Dietary energy density and energy intake in cancer patients

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ABSTRACT

Background & Aims: Cachexia is frequent in advanced cancer and is associated with adverse outcomes; however, definite diagnostic criteria for cachexia are not established. Diet energy density (ED) may affect energy intake (EI) and energy balance. Patient characteristics may also influence such associations. This potentially hampers cachexia treatment and dietary treatment in clinical practice.

The aim was to study associations between ED and EI in palliative cancer patients and whether ED or EI predict energy balance, and the influence of systemic inflammation and survival time. The prevalence of reduced quality of life (QoL), function and survival, in patients classified by different cachexia criteria were compared.

Methods: Dietary intake and ED was assessed by food records (n=251-322). Energy balance was calculated from the change in body energy content by repeated DXA scans in 107 patients for a total of 164 4-month periods. Linear regression and linear mixed model were used to investigate relationships between ED and EI with patient characteristics as covariates. In energy balance analysis systemic inflammation and survival were covariates. Quality of life (QoL) was assessed by questionnaire, physical function by treadmill test.

Results: Diet ED was associated with EI, explaining approximately 16-22 % of the variation in EI. Age, BMI, fatigue and survival were negatively associated and hypermetabolism was positively associated with EI. After covariate adjustment, ED was still positively associated with EI. In unadjusted models, the ED of solid food and EI were both positive predictors of energy balance (P<0.03). Survival was positively and systemic inflammation negatively associated with energy balance (P<0.005). After adjustment for inflammation, only EI remained a significant predictor. Adverse QoL, function and symptoms were associated with weight loss >2%, BMI <20, fatigue and CRP >10mg/L (P<0.05). Short walking distance was associated with fatigue, low grip strength and inflammation (P<0.05). Short survival was associated with weight loss, fatigue, inflammation and S-albumin < 32g/L (P<0.05). The prevalence of cachexia diagnosis varied from 12 to 85 % using different definitions.

Conclusions: Diet energy density and energy intake are positively associated. Age, BMI, fatigue, survival and hypermetabolism are associated

with EI, but do not substantially influence the association between ED and EI. Diet EI and ED of solid food are positively associated with energy balance in patients with advanced cancer. Relations between EI, ED and energy balance are affected by systemic inflammation. Thus, targeting systemic inflammation may be important in nutritional interventions in this patient group.

Weight loss, fatigue and markers of systemic inflammation were consistently associated with adverse QoL, reduced function, more symptoms and shorter survival. The prevalence of cachexia using different definitions varied widely; indicating a need to further explore and validate diagnostic criteria for cancer cachexia.

Keywords: Cancer, cachexia, diagnostic criteria, quality of life, nutritional support, energy intake, energy balance, dietary energy density

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SAMMANFATTNING PÅ SVENSKA

Aptitlöshet och avmagring (kakexi) är vanligt vid avancerad cancer och förknippas med negativa konsekvenser så som försämrad behandlingseffekt, livskvalité, fysisk funktion och kortare överlevnad. Tydliga och välbelagda diagnostiska kriterier för kakexi saknas, vilket försvårar diagnostiken och behandlingen. Minskat födointag är en av de viktigaste faktorerna som leder till avmagring. Ett av de vanligaste kostråden för att öka energiintaget är att öka intaget av energirika livsmedel och drycker. Energitätheten i kosten kan påverka energiintag och energibalans positivt men detta är inte studerat på cancerpatienter.

Syftet med denna avhandling var att studera om energitätheten i kosten kan påverka energiintag och energibalans hos patienter med avancerad cancer. Ett ytterligare mål var att utforska och validera olika diagnostiska kriterier för cancer cachexia genom att se hur dessa relaterar till nedsatt livskvalité, fysisk funktion och överlevnad. För att studera detta analyserades data från interventionsstudier av anti-inflammatorisk behandling, anemibehandling, insulinbehandling och näringsstöd på en palliativ öppenvårdsmottagning, Sahlgrenska Universitetssjukhuset, mellan 1993 och 2005. Mätningar inkluderade blodvärden, fysisk funktion, kroppssammansättning och livskvalitéformulär. Kostintaget uppskattades från kostdagböcker.

Det fanns ett positivt samband mellan kostens energitäthet och energiintaget. Patienter med högre ålder, mer trötthet och kort överlevnad hade ett lägre energiintag men även hos dessa patienter var en hög energitäthet i kosten förknippat med ett högre energiintag. Ett högre energiintag och hög energitäthet i fast föda var förknippat med en förbättrad energibalans under de följande 4 månaderna. Patienter med inflammatoriskt påslag hade en mer negativ energibalans, vilket överskuggade energitäthetens påverkan. Dessa fynd stödjer nuvarande kostråd men belyser även vikten av anti-inflammatorisk behandling.

Viktminskning, trötthet och inflammatoriska markörer var förknippat med nedsatt livskvalité, funktion, fler symtom och kortare överlevnad. Förekomsten av kakexi varierade kraftigt beroende på vilka kriterier som användes, vilket indikerar ett behov av att ytterligare undersöka och validera diagnostiska kriterier för cancer kakexi.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Wallengren O, Lundholm K, Bosaeus I. Diet energy density and energy intake in palliative care cancer patients. Clin Nutr. 2005;24(2):266-73.

II. Wallengren O, Bosaeus I, Lundholm K. Dietary energy density is associated with energy intake in palliative care cancer patients. Support Care Cancer. 2012:20(11):2851-2857.

III. Wallengren O, Bosaeus I, Lundholm K. Dietary energy density, inflammation and energy balance in palliative care cancer patients. Clin Nutr. 2012. Epub 2012/06/26.

IV. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: Relation to quality of life, exercise capacity and survival in patients with advanced cancer. Submitted

CONTENT

ABBREVIATIONS

AMC	Mid-arm muscle circumference
ASMI	Appendicular skeletal muscle mass index
BMI	Body mass index
BW	Body weight
CRP	C-reactive protein
DXA	Dual-energy x-ray absorptiometry
E%	Percentage of energy intake
ED	Energy density
ED_{food}	Energy density of solid food
EI	Energy intake
ES	Effect size
ESR	Erythrocyte sedimentation rate
FR	Food record
EORTC	European Organization for Research and Treatment of Cancer Scale
KPS	Karnofsky Performance Score
ONS	Oral nutritional supplements
QoL	Quality of life
REE	Resting energy expenditure
TSF	Triceps skinfold
WL	Weight loss
W%	Percentage of food weight

1 INTRODUCTION

Cachexia is very common in patients with advanced cancer. It affects treatment, survival, quality of life (QoL) and function negatively, yet it is rarely recognized, assessed, or managed actively [1]. Contributing factors may be the lack of a clear definition and the multifactorial nature of the cachexia syndrome [1, 2]. Recently there have been several articles defining and discussing the definitions of cancer cachexia [2]. The most accepted definition of cancer cachexia have been published as an international consensus and is one from more detailed descriptions of stages and subsets will develop [1, 2]. The currently suggested definitions and staging of cancer cachexia are supported by a clinical and pathophysiological rationale [1, 3-5]; however, the validity and prognostic significance in different patient groups remains limited [4, 6, 7].

Reduced food intake is one of the main domains of anti-cachexia therapy [1, 2, 8-10]. Dietary counseling is in routine practice often recommended as the first line of nutrition therapy [11, 12]. One of the most common strategies to increase energy intake (EI) is to increase the intake of energy-dense food and beverages [11-14]. Dietary energy density (ED) is associated with EI in healthy and obese subjects [15-19]. The effect of dietary advice aimed at increasing ED in patients with advanced cancer has not been studied. This advice is consequently based on expert opinions and interventions in other patient groups [11-14].

The main objective of this thesis was to increase knowledge and efficacy of oral nutrition therapy by investigating if diet ED is important for maintaining an adequate EI in cancer patients (*paper I-III*). An additional objective was to further explore and validate different diagnostic criteria in the diagnosis and staging of cancer cachexia (*paper IV*). To achieve this, a secondary analysis was performed of data from intervention studies of anti-inflammatory treatment, anemia therapy, insulin treatment and nutritional support in an outpatient palliative care program at the Department of Surgery at Sahlgrenska University Hospital (Gothenburg, Sweden) between 1993 and 2005 [20-23].

1.1 Cancer

There were more than 55 000 cases of malignant cancers reported to the Swedish Cancer Registry in 2010. During the last two decades the average

annual increase in number of cases has been 2.0 % for men and 1.4 % for women. The increase is partly explained by the ageing population but also by the introduction of screening activities and improvements in diagnostic practices [24]. The probability of developing cancer before the age of 75 is 31 % among men and 28 % among women. However, the risk of developing cancer varies strongly with both age and by site [24].

The prognosis for cancer patients in Sweden has developed positively in the last four decades. The relative 5-year survival has increased from 35 % for men and 48 % for women to nearly 70 % for both sexes [25].

Gastrointestinal cancers

The major gastrointestinal cancers are cancer of the colon, rectum and anus, stomach, pancreas and biliary tract. Together they constitute about 16 % of all newly diagnosed cancers in Sweden [24].

There is an annual decrease in incidence of upper gastrointestinal cancers for both men and women during the last two decades which is mainly attributed to a reduction in stomach cancer incidence [24]. Overall 5-year survival of stomach cancer is about 20 percent [25].

Cancer of colon and rectum are among the most common cancer sites and the trend is rather stable although colon cancer in women has increased during the last decade [24]. The relative 10-year survival rate is over 50 percent [25].

There is a declining trend in both cancer of the liver and pancreas. Cancer of the pancreas has very poor prognosis. The relative 5-year survival is currently only a few percent [25].

Treatment

The main treatments for cancer care are surgery, radiotherapy and chemotherapy. Although the basic principles are the same, there is a constant improvement and refinement of these methods. Often they are combined in such a way that side effects are reduced, while treatment results are improved [25]. The disease and its treatment still generate a large number of symptoms that can affect nutritional status. All treatments have nutritional consequences, either because they add a nutritional demand or because they have side effects that limit dietary intake [26].

1.1.1 Palliative care

With long time (5-10 year) survival rates ranging from only a few percent to just over 50 % it is clear that a majority of patients with gastrointestinal

cancers are eligible for palliative care. The concept of palliative care and palliative medicine has been around for more than 30 years. The palliative phase begins from the moment cure is not or no longer possible, and lasts until the moment of death. The World Health Organization's current definition of palliative care states that:

"Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"[27].

Palliative care is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life. As such it can include chemotherapy or radiotherapy, symptom management, nutrition support and counseling, preferably in a multimodal team approach [10, 26, 27]. The focus of care may change through the disease trajectory from physiological and functional outcomes to improvement of food enjoyment and QoL [26].

1.2 Cancer cachexia

The term 'cachexia' originates from the Greek words kakós (bad) and hexis (condition or appearance). This 'bad condition' has long been associated with the gravely ill patient and with poor prognosis. The term is regularly used to describe wasting of body tissues or a state of depletion [26].

1.2.1 Definition and diagnostic criteria

Cancer cachexia is a complex and multifactorial syndrome that is not easily defined and several definitions and criteria for diagnosis have been suggested [1-4, 6]. An ongoing loss of muscle mass (with or without loss of fat mass) due to a negative energy and protein balance driven by a variable combination of reduced EI, systemic inflammation and metabolic abnormalities are considered to be main characteristics [1, 2].

Development of cancer cachexia is seen as a continuum with three suggested stages that are clinically relevant: precachexia, cachexia and refractory cachexia [1]. Their definition still remains somewhat imprecise but provide a framework which can evolve over time [1, 2]. Defining the stage and components of cancer cachexia could help select patients suitable for multimodal treatment programs [1, 2, 10]. Early recognition of cachexia is important so that its effects can be reduced or postponed. The proportion of

patients with cachexia diagnosis can vary considerably depending on the definition criteria used [6, 7, 28, 29]. For example, Fox et al. observed a prevalence of cachexia ranging from 2.4 to 14.7 % depending on definition and totaling 23.1 % by any of these definitions in a large sample of cancer patients [29]. In weight losing patients with advanced pancreatic cancer the prevalence ranged from 21.8 to 60 % depending on if a 3 or 2 factor definition of cachexia were used [4]. Thoresen et al. observed a prevalence of cachexia ranging from 22 to 55 % in colorectal cancer patients depending on definition [7]. Bozzetti et al. classified patients by 4 classes (or stages) of cachexia from 'asymptomatic precachexia' to 'symptomatic cachexia' based on weight loss (WL) (≥10%) and presence or absence of symptoms; 36 % had both symptoms and WL, 40 % had WL and 83 % had either WL or symptoms, leaving 17 % with WL <10% and no symptoms [6]. The prevalence of 'nutritional risk' or 'malnutrition' in cancer patients varies widely, ranging from 5 to 85 %, using different criteria (WL, BMI or screening instruments) in different populations and settings [11]. It is clear that a lack of definition and classification is a barrier to getting a clear picture of the prevalence and consequences of cachexia.

Diagnostic criteria should be both sensitive and specific to be of value in clinical practice and in the design of clinical trials. The currently suggested definitions and staging of cancer cachexia are strongly supported by a clinical and pathophysiological rationale [1, 3-5]. However, the validity and prognostic significance in different patient groups remains limited [4, 6, 7].

1.2.2 Etiology, pathology and impact

Cachexia in advanced cancer has a negative impact on outcomes such as QoL, physical function and survival [1, 5, 30]. Approximately 20% of patients with cancer may die from the effects of malnutrition rather than the malignancy [31]. Cachexia is also associated with increased risk of complications in surgery and radiotherapy and impaired response to chemotherapy [31, 32].

Weight loss and loss of muscle mass

Weight loss is a cardinal feature of cancer cachexia and a majority of patients with advanced cancer experience some degree of WL [5]. Weight loss is a significant prognostic variable for survival in most studies in patients with advanced cancer [33]. Various perspectives exist on how to classify WL. Absolute WL can be classified by severity and various cut-offs have been suggested, from 2 to >20 % [1, 26]. Another perspective is intensity of WL, i.e. rate of WL in 1 week, 1, 3 or 6 months [1, 26]. Body mass index (BMI)

can be a measure of body energy and protein reserves, and can together with WL be used to assess the severity of depletion [1]. However, none of these classifications take into account the wide distribution in body composition in cancer patients and also give no information of proportions of fat and lean body mass lost [26].

Weight loss reflects a negative energy balance, in which dietary EI is less than energy expenditure. A reduced EI due to anorexia and metabolic abnormalities, including hypermetabolism driven by systemic inflammation, are considered the primary causes [5, 30, 34]. Other procachectic mechanisms may, however, be involved.

Weight loss is composed of lean and adipose tissues in different degrees. The amount of WL for any unit of energy deficit will be highly dependent on the proportion of fat and fat free mass lost as their energy density are very different (9,417 kcal/kg for fat and 884 kcal/kg for fat-free mass) [35]. The low energy content of lean tissue and concomitant up regulation of proteolytic pathways (particularly the ubiquitin-proteasome pathway) together with hypoanabolism makes loss of muscle mass greater than expected for any level of energy deficit compared to healthy subjects [36-39]. Systemic inflammation is believed to be primarily involved in the metabolic change and loss of muscle in cachexia; hormones, tumor derived factors, bed rest, and inadequate nutrient intake may also contribute [10, 40].

The ensuing loss of function and debilitation makes muscle loss an important feature and treatment target in cancer cachexia [1, 10, 37]. Muscle loss is indeed associated with poor outcome and shorter survival in cancer patients [41].

Assessment of muscle mass and strength are therefore important in diagnosis, staging and follow-up of cachexia; however, there is no consensus as to methodology [1, 42]. Cross-sectional imaging has been suggested as the preferred method (CT or MRI), followed by dual-energy x-ray absorptiometry (DXA), mid-arm muscle circumference (AMC) and bioimpedance analysis [1]. Handgrip strength has been suggested as the preferred method assessing muscle function [1, 3, 42]. There is also no clear consensus as to which cut-off limits should be used in diagnosis of cachexia. Appendicular skeletal muscle mass index (ASMI) consistent with sarcopenia have been suggested when using DXA [1, 3].

Catabolic drivers: Systemic inflammation

The catabolic drive and metabolic abnormalities in cancer cachexia has long been considered to be the result of a variety of interactions between the tumor and the host, of which all are not completely understood [38, 39]. The tumor induces local production of pro-inflammatory (interleukins; IL-1, IL-6, IL-8, interferon-γ and tumor necrosis factor-α) and anti-inflammatory cytokines (IL-4, IL-10 and IL-13) as well as tumor specific cachectic factors (proteolysis inducing factor and lipid mobilizing factor) [38, 39]. The liver responds by increasing the production of positive acute-phase proteins such as C - reactive protein (CRP) and fibrinogen. Concomitantly the level of albumin, a negative acute-phase protein, may fall [38]. Although not completely understood, there also seems to be a neuro-endocrine stress response that results in inadequate neuro-hormonal anabolic activity (insulin, growth hormone and testosterone) and excess catabolic activity (cortisol and myostatin) [38]. These host tumor interactions results in a catabolic state with a deranged protein, lipid and glucose metabolism [38, 39]. Systemic inflammation measured by CRP is associated with WL and poor prognosis [5, 43]. The value of specific cytokines in the assessment of inflammation in cachexia needs further study [5, 10]. Systemic inflammation is therefore considered to be one of the key features of the cachectic state and an important therapeutic target [1, 10, 38].

The most common marker of systemic inflammation in cancer patients has been the level of CRP [1]. Two cut-off levels have been suggested, CRP >5 or >10 mg/L [3, 4]. Alternative markers and prognostic scores include erythrocyte sedimentation rate (ESR), serum albumin, the composite Glasgow Prognostic Score, the Neutrophil Lymphocyte Ratio or the Platelet Lymphocyte Ratio [22, 43, 44]. Additional work is required to establish the value of different measures of inflammatory response as diagnostic criteria and selection in clinical trials [1, 43]

Many different anti-inflammatory therapies have been used in cancer cachexia treatment. Therapies include celecoxib, indomethacin, eicosapentaenoic acid, ibuprofen and thalidomide. The effects have generally been positive but inconsistent and few studies have been carried out that compared treatments [45-52]. Lundholm et al. showed that indomethacin prolongs survival over that achieved with placebo, but the effect of prednisolone is less clear [46]. Mantovani et al. showed that a combination of a progestational agent, eicosapentaenoic acid, L-carnitine and thalidomide is more effective in improving lean body mass, resting energy expenditure (REE) and fatigue reduction than any of the agents given alone [53]. Similarly, a combination of fish oil and COX-2 inhibitors is more effective in

improving weight and strength than fish oil alone [48]. It is clear that further study is needed to determine the most effective mode of anti-inflammatory treatment.

Energy intake and energy expenditure

Loss of appetite is one of the most frequently reported symptoms in cancer patients with on average 65 % of patients reporting anorexia in studies of palliative care [5, 26, 33]. Neuroendocrine and metabolic control of EI and appetite is regulated by peripheral signals to the brain as well as signaling of metabolic sensors in the brain and brainstem. It is clear that cancer anorexia is multifactorial and involves most of the signaling pathways modulating EI [26, 39]. The influence of anorexigenic signals is dominating and the orexigenic signals are reduced so that anorexia develops and EI is reduced [26, 39]. However, reported anorexia is not always associated with reduced intake and WL and vice versa [5].

Reported energy intakes by cancer patients are generally low. Average energy intakes are close to reported basal energy expenditure [26, 54, 55]. As a consequence a significant number of patients consume less energy than is required for basal activities of daily living. Energy intake is associated with WL in several but not all studies [5]. As a diagnostic criteria an EI < 1500 kcal/day have been used classifying patients with low intake [4]. Patients own estimate of intake in relation to normal have also been suggested for assessment of overall food intake [1].

Increased energy expenditure would also contribute to a negative energy balance. Resting energy expenditure has been measured in a variety of studies and results have been variable [5, 39]. Increased, normal and decreased metabolism has all been found [5, 39, 56]. Hypermetabolism may be present in some patients and it has been related to type and stage of tumor and the presence of systemic inflammation [5, 34, 39]. Total energy expenditure may fall due to reductions in physical activity, compensating for reduced EI and any hypermetabolism [57, 58]. Interestingly, it is possible to increase total energy expenditure with oral nutritional supplements (ONS) containing eicosapentaenoic acid [58].

Many drugs have been evaluated for their appetite stimulating properties and effect on EI, including progestins, glucocorticoids, cannabinoids and ghrelin [59-62]. There are some improvements in appetite, EI and body weight (BW); however, several of these drugs have unwanted side effects and no clear benefit towards QoL or survival have been observed which limits their clinical usefulness [10, 26, 59-62].

Nutrition impact symptoms

A number of symptoms may limit food intake in patients with advanced cancer, such as; anorexia, pain, early satiety, nausea, vomiting, dry mouth, dysphagia, dysgeusia, constipation and others, caused by the disease itself or by treatment [26, 63]. Many of these nutrition impact symptoms are present concurrently and psychological factors, such as anxiety, depression and distress, may also contribute [26]. Anorexia, dysphagia, pain and mouth sores are associated with reduced dietary intake, WL and reduced functional capacity [63]. Anorexia, dysphagia, nausea, pain, constipation and depressed mood are also associated with shorter survival [33, 64]. Many of these symptoms can be treated or palliated and there is a need of an integrated approach of these symptoms in the assessment and treatment of cancer cachexia [1, 26, 33].

Quality of life and function

The cachexia syndrome has detrimental effect on QoL. Patients report an impact on their emotions, spirituality, relationships and social functioning. Together with anorexia, pain and fatigue this results in a restricted and isolated life with decreased performance status and QoL [4, 26, 63, 65, 66]. Reduced QoL is associated with shorter survival [64]. There is a significant correlation between physical activity levels and patient reported physical function, role function and fatigue [57, 67]. Nutritional status is also associated with QoL and function and these aspects can also improve with nutritional interventions [65, 68-70].

Fatigue is one of the most common symptoms for patients with advanced cancer [33]. Fatigue can be defined as a subjective feeling of tiredness, weakness or lack of energy [71]. It is a multidimensional syndrome of physical, cognitive and emotional components with difficulty in motivation or in activity. The exact cause of fatigue remains unclear and many contributing factors may exist, such as energy depletion, alterations in muscle metabolism, pro-inflammatory cytokines, anemia, endocrine disorders, infections, medications, depression, and other interfering symptoms [42, 71, 72]. Pharmacological interventions for fatigue have shown some effects of psychostimulant methylphenidate, erythropoietin and darbepoetin [73]. Non-pharmacological interventions support the use of exercise and psychosocial interventions in the management of cancer related fatigue. Overall, more research is warranted, especially to determine potential efficacy in those with advanced disease [73].

Patient centered outcomes, such as patient reported QoL, function and symptoms, are important aspects when assessing the impact of cachexia and

effects of anti-cachectic treatment [1, 74, 75]. In palliative care, QoL and function becomes the principal or only endpoint of consideration [27, 74, 75].

The European Organization for Research and Treatment of Cancer questionnaire (EORTC-QLQ-C30) [76] is recommended in the routine assessment functional and psychosocial effects [1]. Alternatively, physician reported performance status can also be used (e.g. Karnofsky performance score or Eastern Cooperative Oncology Group questionnaire) [1, 77, 78]. Objectively measured physical activity with activity meters can be used to assess physical function, may provide a surrogate marker of QoL and is a meaningful outcome in clinical trials [1, 37, 57].

1.3 Nutrition support to cancer patients

The overall goal of oral nutritional support to cancer patients is to maintain or improve nutritional status and thereby improve treatment tolerance and outcome. Additional goals are to reduce disease or treatment symptoms, maintain or improve functional capacity and ultimately improve the patient's QoL [11-13, 68, 79-82]. Nutrition support in curative treatment aims primarily at increasing treatment tolerance [26, 65]. In the palliative phase, the main goal is to alleviate and prevent adverse symptoms and maintain or increase QoL [26, 65]. For caregivers involved in decisions related to nutritional support in patients with advanced cancer it is important to keep aware of the current state of evidence concerning prognosis in this patient group [26]. Approximation of life expectancy is required to make appropriate decisions in the phases of advanced malignant disease [26].

When *ad libitum* dietary intake is inadequate there are a number of nutrition support strategies available; dietary fortification and counseling, oral nutritional supplements (ONS, ready to drink or reconstituted powder), enteral tube feeding and parenteral nutrition, alone or in combination [11].

Conventional nutrition support cannot fully reverse the loss of muscle or the ensuing functional impairment in cachectic patients [1, 9]. However, multimodal treatment including nutrition support and anti-inflammatory treatment has been shown to partially alter the cachectic trajectory, improving functional capacity, QoL and prolonged survival of advanced cancer patients [20, 49, 53, 68, 83]. End stage catabolic patients with severe muscle wasting, low performance status and unresponsive to oncological treatment may not have clinical important benefits from such multimodal treatments [1].

European, American and Australian guidelines on nutritional support to cancer patients recommend that nutrition receives prompt attention and that intervention is commenced in patients that are malnourished or at risk for developing malnutrition [79-82, 84]. However, these guidelines do not fully capture the potential benefits of oral nutritional support such as dietary counseling and ONS as they rely predominantly on data from studies of enteral or parenteral feeding [68].

1.3.1 Dietary counseling strategies to improve dietary intake

Nutrition counseling is a supportive process, characterized by a collaborative counselor–patient relationship, to set priorities, establish goals, and create individualized action plans that acknowledge and foster responsibility for self-care to treat an existing condition and promote health [85].

Dietary counseling to improve nutrient intake in cancer patients with declining nutrient status is in routine practice often recommended as the first line of diet therapy, prior to using ONS or in combination with ONS [11, 12]. Dietary counseling should be individually tailored to nutritional needs, nutritional status, dietary restrictions, tolerance and feasibility, gastrointestinal function, medical condition and expected side effects of treatment [11, 12]. There are various dietary counseling strategies to support oral nutrient intake, including increasing the intake of energy-dense food and beverages, increasing the frequency of meals and snacks, enhancing flavor, modifying texture or temperature, limit beverage or separate food and beverage intake, retry problem foods, take alcohol as an appetite stimulant and avoid or include foods to remedy symptoms [11-14]. An alternative approach is to not increase quantity, avoid nutritional supplements or be allowed not to eat and that dietary restrictions should be lifted [13].

Psychosocial targeted advice includes eating what you want, can tolerate, are easy to eat, enjoy and that will improve QoL. Some suggest relaxing dietary restrictions and eat whatever negotiated as best by patient and family [13].

Most of these advices are based on expert opinions with little theoretical justification or empirical evidence to support them [13]. Some are based on observational studies, non-randomized trials or interventions in other patient groups [11-14]. Many studies neglect to report or give very brief information about the person giving the dietary counseling, frequency of counseling, which specific advices that were given, counseling methods used or the patients understanding and compliance. Most importantly, randomized trials

comparing the effects of specific dietary advice and their relative efficiency in cancer patients are lacking [11-13]. Consequently, little well supported specific dietary counseling strategies aimed at improving dietary intake in cancer patients are available. This is an area for further study.

1.3.2 Diet energy density

Energy dense foods are used with the intent of increasing the ED of the diet and thereby increase EI. Small meals, in reference to weight and volume, with high ED will provide more energy and are supposed to be less satiating.

Diet energy density is positively correlated with EI in healthy and obese people, both in experimental studies and in studies of people eating self-selected diets in free living conditions [15-19]. Cross-sectional epidemiological studies have shown that ED and BMI are correlated and that ED is associated with weight or waist circumference [86, 87]. This result, while not a general finding, implies that ED is associated with long-term energy balance in healthy and obese people [86, 87].

Experimental studies in institutionalized elderly or with home-delivered meals have shown that EIs increase when ED of the diet are increased [88-91]. However, these were not self-selected diets and all or a large part of the diet were manipulated and supplied to the subjects. This limits the potential for compensatory changes in intake and may not reflect the long term impact of diet ED on energy balance in the context of dietary counseling. With increased ED of the diet a decrease in the amount (weight) of food is usually observed so that EI increases less than expected (i.e. food intake compensation) [11, 15, 19, 92, 93].

The effect of dietary advice aimed at increasing ED in patients with advanced cancer eating self-selected diets in free living conditions has not been studied. Dietary counseling to increase the intake of energy-dense foods may be inappropriate for patients with advanced cancer, if it does not result in increased EI and an improved energy balance. This may be the case, for example, if the patient makes compensatory changes.

Dietary energy density can be defined as the energy per unit of dry or wet weight of food or energy per unit of volume of food. Usually ED is defined as energy per wet weight of food eaten [19]. The energy density of the diet is dependent on the macronutrient composition, amount of water, fiber and air in the diet, where the amount of water and fat is of most practical importance [94].

Different methods of ED calculation have been used, in reference to the types of food included in the analysis [95, 96]. The energy density can be markedly affected by the inclusion or exclusion of specific dietary items, particularly energy-free beverages [94-96]. This has implications for making direct comparisons between studies and interpretation of findings. In addition, associations between ED and dietary intake could vary according to how ED was calculated and therefore make the results of such studies method-dependent [87, 95]. For example, studies in healthy subjects have shown that ED is associated with long-term energy balance but the association depends on whether water and less energy-dense drinks are included in the calculation [87]. Research on healthy subjects suggests that energy-free beverages do not influence EI, though the long term effects of non-energy beverages intake on EI have not been fully explored [19, 97-99].

There is also limited information on the influence of patient characteristics on the association between ED and EI, potentially hampering individual tailoring of dietary treatment in clinical practice. In a heterogeneous sample, dietary associations in a between- or within-subject analysis could be different, due to differences among subjects such as age, sex, BMI, physical activity level, dietary reporting levels and related measurement errors (i.e. attenuation bias) [19, 100, 101].

Clarification of the association between ED, EI and energy balance in patients with advanced cancer is, therefore, necessary to improve dietary advice.

1.3.3 Evidence base for oral nutritional support in cancer patients

To review the evidence base for oral nutritional support to cancer patients meta-analyses, evidence based guidelines, systematic reviews and their bibliographic references were searched to identify studies that studied the effectiveness of oral nutritional support in cancer patients compared to no advice or usual care [11-13, 68, 79-84, 102-105]. Searches were updated with PubMed searches with combinations of exploded MeSH terms including neoplasm, diet therapy and nutritional support and related search terms. Only human randomized controlled trials (RCT) in English or Nordic languages were included. Trials studying the effects of parenteral or enteral nutrition or specific nutraceuticals (e.g. EPA, arginine, and glutamine) were excluded. Twenty-two RCTs with a total of 1847 participants were found [106-127].

Study groups were:

- no advice
- usual care
- the prescription of ONS
- dietary counseling
- dietary counseling and ONS

The no advice or usual care groups were control groups. However, usual care included brief nutritional advice, written or by dietician or other health care professionals in some studies. Oral nutritional supplements were commercially available ready to drink sip feeds but also creams or reconstituted powders that were nutritionally complete or energy/protein dense with vitamin and minerals. Amounts of ONS prescribed were not specified in all studies but ranged from 400 to 2400 kcal [106, 124, 125]. Four studies compared elemental or hydrolyzed diets to standard diets in patients with abdominal radiation [106-109]. In the 19 studies that included some form of dietary counseling or usual care with dietary information this was performed by a dietician in 13 studies [110, 113, 114, 118-127], otherwise it was performed by other health care professionals or not specifically mentioned. In most studies, the dietary counseling strategies used were only briefly described and focused mainly on increasing the intake of energy-dense food and beverages, increasing the frequency of meals and snacks, modifying texture and to avoid or include foods to remedy symptoms.

Effects of oral nutrition support

Overall there were several clinical benefits of the interventions including:

- Improved energy and protein intake [111, 113, 115, 119, 121, 123-125, 127]
- Improved body weight and anthropometry [106, 112, 117, 118, 122, 123, 126]
- Less malnutrition [120, 123-125]
- Improved immune function [106, 107]
- Improved QoL and function [124, 125]
- Less symptoms [116, 124, 125]
- Less complications or improved treatment tolerance [114, 117, 127]
- Reduced length of stay in hospital [114].

Effects of the interventions were mixed and 3 studies did not find any significant effects at all [108-110]. Two of these were comparisons of elemental diet for 33-44 days to standard low fiber diet; however, in 2 similar trials there were improvements in weight and immune function [106, 107]. The 3rd study included only well-nourished patients where positive effects are less likely [11, 110]. In the largest study, comparing dietary counseling, ONS or their combination to a control group, only modest effect on weight were found in the counseling group with no other effects of the interventions [126]. However, compliance to nutritional support was very low, for example; only 19% of patients were able to take their full prescription of ONS by week 6 of the 1 year study and only 17% completed more than one food diary [126].

In the most recent meta-analysis of the effects of oral nutritional support in cancer patients 13 randomized controlled trials with 1414 participants were included [68]. There were no significant differences in mortality between intervention and control groups (RR 1.06, P =0.43, I^2=0%). Nutritional intervention had positive effects on some measures of QoL and symptoms (global QoL, emotional functioning, dyspnea and anorexia). There were significant improvement in BW (mean difference 1.86 kg, P =0.02, I^2=76%) and EI (mean difference 432 kcal/day, P =0.001, I^2=97%). Heterogeneity was high in all significant analyses. Studies showing larger effects were identified as sources of heterogeneity [123-125]. Consequently, after removing these studies no significant effects were found. In a previous meta-analysis with 3 studies [107, 111, 115], of which 2 were not included in the above meta-analysis, found that oral nutrition support increased EI by 381 kcal/day, without significant heterogeneity [83].

The several positive effects of oral nutritional support in cancer patients are also supported by meta-analyses in other patients groups that have consistently shown improvements in nutrient intake, anthropometry and also a number of clinical and functional benefits [11, 102, 104, 105]. Contrary to studies in cancer patients, meta-analyses in several other patient groups have repeatedly shown reductions in hospital admissions and mortality [11, 104, 105]. However, the most recent Cochrane review did not find a consistent effect on survival [102]. Most studies in cancer patients are not adequately designed or powered to study the effects on mortality. For example, Baldwin et al. aimed at a assessing the effects of nutritional interventions on survival. They intended to include 660 patients to reach adequate power but the study was stopped prematurely by advice of a data monitoring committee and only included 358 patients and only half of the predicted deaths had occurred [126].

There are inherent difficulties studying the effects of nutritional interventions. Failure to comply with the treatment, lack of blinding and patients obtaining dietary information from alternative sources all make it difficult to assess the true treatment effect and also decrease the effect size (ES) of the interventions [128]. With these methodological issues and the large clinical heterogeneity between studies in mind, it is not surprising that results are heterogeneous and effects are modest or insignificant. Consequently, it is not yet possible to determine whether this is due to failure of the interventions, due to poor compliance or different effects in diverse patient groups and settings.

In conclusion, oral nutritional support to cancer patients is effective at increasing nutritional intake and BW and can also improve some aspects of QoL and malnutrition related outcomes. No beneficial effects on mortality have been found. Available evidence suggests that oral nutritional support should include dietary counseling with ONS if needed. Few well supported specific dietary counseling strategies aimed at improving dietary intake in cancer patients are available. The effects of diet ED on EI and energy balance have not been specifically studied. Conclusions are clearly limited by the large clinical and statistical heterogeneity and the low to moderate quality data from available studies. Further studies are needed.

2 AIMS

The overall aim of this thesis was to investigate if the energy density of the diet is important for maintaining an adequate energy intake in cancer patients. The thesis also aimed to examine which patient characteristics that may influence dietary intake, all in order to increase knowledge and efficacy of nutrition therapy for disease-related malnutrition in cancer patients.

An additional aim was to study the relation between different diagnostic criteria for cancer cachexia and the prevalence of adverse patient centered outcomes such as reduced QoL, impaired function, symptoms and also the prognostic significance of these criteria on survival.

Specifically, the following questions were addressed:

1. Is diet ED associated with EI in palliative care cancer patients? (*paper I*)
2. Which method of diet ED calculation is most appropriate to describe a possible relationship between EI and ED? (*paper I*)
3. In addition to diet ED, what subject characteristics (i.e. sex, age, BMI, WL, muscle mass, hand grip strength, fatigue and inflammation) are associated with EI? (*paper II*)
4. Do subject characteristics associated with EI influence the association between EI and diet ED? (*paper II*)
5. Is the association between ED and EI different within individuals compared to group level associations when accounting for between subject differences? (*paper II*)
6. Is diet ED and EI associated with energy balance in patients with advanced cancer, and does systemic inflammation influence these possible relationships? (*paper III*)
7. Which diagnostic criteria of cancer cachexia are associated with reduced QoL, more symptoms, reduced functional abilities and shorter survival? (*paper IV*)

3 PATIENTS AND METHODS

3.1 Study population

Patients referred to a palliative care program at the Department of Surgery at Sahlgrenska University Hospital (Gothenburg, Sweden) between 1993 and 2005 were included in the studies. This was a secondary analysis of cross-sectional and longitudinal data from intervention studies of anti-inflammatory treatment with indomethacin, of anemia with erythropoietin, insulin (NCT00329615), dietary counseling and nutritional support in an outpatient palliative care program. [20-23]. Patients were invited to participate in follow-up measurements that included biochemical tests, measurement of body composition and dietary intake every 4 months. None of the patients received radio- or chemotherapy during follow-up or had received any of these therapies within 6 months of the start of our evaluations.

Inclusion criteria were the presence of generalized malignant disease with a solid tumor type without efficient or established tumor treatment available, expected survival of more than six months at first visit. Subjects were also required to have data for BW, height and WL from pre-illness weight. In *paper I, II* and *IV* baseline data at inclusion in the above mentioned studies were used for analysis. In the longitudinal follow-up, all available data that met the study criteria were used for analysis. Measurement of REE was required in *paper I*. For inclusion in *paper I-II* at least one food record (FR) was required. The completion of at least two measurements of body composition and FRs separated by 4 months were required for the longitudinal follow-up (*paper III*). For *paper IV* at least one outcome was required (quality of life questionnaire or a treadmill walk). Exclusion criterion was treatment with parenteral or enteral nutrition at inclusion (*paper I, II and IV*) and during follow-up (*paper III*). Outliers for EI (outside ± 3 SD) were excluded in *paper II*. Only patients with a complete data set were included in *paper I*. In *paper II* and *III* only patients with complete data in the mixed models are presented. An overview of design and analysis is presented in Table 1.

Table 1. Design and analysis.

Paper	I	II	III	IV
Design	Secondary analysis Cross-sectional	Secondary analysis Cross-sectional	Secondary analysis Longitudinal	Secondary analysis Cross-sectional
Participants (n)	259	251	107	405
Inclusion year	1993-2000	1993-2005	1993-2005	1993-2005
Measurements	Weight Height Pre-illness weight 4 day FR REE	Weight Height Pre-illness weight ≥3 day FR REE DXA Survival Fatigue (1-10) Grip-strength Albumin CRP	Weight Height Pre-illness weight ≥3 day FR REE DXA Survival CRP ESR	Weight Height Pre-illness weight ≥3 day FR REE DXA AC TSF Survival EORTC-QLQ Fatigue (1-10) KPS Grip-strength Treadmill Albumin CRP ESR
Exclusion criteria	PN/EN	PN/EN EI outliers (±3SD)	PN/EN	PN/EN
Statistical analysis	Linear regression	Mixed model with repeated measures	Mixed model with repeated measures	Logistic regression, Cox proportional hazards model

Abbreviations: AC, mid-arm circumference; CRP, C-reactive protein; DXA, dual-energy x-ray absorptiometry; EN, enteral nutrition; EORTC-QLQ, European Organization for Research and Treatment of Cancer Scale; ESR, Erythrocyte sedimentation rate; FR, food record; KPS, Karnofsky Performance Score; PN, parenteral nutrition; REE, resting energy expenditure; TSF, triceps skinfold.

3.2 Methods

3.2.1 Anthropometry, body composition and energy balance

Body weight

Body weight (BW) was recorded in light indoor clothing on a calibrated electronic scale. Habitual weight before the onset of disease was reported by

the patients. Weight loss was calculated as the difference between the two, and expressed as percentage of habitual BW. Body height was measured using a wall-mounted stadiometer and body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Weight loss and BMI were classified according to five different criteria; BMI < 20, WL > 2%, 5%, and 10% respectively or WL > 2% and a BMI < 20 [1, 28].

Body composition

Body composition was measured by dual-energy X-ray absorptiometry using a LUNAR DPX-L scanner (Scanexport Medical, Helsingborg, Sweden). Whole-body scans were obtained in fast-scan mode. Body fat and lean tissue mass were analyzed using the extended research mode of the LUNAR DPX-L software (Version 1.31; Scanexport Medical). Appendicular skeletal muscle mass index (ASMI) calculated from appendicular lean soft tissue mass (kg) divided by squared body height were used as a proxy of whole body skeletal muscularity. Low ASMI was defined as ASMI < 7.26 kg/m2 for males and < 5.45 kg/m2 for females [1, 3]. Alternatively, AMC was used with a cut-off below the 10th percentile of a reference population [3, 129]. AMC was estimated using triceps skinfold and mid-arm circumference, measured with a Harpenden skinfold caliper and tape measure at midpoint of the humerus. Low muscle mass was defined as low ASMI or AMC below cut-off.

Resting energy expenditure

Resting energy expenditure (REE) was measured by indirect calorimetry (Deltatrac; Datex, Helsinki, Finland) after an overnight fast. Hypermetabolism was expressed as the percentage of measured REE above or below the predicted basal metabolic rate using the Harris-Benedict equation.

Energy balance

Energy balance was estimated from the difference in body composition from DXA scans separated by 4 months. Changes (gain or loss) in fat or fat-free mass were multiplied by their respective energy value (9,417 kcal/kg for fat and 884 kcal/kg for fat-free mass) and divided by the number of days between scans, giving energy balance per day (kcal/day) [35].

3.2.2 Dietary intake

Food records

A dietician instructed the patients to complete a 4-day FR at home. Amounts of all food and beverages were recorded in household measures. The dietician

interviewed each patient and any ambiguities were resolved upon return of the FRs. The emphasis in dietary intake during the study of palliative nutritional intervention in addition to indomethacin and erythropoietin treatment had been on energy and macronutrients [20]; consequently, the recording of beverages that did not contain energy was not specifically requested. Estimation of serving sizes and conversion to weight units were aided by a previously validated meal model [130]. Intakes of energy and nutrients were calculated with KOSTSVAR (from 1993 to 2000) or with DIET32 (from 2000 to 2005) software (Aivo, Stockholm, Sweden). The National Food Composition table (PC-kost, Statens livsmedelsverk, Uppsala, Sweden) was used as nutrient database. Food records were validated by 24 hr. urinary nitrogen [56].

Dietary characteristics

Energy intake is reported in absolute amounts (kcal), amount per kg of BW (kcal/kg/d), and as a multiple of the measured REE (EI/REE). Macronutrient intake is reported as the percentage of EI (E%). Food weight, water volume and fiber weight are expressed in grams per day and as percentage of the total food weight (W%).

Energy density

"Energy density" is defined as the amount of energy per wet weight of food (kcal/g). Four different methods, with varying exclusions of different beverages and water, were used to calculate the ED in the diet: (ED1) all food and beverages (*paper I-IV*); (ED2) all food and energy-containing beverages (*paper I*); (ED3; ED_{food}) all food and milk (*paper I and III*); and (ED4) food only (*paper I*). These methods have previously been used by Cox and Mela, and were used here in slightly modified form, in that alcoholic beverages were excluded in ED3 and no analysis were performed on all dry matter and macronutrients [95]. In *paper III* ONS were also included in calculation of ED_{food} (ED3). Summaries of methods and the rationale for different calculations of ED are presented in Table 2. The food and beverages were grouped in accordance with Swedish National Food Composition Tables grouping of foods [131]; in addition, a food group was created for energy-free beverages.

Table 2. Methods of energy density calculation. Methods presented in the order of least exclusion of food items.

Method	Includes	Excludes	Rationale
ED 1	Total dietary intake	-	Typical dietary measure. Includes all on the assumption of a complete dietary record.
ED 2	All food and energy-containing beverages	Energy-free beverages, e.g. water, tea, coffee and non-energy sweetened soft drinks	Between meals beverage intake could be incompletely recorded. Uncertain to what extent non-energy beverages affect energy intake.
ED 3 (ED_{food})	All food and milk (ONS)	All other beverages than milk	Milk is consumed both as food and as a beverage.
ED 4	Food only	All beverages	Exclusion of beverages can presumably decrease CV

Abbreviations: CV, coefficient of variation; ONS, oral nutritional supplements.

3.2.3 Biochemistry

Blood tests included measurement of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), S-Albumin and hemoglobin (Hb) levels. The presence of inflammation was defined by two criteria: 1/ An elevated level of CRP (three levels: CRP > 5, CRP > 10, CRP > 15 mg/L) or 2/An elevated ESR (two levels: > 20, > 30 mm/h). The Glasgow Prognostic Score (GPS) was also used to define whether inflammation was present [43]. Hypoalbuminemia was defined as S-Albumin < 32 g/L and anemia as Hb < 120 g/L [3, 28].

3.2.4 Performance and functional status

Karnofsky Performance Score was assessed by the attending clinician and a score of 80 was used as cut-off [4, 77]. Grip strength was measured with a hand-held spring-loaded dynamometer. Low muscle strength was defined as a value in the lowest tertile, adjusted for sex and age [3]. Walking distance was measured on a treadmill. The exercise started with patient standing on the treadmill with all equipment connected for 1 min and thereafter walking 1.5 km/h for 2 min. The test continued with walking at 1.5 km/h at a 12% elevation for 1 min; thereafter, the speed was increased 0.1 km/h every 10th second until the person finished the test. Patients with reduced walking capacity were defined as having walking distance less than the patient group mean, adjusted for sex and age.

3.2.5 Quality of life

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 form were filled out by the patient. The QLQ-C30 was developed for cancer patients and has been validated in multicultural environments [76]. It considers several factors that contribute to QoL, including physical and role functioning, cognitive status, emotional and social factors and global QoL. Symptoms (fatigue, pain, nausea and vomiting, dyspnea, and insomnia) and financial implications are also included in this questionnaire. Answers to specific items were summed and transformed linearly to range between 0 (representing poor health) to 100 (representing optimal health status). Higher scores on the symptom scales indicate a high level of symptoms.

Cluster analysis with a two cluster solution was used to identify relatively homogenous groups of patients into QoL and symptom clusters. Primary outcome were a "QoL and symptom" cluster where all functional and symptom scales and items, except financial implications, were used to form two clusters with patients differing in these two aspects. In addition, two more cluster analyses were run with only QoL and functional scales or only symptoms scales, to form two additional outcomes focusing on each aspect. Patients with lower QoL and function or more disease symptoms were considered to have adverse outcomes.

Patients were also asked to rate their own perception of fatigue on a 10 point scale (1-10). This measure of fatigue was used as diagnostic criteria and after visual inspection of the distribution and comparison with reference values for EORTC QLQ-C30 [132] a value >3 were used as cut-off (*paper IV*).

3.2.6 Cachexia definitions

Patients were classified as having cachexia using three recently published definitions; 1/ The 2- and 3-factor profile definitions described by Fearon et al., incorporating WL (≥ 10%), low food intake (≤ 1500 kcal/day) and systemic inflammation (CRP ≥ 10 mg/L) (Fearon et al. 2006)[4]; 2/ The diagnostic criteria of Evans et al. with WL (> 5%) plus three of the following: decreased handgrip strength, fatigue, low EI, low muscle mass or abnormal biochemistry (CRP > 5 mg/L, anemia or low albumin) (Evans et al. 2008) [3]; and 3/ The 2011 expert panel consensus definition of screening and staging of cachexia using WL, BMI or low muscle mass (Fearon et al. 2011) [1].

3.3 Data analysis

Group data are expressed as mean ± SD unless otherwise stated. Data were checked for normality with one-sample Kolmogorov-Smirnov test. When log-transformation restored normality the transformed data were used. Data were analyzed using SPSS for Windows version 11.5 (*paper I*) and 19.0.0 (*paper II-IV*) (SPSS, Chicago, IL). A *P*-value < 0.05 was considered to be significant.

Group comparisons

Differences in proportions were analyzed with the $\chi 2$-test or Fisher's exact test, as appropriate. Differences between group means were tested with t-test for normally distributed data and with Mann-Whitney U-test for QoL data. Differences in means between more than two groups are assessed by 1-way ANOVA, and *post hoc* differences, by the method of Bonferroni.

Associations

The association between ED and EI were analyzed with Pearson´s correlation coefficient and linear regression (*paper I and II*). Associations between mixed model estimated individual intercepts and slopes and subject characteristics were analyzed with Pearson's correlation coefficient (*paper II*).

Multi-level repeated measures data

Linear mixed models were used to analyze the multi-level repeated measures data in *paper II* and *III*. In *paper II*, a mixed model was used to investigate the relationship between EI and ED and a number of patient characteristics. In *paper III*, the mixed model was used to investigate the relationships between energy balance and ED, ED_{food}, EI, systemic inflammation and survival. Details of the analyses are given below.

Paper II

Energy intake was the dependent variable. Fourteen explanatory variables were included from start: ED, age, sex, BMI, WL, tumor type, survival (tertiles), hypermetabolism, low serum albumin (<32 g/L), high CRP (CRP >5 mg/L), low ASMI (<7.25 in males and <5.45 in females), fatigue, handgrip strength (adjusted for sex and age) and day of dietary record. These variables were entered as fixed effects, which can be interpreted as estimates of group mean effects. Day of dietary record was entered as a repeated effect with a first-order auto-regressive covariance type and as a fixed covariate to model dependence and trend across days. Starting from the full model, the

explanatory variable having the highest p-value was excluded and the model was refitted in a stepwise backward selection procedure until all remaining explanatory variables in the model showed significance.

Apart from the fixed effects, the model includes a random intercept and a random effect for ED. In a random intercept and slope model an intercept and slope is estimated for each individual in addition to the fixed effects. Significant random intercepts indicate that individual EI differs from the group estimate when accounting for explanatory variables in the fixed effects model. Similarly, significant random slopes indicate that individual responses in EI for a change in ED are different from the overall group response (fixed effect).

ED was centralized by subtracting the population mean value from each observation. In this way the estimated variance of the random intercept can be interpreted as the between-subject variation in the mean response at the group mean value of ED.

Paper III

Energy balance was the dependent variable. The measurement period was entered as a repeated effect with a Toeplitz covariance type. If model convergence was not achieved, a first-order auto-regressive covariance was used. The last measurement period before death was considered to be common for all patients, in order to enable modeling of the natural disease progression. Thus, measurement periods were 0-4 (1^{st}), 4-8 (2^{nd}), 8-12 (3^{rd}) and 12-16 (4^{th}) months before the final follow-up appointment. ED and EI at the beginning of measurement periods were entered as continuous predictors. Additionally, models were adjusted at the beginning of each measurement period for (log transformed) survival in days, or by tertiles of survival. The presence of inflammation was defined by three criteria: the patient having an elevated level of CRP (two levels: CRP > 5, CRP > 10 mg/L) or having an ESR > 20 mm/h. The Glasgow Prognostic Score (GPS) was also used to define whether inflammation was present [43]. Schwarz's Bayesian criterion was used to select the inflammatory marker and measure of survival (continuous or tertile-based) that yielded the best model. Differences in patient characteristics and differences in dietary characteristics between patients with or without systemic inflammation were tested with a mixed model with repeated effects and test variable as the dependent variable.

Quality of life clusters

Cluster analyses were performed with K-means cluster analysis with a two cluster solution (*paper IV*).

Adverse outcomes

Logistic regression was used to estimate the odds ratio of having low QoL, more symptoms or short walking distance with each diagnostic criteria or cachexia definition as a single dichotomized predictor (*paper IV*). Additionally, a stepwise forward logistic regression was fitted with all diagnostic criteria as possible predictors for an adverse outcome (*paper IV*).

Survival

Survival analysis was conducted with a Cox proportional hazard regression model with each diagnostic criterion or cachexia definition as a single dichotomized predictor. A stepwise model with all predictors was also fitted (*paper IV*). Differences in survival (days) were tested with the log-rank test (*paper IV*).

4 RESULTS

The largest sample of patients were included in *paper IV* (n = 405) and these included nearly all of patients in the previous papers (Table 1). Thus, as an overview of patient characteristics and dietary intake of patients included in this thesis, data from *paper IV* is presented.

4.1 Subject characteristics

Patient characteristics, WL, functional status and biochemistry of patients are shown in Table 3 and tumor types in Table 4. Patients had advanced disease with 54 % having distant metastases (stage IV), which is reflected in values for health status, functional status and a median survival of less than 6 months (Table 3).

Table 3. Patient characteristics at first visit (baseline)

		n	Mean ± SD	Range
Survival (days; median, IQR)		405	175 ± 235	1–6014
Age (years)		405	68 ± 11	30–89
BMI (kg/m2)		405	23.0 ± 3.8	15.7–38.4
Weight (kg)		405	67.3 ± 13.8	35.4–119.7
Weight loss (%)		405	10.0 ± 9.3	-16–45
Hypermetabolism (%)		400	10.6 ± 13.1	-26–68
CRP (mg/L)		399	32 ± 43	1–300
ESR (mm/h)		375	39 ± 27	3–115
S-Albumin (g/L)		398	34 ± 5	19–47
Hemoglobin (g/L)		405	120 ± 16	67–165
Fatigue (EORTC, 0-100)		331	52 ± 28	0–100
KPS		290	84 ± 11	50–100
Walking distance (m)	Male	159	317 ± 214	34–1241
	Female	145	242 ± 192	3–1400

Abbreviations: CRP, C-reactive protein; EORTC, European Organization for Research and Treatment of Cancer Scale; ESR, Erythrocyte sedimentation rate; KPS, Karnofsky Performance Score.

Weight loss was noted in 84 % of patients before study inclusion. Proportions of patients with WL more than 5, 10 and 15 % were 67, 46 and 27 % respectively. Patients also had low appendicular skeletal muscle mass (67 %) and the prevalence was higher in *men* (76 %, $P < 0.001$). 74 % had elevated

CRP (>5 mg/L) with some differences across tumor types (P = 0.02). Specifically, patients with upper gastrointestinal cancer had lower CRP than those with biliary tract cancer (P = 0.02). Patients with inflammation (CRP > 5) had higher REE than predicted (12.1 vs. 5.8 % of BMR, respectively, P < 0.001) and also experienced slightly more WL before inclusion (10.5 vs. 8.5 %, respectively, P = 0.049). Fatigue (EORTC) was higher in patients with inflammation (median, 56 vs. 33, respectively, P = 0.001). Patients with pancreatic tumors had shorter survival than other tumor types (P = 0.04).

Table 4. Tumor types

Tumor type	n	%
Colorectal	91	22
Biliary tract	59	15
Upper gastrointestinal	107	26
Pancreatic	105	26
Other	43	11
Total	405	100

4.2 Dietary intake

Energy intake ranged from 326 to 4715 kcal/day with mean intake of 1762±639 kcal/day (n = 322) (Table 5). Expressed in relation to BW (kgBW), EI was 27.0±10.3 kcal/kg/day (range, 5.7–76.9 kcal/kg/day). Energy intake, expressed as a multiple of measured REE (EI/REE), ranged from 0.29 to 2.87 with a mean of 1.18±0.41 (n = 318).

Macronutrient intake, expressed as percent of total EI was 36 E% fat, 45 E% carbohydrate and 16 E% protein and thus did not differ from the general population in Gothenburg [133]. Dietary protein intake estimated from 24h urine nitrogen (n=53) according to Bingham and Cummings [134], were not significantly different from protein intake calculated from FRs (mean difference 4.5 ± 22.9 g/day, P = 0.15). Moreover, differences between estimates were not significantly different between sexes or by overweight status. However, there was a trend of FRs to overestimate protein intake at lower intakes and underestimate at higher intakes (r = -0.58, P < 0.001).

Table 5. Dietary intake

n = 322	Mean ± SD
Energy intake (kcal)	1761 ± 639
Energy intake(kcal/kg)	27.0 ± 10.3
Energy intake (EI/REE)	1.18 ± 0.41
Energy density (kcal/g)	0.90 ± 0.23
Fat (g)	73 ± 34
Carbohydrate (g)	201 ± 73
Protein (g)	68 ± 25
Protein (g/kg)	1.03 ± 0.4
Alcohol (g)	3 ± 10
Fiber (g)	13 ± 6
Water (g)	1618 ± 674
Food weight (g)	2042 ± 789
Fat (E%)	36 ± 7
Carbohydrate (E%)	45 ± 7
Protein (E%)	16 ± 3
Alcohol (E%)	1 ± 4
Water (W%)	79 ± 8

4.3 Energy density and energy intake

Paper I

Energy density determined with the 4 different methods ranged from 0.88 ± 0.23 to 1.67 ± 0.35 kcal/g. The lowest ED was measured with ED1 (nothing excluded) and rose with each successive method to ED4 (including solid food only). Means in ED determined with the different methods were significantly different from each other.

The correlation between ED and EI was positive (r = 0.43, $P < 0.001$) and the association between ED and food weight was negative (-0.34, $P < 0.001$). In regression analysis ED explained 18, 15, 22 and 21 % of the variation in EI, for method 1 to 4 respectively (P for all < 0,001). In relation to energy per kg BW and REE, method 3 and 1, respectively, yielded the highest determination coefficient. Overall ED3 yielded the highest determination coefficient (Table 6).

Table 6. Determination coefficient (R^2) in regression of different measures of energy intake (EI, EI/kg BW and EI/REE) and diet energy density, calculated with four different methods (Table 2).

Method	ED1	ED2	ED3	ED4
Energy (kcal)				
R^2	0.18	0.15	0.22	0.21
Energy (kcal/kg)				
R^2	0.16	0.10	0.16	0.16
Energy (EI/REE)				
R^2	0.18	0.16	0.18	0.15

All regressions were significant, $P < 0.001$.
Abbreviations: EI, Energy intake; R^2, Determination coefficient; REE, resting energy expenditure.

Paper II

Age, BMI, fatigue and survival were negatively associated and hypermetabolism was positively associated with EI. Effect estimates (1 SD) were: -1.9 kcal/kg/d for age, -3.8 kcal/kg/d for BMI, -1.5 kcal/kg/d for fatigue and 1.1 kcal/kg/d for hypermetabolism. For tertiles of survival, the effect was -4.3 kcal/kg/d for 1st and -2.6 kcal/kg/d for 2nd compared to 3rd. Patients with shortest survival (<3.7 months) had approximately 17 % lower EI than patients with more than 8.3 months survival.

After adjustment with the above covariates, group mean estimate for ED (1 kcal/g) were 17.5 kcal/kg/d (95% CI, 15.2-19.8) and expressed as 1 SD, 4.5 kcal/kg (17.3 %) ($P < 0.001$) (Figure 1). When entering ED as the only predictor of EI in a mixed model with fixed, random and repeated effects, the group mean estimate for ED (1 kcal/g) was 18.5 kcal/kg/d (95%CI, 16.4-20.6). Using linear regression with mean dietary ED predicting EI in these patients, the β-coefficient was 16.6 kcal/kg/d (95% CI, 11.9-21.3) ($P < 0.001$), explaining 16.2% of the variation in EI. With multiple linear regression with age, BMI, hypermetabolism, fatigue and tertiles of survival as covariates, the β-coefficient for ED was 13.6 kcal/kg/d (95% CI, 9,6-17.6) ($p<0.001$). Thus, estimates of the relationship between EI and ED from the mixed model and simple or multiple linear regression, with or without covariates were not significantly different judged by overlapping 95% confidence intervals.

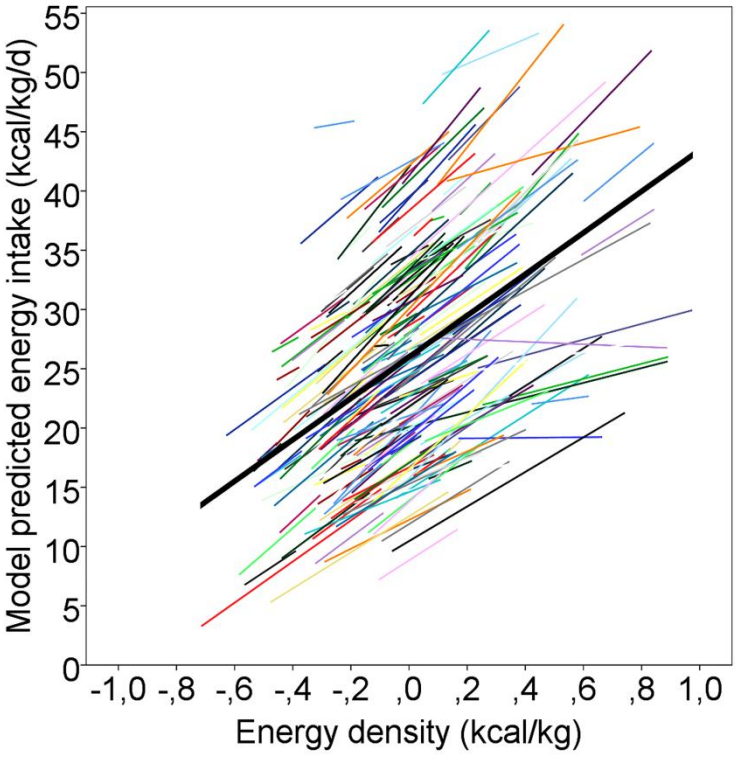

Figure 1. Mixed model output estimating energy intake with selected patient characteristics (see text) and diet energy density (grand mean centered) as predictors. Overall (thick line) and individual (thin lines) estimated energy intake

Day of dietary recording was negatively associated with EI in the mixed model ($P < 0.02$). Each successive day were associated with approximately 1% lower EI. In addition, there was a repeated effect with covariance of EI between days ($P < 0.001$), indicating a positive dependence between days (r = 0.19, $P = 0.003$).

Individual slopes (random effects) for ED were significant ($P < 0.001$), indicating that there was individual variation in the responses in EI for a change in ED that were different from the overall group response (fixed effect). Mixed model output illustrating the estimated individual variation in EI and the overall and individual EI:ED relationship is presented in Figure 1. Individual slopes for ED (subtracting group mean estimates) were negatively correlated with age and fatigue (r = -0.16 and -0.16, respectively, $P < 0.013$) and positively correlated with hypermetabolism (r = 0.16, $P < 0.014$) but not with any other patient characteristic. Individual slopes were positively correlated with EI, food intake (g) and beverage intake (g) (r = 0.30, 0.27 and

0.15 respectively, $P < 0.02$). There was also individual variation in EI that could not be accounted for in the present model as indicated by significant individual (random) intercepts ($P < 0.001$). Individual intercepts (i.e. EI) were negatively correlated with a high proportion of protein (E%) and fiber (W%) in the diet (r = -0.23 and -0.21, respectively, $P < 0.001$). EI were positively correlated with a high proportion of beverages (r = 0.28, $P < 0.001$), both with and without energy (r = 0.18 and 0.16, respectively, $P < 0.013$).

4.4 Energy balance

Paper III

Data from 107 patients who were followed through 164 periods was available to model four measurement periods over the 16 months before the final follow-up. An ESR value greater than 20 and tertiles of survival were the best predictors of energy balance, and these were consequently used in models to adjust for inflammatory status and survival. Missing data meant that 97 patients who were followed through 145 periods remained in models adjusted for survival and inflammatory status. The mean energy balances were -126 ± 250, -25 ± 237, 118 ± 239 and 85 ± 123 kcal/day for measurement periods 1 to 4, respectively.

In an unadjusted model, the ED_{food} and EI were positive predictors of energy balance ($P < 0.03$). A 1-SD increase in ED and EI increased energy balance by 38 and 41 kcal/day, respectively. The total diet ED did not predict energy balance ($P > 0.05$). Survival was positively ($P < 0.001$) and inflammatory status (measured as ESR > 20) was negatively (-98 kcal/day, $P = 0.005$) associated with energy balance over the following 4 months. The estimated energy balance for tertiles of survival from 1st to 3rd were -180 ± 31, -23 ± 30 and 5 ± 23 kcal/day (mean ± SEM), respectively (Figure 2). Only EI remained a significant predictor of energy balance after adjustment for survival and inflammatory status. Patients with inflammation had a lower EI relative to BW (-9%, $P = 0.04$) while the EI was not significantly different (-8%, $P = 0.07$). ED (-9%, $P = 0.02$) and ED_{food} (-8%, $P = 0.01$) were both significantly lower. There were no differences in macronutrient distribution (E%) or water intake between groups, but fiber intake was lower in patients with inflammation (-1.7 g/d, $P = 0.04$).

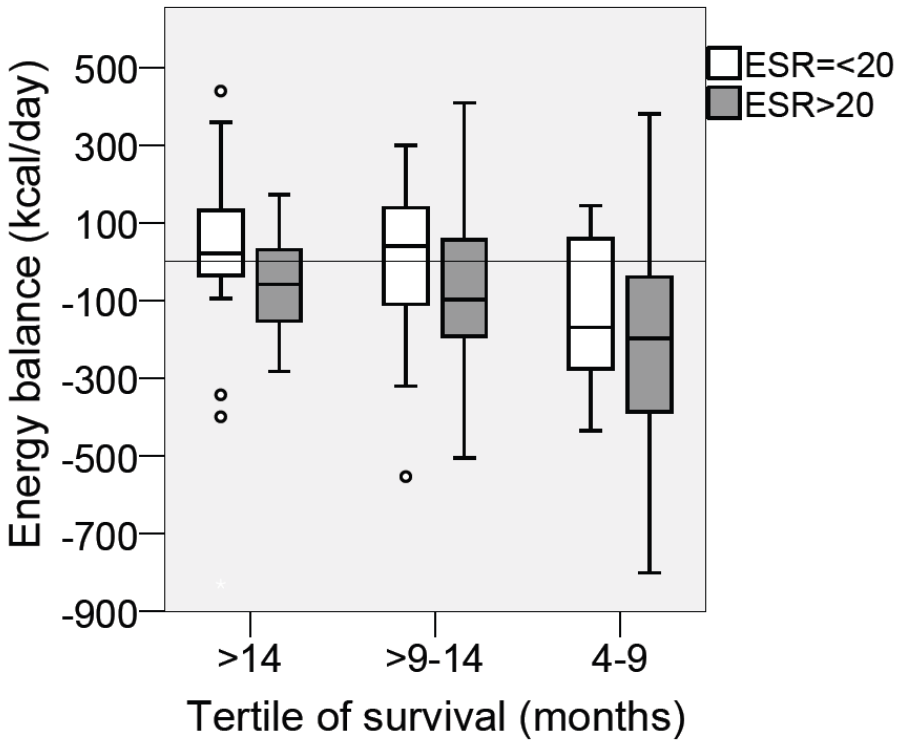

Figure 2. Energy balance per day estimated from change in body energy content by repeated dual-energy X-ray scans separated by 4 months, classified by tertiles of survival and inflammatory status (ESR > 20)

4.5 Diagnostic criteria of cancer cachexia: QoL, function, symptoms and survival

Paper IV

Quality of life data were available for 331 patients. All cluster analyses created groups of patients with significantly different scores for all scales of the EORTC QLQ-C30 ($P < 0.05$). Forty three percent (43 %) of patients were in the adverse "QoL, function and symptom" cluster, 45 % in the adverse "QoL and function" cluster and 39 % in the adverse symptoms cluster. When comparing function scales of the "QoL and symptoms" clusters differences were largest for social function, global QoL and role function with effect sizes (ES) of -2.05, -1.86 and -1.44 respectively. Largest differences in symptoms were found for fatigue, pain and loss of appetite (ES 1.93, 1.53 and 1.33 respectively). There were significant differences in survival, health status (WL, BMI, muscle indexes and biochemistry) and some measures of

physical function (grip strength in *women* and walking distance in *men*) but no difference in dietary intake between "QoL, function and symptom" clusters.

Between clusters formed with only global QoL and function scales, the largest differences were found for social function, role function and global QoL (ES 2.12, 1.95 and 1.92 respectively), with differences in symptoms being less pronounced. Differences between the symptom clusters were largest for loss of appetite and fatigue (ES 2.39 and 1.71 respectively).

Odds ratios for adverse QoL, function, symptoms and short walking distance, classified by different diagnostic criteria for cachexia are shown in Table 7.

In the stepwise forward logistic regression model with all diagnostic criteria as possible predictors for an adverse outcome 162 patients were available for analysis. Low handgrip strength (lowest tertile), fatigue > 3 (10 point scale) and CRP>10 (mg/L) were associated with being in the adverse "QoL, function and symptoms" cluster ($P < 0.05$). The same three predictors with the addition of WL > 5% remained in the model with adverse "QoL and function" cluster as outcome ($P < 0.05$). Weight loss > 10%, fatigue > 3, protein intake < 1.2 (g/kg/day) and hemoglobin <120 (g/L) were significant predictors of being in the cluster with more symptoms ($P < 0.02$). In the stepwise model with walking distance less than average as outcome, fatigue > 3 and ESR > 20 (mm/h) were associated with shorter walking distance (n = 168, $P < 0.001$).

There were 6 censored observations in the survival analyses. Hazard ratios from the Cox proportional hazards model with each diagnostic criterion as predictor and median survival for each classification are shown in Table 8. None of the dietary variables were significant predictors of survival (data not shown).

In the stepwise Cox regression model with all diagnostic criteria as possible predictors for survival, 202 patients were available for analysis. Low handgrip strength, fatigue > 3 (1-10 scale), Karnofsky performance score <80 and CRP>15 (mg/L) were prognostic of shorter survival ($P < 0.03$).

Based on the results from the logistic and Cox regressions an alternative 3-factor diagnostic criterion was constructed: WL >2%, Fatigue >3 (1-10 scale) and CRP > 10 mg/L (Table 7 and 8).

When excluding patients with less than 3 months survival, odds ratios for having an adverse outcome decreased for all cachexia definitions except for those of Fearon et al. 2006 [4]. In survival analysis only the 2 of 3 factor definition of Fearon et al. 2006 [4] and our own alternative 3-factor definition remained significant predictors of survival, with hazard ratios of 1.4 and 1.6 respectively ($P < 0.004$). The prevalence of a diagnosis of cachexia decreased when excluding patients with less than 3 months survival; to 6 % (3-factor, Fearon et al. 2006), 38 % (2 of 3-factors, Fearon et al. 2006), 28 % (Evans et al. 2008), 82 % (Fearon et al. 2011) and 26 % (our 3-factor alternative), respectively.

Table 7. Odds ratio for adverse QoL, function, symptoms and walking distance in patients with advanced cancer (n = 405), classified by different diagnostic criteria for cachexia.

	Odds ratio for adverse outcome[a]					
	QoL and Symptoms	QoL	Symptoms	Short walking distance	Prevalence (%)	Missing (%)
BMI < 20	2,9	2,7	2,6		21	0
BMI < 20 and weight loss > 2%	2,8	2,6	2,5		20	0
Weight loss > 2%	2,1	2,1	1,9		77	0
Weight loss > 5%	1,7	1,8	2,0		67	0
Weight loss > 10%	1,8	1,9	1,9		46	0
Walking distance less than average	2,3	2,2	3,3	-	58	25
Handgrip strength in lowest tertile	2,5	2,3	2,2	2,7	35	31
Fatigue < 3 (1 to 10 scale)	4,0	4,5	4,0	3,3	63	28
Karnofsky performance Score < 80	3,4	2,7	3,6		17	28
EI < 20 (kcal/kg/day)					28	21
EI < 1500 (kcal/day)			2,3	2,0	39	21
EI less than average (1756 kcal/day)	1,9		3,1		53	21
Protein intake < 1.2 (g/kg)			2,0		69	21
ED less than average					49	21
Low AMC	2,3	1,9	2,1		15	1
Low ASMI	2,0	2,1	1,8	2,0	67	4
Low muscle mass	1,8	2,0		2,0	66	0
CRP > 5 (mg/L)	2,1	2,3	2,6	3,9	74	2
CRP > 10 (mg/L)	3,1	3,6	2,4	3,6	59	2
CRP > 15 (mg/L)	3,0	3,0	2,4	3,1	49	2
ESR > 20 (mm/h)	1,7	2,0	1,7	4,2	70	7
ESR > 30 (mm/h)	1,7	1,7	1,6	3,2	50	7
S-Albumin < 32 (g/L)	1,9	2,2	1,7	3,2	30	2
Hemoglobin < 120 (g/L)	1,7	1,6	2,1	1,9	48	0
Cachexia all 3 factors (Fearon 2006)	5,3	4,4	5,1	3,5	12	22
Cachexia 2 of 3 factors (Fearon 2006)	2,1	2,6	2,6	2,1	45	22
Cachexia (Evans 2008)	2,3	2,3	3,1	3,1	33	33
Cachexia (Fearon 2011)	2,6	3,4	2,2		85	0
Cachexia (WL>2%, Fatigue>3, CRP>10)	2,5	3,2	2,6	4,2	37	30

[a]Only statistically significant odds ratios are shown ($P < 0.05$).

Abbreviations: AMC, mid-arm muscle circumference; ASMI, appendicular muscle mass index; CRP, C-reactive protein; ED, diet energy density; EI, energy intake; ESR, Erythrocyte sedimentation rate; WL, weight loss.

Table 8. Table 4. Survival analysis with Cox-proportional hazards model in patients with advanced cancer (n = 405), classified by different diagnostic criteria for cachexia.

		Median survival (days) Diagnostic criteria		
Diagnostic criteria	Hazard ratio[a]	Negative	Positive	Difference
BMI < 20				
BMI < 20 and weight loss > 2%				
Weight loss > 2%	1,4	251	146	-105
Weight loss > 5%	1,3	243	147	-96
Weight loss > 10%	1,2	203	133	-70
Walking distance less than average	1,3	240	146	-94
Handgrip strength in lowest tertile				
Fatigue < 3 (1 to 10 scale)	1,6	249	131	-118
Karnofsky performance Score < 80	1,5	182	101	-81
Low AMC	1,3	183	128	-55
Low ASMI				
Low muscle mass				
CRP > 5 mg/L	1,8	290	138	-152
CRP > 10 mg/L	2,2	291	120	-171
CRP > 15 mg/L	2,3	255	110	-145
ESR > 20	1,6	257	149	-108
ESR > 30	1,7	241	135	-106
S-Albumin < 32g/L	2,0	224	107	-117
Hb < 120g/L	1,4	236	135	-101
Adverse QoL and Symptoms	1,6	249	120	-129
Adverse QoL	1,6	253	126	-127
More Symptoms	1,6	244	120	-124
Cachexia all 3 factors (Fearon 2006)	2,2	202	85	-117
Cachexia 2 of 3 factors (Fearon 2006)	1,7	252	126	-126
Cachexia (Evans 2008)	1,4	197	115	-82
Cachexia (Fearon 2011)	1,3	249	157	-92
Cachexia (WL>2%, Fatigue>3, CRP>10)	2,1	240	91	-149

[a]Only statistically significant hazard ratios are shown ($P < 0.05$).
Abbreviations: AMC, mid-arm muscle circumference; ASMI, appendicular muscle mass index; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; QoL, quality of life; WL, weight loss.

5 DISCUSSION

The present studies are the first attempt to examine dietary ED and its relation to EI in cancer patients using both a between- and within-subject analysis. Energy density of the diet was associated with EI in all analyses. *Paper III* is the first examination of EI and dietary ED and their relationships with energy balance in cancer patients. As expected, EI was positively associated with energy balance; however, only ED_{food} was associated with energy balance. These results support current dietary practice recommending an energy-dense diet to cachectic cancer patients.

When we applied several popularly used criteria for cancer cachexia we found that WL, fatigue and markers of systemic inflammation were most strongly and consistently associated with adverse QoL, reduced functional abilities, more symptoms and shorter survival, which support that these are among the key features that should be assessed to characterize a patient with cachexia.

5.1 Methodological considerations

Subjects

Patients included in this thesis were an unselected and heterogeneous group of cancer patients referred to a palliative care program. A majority of patients had gastrointestinal cancers (89%). Accordingly, the results may not be representative or generalizable to other groups of cancer patients, who may have a different etiology of anorexia and cachexia. We found differences in CRP and survival among tumor types. In the mixed models, both survival and signs of inflammation were used as covariates which would adjust for differences among tumor types. In *paper II* we entered tumor type as a covariate and it was not significant.

Interventions included anti-inflammatory treatment with indomethacin, of anemia with erythropoietin, insulin, dietary counseling and nutritional support [20-23]. The effects of concomitant anti-inflammatory treatment should consequently be considered when evaluating our results. More than 90% of patients were being treated with indomethacin in the analysis of energy balance (*paper III*). Therefore we chose to adjust for signs of inflammation per se, rather than its treatment to assess the effects of inflammation. However, we cannot infer that dietary diaries precisely reflect

the actual eating behavior of advanced cancer patients without anti-inflammatory treatment or that there are no differences in eating behavior between patients with different tumor types. Results in the longitudinal follow-ups do not reflect alterations during disease progression that were fully spontaneous: they present an integrative view over time, according to the evidenced-based treatment offered.

Food records

In the intervention studies emphasis in dietary intake was on energy and macronutrients [20-23]. Consequently, when FRs were returned and checked for incomplete recordings energy-free beverages were not specifically asked for, which may have increased underreporting. Underreporting of energy-free beverages between days or between patients will affect the calculated ED and consequently the estimated relationship between ED of the total diet and EI. Inclusion of energy free-beverages when calculating ED would be expected to decrease the association between ED and EI if under reporting were substantial. In contrast, the inclusion of energy free beverages increased the association between ED and EI (comparing ED1 to ED2, table 6) and consequently does not support that there were substantial under reporting of energy free beverages. Energy and water intake varied widely between subjects; however, it is not possible to classify patients as under or over reporters using cut-off values from healthy populations in this sample of unselected palliative care cancer patients with ongoing WL. An alternative approach was used in *paper II* where patients were excluded if EIs were outside of ±3SD.

Energy intake in relation to BW decreased with increasing BMI in the present study. This could be due to underreporting in people with higher BMI's, assuming that physical activity levels were the same across the BMI range. This is a common phenomenon in dietary surveys [135], but one we didn't expect to find in this population of weight losing cancer patients. Analysis of urinary nitrogen did not indicate underreporting of protein intake in a sub sample of our patients but there could still be underreporting of non-protein rich foods. Dietary protein intake estimated from urine nitrogen were on the contrary 4.5 g/day lower ($P = 0.15$) than estimated intake from FRs even after accounting for incomplete collection of urine according to the method of Bingham and Cummings [134]. Estimates were also not significantly different stratifying by overweight status. However, there was a trend of FRs to overestimate protein intake at lower intakes and underestimate at higher intakes ($r = -0.58$, $P < 0.001$) which may support that there were systematic over- and underreporting at low and high BMI's respectively. Since urine was only collected for only 24h during the 4-days of FR this correlation

could arise by regression to the mean, which would be expected to some degree. The limited number of patients with urine collections prevents any definite conclusions regarding urinary nitrogen and dietary reporting.

The association with decreasing EI with higher BMI's may also be due to high EI in patients with low BMI attempting to counteract WL. In a systematic review Blum et al. found that reported EI related unreliably to WL which, given our results, to some degree could be due to confounding by BMI [5]. Yet another explanation may be that subjects with higher BMI have a higher proportion of adipose tissue to lean body mass and thus lower energy expenditure per kg [136]. BMI or body composition may therefore be important covariates to consider when assessing dietary adequacy from dietary records also in patients with advanced cancer.

Association between energy density and energy intake

It is inherently difficult to study the association between two variables when they are mathematically related, as in the case of EI and ED (i.e. kcal and kcal/g). The variables X and X/Y will be correlated even if X and Y are random numbers. Consequently, diet ED and EI are expected to be correlated. However, in the presence of human EI regulation, EI and ED would not be correlated if any change in diet ED were precisely compensated by a reciprocal change in amount of food eaten to reach a specific EI. This would constitute perfect EI regulation. On the other hand, if people would eat the same amount of food (by weight) every day, then EI would be precisely dependent on diet ED and the two would be perfectly correlated with no apparent EI regulation. It is also possible, however, that humans choose more energy-dense foods when energy demands increase or vice versa, although evidence for this is largely lacking [137-139]. In that case ED will be correlated with EI even in the presence of perfect EI regulation.

Any correlation between EI and ED in these scenarios would thus represent the uncompensated or "true" relation between EI and ED and any measurement error in either variable would obscure this relationship. However, the direction of causality cannot be established.

Strengths and limitations in design and analysis

The cross-sectional design, the short period of dietary recording in the analysis of day-to-day variation and a possible impact of dietary misreporting limit the conclusions that can be drawn. Increased number of days of dietary recording would be preferable but are in our opinion not feasible in this patient group.

Strengths include the use of a multivariate mixed linear model, which correctly models non-independent hierarchical data with repeated measures, in a large sample of patients with advanced cancer. This allowed for a better estimate of the impact of diet ED on EI while accounting for between subject differences.

The inclusion of exercise and non-exercise energy expenditure (apart from REE) in the models might explain part of the unexplained variance in EI and energy balance. Since these variables were not measured, this precludes us from making any conclusions of their impact on these relationships.

Strengths also include the high precision with which energy balance was measured and the longitudinal follow-up. However, the reliability of estimates of the impact of ED and EI on energy balance are limited by imprecision in the measure of food intake and by the low number of patients in that analysis. The requirement for several body composition measurements separated by 4 months limited the number of patients from the cohort that could be included in the analysis.

Strengths in the analysis of different diagnostic criteria and adverse outcomes include the large number of diagnostic variables measured with appropriate methods simultaneously in a relatively large sample of patients with advanced cancer. The use of cluster analysis that clearly separated patients with adverse QoL, function and symptoms may also be considered a strength of this analysis.

Limitations include the number of missing values in some of the variables, which reduced the number of patients available for multi-factor and multivariate analysis. Missing measures is a reality in care of patients with advanced cancer, diagnostic measures should therefore be accessible and easy to perform in routine care [1].

5.2 Dietary energy density and energy intake

Where methods of ED calculation are comparable, the observed dietary ED in this study is close to the observed ED in larger community studies in the U.S. and Spain in healthy populations of similar age, so it appears that the diet ED in this group of cancer patients does not differ much from what has been observed in healthy populations [16, 17, 140].

Dietary energy density was associated with EI regardless of calculation method and both in a between- and within-person analysis. The ED of food predicted energy balance, but the association was not significant when systemic inflammation was considered. Overall, the results were in accordance with findings in elderly, healthy and overweight free-living people in both experimental and observational studies [15-17, 19, 87, 89-92, 141].

Methods of ED calculation and the relationship between ED and EI

The results from *paper I* indicated that the method used when calculating ED had little impact on the association between ED and different measures of EI (absolute, per kgBW and EI/REE). In relation to absolute EI and per kg BW the exclusion of all beverages except milk (ED3) gave the highest determination coefficient (R^2) and overall ED3 seemed to be the best measure (**Table 6)**. It is interesting that the inclusion of non-energy containing beverages increases the association between ED and EI compared to ED calculated including energy containing beverages only (ED2); this in part contradicts earlier research on healthy subjects that non-energy beverages does not influence EI [19, 97, 99, 142]. This could indicate that in cancer patients with limited dietary intake, the total volume of food and drinks is a limiting factor in respect to EI. Stomach filling has indeed been suggested to partially mediate the influence of ED on food intake even in healthy subjects [143]. In the mixed model energy free beverages were positively correlated with EI which would seem contradictory. However, the positive association could arise if patients with a limited food intake reduced their intake of beverages, supposedly to reduce food volume. Alternatively, patients with low intakes may underreport their beverage intake.

In our longitudinal analysis, ED of solid food (including milk) was positively associated with long-term energy balance in an unadjusted model. This association persisted; indeed it increased, after adjustment for survival. In contrast, total ED of the diet were not associated with energy balance in any model. This suggests that it is ED_{food} that affects EI and ultimately energy balance in cancer patients with limited food intake. This result agrees with those of studies in healthy subjects, where ED_{food} is associated with long-term energy balance and the association depend on whether water and less energy-dense drinks are included in the calculation [87]. Accordingly, the effect of the ED of food and energy from beverages should be separated in future analyses.

ED and energy intake regulation

Our results imply that diet ED and in particular ED_{food} affects EI and energy balance to some degree, which supports current dietary practice. If there is no compensatory change in the amount of food, then an ED that is 1 SD higher (an increase of approximately 16-25%) would correspond to an increase in EI of approximately 350-450 kcal. Some compensation is, however, expected. ED was negatively associated with the amount of food ingested (food weight) which indicate EI compensation. The effect of increased ED would thus be compensated for by a smaller portion size or reduced meal frequency. Consequently, an increase in ED_{food} of 1 SD was correlated in this patient group with an increase in EI of approximately 190 kcal (10%). A compensatory change in total energy expenditure may be expected in cancer patients during semi-starvation, mainly due to changes in the level of physical activity [36]. Consequently, only a minor part of a change in EI is reflected in the energy balance. Our results, showing that an increase in ED of 1 SD is associated with an increase in energy balance of approximately 40-50 kcal/day, support this.

Average daily EI decreased during days of dietary recording. This could be an effect of dietary recording in itself (wear-out effect) or an initial effort to increase dietary intake that could not be upheld across the recording period, i.e. EI compensation between days, albeit at low levels of EI. The repeated measures covariance indicates dependence between days which could be due to EI regulation but the positive correlation indicates clustering of high or low EI, possibly due to disease symptoms, environmental or social circumstances [63, 144]. In healthy subjects de Castro reported a 2 to 3 day lag in EI compensation [145]. If the same applies to our patient sample our results would indicate EI regulation between days to some degree.

Dietary characteristics

Lowering the water content of food while increasing the fat content is the most effective way of increasing dietary ED. Increasing the ED by 25% would require a decrease in water content of ~5% and an increase in fat content of ~10 E%. For example, substituting boiled potatoes for pan-fried potatoes would increase the ED by 43%, and substituting natural yoghurt with 3% fat for yoghurt sweetened by sugar and having a fat content of 7% would increase the ED by 215%. Thus, exchanging several foods and beverages for corresponding energy-dense options could increase diet ED substantially.

Diets rich in protein (E%) and fiber (W%) were associated with lower EIs even after accounting for their influence on ED. This could possibly be

explained by the higher satiating properties of protein and fiber, which have been documented in healthy and obese [146, 147] and may consequently also apply to cancer patients. Recommending less energy-dense fiber rich foods to weight losing patients is counterintuitive and our results also support this. The importance of an adequate protein intake in disease related malnutrition is well established and high-protein supplements have been shown to produce clinical benefits, including increased EI and weight gain [103]. High-protein diets should therefore be recommended despite that such diets supposedly are more satiating. Rather, different protein sources should be explored for their anabolic, anti-catabolic and satiating properties to optimize their effect in different disease states [148, 149].

Subject characteristics

The inclusion of between-subject covariates did not substantially impact the positive association between EI and ED. This implies that diet ED is likely to be an important factor when attempts are made to increase EI in malnourished cancer patients with a limited capacity of food intake, similarly to what has been found in elderly [89-91].

In this group of cancer patients there were individual variations in the responses in EI for a change in ED that were different from the overall group response. Specifically, age and fatigue were associated with lower EI and with flatter ED:EI slopes. There was also a positive association between EI and individual ED:EI slopes, which means that patients with low EIs have flatter ED:EI slopes. This implies that some patients could be less likely to respond favorably to an increase in diet ED, particularly the elderly and fatigued with low EI.

5.3 Systemic inflammation

The association between ED of food and energy balance was not significant when systemic inflammation was considered. Patients with an ESR > 20 had lower dietary ED, EI and fiber intake than other patients, while the amount of food and degree of hypermetabolism were similar. While causality cannot be inferred, the results imply that ingestive behavior and choice of food change in the presence of systemic inflammation, which leads to a lower EI and negative energy balance. However, systemic inflammation (CRP > 5 mg/L) was not significant in the mixed model predicting EI and were also not correlated with the individual EI:ED slopes. This could partly be explained by the possible impact of inflammation on fatigue and hypermetabolism and their association with EI, explaining more of the variance in EI than the dichotomized marker of inflammation alone. More importantly regarding the

association between EI and ED is the fact that individual EI:ED slopes were not associated with systemic inflammation. Thus, while EI and ED may be low in patients with inflammation the positive association between EI and ED may still be the same as in patients without.

Energy balance became more negative during the final 5 months of life, and patients with inflammation differed from those without, especially in patients with longer survival (2^{nd} and 3^{rd} tertiles) (Figure 1). Our results thus highlight the importance of targeting systemic inflammation in the prevention and treatment of cancer cachexia with nutrition support [22, 31, 43, 53, 150].

The most common measure of systemic inflammation in cancer patients has been the level of CRP. Interestingly, we found ESR > 20 to be the inflammatory marker that was most closely associated with energy balance. ESR may reflect more accurately a long-standing inflammatory state, while CRP is more sensitive to acute changes, such as incidental infection. However, CRP with a cut-off of 10 mg/L seemed to be the best predictor of adverse QoL, symptoms and shorter survival, although differences between the cut-off levels were small. Our results support that serum CRP level is a useful marker of systemic inflammation and a key feature of cancer cachexia [1]. However, both markers, at different cut-off levels, reflect essentially the same influence on the associations studied, and the limited number of patients precludes further conclusions.

5.4 Diagnostic criteria and adverse outcomes

Weight loss, fatigue and markers of systemic inflammation were the criteria for cancer cachexia that were most strongly and consistently associated with adverse QoL, reduced functional abilities, more symptoms and shorter survival. All cachexia definitions used were associated with adverse outcomes and prognostic of survival.

The use of cluster analysis to separate patients with adverse QoL, function and symptoms worked well and large clinically meaningful differences were found in most scales of the EORTC QLQ-C30 [151]. Between the “QoL, function and symptoms” clusters the largest differences were found in global QoL and all function scales, but also in pain, fatigue and appetite. Similarly, the symptom only clusters weighed heavily on loss of appetite and fatigue, which suggests that the two are related. In agreement with a meta-analysis of studies using the EORTC QLQ-C30 all of the clusters with adverse outcomes

were associated with shorter survival [64]. Our results support that patient-reported functional and psychosocial effects and symptoms are among the key features that should be assessed to characterize a patient with cachexia [1].

Weight loss of any degree was associated with both adverse QoL and shorter survival and might be a better reflection of an ongoing process of negative energy balance and progressive disease than BMI in this population. This agrees with most previous studies showing WL to be a significant prognostic variable for survival in advanced cancer [33].

Patients with shorter survival had substantially lower EIs and increasingly negative energy balance. This could be expected and fits well to the suggested classifications and stages of cancer cachexia (Figure 2) [1, 4]. Energy intake as a dichotomized predictor was not associated with survival and was not consistently associated with adverse outcomes other than more disease symptoms. Diet ED was not associated with any outcome. Reduced food intake is undoubtedly one of the main features of cachexia and should be assessed routinely [1]. In our study however, the dietary assessment with the classification criteria used seemed to be of little prognostic value. Rather the symptom scales of the EORTC QLQ-C30 that capture some of the underlying causes of reduced food intake, such as loss of appetite, nausea, diarrhea, constipation and fatigue appeared to be of better prognostic value. These results question the validity of using FRs as a diagnostic criterion. In *paper III* on the other hand, EI as a continuous predictor was associated with long term energy balance which shows that a 4-day FR has some predictive validity of EI over the following 4 months. For energy intake to be predictive of adverse outcomes it may be more appropriate to evaluate EI compared to estimated expenditure on an individual basis. This is a challenging task that may not be possible as a screening activity or in use as a diagnostic criterion. Fearon et al. suggests in their consensus findings that the patient's own estimate of overall food intake in relation to normal may be used to assess food intake [1] which, given our results, seems like a more appropriate option.

The prevalence of a diagnosis of cancer cachexia varied widely according to the definition used (Table 3). In one end of the spectrum was the 3-factor definition of Fearon et al. [28] with prevalence of 12 % and in the other the consensus definition of Fearon et al. [1] with prevalence of 85 %. The former included patients with more advanced cachexia which was strongly associated with adverse QoL, symptoms and a median survival of less than 3 months and as such may already entered a state of refractory cachexia. The

more inclusive consensus definition [1] was also associated with adverse QoL and symptoms but not with a shorter walking distance. In these patients with less of a functional decline and a longer survival, anti-cachectic treatment may be timely and efficient. Main determinants for a cachexia diagnosis according to the consensus definition [1] were the high prevalence of WL > 5% (67 %) and low muscle mass (66%) together with WL > 2% (77 %), while BMI < 20 contributed marginally (Table 8).

6 CONCLUSION

We found a positive association between diet ED and EI in palliative care cancer patients.

Age, BMI, fatigue, survival and hypermetabolism are associated with EI, but do not substantially influence the association between ED and EI. However, individual variation in response implies that some patients could be less likely to respond positively to an increase in dietary ED, particularly the elderly and fatigued with low EI.

The energy intake and ED of the food consumed are associated with energy balance in patients with advanced cancer. This conclusion justifies current dietary practice and encourages future dietary interventions. Our results suggest also that the associations of EI and ED with energy balance are influenced by systemic inflammation. Thus, targeting systemic inflammation may be important in nutritional interventions in this patient group.

ED of solid food (including milk) was positively associated with long-term energy balance. In contrast, total ED of the diet were not associated with energy balance. This suggests that it is ED_{food} that affects EI and ultimately energy balance in cancer patients with limited food intake. Accordingly, the effect of the ED of food and energy from beverages should be separated in future analyses.

Weight loss, fatigue and markers of systemic inflammation were the criteria for cancer cachexia that were most strongly and consistently associated with adverse QoL, reduced functional abilities, more symptoms and shorter survival. All the cachexia definitions used were associated with adverse outcomes and prognostic of survival, but the prevalence of cachexia using criteria of the different definitions varied widely; especially in patients with more than three months survival – from 6 to 82 per cent – indicating a need to further explore and validate diagnostic criteria for cancer cachexia.

7 FUTURE PERSPECTIVES

Additional studies are required to understand the impact of energy-dense diets in cancer patients on both EI and energy balance. The impact of diet ED should be confirmed in additional longitudinal follow-ups or preferably in dietary interventions. In future studies, the effect and degree of compensation in dietary intake when dietary characteristics that influence ED change should be monitored. Such studies should also pay attention to the effects of ED in solid food as well as the impact of energy containing and energy free beverages. In addition, possible subject characteristics (age, BMI, physical activity level, inflammatory status, stage of disease and cachexia) and nutrition impact symptoms (fatigue, appetite loss, pain and gastrointestinal symptoms) that may influence this relationship should be considered.

To further explore and validate different diagnostic criteria in the diagnosis of cancer cachexia we suggest for future research that several different cut-off values be used for the main features of cachexia, similarly to the approach in this thesis. The diagnostic criteria and classification of the cachexia stages need further validation to better select patients with high enough sensitivity and specificity for interventions that are clinically relevant and tailored for the specific stages: precachexia, cachexia and refractory cachexia [1, 2]. Generally applicable diagnostic criteria would be valuable but clearly there are populations that may need specific modification. Definite cut-offs for the criteria that relate optimally to patient centered outcomes could be developed from large contemporary datasets [1].

Cancer cachexia is by definition a multifactorial syndrome and as such requires a solution that is multidimensional. It is self-evident that optimal oncological management must be achieved to get the best response of anti-cachexia therapy. The development of cachexia is complex and involves a number of partly interrelated factors. Therefore, the best supportive care for cancer cachexia remains unresolved. Any single therapy is unlikely to be fully successful and combination therapies are at present the most logical and promising solution [1, 9, 10, 26, 37].

There are principally two main domains of cachexia therapy; reduced food intake and metabolic disturbances [8-10, 37]. Nutrition support, including dietary counseling, ONS and artificial nutrition as appropriate, possibly together with appetite stimulants will support nutritional intake [11, 20, 60-62, 68]. Optimal management of nutrition impact symptoms is also key

factors that need to be addressed to support food intake and also improve QoL[26, 63].

Anti-inflammatory treatment to modify the host-tumor response together with anabolic and anti-catabolic therapies can reduce the metabolic disturbances and possibly restore the impaired appetite and anabolic response to nutrition and exercise [8, 10, 37, 45, 51, 60]. Anemia therapy and exercise could further improve fatigue and physical activity [73, 152]. These combination therapies could thus result in improvement of important patient centered outcomes such as physical activity, function, QoL and survival. It is clear however that further study is needed to determine the most effective mode of treatment.

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