Clinical Nutrition (2005) **24**, 998–1004

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Clinical Nutrition

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ORIGINAL ARTICLE

# Compliance with nutrition prescription improves outcomes in patients with unresectable pancreatic cancer

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Received 5 January 2005; accepted 22 July 2005

**KEYWORDS**
Nutrition prescription;
Nutrition intervention;
Pancreatic cancer;
Quality of life

**Summary**
*Background & Aims:* There are few well-designed studies evaluating the effect of oral nutrition supplements in patients with cancer cachexia. The aim of this study, in a posthoc analysis, was to examine the effect of dietary compliance on intake and body composition in patients with unresectable pancreatic cancer.
*Methods:* Two hundred patients were randomised to receive 2 cans/day of a protein and energy dense, oral nutrition supplement $\pm$n-3 fatty acids in an international, multi-centre randomised trial over 8 weeks. Dietary compliance was defined a priori as consumption of a minimum of 1.5 cans/day of either supplement. Body composition, dietary intake and quality of life were measured at baseline, 4 and 8 weeks.
*Results:* On average, there were significant differences in energy intake (501 kcal), protein intake (25.4 g) and weight (1.7 kg) between patients who were compliant with the nutrition prescription compared to noncompliant patients controlling for n-3 fatty acid randomisation, baseline weight and quality of life. Over the 8-week period, there was significant improvement in weight only. There was no significant difference in the energy intake from meals of the total group over the 8 weeks.

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0261-5614/$ - see front matter 
doi:10.1016/j.clnu.2005.07.002

*Conclusions:* Compliance with the prescription of 1.5 cans of a protein and energy dense, oral nutrition supplement ±n-3 fatty acids improved nutrition related outcomes in untreated pancreatic cancer patients. This level of supplement intake does not inhibit meal intake.


## Introduction

Surgically unresectable pancreatic cancer is an aggressive and lethal disease. Fewer than 20% of patients survive one year after diagnosis.[1] As the disease progresses, many patients experience increasingly severe pain, nausea, vomiting, anorexia, weight loss and weakness. Their care focuses on relief of symptoms to optimise quality of life.

Although there is extensive literature regarding nutritional advice for patients with cancer, there are few well-designed studies evaluating the effect of oral nutrition supplements in these patients.[2] Stratton and Elia[3] reviewed 11 randomised controlled trials of oral nutrition supplements in patients with cancer and concluded that this approach generally failed to improve outcomes such as body composition, functional capacity or quality of life. A key aspect of the success or otherwise of nutrition intervention studies is the compliance of the patients with the nutrition prescription.[2]

The intent to treat analysis of an international randomised double blind trial with a protein and energy dense, oral nutrition supplement ±n-3 fatty acids in untreated pancreatic cancer patients has been previously reported.[4] In this paper, a posthoc analysis of the effect of dietary compliance with 1.5 cans/day of either the experimental or placebo oral nutrition supplement on body composition, dietary intake and quality of life in the same patient population are presented.

## Methods

Two hundred patients with unresectable adenocarcinoma of the pancreas were enrolled in an international, multi-centre, randomised, double blind study. Inclusion criteria included weight loss of greater than 5% in the previous 6 months, life expectancy of greater than 2 months and a Karnofsky performance score of 60 or more. Exclusion criteria included chemotherapy, radiotherapy or surgical treatment in the previous month, consumption of fish oil capsules or medication such as steroids that could affect metabolism. Patients were asked to consume two cans per day of either a protein and energy dense, n-3 fatty acid (1.1 g EPA) oral nutritional supplement ($n = 95$) or an isocaloric, isonitrogenous control supplement without n-3 fatty acids ($n = 105$). Each can provided 310 kcal and 16 g protein. Dietary intake, weight, lean body mass and quality of life were assessed at baseline, 4 and 8 weeks. The a priori definition of dietary compliance was average consumption over a 4-week period of at least 1.5 cans of either oral nutrition supplement per day (465 kcal and 24 g protein). This was determined from a daily record completed by the patient of the number of cans consumed. Dietary intake was assessed by a food diary completed over 3 consecutive days consisting of two week days and one day of the weekend at baseline, 4 and 8 weeks. Weight was measured to the nearest 0.1 kg using a spring balance scale (Tanita Model 1618, Tanita, Uxbridge, Middlesex, UK). A Xitron multifrequency bioelectrical impedance analyser (Xitron Technologies, San Diego, CA, USA) measured resistance at 5 and 200 kHz. Total body water was estimated using the equation developed by Hannan et al.[5] and lean body mass was determined assuming a hydration constant of 0.732.[6] Quality of life was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQC30).[7]

Statistical analysis was carried out using SPSS Version 11, 2001 (SPSS Inc., Chicago, IL, USA) and SUDAAN version 7.5.2A.[8] All continuous variables were normally distributed. Repeated measures regression models were fitted to consider the effects of compliance with 1.5 cans of either supplement on a series of nutritional outcomes—energy and protein intake, weight, lean body mass and quality of life. As there were substantial (>10%) missing data due to patient attrition over the 8 weeks, a generalised estimating equations approach was used to permit the inclusion of data of patients with incomplete data records. Hence the analyses were based on 200 patients who contributed between one and three time points of information for a total of 399–426 time points depending on the outcome variable being analysed. The posthoc analysis reported here considered the actual dose of either supplement taken. As

there were clinically important differences in quality of life and weight between compliant and noncompliant groups at baseline, outcome variables were adjusted for baseline quality of life and weight. For each of the outcome variables, the interaction between compliance and time and compliance and EPA randomisation were considered. As these interactions were not significant for the outcome variables examined, main effect means are reported.

Statistical significance was reported at the conventional $P<0.05$ level (two-tailed). Due to the posthoc nature of this analysis and resultant inability to rely on power of each association, interpretation of differences was not solely based on statistical testing but also interpreted in light of clinically important differences over 8 weeks. These were defined a priori to be 500 kcal for energy intake, 10 g for protein intake, 1 kg for weight, 0.5 kg for lean body mass, and 5 units for quality of life as determined by the EORTC-QLQC30 questionnaire. The multidisciplinary ethics committee of each of the hospitals approved the study and informed written consent was obtained from all participants.

## Results

Of the 200 patients enrolled in the trial, 185 were assessed at baseline, 148 at 4 weeks and 110 at 8 weeks. Baseline characteristics of compliant and noncompliant patient groups are shown in Table 1. There was no significant difference in stage of disease between complaint and noncompliant groups ($P = 0.309$).

Table 2 shows the effect of compliance with a minimum of 1.5 cans per day of the protein and energy dense, oral nutrition supplement $\pm$n-3 fatty acids on total (meal and supplement) protein and energy intake, weight, lean body mass and quality of life. For each variable, time specific estimates as well as main effect means (average over time) are presented. Apart from weight, these differences were similar irrespective of time point being considered. Hence the following summary emphasises the results averaged over time rather than the time specific estimates, which are presented for completeness. With the exception of lean body mass ($P = 0.555$), on average there were statistically significant ($P<0.050$) or near-significant ($P = 0.075$) differences in all other outcomes between compliant and noncompliant patients (Table 2). There were significant differences in total energy intake by 501 (SEM$\pm$80) kcal/day (Wald $F_1 = 39.1$, $P<0.0001$) and total protein intake by 25.4 (SEM$\pm$3.5) g/day (Wald $F_1 = 53.0$, $P<0.0001$) between patients who were compliant with the nutrition prescription compared to noncompliant patients controlling for baseline quality of life, body weight and EPA randomisation. There was no significant difference in the mean energy intake from meals of the total group at baseline, week 4 and 8 which was 1513 (SEM$\pm$43), 1440 (SEM$\pm$48) and 1441 (SEM$\pm$49) kcal/day, respectively (Wald $F_2 = 0.96$, $P = 0.38$).

Prior to enrolment in the study, patients were losing weight at a rate of 3.3 kg/month. On average, there was a significant difference in body weight by a mean of 1.7 (SEM$\pm$0.4) kg (Wald $F_1 = 19.1$, $P<0.0001$) in patients compliant with the prescription relative to the noncompliant group. Over the 8-week period, patients in the compliant group increased body weight by 0.5 kg whereas the noncompliant group decreased weight by 0.7 kg ($P = 0.052$) overall. There was no difference in lean body mass between the compliant and noncompliant groups and this did not change over the 8-week study period.

Although there was no significant difference in baseline plasma phospholipids EPA levels between

**Table 1** Baseline characteristics (mean$\pm$SEM) of 185 untreated pancreatic cancer patients based on compliance with the nutrition prescription of consumption of a minimum of 1.5 cans/day of an energy and protein dense oral nutrition supplement$\pm$EPA.

| Variable | Compliant ($n = 87$) | Noncompliant ($n = 98$) |
|---|---|---|
| Age (years) | 66.8$\pm$1.0 | 68.3$\pm$1.1 |
| Weight (kg) | 62.9$\pm$1.2 | 59.3$\pm$1.3 |
| BMI (kg/m$^2$) | 22.4$\pm$0.4 | 21.2$\pm$ 0.4 |
| EORTC QLQC30 Global Quality of Life score | 59.6$\pm$2.0 | 53.2$\pm$2.1 |
| Karnofsky performance score | 77.2$\pm$1.1 | 72.6$\pm$1.2 |

*Note*: significance testing was not performed due to posthoc nature of analysis, balance of characteristics was based on clinical assessment of the importance of the magnitude of difference.

**Table 2** The effect of compliance on protein and energy intake, weight, lean body mass and quality of life in 185 untreated pancreatic cancer patients over 8 weeks and averaged over time.

| | Time | Compliant | | Noncompliant | | Level of significance |
|---|---|---|---|---|---|---|
| Total protein intake (g/day) | Baseline | 62.3 | (1.7) | 36.6 | (4.7) | 0.844* |
| | 4 weeks | 88.3 | (2.6) | 62.5 | (3.3) | |
| | 8 weeks | 87.2 | (2.7) | 62.4 | (3.5) | |
| | *Average* | 77.0 | (1.7) | 51.6 | (3.1) | <0.001† |
| Total protein intake (g/kg/day) | Baseline | 1.04 | (0.03) | 0.67 | (0.08) | 0.758 |
| | 4 weeks | 1.42 | (0.05) | 1.05 | (0.06) | |
| | 8 weeks | 1.43 | (0.04) | 1.08 | (0.06) | |
| | *Average* | 1.26 | **(0.03)** | 0.90 | **(0.05)** | <0.001 |
| Total energy intake (kcal/day) | Baseline | 1576 | (36) | 1058 | (112) | 0.729 |
| | 4 weeks | 2054 | (60) | 1537 | (79) | |
| | 8 weeks | 2037 | (63) | 1558 | (74) | |
| | *Average* | 1845 | **(37)** | 1344 | **(72)** | <0.001 |
| Total energy intake (kcal/kg/day) | Baseline | 26.17 | (0.61) | 18.13 | (1.82) | 0.350 |
| | 4 weeks | 33.65 | (0.96) | 25.61 | (1.34) | |
| | 8 weeks | 33.11 | (1.10) | 26.96 | (1.28) | |
| | *Average* | 30.29 | **(0.61)** | 23.04 | **(1.19)** | <0.001 |
| Weight (kg) | Baseline | 61.5 | (0.03) | 60.3 | (0.37) | 0.052 |
| | 4 weeks | 61.9 | (0.24) | 60.7 | (0.29) | |
| | 8 weeks | 62.0 | (0.42) | 59.6 | (0.51) | |
| | *Average* | 61.8 | **(0.2)** | 60.0 | **(0.3)** | <0.001 |
| Lean body mass | Baseline | 43.6 | (0.3) | 42.6 | (1.0) | 0.181 |
| | 4 weeks | 44.8 | (0.5) | 43.7 | (0.7) | |
| | 8 weeks | 44.0 | (0.7) | 44.4 | (0.7) | |
| | *Average* | 44.1 | **(0.4)** | 43.6 | **(0.7)** | 0.556 |
| Quality of Life (EORTC-QLQ-C30) | Baseline | 55.0 | (1.4) | 50.9 | (3.4) | 0.894 |
| | 4 weeks | 57.3 | (2.0) | 53.2 | (2.2) | |
| | 8 weeks | 59.1 | (2.2) | 54.4 | (2.8) | |
| | *Average* | 56.8 | **(1.3)** | 52.4 | (2.2) | 0.075 |

Means (SEM), adjusted for baseline weight and quality of life, and EPA randomisation group.
*Significance of interaction effect of compliance over time.
†Significance of main effect of compliance.

the complaint and noncompliant groups (0.9% and 1.0%; $P = 0.939$), there were significant differences in plasma EPA levels between the groups over time (week 4—2.9% and 1.6%; $P = 0.000$; week 8—2.7% and 1.6%; $P = 0.002$).

## Discussion

The aim of this study was to assess the effect of compliance with the nutrition prescription of 1.5 cans of a protein and energy dense, oral nutrition supplement irrespective of inclusion of n-3 fatty acids on patient outcomes in terms of dietary intake, body composition and quality of life. Although there was an increase in dietary intake in both groups, patients who were compliant with the prescription on average had higher total protein and energy intake both in absolute terms and per kg body weight. An increase in protein and energy intake is consistent with other studies in patients with cancer who were provided with oral nutrition supplements.[9–11]

One of the goals of nutrition intervention for patients with cancer is to minimise weight loss and prevent or correct nutritional deficiencies.[12] In this study, patients who were compliant with the nutrition prescription increased body weight by 0.5 kg compared to patients who were not

compliant who decreased weight by 0.7 kg. This is in contrast to the findings of Oveson et al.[9] who found that despite an increase in protein and energy intake patients did not gain weight. This study does demonstrate however that an adequate amount of protein and energy is required to achieve positive changes in terms of weight. Even though protein and energy increased over the 8 weeks in the noncompliant group, the level of intake achieved was inadequate for weight maintenance.[12] The rate of weight loss experienced by patients with pancreatic cancer is dramatic over short periods of time. DeWys et al.[13] found that in patients with pancreatic cancer, 54% had lost $>5\%$ of their body weight in the previous 2 months, 28% between 5% and 10% weight loss and 26% had experienced $>10\%$ weight loss. Prior to enrolment in this study, patients were losing weight at a rate of 3.3 kg/month. Compliance with the nutrition prescription attenuated this weight loss and resulted in significant weight gain. The gain in weight cannot be attributed to compliance alone as there were significant increases in blood phospholipid EPA levels over the 8-week period in the compliant group. Although there was no significant interaction between compliance and EPA randomisation, Fearon et al.[4] have reported that some patients in the control group had high levels of plasma phospholipid EPA consistent with supplementation.

The effect of oral nutrition supplements on changes in body composition has not been well studied.[3] Several trials with synthetic progesterone agents have demonstrated a beneficial influence on weight, however this is largely due to an increase in fat mass.[14–16] Restoration of lean body mass is essential to improve physical activity and quality of life. In an open trial of 20 patients with untreated pancreatic cancer receiving a protein and energy dense, oral nutrition supplement with n-3 fatty acids, Barber et al.[17] showed an increase in lean body mass of 1.9 kg over 7 weeks with a median intake of 1.9 cans/day. In this study, increases in lean body mass were observed in both groups over the 8 weeks, although the gain was not significant. Bioelectrical impedance analysis was used to estimate total body water from which lean body mass was determined. A key assumption in estimating lean body mass is that of a constant hydration factor. As oedema is a feature of end stage pancreatic cancer, this assumption may have been violated. As the noncompliant group did not achieve the intake required for improvements in body composition, it is likely that the gain attributed to lean body mass in this group may be an increase in total body water.

Two key aspects contributing to the success of nutrition intervention are the nutrition prescription and the implementation of the nutrition care.[2] In this study the prescription and implementation of the nutrition care were standardised. The prescription of 1.5 cans or more per day of supplement was achieved by 51.4% of patients at 4 weeks and 53.6% of patients at 8 weeks of the study. Splett[18] described a model of nutrition intervention depicting a cascade of events that are necessary to achieve positive outcomes. The stages of this model include appropriate access to necessary care, quality nutrition care, change in intermediate outcomes and clinical, cost and patient outcomes. If there is a blockage at any stage of the cascade, such as inadequate dietary intake, then improved outcomes are unlikely to be achieved. Patients achieving a minimum of 1.5 cans of supplement per day had a clinically significant increase in total protein and energy intake and achieved a positive benefit in terms of body weight. Noncompliant patients did not increase intake adequately to demonstrate these positive outcomes.

To enhance compliance, several key strategies in relation to implementation of the nutrition care were used in this study. Weekly contact with patients by either face-to-face interview or telephone contact was maintained for the 8-week study. An experienced clinician assisted patients with dietary advice ensuring that issues related to oral intake, supplement consumption and nutrition impact symptoms were addressed in a timely manner. Patients were encouraged to consider the supplement as an essential component of their treatment, e.g. food as medicine.

A perception by some health professionals and patients is that consumption of oral nutrition supplements has a negative impact on spontaneous food consumption.[3] In this study, there was no significant change is spontaneous food consumption over the 8-week study period. These findings are in agreement with other studies in patients with cancer that have found that habitual food intake did not decline during supplementation.[11,19,20]

A limitation of the present study was that assessment of dietary intake was made over 3 days once per month. These measurements may not have provided an accurate representation of the patients' habitual dietary intake as in patients with cancer, intake may vary greatly from day to day due to presence of nutrition impact symptoms such as nausea, vomiting, pain, etc. This was evidenced by the variation in supplement intake on a daily basis. Although the 3-day food record does have limitations, the burden of completing daily food intake records in terminal cancer patients was not

considered warranted. The validity of the supplement intake records was checked with supplement cans used at each visit and cross-referenced to the food diaries. A further potential limitation relates to the degree of illness of the patients and the potential for this to effect compliance. There were clinically important differences in baseline quality of life between the compliant and noncompliant groups and hence outcome variables were adjusted for baseline quality of life.

The results of this study need to be interpreted with caution, as this was a posthoc analysis. However there were positive outcomes in terms of body weight in those patients who were compliant with the nutrition prescription of 1.5 cans/day of either of the supplements. The large sample size, homogeneous group of patients and the level of significance of the results improve confidence in the data. Further purpose-designed research to address this question is required to provide more definitive confirmation of these results. Future nutrition intervention studies should be encouraged to report compliance with the nutrition prescription.

## Conclusion

Compliance with the prescription of 1.5 cans of a protein and energy dense, oral nutrition supplement $\pm$n-3 fatty acids improved total dietary intake and body weight in untreated pancreatic cancer patients. This level of supplement intake does not inhibit meal intake. Compliance with the nutrition prescription is an important component to monitor in nutrition outcome studies.

## Acknowledgments

Funding: Abbott Laboratories, Chicago, IL, USA

We thank the other dietitians in the Cancer Cachexia Study Group who were involved in analysis of the dietary data; R. Richardson, K. Yuill, J. Maessen, M. Dube and M. Gehami.

The principal investigators in the Cancer Cachexia Study Group are as follows: KCH Fearon (Royal Infirmary of Edinburgh, Edinburgh, UK), M.F. von Meyenfeldt (University Hospital of Maastricht, The Netherlands), A. Roy (Centre Hospitalier de l'Universite de Montreal, Canada), D.J. Gouma (Academisch Medisch Centrum, Amsterdam, The Netherlands), A. Giacosa (Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy), A. Van Gossum (Universite Libre de Bruxelles Erasme, Brussels, Belgium), J. Bauer (The Wesley Hospital, Brisbane, Australia), S. Ash (Princess Alexandra Hospital, Brisbane, Australia).

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