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Meta-analyses

Nutritional counseling for patients with incurable cancer: Systematic review and meta-analysis

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SUMMARY

Background & aims: This systematic review aims to determine whether nutritional counseling by registered dietitians and/or nutritional specialists is recommended for adult patients with incurable advanced or recurrent cancer who are refractory to or intolerant of anticancer therapy.
Methods: This systematic review analyzed randomized controlled trials (RCTs) of nutritional counseling in cancer patients older than 18 years, primarily those with stage 4 cancer. Nutrition counseling was performed by registered dietitians and/or nutritional specialists using any method, including group sessions, telephone consultations, written materials, and web-based approaches. We searched the Medline (PubMed), Medline (OVID), EMBASE (OVID), CENTRAL, Emcare, and Web of Science Core Collection databases for articles published from 1981 to 2020. Two independent authors assessed the risk of bias used the Cochrane Risk of Bias 2 tool. Meta-analysis was performed for results and outcomes that allowed quantitative integration. This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (ID: CRD42021288476) and registered in 2021.
Results: The search yielded 2376 studies, of which 7 assessed 924 patients with cancer aged 24–95 years. Our primary outcome of quality of life (QoL) was reported in 6 studies, 2 of which showed improvement with nutritional counseling. Our other primary outcome of physical symptoms was reported in two studies, one of which showed improvement with nutritional counseling. Quantitative integration of both QoL and physical symptoms was difficult. A meta-analysis of energy and protein intake and body weight was performed for secondary outcomes. Results showed that nutrition counseling increased energy and protein intake, but total certainty of evidence (CE) was low. Bodyweight was not improved by nutrition counseling.
Conclusions: Nutrition counseling is shown to improve energy and protein intake in patients with incurable cancer. Although neither nutrient intake can be strongly recommended because of low CE, nutrition counseling is a noninvasive treatment strategy that should be introduced early for nutrition intervention for patients with cancer. This review did not find sufficient evidence for the effect of nutrition counseling on QoL, a patient-reported outcome. Overall, low-quality and limited evidence was identified regarding the impact of nutrition counseling for patients with cancer, and further research is needed.

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1. Introduction

Cancer is the second most common cause of death globally [1]; in 2017, 24.5 million people received a cancer diagnosis, and 9.6 million died worldwide [1]. These patients are at particularly high risk of malnutrition because their nutritional status is threatened by multiple factors, including disease, treatment modalities, and psychological changes. An estimated 10%–20% of deaths in patients with cancer are caused by malnutrition rather than the malignancy itself [2,3]. In patients with incurable advanced or recurrent cancer, poor clinical outcomes, such as worsening nutritional status and shortened overall survival, occur with disease progression, regardless of whether anticancer therapy is continued or discontinued [4]. Additionally, diminished nutritional status may lead to fewer activities of daily living, lower quality of life (QoL), intolerability to anticancer therapy, unplanned hospitalization, and increasingly poor survival [5]. Even in patients with incurable advanced or recurrent cancer, nutritional intervention is necessary to maintain QoL in those with decreased oral intake [5]. An important consideration is that patients with cancer have the right to survive for a reasonable period and live a high QoL, even if a cure is not possible. Various nutritional therapies for this population, including nutrition counseling and oral nutritional supplements, have been developed and are reported to control or prevent the progression of nutritional deterioration [6,7]. In patients with cancer, nutritional counseling in particular has been identified as the initial nutritional intervention to be provided [4,6,8,9]. To date, however, the effectiveness of nutrition counseling interventions in patients with incurable cancer and the impact on physical symptoms, such as improved QoL and worsening edema, have not been determined. The purpose of this systematic review is to determine whether nutritional counseling by registered dietitians and/or nutritional specialists is recommended for adult patients with incurable advanced or recurrent cancer who are refractory to or intolerant of anticancer therapy.

2. Materials & methods

2.1. Protocol registration

This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (ID: CRD42021288476) and registered in 2021. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed [10].

2.2. Eligibility criteria

The search criteria for this systematic review were limited to full-text, peer-reviewed articles written in English and published between 1981 and 2020. Randomized control trials (RCTs) of patients aged ≥18 years with advanced or recurrent cancer that is not curable and who were histologically or clinically diagnosed with cancer were included and the eligible studies were those with at least 67% of patients with stage 4 cancer. Eligible interventions were nutritional guidance provided by any method, including group sessions, telephone counseling, written materials, or web-based approaches, in addition to standard clinical nutritional counseling that is delivered by a nutritional therapy specialist or health care provider. Also included were studies that assessed oral nutritional supplements or exercise interventions in combination with nutritional interventions; however, studies that analyzed only the effects of interventions with specific nutrients were excluded. Controls included standard cancer care, placebo, or exercise only.

2.3. Information sources

Six databases, namely, Medline (PubMed), Medline (OVID), EMBASE (OVID), CENTRAL, Emcare, and Web of Science Core Collection, were searched. In addition, the reference lists for the studies identified in the electronic literature search were reviewed manually for other potential studies to include. Our last search date was December 11, 2021. We consulted with an information specialist on formula creation and search strategies. To identify appropriate articles, the search strategy used the text in article titles and abstracts, including index terms, such as “incurable cancer,” “recurrent cancer,” “palliative care,” “diet, food, and nutrition,” “nutritional support,” and “therapy.” The detailed search strategies are described in the **Supplementary File**.

2.4. Study selection

The studies retrieved through a search of the six different databases were screened to assess their eligibility for inclusion after removing duplicate records. The screening was performed independently by two authors (J.U. and A.N.) using Rayyan (Qatar Computing Research Institute, Doha, Qatar) [11]. In case of disagreement, the reasons for the disagreement were clarified; then, a third reviewer (K.M.) was consulted on the decision whether to include or exclude the study. After initial screening of the article title and abstracts, 21 studies were selected for full-text review.

2.5. Data extraction

The data extracted were the general study characteristics, types of intervention, and outcomes. Data extraction was independently performed by two authors (J.U. and A.N.) using Microsoft Excel version 2112 (Microsoft, Redmond, WA, USA). Extracted data were cross-checked and discussed to reach an agreement among the authors, including a third author (K.M.).

We designated QoL and physical symptoms, including anorexia, nausea, ascites, digestive symptoms, and fatigue, as the primary outcomes. The secondary outcomes were adverse events, such as edema; physical function, such as gait speed and handgrip strength; overall survival; increased of nutritional intake; medical cost; and anthropometry, including weight gain and muscle mass. All results related to these outcomes were collected. In published articles with missing data, the corresponding authors of the original articles were contacted via e-mail to obtain the necessary information.

2.6. Quality assessment

Two authors (J.U. and A.N.) independently assessed the risk of bias using the Cochrane Risk of Bias 2 tool for RCTs. We used the following components to assess risk of bias: random sequence generation, allocation concealment, blinding of participants, and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Quality assessment was performed independently by two authors (J.U. and A.N.). Disagreements between the authors arising at any stage were resolved through discussion or by the third author (K.M.).

2.7. Summary measures

Because of the diversity of interventions and outcomes across studies, each result was summarized using the indicators as

presented in the individual study. In the meta-analysis, a mean difference (MD) value was used to summarize findings.

2.8. Data synthesis

All three authors (J.U., A.N., and K.M.) analyzed the included studies using qualitative synthesis to characterize the studies. If no response was received despite enquiring of individual study authors regarding missing data, the study was removed from the meta-analysis. The mean change was calculated as required, and standard deviations (SDs) were calculated from the standard error or the 95% confidence interval (CI) was used if the SD was not reported. The results of each study were summarized and presented in a tabular form.

Meta-analysis was performed for results that could be quantitatively synthesized. Revman 5.4 software (The Cochrane Collaboration, 2020) was used for meta-analysis. The MDs were calculated using a random effect model, the DerSimonian–Laird test, on meta-analysis. The results reported in the Median, interquartile range were estimated as mean and SD using the estimate of methods used by Hozo et al. [12] and Wan X et al. [13]. The presence of heterogeneity was evaluated using the Cochran Q test, and the level of heterogeneity was presented as I^2, with I^2 values of 25%, 50%, and 75% corresponding to the low, medium, and high levels of heterogeneity, respectively. If heterogeneity was high, we considered other factors, such as the patient background, intervention details, outcome definitions, and study quality, and conducted subgroup or sensitivity analysis when possible.

Publication bias was evaluated using funnel plots. The bias was then confirmed using Begg's test [14] if > 10 studies were included for each outcome [15]. Finally, based on the Cochrane review procedures, the total certainty of evidence (CE) for each outcome was assessed using five considerations: limitations, inconsistency, indirectness, imprecision, and publication bias [16].

3. Results

A total of 2376 studies were identified from the electronic search of 6 databases and the manual search of the study reference lists. After primary and secondary screening, seven studies [17–23]were qualified for consideration, and five [17,19–21,23] of the seven studies were included in the meta-analysis (Fig. 1). The 7 studies included 924 patients with cancer (age, 24–95 years). In all seven studies, dietitians implemented nutrition counseling (Table 1).

3.1. Primary outcomes: QoL and physical symptoms

The primary outcome of QoL was evaluated in six studies [17–22] (Table 2) and was assessed by four measures. Three or two articles were included for each of these QoL measures: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Functional Assessment of Anorexia/Cachexia Therapy (FAACT). We contacted the authors of these studies regarding the values needed for the meta-analysis, but we did not receive a response, so the meta-analysis could not be performed [18,22]. In the three studies using EORTC QLQ-C30, QoL improved significantly in the intervention group in one study [9], but not in the other two studies [20,22]. In the two studies using FAACT, the total score was significantly improved ($p = 0.05$) in one study [17], but not in the other study [22]. Additionally, two other measures were used: one study used The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative (EORTC QLQ-C15 PAL) as a QoL measure and showed no significant difference in

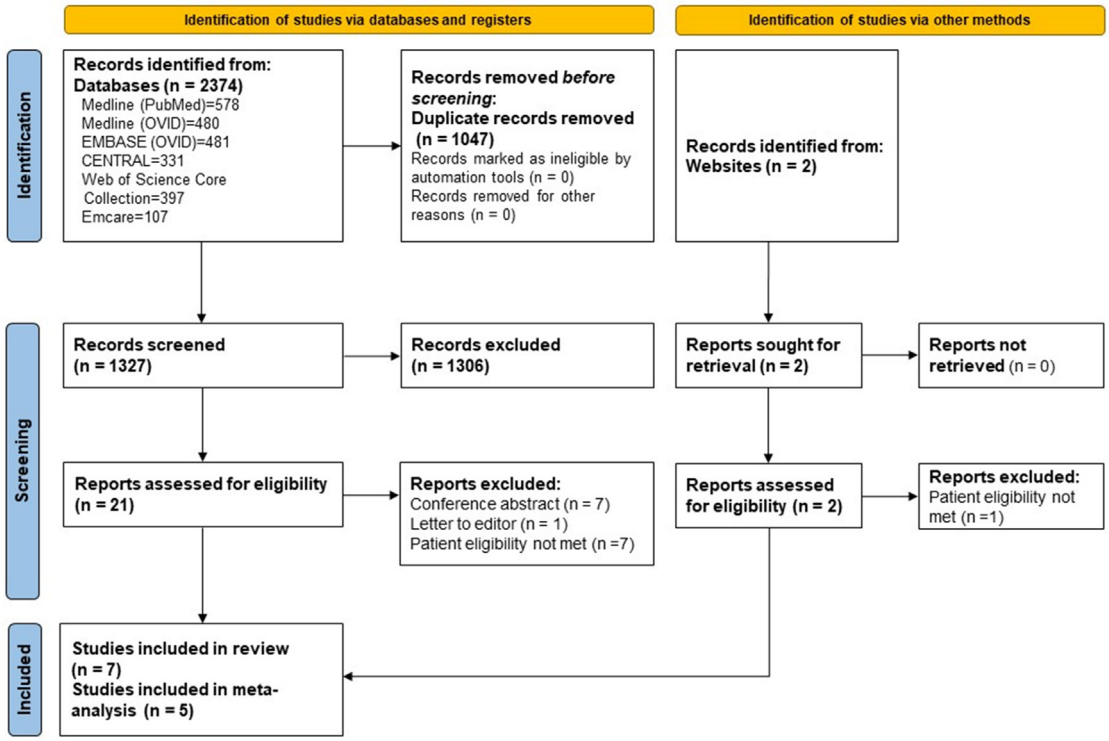

Fig. 1. PRISMA flow diagram of the search. A strategy of electronically searching 6 databases and manually searching reference lists identified 2736 articles, with primary and secondary screening conducted by 2 independent reviewers. Conflict judgments were conducted by an independent third party. Finally, 7 studies met the eligibility criteria.

Table 1
Characteristics of the studies included in review.

Study	Cancer type	Age	Number of patients at baseline	Intervention	Comparison	Duration
Hall 2021[a]	Gastrointestinal Thoracic Breast Urological/ Gynecological Myeloma Head and neck Endocrine	Median (IQR); 78 (69–84)	Total: 45 Intervention: 23 Control: 22	An exercise and nutrition-based rehabilitation program; Individualized guidance by physical therapist and nutrition counselling by dietitian; optimal nutritional intake with oral nutritional supplement twice a day.	Usual care Individualized specialized palliative care available when needed	9 weeks
Keum 2021	Pancreatic ductal adenocarcinoma	Median (IQR); 61.5 (34–78)	Total: 40 Intervention: 20 Control: 20	Nutritional counselling by registered dietitian with use of mobile apps for weight management	No nutritional counselling or use of apps.	12 weeks
Molassiotis 2021[a]	Gastrointestinal Gynecological Lung Skin Urological Breast thyroid	Mean ± SD (range); Patients: 63.7 ± 14.7 (28–86) and 72.4 ± 14 (35–95) Caregivers: 58.5 ± 12.0 (37–71) and 57.7 ± 13.4 (27–84)	Patients: Total: 64 Intervention: 34 Control: 40 Caregivers: Total: 54 Intervention: 23 Control: 31	Family-centered psychosocial nutrition intervention by dietitian	Usual care; Nutritional advice and symptom management by the cancer care team	5 weeks
Uster 2018[a]	Colorectal Oesophago-gastric Non-small cell lung cancer Small cell lung cancer Pancreas	Mean ± SD; 63.0 ± 10.1	Total: 58 Intervention: 29 Control: 29	At least three nutrition counseling sessions with a registered dietitian and exercise therapy twice a week with a physical therapist	Usual care; no exercise intervention; Dietitian intervention only when ordered by the physician	3 months Follow-up after 3 months
Sukaraphat 2016[a]	Lung Cholangiocarcinoma	Mean (range); Intervention:61.3 (45–81) Comparison:62.7 (48–72)	Total: 50 Intervention: 25 Control: 25	The dietary counseling: Individualized and proactive nutritional counseling from a dietitian to maintain and improve energy and protein intake	Usual care; General dietary recommendations by physician or nurse, no involvement of dietitian	Primary endpoint:9–12 weeks Secondary endpoint:18–24 weeks Follow up: 2 months after secondary endpoint
Baldwin 2011	Oesophago-gastric Pancreas Liver and biliary Colorectal Lung	Median (IQR); 66.8 (24–88)	Total: 358 Intervention: 262 Control: 96	Group2: Dietary advice only Group3: Oral nutritional supplement (588 kcal) only Group4: Dietary advice and nutritional Supplement by trained, trial dietitians	Group1:no nutritional intervention	6 weeks Follow up: 1 year or until death
Lundholm 2004[a]	Esophageal/gastric Liver/biliary passages Pancreatic Colorectal Lung Breast Head/neck Melanoma	Mean ± SEM; 68 ± 1	Total: 309 Intervention: 139 Control: 170	Nutritional support by dietitian : nutritional counseling and oral supplements (450–600 kcal per day) Parenteral support provided when dietary intake decreases to 90% of expected level No enteral nutrition	Spontaneous oral nutrient intake	Until death or until the patient was unable or unwilling to participate for any reason.

Abbreviations: IQR, interquartile range; SD, standard deviation, SEM, standard error of the mean.
[a] Studies included in the meta-analysis.

overall QoL [19], and one study [17] used the Thai-Modified Function Living Index Cancer Questionnaire Version 2 and reported higher endpoint QoL in the nutritional guidance group ($p = 0.01$).

The primary outcome of physical symptoms was reported in two studies [19,20]; however, meta-analysis was not possible because different measures were used. A nutritional intervention group showed significant improvement ($p = 0.006$) in emotional functioning on the EORTC QLQ-C15 PAL [19] and significant improvement in subjective assessment of vomiting and nausea on the EPRTC QLQ-C30 ($p < 0.01$) [20] (Table 2).

3.2. Secondary outcomes

For analysis of the increased nutritional intake, four studies [17,20,21,23]. On energy intake could be integrated quantitatively. Results showed that nutritional intervention significantly increased

energy intake, although the degree of heterogeneity was medium (MD 392.82 kcal; 95% CI, 170.04–615.60; p = 0.0005; I^2 = 57%; 71 intervention patients vs. 86 controls; CE, very low quality of evidence). The intervention period was 5 weeks–10 months or longer (Table 3, Supplementary Fig. 1).

For analysis of on protein intake, two studies could be integrated quantitatively [17,20]. Protein intake was significantly increased in intervention group, with low heterogeneity (MD 10.67 g; 95% CI, 1.83–19.51; p = 0.02; I^2 = 0%; 28 intervention patients vs. 25 controls; CE, low quality of evidence) The intervention period was 5 weeks–6 months (Table 3, Supplementary Fig. 2).

All seven studies reported body weight of which four had values available for analysis and could be quantitatively integrated [17,19,20,23]. Meta-analysis showed no significant differences between the intervention and control groups (MD −0.45 kg; 95% CI, −3.68 to 2.78; p = 0.79; I^2 = 11%; 71 intervention patients vs. 84 controls; CE, very low quality of evidence). The intervention period was 5 weeks–10 months or longer (Table 3, Supplementary Fig. 3).

Physical function was evaluated in three studies [19,20,23]. Hand grip strength was evaluated in two studies [20,23]; both reported no significant differences due to nutritional intervention. Numerical data could not be obtained from these two studies and therefore could not be integrated. Additionally, one study [23] measured oxygen uptake and carbon dioxide production on a treadmill and showed increased whole-body oxygen uptake during maximal exercise (p < 0.003) and increased carbon dioxide production and pulse rate near maximal exercise (p = 0.01). Other physical function measures showed no significant differences between the nutrition intervention and control groups (Supplementary Table 1).

Overall survival was evaluated in 3 studies [20,22,23]. For two of these studies, although we contacted the authors, we were unable to obtain the information necessary for quantitative integration [20,23]. Overall survival did not differ between the intervention and control groups in all three studies. Medical costs were evaluated in one study [19], and costs were lower in the intervention group. Muscle mass was evaluated in two studies [18,23], but neither reported an increase in muscle mass with intervention (Supplementary Table 1).

No studies reported edema as an adverse event. However, one study [19] reported abdominal symptoms, including nausea, diarrhea, flatulence, and cramps, related to the oral nutritional supplements used in the intervention.

3.3. Other outcomes

Nutritional status was reported in four studies [17–19,21], of which 2 [19,21] reported the Patient-Generated Subjective Global Assessment (PG-SGA) could be quantitatively integrated. The level of heterogeneity was low, but no significant differences in PG-SGA scores due to nutritional guidance were found (MD −1.52 points; 95% CI, −4.18 to 1.15; p = 0.26; I^2 = 24%; 36 intervention patients vs. 33 controls; CE, very low quality of evidence) The intervention period was 9 weeks to 2 months (Table 3, Supplementary Fig. 4).

Table 2
Primary Outcome (patients only).

	Evaluation tools	Study	Results
QoL	EORTC QLQ-C30	Keum 2021	Significant improvement in QoL in the intervention group (data not shown[a])
		Uster 2018	No significant difference in global health status and QoL Mean (SD) change from baseline: at 3 months; (I) 4.5 (3.4) vs (C) 2.7 (4.0), at 6 months; (I) 5.7 (3.7) vs (C) 2.7 (4.1), p = 0.72
		Baldwin 2011	No significant effect on QoL by oral nutritional intervention (data not shown[a])
	The Functional Assessment of Anorexia/Cachexia Therapy	Molassiotis 2021	Australia site: FAACT QOL total score was significantly improved in intervention group. Other outcomes were improved without significancy. FACCT total score, mean (SD) change score from baseline: (I) 5.39 (3.12) vs (C) −6.58 (4.35), between group effect size 1.09 p = 0.05 FACCT cachexia subscale, mean (SD) change score from baseline: 4.15 (2.23) vs 1.96 (2.12), between group effect size 0.34 p = 0.49 Hong Kong site: FAACT QOL total score and numerically FACCT cachexia subscale improved values with effect sizes being large (FAACT scale) and near large effect size on the FAACT anorexia-cachexia subscale. FACCT total score, mean (SD) change from baseline: (I) 0.47 (6.27) vs (C) 1.16 (3.96), between group effect size 0.13, p = 0.93 FACCT cachexia subscale, mean (SD) change from baseline: (I) 2.75 (1.15) vs (C) 2.85 (3.11), between group effect size 0.72, p = 0.13
		Baldwin 2011	No significant effect on QoL by oral nutritional intervention (data not shown[a])
	EORTC QLQ-C15PAL	Hall 2021	No significant difference in change of overall QoL score between groups. Median (IQR) score: (I) 0.0 (−16.7–12.5) vs (C) 0.0 (−16.7–16.7)
	the Thai-Modified Function Living Index Cancer Questionnaire Version 2	Sukaraphat 2016	Significantly higher QoL scores in nutritional counselling group after 3 or 4 cycles of chemotherapy. Mean (SD) score: (I) 46.16 (7.55) vs (C) 39.40 (10.61), p = 0.01 Higher QoL scores in nutritional counselling group at next two month. Mean (SD) score: (I) 46.45 (7.34) vs (C) 41.10 (11.21), p = 0.08
Physical symptoms	EORTC QLQ-C15 PAL	Hall2021	Significant improvement in emotional function in nutritional intervention group (p = 0.006). No significant improvement in physical (p = 0.846), fatigue (p = 0.449), pain (p = 0.714), dyspnoea (p = 0.589), insomnia (p = 0.92), appetite loss (p = 0.268), nausea (p = 0.812), constipation (p = 0.714).
	EORTC QLQ-C30	Uster 2018	Significant improvement in subjective evaluation of vomiting and nausea. (p < 0.01) No significant improvement in fatigue, pain, dyspnea, sleep disturbance, constipation, diarrhea, appetite loss.

Abbreviations: QoL, Quality of life; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-C15 PAL, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative (I), intervention group (C), control group; SD, standard deviation; IQR, interquartile range.

[a] Inquired with author regarding data, no response.

Table 3
Summary of meta-analysis for outcomes.

Outcomes	Studies, n	Patients (Intervention/control), n	Effect size (MD)	95%CI	p-value	Inconsistency, I^2 (%)	Quality assessment
Energy intake (kcal)	4 [17, 20, 21, 23]	71/86	392.82	170.04, 615.60	0.0005	57	low
Protein intake (g)	2 [17, 20]	28/25	10.67	1.83, 19.51	0.02	0	low
Body weight (kg)	4 [17, 19, 20, 23]	71/84	−0.45	−3.68, 2.78	0.79	11	very low
PG-SGA (points)	2 [19, 21]	36/33	−1.52	−4.18, 1.15	0.26	24	very low

Abbreviations: MD, mean difference; CI, confidence interval; PG-SGA, the Patient-Generated Subjective Global Assessment.

Blood test results were used as an outcome in two studies [21,23] of which one reported [23] significant differences in serum albumin and alkaline phosphatase concentrations between the intervention and control groups (data not shown). Additionally, energy balance—calculated as dietary intake minus resting energy expenditure measured by indirect calorimetry—showed significant improvement in the intervention group [23]. Other outcome measures used were adherence to the intervention [19,22], body mass index [18], length of hospital stay [20], phase angle [20], and quality of sleep [19], none of which statistically differed between the intervention and control groups. Eating-related distress ($p = 0.05$) and eating-related enjoyment ($p = 0.02$) were improved by family-centered nutritional intervention in one study (Supplementary Table 2) [17].

3.4. Summary of findings

A total of 7 studies were identified with 924 patients with cancer, aged 24–95 years, and nutritional counseling was provided by a dietitian in all 7 studies. A primary outcome of this review, QoL, was improved by nutritional counseling in two of the six studies. The other primary outcome, physical symptoms, showed improvement with nutritional counseling in one of the two studies. Quantitative integration of both QoL and physical symptoms was difficult. For secondary outcomes, although four studies on energy intake and two studies on protein intake could be integrated quantitatively, indicating that nutritional counseling may increase intake, the total CE was low. Body weight was reported in all seven studies and could be integrated in four studies, but no effect of nutrition counseling on improvement was found. Low-quality and limited evidence were identified for the effectiveness of nutrition counseling for patients with cancer.

3.5. Quality assessment

Bias in measurement of outcomes was judged as high risk in four of seven studies, and bias in the selection of the reported results was judged as high risk in three of seven studies. Overall risk of bias was judged as high risk in six of seven studies [17–19,21–23], and some concerns for bias were present in one study [20] (Fig. 2).

3.6. Assessment of CE

The total CE ranged from low to very low. All outcomes were downgraded 1–2 levels because of the serious limitations in one or more of the criteria for the risk of bias. Additionally, all outcome grades were lowered by one grade because the sample size was too small to assess the outcome, and the reported events were too few to be precise. Additionally, inconsistency was downgraded by one grade for two outcomes (body weight and PG-SGA) because of inconsistency, and indirectness was downgraded by one grade for one outcome (PG-SGA) because of a non-direct comparison. Publication bias was confirmed by drawing a funnel plot, and no downgrades were needed for all outcomes. The Begg's test was not performed because of the small number of included references (<10) [15].

4. Discussion

This systematic review was conducted to determine the effect of nutrition counseling by registered dietitians and/or nutritional specialists on adult patients with incurable cancer. Results showed that the primary outcomes of QoL and physical symptoms were not quantitatively integrated, and only limited evidence was available. In contrast, the secondary outcomes of energy intake and protein intake were potentially increased by nutritional counseling, whereas body weight was not improved by nutritional counseling.

In patients with cancer, it is important to consider both systemic status and QoL when making treatment decisions [24]. The association between malnutrition and poor QoL has been reported in several studies [24–28]. Nutritional support may also improve QoL in patients receiving palliative care support [5,29,30] and is an essential aspect of the comprehensive intervention. Systematic reviews by Blackwood et al. [7] and Balstad TR et al. [30] have also examined the effect of nutrition counseling on improving QoL. Still, the results are not reliable owing to differences in study design. Our review also had difficulty with quantitative integration and could not determine the effect of nutrition counseling on QoL. In addition, the quality of each study was low, and the evidence was limited. Future high-quality studies of the impacts on QoL are needed. Physical symptoms were reported to show improvement on a fatigue scale in a review by Blackwood et al. [7]. However, the article

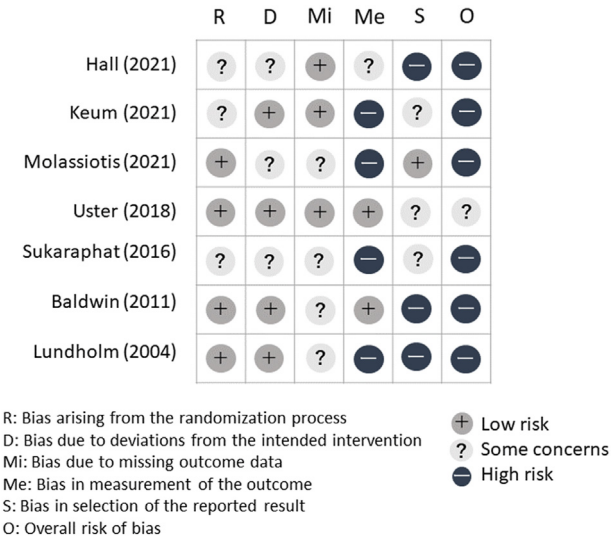

Fig. 2. Assessing risk of bias in included studies. For the seven articles that met the eligibility criteria, two independent reviewers assessed risk of bias, and a conflict judge was assessed by an independent third party. The risk of bias was high for "bias in outcome measurement" and "bias in selection of reported outcomes." The results showed an overall risk of bias in all studies, except the 2018 study by Uster [20].

reported is an exploratory prospective observational study, which looked at adding ice cream as a dietary intervention and not the effect of nutritional counseling. In our review, nutrition counseling improved physical symptoms in one of two cases, but qualitative integration was not possible, and the effect was unclear. Nutritional support, including nutritional counseling, is in high demand from patients and their families, even for patients with cancer at the end of life [31,32], and is recommended in ESPEN practical guideline [33]. Therefore, nutritional counseling should still be provided in actual clinical practice.

Energy intake and protein intake were likely to increase with nutritional counseling. These results support the ESPEN guideline recommendation on oral nutrition. A 2011 Cochrane review of noninvasive interventions for lung cancer patients [26] reported that nutrition counseling positively affected increased energy intake. However, this Cochrane review included only one article on nutritional interventions. A systematic review by Balstad TR et al. [30] also showed an effect of increased energy intake with nutrition counseling, but quantitative integration was not examined. In our review, we conducted a meta-analysis using four articles, which we believe more robustly demonstrate the effect of nutrition counseling on increasing energy intake. Regarding protein intake, the systematic review by Blackwood et al. [7] found increased energy and protein intake with oral nutritional supplements and fortified diets. However, the effect of nutrition counseling on increased protein intake remains unclear. A systematic review of the impact of oral nutritional intervention, including dietary counseling, on adult patients with cancer undergoing chemo (radio)therapy, by De van der Schueren MAE et al. [34] found that oral nutritional intervention increased protein intake. This review includes patients other than those with incurable cancer, which differs from our study population. Our study showed that nutrition counseling for patients with incurable cancer may increase protein intake. However, it should be noted that in our study, the effect of increased energy intake and protein intake is that the CE is low, and the quality of the evidence is insufficient. Additionally, our review results do not allow us to conclude whether the increase in calorific value and protein intake led to good patient outcomes.

Body weight was not improved by nutritional counseling. The study by De van der Schueren MAE et al. [34] also found no weight gain with nutritional counseling intervention. They cite the failure to achieve weight gain because the energy intake of the study participants did not reach energy requirements, noting that weight gain may only be achieved in studies with adequate target intake and high compliance. In the seven studies included in our review, only one study [23] reported whether energy intake reached energy requirements, so the details are unclear. Two guidelines on cachexia management [8,9] recommend offering nutritional counseling to increase body weight, but the evidence is limited and of low quality. In addition, a 2021 Cochrane review [35] on the effects of nutrition counseling for adults with disease-related malnutrition found that in the short term (after 3 months), dietary advice alone and dietary advice plus oral nutritional supplements may increase body weight. However, because of the low CE, the effect of nutritional counseling could not be determined. Furthermore, the population of this Cochrane review was not limited to patients with cancer. In summary, the effect of weight gain from nutritional counseling for patients with incurable cancer remains unclear.

Nutrition counseling for patients with cancer is considered an initial nutritional intervention in the guidelines [6,8,9] and is a noninvasive intervention. We believe that clarifying this effect is highly significant for clinical practice, social policy, and future research in cancer care and that the benefits to patients with cancer will be high.

This study has several limitations. First, in the meta-analysis, many of the individual study authors were contacted, but their data were not available; therefore, it was difficult to perform qualitative integration for the primary outcomes, which affected the certainty of the evidence. Second, data from RCTs were collected, but the small number of articles included made it difficult to assess publication bias by using Begg's test. Furthermore, it was difficult to conduct subgroup analysis. Third, the meta-analyzed studies included a variety of interventions that involved a combination of exercise and nutrition, thereby leading to heterogeneity.

5. Conclusion

Nutrition counseling was shown to have the potential to improve energy and protein intake in patients with incurable cancer. Although neither can be strongly recommended owing to the low CE, we believe that nutrition counseling is a noninvasive treatment strategy that should be introduced as an initial nutritional intervention for patients with incurable cancer. However, although QoL, a patient-reported outcome, is an important outcome of nutrition counseling, the evidence for its effect on QoL is insufficient. Large-scale intervention studies with more significant numbers of patients are needed to corroborate this recommendation, and future research results are expected.

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Author contribution

Junko Ueshima: Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing-Original Draft, Writing-review and editing. **Ayano Nagano:** Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing-Original Draft, Writing-review and editing. **Keisuke Maeda:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Resources, Validation, Visualization, Writing-Original Draft, Writing-review and editing. **Yoshiko Enomoto:** Writing-review and editing, Visualization. **Koshi Kumagai:** Writing-review and editing, Visualization. **Rie Tsutsumi:** Writing-review and editing, Visualization. **Naoki Higashibeppu:** Conceptualization, Writing-review and editing, Visualization. **Yu Uneno:** Conceptualization, Resources, Visualization, Writing-review and editing. **Joji Kotani:** Conceptualization, Project administration, Supervision, Visualization, Writing-review and editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors have no financial or any other kind of personal conflicts with this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.12.013.

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