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REVIEW

Oral Nutritional Interventions in Malnourished Patients With Cancer: A Systematic Review and Meta-Analysis

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Background International guidelines on the nutritional management of patients with cancer recommend intervention with dietary advice and/or oral nutritional supplements in patients who are malnourished or those judged to be at nutritional risk, but the evidence base for these recommendations is lacking. We examined the effect of oral nutritional interventions in this population on nutritional and clinical outcomes and quality of life (QOL).

Methods Electronic searches of several databases including MEDLINE, EMBASE, and CINAHL (from the first record to February 2010) were searched to identify randomized controlled trials of patients with cancer who were malnourished or considered to be at risk of malnutrition and receiving oral nutritional support compared with routine care. We performed a meta-analysis using a fixed effect model, or random effects models when statistically significant heterogeneity was present, to calculate relative risk (mortality) or mean difference (weight, energy intake, and QOL) with 95% confidence intervals (CIs). Heterogeneity was determined by using the χ^2 test and the I^2 statistic. All statistical tests were two-sided.

Results Thirteen studies were identified and included 1414 participants. The quality of the studies varied, and there was considerable clinical and statistical heterogeneity. Nutritional intervention was associated with statistically significant improvements in weight and energy intake compared with routine care (mean difference in weight = 1.86 kg, 95% CI = 0.25 to 3.47, $P = .02$; and mean difference in energy intake = 432 kcal/d, 95% CI = 172 to 693, $P = .001$). However, after removing the main sources of heterogeneity, there was no statistically significant difference in weight gain or energy intake. Nutritional intervention had a beneficial effect on some aspects of QOL (emotional functioning, dyspnea, loss of appetite, and global QOL) but had no effect on mortality (relative risk = 1.06, 95% CI = 0.92 to 1.22, $P = .43$; $I^2 = 0\%$; $P_{heterogeneity} = .56$).

Conclusion Oral nutritional interventions are effective at increasing nutritional intake and improving some aspects of QOL in patients with cancer who are malnourished or are at nutritional risk but do not appear to improve mortality.

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The number of new cancers diagnosed worldwide is increasing. The American Cancer Society estimated that there were 12 million new cancers diagnosed worldwide in the year 2007, with the number expected to more than double in the next 50 years (1). The amount of malnutrition in patients with cancer at first referral varies by the site and the stage of disease (2). Recent data have suggested that as many as 56.0% of patients with gastrointestinal cancers have clinically significant weight loss at first referral (3). Weight loss at presentation (ie, first referral) is associated with poorer survival, reduced likelihood of objective response to treatment, and poorer quality of life (QOL) (2,4,5). The data on weight loss in cancer patients show convincing associations with poorer clinical outcomes, but there is no evidence at present to suggest that there is a causal link between these variables. Despite this, European, American, and Australian guidelines on the nutritional management of malnourished patients with cancer have recommended that nutrition receives prompt attention and that intervention is commenced in malnourished patients or those in whom difficulties with eating are anticipated (6–8). The evidence for these recommendations and ones relating to nutritional intervention during treatment phases is largely lacking and is mainly on the basis of expert opinion.

In the United Kingdom, the National Institute for Health and Clinical Excellence has recommended that health care professionals should consider oral nutrition support to improve nutritional intake for people who can swallow safely and who are malnourished or at risk of malnutrition (9). This recommendation is on the basis of an analysis that included few trials conducted in cancer patients and relied largely on trials conducted in the elderly or perioperative patients. There are no universally accepted cut-offs for defining malnutrition, but there is broad acceptance that a low body mass index or substantial amounts of weight loss in the preceding months are indicative of malnutrition (6,9) and associated with poorer outcome in cancer patients (2,4). Patients at risk of

CONTEXTS AND CAVEATS

Prior knowledge

International guidelines recommend nutritional intervention with dietary advice and/or oral nutritional supplements during treatment for cancer patients who are malnourished or at nutritional risk. However, these recommendations have been made largely on the basis of expert opinion rather than clinical trials.

Study design

Electronic searches of several databases were done for randomized controlled trials of cancer patients comparing oral nutritional intervention with routine care. Outcomes such as mortality, weight, energy intake, and quality of life were investigated by meta-analyses to determine the benefits of nutritional intervention vs routine care.

Contributions

Thirteen studies that included 1414 cancer patients were identified for analysis, although the quality varied and the clinical and statistical heterogeneity was substantial. Nutritional intervention resulted in statistically significant improvements in weight and energy intake, although no difference was observed after removing the studies responsible for heterogeneity. However, some aspects of the quality of life including emotional functioning, dyspnea, loss of appetite, and global quality of life were improved. Nutritional intervention had no effect on mortality.

Implication

Nutritional interventions increase nutritional intake and improve some aspects of a patient's quality of life with no beneficial effect on mortality.

Limitations

The effects of nutritional intervention on weight and energy intake are heterogeneous, and further studies are needed. A clinically meaningful benefit of changes to quality of life associated with nutritional intervention is also unclear. This study was further limited by the low to moderate quality data from available studies with few participants who had cancer at different sites and stages.

From the Editors

becoming malnourished have been defined on the basis of poor intake in the recent past (6,9) and poor intake in combination with illness (10). Three systematic reviews that have included analyses of the effects of oral nutritional interventions in cancer patients have failed to demonstrate any clinical benefit of oral nutritional intervention (11,12) or benefits to QOL (13), but the conclusions were limited. None of the reviews included an analysis of weight, the analysis of QOL was limited to global QOL only, and some key studies were not included in the analysis. More recent trials have provided additional data in this area, and therefore, it is timely to reexamine this question. In addition, guidelines on nutritional support often do not capture the potential benefits of simple oral nutritional interventions and rely on data from studies of enteral and parenteral feeding (8).

The aim of this systematic review was to examine the evidence for an effect of oral dietary interventions in patients with cancer who were malnourished or were at risk of malnutrition. The outcomes examined were survival, QOL, and nutritional indices (ie, weight loss and energy intake).

Methods

A systematic review was conducted, according to the methods recommended by the Cochrane Collaboration (14).

Identification of Studies

The searches undertaken to identify the studies for this analysis were conducted on five occasions between 1998 and February 2010 (two separate but identical searches were undertaken from November 2005 to 2008 and November 2008 to February 2010) (Figure 1). Publications describing randomized controlled trials (RCTs) of oral nutritional interventions in patients with cancer were retrieved by searching electronic databases. The search strategy used to identify studies evolved in line with changes in information technology and development of the search strategy and selection of appropriate databases was undertaken with advice from information specialists. The search strategies are provided in Supplementary Methods (available online). The search was restricted to RCTs only by using an electronic filter. All languages were included, and publications not in English but considered to meet the inclusion criteria from the abstract were translated. Reports of additional trials that may have been missed were sought by assessing the bibliographic references of all retrieved studies, the reference lists of key reviews (6,9,11,12,15), and contacting the authors of all included studies. No hand searching was undertaken. Contact was made with experts in clinical nutrition, manufacturers of oral nutritional supplements, and all registered dietitians in the United Kingdom in the year 2002.

Selection of Studies

Trials were included if they were undertaken in adults with cancer (all sites and stages) who were clearly malnourished or judged to be at risk of malnutrition on the basis of their clinical condition, receiving active treatments or palliative care, and were comparing oral nutritional interventions with usual care. For the purposes of study selection, it was assumed that cancer patients receiving active or palliative treatments could be judged to be at risk of malnutrition. Oral nutritional intervention could consist of: 1) dietary advice, 2) oral nutritional supplements, or 3) dietary advice and oral nutritional supplements given together.

Dietary advice was defined as instruction to modify food intake given with the aim of improving nutritional intake. Oral nutritional supplements were defined as food products that were marketed for the management of disease-related malnutrition. Trials were eligible for inclusion if they were RCTs or quasi-RCTs (ie, trials that describe the method of assignment and group allocation but use methods that are not strictly random, such as alternation or date of birth). Trials were excluded if they did not meet these criteria. The principal reasons for exclusion of trials were that they were not RCTs, that the nutritional intervention and comparisons did not meet the inclusion criteria, or that they were conducted in children.

Data Extraction and Outcome Measures

Titles and abstracts from searches were reviewed on-screen by one reviewer (C. Baldwin). Potentially relevant studies were assessed for inclusion by two investigators (C. Baldwin and A. Spiro),

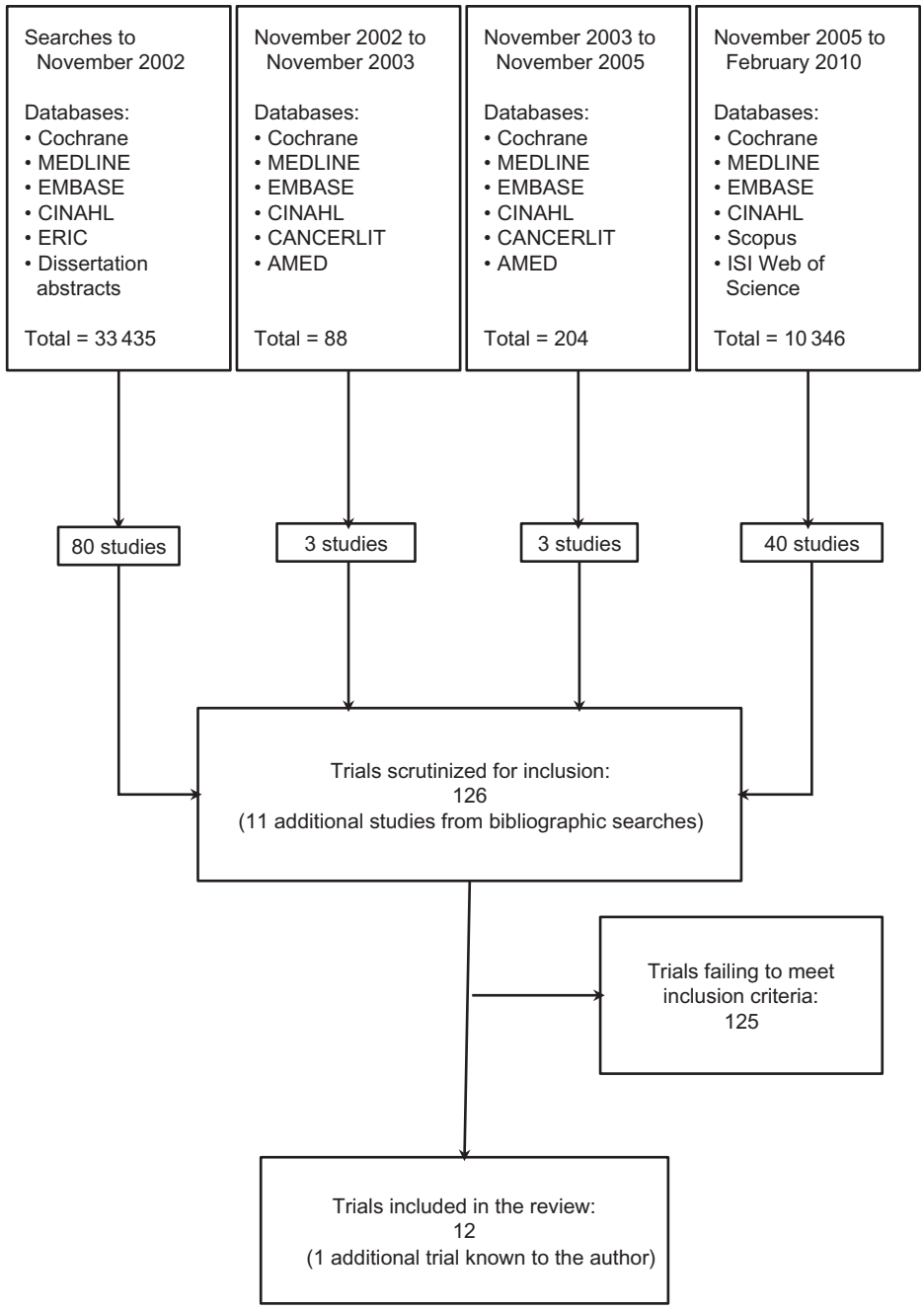

Figure 1. The search strategy and number of trials identified for inclusion in the meta-analysis. The searches were done on five occasions between 1998 and February 2010 (two separate but identical searches were undertaken in November 2008 and February 2010). The search strategy evolved in line with the changes in information technology and was designed with advice from information specialists. The databases searched in the study included Allied and Complimentary Medicine Database (AMED), Cancer Literature (CancerLit), Cochrane Central Register of Controlled Trials (Cochrane), Excerpta Medica Database (EMBASE), Cummulative Index to Nursing and Allied Health Literature (CINAHL), Education Resources Information Center and Dissertation abstracts (ERIC), the Web of Science (ISI), Medical Literature Analysis and Retrieval System Online (MEDLINE), and the Elsevier database of abstracts and citations (SCOPUS).

working independently. The following details of studies were extracted from each trial: year and journal of publication; patient population (cancer type, stage, and treatment intent, as well as demographic information); details of the intervention and the comparison, number of patients randomly assigned to each group and attrition; outcome data on mortality, weight, energy intake, and QOL. Data were extracted from all included studies by both reviewers independently. When information on study design, quality, or data was unclear, authors were contacted for additional information. The primary outcome measures were mortality and QOL. Secondary outcome measures were change in weight and energy intake.

Methodological Quality of Studies

The methodological quality of studies was assessed by two investigators (C. Baldwin and A. Spiro), according to the criteria described by Schulz et al. (16) and the Cochrane Handbook (14). This assessment included an examination of the method of randomization and allocation concealment, whether the study was blinded and whether patient characteristics were compared at baseline to ensure that the groups were comparable. In addition, studies were examined to ensure that the number of participants lost to follow-up or excluded from the study was recorded and that all the outcome variables stated in the "Methods" were presented in the "Results."

Statistical Analysis

For mortality, which was a binary outcome, data were combined using the Mantel–Haenszel method, with results presented as a relative risk with 95% confidence intervals (CIs). Follow-up data at 6 months were used from the studies by Baldwin et al. (17) and Persson et al. (18) to make the time frame comparable with other studies. For all other studies, data were collected at the end of follow-up.

For QOL, weight, and energy intake, which were continuous outcomes, an inverse variance model was used to combine the mean difference and 95% confidence intervals. Fixed effect models were used unless statistically significant heterogeneity was present, for which a random effects model was used. For studies with multiple interventions and one control group (17,19,20), the control group numbers were divided equally between the number of intervention groups for survival data. For continuous data (change in weight and QOL), the mean and SD were kept constant, but the sample size was divided by the number of intervention groups.

Four of 13 studies included in our analysis were completed during a period longer than 6 months. Data were available at several time points for two of these studies (17,18). Analyses were repeated with data at each time point to ensure that choice of timepoint did not have a substantial impact on the overall results. When included studies had data at several time-points, data have been chosen for inclusion in each analysis to make them comparable with data from studies with only one time point. Data at 6 months follow-up from the studies by Baldwin et al. (17) and Persson et al. (18) have been used in the analysis of weight gain and energy intake, and data at 6 weeks and 6 months follow-up, respectively, have been used in the analyses of QOL.

The results of meta-analyses were inspected for heterogeneity and tested using the χ^2 test and by using the I^2 statistic. A P value of less than .1 rather than less than .05 was used as evidence of statistical heterogeneity for the χ^2 test, as recommended by the Cochrane Collaboration (14). The I^2 statistic (0%–100%) describes the percentage of total variation across studies that were because of heterogeneity rather than chance (21). A simplified categorization of heterogeneity [on the basis of recommendations in the Cochrane Handbook (14) and Higgins et al. (21)] was used of low (I^2 = 0%–33.0%), moderate (I^2 = 34.0%–66.0%), and high (I^2 = 67.0%–100.0%). When heterogeneity was high, the data were examined to determine which studies were responsible for the heterogeneity. The data were then reanalyzed without the studies contributing heterogeneity by setting the weighting for those studies to zero.

Initially, data on all interventions were combined to examine the effect of nutritional intervention (any type) compared with no nutritional intervention. Consideration was then given to carrying out subgroup analyses, to examine the effects of study quality, individual types of nutritional intervention, the influence of site of cancer, treatment intent (adjuvant, neoadjuvant, or palliative), type of treatment (radiotherapy or chemotherapy), and nutritional status of the patients at study entry (well- or malnourished). We did not perform subgroup analyses to reflect differences related to gender and ethnicity. All analyses were conducted using RevMan software (version 5.0; Cochrane Collaboration, Oxford, UK). All statistical tests were two-sided.

Results

Study Characteristics

Thirteen studies (17–20,22–30) representing 1414 randomized participants were identified for the systematic review (Table 1, Figure 1). All studies were performed in cancer patients, but there was variability in the type, site, and stage of cancers, both within and between studies (Table 1). Trials included patients with gastrointestinal cancers (esophageal, gastric, pancreatic, and colorectal), gynecological cancers (cervix and ovary), leukemia, lymphoma, and cancers of the bladder, lung, head and neck, and breast. All trials were in patients receiving treatment, but the type and clinical intent of this treatment varied between studies and included both chemotherapy and radiotherapy given as adjuvant, neoadjuvant, or primary treatment.

All trials were of oral nutritional interventions compared with routine care but varied in the exact nature of the intervention offered: Six studies compared dietary advice with routine care, three compared oral nutritional supplements with routine care, and seven compared dietary advice plus supplements if required with routine care. Four of the studies included more than one intervention that met the inclusion criteria of the review (17,19,20,22). The study by Baldwin et al. (17) included groups receiving dietary advice, dietary advice plus supplements, and oral nutritional supplements. The studies by Ravasco et al. (19,20) included groups receiving dietary advice and groups receiving oral nutritional supplements. The study by Dixon (22) included groups receiving dietary advice and dietary advice plus oral nutritional supplements. The data from one study are reported in two different articles (27,31).

All included studies provided nutritional intervention with the aim of improving nutritional status but varied by the baseline nutritional status of the recruited patients. Only four of the 13 studies defined nutritional status as an inclusion criterion (17,18,22,24), using a recent weight loss as a threshold. Six studies included some well-nourished and some malnourished patients (19,20,25–27,30). No specific nutritional thresholds were specified as inclusion criteria in the remaining studies, but these studies were carried out in patients whose conditions exposed them to nutritional risk as defined in the "Methods." The studies reported on a range of outcomes (Table 1), but the aim of this analysis was to examine the effects of nutritional intervention on survival, QOL, and nutritional indices.

Methodological Quality of Studies

In eight studies, the description of the methods of randomization and allocation was adequate (Table 2). Four studies did not report details of the method of randomization and allocation. The study by Macia et al. (23) used a coin toss to randomly assign participants to treatment groups but did not describe the method of allocation concealment. No study stated that quasi-randomization methods were used. Only one study reported blinded assessment of some outcomes (23) and 10 of 13 studies presented the patient characteristics at baseline. In eight of the studies presenting baseline characteristics, similar baseline characteristics were observed between groups; in the study by Moloney et al. (29), the treatment group was older than the comparison group, and in the study by

Table 1. Characteristics and information extracted from studies included in the review*

Trial	No. of participants	Cancer site and treatment intent	Nutritional status	Comparison details	Outcomes	Length of intervention	Length of follow-up	Study funding source(s)
Baldwin et al., 2008 (17)	358	Upper and lower GI cancer and lung cancer (NSC and mesothelioma) receiving palliative chemotherapy	All patients had lost weight at the start of the trial (mean = 10.0%)	Group 1 received no additional intervention, group 2 received dietary advice to increase intake by 600 kcal/d, group 3 received an oral nutritional supplement providing 588 kcal/d, group 4 received dietary advice to increase intake by 600 kcal/d and an oral nutritional supplement	Mortality*, weight*, QOL*, energy intake, grip strength	6 wk	12 mo	Henry Smith Charity and The Special Trustees of Chelsea and Westminster Hospital, London, UK
Dixon, 1984 (22)	36	Cancer (mainly colorectal [27.0%] and lymphoma [16.0%]). 58.0% receiving chemotherapy, 74.0% with palliative intent	>5.0% weight loss in a 2-mo period or persistent difficulties with eating	Nutritional counseling provided by nurses or nutritional counseling plus oral nutritional supplements vs no advice	Mortality, weight	4 mo	4 mo	PHS Grant R18 CA22619 National Cancer Institute, US Department of Health and Human Services
Elkort et al., 1981 (25)	47	Metastatic breast cancer receiving chemotherapy; 21 patients lost to follow-up and only 26 evaluable patients	Described as well nourished and moderately malnourished (only two of 47 eligible patients were malnourished)	Optimal diet (information from author indicated equivalent to dietary advice to meet nutritional requirements) + 500 kcal of nutritional supplement vs routine care + no supplement	Mortality*, weight*, TSF, MAMC	12 mo	12 mo	Mead Johnson and Co, Evansville, IN (Grant No. 675)
Evans et al., 1987 (26)	180	Metastatic cancer (colorectal and NSC lung) receiving chemotherapy	Patients stratified according to amount of weight loss; 83 of 180 patients with >5.0% weight loss	Nutritional counseling to achieve a target caloric intake, using supplements if required vs routine care (ad libitum food intake)	Mortality*, weight, energy intake	12 wk	12 wk (weight and energy intake), 3 y survival	National Institute of Health Contract and the US National Institutes of Health grants
Isenring et al., 2004 and 2007 (27,31)	60	GI and head and neck cancers receiving adjuvant or neoadjuvant radiotherapy	Assessed by PG-SGA; 39 of 60 patients were well nourished and 21 (35.0%) were malnourished, of whom four were severely malnourished	Intensive nutritional counseling and nutritional supplements, if required vs usual care (which included standard booklet and the patient could request a referral to a dietitian). Five of 31 patients saw a dietitian during the 12-wk study	Mortality*, weight*, fat-free mass, QOL*, PG-SGA, energy intake*	12 wk	12 wk	The Wesley Research Institute, Australia

(Table continues)

Table 1 (Continued).

Trial	No. of participants	Cancer site and treatment intent	Nutritional status	Comparison details	Outcomes	Length of intervention	Length of follow-up	Study funding source(s)
Lovik et al., 1996 (28)	61	Cancer (head and neck), early- and late-stage disease receiving radiotherapy	None specified	Intensive dietary instruction including advice to use nutritional supplements if required vs routine care (a standard information sheet providing information on all aspects of treatment, including advice to eat a nutritious diet)	Mortality*, weight*, energy intake	6 wk	6 wk	Support from Meddinova's Research Fund
Macia et al., 1991 (23)	92	Cancer (head and neck, breast, abdominopelvic). No details on the disease stage of patients receiving radiotherapy	None specified	Dietary instruction was given verbally and in writing vs no advice	Weight	Unclear	Unclear	None declared
Moloney et al., 1983 (29)	84	Patients with cancers of the head and neck, breast, lung, bowel, cervix, and bladder, who received radiotherapy, 75.0% of included patients had advanced disease	None specified	Dietary counseling and supplements vs routine care	Mortality*, long-term outcome of disease, energy intake	3–5 wk	3 wk–11 mo	Support from Bristol Myers
Ollenschlager et al., 1992 (24)	31	Acute leukemia (lymphocytic and nonlymphocytic); all patients received chemotherapy	Unintentional weight loss >5.0% or actual weight ≤90% of ideal body weight	Daily dietary instruction and modification of diet vs no advice	Mortality*, weight, energy intake, QOL	Unclear	6 mo	None declared
Ovesen et al., 1993 (30)	137	Patients with NSC lung, breast, and ovarian cancer who received chemotherapy. 56.0% of patients had localized disease and 44.0% had advanced disease.	Patients stratified for degree of previous weight loss: >5.0% or <5.0% in previous 3 mo	Dietary instruction to exceed the Nordic recommended allowances using supplements if required vs routine care	Mortality*, weight*, energy intake*, QOL	5 mo	5 mo	Grant No. 89-402 Danish Cancer Society, Copenhagen, Denmark
Persson et al., 2002 (18)	142	Colorectal or gastric cancer, all post surgery. Some patients received adjuvant chemotherapy and some received palliative chemotherapy	>5.0% weight loss	Dietary advice by phone and in writing to meet the Nordic recommended allowances using supplements if required vs routine care	Mortality*, weight*, energy intake, QOL*	2 y	2 y	Swedish Cancer Society

(Table continues)

Table 1 (Continued).

Trial	No. of participants	Cancer site and treatment intent	Nutritional status	Comparison details	Outcomes	Length of intervention	Length of follow-up	Study funding source(s)
Ravasco et al., 2005 (20)	111 (groups 1, 2, and 3)	Patients with colorectal cancer (mixed stages) who received radiotherapy ± chemotherapy before surgery	Assessed using PG-SGA; 42 (38.0%) of 111 patients were malnourished, 15 were in the dietary advice group, 14 were in the supplement group, and 13 were in the no dietary advice and no supplement group	Dietary counseling to achieve calculated energy and protein requirements vs 400 kcal of supplement vs no advice and no supplement	Mortality*, weight*, BMI, nutrient intake*, PG-SGA, QOL*	3 mo	3 mo	Nucleo Regional do Sul da Liga Portuguesa contra o Cancro: Terry Fox Foundation
Ravasco et al. 2005 (19)	75 (groups 1, 2, and 3)	Patients with head and neck cancers (mixed stages) who received radiotherapy alone, in combination with chemotherapy, or as an adjunct to surgery	Assessed using PG-SGA; 45 (60.0%) of 75 patients were malnourished, 16 were in the dietary advice group, 14 were in the supplement group, and 15 were in the no dietary advice and no supplement group	Dietary counseling to achieve calculated energy and protein requirements vs 400 kcal of supplement vs no advice and no supplement	Mortality*, weight*, nutrient intake*, PG-SGA, QOL*	3 mo	3 mo	Nucleo Regional do Sul da Liga Portuguesa contra o Cancro: Terry Fox Foundation

* Data available for inclusion in the meta-analysis. BMI = body mass index; GI = gastrointestinal; MAMC = mid-arm muscle circumference; NSC = non–small cell carcinoma; PG-SGA = Ottery's Patient-Generated Subjective Global Assessment; QOL = quality of life; TSF = triceps skinfold.

Elkort et al. (25), there were more patients with early disease (stage I) in the control group than the intervention group. On the basis of these observations, all studies were judged to be at risk of bias from one or more characteristics.

Nutritional Intervention and Survival

Data were available on survival for 11 of the 13 studies and 15 comparisons, although in the studies by Ravasco et al. (19,20) (four comparisons), there were no deaths (Table 2). The study by Dixon (22) reports the total number of deaths in the study but not by group allocation, making the data unusable. Study length varied from 6 weeks to 36 months, with two studies having data available at more than one time point (17,18). The duration of six of 11 studies was 6 months or less; therefore, data at 6 months follow-up from the studies by Baldwin et al. (17) and Persson et al. (18) were included in this analysis to make them comparable with other studies. These results were combined in a meta-analysis (Figure 2). There were no statistically significant differences in mortality between the intervention and control groups. Relative risk, using a fixed effects model, and heterogeneity were low (relative risk = 1.06, 95% CI = 0.92 to 1.22, $P = .43$; $I^2 = 0\%$; $P_{\text{heterogeneity}} = .56$).

Nutritional Intervention and QOL

Seven of the 13 studies identified by the systematic review included QOL data, of which five collected data using the same cancer-specific questionnaire from the European Organization for Research and Treatment of Cancer (EORTC) (17–20,27). The remaining two studies (24,30) collected QOL data using other QOL scales and could therefore not be included in the combined analysis.

The 30-item EORTC questionnaire assesses five functional scales (physical, role, cognitive, emotional, and social) and eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, loss of appetite, constipation, and diarrhea), and measures global QOL and perceived financial impact. Of the studies that assessed QOL using the EORTC questionnaire, three reported the results for all components (17,19,20), one reported selected components (18), and one reported only global QOL (27). In view of the difficulties, this posed for completing a meta-analysis; the original data were requested and obtained from authors on all EORTC scales. Follow-up data were available from the studies by Ravasco et al. (19,20) and Isenring et al. (27) at 3 months, which represented the end of the intervention. Data from the study by Baldwin et al. (17) collected after 6 weeks of follow-up (end of intervention) were used in the analysis to make it comparable. Data supplied by Persson et al. (18) was after 6 months of follow-up. When comparing the combined results for all studies of nutritional intervention with routine care in a combined meta-analysis, there were statistically significant improvements in all function scales, seven of eight symptom scales, and global QOL (Table 3). However, there was high heterogeneity for all comparisons other than the constipation and financial scales. For each scale, therefore, the analysis was repeated removing the comparisons accounting for the heterogeneity. The heterogeneity in the combined analyses of "social functioning," "cognitive function," "emotional functioning," "global QOL," and "nausea and vomiting" was due to data from two studies (four comparisons) (19,20) that reported

Table 2. Indicators of study quality in included studies

Study	Generation of sequence	Allocation concealment	Blinded assessment of outcome	Baseline characteristics	Description of dropouts	Selective reporting
Baldwin et al., 2008 (17)	Computer-generated list from independent trials center	Group allocation communicated by independent trials center after consent to participate had been signed	No outcomes assessed, blinded to intervention	Baseline characteristics similar for all groups	Attrition described according to group allocation: 198 deaths and seven withdrawals	All specified outcomes were reported
Dixon, 1984 (22)	Described as randomized but no method stated	None described	Not reported	Groups similar at baseline	Attrition not described according to group allocation: 63.0% of participants completed the study. There were 23 deaths and 10 patients left the trial. Groups were not specified	All specified outcomes were reported but were not in a usable format
Elkort et al., 1981 (25)	Described as randomized but no method stated	None described	Not reported	Groups similar at baseline apart from number of patients with early disease. Five patients with early disease in the control group compared with two in the intervention group	Attrition reported according to group allocation: 55% of participants were evaluable at 12 months. Seven patients died, 10 left the study, one had incomplete records, and 3 completed <12 mo of follow-up	All specified outcomes were reported but only the mortality data were in a usable format
Evans et al., 1987 (26)	Performed by a centralized office	Achieved by using a centralized office	Not reported	Groups similar at baseline	Mortality reported to 3 years: 156 of 180 patients died. No information on patients who left the study	All specified outcomes were reported but only the mortality data were in a usable format
Isenring et al., 2004 and 2007 (27,31)	Random number table (details provided by author)	Sealed opaque envelopes (details provided by the author)	Not reported	Groups similar at baseline	Attrition reported according to group allocation: six participants were lost to follow-up, four from the intervention group	All specified outcomes were reported; data was obtained from the authors for the meta-analysis
Lovik et al., 1996 (28)	Random number table (details provided by author)	Sealed opaque envelopes (details provided by the author)	Not reported	Groups similar at baseline	Attrition reported according to group allocation: three deaths occurred in the intervention arm and no patients left the study	All specified outcomes were reported

(Table continues)

Table 2 (Continued).

Study	Generation of sequence	Allocation concealment	Blinded assessment of outcome	Baseline characteristics	Description of dropouts	Selective reporting
Macia et al., 1991 (23)	Randomization performed using a coin toss	None described	Clinical outcomes assessed by a physician unaware of the group allocation	Baseline data not provided	Attrition not reported	All specified outcomes were reported but were not in a usable format
Moloney et al., 1983 (29)	Described as randomized but no method stated	None described	Not reported	Intervention group were older than the control group	Attrition reported according to group allocation: 53 of 88 patients died, no patients left the study	All specified outcomes were reported but only the mortality data were in a usable format
Ollenschlager et al., 1992 (24)	Described as randomized but no method stated	None described	Not reported	Groups similar at baseline	Attrition reported according to group allocation: two deaths in the intervention arm and no patients left the study	All specified outcomes were reported but only the mortality data were in a usable format
Ovesen et al., 1993 (30)	Random number table	Sealed opaque envelopes	Not reported	Groups similar at baseline	Attrition reported according to group allocation. 30 deaths: 20 in the intervention group and 10 in the no intervention group. 19 patients withdrew: nine in the intervention group and 10 in the no intervention group.	All specified outcomes were reported
Persson et al., 2002 (18)	Performed using an independent center (information from author)	Achieved by using an independent center (information from author)	Not reported	Groups similar at baseline	Information on attrition obtained from author: in the intervention group, there were 137 patients randomized in the study. At 24 months there were 25 deaths, five patients withdrew and three patients were excluded in the intervention group. In the control group, there were 26 deaths, 14 patients withdrew and one patient was excluded	All specified outcomes were reported; data for analysis were obtained from the author
Ravasco et al., 2005a (20)	Computer-generated list of random numbers	Sequentially numbered sealed opaque envelopes	Not reported	Not reported	Attrition reported, no patients left the study or died	All specified outcomes were reported; data for the analysis were obtained from the author
Ravasco et al. 2005b (19)	Computer-generated list of random numbers	Sequentially numbered sealed opaque envelopes	Not reported	Not reported	Attrition reported, no patients left the study or died	All specified outcomes were reported, additional data for analysis were obtained from the author

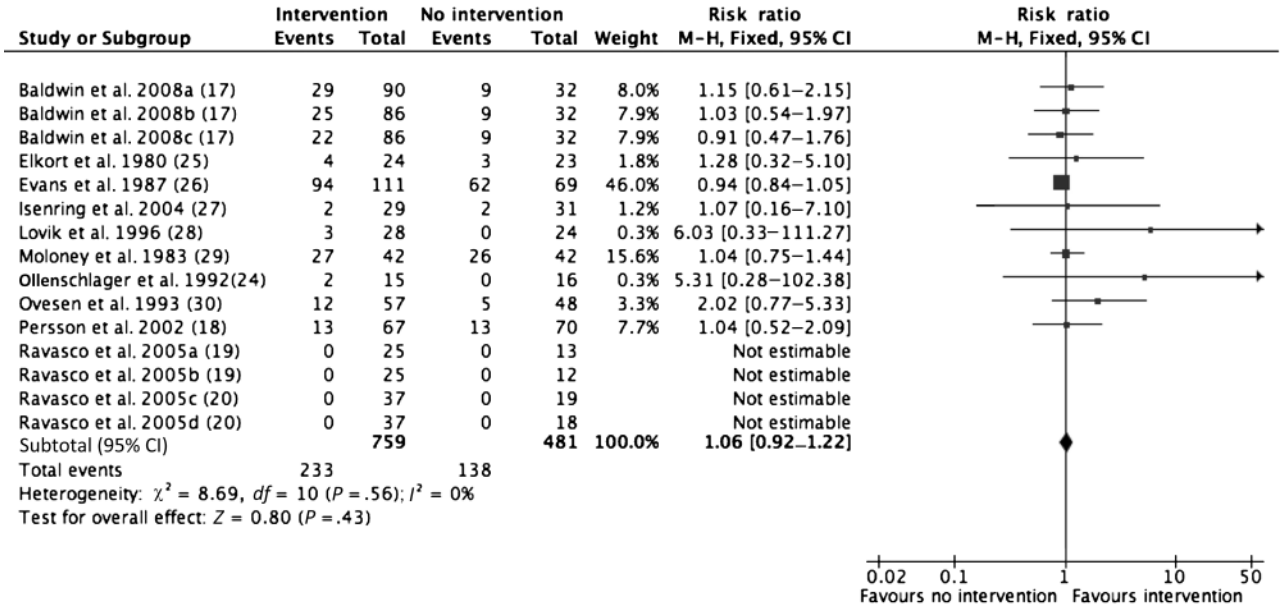

Figure 2. Oral nutritional interventions and mortality meta-analysis. The plot shows the raw data for mortality in each arm together with the total number of participants and risk ratio (**squares**) with 95% confidence intervals (CIs) (**horizontal bars**) analyzed using the Mantel–Haenszel (M-H) fixed effects method of meta-analysis. Data on mortality were extracted for the intervention and comparison groups for each study and combined to obtain a pooled estimate of the overall risk ratio for all studies (**diamond**). The I^2 statistic was used to test for the presence of heterogeneity across studies. The overall effect is given by the Z score. All tests were two-sided. Data were available for several intervention groups and one comparison group in the study by Baldwin et al. (17), and Ravasco et al. (19,20). The numbers in the comparison group have been divided equally between the intervention groups to avoid multiple analyses of data on the same participants. The comparison groups were as follows: Baldwin et al. 2008a, Ravasco et al. 2005a (in head and neck cancer patients), and Ravasco et al. 2005c (colorectal cancer patients)—advice only vs no advice and no supplement; Baldwin et al. 2008b, Ravasco et al. 2005b (head and neck cancer patients), and Ravasco et al. 2005d (colorectal cancer patients)—supplement only vs no supplement and no advice; Baldwin et al. 2008c—advice plus supplements vs no advice and no supplement.

substantially greater improvements in function scales, the symptoms of nausea and vomiting, and global QOL compared with other studies. The heterogeneity in the combined analyses of "physical functioning" and "pain" was because of data from the same two studies as well as one other (27), which found statistically significant improvements in physical functioning and reductions in pain compared with other studies. In the combined analyses of "role functioning," "dyspnea," "sleep disturbance," "loss of appetite," and "diarrhea," the heterogeneity was explained by the inclusion of some of the comparisons from two studies (19,20) (Table 3). The heterogeneity in the combined analysis of "fatigue" could not be explained by any study or combination of studies.

After removing the studies that accounted for the heterogeneity, meta-analysis indicated that oral nutritional interventions were associated with statistically significant improvements in the "emotional functioning" and "global QOL" function scales and the "dyspnea" and "loss of appetite" symptom scales (Table 3). However, changes in other scales did not reach statistical significance. The Forest plot for the global QOL results is shown in Figure 3. For each analysis, when the excluded studies were combined and the previously included studies were excluded, heterogeneity remained unacceptably high (eg, for physical functioning, I^2 = 96.0%).

Nutritional Intervention and Nutritional Status

Data on body weight from eight of 13 studies (12 comparisons) were available for meta-analysis. In one study (19), the effect size was inestimable because the mean and SD weight change for the control group was zero. Five of the eight studies reported data for a follow-up period of 6 months or less. The studies by Baldwin et al. (17) and Persson et al. (18) were of 12 and 24 months' duration, but data were reported at interim time points. Hence, the data from 6 weeks from the study by Baldwin et al. (17) and 6 months from the study by Persson et al. (18) have been included in this analysis. Data at interim time points were sought for the study by Elkort et al. (25) but were unavailable. Oral nutritional intervention was associated with statistically significant improvements to weight (mean difference in weight = 1.86 kg, 95% CI = 0.25 to 3.47, P = .02), but there was statistically significant heterogeneity (Figure 4, A). The heterogeneity was attributed to data from two studies (20,27). When these studies were removed from the analysis, there was no statistically significant overall association between oral nutritional interventions and weight gain (Figure 4, B). Four other studies assessed change in weight, but the data were not reported in a format that enabled entry into a meta-analysis (22–24,26). Nutritional intervention was associated with greater weight gain compared with no intervention in some groups of patients, but in patients with abdominal cancers in the study by Macia et al. (23) and those who had colorectal cancer in the study by Evans et al. (26) was associated with smaller improvements in weight vs the control groups.

Energy intake was measured in 10 of 13 studies. All studies reported an increase in energy intake associated with nutritional intervention. Only four studies (six comparisons) included data in a format that could be used for a meta-analysis (19,20,27,30). Groups receiving nutritional interventions had a statistically

Table 3. Meta-analysis of quality of life data, including all studies combined, and after removal of heterogeneity*

	All studies included						Excluding comparisons causing heterogeneity				
Scale on EORTC questionnaire	No. of comparisons	Mean difference (95% CI)	*P*†	I^2, %‡	$P_{heterogeneity}$†	Studies (and comparisons) accounting for heterogeneity§	No. of comparisons	Mean difference (95% CI)	*P*†	I^2, %‡	$P_{heterogeneity}$†
Function scales											
Physical functioning	9	40.1 (38.5 to 41.8)	<.001	98.0	<.001	19, 20 (all comparisons), 27	4	1.6 (−3.2 to 6.3)	.78	0.0	.39
Role functioning	9	12.7 (11.1 to 14.4)	<.001	99.0	<.001	19, 20 (comparisons a, b, and d)	6	1.4 (−1.8 to 4.6)	.40	8.0	.37
Cognitive function	9	16.0 (14.7 to 17.4)	<.001	98.0	<.001	19, 20 (all comparisons)	5	4.3 (−0.96 to 9.5)	.11	14.0	.33
Emotional function	9	35.4 (33.9 to 36.9)	<.001	98.0	<.001	19, 20 (all comparisons)	5	5.2 (0.8 to 9.7)	.02	0.0	.61
Social functioning	9	36.2 (34.4 to 37.9)	<.001	98.0	<.001	19, 20 (all comparisons)	5	3.3 (−3.1 to 9.5)	.31	0.0	.61
Global QOL	9	38.9 (37.6 to 40.2)	<.001	98.0	<.001	19, 20 (all comparisons)	5	5.5 (0.7 to 10.3)	.02	27.0	.24
Symptom scales											
Fatigue	9	−35.7 (−37.2 to −34.2)	<.001	99.0	<.001	NA	NA	NA	NA	NA	NA
Nausea and vomiting	9	−42.2 (−43.8 to −40.5)	<.001	99.0	<.001	19, 20 (all comparisons)	5	−0.4 (−4.6 to 3.8)	.85	0.0	.71
Pain	9	−48.5 (−50.1 to −46.8)	<.001	98.0	<.001	19, 20 (all comparisons), 27	4	0.02 (−7.6 to 7.7)	1.0	0.0	.39
Dyspnea	9	−7.5 (−8.1 to −6.8)	<.001	94.0	<.001	19, 20 (comparisons a, b, and c)	6	−2.9 (−4.0 to −1.8)	<.001	17.0	.31
Sleep disturbance	9	−24.8 (−26.5 to −23.3)	<.001	99.0	<.001	19, 20 (comparisons a and c)	7	1.08 (−1.22 to 3.39)	.36	0.0	.69
Loss of appetite	9	−19.3 (−20.6 to −18.0)	<.001	98.0	<.001	19, 20 (comparisons a and c)	7	−2.35 (−4.48 to −0.22)	.03	8.0	.36
Constipation	9	−0.3 (−0.7 to 0.1)	.01	0.0	.47	NA	NA	NA	NA	NA	NA
Diarrhea	9	−1.4 (−1.8 to −0.9)	<.001	99.0	<.001	19, 20 (comparisons c and d)	7	−0.01 (−0.49 to 0.47)	.97	0.0	1.0
Financial	9	−0.03 (−0.5 to 0.45)	.91	0.0	.91	NA	NA	NA	NA	NA	NA

* Raw data were collected using the European Organization for Research and Treatment of Cancer questionnaire and are presented as the mean difference in the change in score from the start of the trial to the end of follow-up for each scale with 95% confidence intervals (CIs). NA = not applicable; QOL = quality of life.

† *P* and $P_{heterogeneity}$ were calculated by a two-sided χ^2 test.

‡ The I^2 test statistic was used to test for the presence of heterogeneity across studies.

§ Data from the trial by Baldwin et al. (17) and Persson et al. (18) were presented at more than one time point; therefore, the data are from start of trial to end of 6 weeks and 6 months, respectively, were chosen for inclusion in the analyses to make them comparable with the time points in the other studies. Original data were obtained from the authors for the studies by Persson (18), Isenring (27), and Ravasco (19,20). The comparison groups were as follows: Baldwin et al. 2008a, Ravasco et al. 2005a (in head and neck cancer patients), and Ravasco et al. 2005c (colorectal cancer patients)—advice only vs no advice and no supplement; Baldwin et al. 2008b, Ravasco et al. 2005b (head and neck cancer patients), and Ravasco et al. 2005d (colorectal cancer patients)—supplement only vs no supplement and no advice; Baldwin et al. 2008c—advice plus supplements vs no advice and no supplement.

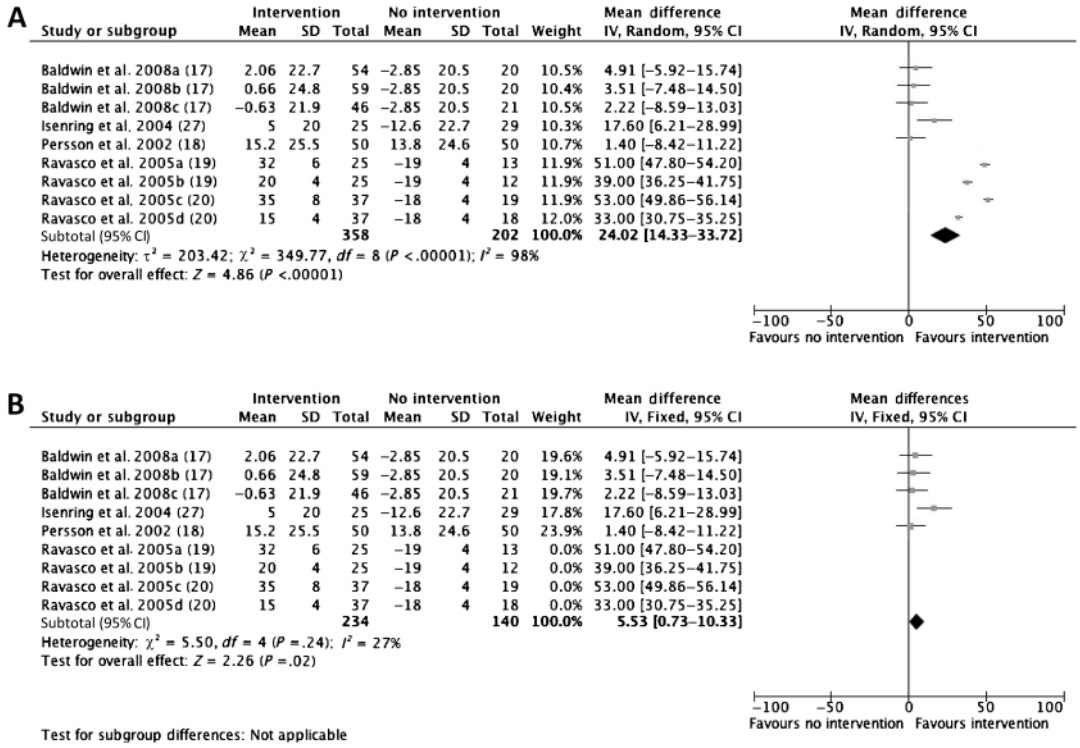

Figure 3. Oral nutritional intervention and global quality of life meta-analysis. Meta-analyses with **A**) all studies and **B**) studies accounting for heterogeneity removed were performed. The raw data are shown for the mean and standard deviation (SD) change in score on the European Organization for Research and Treatment of Cancer global quality of life scale from the beginning of the trial to the end of follow-up. The plot shows the mean difference (**squares**) and 95% confidence intervals (CIs) (**horizontal bars**) for nutritional intervention vs no intervention. The values were combined in a meta-analysis to obtain a pooled estimate of the effect from all studies (**diamond**). The meta-analysis is the inverse variance (IV) method, which uses the inverse of the variance of the effect estimate to weight studies. Larger studies with smaller standard errors are given more weight than smaller studies. Data from the trials by Baldwin et al. (17) and Persson et al. (18) are from the start of the trial to the end of 6 weeks and 6 months, respectively. Data were available for several intervention groups and one comparison group in the study by Baldwin et al. (17) and Ravasco et al. (19,20). The numbers in the comparison group have been divided equally between the intervention groups to avoid multiple analyses of data on the same participants. The comparison groups were as follows: Baldwin et al. 2008a, Ravasco et al. 2005a (in head and neck cancer patients), and Ravasco et al. 2005c (colorectal cancer patients)—advice only vs no advice and no supplement; Baldwin et al. 2008b, Ravasco et al. 2005b (head and neck cancer patients), and Ravasco et al. 2005d (colorectal cancer patients)—supplement only vs no supplement and no advice; Baldwin et al. 2008c—advice plus supplements vs no advice and no supplement. The I^2 statistic was used to test for the presence of heterogeneity across studies. The overall effect is given by the Z score. In (**A**), the heterogeneity was high and therefore a random effects analysis is presented; in (**B**), the heterogeneity is low and therefore a fixed effects analysis was done. All statistical tests were two-sided.

significantly greater energy intake than groups receiving routine care: The mean change in energy intake from baseline to the end of the intervention period (assessed by a random effects model) was 432 kcal/d (95% CI = 172 to 693; $P = .001$). However, heterogeneity was high ($I^2 = 97.0\%$, $P < .001$) and could not be reduced by removing any one study. Removal of data from two studies (four comparisons) (19,20) reduced the heterogeneity to 0% but only left data from two studies (159 participants) in the analysis, and there was no statistically significant difference between groups receiving intervention vs routine care. Although consideration was given to undertaking subgroup analyses, there were insufficient data on any of the outcomes.

Discussion

The primary aim of this systematic review and meta-analysis was to examine the efficacy of oral nutritional interventions in patients with cancer who were malnourished or judged to be at risk of becoming malnourished on survival, QOL, and nutritional indices. The findings suggest that oral nutritional interventions have no effect on survival and that the effect on body weight and energy intake is inconsistent but that statistically significant improvements in some aspects of QOL may be achieved. This review identified few studies, some of which were of poor quality; therefore, more research is needed to characterize the benefits of oral nutritional support in patients with cancer.

There are European guidelines on the nutritional management of malnourished patients with cancer (6), guidelines from the American Dietetic Association (32), the American Society for Parenteral and Enteral Nutrition (8), and practice guidelines and recommendations from the Dietitians Association of Australia (7) that all support the use of nutritional intervention in the management of malnourished patients with cancer or those judged to be at risk of malnutrition. However, these guidelines and recommendations rely heavily on consensus statements and good practice points in the absence of good quality RCT evidence. There have been two previous systematic reviews that have examined the efficacy of nutritional intervention in cancer patients (11,12). The

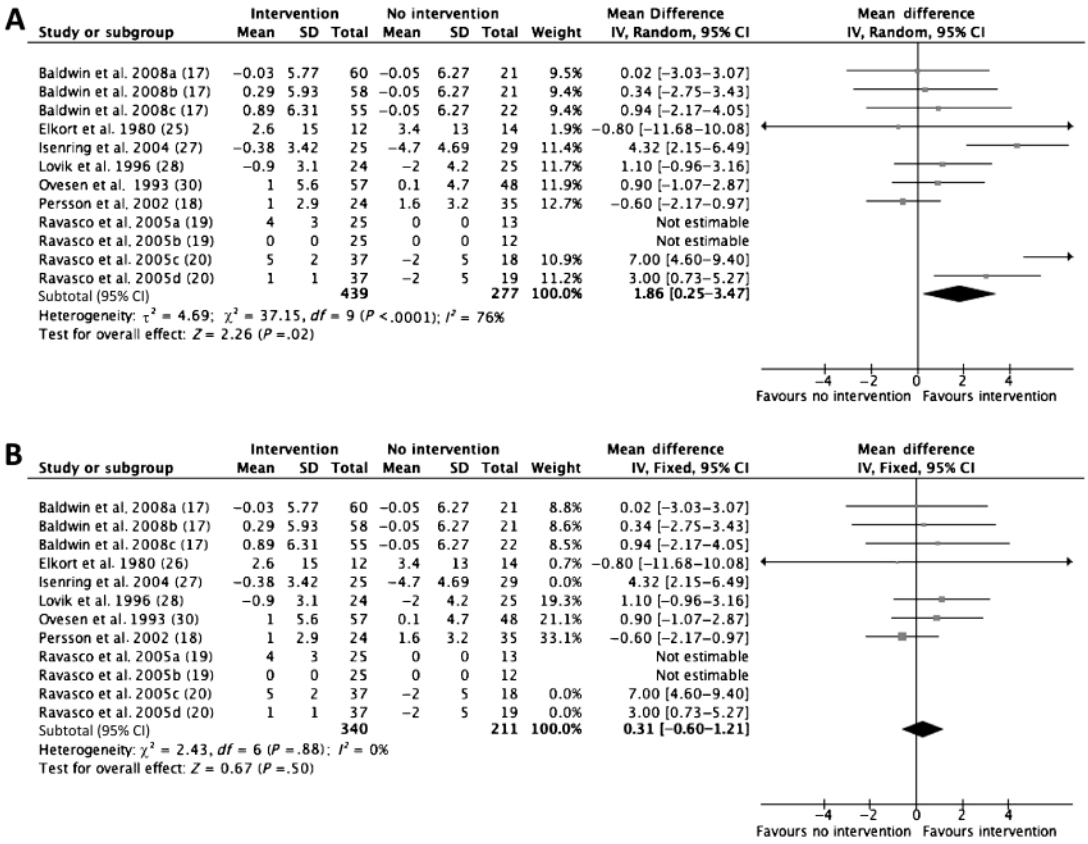

Figure 4. Oral nutritional interventions and weight gain meta-analysis. Meta-analyses of **A**) all studies and **B**) the studies accounting for heterogeneity removed. Raw data are shown for the mean weight change (kg) and the standard deviation (SD) from the beginning of the trial to the end of follow-up. The plot shows the mean difference (**squares**) and 95% confidence intervals (**horizontal bars**) for nutritional intervention vs no intervention. The values were combined in a meta-analysis to obtain a pooled estimate of the effect all studies (**diamond**). The meta-analysis is the inverse variance (IV) method, which uses the inverse of the variance of the effect estimate to weight studies. Larger studies with smaller standard errors are given more weight than smaller studies. Data from the trials by Baldwin et al. (17) and Persson et al. (18) are from the start of the trial to the end of 6 weeks and 6 months, respectively. Data were available for several intervention groups and one comparison group in the study by Baldwin et al. (17) and Ravasco et al. (19,20). The numbers in the comparison group have been divided equally between the intervention groups to avoid multiple analyses of data on the same participants. The comparison groups were as follows: Baldwin et al. 2008a, Ravasco et al. 2005a (in head and neck cancer patients), and Ravasco et al. 2005c (colorectal cancer patients)—advice only vs no advice and no supplement; Baldwin et al. 2008b, Ravasco et al. 2005b (head and neck cancer patients) and Ravasco et al. 2005d (colorectal cancer patients)—supplement only vs no supplement and no advice; Baldwin et al. 2008c—advice plus supplements vs no advice and no supplement. The I^2 statistic was used to test for the presence of heterogeneity across studies. The overall effect is given by the Z score. In (**A**), the heterogeneity was high and therefore a random effects analysis is presented; in (B), the heterogeneity is low and therefore a fixed effects analysis is shown. All tests were two-sided.

review by Brown (11) identified seven RCTs and combined the results into a narrative summary. Elia et al. (12) identified four studies that examined clinical outcomes and three studies that reported on nutritional status. The findings were consistent with the findings of this study in demonstrating no differences in survival or weight following nutritional intervention. The present review represents a larger group of studies and suggests that nutritional interventions are associated with improvements in some aspects of QOL. The heterogeneity among studies means that the magnitude of the effect cannot be predicted accurately. In addition, the findings suggest that some patients showed considerably greater responses to intervention in terms of weight and QOL, and it has not been possible to define the characteristics of this patient group; therefore, caution is needed in extrapolating data from these populations to all patients with cancer. A recent review and meta-analysis by Halfdanarson et al. (13) of the effects of nutritional intervention on global QOL showed no benefits of nutritional intervention. Our review has obtained original data, included more studies, examined the effects of more dimensions of QOL, and suggests that there may be some beneficial effects of oral nutritional interventions.

Although our meta-analysis indicates that oral nutritional interventions are associated with statistically significant benefits to some aspects of QOL, it is not clear whether these are clinically meaningful changes to the patient. King (33) examined 14 studies that assessed QOL in patients with cancer using the EORTC and derived values that represented small and large differences in scores for some of the scales. The mean difference in the emotional function scale in our study was 5.2, which is closer to the value for a large difference than a small difference (7 and 2, respectively) proposed by King (33). On the other hand, the mean difference found for global QOL was 5.5, which is closer to the proposed value for a small difference than the proposed value for a large difference, (2 and 16, respectively). Overall, these data

suggest that the benefits to QOL that may be achieved with simple oral nutritional interventions are limited but may be clinically meaningful. In addition, the QOL data used in our analyses were all collected by assessors who were not blinded to group allocation. Lack of blinding in assessment of this outcome may have resulted in some bias.

This analysis has several limitations that mainly relate to the considerable clinical and statistical heterogeneity in this group of studies. Three studies accounted for most of the heterogeneity (19,20,27) and were similar in that they all included patients receiving radiotherapy, although the stage of disease and treatment intent of radiotherapy appear to vary within and between studies. It has not been possible to identify the factors that account for the differences in effect size found between studies despite considering the site and stage of disease, treatment modality and treatment intent, nutritional status, and performance status. It is not possible, therefore, to explain the differences found between studies, but it is likely that the factors outlined above and indeed variations in the duration, nature, and intensity of the nutritional intervention may account for differences in effects in patients. These factors merit further study in future trials. It is also important to recognize that the data on weight, energy intake, and many aspects of QOL reported in the studies accounting for most of the heterogeneity in this analysis suggested substantial benefit. The studies were conducted in patients receiving radiotherapy with and without chemotherapy, and these observations should be confirmed in follow-up studies.

Another limitation of this analysis is the combining of studies in patients heterogeneous for cancer site and stage. The justification for this combining of studies is that dietetic intervention is pragmatic and always aims to increase nutrient intake, although this may be achieved by a variety of means. The advice given does not vary by the clinical presentation or treatment regimen of the patient when the underlying nutritional problem is malnutrition or the patient is considered to be at nutritional risk. This background underlies the assumptions made in choosing the method of meta-analysis. The fixed effects meta-analysis assumed that the true effect of the intervention (in both magnitude and direction) was the same for every study and that any variation between studies was because of chance (14). For the purposes of the analyses presented here, it was assumed that dietetic intervention would have the same effect on the outcomes of interest in all malnourished cancer patients or those judged to be at risk of malnutrition.

When there was high heterogeneity in the results of different trials, a random effects model was used, which relied on the assumption that the effects being estimated across the studies were not identical but followed a distribution, which was random (14). When heterogeneity was still present with a random effects analysis, attempts were made to account for and explain the heterogeneity. This approach presents a simplistic version of the process. There are other factors that determine the choice of model in a meta-analysis, and a random effects analysis is also a reasonable choice if the intention is to generalize beyond the results. Conversely, a fixed effects analysis usually pertains only to the studies presented. Despite all these considerations, it was not always possible to account for heterogeneity in the presented analyses, and we recognize that there could be factors, perhaps not immediately apparent, that are accounting for variations in the data and that the identified studies should possibly not have been combined.

Another factor, which may have accounted for the heterogeneity between studies, is that the length and the type of dietetic intervention provided differed. Some of the included studies provided only food-based interventions, whereas others provided combinations of food and nutritional supplements. In some studies, the comparison group received no intervention, whereas usual care included the possibility of referral to a dietitian in other studies. The intensity of interventions, assessed by the amount of support following the start of the intervention, also varied between studies, with some providing support weekly for the duration of treatment (17,19,20) and others providing support just eight times within 2 years (18). Differences may also have arisen as a result of variations in the experience, training, and approach of the dietitians. The use of standardized protocols would reduce this aspect of heterogeneity (32). In addition, we found high heterogeneity among the analyses of energy intake; and the reported changes in energy intake did not always correspond with the expected changes in weight. Assessment of energy intake relied on a variety of methods, all of which are associated with weaknesses, in particular, differential misreporting.

The quality of evidence in this review was at best of low to moderate quality and is another limitation of this analysis. The main issue was that very few studies were adequately blinded and most were small and inadequately powered. Additional difficulties related to study design. It is difficult to design a placebo for dietary advice, and it is impossible to prevent some patients in the control arm from seeking other sources of dietary advice and obtaining supplements, which are freely available. The search strategy used for this review was comprehensive, and robust processes were used in the identification and selection of the included studies. Nevertheless, there were few studies identified for this review, and the possibility of publication bias cannot be ruled out. Because of the small number of studies in the analyses presented, it has not been possible to make reliable estimates of bias by using funnel plots.

The final limitation of this analysis relates to multiplicity. In systematic reviews, multiple comparisons can arise from the inclusion of data on multiple outcomes, the use of multiple intervention groups, and the existence of multiple time points within trials (34). Appropriate adjustments have been made within the analyses of studies that compared several intervention groups with one control group, as explained in the "Methods." For studies reporting data at more than one time point, only one set of data have been included in this review. However, there remain difficulties relating to patient attrition and the representativeness of the included data. There is no satisfactory solution to the problem of multiple outcomes (14,33). Hence, the possibility of type I error as a result of multiplicity cannot be ruled out, and the results pertaining to different aspects of QOL in particular should perhaps be regarded as hypothesis generating rather than hypothesis testing.

Despite the weaknesses in the meta-analyses, the data suggest that there are differences in the way patients with cancer respond to oral nutritional interventions. Studies are required to determine the factors, which contribute to the effectiveness of nutritional

interventions in patients with cancer who are malnourished or at risk of malnutrition, to strengthen the evidence base for nutritional management in this patient group.

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