse events among those using branch chain amino acid (BCAA)-enriched total parenteral nutrition (TPN).⁴⁰ Another medium-risk-of-bias study found improvement in postoperative complications with enteral and parenteral nutrition supplemented with

omega-3 fatty acids.⁴⁴ Three studies reported improvements in length of hospital stay across diverse supplements.^{32, 43, 46}

One low- and 10 medium-risk-of-bias studies that examined route and timing of nutrition interventions conducted during cancer treatment demonstrated mixed results.⁴⁷⁻⁵⁷ The majority reported no difference for body weight, adverse events, readmissions, or death, but half reported reduced length of hospital stay. One low-risk-of-bias study reported that postoperative enteral nutrition reduced adverse events length of hospital stay.⁴⁸ Among three low- and eight medium-risk-of-bias studies that examined nutrition support (including oral nutrition) during cancer treatment,⁵⁸⁻⁷² results were mixed for body weight, nutrition status, and adverse events. Two low-^{66, 71} and three medium-risk-of-bias studies^{67, 69, 72} reported improvements in body weight or composition with postoperative nutrition support. Four out of ten studies^{58, 59, 65, 70} reported improvements in adverse events and three reported improvements in length of hospital stay^{58, 59, 70} across diverse enteral and oral nutrition support interventions.

Finally, among studies of the effects of nutrition interventions on symptoms, three medium-risk-of-bias studies in dietary supplements reported mixed results for patient-reported symptoms.^{33 23, 43} One study of probiotics and omega-3 fatty acids reported improved quality of life,³³ while another reported no benefit.²³ Two studies reported mixed outcomes for patient-reported symptoms with one reporting a benefit³³ and one no difference.⁴³ Among five low- and four medium-risk-of-bias study of nutrition support, reported results were mixed.^{13, 15, 16, 18, 28, 66, 68, 69, 71, 72} Two studies showed mixed results on functional status, with one showing a benefit and one no difference.^{28, 66} Two low-risk-of-bias studies reported improvement in nausea for individuals receiving preoperative oral carbohydrate drinks.^{28, 66} A third low-risk-of-bias study reported improvement in treatment tolerance and symptoms after use of oral nutrition supplements and dietary advice.^{66, 68}

While studies addressing Key Questions (KQs) 1-3 enrolled individuals from multiple cancer types, treatments, and stages (KQ 1-3a) across the lifespan (KQ 1-3b), with varying degrees of muscle wasting (KQ 1-3c), and in those with a range of comorbid conditions (KQ 1-3d), no eligible studies specifically evaluated whether the effects of nutrition interventions on preventing negative outcomes varied across these characteristics.

Only four studies reported the effects of nutrition interventions intended for weight loss using special diets among individuals with breast cancer and assessed body weight and composition changes. One study reported on each of the following symptoms: quality of life, symptoms, and treatment tolerance.

Among studies included in our KQ we found that few (4 percent, n=8) published cost or value (e.g., cost-effectiveness, cost-benefit) information related to the intervention. In our grey literature search of additional studies examining cost or value of nutrition interventions, we found few studies that conducted cost-effectiveness or cost-benefit analyses, and, among those, found mixed results on the value of nutrition interventions; most of these studies were conducted in non-U.S. health systems.



Limitations

The methods we used for this systematic review provided a detailed evidence map of the current state of literature on nutrition interventions, highlighting not only concentrations of literature but also gaps in intervention types. We purposefully chose broad definitions of nutrition interventions, thereby increasing the scope, breadth, and heterogeneity of the included literature in order to better assess the range and depth of available evidence. This decision allowed for demonstration of the diffuse literature set on the topic and highlighted the predominantly low quality of studies where there were concentrations of similar intervention types. However, this required focusing on high-level directionality of intervention effects across a broader range of nutrition interventions rather than looking for more detailed, precise estimates of intervention effects. Overall, this approach allowed for high level mapping of the evidence across Key Questions by patient, intervention, comparator, and outcome categories. It also revealed evidence gaps for future research.



Implications and Conclusions

Overall, the RCT evidence focused on a wide range of nutrition interventions, but studies were concentrated in use of dietary supplements (not including vitamins and minerals), nutrition support, and the route or timing of nutrition interventions within gastrointestinal and head and neck cancers in the inpatient setting of hospitals outside of the United States. Among interventions with the highest volume of literature, a majority of studies were evaluated as having high risk of bias. Our findings point to the need for rigorous new U.S.-based research to bolster the evidence base. Specifically, the field needs a more detailed future evaluation of a subset of nutrition interventions contained in this evidence map that focus on priorities most relevant to specific stakeholders (e.g., oncologists, patients, dietitians, researchers, policymakers). Further, studies should be specifically designed to evaluate the main outcomes of interest for clinical practice. Future research would also benefit from creation of standardized taxonomies for interventions and outcomes as well as more rigorous design and reporting of nutrition interventions. As mentioned, heterogeneity of populations, interventions, comparators and outcomes precluded aggregation. Currently, the quality and heterogeneity of the studies limit the ability to translate findings into clinical practice or guidelines. In order to inform development of guidelines, coordinated efforts are required to establish detailed conceptual frameworks for mechanisms of nutrition interventions most relevant to clinical care providers and patients. Such frameworks would help inform priorities for future research as well as guide practice and policy.



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