Improved Nutritional Support in Cancer Patients

BY

CHRISTINA PERSSON
ABSTRACT


Weight loss and other nutritional problems are common in cancer patients. The problems are of importance for response to treatment and survival and the well-being of the patients. Nutritional support can be carried out in different ways. The efforts considered in this thesis are; assessment of nutritional status to find the patients who are at risk to become or already are malnourished, assessment of dietary intake, dietary advice, information and support to the families, information and education to the caregivers, and supplementation with drugs that possibly could influence the weight development. The Swedish version of the Patient Generated Subjective Global assessment of nutritional status, PG-SGA, is useful in assessment of nutritional status in cancer patients. Dietary advice and support to patients and their families combined with information and education to the staff, at the hospital and in the home care, turned out to have a positive influence at the weight development and other parameters related to nutrition. The effects were seen in consecutive patients with small cell lung cancer in comparison with a historical control group, and in patients in a randomised trial. Fish oil and melatonin could stabilise weight development in patients with advanced gastrointestinal cancer, but had no marked influence on factors reflecting cachexia. Problems with nutrition in cancer patients are possible to recognise and various interventions may be beneficial.

Key words: Cancer, weight loss, PG-SGA, dietary advice, education, fish oil, melatonin.

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"Consumed food is good food"

Christina Persson
This doctoral thesis consists of the present summary and the following papers, which are referred to by their Roman numerals.


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INTRODUCTION

Nutritional support for cancer patients includes several aspects. The most central are identification of patients who are at risk to become or who are already malnourished; dietary advice to patient and family; information and education of all staff involved in the care of the patient, at the hospital and at home; drugs and other interventions to relieve symptoms preventing adequate food intake, as well as a variety of intensive interventions like enteral and parenteral supplies of nutrition. It appears today as if an increased energy intake is insufficient to stop weight loss among cancer patients and to achieve weight gain. Several attempts have been made to use possible anti-cachectic and appetite stimulating drugs (1). Earlier nutritional support was often synonymous with parenteral or even total parenteral nutrition. Nutritional deficiencies were often not properly recognised until the terminal stage of the disease, when such development can not be reversed. As many as 20% of patients with cancer die from the effects of malnutrition rather than the malignancy itself (1).

In several articles, Tchekmedyian and co-workers discusses the benefits of nutritional support and the assessment of nutritional status in cancer patients (2-5). He states that the endpoints for clinical treatments traditionally have been the impact on the malignancy and survival time. But having a better quality of life (QoL), e.g. feeling and functioning better and living a worthwhile life are outcome variables of ultimate interest to the patient. The American Society of Clinical Oncology has stated that as a single outcome, not even overall survival is sufficient to adequately describe treatment results (6).
Nutritional assessment is a comprehensive process of identifying individuals and populations at nutritional risk and of planning, implementing and evaluating a course of action (7). In 1979, Maurice Shils emphasised the need for early and recurrent assessments of nutritional status in cancer patients (8). Early identification of patients who are malnourished or who are suspected of developing malnutrition makes it easier to prevent further nutritional deterioration and to maintain or improve QoL (9,10).

**Cachexia**

Cachexia and starvation are separate expressions of malnutrition. Starvation is characterised by pure caloric deficiency, leading to adaptation to conserve lean mass and to increase fat metabolism. Appropriate feeding may reverse these changes. Cachexia includes a wide range of metabolic, hormonal and cytokine-related abnormalities. One characteristic of cachexia is an inability to use nutrients effectively (11,12) and feeding does not reverse the accompanying metabolic changes (13). Patients with cachexia lose roughly equal amounts of fat and fat-free mass, but maintain extracellular water volumes. The acute-phase response (APPR), developed to localise injured cells and to clear tissue debris, has nutritional implications. High rates of hepatic protein synthesis are energy-intensive and require large quantities of essential amino acids, causing loss of skeletal muscle. Changes in fat metabolism are seen in cachexia, including hypertriglyceridemia, an increased hepatic secretion of very-low-density lipoproteins and a decrease of lipoprotein lipase activity. Peripheral insulin resistance alters carbohydrate metabolism. Glucose is redirected to the liver and other viscera and away from skeletal muscle, and the energy needs of muscle are met by oxidation of nonessential amino acids, contributing to a negative nitrogen balance (13). Cancer patients fail to adapt metabolism to save protein stores (14). In
critically ill patients, there is an inability of hypercaloric feeding to increase lean body mass, especially skeletal muscle mass (15,16).

Metabolic abnormalities seen in cancer patients may be caused by cytokines produced by the host in response to tumour presence (17). Various cytokines participate in a complex network. The amount and type of dietary fat may influence cytokine production and activity (11). The tumour necrosis factor α, (TNF-α), is a potent anorexia-producing agent, promoting skeletal protein wasting, reducing the synthesis of lipids by inhibiting lipoprotein lipase, and stimulating neoangiogenesis (18,19). The serum levels of TNF-α are discontinuous and correlated to weight loss (20). High serum levels of Interleukin-1 β (IL-1 β) cause increased resting energy expenditure (REE), skeletal protein wasting, reduction of meal size and meal duration (18,19,21), and are associated with the levels of plasma-fibrinogen and serum C-Reactive Protein (CRP), and with survival (22,23). Interleukin 6 (IL-6) is associated with weight loss and increased levels of CRP and Fibrinogen and a decrease of serum-albumin (S-alb) levels (24, 25). The soluble Interleukin-2 receptor (s IL-2r), necessary for the activity of the immunoregulatory cytokine Interleukin-2, is elevated in cancer patients, and significantly higher in cachectic patients. sIL-2r is suggested to be a nutritional parameter, correlated with P-prealbumin (P-prealb), S-transferrin and survival (26). Interleukin -8 (IL-8), a proinflammatory cytokine, is involved in the regulation of satiety and in modulation of the CRP-levels (27, 28).

The majority of the present studies concern attempts to diminish and reverse weight loss, a clinical sign of cachexia, involving several efforts to increase energy intake and an intervention with two possible anti-cachectic drugs, melatonin and fish oil.
Energy expenditure and requirements in cancer patients

In most nutritional studies of cancer patients, dietary intakes have been compared with the recommended daily intake (RDA) for healthy subjects (29). Such comparisons may be relevant but are plagued by the important question: Is energy expenditure, and thus requirement, higher in cancer patients than in non-cancer individuals?

Total energy expenditure (TEE) involves REE (approximately 70%), voluntary energy expenditure (25%) and energy expended in digestion (5%) (13). REE is defined as the metabolic rate in kilocalories (kcal) per day of a postprandial individual, more than two hours after a meal, lying in bed in a comfortable environment. REE may be measured by the doubly labelled water method (30), by indirect calorimetry (31) or calculated by the equations of Harris and Benedict (H&B), (31, 32) or the World Health Organisation (33).

More than 50% of malnourished cancer patients have an abnormal REE, 33% are hypometabolic and 26% hypermetabolic (34, 35). In one study, hypermetabolic patients had a significantly longer disease duration than did normometabolic patients, 33 vs 13 months (35). The primary tumour site was a major determinant of REE. Oesophageal and colorectal cancer patients were generally normometabolic; patients with pancreatic and hepatobiliary tumours tended to be hypometabolic and patients with gastric cancer tended towards hypermetabolism (34).

REE, measured by indirect calorimetry and calculated by H&B, has been compared between cancer patients, and non-cancer individuals (36) REE was significantly higher in cancer patients, irrespective of weight loss. Predicted energy expenditure (EE) agreed with that measured in weight-losing cancer patients. The conclusion was that
many cancer patients with solid tumours have an elevated REE, but it is unclear if this represents a lack of adaptation to undernutrition or a true increase of the metabolic rate.

In patients with lung cancer, an elevated REE was seen in 70 %, related to the level of inflammation. A statistically significant difference was seen in the REE between patients with a weight loss less than 10%, and those with a greater weight loss, 23.4 and 25.3 kcal/kg body weight (BW), respectively (37).

In patients with newly detected gastric and colorectal cancer, preoperative REE was 20.5 kcal/kg BW and increased moderately postoperatively, or to 22 kcal/kg BW (38). In cachectic patients with pancreatic cancer, REE was significantly higher than in healthy controls, 24 and 19 kcal /kg BW, respectively (39).

The studies cited above do not give a uniform answer to the question about EEs in cancer patients. Thus there is no specific recommendation for cancer patients, why the calculated values in the present studies are compared with the Swedish (SNR) and Nordic recommendations (NNR) (40) for daily intake in healthy subjects.

**Nutritional status**

There are several methods for assessing nutritional status. Anthropometric measurements and laboratory tests are the ones most frequently used. Among the anthropometric measures, weight and weight development are the easiest to obtain, and have been found to be useful (17). Weight loss should be evaluated in relation to usual or pre-illness weight. Loss of subcutaneous fat and muscle wasting are other
aspects that may be used to assess nutritional status (41). Serum proteins, especially S-alb measurements, are often utilised in nutritional studies (42). S-alb measurements have a predictive value by differentiating low-risk from high-risk patients (41). Low S-alb is an independent prognostic factor for survival in patients with lung and colorectal cancer (44-48). However, other data indicate that P-prealb, may be a better marker of nutritional status than is S-alb (49,50). Also, CRP and P-fibrinogen are associated with weight loss and survival (51-53).

In addition to these anthropometric and biochemical variables, a standardised questionnaire may be used to achieve more detailed information, e.g., about diet and gastrointestinal problems (1). Such a questionnaire, the Patient-Generated Subjective Global Assessment of nutritional status (PG-SGA) will be presented and discussed.

**Self-reported weight and height**

Information about BW and height is necessary for calculation of REE, and for the body mass index (BMI,(kg/m²). It is well-known that there are both under- and overreporters of weight, but little is known about cancer patients in this respect.

In NHANES II, the National Health and Nutrition Examination (54), the replies from 11284 participants to questions about "what is your weigh without clothes or shoes?" and "how tall are you without shoes" were compared with measured weight and height. There was an overall tendency for men to overreport their weight whereas women underreported it. Underweight men and women overreported their weight, whereas overweight men and women underreported it. Severely overweight young men and women (20-34 y) underreported more than did the elderly (55-74y). Both
men and women overreported their height, older (45-74 y) more than younger (20-44 y). The association between self-reported and measured weight was calculated in an American-Danish study (55). Data were collected from applicants for medical insurance at seven sites in the USA, of which four were obesity treatment sites, and one site in Denmark. There were strong correlations both in the American (r=0.974) and Danish data (r=0.856). The conclusion was that it is possible to carry out valid studies of weight status by questionnaires and even by telephone interviews. Both methods are used in the present studies.

Allan Detsky (41,56,57) has developed a standardised instrument called the Subjective Global Assessment (SGA). This method classifies patients into SGA A (well-nourished), SGA B (moderately /suspected malnourished) and SGA C (severely malnourished). The SGA has been used for assessment of nutritional status of patients with various diseases (58,59). It has been translated into Swedish and tested for validity and reliability in studies of patients undergoing gastrointestinal surgery and in patients at geriatric clinics (60, 61). A modified version of the SGA has been developed, the PG-SGA, intended for use with cancer patients (62, 63). This version differs from the original SGA, in that the patient completes the first four questions and the clinician, dietician or nurse the remaining ones.

**Weight loss and quality of life**

Malnutrition and weight loss may influence QoL. Previous studies have shown lower QoL scores and more appetite loss and fatigue in patients with weight loss than in those without weight loss (64-67). A significant correlation has been reported between performance status and weight loss in patients with colorectal cancer (66,68). APPR,
with a lowered level of S-alb and an increased level of CRP were seen at baseline in weight losing gastrointestinal (GI) cancer patients. At follow up, CRP continued to increase and performance status decreased in weight losing patients (51). In a study of 199 patients (65) with locally advanced and/or metastatic GI cancer, weight loss and reduction of appetite were related to a reduced QoL. Patients with weight loss, median 17%, had a lower Karnofsky performance score (KPS) (69) than did weight stable patients. Patients with weight loss had significantly more problems with fatigue, nausea and vomiting and appetite. To examine whether weight loss at presentation had an influence on outcome, data were collected from patients with locally advanced or metastatic GI cancer (66). All patients were treated with chemotherapy. Patients continuing to lose weight during the first 120 days of treatment had a lower mean QoL, all sites combined, than did patients with stabilised or increased weight.

The above mentioned relations between weight loss, QoL and performance status reported in previous studies will be further explored in the present studies.

**Weight loss and survival**

Involuntary weight loss, often seen in cancer patients, carries prognostic information in studies of a variety of tumours (45-48,66,68,70-74). In patients with colorectal and gastric cancer, a statistically significant difference in survival has been demonstrated between those with and without weight loss (68). In patients with SCLC, weight loss and a reduced S-alb, are significant determinants of survival (48,74). APPR, and low performance status have been found to be associated with poor survival in GI cancer patients, independent of weight loss (52).
Overall survival was significantly improved in GI cancer patients when a stabilisation of weight loss occurred (66). Average time of treatment was shorter in patients with weight loss. In a multivariate analysis, four independent prognostic variables of overall survival were found: weight loss, performance status, response, and presence of liver metastases.

Preoperative weight loss has predictive value for postoperative mortality and survival in studies including patients with gastric and colorectal cancer (47,68). In surgically treated patients with gastric adenocarcinoma, weight loss (73), low S-alb levels and a high nutritional risk index NRI (47) were significantly correlated to survival.

The predictive value of involuntary weight loss and a deficient nutritional status will be explored in the present studies.

**Dietary assessment**

The objectives of a dietary study are to assess past and/or present dietary intake, long-term effects of diet on nutritional parameters, or the impact of interventions on dietary intake in specific high-risk groups. There are a variety of methods for assessment of dietary intake. The most commonly used are food frequency questionnaires, food records (estimated or weighed) and 24-hour recalls. The 24-hour recall is considered to be reliable for assessing intake of groups (75-78). A comparison has been performed between weighed records, 24-h recalls (unstructured and structured), food-frequency questionnaires and estimated-food diary (79). Data from the food diary, combined with a booklet with photographs of three portion sizes were most closely associated with
the weighed record. However, the unstructured 24-hour recall compared surprisingly well with the weighed records.

Examples of errors that might occur in dietary assessment studies are; foods or eating events are omitted, over- or underestimated amounts, food types are not sufficiently described, amounts of foods are not correctly quantified, an incorrect food code is selected in the nutrient database, and volume to weight conversion factors may be wrong.

The 24-hour interviews may be performed by telephone or face-to-face. Good agreement between the two methods has been reported (80,81). In comparison with observed meals, the accuracy of telephone recalls with respect to portion-size and number of food items appears to be adequate (82,83). As the 24 hour-recall interview implies that the person has to remember everything consumed during the past 24 hours, fading memory can be a problem, and patience and care must be shown by the interviewer. A check-list is helpful to remind the interviewer to ask about snacks, drinks between meals, candy, fruit etc, not always considered to be food. The food items are described in household measurements in terms of glass, cup, spoon and, when possible, in grams or dl. The cooking process should also be described (cooked, fried, grilled or raw).

Other sources of error in dietary assessments are underreporting or bias due to social desirability. Biased reporting in 24-hour recalls may result from selective forgetting of socially undesirable foods, or purposeful fabrication of socially desirable responses (84). The frequency of underreporting has been studied in the NHANES III study, where 24-hour recalls were used (85). Fewer men than women were underreporters, 18
and 28%, respectively. The prevalence of overweight and attempts to lose weight was significantly higher in underreporters, both men and women. The ratio between estimated energy intake and estimated basal metabolic rate was used to evaluate underreporting of dietary intake. Biased over- or underreporting is a characteristic of some persons.

In the present studies, assessment of dietary intake was performed using the 24-h recalls. A 4-day food diary was used in another.

**Fish oil and melatonin, possible anti-cachectic drugs**

Fish oil, containing omega-3 fatty acids has been suggested as a drug for the treatment of cancer cachexia (86). The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) inhibit cytokine production and activity by interfering with the cyclo-oxygenase and lipid-oxygenase pathways (18). Omega-6 fatty acids, linoleic acid and arachidonic acid (AA) may increase the production of prostaglandin E$_2$ (PGE$_2$), whereas omega-3 fatty acids reduce this production. An antitumour effect of fish oil seems to be the result of a reduction of tumour cell proliferation through reduced levels of PGE$_2$ and its metabolites (87). Omega-3 fatty acids modulate the metabolic response to feeding (22), and reduce the levels of CRP, TNF-α and IL-6 (88, 89). In previous studies supplementation with fish oil has shown associations with weight gain, improvement in performance status, better appetite, and survival (90, 87). Fish oil in combination with nutritional supplements prevented progression of APPR and cachexia in patients with advanced cancer (91).
Melatonin is a hormone produced by the pineal gland, and patients with advanced cancer often present with a pineal endocrine hypofunction. This secretion shows a circadian rhythm with the lowest values during the day (92,93). Melatonin reduces the levels of circulating TNF-\(\alpha\), and the degree of weight loss (92,93). An improvement in performance status was seen in patients with metastatic GI cancer treated with melatonin (92).

Corticosteroids have been used for appetite stimulation in cancer patients. Excellent short-term effects have been seen (94). However, chronic use requires increasing doses to maintain the effect, which results in side effects like muscle wasting and weakness, immunosuppression, diabetes, and osteoporosis (94). Progestins, e.g. megesterol acetate (MA) and medoxyprogesterone acetate (MPA) have been used extensively as appetite-stimulating drugs in cachectic cancer patients. MPA vs placebo during 12 weeks led to a statistically significant increase of energy intake and fat mass (95). MA and ibuprofen compared to MA and placebo resulted in a statistically significant increase in appetite scores in both groups. However, median weight decreased in the MA-placebo group, while a significant increase was seen in the MA-ibuprofen group. The authors suggest that the anti-inflammatory effect of ibuprofen contributed to the weight gain (96). In a review of 15 randomised clinical trials, significant improvements were seen in appetite and in body weight gain in patients treated with high dose progestins (97).
AIMS

The aims of the present thesis are twofold: to study weight loss, and to explore the possibility to influence the development of body weight in cancer patients.

The following research questions were formulated:

Is weight loss related to quality of life, response to treatment and survival in patients with colorectal, gastric, biliary and pancreatic cancer? (Study IV)

Does an instrument for assessment of nutritional status, the PG-SGA, facilitate an early identification of cancer patients at risk to be or already malnourished? (Study II)

Is it possible to regain weight or prevent further weight loss among cancer patients by providing dietary advice, support and information to their families, information to and education in nutritional issues of hospital and home care staff? (Study I and Study III)

Does supplementation with two possible anti-cachectic drugs, melatonin and fish oil, influence the weight development and markers of cachexia among patients with advanced gastrointestinal cancer? (Study V)
MATERIAL AND METHODS

Diagnoses and numbers of patients in studies I-V are shown in Table 1.

<table>
<thead>
<tr>
<th>Study I</th>
<th>58 vs 81 historical controls in nutritional, response and survival parameters.</th>
<th>36 vs 22 in QoL parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell lung cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study II</td>
<td>54 vs 33, consecutive patients at the out-patient clinic</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal and urological cancer</td>
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<tr>
<td>Study III</td>
<td>71 randomised to nutritional support vs 73 controls</td>
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</tr>
<tr>
<td>Gastric and colorectal cancer</td>
<td></td>
<td></td>
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<tr>
<td>Study IV</td>
<td>152 patients treated within four randomised studies</td>
<td></td>
</tr>
<tr>
<td>Gastric, pancreatic, biliary and colorectal cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study V</td>
<td>24 patients with weight loss and/ or S-alb below 35</td>
<td></td>
</tr>
<tr>
<td>Gastric, pancreatic, biliary and colorectal cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Assessment methods

Assessment of dietary intake

The 24-hour recall method was used in Study I, and the initial interview was made on the ward the first time the dietician met the patient. The subsequent interviews were made by phone. The same method was used in Study III, the first interview as far as possible conducted in the patient's home and the subsequent interviews by phone. The dietician used a booklet with black-with drawings and photographs of different portion sizes at the first interview. In Study V, a 4-day food diary was employed combined with a booklet with colour photographs, which the patient kept at home during the study. The patients received written information on how to complete the food diary.

In Study I the calculations of dietary intake were made with a computer program from Kost-och Näringsdata (98), and in Studies III and V with the MATS program (99).

Quality of life assessments

Three different questionnaires were used for assessment of quality of life in the included studies (Table 2).

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality of Life assessments</th>
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<tbody>
<tr>
<td>Study I</td>
<td>Cancer Inventory of Problem Situations, CIPS</td>
</tr>
<tr>
<td>Studies III, IV and V</td>
<td>EORTC-QLQ C-30</td>
</tr>
<tr>
<td>Study IV</td>
<td>Uppsala Questionnaire (in part)</td>
</tr>
</tbody>
</table>
The Swedish version of the Cancer Inventory of Problem Situations (CIPS) (101) was used in Study I. The CIPS is a cancer-specific survey instrument designed to assess day-to-day problems and rehabilitation needs. During an interview, patients rated how much they agreed to 131 problem-oriented statements using a scale from 0 to 4, a higher value indicating more problems. CIPS-items were combined into higher-order factors and subscales, representing physical, psychosocial, medical interaction, marital and sexual problem areas, proposed for the original CIPS (102,103).

The EORTC QLQ C-30 is a 30-item questionnaire, often used for assessment of health-related QoL among cancer patients (104). The EORTC QLQ-C-30 is a multidimensional instrument that covers physical, social and psychological functioning as well as cancer-specific symptoms. The 28 items measuring physical, role, emotional, cognitive and social functioning, symptoms and financial difficulties have a four-grade scale. The two remaining items concerning global quality of life has a seven-grade scale. Subscale scores are transformed to 100 grade scales. In the functional scales and in the score for global health/QoL, a higher value means a better QoL. However, a higher value on a 0-100 symptom scale indicates more problems.

The Uppsala Questionnaire is a structured questionnaire centred on problems of daily life (105). It consists of five parts. 1. Pain, location indicated on a schematic drawing, and intensity rated on a 1-10 scale. 2. Symptoms and adverse effects, the occurrence of 25 events e.g. loss of appetite, tiredness, changed tates sensations. 3. Frequency of troublesome events i.e. resting, crying, skipped meals, problems concentrating, and consumption of analgesics was rated on a 4-step scale. 4. Nausea, vomiting, diarrhoea, intensity and frequency, and 5. tiredness and pain in association with everyday activities, rated on a 0-10 scale.
**Performance status**

The Karnofsky Performance Status (KPS) is used for assessment of performance status, yielding a numerical value, in terms of percentage, describing the patient's ability to carry on his/her normal activity and work, his need for a certain amount of care, or dependence on constant medical care (69).

**Dietary advice**

As many of the patients did not manage to eat large portions, they were often advised to have an energy-dense diet to satisfy their energy requirements. The easiest way to increase the energy content of food is to add fat. In the recommendations for diets in Swedish hospitals (100), the recommended level of fat in an energy-dense diet is 35 energy per cent (E%). This should be compared with the Nordic recommendation for healthy people, which is<30% (40). To increase energy intake, the patients were also counselled to have more sweet drinks and desserts, in contrast to the dietary advice to healthy people. The patients were told to have small but frequent meals, and to use commercial supplements and enrichments, both liquid and in powder form.

**Commercial supplements**

The majority of the supplements used were complete liquid supplements containing protein, fat, carbohydrates, vitamins and minerals. There were some without fat, but they were seldom recommended. Enrichments were available as powder or liquids, complete as the liquid products or containing only carbohydrates or protein. The supplements were available in many different flavours.
Statistical analyses

Comparisons of mean values were in Studies I-V performed by the unpaired Student's test in body weight, BMI, KPS, biochemical and QoL variables. The paired t-test was used in Study V, comparing QoL assessments at two different points of time.

The Mann-Whitney U test was used for comparison of median values in biochemical variables and levels of cytokines (Study V).

Analysis of variance was used for between-groups changes over assessments in body weight (Study I) and BMI (Study III). In Study II, analysis of variance was performed for comparison of biochemical variables in the three SGA-classes.

In Study V, the Wilcoxon signed rank test was used for changes within groups over assessments in the biochemical variables and the levels of cytokines.

The Chi-square test was performed to test proportions in weight loss and decreased S-albumin between groups (Study I), and diagnoses in the different SGA-classes (Study II).

Correlations were analysed by the Pearson coefficient between weight loss and biochemical measurements (Study II), weight development and global QoL, and weight development and fatigue (study III), and between symptoms, KPS and global QoL (Study IV).

The Spearman rank coefficient was performed for correlations between the biochemical variables and the levels of cytokines in Study V.
The relationship between the different components of the PG-SGA was analysed by logistic regression (Study II).

Hazards ratios of the significant prognostic variables of survival were calculated using the Cox regression model (Study IV).

Multivariate regression was performed in analysing variables explaining global QoL (Study IV).

The inter-rater reliability was analysed by Kappa statistics (Study II).

Cumulative percent surviving was in all studies calculated with the life-table technique and differences were tested with the log-rank test.

**Study I**

This study is based on a cancer care project financed by the Swedish Cancer Society, which started in February 1987 and was terminated in December 1989. The purpose was to improve patient care, both in general terms as well as in certain specific respects. The patients suffered from one of the following diagnoses: Small cell lung cancer (SCLC), high grade non-Hodgkin lymphoma, Hodgkin's disease, acute leukaemia, myeloma in progressive stage, and breast cancer Stage II to be treated with adjuvant chemotherapy. Only patients with SCLC are included in the present paper. All patients were treated with intensive combination chemotherapy. A description of the project and its overall results has been published elsewhere (102). A special nurse was employed on each ward participating, a contact nurse, who played an important
role in the project. There was also a common "resource group" consisting of a nurse, psychologists, social worker, dietician, occupational therapist and physiotherapist. A care program booklet was produced giving guidelines and detailed descriptions of goals and methods. Some of the main points were information, communication, crisis reactions, activation, and care-taking of families and relatives, nutrition, pain and nausea treatment. For the SCLC patients, the intervention efforts were concentrated on their nutritional situation. Weight and nutritional parameters were recorded repeatedly, in connection with every course.

The study period group (SPG) consisted of fifty-eight patients with SCLC, and in the evaluation of the nutritional and survival outcomes, another 81 patients served as historical controls (S/N-C). They had received the same medical treatment before the project started. The latter group had not had the possibility to meet a contact nurse, to get nutritional support from a dietician or access to the resource group. Data on weight, S-alb, B-Hb, stage and KPS in the control group were collected retrospectively from the clinical records.

The main instrument of evaluation was the CIPS (101). Interviews with patients in the SPG were made before the second treatment course, and in association with the 4th, 8th and 12th course. One month before the care project was initiated, twenty-two patients, treated for a mean of 7.1 courses, were interviewed with the same instrument. In the QoL evaluation, these patients served as a control group (QoL-C) to the thirty-six patients assessed in association with their 8th course.

The SPG patients all met the dietician in connection with one of the first treatment courses and then repeatedly on the ward during treatment. Dietary assessments, 24-
hours recalls by phone, were done at regular intervals, before every 4th treatment course, followed by individual dietary advice. Families and relatives were also involved. They met the dietician on the ward, talked to her on the telephone when the patient was at home and attended meetings arranged during the project.

An extensive educational program was offered to all employees at the wards. The staff was taught the importance of nutritional support and good nutritional status. To facilitate the nutritional care on the ward, a special diet-cardex was compiled with information about diet, such as what supplements the patient preferred, and foods that the patient did not like. The diet-cardex was kept in the kitchen on the ward. During the study, a new way to serve the food was introduced. Food was delivered in deep dishes instead of ready-made trays. Meals were served at laid tables in the day room instead of at the bedside.

**Study II**

The aim of the study was to translate the PG-SGA into Swedish and then evaluate the instrument in an outpatient setting. Two groups of patients were compared, one in which nutritional problems and a poor nutritional status are frequent, i.e. GI cancer, and the other where these are infrequent, i.e. urological cancer. During the period February to December 1996, the nutritional status of 87 consecutive patients was assessed at the outpatient unit of the Department of Oncology, Akademiska hospital, Uppsala. All patients with gastric, pancreatic, biliary and anal cancer had inextricable primary and/or metastatic disease. None of the patients with testicular cancer had known metastases.
The PG-SGA was translated into Swedish and then back-translated by a nurse from the USA. Then it was retranslated into Swedish after comparison of the two versions. The questionnaire is reprinted in Appendix. When arriving to the out-patient unit, the patients received written information about the study, and if they agreed to participate, they completed their part of the SGA (questions 1-4). These questions concerned actual weight, weight six and twelve months ago, gastrointestinal problems, food intake, and physical activity.

The physician completed the remaining questions concerning diagnosis, metabolic demand, loss of subcutaneous fat, muscle wasting and oedema. The classification of each patient’s nutritional status as A, B or C was based on the answers from the patient and the physician. Without knowledge of the doctor's assessment and classification, the dietician completed the same questions as the doctor and made an independent classification. In order to validate the classification, biochemical measurements S-alb, P-prealb, B-neutrophils and B-lymphocytes, were performed.

After answering the PG-SGA, the patients were offered to meet the dietician for dietary advice. When required, prescriptions for commercial supplements were also given.

**Study III**

Within a "Support-Care-Rehabilitation" project, patients with breast, prostate, colorectal or gastric cancer were randomised to one of four alternatives: 1. Individual Support (IS), starting at diagnosis, including intensified primary health care (IPHC), problem-focused psychological support (IPS) and individual nutritional support (NS).
2. Group Rehabilitation (GR) 3. A combination of Individual Support and Group Rehabilitation (IS+GR) and 4. Standard care (SC). Patients were included between October 1st, 1993 and December 31st, 1995. The intensified primary health care (IPHC) included in IS implied that the patient was referred to the home care nurse responsible for the district where the patient lived. The patient's general practitioners (GP) were informed about the cancer diagnosis and the referral to the home care nurse. The IPHC has been evaluated and described elsewhere (107-109). The individual psychological support (IPS) was designed to identify the patient's needs on an individual basis, and to help them to handle problems arising from the diagnosis and medical treatments. The patient was contacted by phone and a first appointment was decided. The psychologist then suggested appropriate psychological interventions based the patient's needs. The IPS has been described and evaluated elsewhere (110,111). The GR intervention was an eight-session group intervention with a booster session, starting approximately 4 months after diagnosis. Each group consisted of 3-9 patients. An oncology nurse, a psychologist and a physiotherapist conducted the sessions. The sessions included cognitive behavioural therapy techniques and light physical training plus relaxation. In one session, an oncologist or a surgeon gave information about disease and treatment, and the dietician participated in one session. The GR intervention has been described elsewhere (112,113). The nutritional support (NS) described in the present paper was offered to patients with colorectal or gastric cancer, randomised to IS. The aim of Study III was to evaluate if NS affects weight development, food intake, QoL and survival in patients with GI cancer.

Sixty-seven patients with GI cancer were randomised to IS+ISGR, the study group, and 70 to GR+SC, the control group. All patients in the IS+ISGR group accepted the NS they were offered. Weight development and QoL aspects were evaluated in both
groups, at diagnosis and after 3, 6, 12 and 24 months. In the study group, dietary intake was assessed by 24-hour recalls on the same occasions. In patients with advanced disease, there were additional assessments of the dietary intake. The first contact was made as soon as possible after diagnosis and randomisation. The living area, Uppsala town or rural district determined whether the contact was made face-to-face or by telephone. The subsequent interviews were all made by telephone, and in connection with the interview, family members had an opportunity to talk to the dietician.

The home care nurses and the general practitioners received education in nutritional issues prior to and throughout the project. A video was made concerning nutritional problems and dietary advice to patients with gastric cancer, which was used in this education. A chapter on nutrition was included in the booklet "Oncology care", prepared prior to the project and distributed to participating staff. The dietician gave lectures on nutritional problems in cancer patients, and dietary advice including enteral nutrition. in seminars arranged by the project group. The dietician also participated in problem-focused supervision offered to the home care nurses.

**Study IV.**

To explore the relations between weight loss, other nutrition-associated parameters, performance status and response to chemotherapy on one hand, and survival and global QoL on the other, data from patients treated within four randomised studies were analysed. All the 152 patients had advanced GI cancer, gastric, colorectal, pancreatic or biliary cancer. Data were gathered from the case record form used in these studies and from the medical records. The analyses of weight loss, nutritional
problems, performance status, and QoL were all based on data at inclusion. in each study. QoL and presence of symptoms were assessed by the Uppsala questionnaire (105) in the first study and by the EORTC QLQ C-30 (104) in the remaining studies. The KPS (68) was used to assess the performance status. Responses to treatment were classified using the UICC criteria (111). Analyses of survival in relation to whether a response occurred or not were made according to the landmark method (112,113), excluding patients who died before the response evaluation or within 120 days.

Study V

Twenty-six patients with advanced GI cancer and a weight loss of ≥ 10% during the last six months, or S-alb ≤ 35g/L were included. Two patients did not participate in the intervention, one due to early death and one due to thrombosis. Baseline assessments were made during the first weeks after inclusion. They included biochemical, QoL and dietary assessments. Patients were then randomised to a 4-week intervention period with fish oil (FO) or melatonin (MLT) followed by study assessments and a 4-week intervention period with FO and MLT, and final assessments. The prescribed amounts of the supplements were 2x15 ml /day FO or 18 g/day MLT.

Dietary intake was measured by 4-day food diaries at baseline, and after the first and the second intervention periods. Patients had dietary advice, based on the diaries, at inclusion, and during the intervention periods. At baseline, and after the first and second period, B-haemoglobin, (B-Hb), S-alb, S-lactate dehydrogenase (S-LDH), CRP and P-fibrinogen as well as the cytokines TNF-α, IL-1β, sIL-2 R, IL-6 and IL-8 were assessed. Levels of fatty acids linoleic acid, AA, EPA and DHA were assessed on the same occasions, and QoL by means of the EORTC QLQ C-30 questionnaire (104) and
the KPS (69). Compliance with the FO regimen was assessed in relation to the
development of plasma levels of EPA. Patients with at least a doubled level of EPA
were estimated to have good compliance. Compliance with the MLT regimen was
assessed in relation to the number of pills consumed. Two empty packages, the
prescribed amount, were considered as good compliance.

RESULTS

Study I (Effects of nutritional support in patients with SCLC)

At diagnosis mean body weight and BMI did not differ between the study group (SPG)
and the control group (S/N-C). However, during the study period, there was a more
pronounced decrease in body weight and BMI in the S/N-C group, than in the study
group (p<0.01 and p<0.05, respectively). Mean S-alb did not differ at diagnosis,
remaining approximately constant in the control group but increased with time in the
study group (p<0.001). Mean energy intake at home was 1530 kcal at the first
interview which increased to 1700 -1800 kcal at the following assessments. Fat
provided 38-42% of the energy.

The routines for nutritional support on the ward were improved, due to the
implementation of the diet-cardex routine and the education. Commercial supplements
were always available as well as popular food like pancakes, meatballs, ice cream, and
milk shakes.
Compared with the QoL-C group, the available patients in the study group expressed fewer problems with weight loss, and appetite in hospital. In patients in the study group the scores for "food tastes bad" in hospital were significantly lower, p<0.01. The mean global score of all 131 CIPS-items was lower in the study group than in the control condition (p<0.001), indicating a better QoL. The changes in CIPS factors/individual items formed a coherent pattern in that scores were better in the study group in aspects dealt with, whereas no differences were found in other respects. There was no statistically significant difference in survival between the two groups.

**Study II (Characteristics of the PG-SGA for nutritional status)**

The inter-observer agreement for the PG-SGA between doctor and dietician was 90%. After a joint re-examination consensus was reached about the classification of the remaining patients. Significantly more patients with urological cancer (91%) than with gastrointestinal tumours (48%) were classified as well nourished, p<0.001.

Patients classified as SGA B and C had lower S-alb and P-prealb levels than did those classified as SGA A, but only the differences between SGA A and SGA B were statistically significant (p<0.05 and p<0.01, respectively). Patients assessed as having an enhanced metabolic demand had significantly lower means of both S-alb and P-prealb (p<0.001). Mean weight loss over the last six months was 4.5% (SD 2.6) in patients rated as SGA A, 7.5% (SD 5.3) in SGA B and 11.2% (SD 5.1) in SGA C. There were positive correlations between the percentage of weight loss, calculated as the difference between actual weight and the weight 6 and 12 months ago, respectively, and the biochemical measurements.
A multivariate logistic analysis revealed independent contributions to the SGA classification by weight loss the last 6 months, altered food intake, problems preventing the patient to eat enough, physical activity and muscle wastage. The SGA A group evidenced a significantly longer survival than did the SGA B+C group, p<0.001.

Study III (Effects of nutritional support in GI cancer patients)

The number of patients decreased with time, mainly due to death caused by the underlying malignancy. At the assessments at 6, 12 and 24 months, the number of patients available were 49 vs 52, 41 vs 44 and 37 vs 30 patients, in the IS+ISGR group and the GR+SC group, respectively.

Despite a tendency for greater weight loss at inclusion (7.2 vs 5.5%), the IS+ISGR group managed to gain weight more rapidly and to a greater extent than the control group. The mean group scores differed significantly at 12 and 24 months (p<0.05). The mean energy intake was rather stable during the study period (1400-1500 kcal/day). However, patients with weight loss at inclusion increased their energy intake and weight more than those without weight loss. Energy provided by fat varied between 35 and 40%. There were no differences between the study group and the control group in the QoL ratings. At inclusion fatigue and loss of appetite had high scores, meaning more problems, but the scores decreased during the study period. A positive correlation was seen between weight development and QoL and a negative correlation between fatigue and weight development. The study group had a numerically longer survival than the control group, but this difference did not reach statistical significance (p=0.3).
Study IV (Effects of weight loss on survival and quality of life)

Seventy-four per cent of the patients had lost weight at inclusion, mean 7.3%. The proportion of patients with weight loss and the degree of weight loss were higher in patients with gastric and pancreatic or biliary cancer than in those with colorectal cancer. Patients with weight loss had a lower KPS score than did those without weight loss (p<0.001). Diagnosis had the strongest association to survival, but poor performance status and weight loss were also independently related to survival. Time of survival was longer in patients without weight loss (p<0.001). Global QoL scores were lower in patients having weight loss than in those without weight loss (p=0.01). Patients who stated problems with pain and fatigue also had lower mean global QoL values. Weight loss, low performance status, high frequency of nutrition-associated problems and low B-Hb levels were associated with a lower probability to respond to treatment.

Study V (Effects of fish oil, melatonin and dietary advice on cachexia)

Among the 24 patients who started with the supplements, FO and MLT, twenty patients accomplished the first and sixteen the second study period. There was one drop-out and one patient died in each randomisation group during the first intervention period. During the second period, there was one drop-out in the FO group and three in the MLT group, all due to progressive disease.

The cytokines TNF-α, s-IL2R and IL-6 were detected in 100%, IL-1β in 42% and IL-8 in 50% of the patients at baseline. The median values for most of the biochemical variables were out of normal range in both groups. The MLT group had generally
higher baseline cytokine values compared with the FO group. However, this was statistically significant only for sIL-2R (p=0.02). During the study period, biochemical variables and cytokines changed, but not in a systematic way. When analysing all patients together, the only statistically significant changes were an increase in IL-6 over the first intervention period and (p=0.04) and in IL-8 over both intervention periods (p=0.02).

At baseline mean plasma levels of fatty acids were similar to those in healthy volunteers. After the first intervention period, EPA and DHA increased in the FO group (p<0.001), whereas there were no changes in the MLT group. The changes in the FO group were similar to those seen in healthy volunteers taking 30 ml FO/day during 4 weeks (117). During the first intervention period, good compliance with the fish oil regimen was seen in 62% and to melatonin in 45% of the patients. In the patients who started with the supplements the second period, corresponding figures were 62 and 36%.

At inclusion there was considerable weight loss in both groups, mean 12%. However, weight stabilised in both groups during the study. During the first intervention period, 4/13 of the patients in the FO-group had a weight stabilisation or gain, compared to 2/11 in the MLT group. The median weight loss was 0.6 kg and 1.8 kg, respectively. During the second period, weight stabilisation or gain was seen 5/11 of the patients in the FO group, and in 4/9 in the MLT group. The median weight gain was 0.2 and 0.8 kg, respectively.

The mean energy intake at the three assessments varied between 1500 and 1850 kcal.
At baseline the MLT had a lower mean energy intake, 1500 kcal, than the FO group did, 1750 kcal. During the study period the energy intake increased in the MLT group, in patients who accomplished the whole study period mean intake increased by 166 kcal. However, in the FO group a reduced energy intake was seen, mean energy intake decreased by 240 kcal during the study period. Fat provided 33-35 E%, the fish-oil not included.

The baseline score for global QoL was low, and problems with fatigue and loss of appetite were common. The global QoL scores increased slightly and problems with appetite decreased markedly during the study period There were no statistically significant differences in KPS or QoL between the two randomisation groups, either at baseline or during the study period.

Neither FO nor MLT or their combination induced major biochemical changes suggesting strong anti-cachectic effects in these patients with advanced GI cancer. However, both FO and MLT, combined with dietary advice showed a weight stabilising effect.
DISCUSSION

Several aspects of nutritional support, all of them important in the care of cancer patients, were dealt with in the present dissertation. The impact of weight loss on QoL, survival and response to treatment was explored; a questionnaire for the assessment of nutritional status was translated and evaluated; and the effects on weight development of dietary advice and support of patients and families by a dietician were studied. An extensive educational program was carried out, including doctors, nurses and assistant nurses at the hospital and in home care. In a pilot study, possible effects on cachexia by two anti-cachectic drugs in addition to dietary advice were explored.

An early identification of patients at risk for malnutrition should make it possible to prevent further nutritional deterioration. Weight and weight development are the primary candidates for parameters that can be used to identify patients at risk for malnutrition or already malnourished. In the present studies, weight loss at inclusion varied between a few percent in patients with testis cancer to above 10 percent in patients with advanced upper abdominal cancer. Weight loss was seen predominantly in patients with advanced disease.

The relation between weight loss and quality of life

For many people a high QoL includes the ability to enjoy food and drink. Loss of appetite, nausea, vomiting and fatigue may prevent cancer patients from participating in and enjoying meals with families and friends. In earlier studies weight loss has been associated with a low QoL (64-66,118). Such associations were also seen in Studies I, III, IV and V. QoL improved when patients gained weight (Study III), and when there
was a less pronounced weight loss (Study I) or a stabilisation of the weight development (Study V).

Fatigue leads to a reduced level of motivation or interest in engaging in activities and to difficulties to complete tasks of daily living (119). This may include less interest in food purchase, cooking and eating. In the Swedish reference population for the EORTC QLQ C-30 (120), age group 60-69 years, the mean value of fatigue was approximately 20. At inclusion in Study III, the mean value was 46, and in Study V corresponding figures were 54 in the FO group and 72 in the MLT group.

Loss of appetite, is a symptom that may lead to weight loss. At inclusion in Study V, appetite loss was a major problem among the patients. The mean score was 60, compared to 4 (women) and 2.4 (men) in the reference population (120). A decrease in the appetite scores was seen during the study period, but the subsequent mean scores, about 40, show that the patients continued to have substantial problems. However, the MLT group who had the lowest intake at baseline managed to increase their energy intake, and a weight stabilisation was seen in both groups. In Study I an improvement of the items "food tastes bad at hospital", and "weight loss" was reported by the study group. This may be related to the change of system of serving the meals, suggesting that the way the food is served may affect appetite.

Still, the most efficient way to improve cancer patient's nutritional problems and poor QoL is to actively control the tumour, but this is not yet possible for many of the cancer diseases. However, efforts to limit weight loss that are implemented as soon as possible may contribute to a better QoL. The loss of appetite, shown to be associated
with lower QoL scores in weight losing cancer patients (64-67) may be stimulated by drugs e.g. progestins (94-96).

The relation between weight loss and survival

The prognostic role of information on weight loss reported in other studies (45-48,66,68,70-74) was also seen in Studies II, III and IV. In Study II weight loss the last 6 months showed an independent contribution to the overall classification of nutritional status. There was a statistically significant difference in time of survival between the patients rated as SGA A and those rated as SGA B+C. In Study III, there was a numerical, but not statistically significant difference in time of survival between the study group, which experienced a more rapid and greater weight gain, and the control group. Weight loss was also independently related to survival in Study IV, with a statistically significantly longer time of survival in patients without weight loss. Weight losing patients had a lower probability to response to chemotherapy treatment (Study IV). Hence, efforts to prevent further weight loss may have an impact on survival in cancer patients.

Assessment of nutritional status

Malnutrition may be present even in the absence of marked weight loss (52). Biochemical variables, e.g. S-alb, B-Hb, CRP and Fibrinogen, often assessed as a routine, may reveal a deteriorated nutritional status (42,44-48,52,53,121). Low S-alb levels have earlier been demonstrated to correlate with a deficient nutritional status as previously assessed by the SGA (58). In study II a similar relationship was demonstrated, now using the PG-SGA.
If reliable biochemical variables are not available, a questionnaire may be employed to assess nutritional status. The PG-SGA (Study II) was shown to be a simple, reliable and cheap method for assessing nutritional status in the two groups of patients that were selected to differ considerably in their nutritional status. However, in patients with advanced cancer the question about the level of food intake last month compared to normal may be less reliable. In these patients the actual food intake may be very small, but considered as normal by that patient for quite some time. It is possible that the PG-SGA is more suitable for newly diagnosed cancer patients, the majority of whom are unlikely to have an advanced disease.

**Assessment of the dietary intake**

Dietary advice should always be based on the patient's actual food intake, assessed in a proper way. The 24-hour recall for assessment of food intake is considered to be the easiest method for the patient, but calls for the interviewer to be very careful. The decision to use this method in Studies I and III was made in view of its simplicity for the patients, still being discriminative and providing relevant information. However, when the food diary method was used in Study V, we realised that even patients with very advanced disease managed to complete this without considering it too burdensome. In future studies, we recommend use of the food diary, based on our experience and the demonstrated stronger correlations with weighed records (79).

One may speculate about under- and overreporters among cancer patients. As many of them have lost weight/are losing weight and have difficulties eating enough, there does not seem to be any reason for them to underreport. Perhaps there are more overreporters to satisfy the interviewer, especially if this is the dietician responsible for
the dietary advice? However, the rather modest dietary intake reported in the 24-hour recalls and in the food diaries do not support this notion.

**Dietary advice, "Consumed food is good food"**

Dietary advice to the patients was based on the notion that the food the patient managed to eat was good for him/her, regardless of nutritional composition. They were told that cream, butter, whole fat milk and cheese, desserts and sweets were "good food", and that the main purpose was to get as many calories as possible. This message was sometimes met with surprise and even suspicion from patients and their families, even if given both by the treating doctors, the nurses and the dietician. This advice is the opposite to that given for prevention of cancer or other diseases, which necessitated considerable explanations. The only disadvantage of this message was that family members sometimes were worried about gaining weight, when they had the same food as the patient.

In Study V, however, the dietary advice was different. The patients were told to reduce their intake of food with a high amount of fat, in order to reduce the competition between "the ordinary" fat and the omega -3 fatty acids, in favour of the latter. The intention was to follow the recommendations for healthy people, ≤ 30E% (40).

**The role of commercial supplements**

In the diet of many cancer patients, commercial supplements contribute a considerable share of the energy and nutrient intake. In a review of randomised control trials including oral supplements and/or dietary advice, the conclusion was that supplements may have a more important role than dietary advice for the improvement of body
weight and energy intake (122). In the study by Evans et al. (44), patients in the counselled group all had commercial supplements, and in Ovesen et al (123), patients were offered commercial supplements if indicated. In these studies, the nutritional support increased energy intake and influenced weight development (44,123). Less weight loss was seen during the first 4 weeks in patients with lung cancer (44). In the study by Ovesen et al (123) of patients with SCLC, ovarian or breast cancer, weight increased more in the counselled group, but the difference was not statistically significant after 5 months.

Commercial supplements were available to patients in all of the present studies. The possibility to prescribe supplements to cancer patients with subscription was introduced in Uppsala County during Study I. Members of the resource group participated in the preparatory work for this. Only two patients received enteral nutrition during the last month before they died (Study III).

However, too many patients do not take their supplements as prescribed, and they must be encouraged and reminded to do so. An opportunity to taste a number of the supplements before the prescription is likely to increase the probability of consumption as recommended, although this has not been properly studied. Patients and families benefit from practical advice about how to vary the supplements, e.g. mixed with milk, cream, ice cream, fruit and berries. However, it appears necessary to stress that the supplements are mainly intended to be supplements, and the primary measure is to improve the intake of food and drinks, e.g. to choose more energy dense alternatives, or to serve the meals at other times or in different ways.
The relation between weight development and dietary intake

In the present studies in which nutritional support was an intervention (Studies I, III and V), a positive change in weight development was seen. In spite of the advice to eat energy dense food, and to have many meals and snacks, the mean energy intake did not increase to a great extent. The percentage of energy provided by fat, 38-42% in Study I and 35-40% in Study III was in accordance with the recommended level in energy dense food (100). In Study V the patients did not succeed to reduce the proportion of fat as intended (mean intake 33-35%). However, on the FO regimen the plasma levels of EPA and DHA still increased as expected.

Although most of the patients with GI cancer in Study III did not reach the energy levels recommended for healthy people of the corresponding age (40), they did not continue to lose weight. A possible reason for this may be that cancer patients have lower energy requirements (35,124), and/or lower energy expenditure than healthy peers due to a lower level of physical activity. Another possibility is that the energy intake before inclusion in the studies was that low that even a modest increase of food intake was enough to have a positive influence on the weight development. The patients with SCLC increased their energy intake, but still continued to lose weight. Presumably they had an increased energy need (37), and should have had a more aggressive nutritional support, possibly including enteral nutrition, to stop their weight loss. The lung cancer patients received intensive and frequently prolonged chemotherapy with the aim to prolong survival and possibly cure some, whereas the GI cancer patients generally received much less chemotherapy. In Study V the energy provided by the fish oil probably contributed to the stabilisation of body weight.
The food at home

Support of and information to family members may improve the cancer patient's dietary intake. Nutritional problems often cause anxiety in the family; to eat and drink is fundamental to our daily life. Families and other caregivers need information, verbal and in writing, on suitable messages, including the "consumed food is good food", and how to best utilise commercial supplements. In Studies I, III and IV, the dietician had continuous contact with the families, on the ward, at the out-patient clinic and by telephone.

The food at the hospital

In order to facilitate for cancer patients to at least try to increase their energy intake, there must be a possibility for them to get what they like to eat and drink at a time when they want it. Thus, a great variety of food and drinks should be available at the hospital. The hospital kitchen menu should include energy dense food, food of varying consistency e.g. fluid, minced, purée, and cold and hot food. In addition, the ward kitchen should offer a large selection of snacks, drinks, commercial supplements and food like pancakes, meatballs, omelettes and soups.

The change of system for serving the food, which was implemented on the ward during Study I, resulted in a more pleasant environment at the meals. The patients could decide the components and the size of the portion at the actual time of the meal, not the day before as in the standard serving system with ready-made trays. At Christmas and Easter the staff and the dietician arranged meals with traditional food, which the patients and the staff ate together.
Information and education to staff at the hospital and in home care

Actions aiming at an improved nutritional support are actually not complicated, but they have to be performed, and thus some knowledge is required. Dieticians are uniquely qualified to provide nutritional intervention in the form of diet instructions and intensive nutritional support, but there is no theoretical reason to believe that other professionals could not give dietary advice (122). However, nutrition is only a minor part in the basic education of physicians and nurses. The possibility of a good nutritional care of the patients increases with repeated information, education and discussion concerning nutritional issues. The dietician meets the patient for dietary recall and dietary advice during a relatively short period of time. The staff, on the wards and in home care, has contact with the patients more frequently and should provide the basic nutritional care.

In Studies I and III, there were extensive educational programs intended for physicians, nurses, and assistant nurses. These were implemented in different ways. The dietician had the main responsibility for the education in nutritional care. Lectures, seminars, educational days and group discussions were used to cover theoretical issues. On the wards there were practical training, teaching and discussions in daily work. The home care nurses in Study III also had the possibility to meet the dietician during problem-focused supervision, and to phone for consultation on individual patients. It may be advantageous if other team members e.g. physiotherapist, occupational therapist, social worker and dental hygienist, are also invited to attend the education and information on nutrition. This was done in Studies I and III. Patients tend to discuss their weight loss and other nutritional problem with most staff involved in the care.
Weight development and the use of anti-cachectic drugs

The potential of omega-3 fatty acids and melatonin to reduce the level of cytokines, involved in cachexia has been demonstrated in earlier studies in the form of associations with weight gain, improvement in performance status, better appetite and survival (87, 90-93). In Study V, these substances were used to explore the effect of each during four weeks, and then their combination during a second period. The included patients had advanced disease, and no further medical tumour controlling treatment was available for most of them. The study was performed to find out if patients would benefit by fish oil, melatonin and dietary advice. The FO and MLT interventions were generally well tolerated. On FO the plasma level of fatty acids changed in a manner similar to that of healthy individuals on a similar dose (117). This suggests that a severe cancer-associated inflammatory state does not inhibit the fatty acid response expected from high dose FO. A stabilisation was seen in the weight development. Considering the weight loss of almost 3kg/month seen in weight losing patients with pancreatic cancer receiving supportive care only (90), this could be regarded as a positive effect. Given the results in earlier and in the present studies, further explorations of the putative beneficial effects of FO and MLT are justified.
**Nutritional support and cancer treatment**

All nutritional interventions, particularly preventive ones, must be performed in close collaboration with the treating physicians, recognising both population risk and individual factors. Intensity and duration of treatments are examples of population risks and certain concomitant diseases, special diets and social support are essentially individual risks.

Many newly diagnosed cancer patients have lost weight prior to diagnosis. Once the tumour growth is entirely eradicated, e.g. by surgical removal of a bowel cancer, weight is usually regained and there is no need for any nutritional support. The surgical trauma, e.g. a total gastrectomy in many patients with gastric cancer, may in some patients cause longstanding problems requiring special attention. Radiotherapy and particularly chemotherapy are frequently given during prolonged time periods. Thus, these patients might be at risk for nutritional problems during many months. Chemotherapy treatments and patient groups vary greatly with respect to risk for nutritional problems. The SCLC patients in Study I were selected for nutritional intervention in addition to all other interventions for this reason. However, patients with breast cancer were not. During adjuvant chemotherapy the experience is rather the opposite: namely that breast cancer patients frequently gain weight. This is probably due to a hormonal influence by the medical therapy (125).
CONCLUSIONS

♦ Weight loss is related to quality of life, response to treatment and survival.

Weight loss was shown to be associated with poor QoL, low performance status, and less probability to respond to cytostatic treatment and poor survival in cancer patients. The result of the present studies add further support to previous research showing that weight loss is a risk factor of poor outcomes in cancer patients.

A routine where all patients are weighed at each visit at the out-patient clinic, at admission on the wards and once a week during their hospital stay, would facilitate an earlier discovery of patients at risk or already malnourished. Preferably this should be the routine not only at the cancer clinics; weight loss might be a risk factor in any patient.

♦ The PG-SGA turned out to be useful for identification of patients at risk for malnutrition.

A more detailed assessment of nutritional status using a simple questionnaire, at least in the weight losing patients, provides information useful for planning the future nutritional care. In patients assessed as SGA B or C, nutritional actions should be instituted such as a referral, if not already done, to a dietician.
Patients benefit from dietary advice and other nutritional support.

It is possible for cancer patients to increase their dietary intake and in this way improve weight development. In addition to dietary advice, often including commercial supplements, directly to the patients, support and information to the families, information to and education to staff should be included in nutritional support. The practical teaching in daily practice used at the lung cancer ward and the co-operation between the specialist clinics and the home care service can be looked upon as good examples.

Supplementation with fish oil and melatonin did result in weight stabilisation.

In the cachectic cancer patient, good nutritional support and care does not seem to be enough. In an exploratory trial, when fish oil and melatonin were used as potential anti-cachectic drugs, there was a stabilisation of body weight development. However, it is difficult to determine which of the interventions, dietary advice, fish oil or melatonin, that had the strongest impact on weight. Neither of the drugs had any systematic impact on the chosen markers for cachexia development.

Considering the results of earlier studies and our experience in Study V, there does not seem to be any reason to advice against the use of fish oil in patients who ask about it. However, they should be advised to comply with the dose recommendations from the manufacture. More knowledge on this issue can only be provided by large randomised trials in homogenous patient groups.
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<tbody>
<tr>
<td>AA</td>
<td>Arachidonic acid</td>
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<td>APPR</td>
<td>Acute phase protein response</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>BW</td>
<td>Body weight</td>
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<td>CIPS</td>
<td>Cancer inventory of problem situation</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<td>DHA</td>
<td>Docosahexaenoic acid</td>
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<tr>
<td>E%</td>
<td>Energy percentage</td>
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<td>EE</td>
<td>Energy expenditure</td>
</tr>
<tr>
<td>EORTC</td>
<td>The European organisation for research and treatment of cancer</td>
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<td>EPA</td>
<td>Eisosapentaenoic acid</td>
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<tr>
<td>FO</td>
<td>Fish oil</td>
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<td>Intensified primary health care</td>
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<td>Individual support</td>
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<td>Nordic nutrition recommendations</td>
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<td>Description</td>
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<td>--------------</td>
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<td>P-prealbumin</td>
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<td>Patient generated subjective global assessment</td>
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<td>Prostaglandin E₂</td>
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<tr>
<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>RDA</td>
<td>Recommended daily allowances</td>
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<td>Resting energy expenditure</td>
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<td>S-alb</td>
<td>Serum-albumin</td>
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<tr>
<td>S-Hb</td>
<td>Serum haemoglobin</td>
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<tr>
<td>S-LDH</td>
<td>Plasma Lactate Dehydrogenase</td>
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<td>SC</td>
<td>Standard care</td>
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<td>SCLC</td>
<td>Small cell lung cancer</td>
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<td>SGA</td>
<td>Subjective global assessment</td>
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<td>soluble Interleukin 2 receptor</td>
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<td>S/N-C</td>
<td>Survival/nutrition control group</td>
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<td>SNR</td>
<td>Swedish nutrition recommendations</td>
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<td>SPG</td>
<td>Study period group</td>
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<td>TEE</td>
<td>Total energy expenditure</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor α</td>
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APPENDIX

Patient Generated Subjective Global Assessment.

Questions answered by the patient.

1. I am about ...........cm tall
   I weigh about ..........kg
   A year ago I weighed about ..........kg
   Six months ago I weighed about ..........kg
   During the past 2 weeks my weight has
   □ decreased ..........kg
   □ not changed
   □ increased ..........kg

2. I would rate my food intake during the past month (compared to my normal) as
   □ no change
   □ more than usual
   □ less than usual
   □ much less than usual
   □ taking only liquids
   □ taking only nutritional supplements
   □ really taking in very little of anything
Appendix 2(4)

3. Over the past 2 weeks I have had the following problems that keep me from eating enough (check all that apply)

- [ ] no problems
- [ ] no appetite, just did not feel like eating
- [ ] nausea
- [ ] vomiting
- [ ] diarrhoea
- [ ] constipation
- [ ] mouth sores
- [ ] dry mouth
- [ ] pain
- [ ] thing taste funny or have no taste
- [ ] smells bother me
- [ ] other .....................................................

4. Functional capacity

Over the past month I would rate my activity as generally

- [ ] normal, no limitations
- [ ] not my normal self, but able to be up and about with fairly normal activity
- [ ] not feeling up to most things bur in bed less than half the day
- [ ] able to do little activity and I spend most of the day in bed
- [ ] pretty much bedridden
Appendix 3(4)

Questions answered by physician or dietician

5. Disease and its relation to nutritional requirements
   Primary diagnosis.............................................
   (stage if known........................................)
   Metabolic demand (stress) □ no stress □ low □ moderate □ high

6. Physical (0=normal, 1=mild, 2=moderate, 3=severe)
   □ loss of subcutaneous fat (triceps, chest)
   □ muscle wasting (quadriceps, deltoid)
   □ ankle oedema □ sacral oedema □ ascites

7. SGA rating
   □ A= well nourished
   □ B = moderately (or suspected of being) malnourished
   □ C = severely malnourished

Patient-Generated Subjective Global Assessment of Nutritional Status
F.D Ottery 1995
Appendix 4(4)

**Guidelines.**

Metabolic demand (stress).
May include: stress, tumour fever, depression, pain, fatigue, affect of the tumour, treatment
Loss of subcutaneous fat.
Subjective impression by palpation
Muscle wasting.
Loss of bulk and tone detectable by palpation
Oedema.
Noted by inspection and palpation.
Ascites.
Noted by inspection and palpation.

**SGA rating.**

SGA A.
A nonfluid weight gain during the last 2 weeks, even if the net loss the last six months was 5-10\% and the patient had a mild loss of subcutaneous fat. Improvements e.g better appetite.

SGA B
> 5\% weight loss the last 2 weeks without stabilisation or weight gain,
definite reduction in dietary intake, mild loss of subcutaneous fat.

SGA C
Obvious signs of malnutrition eg severe loss of subcutaneous fat, muscle wasting and often oedema, weight loss > 10 \%