Malnutrition in the setting of cancer treatment is often foreboding and for good reasons, as it is an independent predictor of poor outcomes (ie, decreased survival, poor response to cancer therapies, increased symptomatology, and impaired functional abilities). Nor is the scope of the problem insignificant, as it has been estimated that when malnutrition progresses to cachexia, it accounts for approximately 30% of cancer-related deaths overall (1,2). Treating malnutrition and ideally preventing its unrelenting transition to cancer cachexia is a goal that clinicians have been seeking for decades. Despite the array of oral therapies available, not all patients will benefit, either in improved survival or improved quality of life (QOL). Several systematic reviews during the past decades have shown that a number of considerations must be taken into account when treating patients at risk for or suffering from cancer-related malnutrition (3–5). These include type and stage of disease, treatment modalities, patient comorbidities, functional performance, and psychosocial status. Research aimed at preventing and treating weight loss, and malnutrition must incorporate these factors, beginning with restrictive eligibility criteria and meaningful patient reported outcomes. With this approach, other endpoints that heretofore have eluded the research community, such as improved survival and weight gain or maintenance, might be achieved. Unfortunately, in this issue of the Journal, results from the meta-analysis of Baldwin et al. (6) suggest these changes and achievements have yet to occur.

The authors are to be commended for their thorough and rigorous review and meta-analysis of oral nutritional interventions in malnourished cancer patients or those at risk for malnourishment. Thirteen randomized controlled studies were included in the analysis representing 1414 participants. Study participants were adults with cancer (all sites and stages) receiving active treatment, including palliative treatment, and an oral nutritional intervention consisting of dietary advice, oral nutritional supplements, or both. All studies compared one of these nutritional interventions with usual care. The outcomes included in the analyses were mortality, QOL, weight loss, and energy intake. QOL was measured using the European Organization for Research and Treatment of Cancer (EORTC) questionnaire, which consists of 30 items assessing five functions, eight symptoms, global QOL, and perceived financial impact. The number of studies used to analyze each outcome varied depending on clinical and statistical heterogeneity. Analyses of mortality (15 studies), QOL (five studies), weight (eight studies), and energy intake (10 studies) were done. Overall, the analyses revealed no effect on mortality, no statistically significant difference in body weight or energy intake, and improvement in global QOL, EORTC domain of emotional functioning, dyspnea, and loss of appetite. These results reflect reanalyzed data excluding studies responsible for heterogeneity.

There are several limitations to the review that the authors carefully outline. With regard to nutritional status, the patient population was very heterogeneous, including those at risk for malnourishment, those who were malnourished, and those who were cachectic. These nutritional statuses are often used interchangeably; yet, they constitute very distinct entities, possibly requiring very different interventions. Experts agree that conventional nutritional support cannot fully reverse the process of cachexia (7). Might the results of the analysis have been more promising if the eligibility criterion for weight loss had been more restrictive? Patients also varied in terms of cancer type, stage, and treatment. Though the authors believe this is justified, Santarpia et al. (8) advocate a tailored/personalized nutritional approach dictated by the underlying etiology. Nutritional deficits resulting from cancer and its treatment vary widely, as do their interventions, which may account for the variation seen in the duration, nature, and intensity of the nutritional interventions in the meta-analyses, which the authors cite as a factor contributing to heterogeneity. The most important limitation is the inclusion of studies that were of poor quality because of inadequate blinding, high risk of bias, small sample sizes, and inadequate power. Regrettably, these limitations reduce the clinical applicability of the findings and underscore the inherent challenges in conducting a meta-analysis in this area of research. Moreover, it speaks to the need for further research in this area.

By outlining the limitations, the authors provide direction for future researchers. A key point made by the authors is that despite the statistical significance of some aspects of QOL, it is unclear how meaningful these changes are to the patient. The challenge that researchers face is explaining how improved emotional well-being resulted from taking an oral nutritional supplement and/or receiving dietary counseling. Was the improvement from the nutritional counseling, the supplement, the combination, or the extra attention to and clinical involvement with the patient? Was the improvement seen in cachectic patients only? If the goal of nutritional clinical studies is to improve QOL, more work is needed to define what aspects of QOL are clinically significant and meaningful to the patient and most importantly, to gain a better understanding of the underlying mechanisms. Consideration must also be given to a uniform definition of malnourishment that should be an eligibility criterion. Future studies should use a common QOL scale so data can be analyzed across multiple...
studies, a standard baseline assessment, and standard clinical nutrition guidelines. A thorough psychosocial and symptom assessment including functionality and financial concerns is critical.

Selecting the right patient for nutritional interventions both in everyday practice as well in the clinical research setting, cannot be overstated. Oral nutritional supplements are often recommended likely, in part, because they are perceived to carry no harm, but who will likely benefit remains an important question. Nutritional supplements may indeed improve outcomes for some patients experiencing malnutrition but not cachexia. Dietary counseling may be beneficial for patients at high risk for malnutrition and their caregivers. However, the research conducted to date is fraught with limitations; hence, it is challenging for clinicians to apply these results to everyday practice. Until future research provides clearer answers regarding who will benefit from nutritional interventions, the use of a comprehensive assessment, published nutritional guidelines, and early interventions are essential.

References

Notes
The authors have no conflicts of interest to declare.

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