Protein anabolic resistance in cancer: does it really exist?

Mariëlle P.K.J. Engelen, Barbara S. van der Meij, and Nicolaas E.P. Deutz

Purpose of review
Preventing unintentional weight and muscle loss is of crucial importance to maintain the condition and well-being of patients with cancer, improve treatment response and tolerance, and prolong survival. Anabolic resistance might explain why some cancer patients do not respond to nutritional intervention, but does recent evidence actually support this? We will discuss recent literature that casts doubt on attenuated anabolic potential in cancer.

Recent findings
Although anabolic resistance was observed in the past, more recent studies have shown that advanced cancer patients have an anabolic potential after intake of high-quality proteins. Furthermore, a consistent linear relationship is observed in cancer between (essential) amino acid availability from the diet and net protein gain. The studied cancer patients, however, were often characterized by a normal or obese body weight, following the trend in the general population, and mild systemic inflammation. Factors like recent chemotherapy, surgery, or cachexia do not seem to attenuate the anabolic potential to feeding.

Summary
Cancer patients have a normal anabolic potential which relates to the amount of essential amino acids in the meal. It remains to be determined if this is also the case in weak cancer patients with a short life expectancy and high systemic inflammation.

Keywords
anabolic resistance, cancer cachexia, dietary essential amino acids, protein anabolic potential

INTRODUCTION

Cachexia in cancer is a complex metabolic syndrome characterized by weight loss because of loss of muscle mass with or without loss of fat mass. Some form of cancer cachexia is commonly present in many cancer types [1▪] and is known to negatively affect performance status [2], the response and tolerance to therapy [3], and survival [4,5▪▪]. A spectrum of cachexia (pre-cachexia, cachexia, and refractory cachexia) often evolves in the cancer trajectory, although not all patients will progress through the full spectrum. About half of all patients with cancer lose some body weight, and the prevalence and severity of weight loss varies greatly according to the tumor site and type [1▪]. In addition, the overall prevalence of weight loss in cancer may rise during anticancer treatment [1▪] and in the last phase prior to death [5▪▪].

MUSCLE WASTING, REDUCED PROTEIN INTAKE, AND DISTURBANCES IN PROTEIN METABOLISM IN CANCER

Despite the fact that the prevalence of cachexia has not changed considerably in the past decades [1▪,6], both the general population and the cancer population show the same trend in the increased prevalence of obesity (Fig. 1). This supports the notion that the overall nutritional condition of cancer patients has improved and that weight loss nowadays results in a shift from obese to overweight rather than from normal weight to underweight [7–9]. Also, the higher BMI in overweight and obese populations is significantly associated with higher values for muscle mass [10]. This most likely has an impact on the metabolic profile of weight-losing cancer patients.

Center for Translational Research in Aging & Longevity, Department of Health and Kinesiology, Texas A&M University, College Station, Texas, USA

Correspondence to Mariëlle P.K.J. Engelen, PhD, Center for Translational Research in Aging & Longevity. Department of Health and Kinesiology, Texas A&M University, Suite 210. 1700 Research Parkway, College Station, TX 77843–4253, USA. Tel: +1 979 220 2282; e-mail: mpkj.engelen@ctral.org

Curr Opin Clin Nutr Metab Care 2016, 19:39–47
DOI:10.1097/MCO.0000000000000236

KEY POINTS

- With the obesity pandemic, cancer patients are likely to be normal or overweight, which may positively affect their metabolic profile and muscle mass, and reduce the negative effects of weight loss.
- Advanced cancer patients are able to obtain a normal protein anabolic response to high-quality proteins (enteral or parenteral).
- When the dose of high-quality proteins or amino acids in the diet increases, protein anabolism is stimulated in cancer patients.
- Optimal protein and amino acid intake is critical in advanced cancer patients and needs to be determined to further improve and personalize their nutritional care.
- The remaining anabolic capacity of very weak cancer patients with a short life expectancy and profound systemic inflammation needs to be established.

Normal or even high values for body weight or fat mass were found in patients with nonsmall cell lung cancer (NSCLC) despite the presence of some skeletal muscle loss [11▪,12,13]. This muscle loss, however, was not associated with muscle weakness. It probably matters whether weight loss in cancer takes place from an initial BMI of 30 or 20 kg/m^2, as the changes in body composition (muscle and fat mass) might differ between both starting BMIs. Recent studies, however, show that low skeletal muscle mass is an independent adverse prognostic indicator in cancer whether or not combined with overweight or obesity [14,15].

To be able to explain the variation in muscle and fat loss among cancer patients, habitual protein intake and the underlying metabolic disturbances need to be assessed. Although the 2006 European Society for Parenteral and Enteral Nutrition non-surgical oncology guidelines on enteral nutrition suggest that cancer patients should consume at least 1.2–2.0 g protein/kg body weight/day [16], most cancer patients do not reach this level via the diet and/or through nutritional supplementation [11▪,17▪,18]. Apart from a reduced appetite [19,20▪], the available nutritional supplements for cancer patients are often energy-dense and have a limited amount of high-quality protein. This might contribute to the loss of muscle mass in cancer patients while their fat mass is maintained.

Although cancer cachexia is often viewed to be associated with marked alterations in skeletal

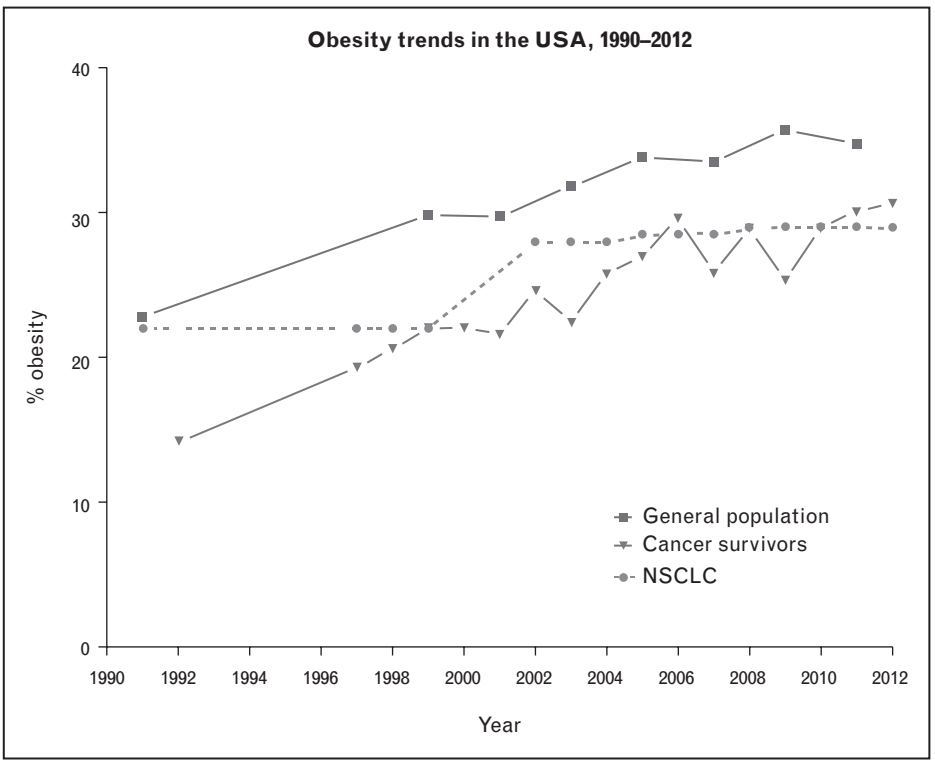

FIGURE 1. Change in demographics as reflected by percentage obesity (BMI $\geq$ 30 kg/m^2) in the general US population, cancer survivors, and patients with nonsmall cell lung cancer at presentation for cancer surgery [7–9]. Cancer survivors were defined as adults ever diagnosed with cancer (except for nonmelanoma skin cancer).

muscle protein metabolism, most of the data were obtained in animal models of cancer cachexia. Underlying disturbances in muscle protein metabolism in patients with cancer have been assessed by measuring the protein fractional synthesis rate of muscle proteins using stable isotope methodology in the postabsorptive state and in response to feeding as a proxy of anabolic capacity. In the postabsorptive condition, skeletal muscle protein fractional synthesis rate was found to be unchanged in cachectic cancer patients [21]. A recent study examining muscle myofibrillar protein synthesis over a period of 1–2 weeks found comparable values between healthy, weight-stable study participants, and weight-losing patients with upper gastrointestinal cancer [22], suggesting that muscle wasting is likely more related to an increased muscle protein breakdown [21]. Furthermore, because of the invasive nature of taking muscle biopsies in cancer patients and the fact that muscle protein synthesis but not breakdown data could easily be obtained, recent studies started focusing more on measuring both protein synthesis and breakdown on whole body level. We recently found in patients with NSCLC with normal body weight and reduced leg muscle mass [11▪] comparable values for postabsorptive whole body protein synthesis and breakdown rates as in the healthy control group. However, in cachectic pancreatic cancer patients, we found elevated values for whole body protein turnover [23]. It remains unclear whether muscle and whole body protein kinetics are uniformly modified among cancer patients.

IS THERE REALLY ANABOLIC RESISTANCE IN CANCER?

'Ongoing loss of skeletal muscle mass that cannot be reversed by conventional nutritional support' is an important part of the definition of cancer cachexia as stated by a panel of experts [24]. We previously confirmed that conventional nutritional supplementation using a commercially available formula is ineffective in stimulating muscle protein synthesis in advanced cancer patients (Table 1) [25]. A blunted response in muscle protein synthesis was also observed in colorectal cancer patients after infusion of a commercially available amino acid mixture [21].

In the past 5 years, more studies have become available showing that cancer patients have an anabolic potential. An euglycemic, hyperinsulinemic clamp study in patients with stage III and IV NSCLC [13] revealed a normal anabolic response to hyperaminoacidemia but a blunted response to low levels of amino acids. This suggests that a substantial protein intake is required to induce protein anabolism in cancer which could be difficult when appetite is reduced. Our recent study in eight cachectic pancreatic cancer patients and seven controls receiving oral sip feeding of a commercially available complete meal [23] showed a comparable protein anabolic response in both groups, albeit through a different pattern of whole body protein kinetics. In the cachectic patients, the anabolic response was because of reduced protein breakdown, whereas in healthy controls, both a decrease in protein breakdown and an increase in protein synthesis were present. We showed in 13 advanced cancer patients (mainly lung and colorectal cancer) that a high-protein formula containing high leucine levels, specific oligosaccharides and fish oil, was able to stimulate muscle protein synthesis [25]. This suggests that the suppressed anabolic responsiveness to a conventional nutritional supplement in advanced cancer can be (at least partly) overcome by providing specially formulated nutrition. We recently confirmed this in a study in 13 patients with advanced NSCLC who did not show an anabolic resistance or attenuated anabolic potential in response to 14 g of either an essential amino acid mixture or a balanced amino acid mixture as present in whey protein [11▪]. The high anabolic potential of free essential amino acids in the NSCLC patients was independent of their body weight, muscle mass, presence of recent weight loss, or disease trajectory. These studies show that diets with high levels of essential amino acids, either free or bound in protein, are anabolic in patients with cancer and healthy study participants.

The presence of anabolic resistance previously observed in some cancer studies but not in others could be related to multiple factors including characteristics of the study population (nutritional status, life expectancy, level of inflammation), dietary intake (protein dosage and amino acid composition), and the presence of anticancer treatment.

Nutritional status and life expectancy: it is possible that anabolic resistance to protein is more prevalent in patients with rapid or significant weight loss and muscle wasting. Although many studies reported a high prevalence of weight loss in cancer, the degree of weight loss differed depending on tumor type, tumor stage, anticancer treatment, and inflammatory state [1▪,6]. These characteristics, as well as the criterion used to define malnutrition, vary between the studies investigating the anabolic potential in cancer. An anabolic potential is absent in 35% of patients in the last phase before death, characterized by severe muscle wasting, disease progression, and reduced dietary intake [5▪▪]. Still 65% of the studied patients were

Table 1. Published studies in past 4 years investigating acute protein anabolic response to nutrition in patients with cancer

Author	Cancer type	Nutritional status/CRP	Provided nutrition	Isotope methods	Results cancer vs. controls	Other results
Deutz (2011) [25]	Advanced cancer mainly NSCLC + colorectal ($n=25$)	Normal weight, BMI: 25 kg/m^2, reduced leg lean mass, CRP: 22–28 ng/ml	EXP (complete meal containing: 40 g protein, free leucine, fish oil) vs. control drink	Muscle fractional synthesis rate: primed continuous L-$^{13}C_6$-phenylalanine	NA	Increase in muscle fractional synthesis rate after EXP drink, no response to control drink
Williams (2012) [21]	Colorectal ($n=13$) vs. controls ($n=8$)	Normal weight, BMI: 28 kg/m^2, low leg lean mass, CRP: 9 mg/l	Commercial IV mixed AA product	Muscle fractional synthesis rate: primed continuous L-$^2H_5$-phenylalanine	Increase muscle fractional synthesis in controls, blunted response in cancer	Surgery restores protein metabolism in cancer
Winter (2012) [13]	Advanced NSCLC ($n=10$) vs. healthy control ($n=10$)	Cachexia, BMI: 22 kg/m^2, CRP: 13 mg/l	IV amino acids	Euglycemic hyperinsulinemic clamp	Comparable whole body anabolic response to hyperaminoacidemia, anabolic resistance to isoaminoacidemia	
Van Dijk (2015) [23]	Unresectable pancreatic cancer ($n=8$) vs. controls ($n=7$)	Cachexia, BMI: 20 kg/m^2, CRP: 8 mg/l	Complete commercial supplement provided as sip feeding	Whole body protein kinetics: primed continuous L-$^2H_5$-phenylalanine, L-$^2H_2$-tyrosine infusion + oral ^{15}N-phenylalanine	No difference in whole body protein anabolism	
Engelen (2015) [11▪]	Advanced NSCLC ($n=13$) vs. controls ($n=13$)	Normal weight, BMI: 26 kg/m^2, low leg FFM, CRP: 10 mg/l	14 g of free essential amino acids vs. balanced amino acids as bolus	Whole body protein kinetics: primed continuous L-$^2H_5$-phenylalanine, L-$^2H_2$-tyrosine infusion + oral ^{15}N-phenylalanine	No difference in whole body protein anabolism	Significant relation anabolic response and dietary essential amino intake

AA, arachidonic acid; CRP, C-reactive protein; EXP, experimental medical food; FFM, fat-free mass; IV, intravenous; NA, not applicable; NSCLC, nonsmall cell lung cancer.

able to increase or maintain their skeletal muscle mass in the last phase before death, suggesting that there is still some exploitable anabolic potential. This was in part confirmed by our recent study in patients with NSCLC showing a preserved anabolic potential to amino acid mixtures in the last 6 months of life [11▪]. Data are needed whether this is also the case for the 3 months refractory period, but this study group is difficult to recruit. Some of the available studies might have unintentionally excluded these patients or these patients feel too weak to participate.

Inflammation: it has often been suggested that protein anabolism is extremely difficult to achieve in cancer in the presence of enhanced systemic inflammation as inflammation induces muscle proteolysis and reduces the sensitivity of skeletal muscle protein synthesis to amino acid supplementation. When reviewing the recent literature examining the acute anabolic response to a meal in cancer in the past years [11▪,13,21,23,25] (Table 1), average C-reactive protein, as marker of systemic inflammatory response, was mostly between 5 and 15 mg/l and independent of the cancer type and nutritional status. In colorectal cancer patients undergoing surgery, no relation was found between alterations in inflammatory mediators and the catabolic changes in protein turnover as the anabolic resistance disappeared 6 weeks after surgery [21]. It remains undetermined whether an attenuated anabolic response is more present in cancer patients with high levels of inflammation (i.e., C-reactive protein >50 mg/l).

Protein dosage and administration: Recent studies show that the dose of daily protein as well as the composition of the proteins and amino acids in a meal are among the most important factors influencing the anabolic response in cancer patients. Figure 2 shows a combined plot of the linear relationships between (essential) amino acid availability coming from the diet and net protein gain in normal weight NSCLC [11▪] and cachectic pancreatic cancer with more than 10% recent weight loss [23]. The relationships between the amount of dietary essential amino acids and net protein anabolism were comparable between both cancer groups and the combined healthy control group, indicating that the anabolic response to feeding is dependent on the amount of essential amino acids in the diet, but independent of the presence of cancer, cancer type, or nutritional status. The linear relationship remained at higher protein and amino acid intakes suggesting that protein accretion is still present at intakes greater than the requirement level and that higher quantities of essential amino acids might be useful to these patients. In line, 40 g of

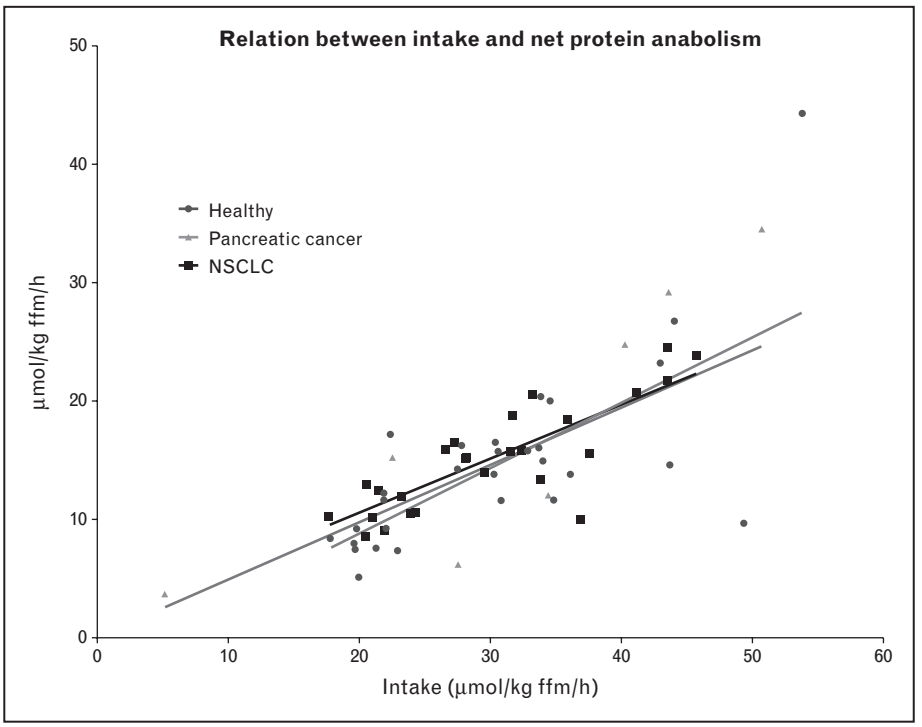

FIGURE 2. Relationship between net protein anabolism and dietary essential amino acid intake in the healthy control (dark grey circles), nonsmall cell lung cancer (light grey triangles), and pancreatic cancer (black squares) groups (calculated with the essential amino acid phenylalanine) [11▪,23].

amino acids incorporated in medical food [25] resulted in acute stimulation of muscle protein synthesis in advanced cancer. It is expected that when the dose of high-quality proteins or amino acids in the diet increases, protein anabolism will go up until factors like digestibility or absorption capacity starts to play a role. Currently, we do not know until what intake level this will occur. The previous critical appraisal of the literature (1984–2000) by Bozzetti and Bozzetti [26▪] also showed that a higher quantity of parenteral amino acids than usually administered via parenteral feeding might be useful to cancer patients as whole body protein synthesis remained high even at an amino acid intake of 1.8–2.0 g amino acid/kg/day, whereas whole body protein breakdown was unchanged or decreased. This indicates that the intravenous dosage of essential amino acids/kg/day should be increased in cancer to at least 1.2 g/kg/day. These data are in line with the recent study by Winter *et al.* [13] showing that hyperaminoacidemia because of intravenous administration of amino acids is able to activate a normal protein anabolic response in cachectic NSCLC patients.

Anticancer treatment: a new area of interest in cancer is the effect of anticancer treatment on protein metabolism and the anabolic response to feeding. Animal studies recently showed that chemotherapeutic agents contribute to muscle and fat wasting by altering lipid metabolism, inducing a rapid inflammatory response, suppressing food intake, and inducing genes involved with the ubiquitin proteasome and autophagy lysosome systems [27,28]. In advanced NSCLC [11▪], we showed that the anabolic response to amino acids in cancer was not affected by previous chemotherapy. In line, oral commercial nutritional supplementation in 92 patients with advanced NSCLC undergoing paclitaxel and cisplatin/carboplatin treatment [29] resulted in a greater energy and protein intake and muscle gain, and lower values for fatigue, loss of appetite, and neuropathy than in the control group who received an isocaloric diet. A positive effect of oral nutritional intervention on body weight and muscle mass during chemotherapy or concurrent chemoradiotherapy in cancer was also observed by us and others in the past years [29–36] (Table 2). Some evidence exists that surgery does not hamper the anabolic response to feeding in cancer as shown by the improved leucine balance to a commercial amino acid infusion in cancer patients within 48 h of undergoing colorectal surgery [37]. The patient's presurgery catabolic state and age were significant determinants of the anabolic effects of the feeding regimen with more catabolic and younger patients showing the greatest benefit. In line, colorectal cancer patients undergoing surgical resection [21] showed normalization of the observed presurgery catabolic changes in protein metabolism 6 weeks after surgery. The recovery in postprandial muscle protein synthesis after surgery was inversely related to the degree of muscle atrophy. The above mentioned studies suggest that the anabolic potential remains exploitable in cancer patients even shortly after undergoing chemotherapy or surgery.

Aging: In our ageing society, cancer patients are older than in the past. As aging is associated with increased splanchnic extraction, a lower response to ingested proteins and alterations in human muscle protein metabolism, older adults need more dietary protein than younger adults to maintain good health and functionality [38,39]. In older cancer patients, the combination of age-related decline of muscle mass (sarcopenia) and the presence of cancer (and related cachexia) could hamper the anabolic response to feeding. Although a lower anabolic response of the skeletal muscle to amino acids was found in older cancer patients than in healthy older controls, older cancer patients were still responsive to amino acids [40].

FUTURE PERSPECTIVES

There is recent evidence that a (genetic) component exists in cachexia among cancer patients [41], although this was not found for cancer-related appetite loss [42]. Furthermore, factors like individual body composition and metabolic phenotype may also play a role in the development of cachexia in cancer. Interindividual differences in metabolic phenotype among cancer patients might be present in substrate levels and intermediary products of proteins (metabolomics), kinetics through related pathways (fluxomics), and/or digestion and absorption of food components. Identification of the metabolic kinetic phenotype possibly can predict cachexia and related outcome in cancer patients and thus could lead to individualized therapeutic approaches to prevent cachexia, thereby improving quality of life, well-being, and clinical and overall outcome in cancer.

Although it is generally accepted that the protein needs of cancer patients are elevated, the existing international guidelines on the optimal dose of protein and amino acid intake in cancer are vague. Recent studies indicate that further fine-tuning of nutritional care is required in cancer which might involve compounding of nutritional formulations containing high levels of essential amino acids. Insight in the optimal protein and amino acid requirements on an individual basis

Table 2. Prospective studies published in past years investigating effects of nutritional intervention in patients with cancer

Author	Cancer type	Nutritional status/mean CRP	Cancer treatment	Provided nutrition	Results intervention vs. control
Baldwin (2011) [30]	Gastrointestinal or lung cancer ($n=358$)	Average weight loss: 11% gastrointestinal, 10% lung	Palliative chemotherapy	No intervention, dietary advice, nutritional supplement, and dietary advice + nutritional supplement before the start of chemotherapy, 6 weeks	No difference in survival, weight, quality of life (between groups)
Van der Meij (2012) [31]	Stage III NSCLC ($n=40$)	Normal weight, 20% malnutrition, CRP: 45 mg/l	Concurrent chemoradiotherapy	Oral nutritional supplement 2 cans/day (high in EPA and DHA) or isocaloric control for 5 weeks	↑ weight and FFM maintenance, ↑ quality of life scores, ↑ Karnofsky performance status
Fietkau (2013) [32]	Head and neck or esophageal ($n=111$)	Malnutrition (SGA B/C or Kondrup score ≥ 3)	Concurrent chemoradiotherapy	Enteral nutrition (high in fat, protein, EPA and DHA, or control) 500 ml/day, 14 weeks	↓ BCM loss (tendency), ↑Karnofsky performance status, no difference in quality of life, ↑ loss of appetite
Vasson (2014) [33]	Head and neck or esophageal ($n=37$)	70% moderate malnutrition, CRP: 10 mg/l	Chemoradiotherapy	Enteral nutrition (high in EPA, DHA, and arginine) or isocaloric isonitrogenous control, minimum 1500 ml, 5 days + 5–7 weeks	↑ weight, ↑ plasma antioxidant capacity, ↑ functional capacity
Sanchez-Lara (2014) [29]	Advanced NSCLC ($n=92$)	48% malnourished, CRP: 35 g/l	Chemotherapy	Oral nutritional supplement (high in EPA) or no supplement, 8 weeks	↑ energy and protein intake, ↑ weight gain, ↓ fatigue, ↓ loss of appetite, ↓ neuropathy, no difference in response rate and overall survival
Vashi (2014) [34]	Advanced cancer ($n=52$)	Malnutrition (SGA B/C)	Chemotherapy and/or radiotherapy	Home parenteral nutrition, ± 3 months	Over time: ↑ weight, ↑ Karnofsky performance status, ↑ quality of life
Culine (2014) [35]	Heterogenous cancer ($n=437$)	98% malnourished	Chemotherapy, radiotherapy and/or surgery	Home parenteral nutrition for 28 day	↑ weight, ↑ quality of life, ↑ well-being
Faber (2015) [36]	Oesophageal ($n=64$)	4–8% weight loss in study groups, CRP: 40 g/l	Planned for esophageal cancer treatment	Oral supplement (high in leucine, EPA, DHA) 4 weeks before start anticancer therapy. Control: <5% weight loss – noncaloric control, ≥5% weight loss isocaloric control	↑ weight, ↑ ECOG performance status

BCM, body cell mass; CRP, C-reactive protein; DHA, docosahexaenoic acid; ECOG, Eastern Cooperative Oncology Group; EPA, eicosapentaenoic acid; FFM, fat-free mass; NSCLC, nonsmall cell lung cancer; SGA, subjective global assessment.

is needed to further improve and personalize nutritional care in patients with cancer.

CONCLUSION

Recent studies indicate that advanced cancer patients are able to obtain a normal protein anabolic response to high-quality proteins or parenteral feeding that contain a high amount of essential amino acids. The studied cancer patients, however, were often characterized by a normal body weight or even obesity, which follows the trend in the general population, and mild systemic inflammation. There is also some evidence that even in more severe catabolic conditions, such as chemotherapy, the anabolic potential of cancer patients remains exploitable although more studies are needed to confirm this. To be sure that there is not a potential selection bias in the published research studies, more research needs to be initiated examining the anabolic potential of very weak cancer patients with a short life expectancy (<3 months) and in those with high levels of systemic inflammation.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

M.P.K.J.E. and N.E.P.D. are sponsored by the research projects from NIH (R01HL095903 and R01GM 084447), Abbott Nutrition (unrelated to Cancer research), and by startup funding from Texas A&M University. B.S.M. is sponsored by a postdoctoral research fellowship from the European Society for Clinical Nutrition and Metabolism (ESPEN).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. ■ Hébuterne X, Lemarié E, Michallet M, *et al.* Prevalence of malnutrition and current use of nutrition support in patients with cancer. JPEN J Parenter Enteral Nutr 2014; 38:196–204.

The differences in the prevalence of malnutrition as well as the use of nutritional support was demonstrated in 1903 patients with different types of cancer.

2. LeBlanc TW, Nipp RD, Rushing CN, *et al.* Correlation between the international consensus definition of the cancer anorexia-cachexia syndrome (CACS) and patient-centered outcomes in advanced non-small cell lung cancer. J Pain Symptom Manage 2015; 49:680–689.
3. Prado CM, Maia YL, Ormsbee M, *et al.* Assessment of nutritional status in cancer: the relationship between body composition and pharmacokinetics. Anticancer Agents Med Chem 2013; 13:1197–1203.
4. Martin L, Birdsell L, Macdonald N, *et al.* Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013; 31:1539–1547.
5. ■■ Prado CM, Sawyer MB, Ghosh S, *et al.* Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? Am J Clin Nutr 2013; 98:1012–1019.

In 368 cancer patients, the clinical course of muscle wasting and the window of possible anabolism was investigated by analyzing computed tomography images over the course of disease. This study showed that cancer patients within 90 days of death have a low likelihood of anabolic potential.

6. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer 2014; 14:754–762.
7. Zogg CK, Mungo B, Lidor AO, *et al.* Influence of body mass index on outcomes after major resection for cancer. Surgery 2015; 158:472–485.
8. Ferguson MK, Vigneswaran WT. Changes in patient presentation and outcomes for major lung resection over three decades. Eur J Cardiothorac Surg 2008; 33:497–501.
9. NCI. Cancer Trends Progress Report 2015. http://progressreport.cancer.gov/prevention/weight [Accessed 30 July 2015].
10. Franssen FM, Rutten EP, Groenen MT, *et al.* New reference values for body composition by bioelectrical impedance analysis in the general population: results from the UK Biobank. J Am Med Dir Assoc 2014; 15:e1–e6.
11. ■ Engelen MP, Safar AM, Bartter T, *et al.* High anabolic potential of essential amino acid mixtures in advanced nonsmall cell lung cancer. Ann Oncol 2015; 26:1960–1966.

In 13 patients with advanced NSCLC, anabolic resistance or attenuated anabolic potential was not observed in response to free dietary essential amino acids, suggesting a key role of essential amino acids in nutritional care of patients with cancer.

12. Op den Kamp CM, Langen RC, Snepvangers FJ, *et al.* Nuclear transcription factor κ B activation and protein turnover adaptations in skeletal muscle of patients with progressive stages of lung cancer cachexia. Am J Clin Nutr 2013; 98:738–748.
13. Winter A, MacAdams J, Chevalier S. Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia. Clin Nutr 2012; 31:765–773.
14. Antoun S, Borget I, Lanoy E. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. Curr Opin Support Palliat Care 2013; 7:383–389.
15. Jung HW, Kim JW, Kim JY, *et al.* Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. Support Care Cancer 2015; 23:687–694.
16. Arends J, Bodoky G, Bozzetti F, *et al.* ESPEN Guidelines on enteral nutrition: nonsurgical oncology. Clin Nutr 2006; 25:245–259.
17. ■ Stobäus N, Müller MJ, Küpferling S, *et al.* Low recent protein intake predicts cancer-related fatigue and increased mortality in patients with advanced tumor disease undergoing chemotherapy. Nutr Cancer 2015; 67:818–824.

In patients with advanced cancer, the level of protein intake was related to the risk of cancer-related fatigue and 6-month mortality, showing a more than two-fold higher risk of cancer-related fatigue and 6-month mortality in patients with a low recent protein intake. This emphasizes the importance of assessing and guaranteeing proper protein intake in patients undergoing chemotherapy.

18. Mardas M, Jamka M, Mądry R, *et al.* Dietary habits changes and quality of life in patients undergoing chemotherapy for epithelial ovarian cancer. Support Care Cancer 2015; 23:1015–1023.
19. Blauwhoff-Buskermolen S, Ruijgrok C, Ostelo RW, *et al.* The assessment of anorexia in patients with cancer: cut-off values for the FAACT-A/CS and the VAS for appetite. Support Care Cancer 2015 [Epub ahead of print].
20. ■ Cooper C, Burden ST, Cheng H, Molassiotis A. Understanding and managing cancer-related weight loss and anorexia: insights from a systematic review of qualitative research. J Cachexia Sarcopenia Muscle 2015; 6:99–111.

Comprehensive overview of the existing qualitative literature on weight loss and anorexia in cancer, discussing the multidimensionality of this syndrome, patients, and caregivers' coping, and the clinical assessment and management of weight loss and anorexia.

21. Williams JP, Phillips BE, Smith K, *et al.* Effect of tumor burden and subsequent surgical resection on skeletal muscle mass and protein turnover in colorectal cancer patients. Am J Clin Nutr 2012; 96:1064–1070.
22. MacDonald AJ, Johns N, Stephens N, *et al.* Habitual myofibrillar protein synthesis is normal in patients with upper GI cancer cachexia. Clin Cancer Res 2015; 21:1734–1740.
23. van Dijk DP, van de Poll MC, Moses AG, *et al.* Effects of oral meal feeding on whole body protein breakdown and protein synthesis in cachectic pancreatic cancer patients. J Cachexia Sarcopenia Muscle 2015; 6:212–221.
24. Fearon K, Strasser F, Anker SD, *et al.* Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12:489–495.
25. Deutz NE, Safar A, Schutzler S, *et al.* Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. Clin Nutr 2011; 30:759–768.
26. ■ Bozzetti F, Bozzetti V. Is the intravenous supplementation of amino acid to cancer patients adequate? A critical appraisal of literature. Clin Nutr 2013; 32:142–146.

Opinion study based on literature review on the effects of amino acid infusions on nutritional, metabolic, and clinical outcomes in cancer patients.

27. Braun TP, Szumowski M, Levasseur PR, *et al.* Muscle atrophy in response to cytotoxic chemotherapy is dependent on intact glucocorticoid signaling in skeletal muscle. PloS One 2014; 9:e106489.

28. Garcia JM, Scherer T, Chen JA, *et al.* Inhibition of cisplatin-induced lipid catabolism and weight loss by ghrelin in male mice. Endocrinology 2013; 154:3118–3129.

29. Sánchez-Lara K, Turcott JG, Juárez-Hernández E, *et al.* Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: randomised trial. Clin Nutr 2014; 33:1017–1023.

30. Baldwin C, Spiro A, McGough C, *et al.* Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. Journal of human nutrition and dietetics: the official journal of the British Dietetic Association 2011; 24:431–440.

31. van der Meij B, Langius J, Spreeuwenberg M, *et al.* Oral nutritional supplements containing n-3 polyunsaturated fatty acids affect quality of life and functional status in lung cancer patients during multimodality treatment: an RCT. Eur J Clin Nutr 2012; 66:399–404.

32. Fietkau R, Lewitzki V, Kuhnt T, *et al.* A disease-specific enteral nutrition formula improves nutritional status and functional performance in patients with head and neck and esophageal cancer undergoing chemoradiotherapy: results of a randomized, controlled, multicenter trial. Cancer 2013; 119:3343–3353.

33. Vasson MP, Talvas J, Perche O, *et al.* Immunonutrition improves functional capacities in head and neck and esophageal cancer patients undergoing radiochemotherapy: a randomized clinical trial. Clin Nutr 2014; 33:204–210.

34. Vashi PG, Dahlk S, Popiel B, *et al.* A longitudinal study investigating quality of life and nutritional outcomes in advanced cancer patients receiving home parenteral nutrition. BMC Cancer 2014; 14:593.

35. Culine S, Chambrier C, Tadmouri A, *et al.* Home parenteral nutrition improves quality of life and nutritional status in patients with cancer: a French observational multicentre study. Support Care Cancer 2014; 22:1867–1874.

36. Faber J, Uitdehaag MJ, Spaander M, *et al.* Improved body weight and performance status and reduced serum PGE_2 levels after nutritional intervention with a specific medical food in newly diagnosed patients with esophageal cancer or adenocarcinoma of the gastro-esophageal junction. J Cachexia Sarcopenia Muscle 2015; 6:32–44.

37. Schricker T, Wykes L, Meterissian S, *et al.* The anabolic effect of perioperative nutrition depends on the patient's catabolic state before surgery. Ann Surg 2013; 257:155–159.

38. Bauer J, Biolo G, Cederholm T, *et al.* Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013; 14:542–559.

39. Churchward-Venne TA, Breen L, Phillips SM. Alterations in human muscle protein metabolism with aging: protein and exercise as countermeasures to offset sarcopenia. Biofactors 2014; 40:199–205.

40. Horstman AM, Sheffield-Moore M. Nutritional/metabolic response in older cancer patients. Nutrition 2015; 31:605–607.

41. Tan BH, Ross JA, Kaasa S, *et al.* Identification of possible genetic polymorphisms involved in cancer cachexia: a systematic review. J Genet 2011; 90:165–177.

42. Solheim TS, Fayers PM, Fladvad T, *et al.* Is there a genetic cause of appetite loss? – an explorative study in 1,853 cancer patients. J Cachexia Sarcopenia Muscle 2012; 3:191–198.