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**Commentary**

# The Pathways to Prevention program: nutrition as prevention for improved cancer outcomes

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## Abstract

Adequate nutrition is central to well-being and health and can enhance recovery during illness. Although it is well known that malnutrition, both undernutrition and overnutrition, poses an added challenge for patients with cancer diagnoses, it remains unclear when and how to intervene and if such nutritional interventions improve clinical outcomes. In July 2022, the National Institutes of Health convened a workshop to examine key questions, identify related knowledge gaps, and provide recommendations to advance understanding about the effects of nutritional interventions. Evidence presented at the workshop found substantial heterogeneity among published randomized clinical trials, with a majority rated as low quality and yielding mostly inconsistent results. Other research cited trials in limited populations that showed potential for nutritional interventions to reduce the adverse effects associated with malnutrition in people with cancer. After review of the relevant literature and expert presentations, an independent expert panel recommends baseline screening for malnutrition risk using a validated instrument following cancer diagnosis and repeated screening during and after treatment to monitor nutritional well-being. Those at risk of malnutrition should be referred to registered dietitians for more in-depth nutritional assessment and intervention. The panel emphasizes the need for further rigorous, well-defined nutritional intervention studies to evaluate the effects on symptoms and cancer-specific outcomes as well as effects of intentional weight loss before or during treatment in people with overweight or obesity. Finally, although data on intervention effectiveness are needed first, robust data collection during trials is recommended to assess cost-effectiveness and inform coverage and implementation decisions.

The role of nutrition in the etiology of cancer has been studied extensively. Although some controversies and uncertainties remain, fundamental knowledge and approaches to further discovery in this area are reasonably well established. In contrast, the role of nutrition in improving outcomes for patients from cancer diagnosis through treatment is not at all clear for researchers, clinicians, dietitians, health systems, and patients. More evidence is needed to clarify which nutritional interventions are effective for which patients, for which cancers, in which settings, and when.

For decades it has been known that malnutrition, including both undernutrition and overnutrition, adversely affects survival among people with cancer (1). However, high rates of malnutrition continue to affect health outcomes and are associated with increased risk of complications, lower treatment tolerance and response to treatments, longer hospital stays, substantial declines in quality of life, and lower survival rates (2-4). Although recent published American Society of Clinical Oncology and American Cancer Society (ACS) guidelines address exercise, diet, and weight management during cancer treatment (5,6), there are no well-defined national clinical guidelines for the prevention or management of cancer-associated malnutrition, nor for nutrition management for specific cancer types. Clinicians can identify risk of malnutrition through nutritional screening, but screening is conducted inconsistently and often with unvalidated tools. Furthermore, evidence remains unclear about the best tools and diagnostic criteria for malnutrition and the related condition of sarcopenia. Neither nutritional screening nor medical nutrition therapy are standard components of outpatient oncology care, where 90% of cancer patients are treated in the United States (1). Finally, there are inconsistencies in how researchers and health professionals define and operationalize basic terms such as malnutrition, cachexia, and sarcopenia.

The questions around proper nutrition for patients with cancer are extremely complex because nutrition-related conditions and outcomes are themselves heterogeneous. Nutritional

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interventions span from dietary education and advice to dietary supplements and special diets, enteral therapies, and total parenteral nutrition. There are also several possible objectives of nutritional interventions, including to increase completion of therapy, retention in trials, quality of life, and survival. Better evidence is needed to establish both the effectiveness of specific nutritional interventions across patients' cancer treatment trajectories and subsequently their cost-effectiveness to inform the implementation of optimal nutritional care.

To address this complex issue, an in-depth evaluation of the existing science and assessment of research needs was cosponsored by 3 institutes and 2 offices of the National Institutes of Health, including the National Cancer Institute, the National Institute on Aging, the Office of Nutrition Research, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the Office of Disease Prevention. The initiative included a systematic evidence review (7) conducted by the University of Minnesota's Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality. In July 2022, the National Institutes of Health convened a Pathways to Prevention Workshop entitled, "Nutrition as Prevention for Improved Cancer Health Outcomes" (7). The workshop included summary presentations of the evidence review and invited experts presenting different domains of oncology nutrition research and care. An independent panel of individuals from multiple disciplines, including dietetics, nutritional science, oncology, nursing, economics, epidemiology, and health services research, was convened to assess, deliberate, and draft a report reflecting key information and recommendations derived from the evidence review and workshop. Before publication, the report was posted for public comment. Four key questions (KQs) and a contextual question guided the evidence review, workshop, and panel deliberations (see Table 1).

Given the complex nature of these KQs and their interactions, the panel designed a conceptual framework (see Figure 1) of critical components encompassed by these questions, their relationships, and associated outcomes. The intent was to encapsulate components of this complex nutrition issue to engage investigators in framing existing gaps in knowledge and weaknesses in evidence that need to be addressed. The framework recognizes that demographic, clinical, system, and social factors can affect the effectiveness of nutritional screening and interventions across the cancer care continuum from diagnosis and treatment to survival. Nutritional interventions before and during treatment can potentially influence intermediate outcomes, such as treatment-related symptoms, and distal outcomes, such as survival. Cost effectiveness may be ascertained based on intermediate or distal outcomes if evidence of effectiveness is available.

Table 2 provides key terms used in this report, which have overlapping features but are not interchangeable. Using the framework and definitions outlined above, the next sections address the KQs and contextual question, outlining what is known and not known in each area, followed by recommendations for moving the field forward while building evidence around nutritional interventions for cancer patients.

## KQs 1 and 2: effects of nutritional interventions before and after cancer treatment

### What is known

Malnutrition reportedly occurs in up to 70% to 75% of people diagnosed with cancer, although the prevalence of the condition varies by cancer type, individual, and social factors (2-4). Most evidence on the risk and prevalence of malnutrition came from studies of patients with gastrointestinal or head and neck cancer, where the ability to consume and digest food was most impaired. Also, most high-quality studies were conducted in inpatient settings outside the United States, so the results of existing research may not be generalizable to cancer patients in the United States. Further, the approaches did not consider the impact of nutritional interventions before cancer treatment (prehabilitation), and there were no standard-of-care nutritional interventions. Therefore, health-care providers must use their discretion to choose whatever they believe will benefit their patients, which may include nutritional counseling, dietary modification or supplementation, nutrition support, use of special diets, or fasting. Common outcomes included adverse events, length of hospital stay, quality of life, and survival. However, substantial heterogeneity was noted in study populations and measurement approaches, and few studies used conceptual frameworks to guide their research.

Overall, nutritional intervention studies (see evidence review Chapter 7 (7)) showed mixed results for the effectiveness of supplementation before or during cancer treatment. High-protein diets (1.2-1.5 g/kg/day; and occasionally higher, 2.0 g/kg/day in

**Table 1.** Key questions posed by the Pathways to Prevention (P2P) program

| | |
|---|---|
| KQs 1 and 2: Effects of nutritional interventions before and after cancer treatment | In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutritional 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? Do the effects of nutritional interventions on preventing the negative outcomes associated with cancer treatment vary by cancer type, treatment type (chemotherapy, radiation, surgery), stage of disease, across the lifespan, or across special populations? |
| KQ 3: Effects of nutritional interventions on side effects and quality of life | In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutritional interventions before or during cancer treatment on associated symptoms such as fatigue, nausea and vomiting, appetite, physical and functional status (eg, frailty), and quality of life? Do the effects of nutritional interventions on preventing the negative outcomes associated with cancer treatment vary by cancer type, treatment type (chemotherapy, radiation, surgery), stage of disease, across the lifespan, or across special populations? |
| KQ 4: Effects of intentional weight loss before or during cancer treatment | In adults with cancer who have overweight or obesity, what is the effect of nutritional 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? |
| Contextual question: cost effectiveness | What evidence is available on the cost-effectiveness of nutritional interventions for preventing negative outcomes associated with cancer treatment? |

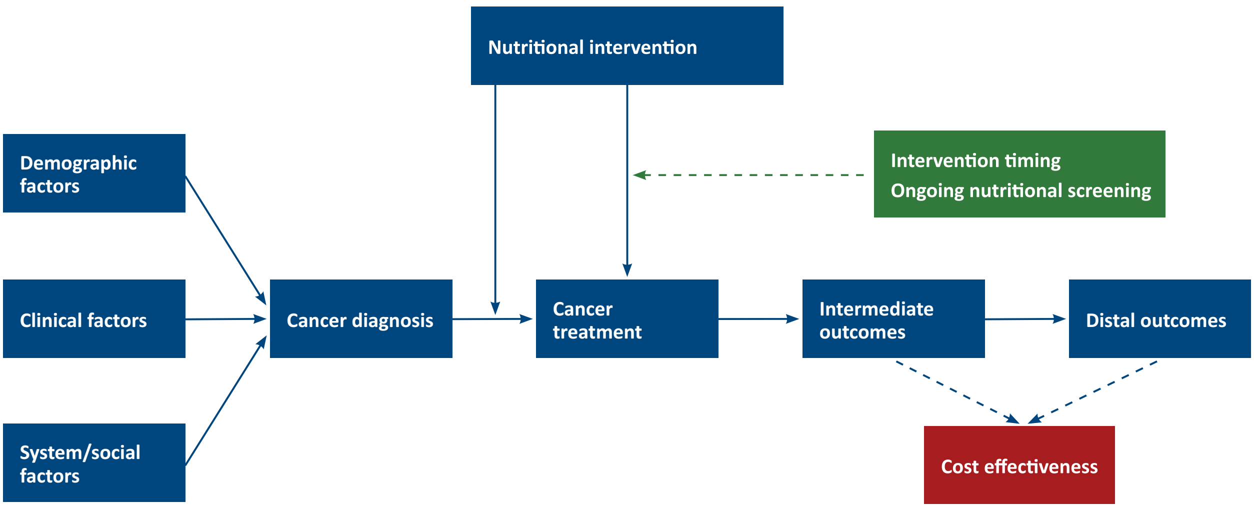


**Figure 1.** Conceptual framework. Dashed lines represent methodological, measurement, or policy considerations. Demographic factors (eg, age, race and ethnicity, socioeconomic status, sex). Clinical factors (eg, cancer type and stage, comorbid conditions, medications, initial or previous nutritional status, body composition). System and social factors (eg, access to care, insurance status, geographical location, food security). Nutritional interventions (eg, dietary modifications, caloric restriction, caloric and protein supplementation, nutrition support). Intermediate outcomes (eg, treatment success and completion, decisions to continue or stop treatment[s], quality of life, nutrition impact symptoms, conditions such as cachexia, sarcopenia, frailty). Distal outcomes (eg, survival, quality of life).

severe protein depletion) were often recommended in major oncology nutrition guidelines (2,4,8), yet even achieving the recommended minimum protein intake can be difficult for some patients. Further, cancer treatment may cause symptoms such as nausea and poor appetite, making food consumption difficult. Unfortunately, given the nature of inpatient nutritional interventions, evaluation for nutritional status and body composition was often conducted later in the cancer treatment trajectory, when interventions may be less effective. Malnutrition was not correctly identified in more than 40% of patients (9) but was generally found to be highest in gastrointestinal cancer patients due to obstruction, lack of absorption, and treatment toxicity. Head and neck cancer patients were also at a high risk of malnutrition and adverse outcomes. Evidence showed that reaching vulnerable patients before treatment may be challenging.

Screening for nutritional status and body composition was rarely and inconsistently undertaken (1). Further, screening approaches varied across studies, with no agreement on minimal screening standards or cutpoints to define malnutrition (10). Many studies used the Patient-Generated Subjective Global Assessment (PG-SGA) for malnutrition screening, which, although validated, required training and did not identify the presence of sarcopenia. Malnutrition is common and is associated with cachexia and sarcopenia (11,12), yet providers often used the “eyeball” method to assess presence of malnutrition. Studies showed that if malnutrition was not perceived, providers did not refer patients for further screening or intervention (11). Patients with high body mass index (BMI) often were not evaluated for malnutrition because physicians were less aware of the risk of malnutrition given a greater body mass. Additionally, cachexia and sarcopenia (indicating changing body composition) may be more difficult to observe without enhanced screening. Initial weight loss associated with cancer diagnosis may be misattributed to healthier dietary behaviors rather than possible malnutrition and potential cachexia and sarcopenia.

There was early evidence of adverse cancer outcomes associated with suboptimal nutritional status before diagnosis. Patients with sarcopenia experienced increased toxicities to standard chemotherapeutic treatments (12). Malnutrition also was associated with weight loss, sarcopenia, and reduced survival (13). Animal model studies demonstrated that cachexia frequently occurred 4 to 14 days after injection with tumor cell lines (14,15). Animal models suggested potential for improved response to treatment when diets that mimic the effects of fasting were used for a few days per month timed to some chemotherapies (15,16). Fast-mimicking diets, which are low in calories, protein, and sugar and proportionally high in fat, are designed to mimic the effects of fasting in reducing hormones and growth factors that promote cancer cell growth (17). Studies in humans on this topic remain sparse (16).

There were limited data on the impact of nutritional interventions for those with sarcopenia and/or cachexia. A summary of meta-analyses (18) concluded that patients with gastrointestinal cancer and sarcopenia experienced a 40% increase in major postoperative complications. Subgroup analyses found that in patients with gastrointestinal cancer who received the nutritional intervention “Enhanced Recovery after Surgery” (19), sarcopenia was not associated with major complications. Further, emerging data from multiple observational studies suggested that sarcopenia was associated with toxicity of various cancer therapies (including chemotherapy, immunotherapy, and targeted therapies), independent of age, sex, BMI, and cancer type (18,20,21).

## What is not known

Overall, the research on nutritional interventions and cancer-associated malnutrition was limited. No conclusive data established the utility of these therapeutic interventions by cancer type, treatment type, cancer stage, age, or muscle wasting status or among patients with multiple comorbidities.

Although optimizing nutritional status of patients before cancer treatment is logical and sensible, it was unclear which interventions to use, when they should be instituted, and how best to measure a successful intervention outcome. Limited emerging evidence in animal models with few human trials suggested potential benefits of various approaches to intermittent fasting and other dietary modifications aimed at influencing hormones

**Table 2.** Definitions for key terms and sample tools[a]

| Key Term | Definition |
|---|---|
| Malnutrition | A condition involving deficiencies, excesses, or imbalance in calorie or nutrient intake or use. Malnutrition may be caused by low (or excessive) dietary intake, high nutrient requirements, compromised ability to assimilate nutrients, disease-associated inflammation, or other mechanisms (25,58,59). |
| Sarcopenia | A progressive and generalized loss of skeletal muscle strength (quantity or quality) and decreased physical performance associated with increased risk of adverse outcomes such as falls, fractures, disability, and mortality (59). Low muscle strength, rather than muscle mass, is the principal determinant of sarcopenia. |
| Sarcopenic obesity | In the context of excess adiposity, obesity exacerbates sarcopenia by increasing fat infiltration into muscle and reducing physical function (35,60). |
| Myosteatosis | Excess fat deposition in muscle tissue that reduces muscles' functional capacity (12). |
| Cancer cachexia | A multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) and abnormal metabolism. It occurs on a continuum that cannot be fully reversed by conventional nutritional support, thus leading to progressive functional impairment (58,61). |
| Nutrition impact symptoms | Any symptom (eg, diarrhea, mucositis) that becomes a barrier to intake, digestion, absorption, or use of nutrients. Symptoms can develop and change rapidly during cancer therapy and should be reassessed at each patient contact. |
| Frailty | A multidimensional geriatric syndrome characterized by cumulative decline in multiple body systems or functions, usually with weight loss, that increases vulnerability to poor health outcomes (4,6). |
| Screening, assessment, and care process terms | |
| Malnutrition screening | To detect nutritional disturbances at an early stage, current recommendations emphasize using a tool validated in the setting in which the tool is intended for use (25,62). The goal is to identify signs and symptoms of anorexia, cachexia, and sarcopenia as early as possible. Several validated screening tools are available, but not all are validated for ambulatory and outpatient settings (5,10). |
| Nutritional assessment | A systematic process initiated following nutrition screening or patient referral in which a registered dietitian gathers and synthesizes data to identify nutrition-related problems and their causes (62,63). This ongoing process can include data about nutritional intake, nutrition impact symptoms, anthropometric measurements, medical tests, nutrition-focused physical examination, and other factors. |
| MST (64) | A valid and reliable tool for identifying malnutrition risk in adult oncology patients in outpatient settings (4,25,65). This 2-question screener, which can be completed by a health-care professional or patient, asks about appetite and unintentional weight loss. A score of 2 or greater indicates risk of malnutrition and warrants referral to a dietitian for further assessment. A workshop presentation on screening noted that although the MST is highly sensitive, it does not assess for nutrition impact symptoms or sarcopenia. |
| PG-SGA (14) | A valid and reliable screening tool in oncology populations (15). The patient-completed portion (the short form, PG-SGA SF) is a quick, valid tool for screening that includes 4 components: weight history, food intake, symptoms, and activity. The complete PG-SGA includes a second portion, completed by a physician, nurse, or dietitian, that adds points based on diagnosis, age, metabolic demand, and physical exam. A workshop presentation noted that although the PG-SGA is validated in cancer patients of all ages and assesses the presence of nutrition impact symptoms, it does not assess for sarcopenia. A well-trained professional is needed to complete the full PG-SGA form. |

[a] MST = Malnutrition Screening Tool; PG-SGA = Patient-Generated Subjective Global Assessment.

and growth factors. Benefits of these approaches compared with nutritional supplementation, nutrition counseling, or behavioral intervention remain unclear. It was unknown whether nutritional interventions could optimize treatment completion and minimize delays, especially for those undergoing systemic therapy (eg, chemotherapy, immunotherapy), thereby improving survival. The relationship between levels of nutritionally regulated hormones and successful cancer treatment was also currently unknown.

Timing of nutritional interventions relative to treatment was relatively understudied. Studies in outpatient settings would further the understanding of the benefits and pragmatic challenges of administering nutritional interventions. It was unknown whether the type and timing of the nutritional intervention vary by cancer type, cancer stage, or treatment type. For example, will a nutritional intervention have the same impact in adults with breast cancer as it had in adults with stomach cancer? It was unknown if nutritional interventions have the same impact in people who differ in demographic characteristics, degree of muscle wasting and malnutrition, or presence of comorbidities. It was unknown whether sarcopenia and cachexia are a result or a cause of cancer progression. Further, the relationship among age, cancer-related muscle loss, and myosteatosis was unknown. Finally, how and when to implement nutritional interventions by body composition was unclear.

## KQ 3: effects of nutritional interventions on side effects and quality of life

### What is known

Debilitating symptoms, such as declining physical and functional status (eg, frailty), fatigue, and decreasing quality of life, may occur as a consequence of cancer or prompt a cancer diagnosis. However, these and other debilitating conditions also may occur during cancer treatment.

Observational data showed that most people with cancer experienced symptoms such as constipation, anorexia, nausea, vomiting, diarrhea, gas or bloating, reflux, indigestion, mucositis, xerostomia, dysphagia, taste and smell alterations, or early satiety (22,23). These are termed nutrition impact symptoms because they are potential barriers to intake, digestion, absorption, and/or use of nutrients. These debilitating conditions interfered with optimal management of associated malignancies. For example, unexplained weight loss was a common presentation before diagnosis of gastrointestinal malignancies (24). These patients often require surgical intervention that may affect their ability to meet nutritional needs due to temporary or permanent loss of intestinal absorptive surfaces (23).

Whether caused by their cancer, its treatment, or both, nutrition impact symptoms and physical and functional decline limited people's ability to consume adequate nutrition and synergistically worsened their nutrition state (2,3). Although more frequently evaluated among people with gastrointestinal, head and neck, lung cancers and advanced cancers, these occurred in all cancer types.

Overall, the evidence review of high- and good-quality studies suggested an uncertain benefit for reducing symptoms with a limited range of dietary supplements and enteral or parenteral nutritional support, with limited evidence on the effects by cancer type or across the lifespan (25). Emerging evidence in older adults with cancer, often from multifactorial interventions involving nutrition and other components, suggested the potential to reduce chemotherapy-related toxicity and improve quality of life (26-28).

### What is not known

Identifying optimal choice and timing of an intervention to avoid or reduce nutrition impact symptoms and improve quality of life, and whether these differ based on cancer or treatment type or an individual's baseline malnutrition risk, were all unknown. Research assessing nutritional interventions in adults during cancer therapy who were underrepresented in biomedical research (older, rural, racially and ethnically diverse, and low socioeconomic status) was extremely limited.

## KQ 4: effects of intentional weight loss before or during cancer treatment

### What is known

Overweight and obesity conferred increased risk of at least 13 cancer types (29-31) and were present in more than 50% of people newly diagnosed with cancer (4,12). Observational studies showed that overall, obesity was associated with increased mortality and higher cancer recurrence rates, although increased survival was seen in people with lung and renal cell cancers and melanoma (32). Evidence showed that increased cancer risk and poor cancer outcomes were associated with inflammation, elevation of insulin and insulin-related growth factors, or changes in reproductive hormones (29-31,33). Research in people without cancer showed that weight loss can improve these factors and likely reduce cancer risk (34). Yet weight loss involved loss of lean body mass and adipose tissue (32), raising concerns about functional status, frailty, and quality of life.

Obesity was associated with poorer functional status, higher mortality rates, and a higher rate of complications across multiple cancer diagnoses and treatment types (32). Limited evidence suggested that differences in fat-free mass among people with obesity may play a role in less optimal chemotherapy dosing (2). Obesity was associated with malnutrition and sarcopenia, with or without unintentional weight loss (35). Without proper screening, sarcopenia may be especially likely to go undetected or unaddressed. Sarcopenia was reported in 36% to 50% of people newly diagnosed with cancer who have overweight or obesity, especially those with head and neck, lung, and gastrointestinal cancers (27).

Randomized controlled trial (RCT) evidence on the potential benefit of intentional weight loss before or during treatment in people with obesity and cancer was limited. Studies in the evidence review and in other RCTs that did not meet inclusion criteria generally involved small sample sizes, a limited range of cancer types, and outcomes related to weight or quality of life (5,36,37). Outcomes did not include cancer survival. Emerging data presented at the workshop from small RCTs suggested that presurgical intentional weight loss provided more beneficial effects when it was slower than the recommended rate of weight loss in noncancer populations (38,39).

Validated, noninvasive imaging methods to reliably quantify body composition, including amount and location of adipose tissue and muscle quantity and structure, have been developed and may be available from imaging studies conducted for other purposes (40). However, imaging methods differed in results provided and were not always interchangeable. Consensus and standardization were lacking regarding measurement, methodology, and appropriate diagnostic cutoff points (40). Patients with similar muscle mass but different amounts of adipose infiltration into muscle tissue experience increased chemotherapy toxicity and quicker tumor progression, yielding shorter overall survival across cancer types (41). Patients with higher BMI were more likely to have sarcopenia that involved changes in muscle quality rather than muscle mass loss; this may be especially pertinent to research involving the effects of intentional weight loss, and results may differ based on loss of fat, lean body mass, or water.

### What is not known

There were many knowledge gaps related to inconsistencies in the observed relationship between BMI and cancer outcomes. It was not known whether people whose BMI is categorized as overweight or obesity at the time of cancer diagnosis were conferred a survival benefit during treatment, perhaps through nutritional reserve. The "obesity paradox" in renal cell cancer (in which obesity is associated with increased risk of this cancer but lower mortality) illustrated the currently incomplete understanding of molecular and physiologic mechanisms in cancer and implications for care (42,43).

Adiposity's influence on treatment outcomes may differ based on cancer or treatment type (32). Workshop presentations provided examples of emerging evidence that suggested differing effects of immunotherapy versus other therapies (44). It was unclear how body composition and modest loss of visceral or total body fat could alter tumor progression and other characteristics. Mechanisms explaining the association of body composition changes with toxicity of systemic cancer therapies need to be identified to better understand differences in muscle loss among individuals during cancer treatment and across cancer diagnoses (25). Emerging evidence showed that variables such as muscle volume, muscle density, and frailty were important to outcome prediction and thus may provide more clarity on mechanisms (45,46).

Given the prevalence of overweight and obesity noted above (4), a vital question is whether intentional weight loss before or during cancer treatment can optimize hormonal and metabolic influences on clinical outcomes or if it increases risk of unintentional cancer-driven or treatment-driven sarcopenia and cachexia. It was also unknown how risks of intentional weight loss vary by cancer types and treatments, baseline lean body mass, functional status, and individual characteristics such as age, ethnicity, and frailty. Evidence was also lacking on whether the risks and benefits of intentional weight loss before and during cancer treatment differ based on methods for achieving weight loss, the degree of calorie reduction, and the combination of dietary change with physical activity.

Most weight loss research was conducted during posttreatment survivorship and produced inconsistent results. Although such research was outside the scope of this panel's charge, evidence supported the value of a healthy diet and physical activity as important influences throughout life (30,31,47). Until further research provides clearer answers, health professionals can capitalize on interest in lifestyle choices stimulated by a cancer diagnosis and encourage patients to follow recommendations that support overall health, such as those provided by the American Institute for Cancer Research, the ACS, and the US Dietary Guidelines. Consistent with recent findings by the American Society of Clinical Oncology- and ACS-sponsored expert panels (5,6), RCTs are needed to test the effects and safety of multifaceted interventions for improved dietary quality and physical activity, with and without weight loss, for people with cancer who have overweight or obesity. Distance-based approaches supported by a centralized institution will help evaluate and increase efficiency and fidelity, expand the diversity of people participating in interventions, and reduce variability within intervention studies.

## Contextual question: cost effectiveness of nutritional interventions

### What is known

The value and cost effectiveness of nutritional interventions delivered in outpatient settings may be key to implementation and adoption of effective strategies to address nutritional status in patients treated for cancer (48-50). Before assessing the value of any intervention, evidence of its effectiveness should be robust. As described in the evidence review, only 5% of the included studies (n = 8) captured any cost-related information. However, the few studies addressing cost or cost-effectiveness of nutritional interventions in outpatient settings supported their use. Most studies were conducted outside of the United States, were specific to the inpatient setting, spanned highly variable interventions (ie, total parenteral nutrition, early enteral nutrition, early oral feeding, or delayed oral feeding), and assessed costs of hospital resources. The grey literature search from the evidence review found 4 additional studies (51-54) that measured costs and/or cost-effectiveness associated with preoperative immunonutrition, or oral nutrition supplements, along with a value analysis of a broad set of nutritional supports, each demonstrating favorable cost findings. Further, 2 reviews of secondary cost analyses of nutritional supports in inpatient settings noted both cost savings and cost-effectiveness (55,56). Lastly, researchers of a Medicare claims modeling study of the clinical and economic impact of nutritional interventions found the potential for both clinical improvements and substantial cost savings (57).

The findings on cost-effectiveness were not generalizable due to the level of heterogeneity of cost data collection, outcome measurement and quality, geographic location, and resource types considered. Any estimates generated insufficient evidence to conclude that nutritional interventions, in general, were cost-effective, particularly in the United States. As previously noted, there were few studies specific to the costs and cost-effectiveness of nutritional interventions in outpatient settings, where 90% (1) of US cancer care occurs. Additional studies are needed that address the factors that can affect resources and costs specific to the patient, provider, and health system, particularly in the outpatient setting. In the absence of insurance coverage for nutritional interventions, it is of utmost importance to consider the financial burden to patients. Moreover, resources and costs associated with nutritional screening and diagnosis (ie, to identify eligible patients) can be costly for certain symptoms and problems and may have upfront and downstream cost implications. Effective and rigorous screening strategies are necessary to assess baseline status, status changes over time affecting nutritional intervention effectiveness, and subsequent potential cost-effectiveness. In some settings, this may require consideration of low-resource and low-cost approaches (eg, urine analysis, dual-energy X-ray absorptiometry vs computed tomography).

Development and use of robust cost-effectiveness analyses could inform 1) insurance coverage decisions at local and national levels, including Medicare coverage; 2) health system investment and prioritization decisions about whether and which nutritional interventions to offer; and 3) novel adaptations for interventions for special populations.

A body of high-quality evidence exists indicating that in people with cancer, malnutrition is associated with adverse effects and poor outcomes. However, the evidence review and workshop revealed large gaps in knowledge, including definitions associated with nutritional status, validated instruments to assess status, and the overall effectiveness and cost-effectiveness of nutritional interventions for patients diagnosed with cancer. Although the effectiveness of nutritional interventions before cancer treatment (KQ1) and during treatment (KQ2) was noted, the evidence was limited by a lack of studies of different cancer sites beyond head and neck and gastrointestinal tract. Other limitations included the lack of studies reflecting different stages at presentation, degree of sarcopenia, comorbidity burden, treatment choices, and among subpopulations defined by age, sex, race, and ethnicity. Evidence also was limited in specificity for interventions that reduce symptoms associated with cancer treatment, such as fatigue, nausea and vomiting, loss of appetite, and diminished physical functioning and quality of life (KQ3). The heterogeneity in methods and patient populations likely created inconsistencies in the evidence for establishing any relationship between BMI and cancer outcomes (KQ4). Moreover, few studies explicitly addressed the cost or cost-effectiveness of nutritional interventions in United States outpatient settings, where 90% of patients receive cancer-related care. Although cost-effectiveness studies and implementation research are needed in this field, evidence of effective interventions are needed first on which to base these kinds of investigations.

In this report, the panel offered a conceptual framework (Figure 1) to assist researchers, funders, and policymakers in illuminating the complexity and noted interactions associated with the KQs. Knowledge gaps were described related to who should be treated, when and how; and the heterogeneity of metrics and outcomes that, to date, were used to evaluate the effectiveness and cost-effectiveness of nutritional interventions. Table 3 shows a set of recommendations that were presented to help the field move forward. Overall, the panel was impressed with the importance of nutritional interventions in producing better outcomes for cancer patients but also acknowledged the lack of data from rigorously designed and implemented research studies. There are many opportunities for advancement in this field that will challenge researchers and funding agencies interested in improving health outcomes through nutritional interventions for people diagnosed and living with cancer.

**Table 3.** Expert panel recommendations for moving the field forward[a]

| | Recommendations | KQ1 and KQ2 | KQ3 | KQ4 | Contextual |
|---|---|---|---|---|---|
| 1 | Rigorous, well-designed nutritional intervention studies conducted in the US in adults diagnosed with cancer who are at risk for or have definite cancer-associated malnutrition to allow for comparisons across studies. | x | x | x | |
| 2 | Studies examining malnutrition across a larger variety of cancer diagnoses, and in outpatient settings. Pragmatic studies embedded in clinical practice or mirroring real world clinical care will help to address issues inherent to both vulnerable populations and varied settings. | x | x | x | |
| 3 | Screening for nutritional status, risk, and body composition using validated and standard measurement approaches with defined cutpoints to identify malnutrition should be routinely integrated throughout the care process and across all cancer care settings. | x | x | x | |
| 4 | Longitudinal studies to examine optimal timing of nutritional interventions that may enhance earlier diagnosis of adverse outcomes of cancer such as cachexia, sarcopenia, adverse events, and quality of life, or avoid or improve nutrition impact symptoms. | x | x | | |
| 5 | Examination of biological mechanisms that would assist in designing approaches such as dietary restriction vs supplementation for specific cancer patients with respect to age, ethnicity, and sex as well as for differing types of cancer diagnoses and treatments. | x | | | |
| 6 | Studies that integrate dietitians and their expertise into the health-care team and that are powered to examine the impact of nutrition interventions on cancer outcomes (eg, cancer treatment tolerance, health-care resources use, treatment-limiting side effects, survival, and quality of life) by cancer type, treatment type, wasting status, comorbidity status, and across the lifespan. | x | x | | |
| 7 | Large nutrition intervention studies to evaluate the efficacy of common interventions on improving important outcomes such as cancer treatment tolerance, health-care resources use, treatment-limiting side effects, survival, and quality of life. | x | x | | |
| 8 | Studies that disentangle age from cancer-related sarcopenia and cachexia. | x | | | |
| 9 | Greater diversity among cancer diagnoses and inclusion of those with differing body composition before and during treatment to better understand the relationships among physiologic muscle wasting and deterioration and cancer treatment and suggest optimal timing for nutritional intervention, screening, and support. This might be accomplished by creating large biobanks of both host and tumor specimens and body composition data to understand mechanisms leading to muscle abnormalities. | x | | x | |
| 10 | Improved screening methods to identify loss of muscle volume or function that can occur even in the presence of obesity. Reliance on edema-dependent markers and BMI alone is ineffective. | | | x | |
| 11 | More direct measures of adiposity and muscle mass to add rigor to the investigation of the relationships between body composition and outcomes of different types of cancer treatment. Prospective studies exploring the role of body composition in predicting dose-limiting toxicities and the relationship between dose modification and clinical outcome to lay a foundation for more customized treatment dosing and timing. | | | x | |
| 12 | Research on weight and cancer outcomes to consider a patient's disease trajectory and body composition changes across time. | x | | x | |
| 13 | Randomized controlled dietary interventions that incorporate intentional weight loss before and during cancer treatment designed to address variables such as timing, rate, and mode of weight loss that may influence outcomes. | | | x | |
| 14 | Because evidence supports physical activity during cancer treatment as beneficial in managing quality of life, its potential to minimize loss of lean body mass during weight loss warrants its inclusion in weight loss intervention trials (5,66). Interventions that test physical activity with and without weight loss to provide insight for optimal treatment of people who have overweight or obesity (67,68). | | | x | |
| 15 | RCTs of nutritional interventions (69,70) that incorporate CEAs. | | | | x |
| 16 | Use of methodologic approaches other than RCTs, such as robust modeling techniques (eg, CISNET, mini-models based on electronic health records and Learning Health Systems), analyses of large population-based data (eg, NHANES, NDI, SEER, health insurance claims, CMMI payment model data, "real-world" data from comparative effectiveness studies), including CEAs to answer "what if?" questions assessing the cost-savings or cost-effectiveness of effective nutritional interventions. | | | | x |
| 17 | Increased adherence to national guidelines and guidance for systematic methods and approaches to CEA (71,72) to enhance generalizability and replication of interventions in diverse settings and promote consistency and clarity with justification for every cost included in analyses. Robust methods include addressing the multiple perspectives (eg, patient, payer, provider, or societal), capturing implementation- and intervention-specific costs, patient out-of-pocket costs, and changes in health-care use that may be attributable or downstream to the intervention. | | | | x |

[a]BMI = body mass index; CEA = cost-effectiveness analyses; CISNET = Cancer Intervention and Surveillance Modeling Network; CMMI = Center for Medicare and Medicaid Innovation; NHANES = National Health and Nutrition Examination Survey; NDI = National Death Index; RCT = randomized controlled trial; SEER = Surveillance, Epidemiology, and End Results.

## Data availability

The data underlying this article are available at National Institutes of Health. Nutrition as prevention for improved cancer health outcomes. https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/nutrition-prevention-improved-cancer-health-outcomes. Accessed March 2, 2023.

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## Conflicts of interest

Authors have no conflicts of interest.

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