American Journal of Hospice & Palliative Medicine®
2025, Vol. 0(0) 1–21

DOI: 10.1177/10499091251335249
journals.sagepub.com/home/ajh
Sage

Nutritional Interventions in Advanced Cancer: Scoping Review

Aynur Aktas, MD[1], Shirley Thomas, MD[2], Michelle Barrett, RGN, MSc[3], Jessica Sui, MD, MSc[4,5], Jake Waldman, BA[1], Ciarán Kenny, PhD[4], Jessica Eustice-Cook, BA[4], Kunal C. Kadakia, MD[1,6], and Declan Walsh, MD, MSc[1,2,3,7,8]

Abstract

Background: It is unclear what evidence supports nutritional advice received by those with advanced cancer. In advanced cancer, the benefits of nutritional interventions are less clear, with no consensus about effectiveness. This uncertainty is compounded by the heterogeneity of nutritional interventions and absence of cohesive, evidence-based approaches. Intervention diversity highlights the need to summarize current dietary and nutritional approaches and their evidence base. **Objective:** To map and summarize the current evidence base for nutritional interventions in advanced cancer. **Methods:** A systematic search included studies on nutritional interventions in adults with advanced cancer, excluding enteral/parenteral nutrition. Five databases (CINAHL Ultimate, Embase, Medline, SCOPUS, Web of Science) were searched from inception until 10/20/2023. Four researchers undertook screening and data extraction. Due to the heterogeneous nature of the studies, data synthesis was narrative. **Results:** The databases search yielded 3290 records. Fifty additional publications were identified through manual searches. Title/abstract screening identified 253 articles for full-text screening, 35 of which met inclusion criteria. Of these, 25 (69%) were randomized controlled trials. The studies were separated into 5 themes: (1) nutraceutical and herbal interventions, (2) ketogenic diet, (3) nutrition advice/support, (4) oral nutrition supplements, (5) other nutritional interventions. Outcome measures reported included anthropometry, biological markers, feasibility, performance status, quality of life, survival, and treatment tolerability. Most provided information about weight and energy intake and a few reported lean body mass. Although some reported positive outcomes, evidence is insufficient for definitive recommendations for any of those interventions. **Conclusions:** Our scoping review provided limited evidence for various nutritional interventions and dietary approaches. Dietary advice and oral nutritional supplements sometimes appeared to enhance treatment tolerance and improve nutritional status; impact on overall survival was inconsistent. Nutraceutical and herbal interventions showed limited clinical benefits despite apparent biological activity. The variability in outcomes underscores the need for personalized nutritional strategies that consider individual patient factors.

Keywords

ketogenic diet, nutritional advice, supplements, neoplasms, nutraceutical and herbal interventions, nutrition support

[1]Department of Supportive Oncology, Atrium Health Levine Cancer Institute, Charlotte, NC, USA
[2]The Lois U. and Harry R. Horvitz Palliative Medicine Program, Department of Palliative and Supportive Care, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA
[3]Academic Department of Palliative Medicine, Our Lady's Hospice & Care Services, Dublin, Ireland
[4]School of Linguistic, Speech and Communication Sciences, Trinity College Dublin, Dublin, Ireland
[5]Donegal Hospice, Letterkenny, Co. Donegal, Ireland
[6]Department of Medical Oncology, Atrium Health Levine Cancer Institute, Charlotte, NC, USA
[7]School of Medicine & Medical Science, University College Dublin, Dublin, Ireland
[8]Hemby Family Endowed Chair in Department of Supportive Oncology, Atrium Health Levine Cancer Institute, Charlotte, NC, USA

Corresponding Author:
Aynur Aktas, MD, Department of Supportive Oncology, Atrium Health Levine Cancer Institute, 1021 Morehead Medical Drive, Suite 70100, Charlotte, NC 28204, USA.
Email: aynur.aktas@atriumhealth.org

Introduction

Cancer remains a significant global health challenge, with high prevalence worldwide.[1] A substantial proportion of cancer cases are diagnosed at an advanced stage and often present with high rates of malnutrition, limited treatment options, and short prognosis. These cases may necessitate a shift in treatment goals, focusing on symptom management and quality of life (QoL) rather than curative efforts. Patients with cancer often seek health information from various sources, including healthcare professionals, online resources, and support groups. However, the quality and reliability of this information (especially regarding nutritional advice) can vary significantly.[2] For early-stage cancer patients undergoing disease-modifying therapy, nutritional interventions can improve clinical outcomes, QoL, symptom management, and treatment tolerance.[3] By contrast, in advanced cancer, the benefits of nutritional interventions are less clear, with no consensus about effectiveness.[4,5] This uncertainty is compounded by the heterogeneity of nutritional interventions and absence of cohesive, evidence-based approaches.[6] Intervention diversity highlights the need to summarize current dietary and nutritional approaches and their evidence base. To bridge this critical gap, we conducted a scoping review to map and synthesize the evidence on nutritional intervention evidence for this specific population.

Methods

A review was conducted to systematically scope and synthesize the evidence on nutritional interventions for people with advanced cancer. The design followed Arksey and O'Malley's[7] scoping review methodological framework, and amendments by the Joanna Briggs Institute.[8] The framework has the following stages:

1) Specify the research question
2) Identify relevant studies
3) Study selection
4) Chart the data
5) Collate, summarize, and report the results.

Each stage is discussed in detail below. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) facilitated the preparation of this research protocol.[9]

Stage 1: Identify the Research Question

This review aimed to answer the research question, "What is known from the existing literature about nutritional interventions for people with advanced cancer?" Based on the initial exploratory research, the following research questions were identified:

1. What are the types of nutritional interventions in current literature?
2. What are the outcomes arising from nutritional information?
3. What are the research gaps identified?
4. What populations have been studied?

Inclusion Criteria. The Population, Concept, and Context framework determined the research question's eligibility.

- Population: Adult participants with advanced solid cancers undergoing nutritional interventions were included. For this review, 'advanced cancer' was defined as stage III or IV disease that has spread beyond the primary tumor site or recurrent cancer unlikely to be cured. Studies were eligible if they explicitly stated advanced/metastatic disease, palliative treatment only, or limited life expectancy (eg, <6 months).
- Concept: Studies with nutritional interventions, including complementary supplements, fortified foods, nutrition counseling, and oral nutritional supplements (ONS) were considered for inclusion.
- Context: There were no restrictions on the duration, frequency, and intensity of interventions nor on intervention settings (eg, home-based, individual/group counseling), and outcome measures.

Exclusion Criteria. We excluded studies of cancer survivors, eating disorders, hematological cancer, non-malignant conditions, and pre/peri or post-operative status. We also excluded publications on artificial nutrition (enteral and parental feeding), studies solely about attitudes and compliance to diet or safety/feasibility, food avoidance, immunonutrition, and nutritional interventions combined with exercise or behavioral interventions. The review process filtered out book chapters, conference abstracts, dissertations, expert opinions, guidelines, letters to the editor, qualitative studies, and review articles. Clinical trial registries were not searched. Additionally, non-English original reports were excluded due to translation resource restraints.

Stage 2: Identify Relevant Studies

A systematic search strategy was developed by the research team in collaboration with a medical librarian (JEC). The Peer Review of Electronic Search Strategies (PRESS) checklist guided the search strategy.[10] All databases were searched from their inception to October 20th, 2023. These included CINAHL Ultimate (EBSCO), Embase (Elsevier), Medline (Ovid), SCOPUS (Elsevier), and Web of Science Core (Clarivate) (Appendix 1). A combination of database index terms, keywords, and synonyms was applied. Terms included studies on nutritional interventions in adults with advanced cancer, excluding enteral/parenteral nutrition. The search strategy used keywords and medical subject headings (MeSH), which included combinations of "diet,"

"nutrition," "cancer diet," "guideline," "guidance," "policy," "recommendation," "plan," "advice," and "cancer patient."

We manually searched 5 key websites: American Cancer Society, Canadian Cancer Society, Cancer Council Australia, Cancer Research UK, and Macmillan UK. The reference list of all included articles and relevant systematic reviews were also searched to ensure no key papers were missed. Authors were contacted for full text if further information was required. That study was excluded if it did not meet inclusion criteria or if no correspondence was obtained within a month of contact.

We used Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) to manage the screening and data extraction processes. The built-in software tools helped streamline our workflow and ensure consistency across reviewers. References were managed using EndNote X9 (Clarivate Analytics, Philadelphia, PA), which facilitated deduplication and citation generation.

Stage 3: Study Selection

All titles and abstracts of the search results were screened independently by 4 reviewers (AA, JS, JW, MB). Discrepancies were resolved by consensus between reviewers; if no agreement could be achieved, other reviewers were consulted for a final decision. After reading the full texts which met the inclusion criteria, data extraction was undertaken.

Stage 4: Chart the Data

An Excel™ spreadsheet (Microsoft Office, Redmond, WA, USA) captured information relevant to the research question. Data were extracted by 4 independent researchers (AA, JS, JW, MB) and compared for accuracy. Data included author(s), publication year, study objective(s), study location, study design, study population (sample size, primary cancer site, disease stage, median/mean age, gender distribution), intervention used, and key findings. We did not conduct a risk of bias assessment of included articles per the Joanna Briggs Institute Methods Manual for Scoping Review.[11]

Stage 5: Collate, Summarize and Report the Results

Nutritional interventions included dietary advice or counseling and specialized food products (modified food, fortified food, and ONS) provided to participants. Nutritional interventions in this review included both positive and negative caloric approaches. While the focus was primarily on increasing caloric intake or nutrient density, we also considered studies on ketogenic diets and fasting regimens due to their potential metabolic effects in cancer. Additionally, we recognize that the type and quality of calories may be as significant as their quantity in cancer nutrition. Dietary advice included increased food intake (eg, larger portion size, added snacks, and nourishing drinks), and greater energy density (food fortification). These interventions were defined according to the European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines[12] (Table 1). Dietary advice was provided by health care providers or research staff, and dietary counseling by a registered dietitian.[13] Nutritional education could be delivered via written pamphlets or individualized counseling in person. The duration of intervention and follow-up were also recorded. The studies were then separated into 5 themes:

1) Nutraceutical and herbal interventions
2) Ketogenic diet (KD)
3) Nutrition advice/support
4) Oral nutritional supplements
5) Other nutritional interventions.

Results

Summary of the Literature Search

Figure 1 outlines the study selection process. The databases search yielded 3290 records, and 50 additional manuscripts were identified through hand searches. Title/abstract

Table 1. Definitions of Nutritional Interventions.

Intervention Type	Description
Nutritional/dietary advice	Advice or counseling on healthy food choices provided by dietitians, health care providers, research staff, or self-help sources.
Nutritional support	Advice or counseling given by dietitians, nurses, and pharmacists for provision of nutrition therapy.
Complementary alternative medicine	Biologically based products found in nature added to diet – herbs, spices, turmeric.
Ketogenic diet	Low carb diet. Aim of getting more calories from protein, fat and less from carbohydrate.
Fortified food	Food products in which vitamins, minerals, energy, other nutrients, or a combination, are added to increase energy or nutrient density. Concentrated source of nutrients (single or mixed) or other substances used to supplement normal diet (eg, ice cream, shakes).
Oral nutritional supplements	Food products that supplement a normal diet are concentrated sources of nutrients (vitamins or minerals) or other substances with nutritional or physiological effects. They can be nutritionally complete or incomplete. Nutritionally complete products can be used as the sole source of nourishment for prolonged periods, whereas nutritionally incomplete products are not suitable as the sole source of nutrients.

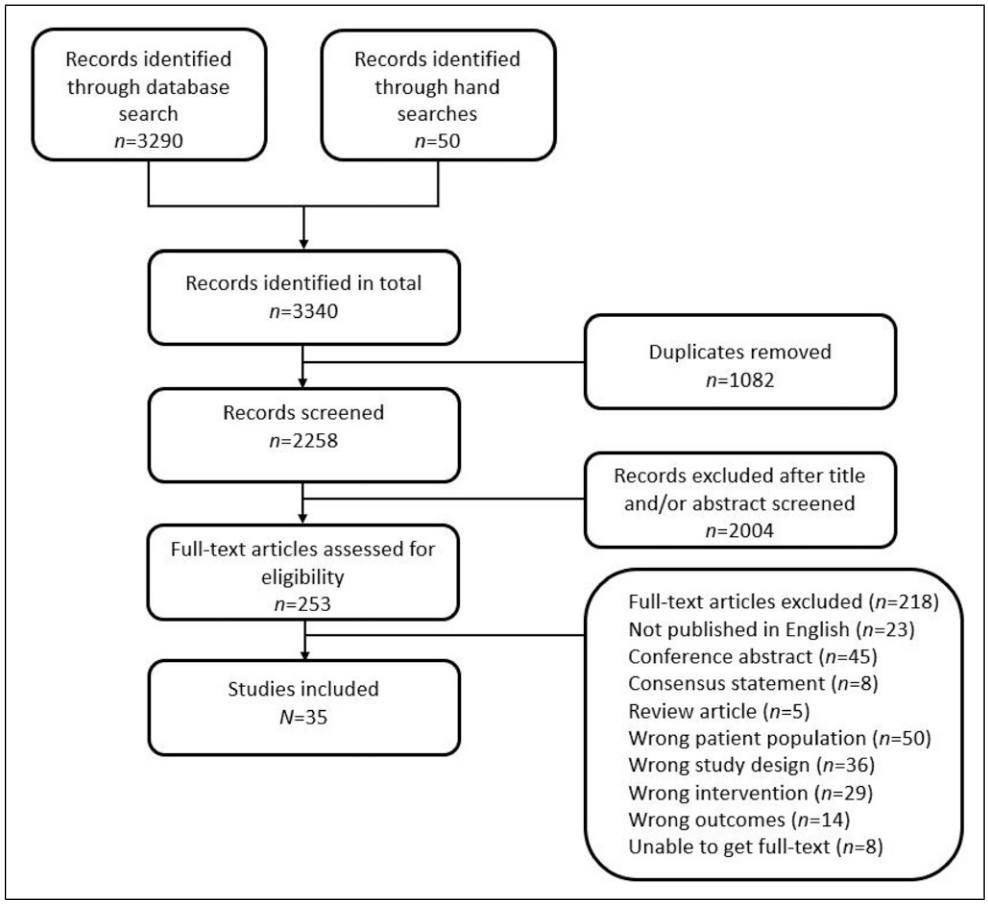

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

screening identified 253 articles for full-text screening, of which 35 met inclusion criteria. We found 2 pairs of studies, each an original study and a re-analysis of the same population, 2 authored by Voss et al[14,15] and 2 by Isenring et al.[16,17] Another study[18] undertook post-hoc analysis of an original study.[19] This second paper was grouped with the first study, counted only once when aggregating data, and acknowledged separately.

Characteristics of Included Studies

Thirty-five studies were published between 1981 and 2023 and included a total sample size of 2518 (Tables 2–6). Twenty[14,15,19-36] studies were conducted in Europe, 5[37-41] in North America, 4 in Australia,[16-18,42] 5 in Asia,[43-47] and one[48] in South America. Randomized control trials (RCT) constituted the main part of the review. Other studies were one observational pilot, 2 open-label Phase I trials, 3 open-label Phase II trials, 3 open-label pilot trials, one cross-sectional study, and one case series. The outcomes included anthropometry, biological markers, feasibility, performance status, QoL, survival, and treatment side effects. Tables 2–6 summarize the study aims, comparators, design, interventions, location, outcomes, population, and setting.

Nutraceutical and Herbal Interventions. Five studies (Table 2) examined the effect of specific nutraceutical and herbal interventions on nutrition status, including beta-glucan,[26] modified citrus pectin (MCP),[25] curcumin,[38] PC-Spes 2,[27] and shark cartilage.[39] While some biological activity was reported for these nutritional interventions, overall clinical benefit was limited.

A prospective clinical trial[26] evaluated the short-term immunomodulatory effects of oral beta-glucan in advanced breast cancer. This showed a significant increase in monocyte count after 2 weeks, indicating that oral beta-glucan can stimulate proliferation and activation of peripheral blood monocytes in these patients despite their initially low white cell counts.

Another study[25] showed MCP was highly tolerable with no systemic toxic effects. Twenty-one percent had an overall clinical benefit with stabile or improved QoL. However, there was a high dropout rate, with many participants unable to complete the 8-week treatment due to poor clinical condition and compliance challenges.

Eight weeks of oral daily curcumin administration down-regulated expression of NF-nB, cyclooxygenase-2 (COX-2), and phosphorylated signal transducer and activator of transcription 3 (pSTAT3) in peripheral blood mononuclear cells, indicating biological activity.[38] However, curcumin absorption was poor.

Table 2. Study Characteristics: Nutraceutical and Herbal Interventions (N = 5).

Study, Year, Location	Study Design/ Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Azémar et al 2007 Germany[25]	Open label, single arm, pilot Multicenter	Assess safety, clinical benefit, QoL, and clinical response rate of MCP	N = 49 Various solid tumors	MCP 15 g/day 8 wks	• 21% (n = 6/29) clinical response (stabilization/improvement) of QoL • After 2 cycles of MCP treatment, 21% (n = 6/24) WG, 45% (n = 13/24) no change, 17% (n = 5/24) WL • 22% (n = 11/49) SD after 2 cycles, 12% (n = 6/49) SD for >24 wks • No significant difference in objective antitumor response • High drop-out rate; 20 discontinued before end of cycle 2
Demir 2007 Turkey[26]	RCT Single center	Assess in vivo effects of oral beta glucan therapy	N = 39 (Breast cancer 23, healthy controls 16)	20 mg soluble 1-3,1-6, D-beta glucan daily	• leukocyte, lymphocyte, platelet counts, and hematocrit levels unchanged • BL monocyte count (326 +124/ mm^3) ↑ to 496 + 194/mm^3 on day 15 (significant) • Monocyte % significantly ↑ from 7% at BL to 12% after 14 days of beta glucan • CD95 + CD45RA expression ↑ (significant)
Dhillon et al 2008 USA[38]	Open label, phase II Single center	Evaluate clinical biological effects of curcumin	N = 25 Pancreatic	Oral Curcumin 8 g/day until disease progression	• Curcumin well-tolerated without toxicity, but poorly absorbed • 19/25 showed NF-κB down-regulation compared with controls (not significant) • COX-2 expression ↓ post-treatment in majority (significant) • Circulating curcumin detected at steady state
Shabbir et al 2008 UK[27]	Prospective, open label, phase I pilot Single center	Evaluate safety and efficacy of PC-Spes2	N = 18 Prostate (hormone refractory)	Herb-based traditional Chinese medicine – (PC-Spes2) 6 mos	• 10/18 withdrew from moderate/ severe diarrhea • Only 3 completed study • Subsequent dose modification ↓ diarrhea • ≥50% reduction in PSA not achieved
Lu et al 2010 USA[39]	RCT, double blind, phase III Multicenter	Determine effect on survival of adding AE-941 to CRT	N = 379 Lung (stage III unresectable) (Experimental 188, control 191)	Standardized aqueous shark cartilage extract (AE-941) + CRT	• OS did not differ between groups • TTP, PFS, tumor rates not significant between groups • CRT toxicity not different between groups

Note. Location identified by first-author affiliation.

Abbreviations: BL, baseline; CRT, chemoradiotherapy; COX: cyclooxygenase; MCP, modified citrus pectin; mos: months; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; OS, overall survival; %, percentage; PFS, progression free survival; PSA, prostate-specific antigen; QoL, quality of life; RCT, randomized control trial; SD, stable disease; TTP, time to progression; wks: weeks; WG, weight gain; WL, weight loss; ↓: decrease; ↑: increase.

Table 3. Study Characteristics: Ketogenic Diet (N = 4).

Study, Year, Location	Study Design/ Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Hagihara et al 2020 Japan[46]	Case series Single center	Investigate efficacy (treatment response) + safety of a new KD regimen in advanced cancer patients receiving chemotherapy	N = 37 Colorectal 8, lung 6, breast 5, pancreatic 4, other cancers 19	MCT oil (50-80 g/day) + ketogenic formula (30 g/day) Wk. 1: KR 2:1 (CHO 10 g, lipid 140 g, protein 60 g); wk. 2-mos 3: KR 2:1 to 1:1 (CHO 20 g, lipid 120-140 g, protein 70 g); mos 3: KR 1:1 (CHO 30 g) + Dietary advice (wks 1, and 1, 2, 3 mos) 3 mos	• Ketone bodies + total CHO + LDL levels ↑ at 3 mos ($P < .001$); 70% moderate/high ketosis • FBS + insulin levels suppressed (significant) for 3 mos after study completion • 50% hyperuricemia + hyperlipidemia • 5 PR at 3-mos; 3 CR, 7 PR at 1 year based on PET-CT; overall response rate 27% • Median OS 32 (max 80) mos; 3-year OS 45% • KD score (serum albumin + blood sugar + CRP) stratified prognosis ($P < .001$) • No significant change in QoL global health score at 3 mos • 12 WL; fat mass ↓ (12.4 ± 6.4 to 10.3 ± 4.8 kg, $P < .001$), but muscle weight did not ($P = .17$) • No serious AEs • Grade 2 constipation, stomach pain, diarrhea reported with stable adherence to KD

(continued)

Table 3. (continued)

Study, Year, Location	Study Design/ Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Khodabakhshi et al 2020 Iran[47]	RCT, open-label Single center	Evaluate safety, tolerability, and effects of a KD on body composition, blood parameters, and survival in patients with breast cancer undergoing neoadjuvant chemotherapy	N = 77 Breast (experimental 40, control 37)	500 mL MCT-based KD (6% CHO, 19% protein, 20% MCT, 55% fat) every 2 wks v. SD (55% CHO, 15% protein, 30% fat) Followed up every 3 wks for 3 mos	• ↓ FBG in KD group (100 ± 12 to 85 ± 11) (significant) • ↑ serum ketone bodies (0.007 ± 0.026 to 0.92 ± 0.69 mmol/l) in KD group (significant) • ↓ BMI (28.47 ± 4.1 to 25.9 ± 3.7), weight (72 ± 12 to 65 ± 11 kg), fat % (35.8 ± 5.1 to 29.1 ± 7.1) in KD group (significant) • ↑ serum TG level in controls (156 ± 61 to 214 ± 90) (significant) • ↑ serum CHO level in KD group (significant) • HDL + LDL levels not different between groups • AST (19 ± 6 v. 24 ± 10 mg/dl) • ↓ Creatinine level in KD group (significant) • ↓ BUN level in both groups (significant) • Significantly ↑ OS in KD group than controls • No severe AEs observed
Voss et al 2020 Germany[14]	RCT, open-label Multicenter	Examine the effect of calorically restricted KD and KD-IF on PFS in patients receiving RT	N = 50 Malignant glioma (KD-IF: 25, SD: 25)	KD-IF (3 days KD + 3 days fasting + 3 days KD with caloric restriction (21-23 kcal/kg/d) + nutrition counseling v. SD (30 kcal/kg/d calorie intake of 60-80 g fat, 5 g/kg CHO, 0.8 g/kg protein) + nutrition counseling 9 days Followed up on day 6, day 12, day 30	• 4 dropped out (KD-IF: 3, SD: 1) • 17 of 20 who completed KD-IF developed ketosis at day 6 + glucose + TG levels ↓ ($P < .01$) • KD-IF group had WL of −2.1 ± 1.8 kg than −0.7 ± 1.4 kg in SD group • KD-IF group who had a glucose level <84 mg/dL on day 6 had ↑ PFS + OS than those >84 mg/dl ($P < .05$) • PFS at 6 mos not different between groups (KD-IF: 20% v. SD: 16%) • OS not different between groups • No severe AEs

(continued)

Table 3. (continued)

Study, Year, Location	Study Design/ Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Voss et al 2022 Germany[15]	RCT, open-label Multicenter	Examine the effect of calorically restricted KD and KD-IF on PFS in patients receiving RT	N = 50 Malignant glioma (KD-IF: 25, SD: 25)	KD-IF (3 days KD + 3 days fasting + 3 days KD with caloric restriction (21-23 kcal/kg/d) + nutrition counseling v. SD (30 kcal/kg/d calorie intake of 60-80 g fat, 5 g/kg CHO, 0.8 g/kg protein) + nutrition counseling 9 days Followed up on day 6, day 12, day 30	• Complete diet data available in 17/20 (85%) KD-IF group • KD-IF group reached diet goals of 21-23 kcal/kg/d + 50 g/d CHO • SD group ↓ calorie intake (21 kcal/kg/d v. 30 kcal/kg/d) • QoL + cognition not affected by diet • Goals for CHO intake + fasting achieved • OS + PFS not different between groups • KPS for SD + 80% for KD-IF with no change at follow-up • EORTC QLQ-C30 global health not different between groups • No change in MMSE for KD-IF + SD at BL + at 1 month

Note. Location identified by first-author affiliation.

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; BL, baseline; BMI, body mass index; BUN, blood urea nitrogen; CHO, carbohydrate; CR, complete response; CRP, C-reactive protein; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FBS, Fasting blood sugar; HDL: high-density lipoprotein; IF, intermittent fasting; KD, ketogenic diet; KPS: Karnofsky performance score; KR, Ketone ratio; LDL, low-density lipoprotein; MCT, medium chain triglycerides; MMSE, Mini-Mental State Examination; mos, months; PET-CT, positron emission tomography-computed tomography; PR: partial response; PFS, progression free survival; PR, partial response; QoL, quality of life; RCT, randomized control trial; RT, radiotherapy; OS, overall survival; SD, standard diet; TG: triglyceride; wk: week; wks: weeks; WG, weight gain; WL, weight loss; ↓: decrease; ↑: increase.

Table 4. Study Characteristics: Nutrition Advice/Support (N = 6).

Study, Year, Location	Study Design/Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Macia et al 1991 Spain[20]	RCT Single center	Prevent malnutrition + RT-related complications	N = 93 Experimental (HN 13, breast 7, abdominopelvic 10) Control (HN 31, breast 14, abdominopelvic 16)	IDC + natural-food supplements v. own diet	• WG in IDC group except breast cancer; other anthropometric parameters stable • Albumin levels stable in IDC group • Controls (breast cancer) maintained weight • RT-related symptoms + treatment delays more common in controls • Dietetic support can improve treatment tolerance HN + abdominopelvic cancers
Isenring et al 2007 Australia[17]	RCT Single center	Determine impact of nutrition intervention on nutrition status and QoL in outpatients receiving RT	N = 60 (HN 53, GI 7)	Nutritional counseling ± ONS + ADA handouts v. SC (general nutrition advice ± ONS)	• Intervention group significantly ↑ total energy (25-29 kcal/kg/day) + protein intake (1.1-1.3 g/kg/day) • Fiber intake in both groups not significant • Intervention group had significantly faster recovery in global QoL + physical function over time • Intensive ADA medical nutrition therapy protocol improved dietary intake + QoL compared to SC
Van den Berg et al 2010 Netherlands[30]	RCT Single center	Assess value of IDC	N = 38 HN (experimental 20, Control 18)	IDC (optimal energy + protein requirement) v. standard nutrition counseling	• IDC + control had similar WL (<3%) 2 wks after RT • 2 mos after RT, IDC group gained weight (1% WG) v. control lost weight (1.5% WL) (P = .03) • BMI for both groups did not differ at any time point • Malnutrition ↓ in IDC (n = 0/20), ↑ in control (n = 5/18) over time (P = 0.02)
Uster et al 2013 Switzerland[34]	RCT Single center	Investigate effects of a nutritional intervention	N = 58 Various cancers (intervention 30, SC 28)	Individualized nutritional care ± ONS v. SC 3 mos	• Nutrition intervention group had ↑ energy (+379 kcal/d) + protein (+10.4 g/d) intake (P = .007) • ↑ dietary intake not associated with improvements in nutritional status, physical function or QoL

(continued)

Table 4. (continued)

Study, Year, Location	Study Design/Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Lee et al 2015 South Korea[44]	Cross sectional Single center	Investigate whether personalized dietary intervention improve clinical measurements	N = 20 Various cancers TD for those receiving chemotherapy (n = 10) or RD for those in remission ≥3 wks (not on chemotherapy or >1 month previously) (n = 10)	Low-glycemic, low-fat, high-plant protein diet. TD contained additional 0.5 g protein Dietary intervention varied between 3 wks and 2 mos	• Daily protein + fat intake in TD group higher than RD group by 8.4 g/d + 3 g/d, respectively ($P < .05$) • CHO intake not different between groups • Vitamin A, C, E, selenium intake ↑ but D-dimer ↓ compared to BL in both groups • Serum albumin ↑ to 4 mg/dL in both groups but only reached statistical significance in TD group
Sukaraphat et al 2016[43] Thailand	RCT Single center	Examine effects of dietary counseling for regular food consumption on nutritional outcomes in patients with advanced or metastatic cancer undergoing chemotherapy	N = 50 Lung (intervention 17, control 18) Cholangiocarcinoma (intervention 8, control 7)	IDC for general dietary recommendations (energy 30-35 kcal/kg/day, protein 0.8 g-1.2 g/kg/day) with a dietitian v. SC with physician + dietitian before starting first cycle of chemotherapy. Followed up at 9-12 wks + 18-24 wks after chemotherapy commencement	• % weight change at 9-12 wks 2.3 (±6.2) in intervention v. −1.7 (±6.2) in control ($P = 0.03$); at 18-24 wks 2.6 (±6.4) in intervention v. −0.3 (±7.1) in control (not significant) • BMI at 9-12 wks 19.70 (±2.72) in intervention v. 18.17 (±2.97) in control • ↑ BMI % change in intervention group 2.27% (±6.09) vs −1.53% (±5.92) in control ($P = .03$) • BMI, at 18-24 wks 2.55 (±6.44) in intervention v. .09 (±6.88) in control (not significant) • ↓ PG-SGA score (better nutritional status) in intervention group than controls at 9-12 wks + 18-24 wks • ↑ QoL score 46.16 (±7.55) in intervention v. control 39.40 (±10.61), ($P = .01$) • At 2-month follow-up, QoL score ↑ in intervention 46.45 (±7.3) v. 41.1 (±11.2) in control (not significant) • No difference in serum albumin + total lymphocyte counts between groups • ↑ energy intake at 18-24 wks in intervention 1847 (±443) kcal/day v. 1616 (±313) kcal/day in controls (not significant)

Note. Location identified by first-author affiliation.

Abbreviations: ADA, American Dietetic Association; BL, baseline; BMI, body mass index; CHO, carbohydrate; CR, complete response; FBS, Fasting blood sugar; FFM, fat free mass; HN, head and neck; IDC, individual dietary counseling; LDL, low-density lipoprotein; mos: months; ONS, oral nutritional supplement; %, percentage; PGA-SGA, Patient-Generated Subjective Global Assessment; PS, performance status; PFS, progression free survival; QoL, quality of life; RCT, randomized control trial; RD, remission diet; RT, radiotherapy; SC: standard care; SD, standard diet; OS, overall survival; TD, treatment diet; wk: week; wks: weeks; WG, weight gain; WL, weight loss; ↓: decrease; ↑: increase.

Table 5. Study Characteristics: Oral Nutritional Supplements (N = 11).

Study, year, Location	Study Design/ Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Bauer et al 2005 Australia[18]	Post-hoc analysis of data from an RCT International, multicenter	Examine effect of compliance with a protein + energy dense ONS (whether or not enriched with n-3 fatty acids) on nutritional outcomes and QoL in cancer cachexia	N = 200 Pancreatic (unresectable)	Energy + protein dense, n-3 PUFA enriched (1.1 g EPA each) ONS (2 cans/day) v. isocaloric ONS (without n-3 PUFA) (2 cans/day) 8 wks	• Compliance with a protein + energy dense ONS (1.5 cans/day) ± n-3 PUFA correlated with significant ↑ in energy intake (501 kcal), protein intake (25 g), and WG (1 .7 kg) compared with noncompliant group • Over 8-week period, significant improvement in weight only • LBM + energy intake not different between groups • ONS intake did not inhibit meal intake
Purasiri et al 1994 UK[22]	Open label, phase II Single center	Examine EFA and cytokine production	N = 30 Colorectal (localized 10, advanced 20)	EFA capsules (4.8 g/day) containing GLA, DHA, EPA 15 days prior to surgery (localized cancer) v. increasing doses every 15 days for 6 mos (advanced cancer) v. own diet (advanced cancer)	• No changes in cytokine levels in EG or CG • 6-mos EFA supplementation significantly ↓ total serum IL-1 levels, IL-4, IL-6, TNF
Fearon et al 2003 UK[19]	RCT International, multicenter	Evaluate protein + energy dense ONS (whether or not enriched with n-3 fatty acids and antioxidants), nutritional outcomes, and QoL in cancer cachexia	N = 200 Pancreatic (unresectable) (Experimental 95, control 105)	N-3 PUFA enriched (1.1 g EPA each) (2 cans/day) + antioxidant enriched ONS daily + own diet v. ONS (without n-3 PUFA or antioxidants) (2 cans/day) + own diet 8 wks	• Mean WL at baseline 3.3 kg/mo • Consumption ONS (1.5 g EPA (1.4) cans/day) below recommended dose • ONS intake significantly correlated with WG + ↑LBM in EG but not in CG • Daily intake correlated with change in LBM between groups ($P = .043$) • WG associated with improved QoL in EG ($P < .01$) • ↑ EPA plasma levels significantly associated with WG + LBM • No difference in survival between groups

(continued)

Table 5. (continued)

Study, year, Location	Study Design/ Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Persson et al 2005 Sweden[24]	Open label, 2-arm, pilot Single hospital	Investigate effect of fish oil, melatonin or their combination and dietary advice on cachexia	N = 24 GI	30 mL/day fish oil (4.9 g EPA+ 3.2 g DHA) v. 18 mg/d melatonin for 4 wks. Then all had both for 4 wks	• Fish oil ↓ in intake by 65 kcal in 4 wks; 196 kcal in 8 wks • In melatonin group, energy intake ↑ by 187 kcal; 19 kcal in 4/8 wks • After 4 wks, median WL 0.6 kg and 1.8 kg in fish oil/ melatonin groups • After 8 wks, both groups gained weight (0.2 kg and 0.8 kg, respectively) (not significant) • Fish oil, melatonin or their combination did not produce anti-inflammatory effects • No difference in OS in both groups • Both interventions stabilized weight
Read et al 2007 Australia[42]	Prospective open label phase II Single center	Assess impact of an EPA-ONS on nutritional and inflammatory status, QoL, and tolerance of Irinotecan	N = 23 Colorectal No control	n-3 PUFA enriched ONS (ProSure™: 300 kcal, 16 g protein, 1.09 g EPA, 0.46 g DHA/240 mL) 2 tetrapacks (480 mL) + own diet + dietary counseling Chemotherapy commenced at wk. 4 + repeated every 2 wks over 9 wks	• WG by 2.5 kg at 3 wks (P = .03); stable during chemotherapy • Energy + protein intake significantly ↓ after chemotherapy • Energy levels + overall wellbeing significantly improved; all other QoL measures maintained (not significant) • LBM maintained (not significant) • No changes in LBM or PG-SGA scores • CRP ↑ at wk 3 (P = .004) but ↓ to BL levels during chemotherapy at wk 9 • Significant correlation between BL plasma IL-6 + IL-10 concentrations, survival and between IL-12 and toxicity

(continued)

Table 5. (continued)

Study, year, Location	Study Design/ Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Trabal et al 2010 Spain[29]	RCT, Open label, phase II pilot Single center	Assess effect of EPA-ONS on chemotherapy tolerability	N = 13 Colorectal (experimental 5, control 6)	Fish oil enriched ONS (1.6 g EPA/day) + dietary counseling v. dietary counseling 12 wks	• WG in EG (4.94 kg) v. control (1.17 kg) (P = .045) • Better scores in QoL • EG reached protein and energy requirements, previous and after chemotherapy cycles more than CG (not significant) • Appetite loss worsened in EG (not significant) • Social function domain improved in EG (significant) • No difference in other QoL domains + global health status between groups • EG showed better compliance to chemotherapy (not significant)
Finocchiaro et al 2012 Italy[33]	RCT, double blind Multicenter	Investigate effect of EPA + DHA on inflammation and oxidative and nutritional status in outpatients receiving chemotherapy (Gemcitabine + Cisplatin)	N = 27 Lung (experimental 13, control 14)	Fish oil 4 capsules/d (510 mg EPA, 340 mg DHA) + dietary counseling v. placebo (olive oil) + dietary counseling followed up at BL (T0), 8 days (T1), 22 days (T2), 66 days (T3) after chemotherapy commencement	• WG (3-4 kg, P < .05) in EG from T0 to T3 • CRP + IL-6 levels ↓ in EG at T3 (P < .05) • Daily energy + protein intakes ↑ in EG (not significant)
Mocellin et al 2013 Brazil[48]	RCT Single center	Assess if fish oil alters production of inflammatory markers, plasma fatty acid profile and nutritional status	N = 11 Colorectal (experimental 6, control 5)	Fish oil 2 g/day (600 mg EPA + DHA + other fatty acids) 9 wks	• No changes in weight, BMI, body fat%, LBM although WG noted in EG (not significant) • No changes between groups in plasma TNF-α, IL-1β, IL-10, IL-17, albumin • EG had significantly improved CRP + CRP/ albumin ratio + plasma fatty acid profile
Poulsen et al 2014 Denmark[35]	RCT Single center	Investigate effect of IDC	N = 61 (esophageal 14, gastric 40, gynecological 7)	IDC + high-protein supplement with 2.2 g EPA v. SC with nurse	• Fewer WL in EG (44% v. 72%, P = .05) • EG had ↑ daily energy + protein intake (P = .05) • No difference in micronutrient deficiencies between groups

(continued)

Table 5. (continued)

Study, year, Location	Study Design/ Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Roca-Rodríguez et al 2014 Spain[36]	RCT Single center	Assess changes induced by an enriched ONS compared to a standard nutritional supplement in outpatients receiving RT	N = 26 HN (intervention 13, control 13)	ONS enriched with n-3 PUFA, fiber + greater amounts of protein + electrolytes v. standard supplement Followed up at 14, 28, and 90 days after starting RT	• No significant differences in inflammation + QoL indices between groups • Greater changes observed in CG (↓ BMI, hematocrit, erythrocyte, eosinophil, albumin and ↑ creatinine + urea levels) • EG showed earlier normalization of these parameters
Sánchez-Lara et al 2014 Mexico[41]	RCT Single center	Compare effect of EPA enriched supplement with an isocaloric diet	N = 92 Lung (intervention 46, control 46)	Regular diet + ONS containing EPA v. isocaloric diet	• EG had ↑ energy + protein intake (significant) • EG gained 1.6 ± 5 kg LBM compared to of 2.0 ± 6 kg in CG • ↓ Fatigue, anorexia, neuropathy in EG (significant) • No difference in response rate or OS between groups

Note. Location identified by first-author affiliation.
Abbreviations: BL, baseline; BCM, body cell mass; BMI, body mass index; CHO, carbohydrate; CG; control group; CR, complete response; CRP, C-reactive protein; DHA, docosahexaenoic acids; EFA, essential fatty acids; EPA, eicosapentaenoic acids; EG, experimental group; FBS, Fasting blood sugar; FFM, fat free mass; GI, gastrointestinal; GLA, HN, head and neck; IDC, individual dietary counseling; IL, interleukin; LDL, low-density lipoprotein; LBM, lean body mass; mos, months; ONS, oral nutritional supplement; OS, overall survival; %, percentage; PGA-SGA, Patient-Generated Subjective Global Assessment; PS, performance status; PUFA, polyunsaturated fatty acids; QoL, quality of life; RCT, randomized control trial; RD, remission diet; RT, radiotherapy; SC: standard care; T, time; TD, treatment diet; wks: weeks; WG, weight gain; WL, weight loss; ↓: decrease; ↑: increase.

PC-Spes2, a herbal dietary supplement containing extracts from 8 herbs, showed limited effectiveness in a Phase I trial in advanced hormone-refractory prostate cancer.[27] Most participants discontinued treatment due to severe diarrhea, and none achieved a significant drop in prostate-specific antigen (PSA). Those who continued treatment had lower PSA doubling time.

The addition of shark cartilage to chemoradiotherapy did not improve overall survival (OS), time to progression, or tumor response rates in non-small cell lung cancer compared to placebo.[39]

Ketogenic Diet. Most data (Table 3) were from open-label RCTs[14,15,47] except one case series.[46] These studies included a median of 50 (range 37-77) participants and a median follow-up period of 8 (range 4-12) weeks. While all KDs were very low in carbohydrates (to induce ketosis), the recommended ratio of macronutrients (carbohydrates, fat, and protein) varied by specific diet.

One case series,[46] reported a decrease in fasting blood sugar and insulin levels after KD. The study completion rate was 67%. Some participants had a reduction in tumor size by positron emission tomography-computed tomography. Lower blood glucose levels correlated with longer OS, although there was no significant change in QoL global health score at 3 months.

Another study[47] found that KD recipients with locally advanced and metastatic breast cancer on neoadjuvant treatment had significantly longer OS than those on a standard diet. The study completion rate was 75%. Survival analysis for the entire study population (which also included patients with metastatic disease) was not presented.

Two studies[46,47] analyzed changes in body composition after a KD. Both showed a significant decrease in body mass index (BMI), fat mass, and weight. One study[46] reported preservation of muscle tissue, the other[47] a loss of muscle mass.

Short-term ketogenic diet-intermittent fasting (KD-IF) compared to standard diet did not show any improvement in progression-free survival or OS among glioblastoma patients receiving radiation therapy.[14] Significant weight loss was noted in those given KD-IF. In a follow-up study,[15] an updated data analysis did not show any improvement in QoL or neurocognition. In both reports,[14,15] lower blood glucose levels were a favorable prognostic factor for OS.

Nutrition Advice/Support. An individualized diet program (Table 4) with natural food supplements improved treatment tolerance compared to a regular diet in abdominopelvic and head and neck cancer patients during radiation treatment.[20] Those with breast cancer in the intervention or control group had no baseline malnutrition.

Table 6. Characteristics of Studies: Other Nutritional Interventions (N = 9).

Study, Year, Location	Study Design/Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Elkort et al 1981 USA[37]	RCT Single center	Evaluate long-term enteral nutritional support in outpatients receiving chemotherapy	N = 47 Breast (experimental 24, control 23)	Isocal® or Sustacal® 500 mL once/day v. own diet 12 mos	• WG or WL in both groups associated with ↑ risk of recurrent disease ($P < .02$) • Improvement in nutritional status did not correlate with ↓ risk of chemotherapy-related toxicity, disease recurrence, treatment response or survival
Ovesen et al 1992 Denmark[21]	RCT Single center	Evaluate nutrition supplementation on nutrition status	N = 20 Experimental (lung 5, breast 5, gynecological 2) Control (lung 5, breast 2, gynecological 1)	Intact milk protein ≥500 mL/day v. partially hydrolyzed soy protein 2 mos	• Energy + protein intake significantly ↑ with soy protein than with milk protein • Progressive WL stopped in both groups • No difference in nutritional status between groups
Isenring et al 2004 Australia[16]	RCT Single center	Determine impact of early and intensive nutrition intervention on nutritional status and QoL in outpatients receiving RT	N = 60 (HN 53, GI 7)	IDC for first 4 days of starting RT and weekly during RT (6 wks) and fort-nightly afterward + telephone reviews/ weekly + ONS (if required) v. SC (general advice + nutrition booklet)	• Body weight maintained in EG compared to SC group who had significant WL • More patients in EG had stable weight • Mean WG of 0.5 kg in EG v. WL of 1.4 kg in SC ($P = .2$) • IDC had ↓ PG-SGA score than SC ($P = .02$) • EG had smaller ↓ + faster recovery in global QoL (not significant) • Early + intensive nutrition intervention improved body weight, nutritional status, physical function, global QoL
Breitkreutz et al 2005 Germany[23]	RCT Single center	Examine effect of high-fat diet on body composition in outpatients receiving chemotherapy	N = 23 Experimental (colorectal 6, gastric 6) Control (colorectal 6, gastric 5)	Fat enriched ONS (20 non-protein kcal/kg/day; 100 mL contained 9.3 g fat equals to 66% of non-protein calories) + natural diet + nutrition counseling every 14 days v. natural diet + nutrition counseling every 14 days 8 wks Nutritional target for both groups was 35 non-protein kcal/kg/day + 1.1 g protein/kg/day	• Energy intake higher (1865 ± 317 kcal/day) in experimental group than controls (1556 ± 497 kcal/day) (not significant) • WG in EG, but controls had WL • FFM ↑ in EG after 8 wks ($P < .05$) • BCM maintained in EG, but declined in CG (not significant) • QoL improved more in EG than CG (not significant)

(continued)

Table 6. (continued)

Study, Year, Location	Study Design/Setting	Aim	Sample	Intervention v. Comparator	Key Findings
Hertz and Lister 2009 Denmark[28]	Observational, pilot Single center	Evaluate effect of Coenzyme Q10 and other antioxidants on survival	N = 41 Various, end-stage cancers	Supplements of Coenzyme Q10 & other antioxidants (vitamin C, selenium, folic acid, β-carotene)	• Median actual survival 17 mos (1 –120 mos) v. 12 mos. (range 3 – 29 mos) predicted survival • Mean survival 29 mos v. 12 mos for predicted survival • 24% (n = 10) shorter survival, 76% (n = 31) longer survival ($P < .002$)
Baldwin et al 2011 UK[31]	RCT Multicenter	Assess effect of dietary advice and/or ONS on survival, nutritional status, and QoL	N = 358 (GI 277, lung or mesothelioma 81)	No intervention v. dietary advice v. ONS + daily multivitamin + mineral supplement v. dietary advice + ONS + multivitamin followed up weekly over a 6-week period	• No differences in survival, weight or QoL between groups • Trial stopped early due to lack of efficacy
Casas et al 2012 Spain[32]	Exploratory prospective study Single center	Assess impact of adapted ice cream as a dietary supplement on QoL in inpatients	N = 70 Various cancers (group I 39, group II 31)	Group I (adapted ice cream): 90 g ice cream (2 servings/d) v. Group II (traditional ONS): 200 mL 2-3 shots/d Duration not stated	• Significant differences in group I for anxiety + depression • QoL significantly different between groups • Global + fatigue scale significantly different from BL between groups
Jatoi et al 2016 USA[40]	RCT Single center	Determine whether wine improves loss of appetite in patients with cachexia (50% were planned to be treated with chemotherapy or RT)	N = 141 Various cancers Experimental 71 (lung 22, GI 16, other 21) Control 70 (lung 22, GI 15, other 22)	White wine (<15% alcohol) twice daily + ONS 3-4 wks v. ONS (no alcohol allowed) Followed up weekly for 4 weeks, then every 6 mos. via electronic medical review for 2 years	• 48% (n = 28) in wine arm; 37% (n = 22) in CG improved appetite (not significant) • 9% weight stability in both groups (not significant) • OS or QoL not different between groups
Kapoor et al 2017 India[45]	RCT Single center	Determine whether nutrition intervention + dietary counseling improves anthropometric indicators and QoL in patients with cachexia	N = 63 Females with various cancers (Intervention 30, control 33)	30-min nutrition counseling + 100 g of improved IAtta (every fortnight 1 packet of flour mix provided to make 3 flat breads) + physical activity encouraged + own diet v. 30-min nutrition counseling (twice a month) + own diet 6 mos	• Significant ↓body weight (n = 15), ↓ mid-upper arm circumference, ↓ body fat in controls • WG trend in EG observed (not significant) • Body fat ↑, fatigue + appetite improved in EG (all significant)

Note: Location identified by first-author affiliation.

Abbreviations: BL, baseline; BCM, body cell mass; BMI, body mass index; CRP, C-reactive protein; CG, control group; DHA, docosahexaenoic acids; EFA, essential fatty acids; EPA, eicosapentaenoic acids; EG, experimental group; FBS, Fasting blood sugar; FFM, fat free mass; GI, gastrointestinal; HN, head and neck; IDC, individual dietary counseling; IL, interleukin; mos, moths; ONS, oral nutritional supplement; OS, overall survival; %, percentage; PGA-SGA, Patient-Generated Subjective Global Assessment; PS, performance status; PUFA, polyunsaturated fatty acids; QoL, quality of life; RCT, randomized control trial; RT, radiotherapy; SD, stable disease; OS, overall survival; TD, treatment diet; wks, weeks; WG, weight gain; WL, weight loss; IG, intervention group; CG; control group.

The American Dietetic Association's medical nutrition therapy protocol, which included 12 weeks of intensive nutrition counseling, specific diet advice, and ONS improved dietary intake, nutritional status, and quality of life (QoL) in gastrointestinal and head and neck cancer patients.[17] Both intervention and standard care (SC) groups had weight loss during the study period, but less in the intervention group. Investigators[17] reported dietary intake in the same study. The nutrition intervention group had a significantly higher energy and protein intake than the SC.

2-months individual dietary counseling (IDC) resulted in less malnutrition and weight loss compared to SC head and neck cancer patients undergoing radiation therapy.[30] In another study,[34] while nutritional interventions (dietary counseling by a dietitian, food fortification, and ONS) increased energy and protein intake in malnourished cancer patients, they did not improve nutritional status or physical function. The study completion rate was 58%.

One study,[44] showed that low glycemic, low fat, high plant protein, and high vegetable diet improved systemic anticoagulant activity and immune function during chemotherapy and remission. Dietary counseling during chemotherapy increased weight and BMI and improved nutrition status and QoL in lung cancer and cholangiocarcinoma.[43] However, there was no significant difference after 2 months of chemotherapy.

Oral Nutritional Supplements. Eleven studies (Table 5) examined the effect of essential fatty acids (EFA) and/or combined with nutritional support or nutritional advice/support. Six were single-center RCTs with a sample size ranging from 13 to 92.[29,33,35,36,41,48] Two were open-label Phase II,[22,42] one open-label pilot,[24] and another a post-hoc analysis.[18] The largest study was an international multicentered RCT that included 200 pancreatic cancer patients.[19] Predominant cancer types were gastrointestinal, lung, and pancreatic cancers; only one study[35] had heterogeneous cancers.

A large RCT[19] showed that addition of omega-3 polyunsaturated fatty acids (PUFA) and antioxidant-enriched oral supplement to regular diet significantly improved body composition, which included lean body mass (LBM) and weight gain. Weight gain was also associated with improved QoL. A post-hoc analysis of this study[18] found compliance with PUFA-supplemented ONS significantly improved energy intake and weight. Nonadherent patients had weight loss.

Another study[42] reported that omega-3 PUFA enriched ONS was significantly associated with a mean weight gain of 2.5 kg at 3 weeks and stabilized weight and LBM for the subsequent 9 weeks. Between weeks 3 to 9, significant improvements were found in energy levels and overall well-being. A separate study[41] showed significantly higher energy and protein intake when a regular diet was supplemented with eicosapentaenoic acid (EPA). Improvement in anorexia, fatigue, LBM, and neuropathy were also reported. No overall difference was seen in treatment response rate or overall survival between groups.

Most studies showed EPA supplementation reduces the production of proinflammatory cytokines like interleukin-1, interleukin-6, and tumor necrosis factor alpha.[22,33,36,42] One study[24] showed no significant changes in inflammatory markers with the use of fish oil or melatonin. Another[48] showed a fall in serum albumin and C-reactive protein (CRP) (but not cytokine levels) with fish oil supplementation. A 9-week supplementation of dietary counseling with fish oil was significantly associated with lower CRP, interleukin-6, and weight gain.[33] Most studies found some benefits in energy levels, stabilizing weight, and well-being with EFA supplementation, but none showed any survival benefits. The effect on inflammatory markers was positive, and prolonged supplementation recommended.

Other Nutritional Interventions. An RCT[37] found no benefit to long-term (12 months) nutritional support with 2 commercial liquid diets (one containing intact milk proteins and the other partially hydrolyzed soy proteins) adjunct to chemotherapy in breast cancer (Table 6). There was little or no correlation between standard nutritional parameters and risk of disease recurrence or chemotherapy response.

Another RCT[16] showed that early and intensive nutrition intervention through individualized dietitian counseling and oral supplements (if required) was associated with stable body weight. This was compared to SC (general advice and nutrition booklet) in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. While not statistically significant, clinically meaningful differences in fat free mass (FFM) were observed between the intervention and SC groups; the intervention group had a mean increase of 0.4 kg and usual care a mean decrease of 1.4 kg.

One study[23] showed that nutritional intervention by individual dietitian counseling, food fortification, and ONS led to a significantly higher energy and protein intake in the intervention group than controls. The intervention group had improved body composition with increased FFM compared to control group. However, higher dietary intake was not associated with better nutritional status (body weight), physical function (hand-grip strength, performance status), or QoL. A long-term, observational pilot study[28] showed that in inoperable or metastatic solid tumors, supplementation with coenzyme Q10 (390 mg/day), vitamin C (7.5 g/day), and other antioxidants had significantly higher survival times than controls after conventional cancer treatment. All patients were followed until death, and the median actual survival was 17 months (range 1−120), ie,>40% longer than the median predicted survival of 2 months (range 3-29). The median difference was 7 months ($P < .002$, 95% CI: 4.0−18.5).

An RCT[31] examined a multi-component intervention initiated before and continued after the start of cancer treatment. This three-arm trial compared dietary advice plus a supplement before chemotherapy vs dietary advice or no intervention in lung cancer. However, the trial was stopped early due to lack of efficacy, with no significant differences in survival or

QoL between groups. At 1 year, intervention patients weighed more than controls, but weight did not differ between those receiving ONS alone or with dietary advice. Weight changes were not significant between survivors and non-survivors, although survivors beyond 26 weeks had less weight loss.

One study[32] reported that the adapted ice cream supplement improved anxiety, depression, fatigue, and QoL in malnourished cancer patients than standard supplements. It did not significantly impact nutritional status as measured by the Patient-Generated Subjective Global Assessment (PG-SGA).[49]

An RCT[40] in advanced cancer with cachexia examined the orexigenic effects of white wine with ≤15% alcohol content twice a day for 3-4 weeks compared to a nutritional supplement (eg, Boost® or Ensure®). Patients assigned to white wine received a nutritional supplement, while control patients in the nutritional supplement arm abstained from alcohol. White wine was tolerated well but did not improve appetite, QoL, or survival compared to the controls who received only a nutritional supplement.

One study[45] reported that 6-month IAtta meal (ie, nutritious flour mixture) supplementation with nutritional counseling in females with advanced cancer improved appetite, fatigue, and QoL in the intervention group but no difference in body weight.

A study[21] on ambulatory cancer patients with progressive weight loss compared soy and milk protein liquid supplements over 2 months. While both groups stopped losing weight, soy protein led to significantly higher energy and protein intake. However, overall nutritional status remained similar between the groups.

Discussion

The studies examined encompass a wide range of nutritional interventions for cancer patients, including nutraceutical and herbal interventions, KDs, nutritional advice/support, and ONS. While some interventions claimed promising results, most had limited clinical benefit or inconclusive outcomes. Studies on nutraceutical and herbal interventions such as beta-glucan, MCP, curcumin, PC-Spes2, and shark cartilage showed varying effectiveness. While these nutritional interventions may have biological effects, clinical benefit was limited or unproven.

Nutraceutical and herbal interventions are proposed to influence biological processes linked to cancer progression, such as immune regulation, inflammation reduction, and malignant cell activity. For example, beta-glucan from mushrooms and yeast may enhance immune responses, while modified citrus pectin could inhibit metastasis by disrupting galectin-3-mediated adhesion. Curcumin's anti-inflammatory and antioxidant properties may mitigate chronic inflammation and oxidative stress associated with cancer. These interventions may help manage symptoms, though clinical evidence remains limited. Further research is needed to standardize formulations, optimize dosing, and validate their effects through rigorous trials.

KD, characterized by high-fat, low-carbohydrate, and adequate-protein intake, aims to lower blood glucose levels and induce ketosis. By significantly reducing carbohydrate intake and promoting ketone body production, KDs create a metabolic environment that is less favorable for cancer cells while providing an alternative energy source for normal cells. KDs have shown beneficial effects on body composition, metabolic parameters like blood glucose, and potentially survival when combined with standard treatment in some cancer types; however, the evidence on outcomes is mixed. Survival outcome may be more influenced by the innate nature of cancer itself rather than dietary intervention. Many patients find it difficult to adhere to the strict KD requirements. There are also concerns about potential risks like elevated cholesterol levels, loss of muscle mass, and nutrient deficiencies, which could be particularly problematic for cancer patients. The evidence on KDs for cancer treatment is limited by diverse study designs, potential biases, and small samples, making it challenging to draw definitive conclusions. To better evaluate the efficacy, safety, and feasibility of KDs across various cancer types and stages, larger, rigorously designed clinical trials are necessary.

Beyond improving energy and protein intake, ONS may offer therapeutic benefits through mechanisms such as reducing inflammation, preserving LBM, and enhancing immune function. Specific nutrients in ONS, including omega-3 fatty acids and antioxidants like vitamin C, have been shown to modulate inflammatory biomarkers and oxidative stress. These effects may help mitigate cancer-associated malnutrition by addressing inflammation-related metabolic alterations and supporting muscle preservation during illness. ONS, particularly those enriched with EFA, showed some interesting results in body composition and inflammatory markers; however, none had significant survival benefits. Long-term nutritional supplementation during chemotherapy did not significantly enhance treatment efficacy in advanced cancer.[37] In contrast, early and intensive nutrition intervention, including individualized counseling and ONS, helped maintain body weight in head and neck cancer.[21] Integrating tailored nutritional support as a standard part of head and neck cancer treatment protocols could potentially improve treatment adherence and enhance overall care quality.

An interesting dichotomy between energy intake and nutritional status emerged in one investigation.[23] Despite achieving higher energy and protein intake, the intervention did not improve overall nutritional status, physical function, or QoL. However, it improved body composition by increasing FFM, despite stable weight, indicating that nutritional interventions can have subtle yet important effects on body composition. Perhaps simply increasing caloric and protein intake may be insufficient to improve all aspects of health and well-being.

While coenzyme Q10, vitamin C, and other antioxidants repeatedly improved survival in end-stage cancer in a single-center pilot study, the results were inconclusive due to the

limited scope of the study.[28] The potential for antioxidant supplementation to interfere with some cancer drug treatments also necessitates careful consideration when recommending any supplements during active treatment. Another multicomponent intervention trial[31] failed to demonstrate significant benefits in survival and QoL in lung cancer. However, those in the intervention group weighed more in one year than the control group, suggesting some benefit in weight maintenance. Although nutritional interventions did not improve overall survival, they might still provide specific benefits in supportive cancer care. This is particularly important given the association between weight loss and poorer prognosis in cancer patients.

One innovative approach using adapted ice cream supplements improved QoL, anxiety, depression, and fatigue more effectively than standard supplements in malnourished cancer patients.[32] However, it did not significantly impact nutritional status on the PG-SGA.[49] These findings highlight the potential of innovative, palatable nutritional interventions to address psychological and QoL aspects in cancer care, even when traditional nutritional markers remain unchanged.

These studies on nutritional interventions in advanced cancer patients reveal diverse outcomes, highlighting the complexity of nutritional interventions in cancer care. The variability in outcomes underscores the need for personalized nutritional strategies that consider individual factors (eg, genetics and lifestyle) rather than generalized nutrition advice.

Our review has several notable strengths. We adopted Arksey and O'Malley's methodological framework, which is generally recognized as the best practice for scoping reviews. The review included various study designs, from RCTs to observational studies, allowing for a broad examination of the available evidence. We also included non-randomized studies, which are convenient study designs that can suggest possible relationships between the intervention and the outcome. Studies spanned multiple countries and continents for a global perspective on nutritional interventions in advanced cancer.

Several limitations were evident. The review only included articles in English, potentially missing relevant studies in other languages. There was a lack of a standardized definition for "advanced cancer" across included studies. We relied on authors' descriptions and made assumptions when not explicitly stated. While not always appropriate for scoping reviews, the absence of quantitative synthesis limits the ability to estimate the overall effect sizes of interventions.

When considering any dietary intervention, it is important to evaluate the available evidence critically on a case-by-case basis, considering factors like study design, sample size, and relevance to specific populations or health conditions. Healthcare professionals should remain current with the latest research and guidelines to provide evidence-based nutritional recommendations tailored to individual needs. More efforts are needed to conduct large-scale, high-quality studies to better understand the potential benefits and limitations of these interventions.

Conclusions

Our scoping review provided limited evidence for various nutritional interventions and dietary approaches. We identified 5 categories of nutritional interventions with varying levels of supporting research, ranging from robust clinical trials to preliminary studies: (1) nutraceutical and herbal interventions, (2) ketogenic diet, (3) nutrition advice/support, (4) oral nutritional supplements, (5) other nutritional interventions. Nutrition advice/support had the best evidence, while interventions like ketogenic diet and nutraceutical and herbal interventions mixed evidence. Dietary advice and oral nutritional supplements sometimes appeared to enhance treatment tolerance and improve nutritional status; however, their impact on overall survival remained inconsistent. Nutraceutical and herbal interventions showed limited clinical benefits despite apparent biological activity. Individualized nutritional strategies tailored to each patient's unique needs can potentially help improve treatment tolerance and quality of life in the cancer care continuum. Larger, well-designed studies focusing on patient-centered outcomes are necessary to establish evidence-based guidelines. Clinicians should carefully evaluate the potential benefits and risks of these interventions to ensure their judicious application in clinical practice.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Aynur Aktas https://orcid.org/0000-0003-3631-7563
Declan Walsh https://orcid.org/0000-0002-9310-1729

Supplemental Material

Supplemental material for this article is available online.

References

1. World Health Organization. *WHO Report on Cancer: Setting Priorities, Investing Wisely and Providing Care for All*. Geneva, Switzerland: World Health Organization; 2020.
2. Barrett M, Ui Dhuibhir P, Njoroge C, et al. Diet and nutrition information on nine national cancer organisation websites: a critical review. *Eur J Cancer Care*. 2020;29(5):e13280. doi:10.1111/ecc.13280
3. Richards J, Arensberg MB, Thomas S, Kerr KW, Hegazi R, Bastasch M. Impact of early incorporation of nutrition interventions as a component of cancer therapy in adults: a review. *Nutrients*. 2020;12(11):3403. doi:10.3390/nu12113403

4. Ueshima J, Nagano A, Maeda K, et al. Nutritional counseling for patients with incurable cancer: systematic review and meta-analysis. *Clin Nutr*. 2023;42(2):227-234. doi:10.1016/j.clnu.2022.12.013
5. Blackwood HA, Hall CC, Balstad TR, et al. A systematic review examining nutrition support interventions in patients with incurable cancer. *Support Care Cancer*. 2020;28(4):1877-1889. doi:10.1007/s00520-019-04999-4
6. Parsons HM, Forte ML, Abdi HI, et al. Nutrition as prevention for improved cancer health outcomes. *JNCI Cancer Spectr*. 2023;7(3):pkad035. doi:10.1093/jncics/pkad035
7. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol*. 2005;8(1):19-32. doi:10.1080/1364557032000119616
8. The Joanna Briggs Institute. *The Joanna Briggs Institute Reviewers' Manual 2015*. Adelaide, SA: The Joanna Briggs Institute, 2015.
9. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:10.7326/m18-0850
10. CADTH. *PRESS – Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration*. Ottawa, ON: CADTH: PRESS E&E; 2016.
11. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Base Healthc*. 2015;13(3):141-146. doi:10.1097/xeb.0000000000000050
12. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr*. 2017;36(1):49-64. doi:10.1016/j.clnu.2016.09.004
13. Orsso CE, Montes-Ibarra M, Findlay M, et al. Mapping ongoing nutrition intervention trials in muscle, sarcopenia, and cachexia: a scoping review of future research. *J Cachexia Sarcopenia Muscle*. 2022;13(3):1442-1459. doi:10.1002/jcsm.12954
14. Voss M, Wagner M, von Mettenheim N, et al. ERGO2: a prospective, randomized trial of calorie-restricted ketogenic diet and fasting in addition to reirradiation for malignant glioma. *Int J Radiat Oncol Biol Phys*. 2020;108(4):987-995. doi:10.1016/j.ijrobp.2020.06.021
15. Voss M, Wenger KJ, von Mettenheim N, et al. Short-term fasting in glioma patients: analysis of diet diaries and metabolic parameters of the ERGO2 trial. *Eur J Nutr*. 2022;61(1):477-487. doi:10.1007/s00394-021-02666-1
16. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer*. 2004;91(3):447-452. doi:10.1038/sj.bjc.6601962
17. Isenring EA, Bauer JD, Capra S. Nutrition support using the American Dietetic Association medical nutrition therapy protocol for radiation oncology patients improves dietary intake compared with standard practice. *J Am Diet Assoc*. 2007;107(3):404-412. doi:10.1016/j.jada.2006.12.007
18. Bauer J, Capra S, Battistutta D, Davidson W, Ash S, Cancer Cachexia Study Group. Compliance with nutrition prescription improves outcomes in patients with unresectable pancreatic cancer. *Clin Nutr*. 2005;24(6):998-1004. doi:10.1016/j.clnu.2005.07.002
19. Fearon KC, Von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut*. 2003;52(10):1479-1486. doi:10.1136/gut.52.10.1479
20. Macia E, Moran J, Santos J, Blanco M, Mahedero G, Salas J. Nutritional evaluation and dietetic care in cancer patients treated with radiotherapy: prospective study. *Nutrition*. 1991;7(3):205-209.
21. Ovesen L, Allingstrup L. Different quantities of two commercial liquid diets consumed by weight-losing cancer patients. *JPEN - J Parenter Enter Nutr*. 1992;16(3):275-278. doi:10.1177/0148607192016003275
22. Purasiri P, Murray A, Richardson S, Heys SD, Horrobin D, Eremin O. Modulation of cytokine production in vivo by dietary essential fatty acids in patients with colorectal cancer. *Clin Sci (Lond)*. 1994;87(6):711-717. doi:10.1042/cs0870711
23. Breitkreutz R, Tesdal K, Jentschura D, Haas O, Leweling H, Holm E. Effects of a high-fat diet on body composition in cancer patients receiving chemotherapy: a randomized controlled study. *Wien Klin Wochenschr*. 2005;117(19-20):685-692. doi:10.1007/s00508-005-0455-3
24. Persson C, Glimelius B, Ronnelid J, Nygren P. Impact of fish oil and melatonin on cachexia in patients with advanced gastrointestinal cancer: a randomized pilot study. *Nutrition*. 2005;21(2):170-178. doi:10.1016/j.nut.2004.05.026
25. Azémar M, Hildenbrand B, Heim ME, Unger C. Clinical Benefit in Patients with Advanced Solid Tumors Treated with Modified Citrus Pectin: A Prospective Pilot Study. *Clin Med Insights Oncol*. 2007;1:73-80. doi:10.4137/CMO.S285
26. Demir G, Klein HO, Mandel-Molinas N, Tuzuner N. Beta glucan induces proliferation and activation of monocytes in peripheral blood of patients with advanced breast cancer. *Int Immunopharmacol*. 2007;7(1):113-116. doi:10.1016/j.intimp.2006.08.011
27. Shabbir M, Thompson C, Jarmulowiczc M, Mikhailidis D, Burnstock G. Effect of extracellular ATP on the growth of hormone-refractory prostate cancer in vivo. *BJU Int*. 2008;102(1):108-112. doi:10.1111/j.1464-410X.2008.07578.x
28. Hertz N, Lister RE. Improved survival in patients with end-stage cancer treated with coenzyme Q (10) and other antioxidants: a pilot study. *J Int Med Res*. 2009;37(6):1961-1971. doi:10.1177/147323000903700634
29. Trabal J, Leyes P, Forga M, Maurel J. Potential usefulness of an EPA-enriched nutritional supplement on chemotherapy tolerability in cancer patients without overt malnutrition. *Nutr Hosp*. 2010;25(5):736-740.
30. van den Berg MG, Rasmussen-Conrad EL, Wei KH, Lintz-Luidens H, Kaanders JHAM, Merkx MAW. Comparison of the effect of individual dietary counselling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. *Br J Nutr*. 2010;104(6):872-877. doi:10.1017/S0007114510001315
31. Baldwin C, Spiro A, McGough C, et al. Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and

weight loss receiving chemotherapy: a randomised controlled trial. *J Hum Nutr Diet*. 2011;24(5):431-440. doi:10.1111/j.1365-277X.2011.01189.x

32. Casas F, Leon C, Jovell E, et al. Adapted ice cream as a nutritional supplement in cancer patients: impact on quality of life and nutritional status. *Clin Transl Oncol*. 2012;14(1):66-72. doi:10.1007/s12094-012-0763-9
33. Finocchiaro C, Segre O, Fadda M, et al. Effect of n-3 fatty acids on patients with advanced lung cancer: a double-blind, placebo-controlled study. *Br J Nutr*. 2012;108(2):327-333. doi:10.1017/S0007114511005551
34. Uster A, Ruefenacht U, Ruehlin M, et al. Influence of a nutritional intervention on dietary intake and quality of life in cancer patients: a randomized controlled trial. *Nutrition*. 2013;29(11-12):1342-1349. doi:10.1016/j.nut.2013.05.004
35. Poulsen GM, Pedersen LL, Osterlind K, Bæksgaard L, Andersen JR. Randomized trial of the effects of individual nutritional counseling in cancer patients. *Clin Nutr*. 2014;33(5):749-753. doi:10.1016/j.clnu.2013.10.019
36. Roca-Rodriguez MM, Garcia-Almeida JM, Lupianez-Perez Y, et al. Effect of a specific supplement enriched with n-3 polyunsaturated fatty acids on markers of inflammation, oxidative stress and metabolic status of ear, nose and throat cancer patients. *Oncol Rep*. 2014;31(1):405-414. doi:10.3892/or.2013.2806
37. Elkort RJ, Baker FL, Vitale JJ, Cordano A. Long-term nutritional support as an adjunct to chemotherapy for breast cancer. *JPEN - J Parenter Enter Nutr*. 1981;5(5):385-390. doi:10.1177/0148607181005005385
38. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res*. 2008;14(14):4491-4499. doi:10.1158/1078-0432.CCR-08-0024
39. Lu C, Lee JJ, Komaki R, et al. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. *J Natl Cancer Inst*. 2010;102(12):859-865. doi:10.1093/jnci/djq179
40. Jatoi A, Qin R, Satele D, et al. "Enjoy glass of wine before eating:" a randomized trial to test the orexigenic effects of this advice in advanced cancer patients. *Support Care Cancer*. 2016;24(9):3739-3746. doi:10.1007/s00520-016-3190-6
41. Sanchez-Lara K, Turcott JG, Juarez-Hernandez E, et al. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: randomised trial. *Clin Nutr*. 2014;33(6):1017-1023. doi:10.1016/j.clnu.2014.03.006
42. Read JA, Beale PJ, Volker DH, Smith N, Childs A, Clarke SJ. Nutrition intervention using an eicosapentaenoic acid (EPA)-containing supplement in patients with advanced colorectal cancer. Effects on nutritional and inflammatory status: a phase II trial. *Support Care Cancer*. 2007;15(3):301-307. doi:10.1007/s00520-006-0153-3
43. Sukaraphat N, Chewaskulyong B, Buranapin S. Dietary counseling outcomes in locally advanced unresectable or metastatic cancer patients undergoing chemotherapy. *J Med Assoc Thai*. 2016;99(12):1283-1290.
44. Lee GY, Lee JJ, Lee SM. Antioxidant and anticoagulant status were improved by personalized dietary intervention based on biochemical and clinical parameters in cancer patients. *Nutr Cancer*. 2015;67(7):1083-1092. doi:10.1080/01635581.2015.1073754
45. Kapoor N, Naufahu J, Tewfik S, Bhatnagar S, Garg R, Tewfik I. A prospective randomized controlled trial to study the impact of a nutrition-sensitive intervention on adult women with cancer cachexia undergoing palliative care in India. *Integr Cancer Ther*. 2017;16(1):74-84. doi:10.1177/1534735416651968
46. Hagihara K, Kajimoto K, Osaga S, et al. Promising effect of a new ketogenic diet regimen in patients with advanced cancer. *Nutrients*. 2020;12(5):1473. doi:10.3390/nu12051473
47. Khodabakhshi A, Akbari ME, Mirzaei HR, Mehrad-Majd H, Kalamian M, Davoodi SH. Feasibility, safety, and beneficial effects of MCT-based ketogenic diet for breast cancer treatment: a randomized controlled trial study. *Nutr Cancer*. 2020;72(4):627-634. doi:10.1080/01635581.2019.1650942
48. Mocellin MC, Pastore e Silva Jde A, Camargo Cde Q, et al. Fish oil decreases C-reactive protein/albumin ratio improving nutritional prognosis and plasma fatty acid profile in colorectal cancer patients. *Lipids*. 2013;48(9):879-888. doi:10.1007/s11745-013-3816-0
49. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition*. 1996;12(-1 Suppl):S15-S19. doi:10.1016/0899-9007(96)90011-8