Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis

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CRD summary
This review found that oral nutritional interventions may be effective in increasing energy intake and improving some aspects of quality of life in patients with cancer and malnutrition, but did not appear to improve survival. Substantial variation in the results across included trials means the results should be interpreted with caution and the reliability of the authors’ conclusion is unclear.

Authors’ objectives
To evaluate the effectiveness of oral nutritional interventions in patients with cancer and malnutrition or at risk of malnutrition.

Searching
MEDLINE, EMBASE, CINAHL, CANCERLIT, AMED and Cochrane Central Register of Controlled Trials were searched up to February 2010; search terms were reported. Bibliographies of retrieved studies were checked. Authors of the included studies were also contacted to identify additional studies. Experts in clinical nutrition, manufacturers of oral nutritional supplements and all registered dieticians in the United Kingdom were also contacted for additional information. There were no language restrictions.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) or quasi-RCTs that evaluated oral nutritional interventions in adult patients who were receiving active or palliative treatment for cancer and were clearly malnourished or at risk of malnutrition. Oral nutrition interventions could include dietary advice, the provision of supplements, and advice and supplements administered together.

Dietary advice was defined as instruction to modify food intake given with the aim of improving nutritional intake and in the trials comprised advice to increase food intake and nutritional counselling. Oral nutritional supplements were defined as food products given to manage disease-related malnutrition. The comparators were usual care with no dietary advice or provision of nutritional supplements. The primary outcome measures were mortality and quality of life. Secondary outcome measures were weight changes and energy intake.

The included patients presented with a range of cancers including gastrointestinal cancers, gynaecological cancers and cancers of bladder, lung, head and neck, and breast. The nutritional status of the patients at baseline was established using amount of weight loss within particular time periods or by Ottery’s Patient-Generated Subjective Global Assessment (where stated). Quality of life was measured using the European Organisation for Research and Treatment of Cancer (EORTC) cancer-specific questionnaire with five functional scales and and eight symptom scales. The interventions ranged in duration from three weeks to two years.

One reviewer performed the title and abstract screening for study selection, two reviewers assessed potentially relevant studies.

Assessment of study quality
Two reviewers assessed methodological quality of included trials using criteria from the Cochrane Collaboration handbook and criteria described by Schulz et al. Criteria assessed included randomisation, allocation concealment, use of blinding, baseline characteristics of patients, the recording of losses to follow-up and reporting of pre-specified outcomes.

Data extraction
Data were extracted by two independent reviewers to calculate relative risks (RR) for the binary outcome (mortality) and mean differences for continuous outcomes (quality of life, weight and energy intake), with 95% confidence.
intervals (CI) for the estimates. Study authors were contacted for missing information.

Methods of synthesis
Pooled relative risks, with 95% confidence intervals, for the estimates were calculated using a Mantel-Haenszel fixed effects model. Weighted mean differences (WMD) and 95% confidence intervals for the summary estimates were calculated using an inverse variance model, where fixed-effect models were used. Statistical heterogeneity was evaluated using $X^2$ and $I^2$. Where heterogeneity was statistically significant, the results were combined using random-effects models. Subgroup analyses were conducted to assess the effect of the removal of some studies on the results.

Results of the review
Thirteen RCTs (1,414 patients) were included in the review. Sample sizes ranged from 31 to 358 patients. Randomisation and allocation concealment was adequately reported in eight trials. One trial reported blinding of outcome assessors. Baseline characteristics were similar between intervention and control groups in eight trials. The length of follow-up duration ranged from three weeks to three years.

Statistically significant benefits were observed with nutritional interventions in weight gain (WMD 1.86kg, 95% CI 0.25 to 3.47; $I^2=76%$; 12 comparisons; 716 patients) and energy intake (432kcal/day, 95% CI 172 to 693; $I^2=97%$; six comparisons). After removal of two heterogeneous trials, the results for these outcomes were no longer statistically significant.

Significant benefits were also observed across all function scales and seven of eight symptom scales and global quality of life (nine comparisons for each scale). Heterogeneity ranged from 94% to 99% for all quality of life outcomes except for constipation and financial scales. When studies causing heterogeneity were removed in the subgroup analyses, oral nutritional interventions were associated with statistically significant improvements in emotional functioning and global quality of life scales, and dyspnoea (shortness of breath) and loss of appetite symptom scales.

There were no benefits observed for survival between patients who received oral nutrition interventions and those who received usual care.

Authors' conclusions
Oral nutrition interventions were effective for increasing nutritional intake and improving some aspects of quality of life, but did not appear to improve survival in patients with cancer who were malnourished or at risk of malnutrition.

CRD commentary
The review addressed a clear question. Inclusion criteria were defined. A range of appropriate databases were searched for relevant studies. There were no language restrictions applied to the search and some attempts were made by the reviewers to identify unpublished studies. Steps were taken at each stage of the review process to minimise errors and biases.

Methodological quality was assessed; the included trials were found to be of low to moderate quality. There was substantial clinical heterogeneity in the trials in cancer type and stage, interventions, length of study and follow-up, which meant that pooling of some of the results may not have been appropriate. Statistical heterogeneity was observed across the results. The authors acknowledged the limitations of the review including clinical and statistical heterogeneity across the trials, and the uncertain clinical significance of the results. Although the authors concluded that oral nutritional interventions were effective for increasing nutritional intake, the removal from the results of two heterogeneous trials showed no statistically significant differences between intervention and comparator groups.

Substantial variation in the results across the included trials means that the reliability of the authors' conclusion is unclear.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that studies were required to determine the components of nutritional interventions which contribute to their effectiveness in patients with cancer and malnutrition to strengthen the evidence base for nutritional and dietary management during cancer treatment.
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