Effect of tumor burden and subsequent surgical resection on skeletal muscle mass and protein turnover in colorectal cancer patients1–4

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ABSTRACT
Background: Cachexia is a consequence of tumor burden caused by ill-defined catabolic alterations in muscle protein turnover.
Objective: We aimed to explore the effect of tumor burden and resection on muscle protein turnover in patients with nonmetastatic colorectal cancer (CRC), which is a surgically curable tumor that induces cachexia.

Design: We recruited the following 2 groups: patients with CRC \( \{n = 13; \text{mean } \pm \text{ SEM age: } 66 \pm 3 \text{ y}; \text{BMI (in kg/m}^2\): 27.6 \pm 1.1\} \) and matched healthy controls \( \{n = 8; \text{age: } 71 \pm 2 \text{ y}; \text{BMI: } 26.2 \pm 1\} \). Control subjects underwent a single study, whereas CRC patients were studied twice before and ~6 wk after surgical resection to assess muscle protein synthesis (MPS), muscle protein breakdown (MPB), and muscle mass by using dual-energy X-ray absorptiometry.

Results: Leg muscle mass was lower in CRC patients than in control subjects \( (6290 \pm 456 \text{ compared with } 7839 \pm 617 \text{ g}; P < 0.05) \) and had an additional decline after surgery \( (5840 \pm 456 \text{ g}; P < 0.001) \). Although postabsorptive MPS was unaffected, catabolic changes with tumor burden included the complete blunting of postprandial MPS \( (0.038 \pm 0.004%/h \text{ in the CRC group compared with } 0.065 \pm 0.006%/h \text{ in the control group}; P < 0.01) \) and a trend toward increased MPB under postabsorptive conditions \( (P = 0.09) \). Although surgical resection exacerbated muscle atrophy \( (-7.2\% \text{, catabolic changes in protein metabolism had normalized } 6 \text{ wk after surgery. The recovery in postprandial MPS after surgery was inversely related to the degree of muscle atrophy } (r = 0.65, P < 0.01) \).

Conclusions: CRC patients display reduced postprandial MPS and a trend toward increased MPB, and tumor resection reverses these derangements. With no effective treatment of cancer cachexia, future therapies directed at preserving muscle mass should concentrate on alleviating proteolysis and enhancing anabolic responses to nutrition before surgery while augmenting muscle anabolism after resection. Am J Clin Nutr 2012;96:1064–70.

INTRODUCTION

The loss of skeletal muscle in cancer is a facet of the cachexia syndrome and a cause of chronic fatigue, deconditioning, morbidity (1–4), and, eventually, a reduced life span because of respiratory failure in cancer (5–7). However, little is known of the catabolic changes in the regulation of protein turnover that underlie human cachexia principally because of 1) the dearth of studies, 2) a paucity in the application of dynamic techniques to quantify protein metabolism, 3) a lack of the characterization of both muscle protein synthesis (MPS)5 and muscle protein breakdown (MPB) under both fasted and fed conditions, and 4) the heterogeneous clustering of distinct cancer pathologies and disease stages (8, 9). Of the existing reports, studies that focused on whole-body protein turnover have reported elevations \( (\sim 20–30\%) \) in synthesis and breakdown \( (10–14) \) or unchanged turnover rates \( (15, 16) \). Studies that directly charted MPS and MPB in cachectic muscle have underlined the need to capture muscle protein turnover in both fasted and fed states to firmly establish the etiology of cachexia. This is needed because perturbations in protein turnover may exist in postabsorptive (17) and fed periods \( (anabolic-resistance) (8, 15) \). Conversely, support for the notion of increased MPB, as reported in preclinical studies, is lacking (9, 17).

Colorectal cancer (CRC) is the second most common cause of cancer-related death in the United Kingdom and has accounted for 42,000 deaths between 2001 and 2003 (18). Although many CRC patients initially present with changes in bowel habits, patients frequently exhibit cachexia at presentation; 28% of patients lose >5% of body weight in the 6 mo before diagnosis (6, 19, 20). Although surgical resection remains the only curative treatment of CRC, the effect of surgery on a patient who is already experiencing cancer cachexia is significant. For exam-

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5 Abbreviations used: AKT, protein kinase B; CRC, colorectal cancer; CRP, C-reactive protein; MAFBs, muscle atrophy F box; MPB, muscle protein breakdown; MPS, muscle protein synthesis; mRNA, messenger RNA; MuRF-1, muscle-ring finger 1; P70S6K1, P70S6 kinase; α-KIC, α-ketoisocaproate; 4E-BP1, eukaryotic translocation initiation factor 4E binding protein 1.

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ple, major abdominal surgery, even in the absence of cancer, has been associated with losses of between 0.5 and 1.5 kg lean tissue mass postoperatively (21), with maximal reductions 14–28 d after surgery. Therefore, the trauma of surgery must also disrupt the equilibrium between MPS and MPB. Indeed, whereas MPS was unchanged compared with preoperative values immediately after major abdominal surgery (22), MPS was depressed 4 h after surgery (23) and is consistently decreased (~30% to ~50%) 1–3 d after surgery (24–26). Such perturbations in MPS result in surgery-induced muscle atrophy (27). After this time, muscle mass stabilizes and begins to recover.

To our knowledge, there have been no investigations that charted the effect of cancer and subsequent curative resection on muscle mass and protein metabolism under fasted and fed conditions in individuals with cancer; therefore, we conducted a study in which individuals were studied before and after curative resection and compared with a healthy age-matched control group.

SUBJECTS AND METHODS

Subject recruitment

We recruited the following 2 groups of subjects: healthy volunteers [mean ± SEM age: 71 ± 2 y; 4 men and 4 women; BMI (kg/m²): 26.2 ± 1.0] and patients with colonic adenocarcinoma booked for curative resection (age: 66 ± 3 y; 6 men and 7 women; BMI: 27.6 ± 1.1) (Table 1), with exclusion of subjects with distant metastasis on preoperative staging. Healthy volunteers were asked to undergo a single acute study, and CRC patients were studied 1 wk preoperatively and 6 wk after resection (hemicolecotomy). Before beginning the study, all subjects were screened by using a medical questionnaire, physical examination, and resting electrocardiogram with exclusions for metabolic, respiratory, or cardiovascular disorders or other contraindications to a healthy status. As a condition of entry to the study, all subjects had normal blood chemistry and were normotensive (blood pressure <140/90 mm Hg). All subjects gave their written, informed consent to participate in the study. The study was approved by the local National Health Service Research Ethics Committee and The University of Nottingham Medical School Ethics Committee and complied with the Declaration of Helsinki. The study ran between August 2005 and August 2010.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Subject characteristics</th>
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<tr>
<td><strong>Control subjects</strong></td>
<td><strong>Cancer patients (n = 13)</strong></td>
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<tr>
<td><strong>(n = 8)</strong></td>
<td>Before surgery</td>
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<tr>
<td><strong>Age (y)</strong></td>
<td>71 ± 2</td>
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<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>26.2 ± 1.0</td>
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<tr>
<td><strong>Plasma IL-10 (pg/mL)</strong></td>
<td>—</td>
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<td><strong>Plasma TNF-α (pg/mL)</strong></td>
<td>—</td>
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<td><strong>Plasma CRP</strong> (mg/L)</td>
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<td><strong>Plasma cortisol (nmol/L)</strong></td>
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1
dAll values are means ± SEMs. There were no significant differences between groups.

2CRP, C-reactive protein.

Metabolic study design

Subjects were instructed to refrain from exercise for 72 h before each study day. Subjects fasted from 2100 the night before each study day (water ad libitum) and reported to the laboratory at 0800. Body composition was measured by using dual-energy X-ray absorptiometry (Lunar Prodigy II; GE Medical Systems), and leg composition was measured on the dominant leg as the area inferior to the level of the lowest visible point of the coccyx. A basal muscle biopsy was taken from the vastus lateralis at 0 min by using the conchotome biopsy technique followed by a primed constant dose of stable isotope-labeled amino acids ([1,2-13C2]-leucine [prime: 0.7 mg/kg; fasted: 1 mg · kg⁻¹ · h⁻¹; fed: 1.43 mg · kg⁻¹ · h⁻¹] and ring-D₃ phenylalanine [prime: 0.3 mg/kg; fasted: 0.6 mg · kg⁻¹ · h⁻¹; fed: 0.91 mg · kg⁻¹ · h⁻¹]). After 120 min in a supine position, measurements of femoral artery blood flow were taken for 60 min by using Doppler ultrasound, and at 180 min, a second muscle biopsy of the vastus lateralis was taken. After this second biopsy, the fed phase of the study began, and subjects received intravenous mixed amino acids infused at a rate that approximately doubled plasma amino acids [Glamin (Fresenius-Kabi); prime: 34 mg/kg; dose: 102 mg · kg⁻¹ · h⁻¹]. Ninety minutes after the start of the amino acid infusion, measurements of femoral artery blood flow were taken for 60 min and were followed by the final vastus lateralis muscle biopsy. Venous and arterialized (by using the hot-hand technique) blood samples were collected every 20 min throughout the study (Figure 1).

MPS

The resulting pellet from the immunoblotting preparation represented the myofibrillar fraction and was used for determination of the myofibrillar protein fractional synthetic rate as a measure of MPS as previously described (28). In brief, the myofibrillar pellet was separated from the insoluble collagen fraction, and the solubilized myofibrillar protein was precipitated out. Protein-bound amino acids were released by using acid hydrolysis and purified by using ion exchange chromatography. Amino acids were derivatized as their N-acetyl-N-propyl esters as previously described (29). The incorporation of [1,2-13C2]-leucine into protein was determined by using gas chromatography–combustion–isotope-ratio mass spectrometry (Delta plus XP; ThermoFisher Scientific) according to our standard techniques (28). Venous plasma α-ketoisocaproate (α-KIC) was chosen as the surrogate precursor for leucyl-t-RNA labeling. The MPS of protein was determined from the increase in incorporation of [1,2-13C2]-leucine between subsequent muscle biopsies by using the labeling of plasma α-KIC as a surrogate for leucyl-t-RNA (the immediate precursor for protein synthesis), as previously described (28). The MPS was calculated by using the standard precursor-product method as follows:

\[
\text{Fractional protein synthesis (percentage per hour)} = \frac{\text{Em} \times \text{Ep}}{1 + t \times 100}
\]

where Em is the change in leucine enrichment between 2 biopsy samples, Ep is the mean enrichment over time of the precursor.
(ie, venous α-KIC labeling), and $t$ is the time between biopsies in hours.

**MPB**

Plasma was used to determine labeling (atom percentage excess) and concentrations of arterIALIZED and venous leucine, phenylalanine, and α-KIC. Plasma was deproteinized with 100% ethanol and dried. Lipids were removed by using ethyl acetate extraction, and the amino acids were converted to their tert-butylidemethylsilyl derivatives. Concentrations and enrichments were determined by using gas chromatography–mass spectrometry (Trace DSQ; Thermo Fisher Scientific) with the use of appropriate internal standards (30). Leg protein flux (ie, breakdown) was calculated from the arteriovenous dilution of [D5]phenylalanine by using the following equation (31):

$$\left(\frac{E_a}{E_v}\right) - 1 \times Ca \times \text{blood flow}$$

(2)

where $E_a$ and $E_v$ are the values of amino acid enrichment at steady state in arterial and femoral venous plasma and $Ca$ is the mean concentration in the arterial blood with blood flow (in mL/100 mL leg) adjusted for leg volume and assessed by using dual-energy X-ray absorptiometry. For each 1.5-h period, values for enrichment and concentration were obtained from the mean of 4 samples collected every 20 min over the past hour. The net amino acid balance was calculated as the difference in arterial and venous concentrations multiplied by the plasma flow adjusted for hematocrit.

**Immunoblotting**

Proteins were extracted from muscle (~20–30 mg) as previously described (32) and standardized to 2 mg/mL by using dilution with Laemmli loading buffer to measure relative phosphorylated protein concentrations. A total of 30 μg protein per lane was loaded on to Criterion XT Bis-Tris 12% SDS-PAGE gels (Bio-Rad) for immunoblotting, which was performed as described (32), with α-actin used to correct for loading on all targets.

**Gene-expression analyses**

Total extracted RNA was quantified, and the integrity and purity were assessed by using both the Nanodrop (Thermo-scientific) and Agilent 2100 Bioanalyzer (Agilent) spectrophotometers. The high quality of RNA was confirmed by the presence of 18S and 28S ribosomal peaks with no evidence of DNA contamination or RNA degradation. Messenger RNA (mRNA) transcripts were analyzed according to previously published protocols (33). The selected targets involved in MPB were the 14-kDa ubiquitin-conjugating enzyme, muscle-ring finger 1 (Murf-1), muscle atrophy F box (MAFBx), C2 proteasome, ubiquitin, myostatin, and tripeptidyl peptidase II. Data were normalized to 28S ribosomal RNA by using the 2-ΔΔCT method (33).

**Cytokine analysis**

Circulating concentrations of plasma IL-10, TNF-α, C-reactive protein (CRP), and cortisol were measured in cancer patients before and after surgery by using ELISA systems (R&D Systems Inc). All ELISAs were processed according to the manufacturer’s instructions.

**Statistics**

Differences in muscle mass were determined by using unpaired (control compared with cancer) or paired (before surgery compared with after surgery) 2-tailed Student’s t tests. Differences in MPS and MPB were assessed by using 2-factor ANOVA with Bonferroni’s post hoc testing. Differences in fasted-fed anabolic signaling were assessed by repeated-measures 1-factor ANOVA (cancer patients) or paired Student’s t test (healthy control subjects) on log-transformed data (data were transformed after failing normality tests). Gene expression was analyzed by using unpaired t tests (healthy control subjects compared with preoperative cancer patients). Correlations were explored (ie, between the postoperative fed-state MPS and muscle loss) by using Pearson’s R correlation (GraphPad Prism, v5.0; GraphPad software), and cytokine concentrations in cancer patients before and after surgery were assessed by using the paired Student’s t test. Data are reported as means ± SEMs with $P < 0.05$ considered significant.
RESULTS

Lean mass

In comparison with healthy controls, lean leg mass was significantly lower in preoperative cancer patients (6290 ± 456 compared with 7839 ± 617 g; \( P < 0.05 \)). After surgery, patients with cancer displayed an additional significant reduction in lean leg mass (6290 ± 456 compared with 5840 ± 456 g; \( P < 0.001 \)) (Figure 2).

MPS and immunoblotting

There was no difference in fasted MPS between preoperative cancer patients and control subjects. In contrast, although increases in MPS after feeding were evident in healthy control subjects (0.038 ± 0.004 compared with 0.065 ± 0.006%/h; \( P < 0.01 \)), there was no change in fed MPS in preoperative cancer patients (0.028 ± 0.004 compared with 0.038 ± 0.004%/h; \( P > 0.05 \)). By the time of the second study after removal of the cancer, fed-state increases in MPS had fully recovered [0.087 ± 0.017 %/h (postprandial after surgery)] compared with 0.038 ± 0.004%/h (postprandial before surgery); \( P < 0.05 \)] (Figure 3). There was a significant inverse correlation between the loss of lean leg mass after surgery and postprandial MPS after surgery (17%, \( P < 0.01 \)) (Figure 4). Thus, restoring the anabolic responses in MPS to feeding limited surgically induced atrophy.

To seek mechanistic explanations for anabolic responses to nutrition, we probed for elements of the protein kinase B (AKT)–mammalian target of rapamycin complex 1 pathway. The healthy control group showed significant increases in P70S6 kinase (AKT)–mammalian target of rapamycin complex 1 pathway. The phosphorylation of P70S6K1Thr389 and 4EBP1Thr37/46 were also significantly lower in preoperative cancer patients (617 g; \( P < 0.05 \)) but were statistically unaffected by feeding (Figure 5).

FIGURE 2. Means (±SEMs) of lean leg mass in healthy control subjects (n = 8) and colon cancer patients before and after resection surgery (n = 13). *Compared with healthy controls, \( P < 0.05 \); **compared with preoperative cancer patients, \( P < 0.001 \). Differences in muscle mass were determined by using unpaired (control subjects compared with cancer patients) or paired (before surgery compared with after surgery) 2-tailed Student’s t tests. Post-Op, postoperative.

MPB and proteolytic gene expression

There was a main effect between conditions (healthy, preoperative, and postoperative) in terms of leg proteolysis from which post hoc testing yielded a trend for increases under both fasted and fed conditions in preoperative cancer patients compared with healthy control subjects [116 ± 37 compared with 50 ± 7 nmol phenylalanine · 100 g lean leg mass\(^{-1}\) · min\(^{-1}\) (\( P = 0.07 \)) and 106 ± 33 compared with 41 ± 8 nmol phenylalanine · 100 g lean leg mass\(^{-1}\) · min\(^{-1}\) (\( P = 0.09 \)), respectively]. Postoperatively, fasted and fed rates of leg proteolysis were reduced in cancer patients such that they were not different from those in healthy controls in either condition (Figure 3). These data support the notion of an increase in MPB that cannot be overcome by an exogenous nutritional supply. To seek mechanistic explanations for increases in MPB, selected genes implicated in MPB expression of C2 proteasome mRNA in preoperative cancer patients compared with in healthy control subjects (3.2 ± 0.75-fold higher in preoperative patients than in control subjects), without changes in other indexes of proteasomal degradation (eg, MAFBx and MuRF-1) (Figure 5).

Plasma cytokine analysis

To assess whether altered cytokine, acute-phase, or stress hormone profiles could be responsible for differences in protein

FIGURE 3. Means (±SEMs) of myofibrillar FSR (MPS) (A) and leg proteolysis (MPB) (B) of healthy controls (n = 8) and colon cancer patients before and after resection surgery (n = 13) in postabsorptive and postprandial conditions. MPS interaction term between feeding and surgery \( P = 0.02 \); MPB, \( P = 0.85 \). **Compared with the same group in the postabsorptive condition, \( P < 0.01 \); *compared with preoperative cancer patients in the same condition, \( P < 0.05 \). Statistical analysis was conducted by using 2-factor ANOVA with Bonferroni’s post hoc analysis. FSR, fractional synthetic rate; MPB, muscle protein breakdown; MPS, muscle protein synthesis; Phe, phenylalanine; Post-Op, postoperative.
metabolism before and after surgical resection, we measured concentrations of these indexes in the plasma of cancer patients. However, there existed no differences in circulating plasma concentrations of IL-10, TNF-α, CRP, or cortisol between cancer patients before and after surgery (Table 1).

DISCUSSION

Although the preservation of muscle mass in cancer is crucial for the maintenance of life quality, outcome, and survival, little is understood about the underlying mechanisms of muscle wasting in cancer cachexia. The paucity of human studies in this area reflects the difficulty in performing invasive studies in cancer patients. Moreover, the few previous studies of muscle protein turnover have reported on histologically and anatomically diverse cancers with patients at differing stages of tumor progression (8, 15, 17). In addition, many of these studies have used younger control groups (15, 17) and reported whole-body protein turnover (14, 34), which does not inform on muscle. in the current article, we have carried out studies to define muscle protein turnover in patients with the same histologic and curable cancer (colonic adenocarcinoma; stage III, T, N 1–2, M0) both before and after primary tumor removal. These data have been compared with an age- and BMI-matched control group (ie, noncancer subjects).

At baseline, CRC patients were cachectic as evidenced by lower lean leg mass than that in the control group. However, in looking for metabolic disturbances to explain this, our results did not support previous findings that depressions in postabsorptive MPS are a universal feature of cachexia (8, 15, 17). Alternatively, we showed that the provision of nutrition normally sufficient to maximize MPS (ie, in healthy controls) is ineffective in stimulating increases in MPS in CRC patients. This inability for nutrition to stimulate MPS is in agreement with a recent report (8) and, on the basis of the crucial role of MPS in the maintenance of muscle mass, at least in part explains muscle wasting in cancer cachexia. Moreover, if the phenomenon of anabolic resistance is a pervasive feature of cancer, this phenomenon likely underpins the global paucity of effective nutritional interventions in alleviating muscle wasting (35).

In terms of MPB, evidence of increased MPB was present under both postabsorptive and postprandial measurement periods. These results suggested that cachexia in nondisseminated colonic adenocarcinoma is due to both anabolic resistance in
fed-state MPS and a paralleled increase in fasted and fed MBP. To seek an explanation for elevated muscle proteolysis, we also measured the expression of a panel of genes that represent obvious candidate markers of MBP (eg, atrogenes) and measured the expression of a panel of genes that represent obvious candidate markers of MBP (eg, atrogenes) and measured the expression of a panel of genes that represent obvious candidate markers of MBP (eg, atrogenes). Although MAFBx and MuRF-1 were not increased in cancer patients, changes in mRNA concentrations of the C2 subunit (previously shown to parallel the chymotrypsin-like activity of the proteasome) were elevated in patients with cancer compared with in control subjects. Although our assessment of proteolytic gene expression was limited to selected mRNA targets measured at a single time-point by reverse transcriptase polymerase chain reaction, we tentatively suggest that these data are in agreement with those derived from preclinical models that showed the active involvement of the ubiquitin proteasome system in cancer cachexia (36). Thus, in addition to improving nutritional strategies to bolster anabolic sensitivity to feeding (eg by providing excessive quantities of nutrition) (8, 37, 38), our data support the notion that therapeutics with which to suppress excessive proteolysis may also be needed to fully reverse features of metabolic dysregulation in cancer cachexia.

Because of the catabolic influence of surgery, we predicted that tumor resection would exacerbate preexisting muscle atrophy. In support of this effect, muscle mass had further declined in the 6-wk period after surgery (−7.2%). Thus, it was surprising that catabolic alterations in protein turnover (ie, increased MBP and anabolic resistance) had normalized at this time. This apparently contradictory observation may be explained if perturbations in protein metabolism are a direct result of the tumor (39). Moreover, the documented catabolic effect of surgery on protein turnover (21, 23–27) that occurs after major abdominal procedures would have passed by 6 wk, albeit with insufficient time to reverse muscle atrophy. In direct support of this catabolic effect of surgery, correlation analysis revealed a relation between the resensitization of MPS to feeding and that of post-surgery muscle maintenance (ie, quicker normalization of protein metabolism after surgery limits the exacerbation of cancer-induced muscle wasting). To search for explanations for the restoration of the anabolic response to feeding after tumor resection, we investigated the phosphorylation of AKT, P70S6K1, and 4EBP1 in response to feeding. However, we were unable to identify reciprocal changes between signaling protein phosphorylation and MPS. This apparent dissociation between protein phosphorylation and dynamically measured MPS may be a feature of any or all of the following: 1) a lack of temporal resolution (ie, a single biopsy time point after feeding (40), 2) a true dissociation between MPS and signaling (29), and 3) MPS being driven by genomic alterations associated with recovering muscle mass rather than acute phosphorylation events (41).

In terms of other explanations for our findings of altered metabolism between cancer patients, preoperatively and postoperatively, we also examined plasma cytokines because inflammation has been suggested as a driver of muscle wasting in cancer cachexia (42). However, there were no differences in circulating plasma cytokine or acute-phase, stress-response protein concentrations (eg, TNF and CRP) in our cancer patients before and ~6 wk after surgery. Thus, although we could not rule out the involvement of cytokines in cachexia (ie, we did not measure a broad spectrum) in the current study, we were unable to link alterations in the cytokines measured to the observed catabolic changes in protein turnover and muscle mass.

In conclusion, in patients with curable colorectal adenocarcinoma, lean leg mass was reduced compared with in control age-matched subjects with a concomitant reduction in postprandial MPS and increases in MBP. Six weeks after surgical resection of the primary tumor, muscle protein synthetic responses to feeding and leg proteolysis had returned to normal with additional decreases in lean leg mass, which was a disparity that we believe to be attributable to the now spent surgical insult (43). With a greater understanding of the processes at work in the skeletal muscle of cancer patients (in different cancers and at different stages), it may be possible to better tailor future therapies to both stimulate MPS, under fasted and fed conditions, and reduce MBP to combat the serious problem of cancer cachexia. Finally, although the detection of significant alterations in protein turnover in mixed-sex populations suggests similarities in responses to cancer burden, additional studies that defined potential sexual dimorphism in protein metabolism (for which current numbers were insufficient) are necessary to explain reports of sexual dimorphism in cancer cachexia.

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The authors’ responsibilities were as follows—MJR, JL, ML, and KS: designed the research; JPW, BEP, KS, SL, DR, and ALS: conducted the research; JPW, BEP, KS, and PJA: analyzed data and wrote the manuscript; and JPW and BEP: had primary responsibility for the final content of the manuscript. None of the authors had a conflict of interest.

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