



## *Comparative Effectiveness Review Disposition of Comments Report*

**Title:** *Nutrition as Prevention for Improved Cancer Health Outcomes*

Draft report available for public comment from July 26, 2022, to August 25, 2022.

**Citation:** Parsons HM, Forte ML, Abdi H, Brandt S, Claussen AM, Wilt TJ, Klein M, Ester E, Landsteiner A, Shaukut A, Sibley SD, Slavin J, Sowerby C, Ng W, Butler M. Nutrition as Prevention for Improved Cancer Health Outcomes. Comparative Effectiveness Review No. 260. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 75Q80120D00008.) AHRQ Publication No. 23-EHC004. Rockville, MD: Agency for Healthcare Research and Quality; May 2023. DOI: <https://doi.org/10.23970/AHRQEPCER260>. [Posted final reports](#) are located on the Effective Health Care Program search page.

### **Comments to Draft Report**

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each draft report is posted to the EHC Program website or the Agency for Healthcare Research and Quality (AHRQ) website for public comment for a 3- to 4-week period. Comments can be submitted via the website, mail, or email. At the conclusion of the public comment period, authors use the commentators' comments to revise the draft report.

Comments on draft reports and the authors' responses to the comments are posted for public viewing on the website approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ.

## **Summary of Peer Reviewer Comments and Author Response**

This research review underwent peer review before the draft report was posted for public comment on the EHC website. Most comments received sought clarity on the categorization of nutritional interventions and the goal of the interventions (cancer outcomes versus treatment outcomes). The following changes were made in response:

- Intervention categories were labeled and clear descriptions of what falls into these categories were added into the Methods section.
- Chapters were reorganized to highlight key points overall followed by basic characteristics and an overview of included studies by intervention type.
- Clarification was added as to whether the nutritional intervention was intended to address cancer outcomes, treatment outcomes, or both. Authors rarely distinguished between the two.

## Public Comments and Author Response

Commentator & Affiliation	Section	Comment	Response
<b>Anonymous</b>	Evidence Summary	I found the Evidence Summary--particularly, the results section--to be difficult to read without citations. For example, there are many statements like the following: "One low-risk-of-bias study with reported a benefit of a preoperative and postoperative carbohydrate drink on functional status." Which study was this? The Executive Study would be far more useful if relevant citations were included throughout.	We have added citations throughout the evidence summary when appropriate to indicate reference to specific studies. We have additionally expanded our references within each of the results sections to reference specific studies. For more information on basic characteristics of individual studies, we reference the relevant appendices where readers may examine study information in more detail.
<b>Valaree Williams &amp; Jose Pimiento</b> <b>ASPEN Oncology Section</b>	Introduction	The introduction section provides a thorough overview of the presence and impact of malnutrition in patients with cancer.	Thank you.



Commentator & Affiliation	Section	Comment	Response
Anonymous	Results	<p>I recognize that the authors found extensive heterogeneity in the published evidence that precluded formal meta-analyses; nevertheless, unless I have missed it, the sub-parts to each Key Question (e.g., a-d) appear to have been almost entirely ignored in this report, outside of their description among the Key Questions. To adequately deliver on these Key Questions that the review was designed to address, it would be important to provide further detail about the studies that are relevant to each of the a-d Key Question sub-parts--even if they cannot be quantitatively summarized, such as through meta-analysis--so that readers can be fully informed on this findings.</p>	<p>Thank you for the comment. We had initially indicated in the discussion section that “During topic refinement, stakeholders were eager to understand the available literature within specific populations of individuals receiving nutrition interventions (e.g., adults ≥ 65 years old, those with muscle wasting, individuals with comorbid conditions). Although the included literature may have enrolled individuals from these important subpopulations, studies rarely reported results according to these characteristics.”</p> <p>To more clearly make the point of the lack of literature reporting according to the sub-questions of interest, we now highlight in each results chapter that studies do not report by these populations. For example, at the end of Chapter 5 (Key Question 1), we have added a section to indicate the lack of literature by key sub-questions:</p> <p>“Variation in the Effects of Nutrition Interventions on Preventing Negative Outcomes</p> <p>While studies enrolled individuals from multiple cancer types, treatments, and stages (Key Question 1a), across the lifespan (Key Question 1b), with varying degrees of muscle wasting (Key Question 1c) and in those with a range of comorbid conditions (Key Question 1d), no eligible studies specifically evaluated whether the effects of nutrition interventions on preventing negative outcomes varied across these characteristics”</p> <p>We have additionally added language to indicate the lack of results by sub-question in the Evidence Summary.</p>

Source: <https://effectivehealthcare.ahrq.gov/products/improved-cancer-outcomes/research>

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Commentator & Affiliation	Section	Comment	Response
<b>Bob Blancato</b> <b>Defeat Malutiriton Today</b>	Results	We were pleased to see that the Draft Report considered the effect of nutrition interventions prior to/during cancer treatment on associated symptoms including functional status and quality of life. While the high heterogeneity in studies reviewed prevented a meta-analysis, such outcomes are important to consider particularly since the outcomes can also be impacted by increasing age.	Thank you.
<b>Bob Blancato</b> <b>Defeat Malutiriton Today</b>	Results	Additional outcomes impacted by increasing age that also remain important to consider for patients with cancer are body composition and muscle mass, although again high heterogeneity in studies reviewed prevented a meta- analysis.	Thank you. As the reviewer indicated, we also considered changes in body composition and muscle mass as indicators of the effect of nutrition intervention. These outcomes are reported as part of the results from Chapters 5,6, and 7.
<b>Valaree Williams &amp; Jose Pimiento</b> <b>ASPEN Oncology Section</b>	Results	To assist readers in understanding the review's findings and reason why certain cancer sites are more frequently studied, it would be beneficial to further discuss the cancer sites that have a higher risk of with malnutrition. This will help to provide context to the populations frequently addressed in the included studies.	We agree with the reviewers that many of the nutrition interventions were focused within head and neck and gastrointestinal populations. As suggested by the reviewer, this is not unexpected as these cancer sites have a higher risk of malnutrition. We have our expanded our discussion to highlight this and now state within the Chapter 11 discussion under "Populations" that "The focus of nutrition interventions within head and neck and gastrointestinal populations is not unexpected due to the higher risk of malnutrition in these populations due to a combination of changes to the digestive tract as a result of the cancer as well as functional changes resulting from the cancer treatments themselves."

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<p><b>Valaree Williams &amp; Jose Pimiento</b></p> <p><b>ASPEN Oncology Section</b></p>	<p>Discussion and Conclusions</p>	<p>Regarding the conclusion section, a more robust discussion on necessary future directions of research to more clearly highlight, and hopefully, prevent the missteps and inadequacies of previous studies is needed. Details regarding which combination of cancer sites, nutrition interventions and outcome measures that are most likely to demonstrate the prevention of negative treatment outcomes would help guide future research efforts. A discussion on this should be included. As demonstrated from the quality of the reviewed studies, additional guidance and standardization, potentially from a large organization, would be helpful as researchers navigate study development. Unfortunately, continued generalized suggestions for the future direction of research in this area is not likely to result in stronger studies and researchers and clinicians need more specific guidance</p>	<p>We agree with the reviewers for the need to bring together a clear research agenda that takes the results from our systematic review and provides actionable guidance on next steps for nutrition research in cancer. As we state in our introduction, the goal of our systematic review was to begin this process by “examining the current evidence for how nutrition interventions before or during cancer therapy affect outcomes of cancer and cancer treatment, with a focus on research gaps and challenges.” The findings from this review were presented to inform discussions of experts and stakeholders at the National Institutes of Health Pathways to Prevention Program conference, held July 26<sup>th</sup>-28<sup>th</sup>, 2022. Based on this evidence, an independent panel developed a draft report to summarize the workshop discussions and identify specific future priorities, as the reviewers suggest.</p> <p>We now highlight the opportunities presented in this independent panel report as a way to take the gaps and challenges identified in our review and create actionable next steps from a collaboration of independent experts. In the beginning of the Chapter 11 Discussion, we state “These results were presented to inform discussion of experts and stakeholders at the National Institutes of Health Pathways to Prevention Program (P2P) conference, held July 26<sup>th</sup>-28<sup>th</sup>, 2022. Based on this evidence, an independent panel developed a draft report to summarize the workshop discussions and identify specific future priorities, which can be found on the P2P Workshop website.</p>

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<p><b>Valaree Williams &amp; Jose Pimiento</b></p> <p><b>ASPEN Oncology Section</b></p>	<p>Discussion and Conclusions</p>	<p>With the mixed results, at best, of the systematic review regarding the impact of nutrition interventions to prevent malnutrition, readers may be discouraged from further exploring the impact of nutrition intervention and developing research to measure interventions to prevent negative treatment outcomes. From reading this report, it appears that there is minimal to no evidence to support common practice including nutrition screening for patients diagnosed with cancer, any type of nutritional intervention for patients with severe malnutrition related to a cancer diagnosis or use enhanced recovery pathways for patients undergoing surgery for cancer diagnosis. It could be disheartening to nutrition clinicians who positively impact patient care daily through optimization of nutrition intervention. We recommend the addition of a brief discussion regarding the impact of the review's results on current practice.</p>	<p>We respectfully disagree that this report should serve to discourage future research. Instead, we believe this report highlights some of the challenges and provides a conceptual roadmap for future work to address most efficiently and effectively high priority questions. We strongly support the role of future clinical and research work in this area and believe our report highlighted the importance of the problems, state of the evidence, gaps in the research, and future pathways for prevention.</p> <p>While we agree with the reviewers regarding the importance of understanding the role of malnutrition screening, our report did not address the question of "screening for malnutrition". We have noted, particularly in the discussion, that definitions of malnutrition (and at risk for malnutrition) are highly varied, focusing on weight loss and other heterogeneous measures, which may be limited in adequately addressing common questions related to malnutrition.</p> <p>Finally, regarding clinical practice, as the reviewers note, our review found the current evidence base is highly heterogeneous and methodologically limited across a wide variety of patients, cancers, interventions and malnutrition status and outcomes. Studies were often conducted in highly refined research settings with carefully selected volunteers. Such limitations challenges implementation of evidence-based clinical practice. We recognize that clinical and policy decisions necessarily are made with factors beyond evidence from randomized trials; however, our results suggest that current strategies may not be supported by high quality information of effectiveness.</p>

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<b>Valaree Williams &amp; Jose Pimiento</b>  <b>ASPEN Oncology Section (cont'd)</b>	Discussion and Conclusions (cont'd)	(comment above)	To highlight these factors, we now state in the discussion: "However, these findings should not serve to discourage, but rather bolster, the rigor and content of future research informing clinical practice on nutrition interventions for cancer, including expansion of investigations of the role of malnutrition screenings, which was not addressed by this review."
<b>Alice Shapiro</b>  <b>Quality Health Consulting, LLC</b>	General	<p>Our paper was not mentioned in your excellent review. (DOI: 10.1016/j.jand.2020.11.007).</p> <p>While it showed a 5% risk of malnutrition in medical oncology pts. in a limited range of cancer DX that are most notably at a lower risk of malnutrition and a 12% risk in radiation pts, it was a well done study and would be of great interest to your readers who would look to your review for a complete review of all good studies. I think it should be included in your references so it is available to the wider audience who look to AHRQ for full review of the topic.</p> <p>Results Over a 20-month period, the average monthly MST completion rate was 74%. Of those with completed MST screens, the average percentage of patients identified at nutritional risk (MST score 2) was 5% in medical oncology and 12% in radiation oncology.</p> <p>Conclusion It is feasible to (1) integrate and standardize data collection of the MST into existing EHR flowsheets and (2) identify and quantify patients at risk for malnutrition on a consistent basis.</p>	Thank you for this additional resource. We have added reference to this article in the Chapter 11 discussion under populations, noting "Prior research examining malnutrition screening in well-defined populations has demonstrated it is feasible to identify and quantify individuals with cancer who are at risk for malnutrition using defined tools."



Commentator & Affiliation	Section	Comment	Response
<p><b>Unhee Lim</b> <b>University of Hawaii</b></p>	<p>General</p>	<p>I'm not sure if this is a relevant comment but it certainly has been a key issue for our dietary/lifestyle intervention studies, over several rounds of grant submissions.</p> <p>I would like to point out that for dietary/lifestyle intervention studies for cancer prevention, which everyone acknowledges we need to do more of as we accrue more evidence from observational studies, it is too extreme to require certain clinical diagnostic criteria as evaluation outcomes. For example, for non-alcoholic fatty liver disease-induced liver fibrosis, some clinical reviewers are very narrow-minded in insisting that dietary/lifestyle interventions propose/implement liver biopsy-based confirmation of NASH or liver fibrosis before and after (and in the middle if long-term) the interventions. There are sensitive imaging (MRI, MRE) methods for liver fat/steatosis and liver stiffness/fibrosis that have been validated against liver biopsy with excellent performance but some clinical reviewers continue criticizing the use. We cannot recruit adequate numbers of participants for dietary/lifestyle interventions while requiring biopsies, as supposed to industry drug trials, where participants are motivated by high monetary compensations. This type of reviewer bias against appropriate use of non-invasive surrogate outcomes really hurts dietary/lifestyle intervention research for cancer prevention and likely also survival. Especially, this accentuates research disparities for under-represented populations (racial/ethnic minorities, non-metro residents) who have less access/coverage/infrastructure for such invasive procedures.</p>	<p>We agree with the reviewers that the choice of diagnostic criteria and outcome measures must be feasible to recruit adequate sample sizes representative of diverse populations for nutrition interventions. This must also be balanced by the need to collect key information on the clinical effectiveness of interventions most relevant to key stakeholders. One of the goals of our systematic review was to create a map of the current evidence to inform discussions about the type and measurement of relevant outcome used in the cancer-related nutrition intervention literature. As we note, there are a diverse set of measures collected using a variety of tools. We have added additional discussion to Chapter 11 in the outcomes section, highlighting that “However, we also recognize that collection of standardized, validated tools for assessment of the most clinically relevant outcomes must be balanced with the feasibility of collection (e.g., imaging, invasive biopsies) that promote recruitment of adequate sample sizes from diverse populations for these nutrition interventions.”</p>



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<p><b>Unhee Lim</b> <b>University of Hawaii</b></p>	<p>General</p>	<p>I see little coverage of disparities studies.</p>	<p>We agree with the reviewer that coverage of disparities in nutrition interventions remains an important topic. While beyond the scope of our current systematic review, we do highlight in the discussion the need to focus on the role of social determinants of health in future nutrition interventions. We also note in our discussion that studies rarely reported race or ethnicity to further understand representativeness of the populations studies. In the current report, we encourage future research to focus on this important area.</p>
<p><b>Alfred Ordman</b> <b>Beloit College</b></p>	<p>General</p>	<p>Unfortunately, requiring clinical trials for nutritional supplements is unrealistic. Vitamin C studies do not provide great profits. The mechanisms by which VC kills cancer cells are well established. VC is almost certain to prevent the recurrence of superficial bladder cancer, without harmful side effects. But as my NIH funded cancer surgeon colleagues explained when our grant was rejected, "no one wants to prevent cancer. Think of all the funding and profit that would end."</p>	<p>In initially scoping this review, our team noted the exceptionally large literature base that examined the effectiveness of nutrition interventions on outcomes for individuals with cancer, including both observational and randomized approaches. After detailed discussion with multidisciplinary stakeholders prior to conducting the review, given limited resources, we focused only on randomized controlled trials randomizing at least 50 participants in this review to identify the literature with the highest likelihood of having statistical power to detect an effect from a nutrition intervention. Even among this literature, we noted that it was not the lack of RCTs, but the heterogeneity and methodological quality around those RCTs. We suspect that observational studies are likely to face similar challenges. Additionally, they have the even greater methodological challenges of selection bias and confounding by indication that are likely very large when attempting to ascertain the association of an intervention on outcomes among individuals selected for such an intervention. We agree well designed observational studies may be helpful but are unlikely to definitively address the KQs. We note the role of observational studies in future work in the discussion.</p>

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<b>Anonymous</b>	General	The report is highly anticipated and extremely important to the field. However, some details are entirely missing from the report, including: the report authors, acknowledgements, key informants, the technical expert panel, and peer reviewers. I would suggest and request that these details be added to the report and that the public comment period be extended (or reopened) so that the public can review and report on the report considering of these details.	Thank you for the comment. Per AHRQ policies, this information is added to the final report and is available online as part of the final report submission.
<b>Anonymous</b>	General	No, not adequately. The Executive Summary is missing important citation information, and reporting on the sub-parts (a-d) for each of the Key Questions is inadequate (largely missing).	We have added citations throughout the evidence summary when appropriate to indicate reference to specific studies. We have additionally expanded our discussion to include discussion of the sub-questions for each relevant Key Question to the Executive Summary.
<b>Bob Blancato</b> <b>Defeat Malutiriton Today</b>	General	We agree with the Draft Report’s statement “Because cancer risk increases with age, the rapidly growing older population in the United States will increase demand for cancer care and, by extension, nutrition support, over the coming decades.”	Thank you.
<b>Bob Blancato</b> <b>Defeat Malnutrition Today</b>	General	As a Coalition focused on achieving greater focus on malnutrition screening and intervention we agree with the background and premise for this systematic review, that for patients with cancer malnutrition is associated with decreased treatment completion, more use of healthcare, and worse survival. And that while malnutrition prevalence is high for patients with cancer, many do not receive nutrition support or intervention. To that end we look forward to sharing the Final Report with our Coalition members and urging them to support coordinated efforts and further research to strengthen the guidelines for clinical practices and policies for nutrition interventions that benefit older adults with cancer.	Thank you. When the Final Report is posted, it will be available on the National Institute’s of Health Pathways to Prevention (P2P) Program website as well as the AHRQ website.

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<b>Valaree Williams &amp; Jose Pimiento</b> <b>ASPEN Oncology Section</b>	General	While the systematic review provides a thorough overview and evaluation of randomized controlled trials (RCTs), we agree with comments in the review regarding utilizing only RCTs is a limitation of the review.	Thank you for the comment.
<b>Valaree Williams &amp; Jose Pimiento</b> <b>ASPEN Oncology Section</b>	General	Moreover, utilizing the term “cancer” as the aggregator produced heterogeneous, non-generalizable results due to the variety of therapies used in oncology care since cancer is not one disease.	As part of this review, we met with a variety of stakeholders and peer reviewers to identify the most useful aggregation of evidence. Based on their consultation, we focused our evidence synthesis by nutrition intervention, cancer type and treatment. We recognize that readers may have additional interests of the role of nutrition intervention by other study and population characteristics and have included a detailed appendix for each included study.
<b>Valaree Williams &amp; Jose Pimiento</b> <b>ASPEN Oncology Section</b>	General	We believe that the data would be more robust with the inclusion of non-randomized intervention or high-quality observational studies. With there being an overall low number of studies regarding the impact of nutrition interventions on outcomes in patients with cancer, wider inclusion criteria may have provided more clinically useful conclusions.	We agree with the reviewer that the inclusion of observational studies may provide important additional context on the real-world effectiveness of nutrition interventions for cancer. As noted above, due to the large and heterogeneous literature for these interventions, after extensive discussion with diverse stakeholders, we chose to focus the review on randomized controlled trials randomizing at least 50 participants in this review to identify the literature with the highest likelihood of having statistical power to detect an effect from a nutrition intervention. Even among this literature, we noted that it was not the lack of RCTs, but the heterogeneity and methodological quality around those RCTs. We suspect that observational studies are likely to face similar challenges. However, we recognize the important contribution of observational literature on answering contextual and implementation questions in diverse populations that would be infeasible or unethical to evaluate in RCTs. In the discussion, we note the important role that these observational studies can play in examining factors such as the role of social determinants of health on outcomes of nutrition interventions.

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<b>Valaree Williams &amp; Jose Pimiento</b>  <b>ASPEN Oncology Section</b>	General	Ultimately, our key takeaway message from the systematic review is the need for additional, high-quality and focused research regarding the impact of nutrition interventions on preventing negative treatment outcomes. While we agree with this statement, the absence of actionable next steps or a call to action for individuals, cancer centers and professional organizations is lacking. The addition of next steps and a call to action must be included along with potential resources in order to assist with filling the research gap and ultimately lead to the guidance that is needed to optimize outcomes.	Thank you for this comment. We now highlight the opportunities presented in an independent panel report that this review informed as a way to address the gaps and challenges identified in our review and create actionable next steps. In the Chapter 11 Discussion, we state “These results were presented to inform discussion of experts and stakeholders at the National Institutes of Health Pathways to Prevention Program (P2P) conference, held July 26 <sup>th</sup> -28 <sup>th</sup> , 2022. Based on this evidence, an independent panel developed a draft report to summarize the workshop discussions and identify specific future priorities, which can be found on the P2P Workshop website.”

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