Original article

Determinants of change in resting energy expenditure in patients with stage III/IV colorectal cancer

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Background & aims: Resting energy expenditure (REE) is variable in cancer and might be influenced by changes in tumor burden, systemic inflammation, and body composition. The objective of this study was to assess REE change and the predictors of such in patients with stage III or IV colorectal cancer.

Methods: REE was measured via indirect calorimetry and fat mass and fat-free mass (FFM) were assessed using dual X-ray absorptiometry as part of a unique analysis of two studies. C-reactive protein (CRP) was measured as an inflammatory marker. Linear regression was used to assess the determinants of REE at baseline and REE change, with days between baseline and follow-up measures included as a covariate.

Results: One-hundred and nine patients were included at baseline (59.6% male; 67.5 ± 12 years; body mass index 24.1 ± 4.3 kg/m²); 49 had follow-up data (61.2% male; 65 ± 12 years; body mass index 25.4 ± 4.3 kg/m²), with median follow-up of 119 days (interquartile range: 113–127 days). At baseline, age, FFM, and CRP explained 68.9% of the variability in REE. A wide variability in REE change over time was observed, ranging from −156 to 370 kcal/day, or −13.0 to 15.7%/100 days. CRP change (1.7 ± 0.4 mg/L, p < 0.001) and stage (81.3 ± 38.7, p = 0.042) predicted REE change in multivariate analysis, controlling for age, FFM change, and days between visits (R²: 0.417 ± 0.042).

Conclusions: Age, FFM, and CRP predicted REE at a single time point. REE change was highly variable and explained by inflammation and stage. Future research should investigate the validity and feasibility of incorporating these measures into energy needs recommendations.

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1. Introduction

Resting energy expenditure (REE, the largest component of total energy expenditure, TEE) is often measured or estimated for energy needs assessment. While REE in healthy populations is predictable, REE is variable in patients with cancer and might be influenced by several factors [1]. As body composition (particularly fat-free mass, FFM) is a major determinant of REE in healthy populations, substantial changes in FFM could affect REE in these patients. Furthermore, inflammation is also associated with REE at a single timepoint [2], and may change throughout disease trajectory [3]. The energetic demand of the tumor itself can also substantially impact energy metabolism, especially in the presence of metastases [4,5].

Furthermore, different types of cancer might induce unique alterations in energy expenditure. For example, higher REE is more common in patients with lung, pancreatic, or liver cancer compared to gastrointestinal or urologic cancer [6]. Colorectal cancer is one of the most commonly diagnosed cancers worldwide [7]. These patients have highly variable body composition, independent of body weight [8], which might substantially impact REE.

Previous literature suggests REE may decrease [9], increase [10], or stay the same [11] in patients with cancer. However, the influence of changes in body composition and other variables such as inflammation on REE change per se has not been investigated in

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colorectal cancer. Furthermore, the methodological issue of dividing REE by measures of body weight or composition precludes accurate conclusions about energy expenditure, as we and others have discussed [1,12].

While the impact of tumor burden on REE has been previously investigated in colorectal cancer [5,11] and average REE change has been reported [13], the variability in REE change and the determinants of such have not been described. Therefore, the objective of this study was to assess REE change and the influence of several variables in patients with stage III or IV colorectal cancer. Our hypothesis was that tumor stage and changes in FFM and inflammation would predict REE change.

2. Materials and methods

2.1. Patients

This is a unique analysis of data collected as part of two previously published studies [14,15]. Data from study 1 was collected at the Department of Surgery at Sahlgrenska University Hospital (Gothenburg Sweden) between 1993 and 2005 and was approved by the Committee for Ethics at the Faculty of Medicine, University of Gothenburg. Patients with stage III or IV colorectal cancer were included in the present analysis. Individuals in this study were not undergoing chemotherapy or radiotherapy but were offered an intervention with anti-inflammatory treatment with indomethacin [16], insulin [17], erythropoietin for anemia [18,19], dietary counseling, and nutritional support [20]. Inclusion criteria were weight loss (3–5% over 3 months), no effective treatment available, and expected survival > 6 months. Exclusion were brain metastases, treatment with anti-inflammatory drugs, kidney function impairment (serum creatinine > 200 µmol/L), body temperature > 37.8 °C, or persistent cholestasis. Patients had not received radiation or chemotherapy in the six months prior to baseline measures or during follow-up. Median survival from baseline assessments in this study was 183 days (interquartile range [IQR]: 104–320 days).

Data from study 2 [15,21] was gathered at the Cross Cancer Institute in Edmonton, Alberta, Canada between January 2005 and October 2006 and approved by the Alberta Cancer Board Research Ethics Board. Patients with newly diagnosed advanced (stage IV) colorectal cancer, age ≥18 years and able to communicate in English were included. Exclusion criteria were pregnancy, human immunodeficiency virus +, or presence of a pacemaker. Median survival from baseline assessments was 453 days (IQR: 303–742 days). Informed consent was collected from all participants in both studies, in line with the Declaration of Helsinki.

2.2. Anthropometrics and body composition

In study 1, body weight was measured by a calibrated electronic scale and height was assessed via a wall-mounted stadiometer (Hultafors Group AB, Sweden). Body composition was quantified using dual X-ray absorptiometry with a LUNAR DPX-L for the first 77 patients, and a LUNAR Prodigy High Speed Digital Fan Beam Densitometer with enCORE 9.20 software. FFM and fat mass (FM) were expressed in absolute terms and adjusted by height in m² (fat-free mass index, FFMI, and fat mass index, FMI).

Body mass index (BMI, kg/m²) for all patients was calculated and categorized according to the World Health Organization [23].

2.3. Resting energy expenditure

Both studies utilized indirect calorimeters after an overnight fast. Study 1 used a Deltatrac machine (Datex, Helsinki, Finland) and study 2 used a Vmax 29N (SensorMedics, Yorba Linda, CA). Previous research has shown the Vmax system to have the best agreement with the Deltatrac indirect calorimeter [24]. The Weir equation [25] was used to calculate REE and respiratory quotient was calculated as the ratio of CO₂ volume to O₂ volume. A rest period of 30 min before REE was conducted in each study. Study 1 measured gas exchange from 30 min (after the first 3 min were discarded) and study 2 collected a minimum of 15 min steady state measurements. REE was not divided by body weight or any measure of body composition, as this creates a statistical bias and might lead to false conclusions about energy expenditure (REE) [1].

2.4. Biochemical assessments

C-reactive protein (CRP, mg/L) was investigated in both studies as a potential influence of REE and body composition. In study 1, CRP analyses were part of routine care and assessed in the certified Department of Clinical Chemistry at Sahlgrenska University Hospital. Study 2 used rate nephelometry on Beckman Image (CV = 10%) as analyzed by a clinical laboratory provider (Dynacare Kasper Medical Laboratories).

2.5. Dietary intake and performance status

As previously described [26–28], dietary intake in study 1 was collected using 4-day food records with KOSTSVAR (from year 1993–2000) and DIET32 (from year 2000–2005) software (Aivo, Stockholm, Sweden), paired with the National Food Composition Tables database (Statenslivsmedelsverk, Uppsala, Sweden). In study 2 [15,21], dietary intake was ascertained using 3-day food records and analyzed using FoodProcessor (ESHA Research, Salem, OR). Food records in both studies were checked for completeness by a registered dietitian. Only energy intake was presented for descriptive analyses because the relationship between energy expenditure and energy intake and macronutrient distribution has been previously described in detail within each cohort [21,28]. Energy intake was expressed in absolute amounts and per kilogram body weight.

The Karnofsky performance status (study 1) [29] or the “Activities and Function” (box 4) score from the Patient-Generated Subjective Global Assessment (PG-SGA; study 2) [30] were used to assess functional status. Box 4 of the PG-SGA is a lay-language version of the European Cooperative Oncology Group (ECOG) performance status score [31] and was used as such. Karnofsky scores were converted to ECOG scores as follows [32]: 100 = 0; 80 to 90 = 1; 60 to 70 = 2; 40 to 50 = 3; 10 to 30 = 4.

2.6. Statistical analyses

All tests were completed in SPSS version 24 (IBM Corp., Armonk, NY, USA) and presented as mean ± standard deviation or median (IQR) where appropriate. Significance was defined as p ≤ 0.05 and normality was assessed using the Kolmogorov–Smirnov test. Overall change in variables between baseline and follow-up were assessed using paired-samples t-test; in the case of non-normality in the differences between baseline and follow-up variables, Wilcoxon signed rank test was used. Differences between groups was assess using independent samples t-tests for continuous variables.
or Chi-square test for nominal variables. In the case of non-normally distributed variables, Mann–Whitney U-test was used. Differences between patients grouped by ECOG performance status was assessed using one-way analysis of covariance (when there was normal distribution within each ECOG category) or Kruskal–Wallis test (non-normal distribution). Changes in body weight, FM, FFM, CRP, REE, and respiratory quotient were expressed in absolute terms and as percentage change/100 days (percent weight, FM, FFM, CRP, REE, and respiratory quotient were expressed as change values in order to meet the assumption of independence. A sample size of 45 was determined to be adequately powered to detect predictors of REE change based on a medium effect size (0.25), x 0.05, β 0.90, and six independent variables. Study (1 or 2) and days in between measurements were included as independent variables to control for heterogeneity between and within studies. Interaction of study and stage to other variables. Study (1 or 2) and days in between measurements were included as independent variables to control for heterogeneity between and within studies. Linear regression was used to predict REE at baseline and REE change in absolute values. Several predictive variables were investigated including age, sex, height, body weight, cancer stage, presence of liver metastases, FM, FFM, and CRP, with stepwise linear regression used to identify the best model to predict REE at baseline. When predicting REE change, independent variables were expressed as change values in order to meet the assumption of independence. When predicting REE change, independent variables were expressed as change values in order to meet the assumption of independence.

Caloric intake in absolute terms was higher in males, but this difference was not apparent after dividing by body weight, Table 1. Twenty-six patients (25.2% of 103 with dietary intake data) reported energy intakes below REE in absolute terms. ECOG scores were available for 94 individuals; of those, most (n = 57, 60.6%) had a score of 1, indicating ‘restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature’. The remaining patients had scores of 0 (n = 26, 27.7%) or 2 (n = 11, 11.7%). There were no differences in age, BMI, REE, FFM or FMI among patients with ECOG of 0, 1, or 2, nor were there differences in ECOG scores between patients with stage III versus stage IV disease (p = 0.125).

In univariate analysis, age (−7.7 ± 2.0, R²: 0.126, p < 0.001), sex (294.3 ± 41.7, R²: 0.318, p < 0.001), height (19.1 ± 2.2, R²: 0.416, p < 0.001), body weight (10.2 ± 1.3, R²: 0.373, p < 0.001), stage (135.8 ± 65.3, R²: 0.039, p = 0.040), FM (6.4 ± 2.6, R²: 0.053, p = 0.016), FFM (18.5 ± 1.7, R²: 0.532, p < 0.001), and CRP (1.2 ± 0.5, R²: 0.056, p = 0.015) were significant predictors of REE. In stepwise regression, age, FM, and CRP explained 68.5% of the variability in REE, Table 2. All other variables were not significant predictors of REE in multivariate analyses and were therefore not included in the model. When only patients with stage IV cancer were assessed, similar results were observed with age (−76 ± 2.2, R²: 0.118, p = 0.001), sex (290.2 ± 49.6, R²: 0.277, p < 0.001), height (20.7 ± 2.5, R²: 0.428, p < 0.001), body weight (10.2 ± 1.5, R²: 0.351, p < 0.001), FM (6.4 ± 2.9, R²: 0.051, p = 0.031), FFM (19.3 ± 1.9, R²: 0.527, p < 0.001), and CRP (1.1 ± 0.5, R²: 0.052, p = 0.033) significant in univariate analysis, and age, FFM, and CRP generating the strongest predictive model in multivariate analysis (R²: 0.678 ± 150.0, p < 0.001; age: −5.7 ± 1.4; FFM: 19.1 ± 1.6; CRP: 1.3 ± 0.3, all p < 0.001). Inclusion of ECOG score or indomethacin treatment into the regression model did not impact results (data not shown).

3. Results

3.1. Baseline

A total of 109 patients had baseline data available, Table 1. Most (n = 86, 78.9%) had undergone previous surgery. A small number of patients received chemotherapy or were undergoing chemotherapy at the time of assessment (n = 12, 11.0%), which included five different regimens (folinic acid/fluorouracil/oxaliplatin, folinic acid/fluorouracil/irinotecan, oxaliplatin/capecitabine, irinotecan/capecitabine, or raltitrexed). In study 1, there were no differences in REE between those taking any modality of the intervention medication and those not taking medication and they were therefore grouped for analysis. Most patients (n = 59, 54.1%) had a BMI in the normal range. Sixty-five (58.6%) were male and most had stage IV disease (n = 91, 83.5%). Compared to stage IV cancer, individuals with stage III cancer were older (median: 74 [IQR: 68–80] vs. 65 [IQR: 58–75] years, p = 0.002) and had lower REE (1442 vs. 1577 kcal/day, p = 0.040).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Entire sample (n = 109)</th>
<th>Males (n = 65)</th>
<th>Females (n = 44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.5 (59.6, 76.0)</td>
<td>67.0 (60.3, 75.9)</td>
<td>67.5 (58.2, 79.0)</td>
<td>0.583</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>71.0 ± 15.3</td>
<td>77.3 ± 14.2</td>
<td>61.1 ± 11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.1 ± 4.3</td>
<td>24.9 ± 4.2</td>
<td>23.1 ± 4.2</td>
<td>0.033</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>49.6 ± 10.2</td>
<td>56.3 ± 7.1</td>
<td>39.7 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat-free mass index, kg/m²</td>
<td>18.1 ± 1.9</td>
<td>14.8 ± 1.2</td>
<td>14.8 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>20.5 ± 9.2</td>
<td>20.2 ± 8.9</td>
<td>20.9 ± 9.6</td>
<td>0.706</td>
</tr>
<tr>
<td>Fat mass index, kg/m²</td>
<td>7.0 ± 3.2</td>
<td>6.5 ± 2.8</td>
<td>7.8 ± 3.5</td>
<td>0.036</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>14.9 (5.0, 40.0)</td>
<td>14.0 (5.0, 37.0)</td>
<td>18.2 (5.0, 47.3)</td>
<td>0.668</td>
</tr>
<tr>
<td>Energy intake, kcal/day</td>
<td>1860 (1535, 2323)</td>
<td>2004 (1619, 2458)</td>
<td>1625 (1477, 1962)</td>
<td>0.002</td>
</tr>
<tr>
<td>Energy intake, kcal/kg/day</td>
<td>27.8 ± 8.5</td>
<td>28.1 ± 9.3</td>
<td>28.1 ± 9.3</td>
<td>0.794</td>
</tr>
<tr>
<td>Measured REE, kcal</td>
<td>1555 ± 257</td>
<td>1674 ± 229</td>
<td>1380 ± 187</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.79 ± 0.06</td>
<td>0.80 ± 0.06</td>
<td>0.77 ± 0.06</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Presented as mean ± standard deviation for normally distributed variables or median (interquartile range) for non-normally distributed variables (age and C-reactive protein). Significance was derived from independent samples t-test for normally distributed variables or Mann–Whitney U-test for non-normally distributed variables. REE: resting energy expenditure.

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two months (64 days, IQR: 56–77 days). Differences in several variables between these studies are shown in Supplementary Table 1 and Supplementary Table 2. Absolute REE without adjusting for days between measurements increased in study 1 (1559 ± 223 to 1603 ± 265 kcal/day, p = 0.023), but not in study 2 (1557 ± 305 to 1562 ± 288, p = 0.836). Nonetheless, no differences between studies were observed when the values were adjusted for follow-up time, Supplementary Table 3.

Forty-six patients had dietary data available at baseline, 45 had this information at follow-up, and 44 had both baseline and follow-up dietary data available. While average energy intake in absolute or weight-adjusted terms did not change over time (Table 3), most patients decreased energy intake (n = 26, 59.1%, expressed in kcal/day and kcal/kg/day). The proportion of patients with energy intake lower than REE was similar at baseline and follow-up (n = 11, 23.9% baseline versus n = 11, 24.4% follow-up).

Most patients had an ECOG score of 1 at baseline (n = 26 out of 42, 61.9%) and follow-up (n = 31, 73.8%), with one patient at baseline and three patients at follow-up reporting a score of 2. Most (n = 31 out of 41 with both baseline and follow-up) 75.6% did not have altered ECOG scores over time; one individual had a reduced score (indicating improved performance status over time) and the remaining patients had a 1-point (n = 8, 19.5%) or 2-point (n = 1, 2.4%) score increase. Only three patients with stage III disease had ECOG scores available at both timepoints, precluding comparisons of performance status between stages.

Overall, absolute REE increased by 35 kcal/day (1559 ± 240 to 1594 ± 268 kcal/day, p = 0.026), Table 3. FFMM (50.2 ± 10.0 to 50.9 ± 9.1 kg, p = 0.037) and CRP (7.5, IQR: 3.2–23.0 to 10.3 IQR: 5.0–45.5, 0.049) also increased. Seven (14.3%) patients had stage III disease at baseline and follow-up (all from study 1). REE decreased in patients with stage III disease (−40 ± 78 kcal/day, −2.3 ± 3.9%/100 days) and increased in patients with stage IV disease (47 ± 107 kcal/day, 2.4 ± 3.9%/100 days); change in both kcal/day (p = 0.044) and % change/100days (p = 0.044) were different between stages. A wide variability in REE change was observed, ranging from −156 to 370 kcal/day, or −13.0 to 15.7%/100 days, Fig. 1.

Six independent variables were initially chosen for linear regression analysis. In addition to our hypothesized predictor variables (stage, FFMM change, CRP change), age was included since it significantly predicted REE at baseline and might influence REE independently of FFMM [33]. Study and days in between visits were originally included as covariates to mitigate potential bias from combining two datasets and control for follow-up heterogeneity, respectively. However, since study was not significant in any models and our results were similar without this variable, it was not included in final predictive models. Days between visits was included in models since REE, FFMM, and CRP changes were time-dependent. Results of the linear regression for predictors of REE change are shown in Table 4. In univariate analysis only stage (87.5 ± 42.2, R²:0.084, p = 0.044), CRP at follow-up (0.8 ± 0.3, R²: 0.135, p = 0.010), and CRP change (1.9 ± 0.4, R²: 0.342, p < 0.001) were significant predictors of REE change. Stage and CRP change remained significant predictive factors when controlling for days between visits, age, and FFMM change. Table 4. Results were similar when indomethacin treatment (n = 14) was included as a covariate (R²: 0.467; standard error of the estimate: 86.5; CRP change: 1.7 [95% confidence interval: 0.9, 2.6], p < 0.001; stage: 871 [9.0, 165.2], p = 0.030; no other variables were significant). There were also no differences in percent change/100 days of REE or CRP in those taking indomethacin versus those not taking this medication.

4. Discussion

This study is the first to collectively assess changes in REE, body composition, and inflammation in individuals with colorectal cancer. We found that age, FFMM and CRP were significant predictors of REE at baseline. REE change was highly variable and inflammation and advanced stage predicted alterations in REE, independent of age and FFMM change.

In healthy adults, FFMM is a significant predictor of REE [34]. Decreases in FFMM explain approximately 60% of decrease in REE observed with age [35], but other age-related factors affect REE independently of FFMM [33]. FFMM and age were therefore expected to predict REE in our sample at baseline. Although it was anticipated that FFMM change would be a significant predictor of REE change, this was not observed in our data. Notably, FFMM is a heterogeneous body composition compartment that comprises of tissues with differing metabolic activity. In metastatic cancer, it is unable to distinguish between changes in tissue, organs, and tumors. Furthermore, FFMM alterations might change in oppositional proportion to inflammatory alterations; namely, skeletal muscle (a large portion of FFMM) atrophy is associated with inflammatory cytokines [36]. It is therefore possible that the impact of body composition alterations are obscured in the face of high systemic inflammation, although further research is needed. According to the findings presented here, FFMM is a useful determinant of REE at a single timepoint, but cannot detect tumor burden or metastases, which—along with inflammation—impact REE change to a greater extent than body composition changes.
We found that REE on a group level increased significantly over time. These findings differ from previous studies in colorectal cancer where average REE in absolute terms did not change over 6 weeks of radiation (1573 vs. 1568 kcal/day, p > 0.05) [13] or was not different than control subjects (29 kcal/kg FFM in patients with cancer, non-malignant gastrointestinal diseases, and healthy controls) [37]. Although group REE alteration was significant, it is important to note the small overall change of 35 kcal, which may or may not impact energy balance in the long term. Regardless of the overall group-level change, we observed a high individual variability in REE change, ranging from –156 to 370 kcal/day or –13.0 to 15.7%/100 days. Expected REE intra-individual variation over two weeks in healthy adults is 3.3% [38]; over half (n = 32, 65.3%) of patients in the present study had REE changes outside of this range. Therefore, a high variability in metabolic alterations is apparent beyond that expected from normal individual variation. 

An emerging and persistent theme in nutrition interventions is the need for personalized recommendations due to substantial intra-individual variation in dietary habits, anthropometrics, blood parameters, physical activity, and gut microbiota [39,40]. The same concept can be applied to energy balance where understanding the contributors of REE and TEE change alongside energy intake alterations are a vital component in precision medicine. In the context of advanced cancer, anticipating changes in energy needs is especially important for preventing weight change.

Change in CRP was a predictor of REE change in our study, after controlling for several variables. At a single time point, markers of systemic inflammation such as CRP have been positively related to REE [16,41] and may predict survival [42,43] in various cancer types. The presence of a tumor induces a chronic inflammatory response associated with the production of T helper 1 cytokines [44] and an ensuing ‘energy appeal reaction’ consumes glucose from the liver, protein from muscle, and lipids from fat tissue, perpetuating high REE [1,45]. Therefore, although FFM can effectively predict REE at a single timepoint, dramatic changes in CRP could indicate underlying metabolic changes that might affect energy metabolism. Our results suggest that markers of inflammation might also play a role in the variability of REE change.

In the present analysis, overall REE decreased in patients with stage III disease and increased in patients with stage IV disease, which could be indicative of extra tumor burden in patients with metastatic disease. Previous studies have assessed the impact of tumor burden on REE. In 101 patients with colorectal cancer undergoing neoadjuvant radiotherapy, more advanced stage (III/IV vs. I/II), aggressive histology, and higher pro-inflammatory cytokines were major determinants of REE before and after therapy [2,11]. Mathematical calculations of tumor energy consumption are estimated to fall between 100 and 1400 kcals/day, depending on tumor size and anaerobic glucose production [4]. Given that the liver is a highly metabolically active organ (200 kcal/kg/day) [46], metastases at this site might consume considerable energy. Mathematical estimates suggest a figure of over 200 kcal/kg metastases/day [4]. In theory, extensive metastatic disease (especially in the liver) would impact REE to a greater extent than inflammation. Indeed, liver volume increases close to death and is positively associated with REE in patients with colorectal cancer [5], although other studies found that liver metastases had no impact on REE [37,47]. In the present analysis, liver metastases did not impact REE at baseline or REE change, although we found that metastatic disease in general (i.e. stage IV vs. stage III) predicted REE increase. Notably, metastases might be extensive in tissues and organs in the absence of liver metastases and there is currently no expedient way to quantify overall tumor burden in vivo for each patient. Therefore, although stage IV disease predicts REE increase, the impact and extent of the metastatic site is unknown.

Despite an overall increase in REE in this sample, most individuals decreased energy intake, and several patients at baseline and follow-up had energy intakes below REE. While this could represent dietary under-reporting, such incongruity between energy metabolism and energy intake has been previously comprehensively characterized and is often emblematic of advanced, progressive cancer [11,27]. Continuous decline in performance status is also a characteristic of advanced cancer [48] and might be a consequence of weight loss due to energy imbalance or directly related to tumor-associated symptoms such as fatigue. This cluster of physiological alterations — increases in REE and inflammation with decreases in energy intake and performance status — are related and represent potential explanatory or outcome variables in interventions aimed at preventing weight loss. In addition, measured REE might predict toxicity [49] and survival [50] and can be potentially used to develop accurate nutrition interventions [51].

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**Table 4**

Linear regression analysis showing the determinants of resting energy expenditure change in patients with colorectal cancer (n = 46).

<table>
<thead>
<tr>
<th>Model</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>R²</th>
<th>SEE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>−369.7</td>
<td>−751.9, 12.6</td>
<td>0.058</td>
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<td></td>
</tr>
<tr>
<td>FFM change, kg</td>
<td>1.5</td>
<td>−16.7, 13.8</td>
<td>0.975</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP change, mg/L</td>
<td>1.7</td>
<td>0.8, 2.5</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>0.7</td>
<td>−1.7, 3.0</td>
<td>0.579</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stagea</td>
<td>81.3</td>
<td>3.1, 159.5</td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days between visits</td>
<td>0.3</td>
<td>−0.4, 0.9</td>
<td>0.405</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; CRP: C-reactive protein; FFM: fat-free mass; SEE: standard error of the estimate.

* Compared to stage III.

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**Fig. 1. Variability in resting energy expenditure (REE) change, expressed as kcal/day (A) and percent change/100 days (B).** Change ranged from –156 to 370 kcal/day or –13.0 to 15.7%/100 days.

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It is therefore plausible that REE measurements are a valid way to anticipate negative outcomes (i.e. the development of cachexia or malnutrition) and serve a vital role in making accurate energy needs recommendations. Our results suggest that measures of body composition, inflammation, and cancer stage might impact REE and/or REE change and should also be considered when measuring or estimating REE in cancer populations.

In terms of total energy needs, while REE might be higher in stage IV disease compared to earlier stages [52], this difference may not substantially impact total energy needs since physical activity levels may also shift. Some have suggested that physical activity is substantially diminished in cancer [53], and might decrease over time in patients with cancer cachexia [54]. Furthermore, while REE has been related to weight loss in some cohorts [27], several other publications have reported no such association [55]. Unfortunately, accurate methods to measure free-living TEE and physical activity such as doubly labeled water have been primarily utilized in advanced cancer patients with cachexia (i.e. high rates of weight loss and inflammation) [56,57]. Exploring REE and TEE in the context of colorectal cancer and in those with earlier stages of cancer will guide future energy recommendations, perhaps based on body weight or composition, inflammation, physical activity, and disease stage. If these are the factors we are actively pursuing [58].

The strengths of this study include the measurement of REE in conjunction with body composition and systemic inflammation in a homogeneous sample of patients. A limitation is the different follow-up times; however, this was controlled for in both descriptive analyses (3×REE change/100 days) and the primary statistical analyses (linear regression with days between measurements as an independent variable). Additionally, although combining data from different groups of patients provides larger sample sizes, we noted that CRP at baseline and follow-up and respiratory quotient at follow-up were different between studies. However, the findings for REE change were similar when study (1 or 2) was included as a covariate in the linear regression and therefore did not impact our findings in analyses assessing REE at baseline or change over time. In addition, dietary data was collected using a 4-day food record in European adults (study 1) versus a 3-day food record in North American individuals (study 2) which might have introduced bias in dietary data.

In conclusion, age, FFM, and CRP were associated with REE at one time point and inflammation and stage explained variability in REE change. Further exploration of these variables in relation to REE and TEE will shed light on the relevant and over-looked area of energy needs in cancer.

Statement of authorship

All authors approve the final version of the manuscript submitted. SAP contributed to the analysis and interpretation of the data, drafting and revising the article for intellectual content. OW contributed to the analysis and interpretation of the data and revising the article for intellectual content. VEB contributed to the design of the study, acquisition of the data, and interpretation of the data and revising the article for intellectual content. KL contributed to the design of the study, acquisition of the data, and revising the article for intellectual content. BI contributed to the acquisition of the data and revising the article for intellectual content. QSC contributed to the interpretation of the data and revising the article for intellectual content. CMP contributed to the acquisition of data, analysis and interpretation of the data and revising the article for intellectual content.

Conflict of interest and funding sources

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.12.038.

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