Examining Resting and Total Energy Expenditure in Patients with Cancer

by

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Abstract

Energy expenditure forms the basis of all dietary recommendations. In patients with cancer, resting energy expenditure (REE) can be impacted by tumor burden, high systemic inflammation, and/or altered body composition. Total energy expenditure (TEE) and physical activity levels (PAL) have been characterized primarily in patients with advanced disease or severe weight loss, which may not represent many individuals with cancer.

The overall aims of this research were to investigate the determinants of REE and to characterize TEE in relation to body weight, body composition, PAL, and current energy recommendations in patients with colorectal cancer (CRC). Additionally, this research aimed to examine the validity of REE predictive equations and a portable indirect calorimeter in patients with solid tumors. REE was measured by indirect calorimetry and TEE was ascertained using doubly labeled water. Body composition was determined using dual X-ray absorptiometry or computerized tomography image analysis.

This research showed that REE was not accurately estimated by predictive equations; even the most accurate equation (Mifflin St.-Jeor) still under-predicted REE by up to 32.4 % (-440 kcal/day) and over-predicted REE by up to 18.1% (261 kcal/day). Error was influenced by age and fat mass. A portable indirect calorimeter also did not accurately measure REE (average error ± two standard deviations: -467 to 363 kcal/day). In newly diagnosed patients with CRC, body weight, body composition, age, and sex predicted approximately 80% of REE variability. However, inflammation change and stage IV cancer predicted the REE change over time in patients with stage III or IV CRC. In individuals with mostly earlier stage CRC, TEE was 2473 ± 499 kcal/day (range: 1562 to 3622 kcal/day), or 29.7 ± 6.3 kcal/kg body weight (range: 20.4 to 48.5 kcal/kg body weight/day). Average PAL was 1.43 ± 0.27, which was higher than previously

reported in cancer, despite a high prevalence of elevated REE. Energy estimation using 25 kcal/kg underestimated TEE (-12.6 ± 16.5%, p=0.002) and individual agreement with all other energy recommendations was poor.

The major finding of this research was that REE and TEE (and consequently PAL) were highly variable in patients with cancer, which is not captured by current predictive equations, portable tools, or energy recommendations. Furthermore, body composition is a major determinant of REE at one timepoint and factors such as inflammation and cancer stage impact REE change across time. This research highlights the heterogeneity in energy metabolism in patients with cancer and will contribute to the formation of evidence-based dietary recommendations, considering disease stage, cancer type, body weight, body composition, and/or physical activity, with the ultimate goal of improving cancer care.

Preface

This preface is an overview of the work completed in partial fulfillment of the requirements of a Ph.D.; it is complemented by more detailed and extensive prefaces before each chapter. Some of the research conducted for this thesis uses data that was previously collected by individuals other than me. Data from an investigation of nutritional and metabolic characteristics of patients with advanced non-small cell lung or colorectal cancer at the Cross Cancer Institute (Edmonton, Alberta, Canada) and led by Dr. Vickie Baracos was used in several chapters ('Study 1' in Chapters 3 and 5; 'Study 2' in Chapter 6). Research from that study was approved by the Alberta Cancer Board Research Ethics Board ("A Comprehensive Nutritional Evaluation for Advanced Lung and Colorectal Cancer Patients Who are at Risk for Involuntary Weight Loss", ID:ETH21612). Data from Study 1 in Chapter 6 was also collected as part of several investigations lead by Professor Kent Lundholm and approved by the Committee for Ethics at the Department of Surgery at Sahlgrenska University Hospital (Gothenburg, Sweden) ("Effects of Indomethacin or Prednisolone on Disease Progression in Patients with Solid Cancer", ID: 1-90; "Study of the Effects on Body Composition and Quality of Life in Patients with Solid Cancer of Treatment with Indomethacin, Inderal, Erythropoietin and Home Parenteral Nutrition", ID: 288-93; "Insulin Treatment in Progressive Cancer Cachexia", ID: S141-02; "The Effect of an Appetite-Stimulating Hormone Ghrelin on Appetite, Actual Dietary Intake and Nutritional Status in Cancer Patients with Anorexia and Progressive Cancer Cachexia Development", ID: S543-03). Data on resting energy expenditure, anthropometrics, and patient-reported characteristics in several chapters were conducted by me as part of an investigation I designed in consultation with my supervisor, Dr. Carla Prado, and supervisory committee members, Dr. Vickie Baracos and Dr. Quincy Chu (approved by the Health Research Ethics Board of Alberta: "Resting Energy Expenditure in Cancer: Associations with Body Composition, Dietary Intake, and Exercise Habits", ID:CC-15-0204). Research from this study was used in Chapters 3 and 5 ('Study 2') combined with research collected by individuals other than me. In Chapters 4 and 7, I used data only from this study. For data collection in Chapter 7, I administered the doubly labeled water and collected and processed the biological samples, but isotope enrichments were assessed using mass spectrometry by Dr. Peter J. Walter and Dr. Hongyi Cai at the National Institutes of Health. The discussion in Chapter 8 is original work. All work presented in this thesis was critically

assessed for intellectual content by my supervisor, Dr. Carla Prado, supervisory committee members, Dr. Vickie Baracos and Dr. Quincy Chu, and external committee members, Dr. Diana Mager and Dr. Éric Doucet. Versions of some chapters have led to accepted or published journal articles:

Purcell SA, Xiao J, Ford KL, Prado CM. The role of energy balance on colorectal cancer survival. Current Colorectal Cancer Reports. December 2018; 14(6):266-73. *Located in Chapter 2.*

Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. European Journal of Clinical Nutrition June 2016;70(11):1230-8. *Located in Chapter 2.*

Purcell SA, Elliott SE, Ryan AM, Sawyer MB, Prado CM. Accuracy of a portable indirect calorimeter for measuring resting energy expenditure in individuals with cancer. Journal of Parenteral and Enteral Nutrition 2019; 43(1):145-151. E-Published June 5, 2018. *Located in Chapter 3.*

Purcell SA, Wallengren O, Baracos VE, Lundholm K, Iresjö BM, Chu QSC, Ghosh S, Prado CM. Determinants of change in resting energy expenditure in colorectal cancer. Accepted to Clinical Nutrition December 26, 2018. ID: YCLNU-D-18-00957R1. *Located in Chapter 6.*

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I am also incredibly grateful to Dr. Vickie Baracos for continually sharing her wealth of knowledge with me. She is a leading expert in this field and I feel very fortunate to have learned so much from her. I thank her for always pushing me to be a more insightful researcher.

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List of Abbreviations

AEE: activity energy expenditure

BMI: body mass index

CO_2: carbon dioxide

CRC: colorectal cancer

CRP: C-reactive protein

CT: computerized tomography

CV: coefficient of variation

DLW: doubly labeled water

DRI: Dietary Reference Intake

FFM: fat-free mass

FM: fat mass

NEAT: non-exercise activity thermogenesis

O_2: oxygen

PAL: physical activity level

PG-SGA: patient-generated subjective global assessment

RAEE: residual activity-related energy expenditure

REE: resting energy expenditure

RQ: respiratory quotient

TEE: total energy expenditure

TEF: thermic effect of food

WBCU: whole-body calorimetry unit

Glossary of Terms

Bias: In the context of validation studies, bias is the difference between the criterion method and the method being validated.

Body composition: General term used to describe the different components that make up total body weight.

Cachexia: A severe wasting syndrome that cannot be fully reversed by conventional nutritional support.

Doubly labeled water: A mixture of the isotopes oxygen 18 (^{18}O) and deuterium (^{2}H) that can measure total energy expenditure.

Dietary Reference Intakes: A general term for reference values used to plan and assess nutrient intakes.

Limits of agreement: Bias (error between methods) plus or minus 1.96 standard deviations.

Non-exercise activity thermogenesis: Energy needed for any movement outside of structured exercise.

Physical activity level: The ratio between total energy expenditure and resting energy expenditure.

Resting energy expenditure: Energy needed to maintain basic bodily functions at rest plus the energy cost of arousal.

Respiratory quotient: The ratio of carbon dioxide production to oxygen consumption, with normal values laying between 0.7 (indicative of fat oxidation) to 1.0 (indicative of carbohydrate oxidation).

Thermic effect of food: The energy expended in digestion, absorption, and storage of consumed energy (food).

Total energy expenditure: The amount of energy used by the body on a daily basis; it is the sum of resting energy expenditure, thermic effect of food, and activity energy expenditure.

Chapter 1 Introduction

1.1 Thesis Organization

This thesis has been prepared as a paper format according to specifications provided by the Faculty of Graduate Studies and Research at the University of Alberta. Following the introduction, Chapter 2 is included as a literature review and Chapters 3, 4, 5, 6, and 7 are included as individual manuscripts. A preface precedes Chapters 3, 4, 5, 6, and 7 with a brief description of each study and collaborator contributions.

1.2 Rationale

Approximately 38% of individuals will be diagnosed with cancer at some point during their lifetimes (1). In 2018, an estimated 1.7 million new diagnoses of cancer were made in the United States alone (1). Even with improvements in cancer prevention, screening, and treatment, an estimated 609,640 individuals die from cancer each year and there are an estimated 15.5 million cancer survivors in the United States. Similarly, 1 in 2 Canadians are expected to be diagnosed with cancer at some point during their lifetime and 1 in 4 are expected to die from the disease, despite steadily improving survival rates over the past three decades (2). Cancer also causes a substantial economic impact, with an estimated $1.16 trillion United States dollars per year spent on cancer care globally (3), $147.3 billion in cancer-related expenditures per year in the United States (1), and $7.5 billion Canadian dollars spent within Canada annually (4).

Colorectal cancer (CRC) is among the most common sites of cancer, making up approximately 10% of all new cancer diagnosis (5). Since obesity is a risk factor for this type of cancer (6), many of these patients have excess fat mass (FM) at diagnosis. Conversely, low fat-free mass (FFM) among individuals with newly-diagnosed cancer is common, independent of body weight and cancer stage (7, 8). Importantly, the presence of both low FFM and high FM is associated with worse prognosis compared to either condition alone (9, 10). Similarly, loss of body weight (11) or FFM (12) is also associated with poorer outcomes during treatment. Therefore, adequate nutritional status is necessary for preventing body weight and FFM loss and improving cancer treatment and survivorship (2).

Energy requirements form the basis of all nutrition recommendations; insufficient energy consumption over time leads to weight loss, i.e. a “negative” energy balance. In this state, maintaining and synthesizing skeletal muscle (a large component of FFM, responsible for

mobility, balance, and several metabolic processes) is difficult if not unattainable, even in highly trained athletes (13). To determine energy intake required for weight maintenance, total energy expenditure (TEE) must be characterized. While understanding TEE is undoubtedly necessary for accurate nutrition recommendations, it is inherently costly to measure. Therefore, the basis of current understanding of energy expenditure in cancer mainly originates from resting energy expenditure (REE), the largest component of TEE. In patients with cancer, REE might be impacted by tumor burden, systemic inflammation, brown adipose tissue activation, and changes in body composition (14). However, the relative impact of such variables on REE at one timepoint or its change over time is unclear and precludes complete understanding of altered metabolism. Quantifying such alterations in clinical settings is challenging and the accuracy of REE predictive equations has been questioned (15, 16) and has not been systematically investigated in patients grouped by body weight, cancer type, or cancer stage. Furthermore, individual-level accuracy of clinically practicable portable indirect calorimeters is poor in patients with cancer (17), although the performance of newer models has not been investigated.

In addition to potential REE alterations, physical activity and dietary composition might also affect TEE and consequential energy needs (14). Nonetheless, TEE has mostly been characterized in advanced disease (18) or in those with cachexia (a severe wasting syndrome) (18, 19), which might not be applicable to all individuals with cancer.

Due to the paucity of data on energy requirements in cancer, current energy recommendations (14) are based on body weight alone and do not consider the dynamic nature of REE or TEE across the disease continuum. Given the present state of the literature and gaps that exist, investigating energy expenditure in cancer is a timely and essential endeavor.

1.3 Purpose

The overall purpose of this research was to investigate REE and the determinants of such and to characterize TEE in patients with CRC. Additionally, this research aimed to examine the validity of predictive equations and a portable indirect calorimeter in the assessment of REE in patients with various types of cancer.

1.4 Research Questions

In patients with solid tumours:

1. Do commonly used prediction equations accurately predict REE?

2. Can a portable indirect calorimeter accurately measure REE?

In patients with CRC:

1. What are the determinants of REE at diagnosis?
2. What are the predictors of REE change in patients undergoing treatment?
3. Are current energy recommendations (25-30 kcal/day or Dietary Reference Intakes) accurate?
4. Do body weight, body composition, and physical activity associate with TEE?

1.5 Objectives and Hypotheses

1.5.1 Accuracy of Resting Energy Expenditure Predictive Equations in Patients with Cancer (Chapter 3)

In patients with solid tumors:

Objectives:

1a. To assess accuracy of commonly used REE prediction equations compared to measured REE.

1b. To assess differences in equation accuracy among sub-groups of body mass index (BMI) classes, cancer stage (I-III or IV), and cancer type (lung, rectal or colon).

1c. To determine whether age, weight, FM and FFM are associated with REE prediction equation inaccuracy

Hypotheses:

1a. Compared to measured REE, all REE prediction equations will have acceptable group-level agreement (bias ± 5%), but poor individual-level agreement (absolute limits of agreement > 20%).

1b. REE equation bias and limits of agreement will be poorer in patients with obesity.

1c. REE equation bias will be lower in patients with stage IV disease compared to stages I-III.

1d. REE equation bias will be negatively correlated to FFM and positively correlated with age, body weight, and FM in the majority (>50%) of equations.

1.5.2 Accuracy of a Portable Indirect Calorimeter for Measuring Resting Energy Expenditure in Individuals with Cancer (Chapter 4)

In patients with solid tumors:

Objective:

2a. To determine the accuracy of a portable indirect calorimeter (FitMate GS) in measuring REE compared to a metabolic cart.

Hypotheses:

2a. Average measured REE between the FitMate GS and metabolic cart will not be different.

2b. Limits of agreement of measured REE from the FitMate GS will be wider than common REE prediction equations.

1.5.3 Predictors of Resting Energy Expenditure in Colorectal Cancer (Chapter 5)

In patients with stage II-IV CRC:

Objectives:

3a. To characterize the determinants of REE.

Hypotheses:

3a. Body weight, height, age, sex, cancer stage, lean soft tissue, and FM will independently predict REE, after controlling for confounding covariates.

1.5.4 Determinants of Change in Resting Energy Expenditure in Patients with Stage III/IV Colorectal Cancer (Chapter 6)

In patients with stage III or IV CRC:

Objectives:

4a. To characterize REE change during treatment.

4b. To describe predictors of REE change during treatment.

Hypotheses:

4a. Average REE at follow-up will not be different than REE at baseline.

4b. FFM change, inflammation (C-reactive protein, CRP) change, and stage (III or IV) will independently predict REE change, after controlling for confounding variables.

1.5.5 Total Energy Expenditure in Relation to Body Composition, Physical Activity, and Current Energy Recommendations in Patients with Colorectal Cancer (Chapter 7)

In patients with stage II-IV CRC:

Objectives:

5a. To compare TEE to current energy recommendations according to body weight (25-30 kcal/kg/day) and Dietary Reference Intakes (DRIs).

5b. To characterize TEE in relation to body weight, body composition and physical activity.

Hypotheses:

5a. Average energy recommendations will not be different than measured TEE, but will have wide variation in individual-level agreement.

5b. Patients with higher TEE per kilogram of body weight will have lower BMI and FM:FFM and higher PAL.

1.6 References

1. National Cancer Institute. Cancer Statistics. April 27, 2018. Available from: https://www.cancer.gov/about-cancer/understanding/statistics.

2. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2018. Toronto, ON: Canadian Cancer Society; 2018. Available at: cancer.ca/Canadian-Cancer-Statistics-2018-EN (accessed [September 2018])

3. International Agency for Research on Cancer. World Cancer Report 2014. Lyon, France: 2014.

4. de Oliveira C, Weir S, Rangrej J, Krahn MD, Mittmann N, Hoch JS, et al. The economic burden of cancer care in Canada: a population-based cost study. CMAJ Open. 2018;6(1):E1-E10.

5. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. Cancer incidence and mortality worldwide: International Agency for Research on Cancer. CancerBase No. 11 Lyon, France: World Health Organization 2012.

6. Jochem C, Leitzmann M. Obesity and colorectal cancer: recent results. Cancer Res. 2016;208:17-41.

7. Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, Birdsell L, et al. The association of nutritional assessment criteria with health-related quality of life in patients with advanced colorectal carcinoma. Eur J Cancer Care (Engl). 2012;21(4):505-16.

8. Xiao J, Caan BJ, Weltzien E, Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. J Cachexia Sarcopenia Muscle. 2018;9(4):654-663.

9. Baracos VE, Arribas L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. Ann Oncol. 2018;29(suppl_2):ii1-ii9.

10. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr. 2012;31(5):583-601.
11. Meyerhardt JA, Kroenke CH, Prado CM, Kwan ML, Castillo A, Weltzien E, et al. Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente Northern California population. Cancer Epidemiol Biomarkers Prev. 2017;26(1):30-7.
12. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, den Braver NR, Berkhof J, Langius JA, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. J Clin Oncol. 2016;34(12):1339-44.
13. Helms ER, Zinn C, Rowlands DS, Brown SR. A systematic review of dietary protein during caloric restriction in resistance trained lean athletes: a case for higher intakes. Int J Sport Nutr Exerc Metab. 2014;24(2):127-38.
14. Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr. 2016;70(11):1230-8.
15. Reeves MM, Capra S. Predicting energy requirements in the clinical setting: are current methods evidence based? Nutr Rev. 2003;61(4):143-51.
16. Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition. 2006;22(6):609-15.
17. Reeves MM, Capra S, Bauer J, Davies PS, Battistutta D. Clinical accuracy of the MedGem indirect calorimeter for measuring resting energy expenditure in cancer patients. Eur J Clin Nutr. 2005;59(4):603-10.
18. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996-1002.
19. Skipworth RJ, Stene GB, Dahele M, Hendry PO, Small AC, Blum D, et al. Patient-focused endpoints in advanced cancer: criterion-based validation of accelerometer-based activity monitoring. Clin Nutr. 2011;30(6):812-21.

Chapter 2 Literature Review

2.1 Preface

Sections of this chapter that describe energy expenditure and energy balance in cancer have been adapted from a published article in the European Journal of Clinical Nutrition (Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. 2016;70[11]:1230-8) or Current Colorectal Cancer Reports (Purcell SA, Xiao J, Ford KL, Prado CM. 2018;14[6]:266-73). Within these articles, I was responsible for the review of the literature, critical analysis, and preparing the initial manuscript draft. All authors contributed to the interpretation of the literature and revised the manuscript for intellectual content.

2.2 Energy Expenditure

In the most simplistic terms, energy balance is the equality of total energy expenditure (TEE) and energy intake over time, assuming body weight and body composition are stable (1). Given that energy intake forms the basis of all individual dietary requirements and recommendations, understanding TEE and its components is essential for accurate energy recommendations for long-term weight maintenance. TEE consists of three components: resting energy expenditure (REE), thermic effect of food (TEF), and activity energy expenditure (AEE) (1). Cumulative perturbations in any component of TEE might substantially impact energy requirements. Given the importance of TEE in body habitus, the basic principles of each TEE component and measurement technique are herein discussed.

2.2.1 Resting Energy Expenditure

REE represents the energy cost of the body at rest under steady state conditions. REE differs from basal metabolic rate or sleeping metabolic rate in that REE includes the additional cost of arousal. It is the largest component of TEE, making up approximately 50 - 70% of TEE (2).

Since REE is the largest component of TEE, quantifying factors that can impact REE is essential for understanding energy metabolism, and has been extensively described in the past several decades. Body size and composition are the strongest predictors of REE. In particular, fat-free mass (FFM) alone accounts for 50 - 70% of the variability in REE (3) and is a heterogeneous component of body composition. For example, although high-metabolic rate organs such as the heart, liver, kidney, and brain make up approximately 5 - 6% of body weight, these organs account for approximately 60% of the variability in REE in healthy adults (4). Resting skeletal muscle has a relatively lower metabolic rate (13 kcal/kg/day [4]), but because it is present in large quantities (i.e. 31.9 kg in the reference male and 21.2 kg in the reference female, [5]) it is also a considerable predictor of REE (6). Adipose tissue is relatively energetically inactive compared to other body composition components (4 kcal/kg/day [4]); however, it may also impact REE, especially in individuals with excess body weight (7). Skeletal muscle, adipose tissue, and bone together contribute about 30% to REE variability (6, 8).

REE also decreases with advancing age (9), primarily driven by declining FFM (10). Age also influences REE in ways independent of body composition alterations. Gallagher *et al.* (11)

observed that organ- and tissue-specific metabolic rate values developed in young adults are different than those in elderly individuals. This phenomenon is likely explained by reductions in the cellular fraction of organs and tissues with age (12), driven by decreased sodium-potassium adenosine triphosphatase activity, declines in norepinephrine from diminished exercise and food intake, and reduced protein synthesis rates (13).

In addition, REE might be modified in disease states with high systemic inflammation. In chronic inflammatory conditions, fuel metabolism and allocation are altered because of the large energy requirements of an activated immune system. In the basal state without immune activation, leukocytes need ~380 kcal/day (14). High local inflammation results in spillover of cytokines (i.e. interleukins 1β and 6, tumor necrosis factor-α), leading to increased circulating activated immune cells. Stimulation of local sensory nerves also further perpetuate systemic inflammation (14). This activated immune system might increase REE up to ~40 to 120 kcal/day, through the activation of leukocytes (14). One acute phase protein that is often used as an indicator of systemic inflammation is C-reactive protein (CRP), which triggers the complement pathway of innate immunity (15). CRP is a positive predictor of REE (along with lean soft tissue and age [negative predictor]) in patients with chronic kidney disease (β 27.1 kcal/day per 1 unit increase in CRP in mg/dL; 95% confidence interval [CI]: 5.71, 48.5, p=0.01) (16). Similar findings were reported in a separate sample of patients undergoing hemodialysis (β 23.6; 95% CI: 6.4, 39.7, p<0.01) (17). Variables such as body temperature, minute ventilation, and heart rate are used to identify systemic inflammatory response syndrome in trauma (18). Because of the close relationship between inflammation and REE, these indices have been incorporated into several REE equations for trauma patients (19). In sum, inflammation might contribute to REE variability in some clinical conditions; a brief description of inflammation and REE in cancer is provided in Section 2.4.4.1.

2.2.2 Thermic Effect of Food

TEF is the energy expended to digest, absorb, and store food as well as associated increased sympathetic nervous system activity and accounts for approximately 10% of TEE in energy balance. However, TEF is highly variable, with reported within-subject CV over 20% (20). The magnitude of TEF is positively proportional to the energy and macronutrient content of food in a meal, with protein and alcohol eliciting a greater energetic response than fat or

carbohydrate (21). Besides macronutrients, several factors might impact TEF. Weight loss, weight gain, obesity, insulin resistance, advanced age, physical fitness, genetic factors (i.e. β_3-adrenoceptor or intestinal fatty acid binding proteins variations) might all contribute to TEF variability (22). Notably, TEF measurement requires six or more hours of continued rest after meal consumption (23). These procedures are burdensome and TEF is therefore assumed to be 10% of TEE in most research studies.

2.2.3 Activity Energy Expenditure

AEE is defined as all energy expended beyond REE and TEF (i.e. AEE = TEE – REE – TEF). It is the most variable element of TEE and is determined by body size and body movement. AEE can be further divided into structured exercise and non-exercise activity thermogenesis (NEAT) which includes energy expenditure of all occupation, sitting, standing, and ambulation activities (24).

The most common way to describe energy expended in activity is though physical activity level (PAL), which is the ratio of TEE to REE and therefore does not consider TEF. The definition of PAL also means that values <1 are not physiologically possible as it would imply the REE is greater than TEE. There is a wide variability in PAL in free living conditions. For example, mean PAL is 1.2 in non-ambulating chair-bound individuals or non-exercising individuals confined to a whole-body calorimetry unit (WBCU) (25). On the other end of the spectrum, PAL values >4 have been recorded, but are not sustainable (i.e. Tour de France cyclists, sled hauling across the Arctic, or Nordic skiers) (25). The highest sustainable PAL values around 2.8 - 3.0 occur in elite athletes during rigorous training but likely do not represent year-round averages (25). Therefore, PAL values in the general population are expected to lie between 1.2 - 2.5.

PAL heterogeneity is influenced by several factors. Firstly, PAL peaks around middle age and begins to decline around age 50 (26). Furthermore, structured exercise elicits increased overall physical activity in younger subjects, but this is not the case in older individuals (27), explained by a greater reduction in spontaneous physical activity with aging (28). Age also interacts with sex to impact AEE. One study reported that before age 52, females have lower PAL and REE, which explains approximately 60% of the overall difference in TEE observed

between sexes (26). However, after around 50 years of age, sex differences were no longer apparent (26).

Body weight is a primary determinant of AEE in absolute terms (kcal/day) since more energy is required to move a larger body. Individuals with obesity have higher absolute AEE compared to individuals without obesity, but these differences are not apparent after adjusting for body size or FFM (29, 30). In fact, AEE measured by accelerometry might be lower in individuals with obesity (29, 30). In terms of body composition, although FFM is the major determinant of REE, it is not associated with more physical activity at any age, although targeted resistance training can increase the proportion of FFM that is skeletal muscle (26).

Energy intake and AEE – NEAT in particular – are also closely related, which is an important consideration in modern obesogenic environments. There is high heterogeneity in the response to long-term overfeeding. For example, Levine *et al*. attributed 8-week fat gain from overfeeding that ranged from 0.36 to 4.23 kg to changes in NEAT, ranging from -98 to 692 kcal/day (31). Underfeeding, however, generally reduces NEAT (24). The pioneering Minnesota Starvation Experiment showed marked reduction in physical activity and REE in acute and severe starvation (32, 33). Even less extreme, prolonged energy restriction might impact AEE. In the Biosphere 2 experiment, TEE and spontaneous physical activity six months after study completion (with weight regain) were reduced compared to that of healthy control subjects (34). Such reductions in NEAT are hypothesized to be part of a mechanistic perseveration of body energy stores and a biological method to return individuals back to their initial body weight (24).

Factors such as genetics and environment might also impact AEE. An estimated 29 - 78% of variance in physical activity and sedentary behavior is explained by genetics (35, 36). Furthermore, physical activity patterns are also affected by season, with lower amounts of both light activities and moderate/vigorous activities in winter months (37).

Because of high within-subject and between-subject variation, AEE is challenging to accurately capture in free-living conditions. Methods to quantify AEE include direct observation, direct calorimetry, indirect calorimetry (i.e. WBCU), and non-calorimetric techniques such as physical activity logs, kinemetric measures, heart rate monitoring (2).

2.3 Energy Expenditure Measurement Techniques

Energy expenditure can be measured using tools from three general categories: 1) direct calorimetry, which measures the rate of bodily heat loss, 2) indirect calorimetry which measures oxygen consumption and/or carbon dioxide production that is converted to energy using a formula, or 3) non-calorimetric techniques which use extrapolated physiological measurements and observations (23). Only techniques relevant to this thesis will be discussed here.

REE is most often measured with open-circuit indirect calorimeters such as metabolic carts (usually with canopy hoods) or WBCU. Within-subject coefficient of variation (CV) with such metabolic carts in healthy adults is around 3.3 – 5.0% (38). In addition, several portable indirect calorimeters are available for gas collection; most of these machines measure O_2 consumption alone with an assumed respiratory quotient (RQ, CO_2:O_2), which could introduce error (39). Despite lower cost and ease of use of these portable units, the accuracy of these units might be negatively influenced by lower actual RQ since CO_2 production is assumed rather than measured (39). Furthermore, many of these tools use a small facemask with nose clip or mouth piece, which could leak air and/or induce participant discomfort, impacting breathing patterns (39). Many of these units report average REE similar to criterion methods, but with high individual error (39). However, newer models of these portable units use a canopy hood, which could, in theory, mitigate some error produced from facemasks or mouthpieces. One such tool – the FitMate GS^{TM} (COSMED, Chicago, IL, USA) – produces repeatable (same-day intraclass correlation coefficient = 0.999, p=0.0001) and accurate (REE=1779 ± 480 vs. 1785 ± 409 kcal/day from metabolic cart) values of REE on a group level in healthy individuals (40). However, the accuracy of this device in determining REE on an individual level in clinical settings has not been determined.

There are hundreds of equations designed to estimate REE, when measurements are unfeasible to attain. One of the largest assessments of equation accuracy in clinical settings (n=1,726) compared 28 equations to measured REE in outpatients with malnutrition, eating disorders, or obesity (41). Calculated REE from the Harris-Benedict equation provided the largest proportion of predictions within 10% of measured (72.9% of patients) and inaccuracies were higher in underweight patients and individuals with obesity. Indeed, factors such as obesity

and older age are associated with greater error in predictive REE, as extensively reviewed elsewhere (42). REE equation accuracy should therefore be assessed in relation to these factors.

Because of the variability in AEE, TEE is difficult to accurately measure. Whole-body calorimetry units (usually indirect calorimetry) can assess distinct parts of energy expenditure such as TEF, structured exercise metabolism, and sleep energy expenditure. However, subjects are in a confined space in these units and often on restricted, specific time schedules. Therefore, free-living PAL and TEE are not captured.

A calorimetric alternative to these units is doubly labeled water (DLW), first used in humans by Schoeller and van Santen in 1982 (43). This method works by dosing a subject with non-radioactive amounts of hydrogen (^{2}H, deuterium) and oxygen (^{18}O) isotopes; ^{2}H exits the body as water and ^{18}O exits the body through both water and carbon dioxide (CO_2). The enrichment elimination rates of these isotopes excreted in bodily fluids are measured using mass spectrometry. The difference in disappearance of these isotopes is indicative of CO_2, collected over a span of 4 - 21 days (44).

DLW is the most accurate way to measure free-living TEE, with estimated error around 1 - 3% in a variety of clinical and healthy populations (45). There are four primary assumptions of DLW, which are all robust in human subjects (44). These include: 1) body water behaves as a steady, single compartment with rapid equilibration (i.e. approximately three to six hours) within the total body water pool; 2) the isotopes leave the body water only as water or carbon dioxide; 3) isotopes exit the body only in isotopic equilibrium with body water; 4) none of the isotope tracers re-enter the body after excretion.

Although DLW is highly accurate for assessing TEE and AEE, it cannot provide details about the nature or intensity of physical activity patterns. Activity monitors are better suited for such objectives, with a variety of different tools available. These can be broadly categorized into pedometers, which detect vertical acceleration only (i.e. step counts), and accelerometers which can detect movement in one axis (uniaxial) or three axes (triaxial) (2). For example, the Actical monitor (Respironics, Bend, OR, USA) accurately assesses step counts at self-selected, moderate, and fast walking paces, but underpredicts steps taken at lower speeds (46). However, the efficacy of accelerometers to estimate TEE is questionable. A recent systematic review of 60 studies noted that even the most accurate accelerometer (SenseWear Armband Mini) had error

ranging from -21.3 to 14.8% in the assessment of energy expenditure (47). These devices do not provide accurate assessment of individual PAL or TEE, but rather different entities of PAL such as step count and time spent in sedentary, light, or moderate-to-vigorous physical activity.

2.4 Energy Balance in Cancer

Approximately 38% of individuals will be diagnosed with cancer during their lifetimes and the disease is a significant public health burden (48). Improving prognosis and survival are therefore valuable clinical targets. Energy balance in cancer is a particularly important concept since low BMI is associated with shorter survival (49) and weight loss after diagnosis is predictive of poor survival, independent of body weight (50-53).

Although body weight is an accessible and potentially useful tool for prognostication, body composition (e.g. skeletal muscle and adipose tissue) is also a valuable aspect of energy balance and whole-body substrate metabolism. Low skeletal muscle among individuals with cancer is common, independent of body weight and cancer stage (54, 55) and is associated with worse physical function, greater risk of chemotherapy toxicity, shorter time to tumor progression, and shorter survival (56). Importantly, the presence of both low muscle and high adiposity is associated with poorer outcomes compared to either condition alone (57, 58). Therefore, understanding the impact of energy balance and subsequent causes of poorer prognosis are important for improving patient risk stratification and selection for targeted nutrition and exercise interventions. Given the importance of understanding energy balance in cancer, dietary intake, TEE, physical activity, and REE (including the determinants of REE, REE change, and REE in colorectal cancer) will be herein discussed.

2.4.1 Dietary Intake

Most research to date has investigated dietary intake only in patients with advanced cancer (i.e. stage IV). Many of these individuals will experience decreased appetite, driven by symptoms such as taste and smell alterations, constipation, abdominal pain, dysphagia, and epigastric pain, abdominal bloating, constipation, or diarrhea (59). Reduced food intake assessed by tools such as the patient-generated subjective global assessment (PG-SGA) or low energy intake from tools such as 24-hour recalls are independently associated with weight loss in some studies (60). Energy intake is also highly variable. In patients with advanced colorectal or non-small cell lung cancer, energy intake collected from 3-day food records ranged from 13.7 to 55.4

g/kg body weight (or 1100 to 3900 kcal/day) (61). In 297 patients with advanced cancer of several tumor types, energy intake (4-day food records) ranged from 248 to 4,650 kcal/day (1716 ± 627), with no differences across tumor types, weight losing patients, or underweight patients (62).

Notably, long-term dietary intake is notoriously difficult to describe and current assessment tools (i.e. questionnaires, food diaries or records, appetite assessments) are not accurate for long-term dietary patterns (63). While methods such as food photography or tools that count bites or measure chewing and swallowing might improve the accuracy of capturing dietary intake, these can be burdensome. Furthermore, characterizing long-term energy intake is not possible at this time (63). Further elucidation of energy intake and dietary patterns in cancer may yield a deeper understanding of this component of energy balance, although further research with accurate tools is needed. For example, repeated assessments of TEE and body composition (coupled with energy equivalents of tissues) would provide objective energy intake data.

2.4.2 Total Energy Expenditure and Physical Activity

To date, few studies (aggregate number of patients = 42) have characterized TEE using objective methods in cancer (64-67). Because of the paucity of available research, current internationally-accepted cancer nutrition guidelines from the European Society for Clinical Nutrition and Metabolism are 25-30 kcal/kg body weight/day (68). These recommendations are designed as "one size fits all" and do not consider disease type, stage, body composition, age, or physical activity, which might all impact energy requirements. Notably, the guidelines indicate a low evidence level for energy requirements with a call to *'improve prediction of energy requirements in the individual patient'* (68).

Within the limited studies that have investigated TEE in cancer, most of those studied presented with advanced cancer (66) and/or severe weight loss (64). The largest study to date that measured TEE (64) included 24 patients pancreatic cancer and cachexia, which is a severe wasting syndrome that cannot be fully reversed by conventional nutritional support (69). Average previous weight loss was 19% of their pre-illness stable weight and average BMI was 20 kg/m^2 (standard error of the mean: 1 kg/m^2). Average REE was higher than predicted and TEE measured by DLW was lower than predicted. Consumption of a nutritional supplement enriched with n-3 fatty acids increased TEE, although these changes were not different than

subjects in the control arm (64). In six patients with advanced cancer of varying tumor types, TEE and PAL measured with DLW were lower than healthy controls (66). Notably, a high variability in TEE (range: 2478 - 5309 kcal/day) and PAL (1.33 - 2.82) was observed in the nine healthy subjects reported in this study, with less heterogeneity in patients with cancer (TEE range: 2017 - 2795 kcal/day; PAL: 1.21 - 1.84). In another study, eight patients with small cell lung cancer with previous chemotherapy or radiotherapy had TEE measured via 24-hour stay in WBCU (n=5) and bicarbonate-urea method (n=8, 5 of whom also stayed in WBCU) as part of a validation study (65). Free-living TEE was 2085 ± 564 kcal/day and PAL was 1.36 ± 0.22, with most (7/8, 87.5%) PAL values < 1.4 in free-living conditions (65). In four patients post-peripheral blood stem cell transplantation due to various types of cancer, participation in a three-month aerobic- and resistance-based exercise program increased TEE/FFM kcal/kg$^{0.5}$ (TEE measured by DLW) (67). Collectively, these studies suggest TEE and PAL are lower than what would be expected in healthy adults and might be improved with nutritional supplements and exercise. Importantly, results to date suggest that although REE might be elevated, TEE and PAL may be lower than controls or expected values. Decreased PAL associated with increased REE might reflect an adaptive response to reduced activity in response to decreased dietary intake or could represent reduced physical activity secondary to cancer and its associated side effects.

In addition to TEE and PAL values outlined above, physical activity in different cancer types have also been described using tools such as accelerometers and questionnaires. For example, one study reported that estimated TEE from accelerometers (which might have limited accuracy for determining individual energy expenditure [70]) did not change during chemotherapy in patients with gastrointestinal cancer, although large interindividual variations were reported (71). In patients undergoing chemotherapy for lymphoma, physical activity and step count non-significantly decreased during treatment with a concomitant increase after treatment, with large interindividual differences (72). It is unclear what proportion of this reduced activity is from NEAT in patients with cancer, though evidence suggests that NEAT decreases during underfeeding in healthy individuals (24).

Physical activity is feasible in patients with cancer and positively impacts several patient-centered and treatment-related outcomes (73). It can also be used as a primary outcome in clinical trials, especially those focused on quality of life and physical function as both

dimensions are captured in physical activity (74). Physical activity is therefore an important clinical target, although objective data regarding its impact on energy requirements for these patients is lacking.

2.4.3 Thermic Effect of Food in Cancer

In cancer, side effects such as anorexia, taste alterations, mucositis, nausea, and vomiting may decrease dietary intake and thus decrease the TEF in these patients (67). Furthermore, taste alterations are a significant problem in many cancer patients and can cause food aversions, which may change the composition of the diet (75) and consequently, TEF. One study quantified the TEF as the average difference, expressed as kcal/kg/day, between postprandial REE and baseline REE during a 2.5-hour measurement period in groups of weight-stable and weight losing patients with gastrointestinal adenocarcinoma. Interestingly, the TEF was lower in weight losing cancer patients in response to an identical meal (2.9 ± 1.7 vs 7.6 ± 1.5 kcal/kg/day, $p<0.05$; exact p-value not indicated) (76), which was a similar result reported in a separate sample of weight-losing patients with pancreatic cancer (77). Individuals with advanced cancer might also have autonomic nervous system insufficiency (78), contributing to the lower thermogenic response to a meal. In a study of 18 individuals undergoing adjuvant chemotherapy for breast cancer, TEF was measured as increase in energy expenditure above REE after administration of a nutritional supplement at 5 mL/kg body weight (79). TEF trended towards a decrease during chemotherapy that rebounded to pre-therapy levels at the commencement of therapy; however, these differences in TEF among these timepoints did not reach significance (79). While TEF might be lower than expected, the specific interactions between nutrient digestion, absorption and metabolism and its impact on the TEF (and, consequently, TEE) in cancer has been scarcely investigated.

2.4.4 Resting Energy Expenditure in Cancer

REE in individuals with cancer has been characterized for decades, with the first apparent case study in 1869 (80) and increase in reports occurring in the latter half of the 20th century. As there are nearly 100 publications measuring or reviewing REE in cancer, the ensuing section is focused only on publications that are relevant to this thesis based on cancer type, analysis, or variables collected (i.e. body composition, inflammation).

While most healthy adults have a measured REE that is within 10% of predicted (i.e. "normal" REE [81]), a substantial proportion of patients with cancer may present with an REE that falls outside of this range (9, 19). In other words, individuals with cancer often have high REE (hypermetabolism) or low REE (hypometabolism). If TEE remains unchanged, PAL might be impacted, since it is a ratio between TEE and REE. Studies investigating REE in individuals with cancer are inconsistent, with some reporting elevated or lower than expected REE, and others reporting no abnormal REE (5, 9). Primary factors that might impact REE in cancer include tumor burden, systemic inflammation, and body composition alterations, which are herein discussed.

2.4.4.1 Tumor Burden, Systemic Inflammation, and Brown Adipose Tissue

The presence of a tumor may induce aberrant REE, in part due to futile substrate cycles. Despite their small size, tumors undergo high rates of glycolysis and lactate production regardless of their oxygen supply (82). Surplus lactate is converted back to glucose in the liver (Cori cycle), leading to a net consumption of adenosine triphosphate (14, 83). This increased glucose turnover may contribute a great deal to high REE and muscle catabolism in patients with cancer (84).

One study advanced our understanding of the energetic demand of a tumor *in vivo* using by using a quantitative theoretical model (85). Mathematical models considering the level of anaerobic glucose production and tumor burden up to 3kg were constructed using two available datasets that measured REE, glucose turnover, glucose recycling, and oxygen consumption in cancer. Estimations of additional energy expenditure associated with the tumor-bearing state ranged from 100 - 1400 kcal/day based on tumor size and glycolytic activity (85).

Another factor that may contribute to higher REE is tumor metastases in the liver. Although the liver makes up a relatively small amount of body weight, it may consume approximately 15 - 20% of total REE (~200 kcals/day) in healthy individuals (86). A retrospective review of computerized tomography (CT) images of patients with advanced colorectal cancer revealed decreased skeletal muscle and adipose tissue over time with simultaneous increases in liver mass, with the most dramatic changes closest to death (87). Average liver mass of these patients (2.3 ± 0.7 kg) was also larger than reported for healthy adults (1.4 - 1.8 kg). The same study explored liver volume in a prospective cohort and found

that liver mass was positively correlated to REE (r^2= 0.35, p=0.010). For every 1 kg increase in liver mass due to metastases, an estimated 343 additional kcal/kg/day were oxidized, which is much higher than the 200 kcal/kg/day reported in healthy individuals (86). This study suggested that the energetic demand of liver metastases is partly responsible for higher REE observed in advanced cancer. Importantly, increased liver volume and changes in body composition occurred most rapidly closest to death, resulting in a shift to a larger proportion of FFM occupied by tissues with a high metabolic rate. Other findings indicate no relationship between liver metastases and REE in newly detected cancer (88, 89). Thus, REE changes resultant of tumor metastases may occur only in late stages of the disease, indicating that REE is highly dependent on the disease trajectory and tumor energetic demand.

An array of metabolic derangements may also occur in the presence of a tumor, such as upregulation of metabolic cycling and systemic inflammation (86, 90, 91). Proinflammatory cytokines arise from crosstalk between the immune system and tumor and act directly on several tissues throughout the body and the central nervous system (91). Inflammation as assessed by members of the interleukin-6 family, tumor necrosis factor-α, interleukin-1, and interferon-γ are associated with changes in the hypothalamic-pituitary axis, oxidative stress, subdued muscle protein synthesis, increased muscle proteolysis (through up-regulated ubiquitin-proteosome pathway), and hypermetabolism (92). The link between inflammation and energy balance is complex but may be due in part to melanocortins, which are a group of peptide hormones derived from pro-opiomelanocortin (POMC) neurons in the pituitary gland. Proinflammatory cytokines upregulate melanocortin signaling through the activation of POMC neurons and inhibition of orexigenic neuropeptides such as agouti-related proteins. This collectively leads to increased REE and/or diminished appetite by up-regulating the activation of melanocortin type 4 receptors, which are widely distributed throughout the brain (93, 94). As a consequence of systemic inflammation concomitant with a tumor, many findings report an association between inflammation and REE (95-98) and weight loss (98-102), though this is not always the case (103). An activated immune system might increase REE ~ 40 to 120 kcal/day (14), as discussed in Section 2.2.1. Higher CRP as an indicator of systemic inflammation has been associated with higher REE in patients with pancreatic (104), lung (97), or mixed tumor types (101). Therefore,

an activated immune system and associated increase in inflammation may relate to REE in much the same way as other clinical conditions (discussed in Section 2.2.1).

Brown adipose tissue dissipates heat through the action of uncoupling protein-1 which facilitates fuel oxidation without the generation of adenosine triphosphate (105). In rodent models of cachexia, browning of white adipose tissue is apparent before the development of cachexia (i.e. "pre-cachexia") and is related to energy expenditure (106), likely through the action of parathyroid hormone-related protein and several other tumor-derived mediators (107, 108). An analysis in a sample of patients with lung or colorectal cancer revealed that patients who displayed detectable levels of serum parathyroid hormone-related protein had lower FFM and higher REE/FFM (107), suggesting a key role of parathyroid hormone-related protein in brown adipose tissue browning which could potentially impact REE. Though these results suggest brown adipose tissue might be potential source of hypermetabolism, the extent to which it contributes to REE and TEE in humans has not been delineated in cancer. Fully activated brown adipose tissue through administration of β3-adrenergic receptor agonist in healthy males elicited increased REE by an average of 203 ± 40 kcals/day (109). Although this could potentially contribute to TEE, this excess energy expenditure was with fully activated brown adipose tissue, which is unlikely to occur in all patients with cancer. Furthermore, although cold exposure might transiently increase energy expenditure in healthy individuals with active brown adipose tissue, this does not translate to higher REE in kcal/day in short-term studies (110, 111), or after a six-week intervention of daily, one-hour cold exposure (112). The prevalence of brown adipose tissue activation among individuals with cancer and the degree to which it impacts REE or TEE is unknown. Given the current understanding of the impact of brown adipose tissue on REE in healthy individuals, it seems unlikely that this tissue substantially contributes to REE in individuals with cancer.

2.4.4.2 Body composition

As a catabolic condition, cancer leads to losses of skeletal muscle (69) and therefore, a reduction in REE is expected as a result. However, some findings point to the presence of elevated REE despite similar or lower than average measures of body weight or skeletal muscle compared to control subjects (113, 114); conversely, others have found no difference in REE between patients with cancer and control subjects (103, 115, 116).

Both body composition and REE may be affected by the disease state and therapy modalities (117), but do not always change in accordance with each other (118-124). Thus, alterations in REE must be considered in the context of body weight and composition variations, which occur throughout the disease trajectory.

When assessing the effect of body composition on REE, proper interpretation of many studies has been limited since studies to date have expressed REE as a ratio to measures of muscularity (REE/FFM) or body weight (REE/body weight). An increase in the proportion of FFM as low-metabolic-rate tissues (bone, adipose tissue) and a decrease in the proportion as high-metabolic rate tissues (such as heart, brain, liver, kidneys) with greater body weight has been reported in the general population (8). This creates a bias wherein a lowering of REE/FFM is observed with increasing body weight and FFM (8, 125). When comparing energy expenditure between groups of individuals, adjustments such as log-log regression (126), multiple linear regression (127)(i.e. group mean REE + individual measured REE – predicted REE from linear regression), analysis of covariance, or generalized liner modeling (128) are preferred.

2.4.4.3 Knowledge Translation: Predicting and Measuring Resting Energy Expenditure

Because of metabolic alterations that might occur in cancer, equations to estimate energy expenditure (mainly developed from healthy, young populations) might logically yield inaccurate results. To date, no study has assessed the accuracy of TEE estimations, but some have addressed REE accuracy in small sample sizes (largest to date: n=18, [101]). Other findings have observed that adding an injury factor of 1.3 to the ubiquitous Harris-Benedict equation (129, 130) vastly overestimates energy requirements by as much as 716 kcal/day in weight-losing cancer patients (131) but forgoing an injury factor may underestimate true REE by an average of 111 ± 234 kcal/day (132). Johnson *et al.* (101) showed wide ranges of limits of agreement (difference ± 2 standard deviations) between measured and predicted REE that ranged from -37% to 17% in weight losing cancer patients (n=18) and -28% to 17% in those who were weight stable (n=18). Predicted REE was within clinically acceptable limits (10%) for little more than half of all patients. Other findings indicate that the limits of agreement between measured and predicted REE in patients with cancer were as much as 40% below and up to 30% above measured REE using a variety of prediction equations (133), which has been corroborated in other studies (134-136).

Since metabolic carts are not readily available or feasible to use in clinical settings, portable indirect calorimeters have been used in some studies in oncology (137, 138). However, such devices might introduce substantial error in REE estimates, similar to that produced in healthy individuals, discussed in Section 2.3. In 18 individuals with mixed cancer types, the MedGem^{TM} (HealtheTech, USA) with a mouthpiece and nose clip was validated against a metabolic cart (139). The MedGem underestimated REE (1351 ± 282 vs. 1526 ± 248 kcal/day), with limits of agreement ranging from -42% to 21% of REE from the metabolic cart (139). However, the accuracy of portable tools with a canopy hood rather than face mask has not been assessed in individuals with cancer.

2.4.4.4 Resting Energy Expenditure Change

In addition to the variability in REE before beginning cancer therapy, some evidence suggests that REE may decrease (29), increase (30), or stay the same (31) throughout disease trajectory. While no studies have investigated the exact mechanisms driving these inconsistent findings in REE change, there are plausible hypotheses. Firstly, if a patient is positively responding to treatment (i.e. tumor mass is decreasing), then the consumption of energy by the tumor and the associated metabolic derangements such as inflammation will subside. This has been corroborated by publications that assess REE according to tumor response (31, 32). Another possibility is that changes in body composition such as reduced skeletal muscle or changes in organ sizes due to cancer therapy and the associated side effects drive altered REE. Furthermore, some therapies might induce more direct changes in body composition or organ composition. For example, many chemotherapy agents used to treat colorectal cancer have been shown to induce steatosis (accumulation of lipids in hepatocytes) (33), although the exact mechanism driving this phenomenon and its potential impact on energy expenditure is unknown. Drawing definite conclusions on REE change is challenging, as the available evidence is varied in terms of study design. For example, some studies choose an arbitrary number of weeks or months to follow-up, regardless of treatment scheduling and without any mathematical adjustment for aberrant follow-up times (30). Others report changes in heterogeneous samples undergoing several different therapies (34). Nevertheless, REE might change throughout the disease trajectory possibly influencing energy requirements.

2.4.4.5 Resting Energy Expenditure in Colorectal Cancer

Most reports assess several different cancer types and stages together. While these shed light on overall energy metabolism in cancer and the potential applicability of prediction equations, REE might differ among cancer types (89). Since cancer type might influence REE, assessing energy metabolism in homogenous samples of patients or comparing energy metabolism between different cancer types might provide a better platform to understand metabolic alterations associated with cancer. Colorectal cancer is of particular interest since it is the second most common type of cancer in Canada (140) and third most common cancer worldwide (141). Studies that report REE in patients with colorectal cancer are herein discussed and presented in **Table 2.1**.

The first known study to report REE in these patients was published in 1986 in 51 patients with colorectal cancer (n=13, 25.5% with hepatic metastases) compared to 22 patients with gastric cancer and 11 patients with non-small cell lung cancer (142). There were no differences in REE/FFM among cancer groups or between patients with and without hepatic metastases. Similar findings were echoed soon after, when 45 patients with colon cancer were found to have similar REE (in kcal/hour, kcal/hour/kg body weight, kcal/hour/body surface area, and kcal/hour/FFM) compared to patients with non-small cell lung cancer; there was also no difference between REE in weight losing versus weight stable colon cancer patients (143). A more recent publication in 148 patients with colorectal cancer found that there were no differences in absolute REE in kcal/day, kcal/kg FFM/day or % predicted REE between patients with colorectal cancer and controls (89).

Others have described REE change in this group of patients. In 24 patients with colorectal cancer, REE was measured before and after surgery (no specific time frame reported) (144). Patients with stage IV disease (n=9) lost body weight over time, while body weight remained stable in patients with non-advanced cancer. However, there were no differences in REE between groups at either timepoint, or REE change within groups (144). During six weeks of radiotherapy, REE (kcal/day) did not change in 14 males with liver metastases (145). In a pair of similar reports, Ravasco *et al*. found no significant increase in REE median values during neoadjuvant radiotherapy in 101 patients with colorectal cancer (100, 146). Higher REE before and after treatment was associated with advanced stage (III/IV), poor histological differentiation

(146), and higher levels of several pro-inflammatory cytokines (100). In the months before death, patients with stage IV colorectal cancer experience a marked decrease in skeletal muscle and adipose tissue mass, and increase in liver mass, which is related to REE, as discussed above (Section: 2.4.4.1[87]).

These findings suggest that at one timepoint, patients with colorectal cancer do not have different average REE compared to controls or other cancer types on a group level. Notably, however, these studies expressed REE by dividing by measures of FFM and/or body weight that creates a statistical bias explained in Section 2.4.4.2. Therefore, REE expressed in this way might reflect changes in body weight or body composition or a mathematical error rather than actual altered REE. Furthermore, although some studies have suggested that REE might be affected by disease state and related systemic inflammation, the predictors of REE at one time point have not been characterized. Predictors of REE change in the individual patient are also unknown. These represent significant knowledge gaps in understanding energy metabolism in cancer since REE is a substantial portion of TEE. There is also a growing need for more personalized nutrition recommendations because of high intra-individual physiological variation (147). In addition, the potential impact of body composition, cancer stage, and systemic inflammation on TEE, REE, and PAL and have also not been characterized in cancer.

2.5 Summary

In conclusion, REE is the largest proportion of TEE in healthy individuals, although AEE (or PAL, if not subtracting TEF) is the most variable. In cancer, TEE and PAL have been scarcely characterized, limiting current understanding of energy requirements. Most understanding of energy metabolism in cancer arises from studies of REE, which might be impacted by tumor burden, inflammation, and alterations in body composition. REE has been longitudinally characterized in several publications, but the determinants of individual REE change are poorly understood. Given current knowledge gaps, characterizing the most accurate methods to estimate or measure energy metabolism and elucidating the determinants of REE and TEE in individuals with cancer is necessary to improve metabolic and nutritional care in these patients.

Table 2.1 Summary of studies assessing resting energy expenditure (REE) in patients with colorectal cancer

Study	Participants	Study Methods	Main Results
Hansell DT, Davies JW, Burns HJ. The effects on resting energy expenditure of different tumor types. Cancer. 1986;58(8):1739-44 (142)	N=51 patients with colorectal cancer; 13 (25.5%) had hepatic metastases (n=84 total, n=22 gastric, n=11 non-small cell lung cancer)	• Observational study to compare differences between groups • REE measured by indirect calorimetry and expressed as kcal/kg body weight/day and kcal/kg FFM/day. Also compared to predicted from Harris-Benedict equation • FFM by tritium dilution • Linear regression in separate groups then compared using independent t-test	• There were no differences in REE/FFM between groups • No differences in REE between patients with and without hepatic metastases
Nixon DW, Kutner M, Heymsfield S, Foltz AT, Carty C, Seitz S, *et al.* Resting energy expenditure in lung and colon cancer. Metabolism. 1988;37(11):1059-64 (143)	45 patients with colon cancer (n=37 metastatic or recurrent disease); compared to 38 patients with non-small cell lung cancer, 60 healthy controls, 5 patients with anorexia nervosa, 9 patients with benign GI disease, 21 patients with miscellaneous causes of weight loss, and 9 patients with advanced chronic obstructive pulmonary disease	• Observational study to compare differences between groups • REE measured by indirect calorimetry and expressed as kcal/hour, kcal/hour/kg body weight, kcal/hour/BSA, and kcal/hour/FFM • Comparisons between groups: ANOVA with Tukey's post-hoc analyses	• No differences in REE were found between the colon and lung cancer patient groups • No differences in REE between weight losing (>5%, no specific time period) vs. weight stable colon cancer patients • Patients with anorexia nervosa had lower kcal/hour/FFM compared to female lung cancer patients • No other differences in REE were observed
Hansell DT, Davies JW, Burns HJ. Effects of hepatic metastases on resting energy expenditure in patients with colorectal cancer. Br J Surg. 1986;73(8):659-62 (144)	24 patients with colorectal cancer (n=9 with stage IV disease)	• Indirect calorimetry before and after surgery (a few months later - no specific time given) • REE expressed as kcal/kg body weight/day, kcal/kg$^{0.75}$/day, and kcal/kg LST	• Stage IV patients lost body weight over time while non-advanced patients' body weights remained stable. • No differences between groups at baseline or follow-up

Study	Participants	Study Methods	Main Results
		• Predicted REE via Harris-Benedict equation • Tritiated water for fat-free mass • Comparisons between groups: Independent or dependent samples t-tests	• No differences within groups in change over time • REE compared to predicted was higher in both groups and at each timepoint
Maguire R, McMillan DC, Wallace AM, McArdle C. A longitudinal study of leptin and appetite, resting energy expenditure and body fat mass in weight-stable cancer patients. Cytokine. 2002;20(4):174-7 (145)	14 male weight-stable patients with stage IV (with liver metastases) colorectal cancer	• Indirect calorimetry before beginning 5-fluorouracil-based chemotherapy and 6 weeks later • REE expressed in kcal/day • Wilcoxon signed rank test for baseline vs. follow-up	REE did not change (numbers not presented) and was not associated with changes in leptin (primary objective)
Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest. 2007;25(5):308-14 (146)	101 patients with colorectal cancer undergoing neoadjuvant radiotherapy	• Indirect calorimetry before and after radiotherapy and expressed as kcal/day and kcal/kg body weight/day • General linear model analysis for determinants of REE at baseline and REE at follow-up	• REE was higher in stage III/IV vs. I/II (numbers not reported) at baseline and follow-up • No significant increase in median REE values • Advanced stage (III/IV) and poorer histological differentiation were the major determinants of REE increase • Higher baseline REE were determined 25% by cancer stage, 25% by histology, 3% nutritional intake, 4% weight loss. Results were similar after treatment • Treatment non-responders: median increase of 390 ± 165 kcal/day; responders: -153 ± 65 kcal/day in REE

Study	Participants	Study Methods	Main Results
Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? Cancer J. 2007;13(6):392-8 (100)	101 patients with colorectal cancer undergoing neoadjuvant radiotherapy	• Indirect calorimetry before and after radiotherapy and expressed as kcal/day and kcal/kg body weight/day • General linear model analysis for determinants of REE at baseline and REE at follow-up	• Higher baseline REE, weight loss ≥ 10%, and intake reduction ≥ 25% were "more prevalent" in patients with higher concentrations if several pro-inflammatory cytokines (exact values or cut-off points not reported) • Higher concentrations of several pro-inflammatory cytokines were major determinants of REE. 27 kcal/kg/day, ≥5% weight loss, and ≥25% intake reduction (dependent variables grouped together). • Treatment non-responders with decreased cytokine levels: median increase of 7.2 ± 1.3 kcal/kg/day; responders: -2.8 ± 0.4 kcal/kg/day • At the end of radiotherapy, patients with higher baseline IL-1ra, IL-6, and TNF-α had greater REE after radiotherapy
Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr.	Three parts: 1) n=34 retrospective longitudinal CT image review (% change/100 days) in patients with colorectal cancer in the year before death, 2) prospective investigation in 18 patients with stage IV colorectal cancer, and 3) mathematical stimulation of REE	• REE by metabolic cart in prospective data and expressed as kcal/day and kcal/kg FFM/day • Repeated-measures ANOVA for change in tissue mass in retrospective cohort; linear regression in prospective cohort	• Retrospective cohort: liver and spleen mass increased, skeletal muscle and adipose tissue decreased • Prospective: REE was correlated to liver mass and % FFM occupied by the liver • Mathematical simulation: New cachexia simulation cumulated

Study	Participants	Study Methods	Main Results
2009;89(4):1173-9 (87)	trajectories for healthy, reduced energy intake, previous stimulation, and current cachexia model		at 1900 kcal/day REE (39.7 kcal/kg FFM/day), 294 kcal/day higher than healthy reference, 331 kcal/day above reference reduced energy stimulation, and 144 kcal/day above previous stimulation
Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, *et al.* Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr. 2010;29(1):72-7 (89)	N=714 patients with cancer, mixed types 642 controls with mixed non-malignant disease; n=148 with colorectal cancer	• REE by indirect calorimetry (>3 hours post-prandial) and expressed as kcal/day, kcal/kg FFM/day, and % predicted from Harris-Benedict • FFM by bioelectric impedance analysis • ANOVA or Kruskal-Wallis test for comparisons between groups	• No differences in absolute REE in kcal/day, kcal/kg FFM/day or % predicted REE between patients with colorectal cancer and controls. • All patients with stage IV disease had higher REE in kcal/day, kcal/kg FFM/day or % predicted REE

ANOVA: analysis of variance; BSA: body surface area; FFM: fat-free mass by dual X-ray absorptiometry unless otherwise specified; GI: gastrointestinal; IL-1ra: interleukin 1 receptor antagonist; IL-6: interleukin-6; LST: lean soft tissue; REE: resting energy expenditure; TNF- α: tumor necrosis factor-α

2.6 References

1. Westerterp KR. Exercise, energy expenditure and energy balance, as measured with doubly labelled water. Proc Nutr Soc. 2018;77(1):4-10.
2. Lam YY, Ravussin E. Analysis of energy metabolism in humans: a review of methodologies. Molecular Metabolism. 2016;5(11):1057-71.
3. Speakman JR, Selman C. Physical activity and resting metabolic rate. Proc Nutr Soc. 2003;62(3):621-34.
4. Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN, editors. Energy Metabolism: Tissue Determinants and Cellular Coeollaries. New York: Raven Press; 1992. p. 61-80.
5. Later W, Bosy-Westphal A, Kossel E, Gluer CC, Heller M, Muller MJ. Is the 1975 Reference Man still a suitable reference? Eur J Clin Nutr. 2010;64(10):1035-42.
6. Gallagher D, Belmonte D, Deurenberg P, Wang Z, Krasnow N, Pi-Sunyer FX, et al. Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass. Am J Physiol. 1998;275(2 Pt 1):E249-58.
7. Bosy-Westphal A, Müller MJ, Boschmann M, Klaus S, Kreymann G, Lührmann PM, et al. Grade of adiposity affects the impact of fat mass on resting energy expenditure in women. Br J Nutr. 2008;101(4):474-7.
8. Heymsfield SB, Gallagher D, Kotler DP, Wang Z, Allison DB, Heshka S. Body-size dependence of resting energy expenditure can be attributed to nonenergetic homogeneity of fat-free mass. Am J Physiol Endocrinol Metab. 2002;282(1):E132-8.
9. Elia M, Ritz P, Stubbs RJ. Total energy expenditure in the elderly. Eur J Clin Nutr. 2000;54 Suppl 3:S92-103.
10. Kyle UG, Genton L, Hans D, Karsegard L, Slosman DO, Pichard C. Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. Eur J Clin Nutr. 2001;55(8):663-72.
11. Gallagher D, Allen A, Wang Z, Heymsfield SB, Krasnow N. Smaller organ tissue mass in the elderly fails to explain lower resting metabolic rate. Ann N Y Acad Sci. 2006;904(1):449-55.

12. Wang Z, Heshka S, Heymsfield SB, Shen W, Gallagher D. A cellular-level approach to predicting resting energy expenditure across the adult years. Am J Clin Nutr. 2005;81(4):799-806.
13. Manini TM. Energy expenditure and aging. Ageing Res Rev. 2010;9(1):1-26.
14. Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med. 2010;267(6):543-60.
15. Sproston NR, Ashworth JJ. Role of C-Reactive protein at sites of inflammation and infection. Front Immunol. 2018;9:754.
16. Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. Am J Clin Nutr. 2005;82(4):801-5.
17. Kamimura MA, Draibe SA, Avesani CM, Canziani ME, Colugnati FA, Cuppari L. Resting energy expenditure and its determinants in hemodialysis patients. Eur J Clin Nutr. 2007;61(3):362-7.
18. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992;101(6):1644-55.
19. Frankenfield D. Energy expenditure and protein requirements after traumatic injury. Nutr Clin Pract. 2006;21(5):430-7.
20. Miles CW, Wong NP, Rumpler WV, Conway J. Effect of circadian variation in energy expenditure, within-subject variation and weight reduction on thermic effect of food. Eur J Clin Nutr. 1993;47(4):274-84.
21. Westerterp KR. Diet induced thermogenesis. Nutr Metab (Lond). 2004;1(5).
22. Donahoo WT, Levine JA, Melanson EL. Variability in energy expenditure and its components. Curr Opin Clin Nutr Metab Care. 2004;7(6):599-605.
23. Levine JA. Measurement of energy expenditure. Public Health Nutr. 2005;8(7a):1123-32.
24. Levine JA. Non-exercise activity thermogenesis (NEAT). Best Pract Res Clin Endocrinol Metab. 2002;16(4):679-702.

25. Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. Eur J Clin Nutr. 1996;50(2):72-92.
26. Speakman JR, Westerterp KR. Associations between energy demands, physical activity, and body composition in adult humans between 18 and 96 y of age. Am J Clin Nutr. 2010;92(4):826-34.
27. Westerterp KR. Physical activity and physical activity induced energy expenditure in humans: measurement, determinants, and effects. Front Physiol. 2013;4:90.
28. Meijer EP, Westerterp KR, Verstappen FT. Effect of exercise training on total daily physical activity in elderly humans. Eur J Appl Physiol Occup Physiol. 1999;80(1):16-21.
29. DeLany JP, Kelley DE, Hames KC, Jakicic JM, Goodpaster BH. High energy expenditure masks low physical activity in obesity. Int J Obes (Lond). 2013;37(7):1006-11.
30. Carneiro IP, Elliott SA, Siervo M, Padwal R, Bertoli S, Battezzati A, et al. Is obesity associated with altered energy expenditure? Adv Nutr. 2016;7(3):476-87.
31. Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. Science. 1999;283(5399):212-4.
32. Keys A, Brozek J, Henschel A. Michelson O, Taylor HL. The Biology of Human Starvation: University of Minnesota Press; Minneapolis, Minnesota. 1950.
33. Taylor HL, Keys A. Adaptation to caloric restriction. Science. 1950;112(2904):215-8.
34. Weyer C, Walford RL, Harper IT, Milner M, MacCallum T, Tataranni PA, et al. Energy metabolism after 2 y of energy restriction: the Biosphere 2 Experiment. Am J Clin Nutr. 2000;72(4):946-53.
35. Perusse L, Tremblay A, Leblanc C, Bouchard C. Genetic and environmental influences on level of habitual physical activity and exercise participation. Am J Epidemiol. 1989;129(5):1012-22.
36. Joosen AM, Gielen M, Vlietinck R, Westerterp KR. Genetic analysis of physical activity in twins. Am J Clin Nutr. 2005;82(6):1253-9.
37. Buchowski MS, Choi L, Majchrzak KM, Acra S, Matthews CE, Chen KY. Seasonal changes in amount and patterns of physical activity in women. J Phys Act Health. 2009;6(2):252-61.

38. Adriaens MP, Schoffelen PF, Westerterp KR. Intra-individual variation of basal metabolic rate and the influence of daily habitual physical activity before testing. Br J Nutr. 2003;90(2):419-23.
39. Hipskind P, Glass C, Charlton D, Nowak D, Dasarathy S. Do handheld calorimeters have a role in assessment of nutrition needs in hospitalized patients? A systematic review of literature. Nutr Clin Pract. 2011;26(4):426-33.
40. Vandarakis D, Salacinski AJ, Broeder CE. A comparison of COSMED metabolic systems for the determination of resting metabolic rate. Res Sports Med. 2013;21(2):187-94.
41. Jesus P, Achamrah N, Grigioni S, Charles J, Rimbert A, Folope V, et al. Validity of predictive equations for resting energy expenditure according to the body mass index in a population of 1726 patients followed in a nutrition unit. Clin Nutr. 2015;34(3):529-35.
42. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. J Am Diet Assoc. 2005;105(5):775-89.
43. Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. J Appl Physiol Respir Environ Exerc Physiol. 1982;53(4):955-9.
44. International Atomic Energy Agency. Assessment of Body Composition and Total Energy Expenditure in Humans Using Stable Isotope Techniques. IAEA Human Health Series No. 3. Vienna, Austria. 2009.
45. Schoeller DA. Measurement of energy expenditure in free-living humans by using doubly labeled water. J Nutr. 1988;118(11):1278-89.
46. Johnson M, Meltz K, Hart K, Schmudlach M, Clarkson L, Borman K. Validity of the Actical activity monitor for assessing steps and energy expenditure during walking. J Sports Sci. 2015;33(8):769-76.
47. O'Driscoll R, Turicchi J, Beaulieu K, Scott S, Matu J, Deighton K, et al. How well do activity monitors estimate energy expenditure? A systematic review and meta-analysis of the validity of current technologies. Br J Sports Med. 2018:bjsports-2018-099643.
48. United States Department of Health and Human Servies. National Institutes of Health. National Cancer Institute. Cancer Statistics April 27, 2018. Available from: https://www.cancer.gov/about-cancer/understanding/statistics.

49. Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. Am J Clin Nutr. 2014;99(5):999-1005.
50. Meyerhardt JA, Kroenke CH, Prado CM, Kwan ML, Castillo A, Weltzien E, et al. Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente Northern California population. Cancer Epidemiol Biomarkers Prev. 2017;26(1):30-7.
51. Kocarnik JM, Hua X, Hardikar S, Robinson J, Lindor NM, Win AK, et al. Long-term weight loss after colorectal cancer diagnosis is associated with lower survival: The Colon Cancer Family Registry. Cancer. 2017;123(23):4701-8.
52. Park YS, Park DJ, Lee Y, Park KB, Min S-H, Ahn S-H, et al. Prognostic roles of perioperative body mass index and weight loss in the long-term survival of gastric cancer patients. Cancer Epi Biomark Prev. 2018;27(8):955-62.
53. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015;33(1):90-9.
54. Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, Birdsell L, et al. The association of nutritional assessment criteria with health-related quality of life in patients with advanced colorectal carcinoma. Eur J Cancer Care (Engl). 2012;21(4):505-16.
55. Xiao J, Caan BJ, Weltzien E, Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. J Cachexia Sarcopenia Muscle. 2018; 9(4):654-63.
56. Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. Proc Nutr Soc. 2016:1-11.
57. Baracos VE, Arribas L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. Ann Oncol. 2018;29(suppl_2):ii1-ii9.
58. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr. 2012;31(5):583-601.
59. Omlin A, Blum D, Wierecky J, Haile SR, Ottery FD, Strasser F. Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions: a case–control study. J Cachexia Sarcopenia Muscle. 2013;4(1):55-61.

60. Martin L, Kubrak C. How much does reduced food intake contribute to cancer-associated weight loss? Curr Opin Support Palliat Care. 2018:12(4):410-9.
61. Prado CM, Lieffers JR, Bergsten G, Mourtzakis M, Baracos VE, Reiman T, et al. Dietary patterns of patients with advanced lung or colorectal cancer. Can J Diet Pract Res. 2012;73(4):e298-303.
62. Bosaeus I, Daneryd P, Lundholm K. Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. J Nutr. 2002;132(11 Suppl):3465s-6s.
63. Chow CC, Hall KD. Short and long-term energy intake patterns and their implications for human body weight regulation. Physiol Behav. 2014;134:60-5.
64. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996-1002.
65. Gibney E, Elia M, Jebb SA, Murgatroyd P, Jennings G. Total energy expenditure in patients with small-cell lung cancer: results of a validated study using the bicarbonate-urea method. Metabolism. 1997;46(12):1412-7.
66. Skipworth RJ, Stene GB, Dahele M, Hendry PO, Small AC, Blum D, et al. Patient-focused endpoints in advanced cancer: criterion-based validation of accelerometer-based activity monitoring. Clin Nutr. 2011;30(6):812-21.
67. Hayes S, Davies PS, Parker T, Bashford J. Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme. Bone marrow transplantation. 2003;31(5):331-8.
68. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2016;36(1):11-48.
69. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-95.
70. Johannsen DL, Calabro MA, Stewart J, Franke W, Rood JC, Welk GJ. Accuracy of armband monitors for measuring daily energy expenditure in healthy adults. Med Sci Sports Exerc. 2010;42(11):2134-40.

71. Viggiani MT, Lorusso O, Natalizio F, Principi M, Di Leo A, Barone M. Influence of chemotherapy on total energy expenditure in patients with gastrointestinal cancer: A pilot study. Nutrition. 2017;42:7-11.
72. Vermaete N, Wolter P, Verhoef G, Gosselink R. Physical activity and physical fitness in lymphoma patients before, during, and after chemotherapy: a prospective longitudinal study. Ann Hematol. 2014;93(3):411-24.
73. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv. 2010;4(2):87-100.
74. Broderick JM, Ryan J, O'Donnell DM, Hussey J. A guide to assessing physical activity using accelerometry in cancer patients. Support Care Cancer. 2014;22(4):1121-30.
75. Ravasco P. Aspects of taste and compliance in patients with cancer. Eur J Oncol Nurs. 2005;9 Suppl 2:S84-91.
76. Weston PM, King RF, Goode AW, Williams NS. Diet-induced thermogenesis in patients with gastrointestinal cancer cachexia. Clin Sci (Lond). 1989;77(2):133-8.
77. Barber MD, McMillan DC, Preston T, Ross JA, Fearon KC. Metabolic response to feeding in weight-losing pancreatic cancer patients and its modulation by a fish-oil-enriched nutritional supplement. Clin Sci (Lond). 2000;98(4):389-99.
78. Walsh D, Nelson KA. Autonomic nervous system dysfunction in advanced cancer. Support Care Cancer. 2002;10(7):523-8.
79. Demark-Wahnefried W, Hars V, Conaway MR, Havlin K, Rimer BK, McElveen G, et al. Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. Am J Clin Nutr. 1997;65(5):1495-501.
80. Fenninger LD, Mider GB. Energy and nitrogen metabolism in cancer. Adv Cancer Res. 1954;2:229-53.
81. Boothby WM, Berkson J, Dunn HL. Studies of the energy of metabolism of normal individuals: a standard for basal metabolism, with a nomogram for clinical application. Am J Physiol. 1936;116(2):468-84.
82. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324(5930):1029-33.

83. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012;16(2):153-66.
84. Lundholm K, Edstrom S, Karlberg I, Ekman L, Schersten T. Glucose turnover, gluconeogenesis from glycerol, and estimation of net glucose cycling in cancer patients. Cancer. 1982;50(6):1142-50.
85. Friesen DE, Baracos VE, Tuszynski JA. Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia. Theor Biol Med Model. 2015;12(1):17.
86. Heymsfield SB. Measurements of energy balance. Acta Diabetol. 2003;40 Suppl 1:S117-21.
87. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr. 2009;89(4):1173-9.
88. Fredrix EW, Soeters PB, Rouflart MJ, von Meyenfeldt MF, Saris WH. Resting energy expenditure in patients with newly detected gastric and colorectal cancers. Am J Clin Nutr. 1991;53(5):1318-22.
89. Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr. 2010;29(1):72-7.
90. Hall KD, Baracos VE. Computational modeling of cancer cachexia. Curr Opin Clin Nutr Metab Care. 2008;11(3):214-21.
91. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105.
92. Baracos VE. Metabolism and physiology. In: Del Fabbro E, Baracos V, Demark-Wahnefried W, Bowling T, Hopkinson JB, Bruera E, editors. Nutrition and the Cancer Patient. Oxford, United Kingdom: Oxford University Press; 2010. p. 7-18.
93. Grossberg AJ, Scarlett JM, Marks DL. Hypothalamic mechanisms in cachexia. Physiol Behav. 2010;100(5):478-89.
94. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10(2):90-9.
95. Wu J, Huang C, Xiao H, Tang Q, Cai W. Weight loss and resting energy expenditure in male patients with newly diagnosed esophageal cancer. Nutrition. 2013;29(11-12):1310-4.

96. Simons JP, Schols AM, Buurman WA, Wouters EF. Weight loss and low body cell mass in males with lung cancer: relationship with systemic inflammation, acute-phase response, resting energy expenditure, and catabolic and anabolic hormones. Clin Sci (Lond). 1999;97(2):215-23.
97. Staal-van den Brekel AJ, Dentener MA, Schols AM, Buurman WA, Wouters EF. Increased resting energy expenditure and weight loss are related to a systemic inflammatory response in lung cancer patients. J Clin Oncol. 1995;13(10):2600-5.
98. Scott HR, McMillan DC, Watson WS, Milroy R, McArdle CS. Longitudinal study of resting energy expenditure, body cell mass and the inflammatory response in male patients with non-small cell lung cancer. Lung Cancer. 2001;32(3):307-12.
99. Deans DA, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. Br J Cancer. 2009;100(1):63-9.
100. Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? Cancer J. 2007;13(6):392-8.
101. Johnson G, Salle A, Lorimier G, Laccourreye L, Enon B, Blin V, et al. Cancer cachexia: measured and predicted resting energy expenditures for nutritional needs evaluation. Nutrition. 2008;24(5):443-50.
102. Lundholm K, Daneryd P, Korner U, Hyltander A, Bosaeus I. Evidence that long-term COX-treatment improves energy homeostasis and body composition in cancer patients with progressive cachexia. Int J Oncol. 2004;24(3):505-12.
103. Trutschnigg B, Kilgour RD, Morais JA, Lucar E, Hornby L, Molla H, et al. Metabolic, nutritional and inflammatory characteristics in elderly women with advanced cancer. J Geriatr Oncol. 2013;4(2):183-9.
104. Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg. 1994;219(4):325-31.
105. Freake HC. Uncoupling proteins: beyond brown adipose tissue. Nutr Rev. 1998;56(6):185-9.

106. Petruzzelli M, Schweiger M, Schreiber R, Campos-Olivas R, Tsoli M, Allen J, et al. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. Cell Metab. 2014;20(3):433-47.
107. Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE, et al. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature. 2014;513(7516):100-4.
108. Schiessel DL, Baracos VE. Barriers to cancer nutrition therapy: excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. Proc Nutr Soc. 2018;77(4):394-402.
109. Cypess AM, Weiner LS, Roberts-Toler C, Franquet Elia E, Kessler SH, Kahn PA, et al. Activation of human brown adipose tissue by a beta3-adrenergic receptor agonist. Cell Metab. 2015;21(1):33-8.
110. Yoneshiro T, Aita S, Matsushita M, Kayahara T, Kameya T, Kawai Y, et al. Recruited brown adipose tissue as an antiobesity agent in humans. J Clin Invest. 2013;123(8):3404-8.
111. Orava J, Nuutila P, Lidell ME, Oikonen V, Noponen T, Viljanen T, et al. Different metabolic responses of human brown adipose tissue to activation by cold and insulin. Cell Metab. 2011;14(2):272-9.
112. Romu T, Vavruch C, Dahlqvist-Leinhard O, Tallberg J, Dahlström N, Persson A, et al. A randomized trial of cold-exposure on energy expenditure and supraclavicular brown adipose tissue volume in humans. Metabolism. 2016;65(6):926-34.
113. Xu WP, Cao DX, Lin ZM, Wu GH, Chen L, Zhang JP, et al. Analysis of energy utilization and body composition in kidney, bladder, and adrenal cancer patients. Urol Oncol. 2012;30(5):711-8.
114. Jatoi A, Daly BD, Hughes VA, Dallal GE, Kehayias J, Roubenoff R. Do patients with nonmetastatic non-small cell lung cancer demonstrate altered resting energy expenditure? Ann Thorac Surg. 2001;72(2):348-51.
115. Langius JA, Kruizenga HM, Uitdehaag BM, Langendijk JA, Doornaert P, Leemans CR, et al. Resting energy expenditure in head and neck cancer patients before and during radiotherapy. Clin Nutr. 2012;31(4):549-54.

116. Vaisman N, Lusthaus M, Niv E, Santo E, Shacham-Shmueli E, Geva R, et al. Effect of tumor load on energy expenditure in patients with pancreatic cancer. Pancreas. 2012;41(2):230-2.
117. Garcia-Peris P, Lozano MA, Velasco C, de La Cuerda C, Iriondo T, Breton I, et al. Prospective study of resting energy expenditure changes in head and neck cancer patients treated with chemoradiotherapy measured by indirect calorimetry. Nutrition. 2005;21(11-12):1107-12.
118. Jebb SA, Osborne RJ, Dixon AK, Bleehen NM, Elia M. Measurements of resting energy expenditure and body composition before and after treatment of small cell lung cancer. Ann Oncol. 1994;5(10):915-9.
119. Kutynec CL, McCargar L, Barr SI, Hislop TG. Energy balance in women with breast cancer during adjuvant treatment. J Am Diet Assoc. 1999;99(10):1222-7.
120. Harvie MN, Campbell IT, Baildam A, Howell A. Energy balance in early breast cancer patients receiving adjuvant chemotherapy. Breast Cancer Res Treat. 2004;83(3):201-10.
121. Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. Head Neck. 2007;29(10):893-900.
122. Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, et al. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol. 2001;19(9):2381-9.
123. Campbell KL, Lane K, Martin AD, Gelmon KA, McKenzie DC. Resting energy expenditure and body mass changes in women during adjuvant chemotherapy for breast cancer. Cancer Nurs. 2007;30(2):95-100.
124. Reis C, Liberman S, Pompeo AC, Srougi M, Halpern A, Filho WJ. Body composition alterations, energy expenditure and fat oxidation in elderly males suffering from prostate cancer, pre and post orchiectomy. Clinics (Sao Paulo). 2009;64(8):781-4.
125. Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr. 2016;70(11):1230-8.

126. Hill RJ, Cleghorn GJ, Withers GD, Lewindon PJ, Ee LC, Connor F, et al. Resting energy expenditure in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2007;45(3):342-6.
127. Ravussin E, Bogardus C. Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization. Am J Clin Nutr. 1989;49(5 Suppl):968-75.
128. Tschop MH, Speakman JR, Arch JR, Auwerx J, Bruning JC, Chan L, et al. A guide to analysis of mouse energy metabolism. Nat Methods. 2011;9(1):57-63.
129. Okamoto H, Sasaki M, Johtatsu T, Kurihara M, Iwakawa H, Akabane M, et al. Resting energy expenditure and nutritional status in patients undergoing transthoracic esophagectomy for esophageal cancer. J Clin Biochem Nutr. 2011;49(3):169-73.
130. Khor SM, Mohd BB. Assessing the resting energy expenditure of cancer patients in the Penang General Hospital. Malays J Nutr. 2011;17(1):43-53.
131. Bauer J, Reeves MM, Capra S. The agreement between measured and predicted resting energy expenditure in patients with pancreatic cancer: a pilot study. JOP. 2004;5(1):32-40.
132. Becker Veronese CB, Guerra LT, Souza Grigolleti S, Vargas J, Pereira da Rosa AR, Pinto Kruel CD. Basal energy expenditure measured by indirect calorimetry in patients with squamous cell carcinoma of the esophagus. Nutricion hospitalaria. 2013;28(1):142-7.
133. Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition. 2006;22(6):609-15.
134. Zuconi CP, Ceolin Alves AL, Toulson Davisson Correia MI. Energy expenditure in women with breast cancer. Nutrition. 2015;31(4):556-9.
135. Pirat A, Tucker AM, Taylor KA, Jinnah R, Finch CG, Canada TD, et al. Comparison of measured versus predicted energy requirements in critically ill cancer patients. Respir Care. 2009;54(4):487-94.
136. Ceolin Alves AL, Zuconi CP, Correia MI. Energy expenditure in patients with esophageal, gastric, and colorectal cancer. JPEN J Parenter Enteral Nutr. 2016;40(4):499-506.
137. Vazeille C, Jouinot A, Durand JP, Neveux N, Boudou-Rouquette P, Huillard O, et al. Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. Am J Clin Nutr. 2017;105(5):1139-47.

138. Jouinot A, Vazeille C, Durand JP, Huillard O, Boudou-Rouquette P, Coriat R, et al. Resting energy expenditure in the risk assessment of anticancer treatments. Clin Nutr. 2018;37(2):558-65..
139. Reeves MM, Capra S, Bauer J, Davies PS, Battistutta D. Clinical accuracy of the MedGem indirect calorimeter for measuring resting energy expenditure in cancer patients. Eur J Clin Nutr. 2005;59(4):603-10.
140. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2018. Toronto, Ontario: Canadian Cancer Society 2018. Available at: cancer.ca/Canadian-Cancer-Statistics-2018-EN (accessed [September 2018]).
141. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.
142. Hansell DT, Davies JW, Burns HJ. The effects on resting energy expenditure of different tumor types. Cancer. 1986;58(8):1739-44.
143. Nixon DW, Kutner M, Heymsfield S, Foltz AT, Carty C, Seitz S, et al. Resting energy expenditure in lung and colon cancer. Metabolism. 1988;37(11):1059-64.
144. Hansell DT, Davies JW, Burns HJ. Effects of hepatic metastases on resting energy expenditure in patients with colorectal cancer. Br J Surg. 1986;73(8):659-62.
145. Maguire R, McMillan DC, Wallace AM, McArdle C. A longitudinal study of leptin and appetite, resting energy expenditure and body fat mass in weight-stable cancer patients. Cytokine. 2002;20(4):174-7.
146. Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest. 2007;25(5):308-14.
147. de Roos B, Brennan L. Personalised interventions—a precision approach for the next generation of dietary intervention studies. Nutrients. 2017;9(8):847.

Chapter 3 Accuracy of Resting Energy Expenditure Predictive Equations in Patients with Cancer

3.1 Preface

The following chapter is based on data from 125 individuals recruited from the Cross Cancer Institute with solid tumors and aimed to determine the accuracy of several REE equations. It is the first analysis to investigate the potential impact of body weight, cancer stage, cancer type, age, and body composition on REE equation error. A version of Chapter 3 is being prepared for submission to the European Journal of Clinical Nutrition with the following co-authors: Dr. Sarah A. Elliott, Dr. Vickie E. Baracos, Dr. Quincy S.C. Chu, Dr. Michael B. Sawyer, Dr. Marina Mourtzakis, Dr. Jacob Easaw, Dr. Jennifer Spratlin, and Dr. Carla M. Prado.

All data from Study 1 was previously collected by individuals other than me. I was responsible for measuring resting energy expenditure and collecting anthropometric and demographic data from individuals in Study 2; I also applied for and maintained ethical approval for this study. Body composition was assessed by dual energy X-ray absorptiometry, which was measured by a radiographic technician. I contributed to formulating the research question, study design and implementation of Study 2, data analysis and interpretation, and chapter/manuscript preparation (~70% total proportion of contribution to research and writing); Dr. Sarah Elliott contributed to formulating the research question and data analysis and interpretation; Dr. Vickie Baracos contributed to study design and implementation (Study 1) and data interpretation; Dr. Carla M. Prado contributed to formulating the research question, study design and implementation (Study 1 and 2), data analysis and interpretation, and chapter/manuscript preparation; all other authors contributed to data interpretation and revising the manuscript for intellectual content.

3.2 Abstract

Equations are often used to estimate resting energy expenditure (REE). Our purpose was to assess the accuracy of REE equations in patients with newly diagnosed stage I-IV non-small cell lung, rectal, colon, renal, or pancreatic cancer. In this cross-sectional study, REE was measured using indirect calorimetry and compared to 23 equations. Agreement between measured and predicted REE was assessed via paired t-tests and Bland-Altman analysis, and percent of estimations ≤10% of measured values. Accuracy was measured among sub-groups of body mass index (BMI), stage (I-III vs. IV) and cancer type (lung, rectal, and colon) categories. Fat mass and fat-free mass were assessed using dual X-ray absorptiometry. Most of the 125 patients had lung, colon, or rectal cancer (92.0%, BMI: 27.5 ± 5.6 kg/m^2, age: 61 ± 11 years, REE: 1629 ± 321 kcal/day). Sixteen (66.6%) equations yielded REE values different than measured ($p<0.05$). Limits of agreement were wide for all equations, with Mifflin St. Jeor equation having the smallest limits of agreement, -21.7 to 11.3% (-394 to 203 kcal/day). Equations that used fat-free mass were not more accurate except for one equation (Huang with body composition, bias and limits of agreement: -0.3 ± 11.3% versus without body composition: 2.3 ± 10.1%, $p<0.001$). Bias in body composition equations was consistently positively correlated with age and frequently (7/10 equations) negatively correlated to fat mass. REE cannot be accurately predicted on an individual level; REE equations should therefore not be used in energy needs estimations.

3.3 Background

Estimation of energy needs is important for individuals with cancer as weight loss and body composition alterations (namely loss of fat-free mass, FFM) are detrimental to health outcomes (1, 2). Energy balance (weight maintenance) occurs when energy intake is equivalent to total energy expenditure (TEE) over time. Resting energy expenditure (REE) is the largest component of TEE and can be used to estimate energy needs (i.e. factorial approach [1]). Since TEE is costly and burdensome to measure, REE is not routinely measured in clinical settings and portable indirect calorimeters may not yield accurate values (2, 3), predictive equations for REE are often used. However, previous research in small samples ($n \leq 18$) has shown some of these equations are inaccurate in patients with different tumor types (4-7), and oncology nutritional guidelines highlight the need for improved prediction of energy needs in individual patients (8).

Inaccuracies in estimating REE in cancer patients may be due to several factors. Firstly, most REE equations were developed in healthy cohorts that are not affected by metabolic abnormalities which might impact patients with cancer (3). In addition, many cancer patients may be paradoxically obese (9) and REE prediction equations developed in populations of primarily normal weight individuals are not as accurate at higher body masses (10). Furthermore, body composition is highly variable in people with cancer, independent of body weight (11). Body composition, particularly FFM, is a primary determinant of REE, and could impact the ability to capture energy needs using body weight-based equations, as previously discussed (3). Lastly, advanced cancer stage has been associated with higher REE (12) and physiological and metabolic heterogeneity between cancer types (13) may impact REE prediction accuracy. As such, performance of REE prediction equations may be impacted by body size, body composition, cancer stage, and/or cancer type.

To date, most research investigating accuracy of REE prediction equations in cancer have been carried out in small samples or compared to a limited number of equations; none have assessed whether the accuracy of these equations is different across body mass index (BMI) classes, cancer types, or stages, or if inclusion of body composition improves the predictive ability of equations. Our aim was to assess the accuracy of the most commonly used clinical REE prediction equations compared to measured REE in patients with solid tumors. Additional objectives included assessing differences in equation accuracy among sub-groups of patients grouped by body mass index (BMI) classes, cancer stage (I-III or IV), and cancer type (lung, rectal or colon) and to determine whether age, weight, FM and FFM were associated with REE prediction equation inaccuracy. It was hypothesized that all REE prediction equations would have acceptable group-level agreement (bias ± 5%), but poor individual-level agreement (absolute limits of agreement > 20%), based on the assumption that indirect calorimetry varies <5% (14) and most healthy adults should have REE that falls within 10% of the Harris-Benedict equation (15). In line with the research discussed above in this introduction, it was also hypothesized that 1) REE equation bias and limits of agreement would be poorer in patients with obesity, 2) REE equation bias will be lower in patients with stage IV disease compared to stages I-III, and 3) REE equation bias will be negatively correlated to FFM and positively correlated with age, body weight, and FM in the majority (>50%) of equations.

3.4 Methods

3.4.1 Participants

The participant data presented in this paper were collected from two distinct studies: 1) a study that profiled nutritional, metabolic and functional characteristics of patients with advanced lung or colorectal cancer, described elsewhere (16, 17) (Study 1), and 2) data from a cross-sectional study investigating energy metabolism, body composition, exercise, and dietary intake in patients with several tumor types (18) (Study 2). Collectively, both studies included patients with recently diagnosed stage I-IV non-small cell lung, rectal, colon, renal, or pancreatic cancer who were recruited from a cancer center serving northern Alberta (Cross Cancer Institute in Edmonton, Alberta, Canada). Both studies were approved by the Health Research Ethics Board of Alberta and informed consent was obtained from all participants prior to any study procedures being carried out. Exclusion criteria included use of medications that might interfere with REE (unstable thyroid medication dose, steroids, or hormones), surgery in the previous 4 weeks, pregnancy or breastfeeding, or confinement to a wheelchair. Exclusion criteria for Study 1 were similar and published elsewhere (16, 17).

3.4.2 Anthropometrics and Body Composition

Height and weight were measured using a Health-O-Meter Professional digital scale with height rod (McCook, IL, USA; model number: 597KL) or a QuickMedical Heightronic digital standiometer (Northbend, WA, USA) for height and a SECA 766 digital scale (Hannover, MD, USA) for weight. BMI was calculated [weight (kg)/ height (m^2)] and classified according to World Health Organization (19): underweight $\leq$18.5 kg/m^2, normal weight 18.6 – 24.9 kg/m^2, overweight 25.0 – 29.9 kg/m^2, obese $\geq$ 30.0 kg/m^2 . Underweight and normal weight patients were grouped together due to sample size (n=3 underweight patients, all within 2 standard deviations of mean BMI).

Body composition was assessed via dual X-ray absorptiometry (DXA), using a General Electric LUNAR Prodigy High Speed Digital Fan Beam Densitometer with enCORE 9.20 software or iDXA with enCORE 13.60 software (General Electric, Madison, WI, USA). Measures of total body lean soft tissue, fat mass, or body fat percent are not different between these machines (20), and data were therefore combined. DXA was completed as part of study protocol for patients in Study 1, while 20 patients in Study 2 underwent DXA scans as part of a

separate study objective. Fat mass (FM) and FFM were adjusted for height (fat mass index, FMI, and fat-free mass index, FFMI, both kg/m^2) since body weight and composition scale to height; this value was used only in the descriptive analysis to profile our population in relation to other cohorts.

3.4.3 Resting Energy Expenditure

REE was measured using indirect calorimetry with a ventilated hood system (VMax 29N; Sensor-Medics, Yorba Linda, CA, USA), which is a standard machine in the field of energy metabolism research. The test was conducted after an overnight fast; patients were asked to avoid food, smoking, caffeine, and physical activity the morning of testing. The flow meter (including volume and air flow) was calibrated before each measurement using a three-liter syringe. Although burn tests were not performed on this machine, gas analyzers were automatically calibrated prior to each test using known standard gas concentration (20.95% O_2, 0.03% CO_2). Patients rested for a minimum of 10 minutes before a canopy was placed over their head and shoulders for 30 minutes to assess oxygen (O_2) consumption and carbon dioxide (CO_2) production. Only breath samples in steady state were used for analysis. Steady state was defined as variations in volume of O_2 and CO_2 of $\leq$ 10% over the previous five minutes (21). No steady state data was selected in the first ten minutes of the measurement period to ensure that each individual had a minimum of 20 minutes of complete rest, according to current guidelines (21). A minimum of 10 minutes of steady state data was collected. The abbreviated Weir equation was used to calculate REE (22).

Measured REE was compared to predicted REE estimated from a total of 23 equations, ten of which incorporated a measure of body composition (FFM and/or FM) (23-35), **Table 3.1**. Some equations used megajoules or kilojoules as units of expression; these values were then converted to kilocalories to allow for uniform comparison. Equations were chosen because they 1) are frequently used in clinical or research settings, 2) were previously used in REE equation validation studies in cancer (4, 5), 3) incorporated a measure of body composition, or 4) were derived specifically from a cancer population (34). Actual body weight was used in all equations, since adjusted body weight introduces error in individuals with obesity (36). No injury factor was used since this largely overestimates REE in ambulatory patients with cancer (4). Aggregate REE was also calculated as the sum of each predicted REE (37, 38). This method reduces error

associated with using multiple equations and allows for comparisons of REE prediction equation accuracy between groups of patients. Because only a portion of the sample had measures of body composition, body weight-based and body composition-based equation REE estimations were aggregated separately.

3.4.4 Statistical Analyses

Data were analyzed using SPSS version 24 (IBM Corporation, Armonk, NY, USA) and are presented as mean ± standard deviation; significance was considered at $p \leq 0.05$. A sample size of 93 patients was deemed adequate to detect differences in measured REE and the Harris-Benedict equation (the most commonly used in clinical settings) using a two-tailed dependent samples t-test. Power (β) was 0.95 and effect size was assumed to be 0.38, based on the difference between the Harris-Benedict equation and measured REE observed in the largest study of REE equation accuracy in cancer to date (4). Data collection continued after sample size reached 93 to facilitate comparisons between patient sub-groups according to our exploratory objectives.

Independent samples t-tests (with degrees of freedom adjustment using the Welch-Satterthwaite method in the case of non-equal variances) and t-test for independent proportions were used to compare characteristics between patient groups. To assess group-level agreement between measured and predicted REE, paired t-tests and Pearson correlation were utilized. The Shipiro-Wilk test assessed normality of differences between measured versus predicted REE; in cases of non-normality, Wilcoxon signed-ranks test was utilized. Agreement between values was also assessed via the Bland-Altman approach (39). This method was chosen as a primary determinant of individual-level accuracy because it accounts for random error in both measured and predicted REE (i.e. the reference method is not truly infallible) (40) and considers individual differences on a scale according to standard deviations rather than binomial categories. Bias was calculated as average difference between predicted REE minus measured REE (group-level agreement). Positive values represent overpredictions of measured REE and negative values represent underpredictions of measured REE. Limits of agreement were defined as bias ± 1.96 standard deviations (individual level agreement). These values were primarily expressed as percentages from baseline REE to account for variability in body size. Pearson correlation coefficient between mean of measured and predicted REE and bias were used to determine if

there were any trends in the magnitude of bias with increasing REE measurement (proportional bias). The proportion of patients with predicted REE within ± 10% of measured REE for each equation was also calculated, based on the assumption that measured REE would fall within ± 10% of predicted (23, 41). Pearson correlation coefficients were utilized to assess whether age, body weight, FM, or FFM would be significantly associated with bias. Paired t-test assessed bias between equations with and without body composition.

The primary purpose of this study was to assess the accuracy of REE equations which are not tumor-specific; patients were therefore assessed as a single group. Cancer types also have metabolic differences and equation error was therefore also assessed according to tumor group. Due to the small number of patients with pancreatic or renal cancer, patients with tumors located in the lung, rectum, or colon were used for cancer-type specific comparisons. Patients were also grouped by BMI class and advanced (IV) versus non-advanced (I-III) stages. Bias between sub groups of BMI categories and cancer types (lung vs. rectal vs. colon) was compared using one-way analysis of variance (ANOVA) with Tukey's post-hoc analysis where appropriate. Since Study 1 consisted primarily of individuals with stage IV disease and Study 2 of individuals with stage I-III disease, analysis of covariance assessed differences in percent bias between these groups, with study as a covariate. Mann-Whitney U test (two groups) or Kruskal-Wallis test (three groups) determined differences between groups with when bias was non-parametric. Equation biases between metastatic patients with and without liver metastases and between patients scheduled to begin either neoadjuvant or adjuvant anti-cancer therapy were also assessed with independent samples t-test or Mann-Whitney U-test. Levene's test for homogeneity of variances described variance in anthropometric and body composition measures between groups of patients (BMI class, cancer type, and stage).

3.5 Results

A total of 125 patients with non-small cell lung cancer (n=28), rectal cancer (n=24), colon cancer (n=63), renal cell carcinoma (n=7), or pancreatic cancer (n=3) were included, **Figure 3.1**. Fifty-two (41.6%) of these patients had stage IV cancer and approximately one-third had obesity (n=39, 31.2%). Anthropometric, demographic, and body composition characteristics are shown in **Table 3.2**. Biases using most equations were not different between sexes; males and females were therefore analyzed together without further sex stratification. Sixty-five

(52.0%) patients had body composition measured; there was a higher proportion of patients with lung cancer and stage IV disease and a lower proportion of patients with rectal cancer and stage I-III disease, **Table 3.3**.

Average measured REE was 1629 ± 321 kcal/day and ranged from 1012 to 3158 kcal/day. All predicted REE values were correlated to measured REE (ranges from r = 0.364 - 0.886, p = 0.003 - <0.001). **Table 3.4** shows results of paired t-tests and Bland-Altman analysis and minimum and maximum errors. Thirteen (56.5%) equations yielded REE values that were significantly different than measured REE, with nine under predicting and four overpredicting REE. All but one equation (Souza-Singer) had bias within 10% of measured REE. Individual variability was high in all equations. The Mifflin St. Jeor equation with age, sex, height, and weight had the smallest limits of agreement, ranging from -21.7 to 11.3% (or -394 to 203 kcal/day). The aggregate REE bias from body-weight based equations was 0.1 ± 8.8% and aggregate REE bias from body composition-based equations was -1.5 ± 11.0%.

The proportion of equations predicting REE within 10% of measured REE is presented in **Figure 3.2**. Equations with the highest prevalence of predicted REE within 10% of measured were the Harris-Benedict, Huang with age, sex, height, weight, and aggregate calculation from body weight-based equations (n=93, 74.4). Most of the remaining equations predicted REE within 10% of measured in about half of patients.

Associations between percent bias and age, weight, FM and FFM are shown in **Table 3.5**. No discernable pattern in biases were observed among equations without body composition. However, in those incorporating body composition, age was consistently positively correlated to bias and FM was frequently negatively correlated to bias. Among body composition equations, FFM was negatively correlated to bias only in the Souza-Singer equation.

Figure 3.3 shows percent bias for equations with and without body composition. Bias was significantly lower (farther from 0) using Mifflin St.-Jeor and Owen body composition equations compared to body weight equations. Bias from the Huang equation incorporating body composition was closer to zero and different than the Huang equation with age, sex, height, and weight. Significant differences were also observed in aggregate biases, with body weight-based equations yielding an aggregate bias above zero and body composition-based equations yielding an aggregate bias below zero.

Percent bias and limits of agreement in sub-groups of patients are presented in **Figures 3.4a-c**. Age was not different among all groups and BMI, FMI, and FFMI were not different among cancer type and stage groups. Patients with obesity had high variance in FFM ($F=3.94$, $p=0.025$), body weight ($F=4.23$, $p=0.017$), and BMI ($F=15.91$, $p<0.001$). In patients with obesity, the equation using 21 kcal/kg body weight significantly over predicted REE (14.1 ± 12.8 %, $F=24.61$, $p<0.001$) compared to patients who were under/normal weight (-4.1 ± 11.1%, $p<0.001$) or overweight (5.2 ± 11.4%, $p=0.003$). Furthermore, percent bias from the Souza-Singer equation was significantly different between groups (underweight/normal weight: -0.6 ± 14.6%; overweight: -16.1 ± 8.2 %; obese: -25.1 ± 12.1%, $p<0.001$; Kruskal-Wallis test). Aggregate bias was not different among BMI groups and limits of agreement were similar. Patients with rectal cancer had greater variance in FM ($F=5.24$, $p=0.008$), although this effect was not present when one outlier within the rectal tumor group was removed ($F=1.23$, $p=0.300$). When comparing REE accuracy in patients with lung, colon or rectal cancer, similar patterns in bias and limits of agreement were observed among groups with exception of the Huang-body weight equation ($F=3.18$, $p=0.045$; lung: 5.2 ± 11.6 % vs. rectal -1.82 ± 8.9%, $p=0.038$). Bias was not different in any equation comparing patients with stage IV versus stages I-III disease, after controlling for study. No biases were different between patients with and without liver metastases or between patients scheduled to undergo neo-adjuvant or adjuvant anti-cancer therapy (data not presented).

3.6 Discussion and Conclusions

An understanding of energy expenditure is essential for providing accurate energy intake recommendations for patients with cancer. This is the largest investigation of REE equation accuracy in oncology, which allowed for assessment of equation performance in subgroups of patients (i.e. BMI classes, cancer types, and cancer stage). Our results suggested that all equations have poor individual-level accuracy (wide limits of agreement) and bias was frequently correlated to age and FM.

Several equations were significantly different than measured REE (t-test) and individual variability was high, as revealed by wide limits of agreement; in addition, a considerable portion of individuals had > 10% error in predicted REE values, and large minimum and maximum error values were observed. Similar to these findings, a previous study in 18 patients with cancer

reported that while most mean biases were small, limits of agreement were poor for all equations (all >20%) (4). In our sample, the best equation for individual prediction (Mifflin St. Jeor with age, sex, height and weight) still under-predicted REE by up to 32.4 % (-440 kcal/day) and over-predicted REE by up to 18.1% (261 kcal/day). Dietary recommendations based on such an equation may perpetuate unwanted weight change and should therefore not be used to predict energy needs for individual patients.

A REE equation was recently developed in patients with head and neck cancer using bioelectrical impedance analysis to measure body composition (34). Although this equation was anticipated to be more accurate than equations developed from healthy populations, this was not observed in our sample. Notably, the present study measured body composition using DXA and discrepancies between bioelectrical impedance analysis and DXA have been previously reported (i.e. the former may underestimate FFM) (42), which might have influenced the observed bias. Furthermore, patients with head and neck cancer might have different REE and body composition than other cancer types (13), further limiting the use of this new equation. Although a similar population to that reported in Souza *et al*. (i.e. head and neck cancer with body composition measured using bioelectrical impedance analysis) would likely yield better individual-level agreement, this equation is not applicable to all cancer types. More accurate cancer-specific REE equations are therefore needed. Such equations should include validation with a separate cohort of individuals for external validity to be used in clinical practice.

Correlation analysis was conducted between bias and age, weight, FM, and FFM to identify potential relationships between error and patient characteristics. In equations using body composition, age was positively correlated to bias, indicating that REE over-prediction was associated with advancing age. A previous study in 32 adults age 64 - 87 years old did not report frequent correlations between age and bias, although only equations with body weight were used (43). We also found that higher FM negatively correlated with bias, indicating under-prediction at higher FM. Only three of ten body composition equations utilized age and FM, while remaining equations used FFM alone or FFM in combination with sex and body weight (34). Notably, three equations that used age, FM, and FFM (Müller, Huang, and Johnstone) were not significantly different than measured REE. REE generally decreases with age due to reduced FFM, decreases in norepinephrine from diminished exercise and food intake, reduced protein

synthesis rates, and lower cellular fraction of FFM (namely from decreased sodium-potassium adenosine triphosphatase activity) (44). FM is also highly variable (45), and it appears that these factors influence the error in REE predictions. Including age and FM alongside FFM could potentially improve prediction equations using body composition.

Given that FFM is a primary determinant of REE and body composition varies widely in healthy people, equations that incorporate body composition would be expected to have higher accuracy compared to equations that use measures of body weight and height alone. However, body composition equations were not more accurate in the present sample, except for the Huang equation which was created in a sample of individuals with BMI $\geq$ 35.0 kg/m^2 (30). This lower accuracy could be because FFM is a heterogenous compartment containing organs and tissues with different metabolic rates; shorter individuals also have a higher proportion of organs with high metabolic rate in the FFM compartment (46). Including high metabolic rate organ weights in prediction models makes the intercept not significantly different than zero (47). Therefore, small differences in organ size could affect REE, which is not captured using FFM and FM alone. In addition, most of these equations were developed using techniques other than DXA (i.e. bioelectric impedance analysis, air displacement plethysmography, total body potassium counting, deuterium dilution, skin-folds), which might contribute to accuracy being lower than expected since precision to measure FFM is highly variable among these techniques (48).

Previous reports have established that REE prediction equations in adults with obesity have higher variability compared to adults who are overweight or normal weight. In 1,726 patients with malnutrition, eating disorders, or obesity, REE equations were not accurate for people with BMI $\geq$ 40.0 kg/m^2 (49). Marra *et al*. 2017 (50) found that error was greatest in individuals with BMI $\geq$40 kg/m^2 and bias was worse in females. A systematic review of equations for people with obesity noted that the Mifflin St.-Jeor equation is most likely to estimate REE within 10% of measured, although large individual variability still exists, and this is greater than variability in non-obese adults (10). Although limits of agreement in some specific equations were wider in patients with obesity in the present sample, this pattern was not reflected in aggregate bias calculations from body weight- or body composition-based equations. Therefore, overall accuracy does not differ according to body weight class in individuals with cancer, which might be explained by the relatively low number of individuals with BMI > 40

kg/m^2 compared to previous research. Notably, using body weight alone (21 kcal/kg body weight) significantly overestimated REE in patients with obesity, likely because this method assumes that height, FM, and FFM increases in a linear fashion to body weight. However, this is not the case in obesity where individuals frequently have a higher proportion of FM (which is less metabolically active than FFM) relative to height and the relationship between FM and REE is altered at high levels of adiposity (51). REE equations with body weight alone should therefore not be used in patients with obesity.

We found that most equations had similar bias and limits of agreement across tumor types; even when colon and rectal patients were grouped together, bias and limits of agreement were similar (data not shown). Furthermore, results were similar when patients were grouped according to broad treatment categories (i.e. neoadjuvant vs. adjuvant). While it is possible that previous and current anti-cancer therapies might impact REE, this type of analysis was not possible in this data due to the heterogeneity of treatment regimens. Bias and limits of agreement were also similar when comparing results between patients with stage IV versus stages I-III cancer. To our knowledge, no other study has assessed REE agreement according to cancer stage, although some reports indicated that patients with advanced (III/IV) cancer had higher REE than patients with earlier stages (I/II) (12). Patients with stage IV colorectal cancer often have increasing liver mass with disease progression (presumably from metastases) which is positively associated with REE (52). It was therefore anticipated that under-prediction would have been more prevalent in patients with stage IV disease; surprisingly, this was not the case. All equations - including aggregate calculations - had a proportion of individuals with predicted REE 10% greater or less than measured REE. Therefore, overall "hypermetabolism" compared to predictive equations is not uniformly apparent early in the disease trajectory in patients with more advanced disease. Notably, however, defining hypo- or hypermetabolism by comparing REE to equations that are not specific for cancer may elicit false conclusions about metabolism since such equations may have limited accuracy in healthy cohorts (36). The purpose of the present study was not to characterize the determinants of REE, but elucidation of such determinants and the feasibility of incorporating these into REE and energy needs assessment warrants further investigation (Chapters 5, 6, and 7).

One limitation of our study is that only REE was compared to predicted estimations. It is important to consider that REE is one part of TEE (albeit the largest component). REE might be altered in the tumor-bearing state, but little evidence is available on TEE. Current energy requirement guidelines for individuals with cancer (8) are based on body weight alone and do not consider factors such as body composition, inflammation, physical activity, or tumor location or stage, which may all impact energy needs. While REE might be different than expected, accuracy of TEE estimations in earlier stage patients is unknown and is an area we are actively pursuing (18). In order to meet our sample size calculation and increase the generalizability of our findings, data was aggregated from two studies, potentially introducing heterogeneity. Both studies included individuals recruited from the same cancer center and used the same indirect calorimeter. Differences in variables between studies was also assessed and accounted for in statistical analyses, where appropriate. Therefore, while data aggregation could have introduced error, this was minimized in all possible manners. Furthermore, there was a higher proportion of patients with lung cancer and stage IV disease that had completed DXA scans. This was not a reflection of patient health but rather of study design; as we assessed equation agreement among tumor types and stages, this discrepancy likely did not affect our conclusions. Additionally, total patient rest prior to collection of steady state CO_2 and O_2 data was less than 30 minutes and might have introduced error, although current recommendations (21) note that 20 minutes is sufficient for many adults. Furthermore, extreme perturbations in long-term macronutrient consumption – such as the ketogenic diet – could impact interpretation of REE results. However, 24-hour dietary recalls (not reported) suggest that no individual was following such a diet and likely did not influence the REE in this study.

In conclusion, REE cannot be accurately estimated for each individual and is influenced by age, FM, and cancer stage. Therefore, REE prediction equations for individual dietary recommendations should not be used in energy needs assessment in individuals with cancer. Since adequate energy intake is an integral part of successful cancer care, more accurate equations and/or tools to easily estimate energy needs should be developed.

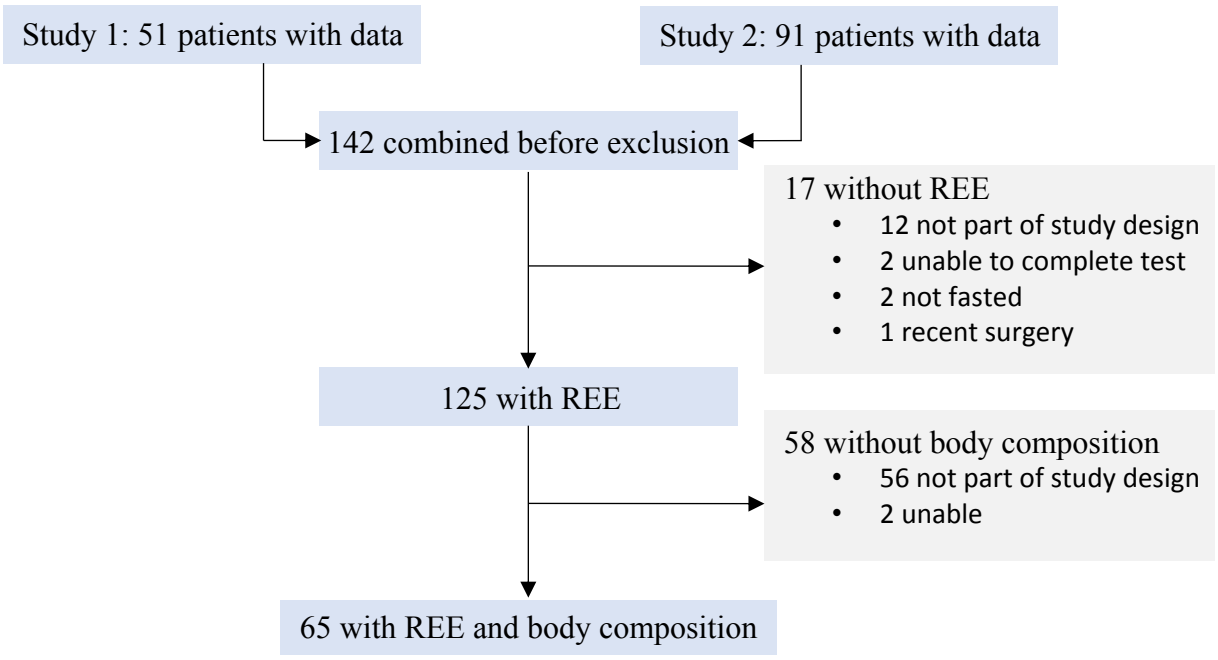


Figure 3.1. Flow diagram of inclusion and exclusion of patients. REE, resting energy expenditure

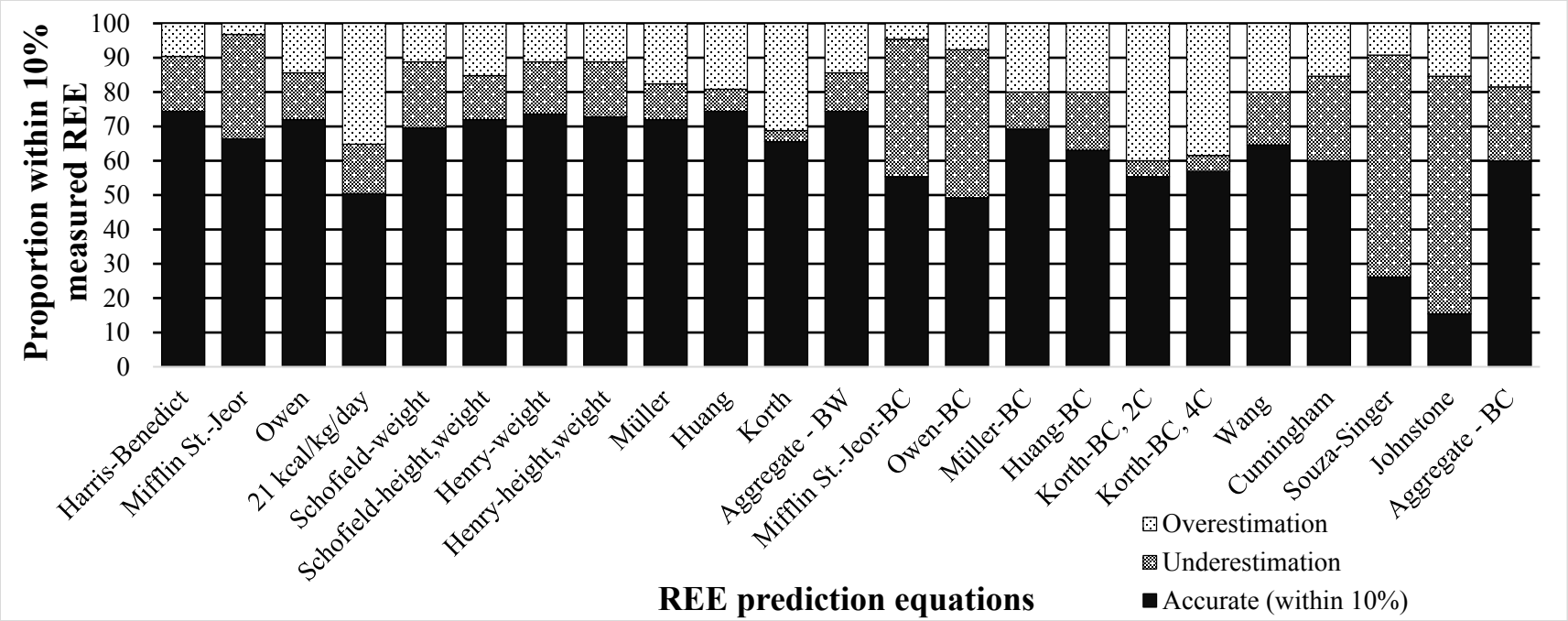


Figure 3.2 Proportion of predicted resting energy expenditure (REE) equations within 10% of measured REE. 2c: equation derived from two compartment body composition model; 4c: equation derived from four compartment body composition model; BC: body composition; BW: body weight. N=125 for body weight-based equations and n=65 for body composition-based equations.

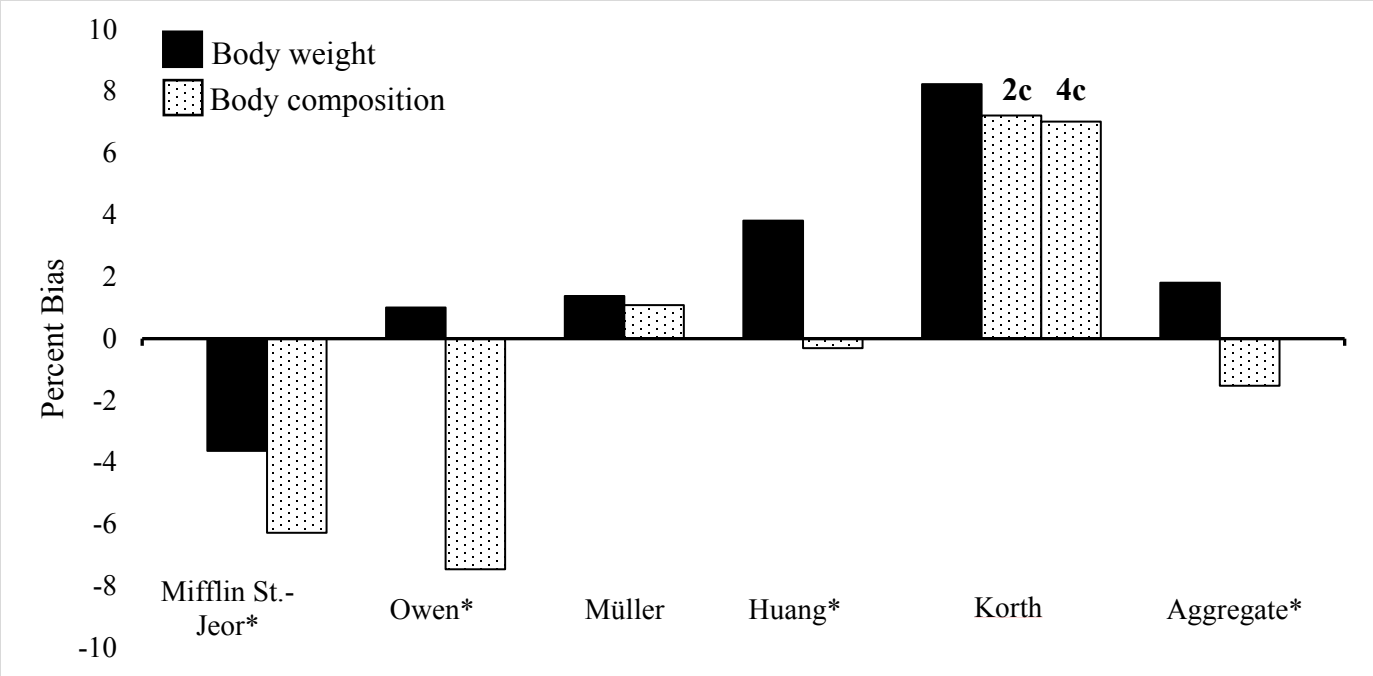
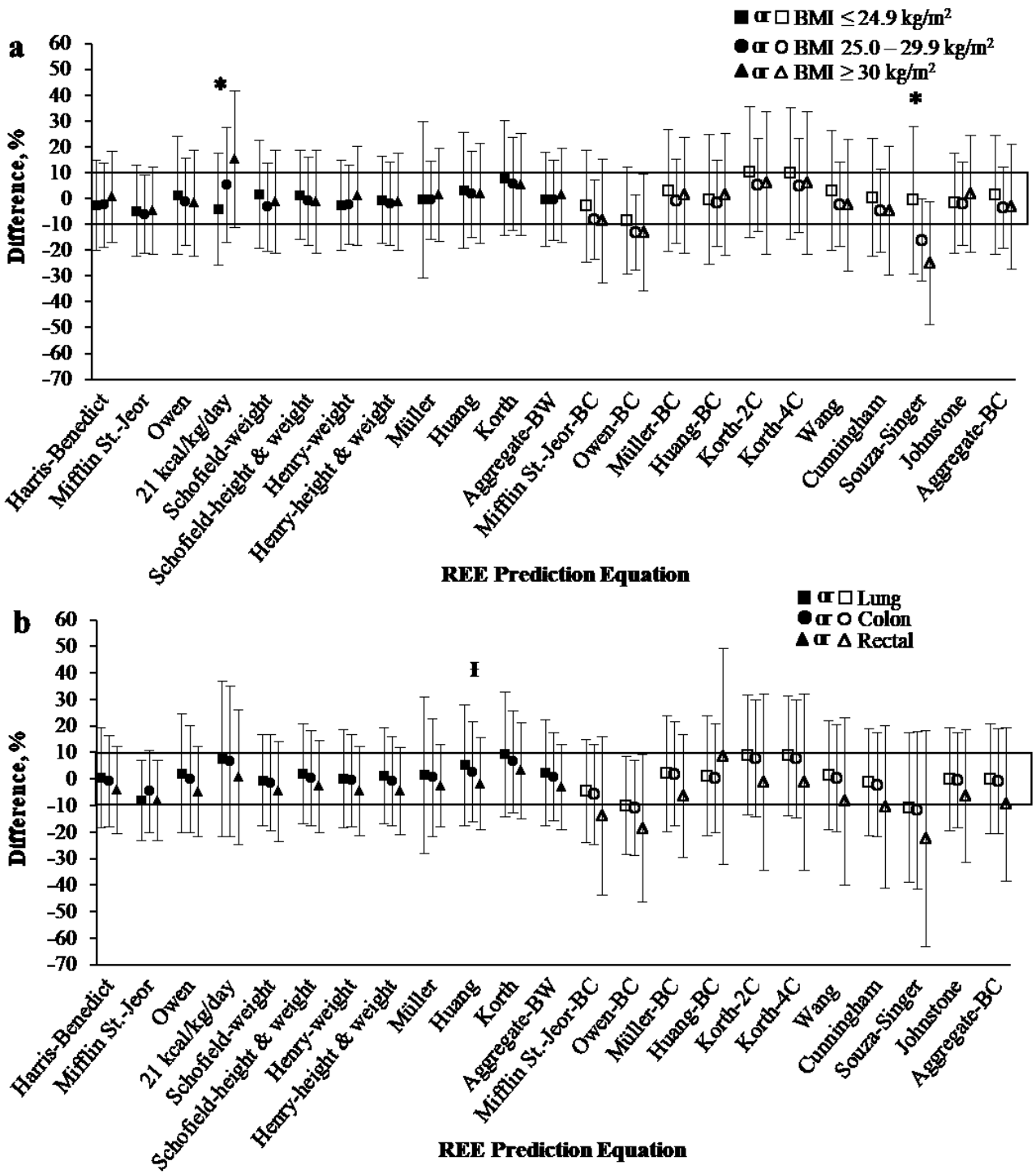
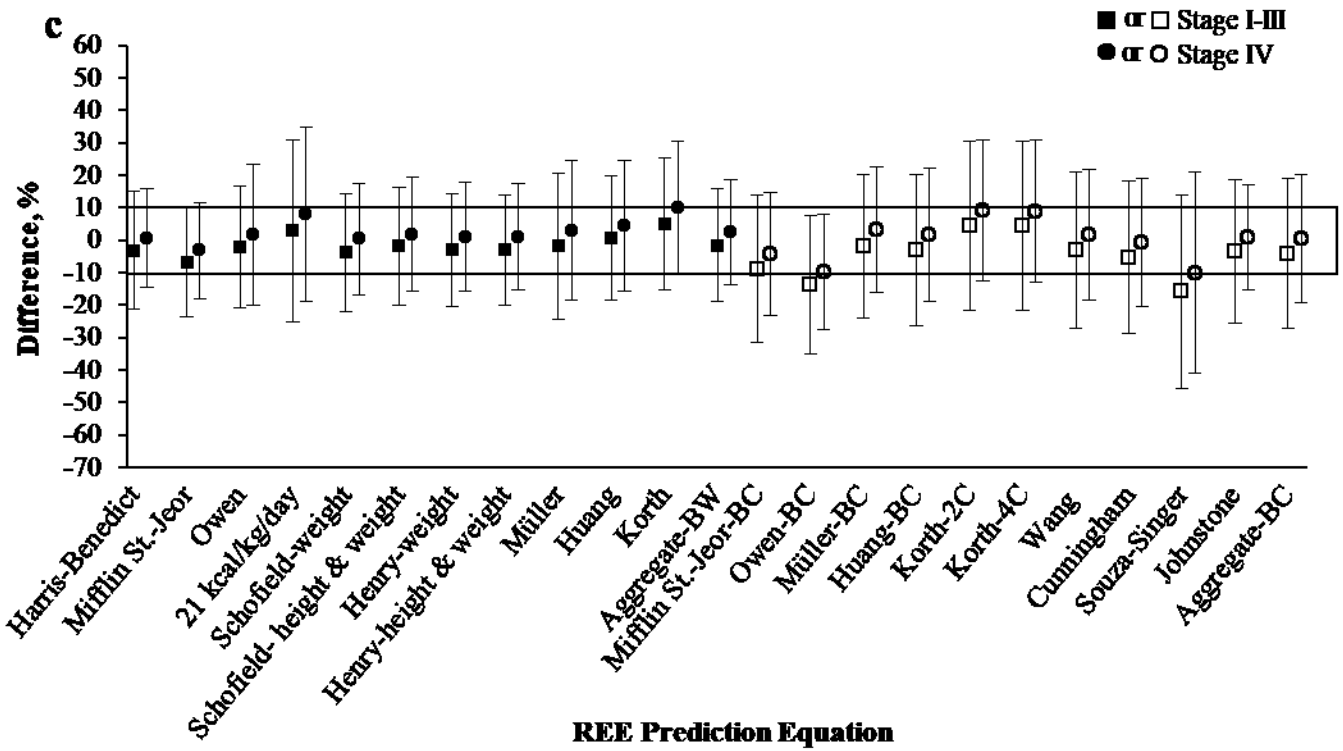


Figure 3.3 Percent bias of equations with body weight and anthropometrics alone versus body composition (n=65). 2c: two compartment body composition model; 4c: four compartment body composition model. *=bias ≤0.05, paired samples t-test, body composition equation versus body weight equation percent differences


a
■ or □ BMI ≤ 24.9 kg/m²
● or ○ BMI 25.0 – 29.9 kg/m²
▲ or △ BMI ≥ 30 kg/m²
Difference, %
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
*
*
Harris-Benedict
Mifflin St.-Jeor
Owen
21 kcal/kg/day
Schofield-weight
Schofield-height & weight
Henry-weight
Henry-height & weight
Müller
Huang
Korth
Aggregate-BW
Mifflin St.-Jeor-BC
Owen-BC
Müller-BC
Huang-BC
Korth-2C
Korth-4C
Wang
Cunningham
Souza-Singer
Johnstone
Aggregate-BC
REE Prediction Equation
b
■ or □ Lung
● or ○ Colon
▲ or △ Rectal
Difference, %
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
I
Harris-Benedict
Mifflin St.-Jeor
Owen
21 kcal/kg/day
Schofield-weight
Schofield-height & weight
Henry-weight
Henry-height & weight
Müller
Huang
Korth
Aggregate-BW
Mifflin St.-Jeor-BC
Owen-BC
Müller-BC
Huang-BC
Korth-2C
Korth-4C
Wang
Cunningham
Souza-Singer
Johnstone
Aggregate-BC
REE Prediction Equation



Figures 3.4 a-c Percent bias and limits of agreement for predicted resting energy expenditure (REE) in subgroups of patients. Each point represents the equation percentage bias (mean percentage difference between predicted and measured), and vertical lines are the percentage limits of agreement. Shapes with fill are from body weight equations and shapes without fill are from body composition-based equations. The box indicates error within 10% of measured REE. *bias significantly different than under/normal weight and overweight ǂbias significantly different than rectal. One-way analysis of variance assessed differences in bias among patients grouped by BMI and cancer type. Analysis of covariance assessed differences in bias between early and advanced stages, controlling for study, since study 1 consisted primarily of patients with stage IV disease and study 2 consisted primarily of patients with stages I-III disease. BMI: body mass index

Table 3.1 Equations used to predict resting energy expenditure

Equation	Formula
Equations without body composition	
Harris-Benedict	Men: 66.5 + (13.75 x weight) + (5.003 x height) – (6.755 x age) Women: 655 + (9.563 x weight) + (1.85 x height) – (4.676 x age)
Mifflin St.-Jeor	Men: (9.99 x weight) + (6.25 x height) – (4.92 x age) + 5 Women: (9.99 x weight) + (6.25 x height) – (4.92 x age) – 161
Owen	Men: 879 + (10.2 x weight) Women: 795 + (7.18 x weight)
21 kcal/kg/day	21 x weight
Schofield - weight only[a]	Men age 30-60: 0.048 x weight + 3.653 Men age > 60: 0.049 x weight + 2.459 Women age 30-60: 0.034 x weight + 3.538 Women age > 60: 0.038 x weight + 2.755
Schofield - height & weight[a,b]	Men age 30-60: 0.048 x weight – 0.011 x height + 3.670 Men age > 60: 0.038 x weight + 4.068 x height – 3.491 Women age 30-60: 0.034 x weight + 0.006 x height + 3.530 Women age >60: 0.033 x weight + 1.917 x height + 0.074
Henry weight only	Men age 30-60: 14.2 x weight + 593 Men age >60: 13.5 x weight + 514 Women age 30-60: 9.7 x weight + 694 Women age >60: 10.1 x weight + 569
Henry - height and weight[b]	Men age 30-60: 11.4 x weight + 541 x height – 137 Men age >60: 11.4 x weight + 541 x height – 256 Women age 30-60: 8.18 x weight + 502 x height -11.6 Women age >60: 8.52 x weight + 421 x height + 10.7
Müller[a]	BMI ≤18.5: 0.0219.77122 x weight – 0.02149 x age + 0.82 x sex + 0.731 BMI >18.5-25: 0.02219 x weight + 0.02118 x height + 0.884 x sex – 0.01191 x age + 1.233

	BMI >25-<30: 0.04507 x weight + 1.006 x sex – 0.01553 x age + 3.407 BMI ≥30: 0.05 x weight + 1.103 x sex – 0.01586 x age + 2.924
Huang	10.158 x weight + 3.933 x height– 1.44 x age +273.821 x sex + 60.655
Korth	41.5 x weight – 19.1 x age + 35.0 x height + 1107.4 x sex – 1731.2
Aggregate - body weight	Mean REE from all body weight-based equations above
Equations with body composition	
Mifflin St.-Jeor	19.7 x FFM + 413
Owen	Men: 22.3 x FFM + 290 Women: 19.7 x FFM + 334
Müller[a]	BMI ≤18.5: 0.08961 x FFM + 0.05662 x FM + 0.667 BMI >18.5-25: 0.0455 x FFM + 0.0278 x FM + 0.879 x sex – 0.01291 x age + 3.634 BMI >25-<30: 0.03776 x FFM + 0.03013 x FM + 0.93 x sex – 0.01196 x age + 3.928 BMI ≥30: 0.05685 x FFM + 0.04022 x FM + 0.808 x sex – 0.01402 x age + 2.818
Huang	14.118 × FFM + 9.367 × FM – 1.515 × age + 220.863 × sex + 521.995
Korth - 2 compartment[a]	105.1 x FFM + 1422
Korth - 4 compartment[a]	106.8 x FFM + 1322
Wang	21.5 x FFM + 407
Cunningham	21.6 x FFM + 370
Souza-Singer	1042.34 + (124.28 x sex) – (10.08 x weight) + (19.32 x FFM)
Johnstone[a]	90.2 x FFM + 31.6 x FM – 12.2 x age +1613
Aggregate - body composition	Mean REE from all body composition-based equations above

2 compartment=equation derived from body composition measurements from dual X-ray absorptiometry; 4 compartment=equation derived from body composition measurements from dual X-ray absorptiometry, air displacement plethysmography, and deuterium oxide dilution; BMI=body mass index; FFM=fat-free mass in kg; FM=fat mass in kg. Age is in years, sex is expressed as 0 for females and 1 for males, weight is in kg. [a]REE was calculated as MJ/day or kJ/day (per the original publication) and then converted to kcal/day [b]height expressed as meters. All other equations use centimeters for height.

Table 3.2 Overall characteristics of patients

	All patients (n=125)[a]	Males (n=82)[a]	Females (n=43)[a]	p
Age (yr)	61 ± 11 (30 – 84)	62 ± 10 (34 – 79)	59 ± 13 (30 – 84)	0.150
Body weight (kg)	81.3 ± 18.7 (39.7 – 142.4)	85.7 ± 17.1 (53.7 – 131.6)	72.8 ± 18.7 (39.7 – 142.4.6)	<0.001
Body mass index (kg/m^2)	27.5 ± 5.6 (17.0 – 51.1)	27.7 ± 4.9 (19.6 – 41.0)	27.2 ± 6.7 (17.0 – 51.1)	0.628
Fat mass, DXA (kg)	26.4 ± 10.1 (5.9 – 59.8)	26.4 ± 11.0 (9.0 – 59.8)	26.5 ± 8.8 (5.9 – 41.4)	0.961
Fat mass index (kg/m^2)	8.9 ± 3.4 (2.3 – 18.0)	8.3 ± 3.3 (2.8 – 18.0)	9.8 ± 3.3 (2.3 – 16.2)	0.085
Fat-free mass, DXA (kg)	53.2 ± 11.2 (33.9 – 73.3)	60.2 ± 7.7 (42.3 – 73.3)	41.9 ± 4.5 (33.9 – 51.9)	<0.001
Fat-free mass index (kg/m^2)	17.8 ± 2.6 (12.5 – 22.7)	19.2 ± 2.0 (15.0 – 22.7)	15.5 ± 1.7 (12.5 – 19.8)	<0.001
Resting energy expenditure, indirect calorimetry (kcal/day)	1629 ± 321 (1012 – 3158)	1755 ± 297 (1133 – 3158)	1389 ± 210 (1012 – 2130)	<0.001
Tumor type (n, %)				
Lung	28, 22.4	17, 20.7	11, 25.6	0.537
Rectal	24, 19.2	17, 20.7	7, 16.3	0.548
Colon	63, 50.4	39, 47.6	24, 55.8	0.381
Renal	7, 5.6	6, 7.3	1, 2.3	0.249
Pancreatic	3, 2.4	3, 3.7	0, 0	0.204
Stage (n,%)				
I	1, 0.8	1, 1.2	0, 0	0.467
II	16, 12.8	11, 13.4	5, 11.6	0.776
III	56, 44.8	38, 46.3	18, 41.9	0.632
IV	52, 41.6	32, 39.0	20, 46.5	0.420

DXA=dual X-ray absorptiometry. Values are presented as mean ± standard deviation (range) or number, percent where appropriate
[a]Body composition measures: n=65 total, n=40 males, n=25 females

Table 3.3 Characteristics of patients with and without body composition measurements

	With body composition (n=65)	Without body composition (n=60)[a]	p
Age (yr)	61 ± 10 (30 – 84)	61 ± 10 (34 – 79)	0.936
Body weight (kg)	79.6 ± 17.6 (45.9 – 131.1)	83.1 ± 19.8 (39.7 – 142.4)	0.294
Body mass index (kg/m^2)	26.7 ± 4.7 (17.0 – 39.5)	28.4 ± 6.3 (17.7 – 51.1)	0.091
Resting energy expenditure (kcal/day)	1584 ± 344 (1022 – 3158)	1679 ± 288 (1012 – 2420)	0.098
Sex (n, % male)	40, 61.5	42, 70.0	0.320
Tumor type (n, %)[a]			
Lung	22, 33.8	6, 12.0	0.007
Rectal	7, 10.8	17, 34.0	0.002
Colon	36, 55.4	27, 54.0	0.882
Stage (n, %)			
I-III	26, 40.0	46,76.7	<0.001
IV	39, 60.0	14, 23.3	<0.001

[a]n=50 for proportions of tumor types
All p≥0.05

Table 3.4 Predicted resting energy expenditure (REE), bias, limits of agreement, and maximum and minimum errors

	REE, mean ± SD	Bias ± SD, %	Proportional bias[b]		Limits of agreement, %	Absolute limits of agreement, %	Min. negative error	Max. positive error
Equations without body composition			r	p				
Measured REE	1629 ± 321							
Harris-Benedict	1593 ± 296*	-1.6 ± 8.8	-0.173	0.053	-18.9, 15.6	34.5	-24.5	24.1
Mifflin St.-Jeor	1534 ± 271*	-5.2 ± 8.4	-0.338	<0.001	-21.7, 11.3	33.0	-32.4	18.1
Owen[a]	1600 (1340, 1815)	-0.6 ± 10.3	-0.342	<0.001	-20.9, 19.7	40.6	-29.8	29.5
21 kcal/kg/day	1707 ± 392*	5.0 ± 14.2	0.316	<0.001	-22.9, 32.9	55.8	-29.1	41.4
Schofield, weight only	1582 ± 273*	-2.1 ± 9.2	-0.311	<0.001	-20.1, 16.0	36.2	-24.8	19.5
Schofield, height and weight	1609 ± 265	-0.3 ± 9.2	-0.360	<0.001	-18.4, 17.8	36.2	-24.8	18.7
Henry, weight only	1596 ± 295*	-1.5 ± 8.9	-0.175	0.052	-18.9, 16.0	34.9	-24.1	26.5
Henry, height and weight	1595 ± 273*	-1.3 ± 8.7	-0.321	<0.001	-18.5, 15.8	34.3	-25.8	23.1
Müller[a]	1622 (1413, 1824)	0.1 ± 11.5	-0.128	0.154	-22.4, 22.5	44.9	-29.2	28.9
Huang	1653 ± 289	2.2 ± 10.1	-0.199	0.026	-17.5, 22.0	39.5	-26.1	31.2
Korth	1723 ± 316*	6.4 ± 10.3	-0.028	0.756	-13.8, 26.5	40.3	-24.1	33.7
Aggregate	1620 ± 286	0.1 ± 8.8	-0.241	0.007	-17.1, 17.4	34.7	-26.6	26.8
Equations with body composition[c]								
Measured REE	1584 ± 344							
Mifflin St.-Jeor	1460 ± 220*	-6.3 ± 10.6	-0.590	<0.001	-27.1, 14.5	41.6	-43.1	16.7
Owen	1451 ± 274*	-7.4 ± 11.4	-0.442	<0.001	-29.7, 14.8	44.5	-45.6	9.0
Müller	1580 ± 258	1.1 ± 10.7	-0.484	<0.001	-19.9, 22.1	42.0	-27.8	27.3
Huang	1564 ± 292	-0.3 ± 11.2	-0.281	0.023	-22.3, 21.7	44.0	-29.0	27.5
Korth – 2 compartment	1675 ± 281*	7.2 ± 12.2	-0.309	0.012	-16.7, 31.1	47.8	-33.3	30.8
Korth – 4 compartment	1673 ± 286*	7.0 ± 12.2	-0.286	0.021	-16.9, 31.0	47.9	-33.2	30.9
Wang	1555 ± 242	-0.3 ± 11.3	-0.498	<0.001	-22.4, 21.9	44.3	-39.0	23.5
Cunningham	1518 ± 242*	-2.7 ± 11.0	-0.498	<0.001	-24.3, 18.9	43.2	-40.2	19.9
Souza-Singer[a]	1372 (1193, 1482)*	-12.6 ± 15.7	-0.648	<0.001	-43.3, 18.1	61.5	-61.9	28.9

Johnstone	1553 ± 285	-1.0 ± 9.8	-0.339	0.006	-20.2, 18.3	38.5	-28.7	23.4
Aggregate	1537 ± 247	-1.5 ± 11.0	-0.488	<0.001	-23.0, 20.0	43.0	-37.7	21.7

2 compartment=equation derived from body composition measurements from dual X-ray absorptiometry; 4 compartment=equation derived from body composition measurements from dual X-ray absorptiometry, air displacement plethysmography, and deuterium oxide dilution

[a]Wilcoxon signed-rank test, measured versus predicted REE, presented as median (interquartile range)

[b]Pearson correlation coefficient between the mean of measured and predicted REE and bias

[c]n=65

*p≤0.05, measured versus predicted REE, paired samples t-test

Table 3.5 Correlation of resting energy expenditure percent bias with age, body weight, fat mass (FM), and fat-free mass (FFM)

	Age, yr	Weight, kg	FM, kg	FFM, kg
Equations without body composition				
Harris-Benedict	-0.014	0.160	0.195	0.044
Mifflin St.-Jeor	0.096	0.065	-0.009	0.027
Owen	0.473*	-0.155	-0.173	0.041
21 kcal/kg/day	0.237*	0.534*	0.539*	0.199
Schofield, weight only	-0.069	-0.074	0.031	-0.059
Schofield, height and weight	0.063	-0.140	-0.061	-0.97
Henry, weight only	0.144	0.147	0.133	0.140
Henry, height and weight	0.179*	-0.006	-0.001	-0.028
Müller	0.232*	0.118	0.065	0.101
Huang	0.398*	0.003	-0.100	0.127
Korth	0.196*	0.037	-0.107	0.221
Aggregate	0.210*	0.093	0.061	0.089
Equations with body composition[a]				
Mifflin St.-Jeor	0.527*	-0.284*	-0.392*	-0.094
Owen	0.488*	-0.047	0.332*	0.227
Müller	0.455*	-0.161	-0.161	-0.082
Huang	0.487*	0.069	-0.055	0.156
Korth – 2 compartment	0.512*	-0.160	-0.343*	0.058
Korth – 4 compartment	0.508*	-0.138	-0.334*	0.084
Wang	0.524*	-0.252*	-0.380*	-0.054
Cunningham	0.521*	-0.224	-0.369*	0.020
Souza-Singer	0.401*	-0.705*	-0.788*	-0.397*
Johnstone	0.366*	0.105	0.054	0.121
Aggregate	0.506*	-0.212	-0.353*	-0.015

2 compartment=equation derived from body composition measurements from dual X-ray absorptiometry;
4 compartment=equation derived from body composition measurements from dual X-ray absorptiometry, air displacement plethysmography, and deuterium oxide dilution [a]n=65 *p<0.05

3.6 References

1. Food and Agricultural Organization, World Health Organization, and United Nations University. Human Energy Requirements. Report of a Joint FAO/WHO/UNU Expert Consultation Rome, Italy: 2001. [accessed September 2018]. Available at: http://www.fao.org/3/a-y5686e.pdf
2. Reeves MM, Capra S, Bauer J, Davies PS, Battistutta D. Clinical accuracy of the MedGem indirect calorimeter for measuring resting energy expenditure in cancer patients. Eur J Clin Nutr. 2005;59(4):603-10.
3. Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr. 2016;70(11):1230-8.
4. Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition. 2006;22(6):609-15.
5. Bauer J, Reeves MM, Capra S. The agreement between measured and predicted resting energy expenditure in patients with pancreatic cancer: a pilot study. JOP. 2004;5(1):32-40.
6. Johnson G, Salle A, Lorimier G, Laccourreye L, Enon B, Blin V, et al. Cancer cachexia: measured and predicted resting energy expenditures for nutritional needs evaluation. Nutrition. 2008;24(5):443-50.
7. Pirat A, Tucker AM, Taylor KA, Jinnah R, Finch CG, Canada TD, et al. Comparison of measured versus predicted energy requirements in critically ill cancer patients. Respir Care. 2009;54(4):487-94.
8. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2016;6(1):11-48.
9. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, 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(12):1539-47.
10. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. J Am Diet Assoc. 2005;105(5):775-89.

11. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35.
12. Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest. 2007;25(5):308-14.
13. Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr. 2010;29(1):72-7.
14. Adriaens MP, Schoffelen PF, Westerterp KR. Intra-individual variation of basal metabolic rate and the influence of daily habitual physical activity before testing. Br J Nutr. 2003;90(2):419-23.
15. Boothby WM, Berkson J, Dunn HL. Studies of the energy of metabolism of normal individuals: a standard for basal metabolism, with a nomogram for clinical application. Am J Physiol. 1936;116(2):468-84.
16. Prado CM, Lieffers JR, Bergsten G, Mourtzakis M, Baracos VE, Reiman T, et al. Dietary patterns of patients with advanced lung or colorectal cancer. Can J Diet Pract Res. 2012;73(4):e298-303.
17. Prado CMM, Mourtzakis M, Baracos V, Reiman T, Sawyer MB, McCargar LJ. Overweight and obese patients with solid tumors may have sarcopenia, poor prognosis and early features of cachexia. Int J Body Compos Res. 2010;8(1):7-15.
18. clinicaltrials.gov. Identifier: NCT03131921. Resting Energy Expenditure in Cancer - Associations With Body Composition, Dietary Intake, and Exercise Habits Bethesda, MD: National Library of Medicine; 2017 [updated May 3, 2017. Accessed February 2, 2018].
19. World Health Organization Consultation. Obesity: Preventing and managing the global epidemic: Report of a WHO consultation. WHO Technical Report Series: 894. Geneva, Switzerland 2000;894:1-253.
20. Morrison SA, Petri RM, Hunter HL, Raju D, Gower B. Comparison of the Lunar Prodigy and iDXA dual-energy x-ray absorptiometers for assessing total and regional body composition. J Clin Densitom. 2016;19(3):290-7.

21. Fullmer S, Benson-Davies S, Earthman CP, Frankenfield DC, Gradwell E, Lee PS, et al. Evidence analysis library review of best practices for performing indirect calorimetry in healthy and non-critically ill individuals. J Acad Nutr Diet. 2015;115(9):1417-46 e2.
22. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1-2):1-9.
23. Harris JA, Benedict FG. A biometric study of human basal metabolism. Proc Natl Acad Sci U S A. 1918;4(12):370-3.
24. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241-7.
25. Owen OE, Holup JL, D'Alessio DA, Craig ES, Polansky M, Smalley KJ, et al. A reappraisal of the caloric requirements of men. Am J Clin Nutr. 1987;46(6):875-85.
26. Owen OE, Kavle E, Owen RS, Polansky M, Caprio S, Mozzoli MA, et al. A reappraisal of caloric requirements in healthy women. Am J Clin Nutr. 1986;44(1):1-19.
27. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39 Suppl 1:5-41.
28. Henry CJ. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr. 2005;8(7A):1133-52.
29. Müller MJ, Bosy-Westphal A, Klaus S, Kreymann G, Lührmann PM, Neuhäuser-Berthold M, et al. World Health Organization equations have shortcomings for predicting resting energy expenditure in persons from a modern, affluent population: generation of a new reference standard from a retrospective analysis of a German database of resting energy expenditure. Am J Clin Nutr. 2004;80(5):1379-90.
30. Huang KC, Kormas N, Steinbeck K, Loughnan G, Caterson ID. Resting metabolic rate in severely obese diabetic and nondiabetic subjects. Obes Res. 2004;12(5):840-5.
31. Korth O, Bosy-Westphal A, Zschoche P, Gluer CC, Heller M, Muller MJ. Influence of methods used in body composition analysis on the prediction of resting energy expenditure. Eur J Clin Nutr. 2007;61(5):582-9.

32. Wang Z, Heshka S, Gallagher D, Boozer CN, Kotler DP, Heymsfield SB. Resting energy expenditure-fat-free mass relationship: new insights provided by body composition modeling. Am J Physiol Endocrinol Metab. 2000;279(3):E539-45.
33. Cunningham JJ. Body composition as a determinant of energy expenditure: a synthetic review and a proposed general prediction equation. Am J Clin Nutr. 1991;54(6):963-9.
34. Souza MTP, Singer P, Ozorio GA, Rosa VM, Alves MMF, Mendoza López RV, et al. Resting energy expenditure and body composition in patients with head and neck cancer: an observational study leading to a new predictive equation. Nutrition. 2018;51-52:60-5.
35. Johnstone AM, Rance KA, Murison SD, Duncan JS, Speakman JR. Additional anthropometric measures may improve the predictability of basal metabolic rate in adult subjects. Eur J Clin Nutr. 2006;60(12):1437-44.
36. Frankenfield DC. Bias and accuracy of resting metabolic rate equations in non-obese and obese adults. Clin Nutr. 2013;32(6):976-82.
37. Siervo M, Bertoli S, Battezzati A, Wells JC, Lara J, Ferraris C, et al. Accuracy of predictive equations for the measurement of resting energy expenditure in older subjects. Clin Nutr. 2014;33(4):613-9.
38. Wells JC, Williams JE, Haroun D, Fewtrell MS, Colantuoni A, Siervo M. Aggregate predictions improve accuracy when calculating metabolic variables used to guide treatment. Am J Clin Nutr. 2009;89(2):491-9.
39. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.
40. Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. JPEN J Parenter Enteral Nutr. 2015;39(7):787-822.
41. Boothby WM, Sandiford RB. Nomographic charts for the calculation of the metabolic rate by the gasometer method. Boston Med Surg J. 1921;185(12):337-54.
42. Ræder H, Kværner AS, Henriksen C, Florholmen G, Henriksen HB, Bøhn SK, et al. Validity of bioelectrical impedance analysis in estimation of fat-free mass in colorectal cancer patients. Clin Nutr. 2018;37(1):292-300.

43. Itoi A, Yamada Y, Yokoyama K, Adachi T, Kimura M. Validity of predictive equations for resting metabolic rate in healthy older adults. Clin Nutr ESPEN. 2017;22:64-70.
44. Manini TM. Energy expenditure and aging. Ageing Res Rev. 2010;9(1):1-26.
45. Prado CM, Siervo M, Mire E, Heymsfield SB, Stephan BC, Broyles S, et al. A population-based approach to define body-composition phenotypes. Am J Clin Nutr. 2014;99(6):1369-77.
46. Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN, editors. Energy Metabolism: Tissue Determinants and Cellular Coeollaries. New York: Raven Press; 1992. p. 61-80.
47. Javed F, He Q, Davidson LE, Thornton JC, Albu J, Boxt L, et al. Brain and high metabolic rate organ mass: contributions to resting energy expenditure beyond fat-free mass. Am J Clin Nutr. 2010;91(4):907-12.
48. Achamrah N, Jesus P, Grigioni S, Rimbert A, Petit A, Dechelotte P, et al. Validity of predictive equations for resting energy expenditure developed for obese patients: impact of body composition method. Nutrients. 2018;10(1).
49. Jesus P, Achamrah N, Grigioni S, Charles J, Rimbert A, Folope V, et al. Validity of predictive equations for resting energy expenditure according to the body mass index in a population of 1726 patients followed in a nutrition unit. Clin Nutr. 2015;34(3):529-35.
50. Marra M, Cioffi I, Sammarco R, Montagnese C, Naccarato M, Amato V, et al. Prediction and evaluation of resting energy expenditure in a large group of obese outpatients. Int J Obes (Lond). 2017;41(5):697-705.
51. Bosy-Westphal A, Müller MJ, Boschmann M, Klaus S, Kreymann G, Lührmann PM, et al. Grade of adiposity affects the impact of fat mass on resting energy expenditure in women. Br J Nutr. 2008;101(4):474-7.
52. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr. 2009;89(4):1173-9.

Chapter 4 Accuracy of a Portable Indirect Calorimeter for Measuring Resting Energy Expenditure in Individuals with Cancer

4.1 Preface

This chapter aimed to validate a novel and potentially useful tool – the FitMate GS – for measuring resting energy expenditure. Individuals with solid tumors and mixed cancer types were included to represent clinical settings where the FitMate GS might be used. A version chapter has been published: Sarah A. Purcell, Dr. Sarah A. Elliott, Dr. Aoife M. Ryan, Dr. Michael B. Sawyer, and Dr. Carla M. Prado. Accuracy of a portable indirect calorimeter for measuring resting energy expenditure in individuals with cancer. Journal of Parenteral and Enteral Nutrition 2019; 43(1):145-151. E-Published June 5, 2018

I contributed to study design formation and was responsible for data collection, data analysis, and interpretation and writing the initial chapter/manuscript. I also applied for and maintained ethical approval for this study (~90% total proportion of contribution to research and writing). Dr. Sarah A. Elliott, Dr. Aiofe M. Ryan, and Dr. Carla M. Prado contributed to formulating the research question and data analysis and interpretation; Dr. Michael B. Sawyer contributed to data interpretation. All collaborators revised the manuscript for intellectual content.

4.2 Abstract

Determining optimal caloric intake for an individual with cancer is complicated by metabolic changes that occur, namely alterations in resting energy expenditure (REE). There is currently no validated clinically available equation or tool to measure energy expenditure in these patients. In this study, patients with newly diagnosed solid tumors underwent REE assessments using the FitMate GS™ portable indirect calorimeter and reference VMax™ metabolic cart; both used canopy hoods. REE was also estimated from the Harris-Benedict, Mifflin St. Jeor, and Henry equations for comparison. Data were analyzed using paired samples t-test and the Bland-Altman approach to assess group- and individual-level agreement compared to the metabolic cart. Twenty-six patients (19 males; body mass index: 27.8 ± 5.5; age: 62 ± 10 years) participated in the study. Biases for the FitMate GS and both equations were low (ranging from -44 to -92 kcal or -2.3% to -5.1%), indicating good group-level accuracy. Although the FitMate GS had small bias, REE from this machine had the widest limits of agreement (-28.0 to 21.2%) compared to the three equations (Harris-Benedict: -15.8 to 11.2%; Mifflin St. Jeor: -17.1 to 6.9%; Henry: 15.4 to 11.5%). These differences were not due to volume of oxygen, BMI category, or sex. The FitMate GS performed well on a group level, but its accuracy was poor on an individual level. Further research should develop better equations and validate tools to measure energy expenditure for accurate dietary recommendations for patients at nutritional risk.

4.3 Introduction

Energy needs are based on total energy expenditure, the largest component being REE. REE is often measured using indirect calorimetry (usually in research settings) or calculated using a variety of prediction equations (clinical settings) with or without activity and/or injury factors to determine total energy needs.

Individuals with cancer are particularly prone to experience changes in REE. Factors substantially altering REE in cancer include changes in body composition (especially decreased lean mass, the main determinant of REE), increased systemic inflammation, tumor energetic demand, and possible brown adipose tissue activation (1). In fact, many studies report up to 48% of patients have a measured REE >10% of predicted (suggesting hypermetabolism) and up to a third present with a REE <10% of their predicted needs (suggesting hypometabolism) (2, 3). Consequently, estimating energy needs in oncology patients is challenging and predictive

equations developed in healthy populations are unlikely to accurately depict REE for an individual with cancer (4); thus, these equations have limited use in clinical settings.

Accurate estimates of energy needs are also essential to avoid weight loss in patients who are at risk for becoming malnourished, which is prevalent in individuals with cancer and associated with negative prognosis such as functional impairment, poorer quality of life, and shorter survival regardless of body weight (5, 6). At the other end of the spectrum, overweight or obese patients' energy recommendations should not be overestimated, as to avoid increases in fat mass and worsening comorbidities (7, 8).

Given the importance and variability of REE in these patients, and the lack of targeted predictive equations, quick, accessible, and low-burden tools that assess REE should be explored to obtain a more accurate prediction of total energy expenditure. Portable indirect calorimeters are a potential solution to this issue. Such a tool would need to be more accurate at measuring REE than current prediction equations to justify its use for individuals at nutritional risk. Some instruments such as the MedGem™ (MicroLife Home Medical Solutions, Golden, CO, USA) have been extensively studied in various populations, with reports of overestimation, underestimation, or relative accuracy (9). In patients with solid tumors, the MedGem with mouthpiece and noseclip was found to have poor accuracy (10). However, few studies have assessed the accuracy of portable indirect calorimeters other than the MedGem or those with a canopy hood instead of a facemask (9). Some publications also only assess group-level agreement tested using paired samples t-test or correlation and do not elaborate on how well these machines perform for each individual (11-14). Furthermore, little is known about the performance of such devices in the cancer population. A portable indirect calorimetry model, the FitMate GS™ has recently become commercially available (COSMED, Chicago, IL USA), **Figure 4.1**. This machine differs from units such as the MedGem in that it uses a canopy hood rather than facemask, thereby reducing error associated with patient discomfort and also measures oxygen with a different kind of sensor (galvanic fuel cell in the FitMate GS versus fluorescent-quenching sensor in the MedGem). Although this system accurately measures REE in healthy individuals (14), it does so using only O_2 measurements without assessing CO_2; the accuracy may therefore be impacted in conditions associated with altered CO_2 and O_2, such as cancer. As such, the objective of the present study was to assess the accuracy of the FitMate GS

in a sample of individuals with solid tumors. It was hypothesized that average measured REE between the FitMate GS and metabolic cart would not differ, but limits of agreement of REE from the FitMate GS will be wider than common REE prediction equations (in line with a previous validation of a different portable indirect calorimeter in individuals with cancer [10]).

4.4 Methods

4.4.1 Participants

Patients with all stages of newly diagnosed colorectal, pancreatic, non-small cell lung, or kidney cancer were recruited from April to December 2016 from a cancer center serving northern Alberta (Cross Cancer Institute in Edmonton, Alberta, Canada). This study was approved by the Health Research Ethics Board of Alberta and informed consent was obtained from all participants prior to data collection. Inclusion criteria were: recent cancer diagnosis; aged 18-90 years; able to communicate freely in English. Excluded patients were those who had undergone anti-cancer therapy or surgery within the past four weeks, had severe mobility issues, used medications that might affect body composition or metabolism (corticosteroids, hormone replacement, thyroid medication), were unable to breathe under the calorimetry hood for 20-30 minutes, or women who were pregnant or breastfeeding.

4.4.2 Measurement Protocols

Height and weight were measured using a Health-O-Meter Professional digital scale with height rod (McCook, IL, USA; model number: 597KL) without shoes or heavy clothing. Body mass index (BMI) was calculated [weight (kg)/ height (m^2)] and classified according to the World Health Organization's cut-points (15).

REE measurements (both techniques) were conducted consecutively on the same morning at the Human Nutrition Research Unit at the University of Alberta. Patients were asked to avoid food, smoking, caffeine, and physical activity overnight and the morning of testing. Patients rested in a supine position for approximately 10 minutes before any testing began, which is a sufficient time to ensure activities of daily living had no influence on REE measurements (16).

In order to quantify if the FitMate GS was a more suitable method than current standards for determining energy needs, three commonly used equations were used to estimate REE: Harris-Benedict (17), Mifflin St. Jeor (18), and Henry (19). The agreement between the FitMate

GS and metabolic cart was compared to the agreement between these equations and the metabolic cart. After anthropometric tests, the FitMate GS test was conducted followed by the metabolic cart.

4.4.3 FitMate GS

The FitMate GS is a portable indirect calorimeter with a ventilated hood. It contains an analyser that assesses the concentration of oxygen, assumes a respiratory quotient (RQ) of 0.85 (default setting), and uses the abbreviated Weir equation (20) to calculate REE. Before each measurement, the FitMate self-calibrated (up to 5 minutes), after which the test started automatically. The flow meter was manually calibrated on a regular interval (~once/week). Patients laid in a supine position and stayed under the hood for 20 minutes and were asked to breath normally.

4.4.4 Metabolic Cart

The metabolic cart with ventilated hood system (VMax^{TM} 29N; Sensor-Medics, Yorba Linda, CA, USA) was used as our reference method and this test commenced directly after the FitMate GS test. This system was chosen as a criterion as it is one of the most accurate metabolic carts (21) and has been used as a gold standard in other studies previously (10, 22). Volume and air flow were manually calibrated before each measurement using a three liter syringe. Although burn tests were not performed on this machine, gas analysers were automatically calibrated prior to each test using known standard gas concentration (20.95% O_2, 0.03% CO_2). The fraction of expired carbon dioxide was kept in between 0.75 and 0.80 for as much time as possible. Breath samples were collected for 30 minutes and only steady state data was used to calculate REE. Steady state was defined as the variations in VO_2 and CO_2 of $\leq$ 10% over the previous five consecutive minutes. No steady state data was selected in the first ten minutes of the measurement period to ensure that each individual had a minimum of 20 minutes of complete rest, according to current guidelines (23). A minimum of 10 minutes of steady state data was collected. The abbreviated Weir equation was used to calculate REE (20). Respiratory quotient was calculated as the ratio between carbon dioxide produced and oxygen consumed (CO_2/O_2).

4.4.5 Statistical Analysis

A sample size of 19 was needed to detect differences between groups based on a two-tailed paired samples t-test with a power of 0.95, error of 0.05, and effect size of 0.89 (calculated

from our unpublished data of FitMate GS validation in healthy individuals). Data were analyzed using SPSS version 24 (IBM Corp., Armonk, NY, USA) and presented as mean ± standard deviation or percentages where appropriate.

Paired samples t-tests and Pearson correlation coefficients were utilized to describe group-level agreement between REE results collected from both indirect calorimeters and prediction equations as well as to assess differences in VO_2 and RQ. Agreement between predicted and measured REE was also assessed using the Bland-Altman approach (24). Bias is indicative of group-level agreement between two assessments and was calculated as the average difference between the mean predicted and measured REE. Limits of agreement provide insight into how well two measures agree on an individual level; numbers that are closer together indicate that two measurements agree better for each individual. These values were calculated as bias ± 1.96 standard deviations. In order to conceptualize bias and limits of agreement, these numbers were expressed as a percentage of REE measured by the metabolic cart. An acceptable difference in agreement was set at 5% between REE from the metabolic cart versus REE from the FitMate GS and prediction equations, based on inter-individual variations of 2 - 5% (25, 26). Pearson correlation coefficient between the mean of measured and predicted REE and bias were used to determine if there were any trends in the magnitude of bias with increasing REE measurement (proportional bias). The results were displayed in Bland-Altman plots to visually describe agreement on an individual level.

As an exploratory analysis, we sought to assess the validity of using a different RQ setting for the FitMate GS. VO_2 collected from the FitMate GS was multiplied by each individual's RQ obtained from the metabolic cart to obtain calculated VCO_2. This estimated VCO_2 was then used to calculate an alternative REE using the abbreviated Weir equation, below.
REE (kcal) = (3.9 x VO_2 [liters] + 1.1 x CO_2 [liters]) x 1440 minutes/day

4.5 Results

A total of 26 patients (19 males; BMI: 27.8 ± 5.5 kg/m^2; age: 62 ± 10 years) participated in the study; all females except one were post-menopausal. The majority of patients presented with colorectal or non-small cell lung cancers, **Table 4.1**. One patient had stage 1 disease (4%), 6 had stage 2 (23%), 11 had stage 3 (42%), and 8 had stage 4 (31%). According to BMI

classification, ten patients (38%) were normal weight, eight (31%) were overweight, and eight (31%) had obesity.

Respiratory quotient from the metabolic cart was 0.80 ± 0.05 (range: 0.69 to 0.92) which was significantly different than the constant FitMate GS RQ of 0.85 (t=-6.09, p<0.001). VO_2 from the metabolic cart was correlated to than that collected by the FitMate GS (r=0.796, =<0.001), and these values did not differ on average (0.239 ± 0.042 vs. 0.230 ± 0.052 L/min, p=0.161).

All measurements and predictions of REE were significantly correlated (r=0.68 to 0.98, all p<0.001). Mean measured and predicted REE, bias, proportional bias, and limits of agreement are presented in **Table 4.2**. In the group-level agreement analysis via paired samples t-test, no differences were observed between the metabolic cart (as a reference method) compared to the FitMate GS, Harris-Benedict equation, or Henry equation. However, REE calculated using the Mifflin St. Jeor equation was lower than the metabolic cart measurement (1560 ± 233 vs. 1652 ± 280 kcal respectively, p<0.001), and proportional bias using this equation was present (r=-0.430, p=0.028). When using each individual's RQ to calculate FitMate GS VCO_2, no improvement in accuracy was observed. REE using this method (1601 ± 360 kcal) was not significantly different than the metabolic cart (p=0.224); bias was -3.4% (-52 kcal) and limits of agreement were -27.8 to 21.1% (-465 to 362 kcal).

Eight (31%) REE FitMate GS measurements fell within clinically acceptable limits (±5% measured REE). Although REE from the FitMate GS was accurate on a group level (bias: -3.4%, -52 kcal), this method produced the widest limits of agreement (-28.0 to 21.2%, -467 to 363 kcal)(**Table 4.2**). When assessing individual data, the FitMate GS measured REE from 18.7% (294 kcal) below to 34.0% (592 kcal) above REE measured by the metabolic cart.

Bland-Altman plots were used to visually examine the spread of bias and limits of agreement using each REE method (**Figures 4.2a-d**). REE from FitMate GS had a fanning effect wherein lower REE values had a narrower spread of biases and positive proportional bias was present. Because of this data pattern, we also explored stratifying patients by BMI status (normal weight [BMI 18.5 – 24.9 kg/m^2] and overweight/obese [BMI ≥ 25.0 kg/m^2]). Bias and limits of agreement for each method were similar as that produced from the entire sample (data not shown). One subject had a bias from the FitMate GS that was a positive outlier. However, when

this subject was excluded, overall bias was farther from zero (-4.9%, -78 kcal) and limits of agreement were still wide (-24.8 to 15.0%, -410 to 255 kcal).

When the sample was divided by sex, bias and limits of agreement for the FitMate GS REE were similar to those reported in the entire sample (males: bias = 2.3%, limits of agreement = -28.3 to 23.7%; females: bias = -6.4%, limits of agreement = -27.2 to 14.4%). We also excluded the female who was pre-menopausal and had similar patterns of results for all analyses.

4.6 Discussion and Conclusions

To our knowledge, our study is the first to assess the accuracy of a portable indirect calorimeter with a hood system in individuals with cancer. In this cohort of patients with solid tumors, FitMate GS was accurate on a group level compared to REE from a metabolic cart. However, limits of agreement were wider on an individual level, and a higher proportion of individuals had REE outside of clinical accuracy (>5% difference) compared to traditional prediction equations.

The FitMate GS had a low bias, similar to bias from traditional equations, indicating its accuracy on a group level. Nevertheless, limits of agreement were wide even when the same RQ collected from the metabolic cart was used to predict REE, indicating poor agreement between the FitMate GS and the metabolic cart. The accuracy of a different FitMate device (which uses a mouthpiece and nose clip without canopy hood) has been previously explored in 60 healthy males and females (age 19-65, BMI 19.2-44.8 kg/m^2) compared with REE using a Douglas bag (14). There were no differences between these tests on a group level (dependant samples t-test and bias [-6 kcal]) and the limits of agreement were much smaller than the data reported within our study (-164, 152 kcal/day). REE differences compared to the present study could be due to study cohorts, as healthy adults are not affected by metabolic derangements that cause highly variable REE in cancer (1).

In the clinical setting, Lupinsky *et al.* (13) assessed the accuracy of the FitMate with facemask (14) compared to a metabolic cart and predictive equations in four groups of patients: 1) receiving home parenteral care; 2) diabetic and overweight; 3) hospitalized and receiving artificial nutrition; 4) heart disease (13). The FitMate performed well on a group level (bias -34 kcal), yet the limits of agreement were wide: -403 to 335 (absolute range of 738 kcal). Although the authors concluded this to be an acceptable range, energy recommendations of approximately

400 under- or 300 kcal over-prediction would be expected to contribute to weight loss or gain over time.

Numerous other studies, mostly in healthy cohorts and populations other than cancer, have attempted to validate various portable indirect calorimeters, with mixed results, as reviewed by Hipskind *et al.* (9). The MedGem is the most commonly studied portable indirect calorimeter. Reeves *et al*. (10) investigated the accuracy of the MedGem against a metabolic cart (VMax 229) in a sample of patients with cancer (n=18, mixed tumor types) and healthy individuals (n=17). Compared to the criterion method (metabolic cart), limits of agreement for the MedGem and Harris-Benedict equation were wide, indicating low accuracy. The authors speculated that differences in the collection system could have led to these findings as the MedGem mouthpiece was smaller than the metabolic cart mouthpiece, and larger mouthpieces might increase ventilation. The FitMate GS used in the present study, however, collected oxygen via a hood, almost identical to the metabolic cart. Therefore, wide biases observed in our study are unlikely to be explained by differences in the collection mechanism alone.

Metabolic alterations that occur in a tumor bearing state are sometimes reflected in fat and carbohydrate oxidation rates. More specifically, various studies have reported lower RQs in oncology patients than that of healthy controls (27-31), which is indicative of higher fat oxidation. Although speculative, higher fat oxidation could therefore be a result of abnormal fat metabolism including increased lipolysis, leading to elevated plasma free fatty acids and glycerol that are associated with negative energy balance that often occurs in cancer (32). The average RQ of patients included in the present study was 0.80, which was significantly lower than the assumed value of 0.85 from the FitMate GS ($p<0.001$). Since RQ is an expression of VO_2 and VCO_2, both used in Weir equation for REE from the metabolic cart, we speculated this could be a source of mismatch between FitMate GS versus metabolic cart measurements. As such, we used each individual's measured FitMate GS VO_2 with their measured RQ from the metabolic cart to calculate VCO_2, consecutively using these values in the abbreviated Weir equation to produce a theoretical REE. However, bias and limits of agreement were similar between the measured and calculated FitMate GS measurements, which indicate that the set RQ of 0.85 was not a significant source of error in our study. Furthermore, results were similar when patients

with pancreatic cancer whose REE might be elevated (33) were excluded from our analysis (data not shown).

The FitMate GS software gives an option to stop testing when the system deems there is sufficient data or allow the test to continue, 5 minutes of which are a calibration and are discarded. The present study limited data collection to 20 minutes, although the user has the option to collect additional data points. The FitMate GS in this protocol collected data based on a single time interval, while steady state was selected according to indication of such on the metabolic cart. Not achieving steady state can introduce inaccuracies in REE calculations (34). Steady state measures are more accurate, precise, and less biased compared to any time interval (e.g. 6-10 minutes, 6-15 minutes) collected from indirect calorimetry in healthy adults (35). It is therefore possible that the method of assuming all data is a steady state introduces inaccuracies for each individual. Although we did not alternate the order of the REE tests, each participant had adequate time to lay supine and relax before the FitMate GS test commenced. Each participant rested for 10-15 minutes before testing and no steady state data was collected in the first 10 minutes. This means that each individual had at least 20 minutes of rest before data collection began, as recommended by the Academy of Nutrition and Dietetics (23).

Our data showed a fanning effect wherein higher mean REE from the FitMate GS and metabolic cart had slightly wider biases (positive proportional bias). Since body size is the main determinant of REE, our findings indicate that individuals with obesity are more likely to have a higher mean REE with consequently larger bias. However, our results did not change when we assessed bias and limits of agreement across different BMI categories or by sex. This indicates the Fitmate GS is not exceptionally better or worse at measuring REE among sub-groups of patients, although this conclusion should be interpreted with caution due to our limited sample size (n=10 normal weight, n=16 overweight/obese and n=19 males, n=7 females).

The Harris-Benedict, Mifflin St. Jeor, and Henry equations were included only for comparative purposes in this study, noting we are aware of a large body of literature investigating which predictive equations are most suitable for a given population. Another investigation in 18 cancer patients with various types of tumors (lung, gastrointestinal, and "other", which included bladder, cervical, and testicular cancer) found that most equations predicted REE within 10% of measured REE for approximately 50% of individuals (4). While

the Mifflin St. Jeor equation in this study did not have proportional bias, other equations had a negative proportional bias, similar to the data hereby presented. Of note, the standard deviation for measured REE for our data was larger than that captured by Reeves *et al.* (4) (280 versus 90 kcal). Thus, the proportional bias observed in our data could be a result of a diverse patient selection (i.e. both studies recruited individuals with numerous types of cancer types) and larger sample size in our data. These results and the data presented here indicate that prediction equations were not accurate for many individuals with cancer; and the use of the FitMate GS did not improve REE prediction compared to equations.

Our study collected sufficient data to assess the accuracy of the FitMate GS in a single group of patients. However, separating our data by BMI class, tumor type, or another characteristic was not possible. Larger sample sizes might show sub-groups of patients in which the FitMate GS performs better. Metabolic carts are used in nearly all validation studies due to its high availability and lower cost (compared to whole-body calorimetry), patient burden, and technical skill (36). However, validation against other tools such as whole body calorimetry units would be ideal to validate the use of Fitmate GS in oncology patients, either revealing more or less individual accuracy. These data were also not compared to our own data of FitMate GS accuracy from healthy individuals, although the individual error is higher than that reported in a separate sample of healthy adults (14). Of note, one individual had RQ < 0.70, which could indicate ketosis or metabolic cart error, which was not confirmed by 24-hour dietary recalls or calibration procedures. All calibration procedures and test protocols were completed to minimize such error. In addition, simultaneous measurement of O_2 from each machine using the same ventilated hood and three-way valve would eliminate the effect of order of testing in future studies. Our findings nonetheless showed that while the FitMate GS was accurate on a group level, individual level agreement was poor and inferior to three predictive equations when compared to a metabolic cart in a sample of patients with solid tumours.

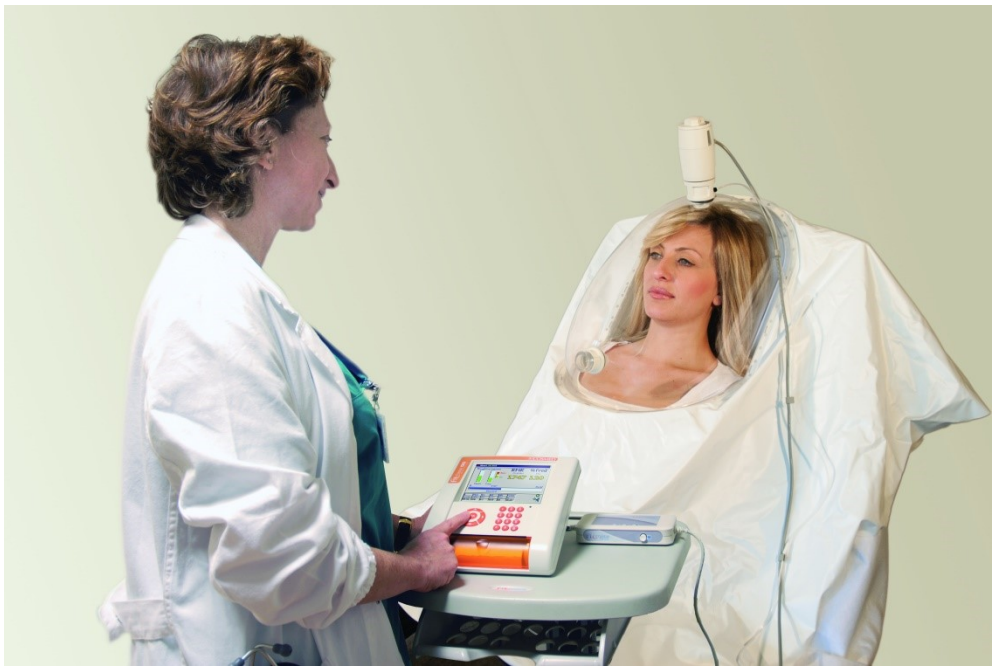
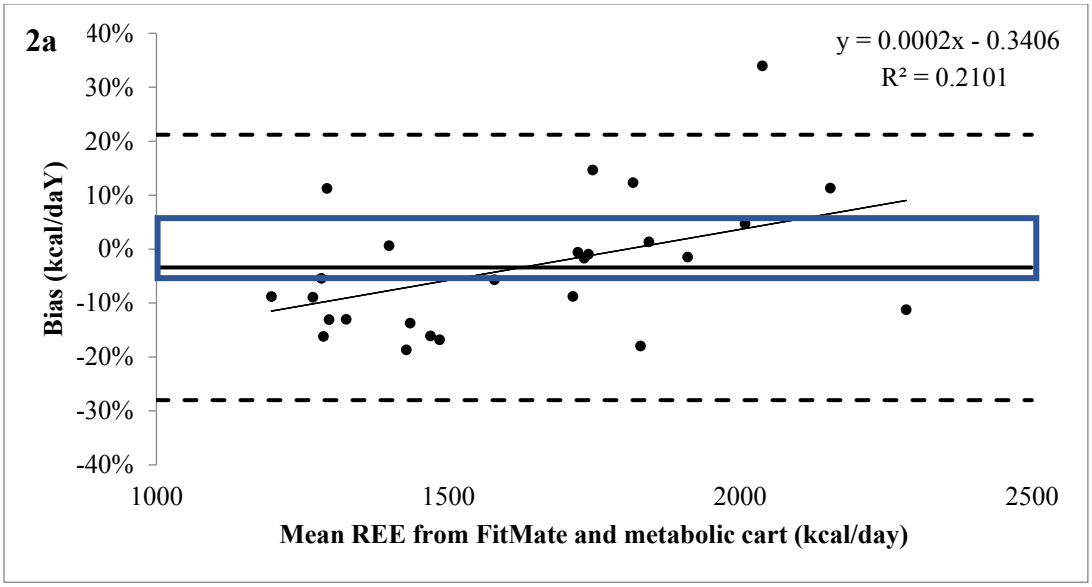
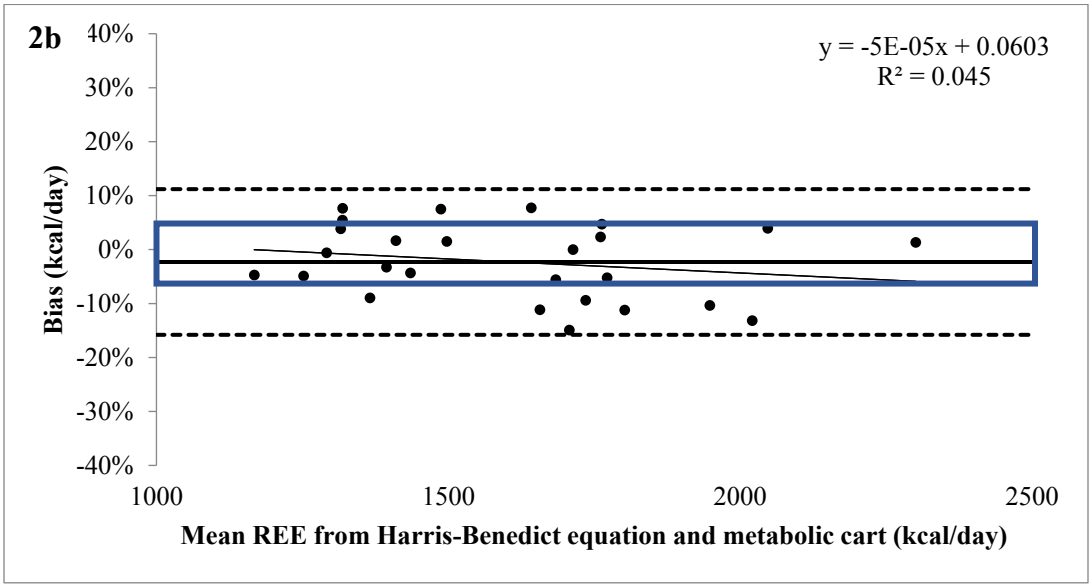
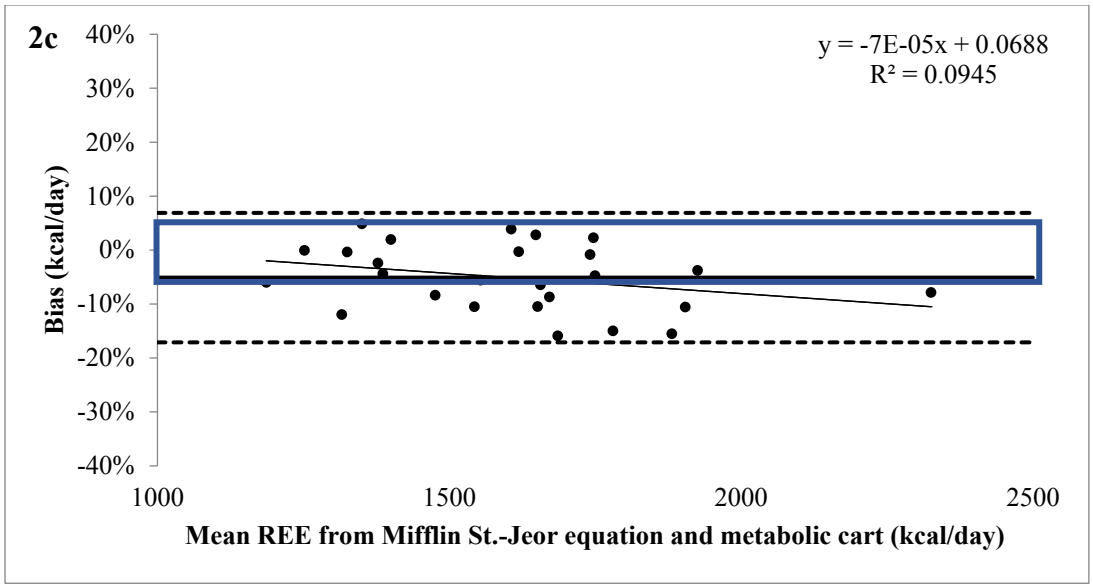
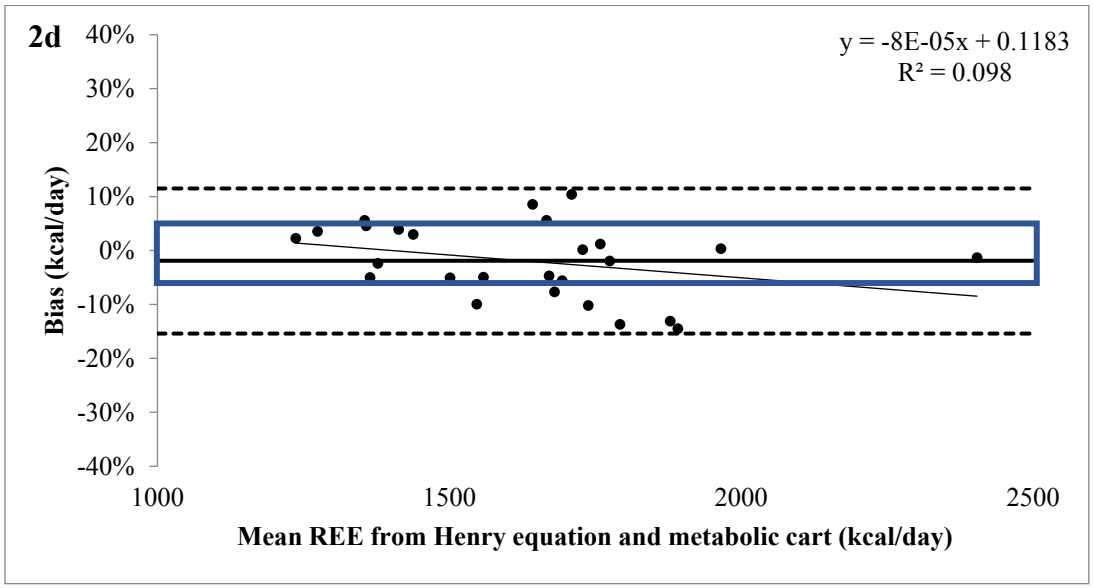


Figure 4.1 The FitMate GS™ with ventilated hood system.
Photograph provided courtesy of COSMED USA, Inc – Concord, CA


2a
y = 0.0002x - 0.3406
R² = 0.2101
Bias (kcal/daY)
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
1000
1500
2000
2500
Mean REE from FitMate and metabolic cart (kcal/day)


2b
y = -5E-05x + 0.0603
R² = 0.045
Bias (kcal/day)
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
1000
1500
2000
2500
Mean REE from Harris-Benedict equation and metabolic cart (kcal/day)





Figures 4.2 a-d. Bland-Altman plots to characterize the difference for average values between resting energy expenditure (REE) measured by metabolic cart and the (a) FitMate GS, (b) Harris-Benedict equation, (c) Mifflin St-Jeor equation and (d) Henry equation. The middle solid line represents bias (mean difference between measured and predicted REE) and the two dotted lines represent the 95% limits of agreement (bias ± 1.96 standard deviations). Blue areas are clinically significant, or within 5% of measured REE from metabolic cart.

Table 4.1 Overall characteristics of patients with solid tumors

	All (n=26)	Males (n=19)	Females (n=7)
Age (years)	62 ± 10 (35 – 84)	63 ± 5 (55 – 73)	59 ± 17 (35 – 84)
Body weight (kg)	83.1 ± 18.4 (57.4 – 118.3)	82.3 ± 17.8 (57.4 – 131.6)	84.4 ± 22.2 (58.6 – 118.3)
Height (cm)	172.7 ± 8.3 (156 – 189.5)	175.0 ± 7.3 (161.0 – 189.5)	166.5 ± 8.6 (156.0 – 180.0)
BMI (kg/m^2)	27.8 ± 5.5 (20.8 – 39.5)	26.8 ± 4.8 (20.8 – 37.2)	30.3 ± 7.0 (22.5 – 39.5)
Cancer type (n, %)			
Colorectal	10 (38)	7 (37)	3 (43)
Non-small cell lung	8 (31)	4 (21)	4 (57)
Renal cell carcinoma	4 (11)	4 (21)	0 (0)
Pancreatic	4 (11)	4 (21)	0 (0)
REE (metabolic cart)	1652 ± 280 (1223-2420)	1708 ± 268 (1252 – 2420)	1500 ± 273 (1223 – 2010)

BMI: body mass index. REE: resting energy expenditure. Data are presented as mean ± standard deviation (range) or number (percent) where appropriate

Table 4.2 Agreement between resting energy expenditure (REE) from the FitMate GS, metabolic cart, and prediction equations (n=26)

	REE Mean ± SD (range)	REE vs. metabolic cart*		Proportional bias		Bias Mean ± SD	Limits of agreement	Bias %	Limits of agreement %
		t-value	p-value	r-value	p-value				
Metabolic cart	1652 ± 280 (1223 - 2420)								
FitMate	1600 ± 360 (1142 - 2334)	1.24	0.223	0.394	0.046	-52 ± 212	-467, 363	-3.4	-28.0, 21.2
Harris-Benedict	1608 ± 267 (1193 - 2453)	1.86	0.085	-0.229	0.263	-44 ± 120	-279, 191	-2.3	-15.8, 11.2
Mifflin St. Jeor	1560 ± 233 (1150 - 2230)	4.23	<0.001	-0.430	0.028	-92 ± 111	-311, 126	-5.1	-17.1, 6.9
Henry	1611 ± 242 (1251 - 2388)	1.74	0.095	-0.328	0.102	-41 ± 121	-279, 197	-1.9	-15.4, 11.5

* $p \leq 0.05$, paired t-test.

4.7 References

1. Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr 2016;70(11):1230-8.
2. Bosaeus I, Daneryd P, Lundholm K. Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. J Nutr 2002;132(11 Suppl):3465s-6s.
3. Knox LS, Crosby LO, Feurer ID, Buzby GP, Miller CL, Mullen JL. Energy expenditure in malnourished cancer patients. Ann Surg 1983;197(2):152-62.
4. Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition 2006;22(6):609-15.
5. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer 2013;21(6):1569-77.
6. Ryan AM, Power DG, Daly L, Cushen SJ, Ni Bhuachalla E, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. Proc Nutr Soc 2016;75(2):199-211.
7. Prado CM, Gonzalez MC, Heymsfield SB. Body composition phenotypes and obesity paradox. Curr Opin Clin Nutr Metab Care 2015;18(6):535-51.
8. Tappy L. Metabolic consequences of overfeeding in humans. Curr Opin Clin Nutr Metab Care 2004;7(6):623-8.
9. Hipskind P, Glass C, Charlton D, Nowak D, Dasarathy S. Do hand-held calorimeters have a role in assessment of nutrition needs in hospitalized patients? A systematic review of literature. Nutr Clin Pract 2011;26(4):426-33.
10. Reeves MM, Capra S, Bauer J, Davies PS, Battistutta D. Clinical accuracy of the MedGem indirect calorimeter for measuring resting energy expenditure in cancer patients. Eur J Clin Nutr 2005;59(4):603-10.
11. Rubenbauer JR, Johannsen DL, Baier SM, Litchfield R, Flakoll PJ. The use of a handheld calorimetry unit to estimate energy expenditure during different physiological conditions. JPEN J Parenter Enteral Nutr 2006;30(3):246-50.
12. Stewart CL, Goody CM, Branson R. Comparison of two systems of measuring energy expenditure. JPEN J Parenter Enteral Nutr 2005;29(3):212-7.

13. Lupinsky L, Singer P, Theilla M, Grinev M, Hirsh R, Lev S, et al. Comparison between two metabolic monitors in the measurement of resting energy expenditure and oxygen consumption in diabetic and non-diabetic ambulatory and hospitalized patients. Nutrition 2015;31(1):176-9.
14. Nieman DC, Austin MD, Benezra L, Pearce S, McInnis T, Unick J, et al. Validation of Cosmed's FitMate in measuring oxygen consumption and estimating resting metabolic rate. Res Sports Med 2006;14(2):89-96.
15. World Health Organization Consultation. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. WHO Technical Report Series: 894. Geneva, Switzerland 2000;894:1-253.
16. Compher C, Frankenfield D, Keim N, Roth-Yousey L. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc 2006;106(6):881-903.
17. Harris JA, Benedict FG. A biometric study of human basal metabolism. Proc Natl Acad Sci U.S.A 1918;4(12):370-3.
18. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr 1990;51(2):241-7.
19. Henry CJ. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr 2005;8(7A):1133-52.
20. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949;109(1-2):1-9.
21. Cooper JA, Watras AC, O'Brien MJ, Luke A, Dobratz JR, Earthman CP, et al. Assessing validity and reliability of resting metabolic rate in six gas analysis systems. J Am Diet Assoc 2009;109(1):128-32.
22. Woo P, Murthy G, Wong C, Hursh B, Chanoine J-P, Elango R. Assessing resting energy expenditure in overweight and obese adolescents in a clinical setting: validity of a handheld indirect calorimeter. Pediatr Res 2016;81:51.
23. Fullmer S, Benson-Davies S, Earthman CP, Frankenfield DC, Gradwell E, Lee PS, et al. Evidence analysis library review of best practices for performing indirect calorimetry in healthy and non-critically ill individuals. J Acad Nutr Diet 2015;115(9):1417-46 e2.

24. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307-10.
25. Bader N, Bosy-Westphal A, Dilba B, Müller MJ. Intra- and interindividual variability of resting energy expenditure in healthy male subjects – biological and methodological variability of resting energy expenditure. Br J Nutr 2007;94(5):843-9.
26. Garby L, Lammert O. Within-subjects between-days-and-weeks variation in energy expenditure at rest. Hum Nutr Clin Nutr 1984;38(5):395-7.
27. Chen WJ, Chung YC. Energy expenditure in patients with hepatocellular carcinoma. Cancer 1994;73(3):590-5.
28. Vaisman N, Lusthaus M, Niv E, Santo E, Shacham-Shmueli E, Geva R, et al. Effect of tumor load on energy expenditure in patients with pancreatic cancer. Pancreas 2012;41(2):230-2.
29. Trutschnigg B, Kilgour RD, Morais JA, Lucar E, Hornby L, Molla H, et al. Metabolic, nutritional and inflammatory characteristics in elderly women with advanced cancer. J Geriatr Oncol 2013;4(2):183-9.
30. Korber J, Pricelius S, Heidrich M, Muller MJ. Increased lipid utilization in weight losing and weight stable cancer patients with normal body weight. Eur J Clin Nutr 1999;53(9):740-5.
31. Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr 2010;29(1):72-7.
32. Ebadi M, Mazurak VC. Evidence and mechanisms of fat depletion in cancer. Nutrients 2014;6(11):5280-97.
33. Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg 1994;219(4):325-31.
34. Haugen HA, Chan L-N, Li F. Indirect calorimetry: A practical guide for clinicians. Nutr Clin Pract 2007;22(4):377-88.
35. Irving CJ, Eggett DL, Fullmer S. Comparing steady state to time interval and non–steady state measurements of resting metabolic rate. Nutr Clin Pract 2016;32(1):77-83.
36. Lam YY, Ravussin E. Analysis of energy metabolism in humans: A review of methodologies. Mol Metab 2016; 5(11):1057-71.

Chapter 5 Predictors of Resting Energy Expenditure in Colorectal Cancer

5.1 Preface

The following chapter is derived from patients diagnosed with stage II-IV colorectal cancer at the Cross Cancer Institute around the time of diagnosis (n=86). This is the first study to characterize the determinants of REE in this population. A version of Chapter 5 is being prepared for submission to Applied Physiology, Nutrition, and Metabolism with the following co-authors: Dr. Vickie E. Baracos, Dr. Quincy S.C. Chu, Dr. Michael B. Sawyer, Dr. Marina Mourtzakis, Dr. Jessica Lieffers, Dr. Diane Severin, and Dr. Carla M. Prado.

All data from study 1 was previously collected by other individuals. I was responsible for measuring resting energy expenditure and collecting anthropometric and demographic data from individuals in Study 2. I collected patient-reported measures and information from medical records in Study 2. I also applied for and maintained ethical approval for this study. Body composition was assessed by computerized tomography, which was collected from medical records and coded for body composition by a research assistant. I contributed to formulating the research question, study design and implementation of Study 2 as well as data analysis and interpretation and initial chapter/manuscript preparation (~70% total proportion of contribution to research and writing).

5.2 Abstract

Resting energy expenditure (REE) might be impacted by tumor burden, inflammation, and altered body composition in patients with cancer. The objective of this study was to characterize the determinants of REE in patients with stage II-IV colorectal cancer (CRC). REE was measured via indirect calorimetry and computerized tomography images ascertained skeletal muscle and total adipose tissue cross-sectional areas, which were transformed to lean soft tissue (LST) and fat mass (FM) values (in kg). Linear regression assessed the determinants of REE. Eighty-six patients were included (n=55, 64.0% male; 60 ± 12 years old; median body mass index: 27.6, interquartile range: 24.3 - 31.2 kg/m^2), with most (n=40) having stage III disease. Age, sex, and weight were significant predictors of REE (R^2=0.829, standard error of the estimate [SEE]: 128, $p<0.001$). Replacing weight with LST and FM yielded a similar model, with age, sex, LST and FM predictive of REE (R^2=0.820, SEE: 129, $p<0.001$). In conclusion, age, sex, weight, LST, and FM were the main contributors to REE. Further investigation of REE changes over time and its relationship to TEE, dietary intake, and clinical outcomes should be explored.

5.3 Introduction

Cancer might induce several physiological alterations such as metabolic demand of the tumor itself and associated systemic inflammation, altered body composition, and/or brown adipose tissue activation (1), which might impact resting energy expenditure (REE). Since REE is the largest component of total energy expenditure (TEE), substantial alterations in REE might change energy requirements. REE has also been associated with chemotherapy toxicity and shorter survival (2, 3). As such, characterizing factors that predict REE is an essential step in improving nutritional care in oncology.

Characterizing REE in cancer is complicated by differences among tumor types (4). Therefore, assessing energy metabolism in homogenous samples of patients or comparing energy metabolism between different cancer types might provide a better platform for understanding metabolism. Colorectal cancer (CRC) is of particular interest since it is the second most common type of cancer in Canada (5) and third most common cancer worldwide (6). Previous research has suggested that REE in individuals undergoing radiotherapy for CRC is influenced by advanced stage (III/IV) and systemic inflammation (7, 8). However, the relative influence of

body composition has not been explored in this cohort, although computerized tomography (CT) images are expedient and readily available in medical records for body composition assessment. Skeletal muscle (SM) and adipose tissue are highly variable in CRC (9) and associate with energy metabolism in cohorts of healthy individuals (10, 11). Large variation in body composition is frequently observed in cancer and might therefore impact REE, although the extent to which this might occur has been scarcely characterized. Given these research gaps and importance of understanding energy metabolism in cancer, the aim of the current study was to characterize the determinants of REE in patients with stage II-IV CRC using data collected from medical records. It was hypothesized that age, sex, height, and weight would independently predict REE, given that these are the main determinants of REE in healthy populations (12). It was also hypothesized that estimations of lean soft tissue (LST) and fat mass (FM) would predict REE because body composition impacts REE in healthy populations (10, 11, 13). Cancer stage was also hypothesized to predict REE since stage IV disease has been previously associated with higher REE because of the presumed higher average metabolic demand of metastases (4, 14).

5.4 Methods

5.4.1 Participants

All patients were recruited from the Cross Cancer Institute in Alberta, Canada with approval by the Health Research Board of Alberta. Written informed consent was provided prior to any study measurements. The data presented here is a unique analysis of data from 1) an investigation of nutritional, metabolic, and functional status in patients with advanced non-small cell lung cancer or CRC, described elsewhere (15, 16) (hereby referred as Study 1) and 2) a cross-sectional study profiling energy expenditure, body composition, exercise, and dietary intake in patients with several tumor types (17) (hereby referred Study 2). Exclusion criteria included use of medications that might interfere with REE (unstable thyroid medication dose, steroids, or hormones), surgery in the previous 4 weeks, pregnancy, or current breastfeeding. Only patients with stage II-IV CRC were included in the present analysis as patients with stage I cancer receive no further treatment after tumor removal.

5.4.2 Anthropometrics

Height and weight were measured using a Health-O-Meter Professional digital scale with height rod (McCook, IL, USA; model number: 597KL) or a QuickMedical Heightronic digital

standiometer (Northbend, WA, USA) for height and a SECA 766 digital scale (Hannover, MD, USA) for weight. Body mass index (BMI) was computed as weight (kg)/height (m^2) and classified according to World Health Organization cut-points (18).

5.4.3 Body Composition

CT images originally collected for diagnostic purposes were used for body composition analysis using sliceOmatic software (V4.3 [Study 1] and V5.0 [Study 2], TomoVision, Montreal, Canada, TomoVision, Montreal, Canada). Only images taken within 100 days of REE measurement were used. Cross sectional areas for each tissue were computed by summing tissue pixels and multiplying by the surface area. Tissues at the third lumbar vertebra were used, as SM and adipose tissue at this landmark are highly correlated to whole-body SM and adipose tissue mass (19). The rectus abdominus, erector spinae muscles, quadratus lumborum, psoas, and internal, transverse and external oblique muscle groups were quantified for SM cross-sectional area. Total adipose tissue (TAT) was measured as the sum of visceral, subcutaneous, and intramuscular adipose tissue cross sectional areas. Hounsfield unit thresholds for determining tissues were as follows: -29 to 150 for SM, -150 to -50 for visceral adipose tissue, -190 to -30 for subcutaneous adipose tissue, and -190 to -30 for intermuscular adipose tissue. Only TAT was used in the analysis. For descriptive analysis, SM and TAT were adjusted by height in m^2 (SM index, SMI, and TAT index, TATI). SM was transformed to lean soft tissue (LST) in kg by the equation: 0.30 x SM + 6.06, (20). This value was subtracted from total body weight as a rough estimate of fat mass (FM) and bone (herein referred to only as FM). Sarcopenia was defined as: SMI < 43cm^2/m^2 in underweight and normal weight males, < 53 cm^2/m^2 in overweight and obese males and < 41 cm^2/m^2 in females (21). Notably, CT image analysis is not prone error caused by fluid retention that might impact the accuracy of body composition measurements from bioelectrical impedance analysis or dual energy X-ray absorptiometry; edema was therefore not considered an exclusion criterion for CT image analysis in this study.

5.4.4 Resting Energy Expenditure

REE in both studies was assessed using indirect calorimetry with a canopy hood system (VMax Spectra 29N; Sensor-Medics, Yorba Linda, CA, USA). The test was conducted after an overnight fast, with patients avoiding food, smoking, caffeine, and physical activity the morning of testing. Air flow and volume were manually calibrated before each measurement using a

three-liter syringe. Gas analyzers were also automatically calibrated prior to each test using known standard gas concentrations of 20.95% oxygen (O_2) and 0.03% carbon dioxide (CO_2), without structured burn tests. Patients rested for a minimum of 10 minutes before a canopy was placed over their head and shoulders for approximately 30 minutes to measure O_2 consumption and CO_2 production. Only breath samples wherein variations in volume of O_2 and CO_2 of $\leq 10\%$ over five consecutive minutes (steady state) were used for analysis. No steady state data was collected in the first 10 minutes of REE measurement, thereby ensuring that all patients had a minimum of 20 minutes total rest before including data in the calculation of REE (in line with current guidelines [22]). The modified Weir equation was used to calculate REE (23).

5.4.5 Clinical and Medical Variables

Patients completed the Patient-Generated Subjective Global Assessment (PG-SGA) – short form (24), which includes information regarding 1-month and 6-month weight change, changes in food intake, nutrition impact symptoms, and physical function. Cancer staging was determined from medical record notes.

5.4.6 Statistical Analysis

Data were assessed using SPSS version 25 (IBM Corp., Armonk, NY, USA) and are presented as mean ± standard deviation or median (interquartile range, IQR); significance was considered at $p \leq 0.05$. A post-hoc power analysis from model 1 yielded β 0.999 with our observed R^2, nine independent variables, and $\alpha = 0.05$.

Normal distribution was evaluated using the Shapiro-Wilk test. Correlation was determined using Pearson's correlation coefficient or Spearman's rho for non-parametric variables. Differences between two groups was determined via independent samples t-test or Mann-Whitney U-test in the case of continuous non-parametric variables. Paired-samples t-test evaluated within-group differences. T-test for independent proportions assessed group differences in categorical variables. Similarly, one-way analysis of covariance or Kruskal-Wallis test (for non-parametric variables) assessed differences between three independent groups. Where appropriate, analysis of covariance compared differences between groups, controlling for a variable.

Univariate linear regression models were first constructed to identify potential explanatory variables in multivariate models. Two multivariate linear regression models were

conducted with REE as a dependent variable and independent variables entered simultaneously (i.e. "enter" method). Explanatory variables in model 1 included age, sex, height, weight; in model 2 these included age, sex, height, LST, and FM. Covariates in all models included study (1 or 2), cancer type (colon or rectal), or cancer stage (II/III or IV). Results from regression models are presented as β-coefficients and standard error of the coefficient. Standardized residuals of the regression line were checked for each independent variable. Homoscedasticity was visually confirmed using plots of the independent variable against the residuals of dependent variable (REE). Co-linearity among independent variables within each regression model was assessed by variance inflation factors, with values < 5 indicating no co-linearity was present. Homoscedasticity of standardized residuals and predicted values were visually assessed using scatterplots. Several interaction terms were calculated and included in models, only if significant.

5.5 Results

A total of 86 patients had REE and anthropometric measurements, **Table 5.1**. Most patients had BMI within the normal or obese categories (n=31, 36% each); only 2 (2.3%) patients were underweight. There was a higher number of patients with colon cancer (n=61, 70.9%) and most patients (n=40, 46.5%) had stage III cancer. Median 1-month weight change was 0% (IQR: -2.4 to 1.2%) and median 6-month weight change was -3.2% (IQR: -7.6 to 0%). Few patients had undergone previous radiation therapy (n=12, 13.9%) and there were no differences in age, height, weight, body composition (SMI, TATI, LST or FM) or REE between these patients and those without previous radiation therapy. Median days between CT image acquisition and study measurements was 29 (IQR: 15 – 54 days).

Differences in age, sex, height, weight, LST, FM (in absolute terms and adjusted by height), and 1-month and 6-month % weight change were assessed between groups of patients according to study, cancer type, and stage. Individuals with advanced disease were shorter (168.0 ± 9.2 vs. 172.7 ± 8.9 cm, p=0.024) and individuals with rectal cancer were younger (56 ± 10 vs. 61 ± 12 years, p=0.048). Disease stage (I-III vs. IV), cancer type (rectal vs. colon), and study (1 versus 2, since study 1 only included patients with stage IV CRC) were therefore included as covariates in all linear regression models.

Of the 76 patients with body composition data available, 23 (30.3%) had sarcopenia. Individuals with sarcopenia had lower BMI than those without sarcopenia (26.2 vs. 29.0 kg/m^2,

p=0.025), but no other differences were observed. Inclusion of sarcopenia in regression models outlined below did not improve the predictive capabilities of any model; therefore, LST was entered as a continuous variable.

Mean measured REE was 1632 ± 296 kcal/day, and two models were created to determine predictors of REE. One outlier was identified and violated the assumptions of normal residuals and homoscedasticity for several variables in linear regression and was therefore excluded from further analyses. In univariate analyses, sex (349.3 ± 55.2, R^2: 0.326, p<0.001), age (-5.9 ± 2.8, R^2: 0.051, p=0.038), height (21.4 ± 2.6, R^2: 0.445, p<0.001), weight (12.5 ± 1.0, R^2: 0.649, p<0.001), LST (20.3 ± 2.0, R^2: 0.578, p<0.001), and FM (11.0 ± 2.3, R^2: 0.245, p<0.001) were significant predictors of REE. In multivariate model 1, age, sex, and weight were significant predictors of REE, with 82.9% of variance in REE explained (SEE: 128 kcal/day), **Table 5.2**. In multivariate model 2, age, sex, LST and FM were significant predictors of REE, with 82.0% of variance in REE explained (SEE: 129 kcal/day), **Table 5.2**.

5.6 Discussion and Conclusions

Characterizing energy metabolism in cancer is an essential endeavor, since REE is a large part of energy requirements and might associate with clinical outcomes (2, 3). Here, we report that age, sex, and weight are significant predictors of REE close to diagnosis. Inclusion of body composition variables did not improve predictive ability of the model, although both LST and FM were independent predictors of REE.

Body size is a determinant of energy expenditure (25) and forms the basis of most REE predictive equations. Although body composition is a primary determinant of REE heterogeneity (26) and individuals with cancer have highly variable body composition at diagnosis (15), replacing body weight with LST and FM did not result in a stronger predictive model in our sample. While SM, TAT, and bone make up a large proportion of body weight, these tissues only account for about 30% of the variability in REE in healthy individuals (10, 11). In patients with cancer, metastatic disease progression in may eclipse REE alterations which would occur with extreme values of LST and FM in healthy adults (14). For example, an estimated average liver mass increase of 0.74 kg over an 9.5 months (14) would equate to an REE increase of ~150 kcal/day, assuming a 200 kcal/kg/day energy consumption of hepatic tissue (27). Skeletal muscle uses ~13 kcal/kg/day and adipose tissue uses ~4.5 kcal/kg/day (27). It would therefore take an

exceptionally larger mass of skeletal muscle and adipose tissue loss to negate the additional metabolic demand of a few grams of cancerous tissue in organs with high metabolic rates. Notably, however, the evolution of tumor metabolic demand is unknown in each individual without multiple accurate assessments of REE, tumor size, and body composition. Although advanced stage was hypothesized to affect REE (since metastatic disease has previously been associated with elevated REE [4]), this was not apparent in our analysis. It is therefore plausible that the impact of cancer stage on REE becomes apparent only later in the disease trajectory. For example, metabolic demand of a tumor can range anywhere from 100 to 1400 kcal/kg/day, depending on size and glycolytic activity (28), with presumed increased metabolic demand in patients with extensive metastases. Significant REE increase in patients with stage IV CRC may theoretically only be apparent after failure or discontinuation of anti-cancer treatments, wherein metastases might continue to worsen. Further exploration of the evolution of REE in relation to disease progression, dietary intake, and overall TEE might aid in the process of triaging patients for intensive nutrition interventions. The relationship between body composition with other aspects of metabolism (metabolic flexibility, TEE, physical activity) also warrants further exploration in this population.

Body weight, age, and sex were the primary determinants of REE in this investigation, which form the basis of most REE predictive equations. Although ~80% of the variability in REE was explained in both models, 20% of REE was left unexplained and currently available REE equations are not accurate for each individual with cancer (reference [29] and Chapter 3 results). Use of predictive equations for dietary recommendations can therefore *not* be endorsed as an accurate assessment of energy requirements at this time. Improved REE equations should be developed, requiring large validation datasets, cross-validation with other cancer populations for external validity, and REE measured by metabolic carts (rather than portable calorimeters).

Assessing abnormal REE is useful since wide deviations from these values might indicate alterations in whole-body metabolism which may affect energy requirements. However, methods to define abnormal metabolism are controversial and there is no consensus on the most accurate method to identify altered REE. In nutritional oncology, hyper- or hypo-metabolism is often defined in relation to predicted REE from the Harris-Benedict (30) or Mifflin St. Jeor (31) equations (2, 3). However, expressing REE in relation to published equations designed for

healthy individuals assumes that these equations are accurate, which is not always the case (32). Our study was also not powered to investigate potential physiological differences between individuals with "normal" or "abnormal" metabolism, nor were tumor volume calculations attained (which may explain apparent altered REE to a greater degree than body composition). Larger sample sizes of individuals with cancer with repeated measures of inflammation, tumor size, and body composition might shed light on the determinants of unusually high or low values of REE.

Although REE has been postulated to play a significant role in cancer-associated weight change (33), REE was not correlated to previous weight change in our sample. However, REE might arguably influence weight change over time or play a larger role in certain cancers (e.g. lung or pancreatic) where high REE and substantial wasting are prevalent (34, 35). In addition, disease progression may not be apparent in patients with earlier stages of disease but is inevitable in individuals with stage IV cancer. While REE is the largest part of TEE, physical activity is highly variable and high REE is not associated with TEE in patients with newly diagnosed CRC (Chapter 7). Therefore, the impact of REE on energy requirements and subsequent weight change might play a lesser role on energy balance than originally anticipated in patients with CRC, at least early in the disease trajectory.

Although this study is the one of the largest investigations of a group of patients with the same type of cancer, some limitations should be considered. Systemic inflammation might associate with REE (7) but was not measured in this study. Our institution, like many others, does not routinely measure indices of inflammation (i.e. C-reactive protein). We sought to explore the determinants of REE using data available in medical records to potentially translate our findings to clinical practice and reduce unnecessary patient burden. Data was also aggregated from two separate investigations to increase statistical power. These studies recruited patients from the same cancer center and used the same indirect calorimeter; study was also controlled for in the statistical analyses. Nevertheless, error is inherent in data aggregation and might have impacted our results. Furthermore, REE in the context of TEE was not described and we can therefore not comment on overall energy balance or which energy needs equations might be more appropriate.

In conclusion, age, sex, weight, LST, and FM were the main contributors to REE in this sample of individuals with stage II-IV CRC. Further exploration of REE changes over time and its relationship to TEE, dietary intake, and clinical outcomes should be explored.

Table 5.1 Characteristics of 86 patients with stage II-IV colorectal cancer

	All (n=86)*	Males (n=55)*	Females (n=31)*	p
Age, years	60 ± 12	61 ± 11	58 ± 13	0.267
Height, cm	171.1 ± 9.3	175.6 ± 7.1	163.0 ± 6.8	<0.001
Weight, kg†	80.9 (68.1 – 95.1)	70.8 (59.9 – 81.1)	89.0 (72.1 – 98.8)	0.001
Body mass index, kg/m^2 †	27.6 (24.3 – 31.2)	28.4 (25.2 – 31.3)	25.1 (22.7 – 30.6)	0.226
Skeletal muscle cm^2	151.7 ± 36.0	168.0 ± 30.0	119.1 ± 22.1	<0.001
Skeletal muscle index, cm^2/m^2	51.0 ± 9.6	54.1 ± 9.1	44.7 ± 7.6	<0.001
Total adipose tissue, cm^2	367.7 ± 191.3	391.1 ± 197.7	321.0 ± 172.2	0.136
Total adipose tissue index, cm^2/m^2	124.0 ± 62.6	125.9 ± 62.6	120.3 ± 63.7	0.714
Resting energy expenditure, kcal/day	1603 (1412 – 1862)	1783 (1575 – 1968)	1405 (1259 – 1500)	<0.001
Tumor type (n, %)				
Colon	61, 70.9	38, 69.1	23, 74.2	0.617
Rectal	25, 29.1	17, 30.9	8, 25.8	0.617
Stage (n, %)				
II	14, 16.3	9, 16.4	5, 16.1	0.977
III	40, 46.5	29, 52.7	11, 35.5	0.124
IV	32, 37.2	17, 30.9	15, 48.4	0.107

Presented as mean ± standard deviation, median (interquartile range), or n, column %

*n=75 total, n=50 males, n=25 females with body composition available.

†non-normally distributed within one or both groups; presented as median (interquartile range); Mann-Whitney U-test for differences between groups. Note: resting energy expenditure was normally distributed when one outlier was removed (all: 1631 ± 296 kcal/day; males: 1759 ± 251 kcal/day; females: 1410 ± 235 kcal/day, p<0.001).

Table 5.2 Multiple linear regression of predictors of resting energy expenditure in patients with colorectal cancer

	Coefficient ± SE	p-value	R^2	SEE
Model 1		<0.001	0.829	128
Age, y	-5.6 ± 1.3	<0.001		
Sex	202.4 ± 39.5	<0.001		
Height, cm	2.6 ± 2.3	0.219		
Weight, kg	9.8 ± 0.9	<0.001		
Model 2*		<0.001	0.820	129
Age, y	-5.0 ± 1.4	0.001		
Sex	174.8 ± 49.1	0.001		
Height, cm	9.06 ± 2.90	0.332		
Lean soft tissue, kg	12.1 ± 2.1	<0.001		
Fat mass, kg	8.5 ± 1.3	<0.001		

All models included study (1 or 2), cancer type (colon or rectal), and stage (II/III or IV) as covariates; none of these covariates were significant predictors. Sex: 0=female, 1=male
SE: standard error; SEE: standard error of the estimate
*n=74. Model 1: n=85

5.7 References

1. Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr. 2016;70(11):1230-8.
2. Vazeille C, Jouinot A, Durand JP, Neveux N, Boudou-Rouquette P, Huillard O, et al. Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. Am J Clin Nutr. 2017;105(5):1139-47.
3. Jouinot A, Vazeille C, Durand JP, Huillard O, Boudou-Rouquette P, Coriat R, et al. Resting energy expenditure in the risk assessment of anticancer treatments. Clin Nutr. 2018;37(2):558-65.
4. Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr. 2010;29(1):72-7.
5. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2018. Toronto, Ontario: Canadian Cancer Society 2018. Available at: cancer.ca/Canadian-Cancer-Statistics-2018-EN (accessed [September 2018])
6. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.
7. Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? Cancer J. 2007;13(6):392-8.
8. Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest. 2007;25(5):308-14.
9. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the obesity paradox: The association between body composition and colorectal cancer survival (C-SCANS Study). Cancer Epidemiol Biomarkers Prev. 2017;26(7):1008-15.
10. Gallagher D, Belmonte D, Deurenberg P, Wang Z, Krasnow N, Pi-Sunyer FX, et al. Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass. Am J Physiol. 1998;275(2 Pt 1):E249-58.
11. Heymsfield SB, Gallagher D, Kotler DP, Wang Z, Allison DB, Heshka S. Body-size dependence of resting energy expenditure can be attributed to nonenergetic homogeneity of fat-free mass. Am J Physiol Endocrinol Metab. 2002;282(1):E132-8.

12. Müller MJ, Bosy-Westphal A, Klaus S, Kreymann G, Lührmann PM, Neuhäuser-Berthold M, et al. World Health Organization equations have shortcomings for predicting resting energy expenditure in persons from a modern, affluent population: generation of a new reference standard from a retrospective analysis of a German database of resting energy expenditure. Am J Clin Nutr. 2004;80(5):1379-90.
13. Bosy-Westphal A, Müller MJ, Boschmann M, Klaus S, Kreymann G, Lührmann PM, et al. Grade of adiposity affects the impact of fat mass on resting energy expenditure in women. Br J Nutr. 2008;101(4):474-7.
14. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr. 2009;89(4):1173-9.
15. Prado CMM, Mourtzakis M, Baracos V, Reiman T, Sawyer MB, McCargar LJ. Overweight and obese patients with solid tumors may have sarcopenia, poor prognosis and early features of cachexia. Int J Body Compos Res. 2010;8(1):7-15.
16. Prado CM, Lieffers JR, Bergsten G, Mourtzakis M, Baracos VE, Reiman T, et al. Dietary patterns of patients with advanced lung or colorectal cancer. Can J Diet Pract Res. 2012;73(4):e298-303.
17. clinicaltrials.gov. Identifier: NCT03131921. Resting Energy Expenditure in Cancer - Associations With Body Composition, Dietary Intake, and Exercise Habits Bethesda, MD: National Library of Medicine; 2017 [updated May 3, 2017. Accessed February 2, 2018].
18. World Health Organization Consultation. Obesity: Preventing and managing the global epidemic: Report of a WHO consultation. WHO Technical Report Series: 894. Geneva, Switzerland 2000;894:1-253.
19. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333-8.
20. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.

21. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, 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(12):1539-47.
22. Fullmer S, Benson-Davies S, Earthman CP, Frankenfield DC, Gradwell E, Lee PS, et al. Evidence analysis library review of best practices for performing indirect calorimetry in healthy and non-critically ill individuals. J Acad Nutr Diet. 2015;115(9):1417-46 e2.
23. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1-2):1-9.
24. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.
25. Westerterp KR. Control of energy expenditure in humans. Eur J Clin Nutr. 2016;71:340.
26. Speakman JR, Selman C. Physical activity and resting metabolic rate. Proc Nutr Soc. 2003;62(3):621-34.
27. Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN, editors. Energy Metabolism: Tissue Determinants and Cellular Coeollaries. New York: Raven Press; 1992. p. 61-80.
28. Friesen DE, Baracos VE, J.A. T. Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia. Theor Biol Med Model. 2015;12(1):17.
29. Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition. 2006;22(6):609-15.
30. Harris JA, Benedict FG. A biometric study of human basal metabolism. Proc Natl Acad Sci U.S.A. 1918;4(12):370-3.
31. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241-7.
32. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. J Am Diet Assoc. 2005;105(5):775-89.

33. Bosaeus I, Daneryd P, Svanberg E, Lundholm K. Dietary intake and resting energy expenditure in relation to weight loss in unselected cancer patients. Int J Cancer. 2001;93(3):380-3.

34. Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg. 1994;219(4):325-31.

35. Staal-van den Brekel AJ, Dentener MA, Schols AM, Buurman WA, Wouters EF. Increased resting energy expenditure and weight loss are related to a systemic inflammatory response in lung cancer patients. J Clin Oncol. 1995;13(10):2600-5.

Chapter 6 Determinants of Change in Resting Energy Expenditure in Patients with Stage III/IV Colorectal Cancer

6.1 Preface

Chapter 6 uses data from patients diagnosed with stage III or IV colorectal cancer diagnosed at the Department of Surgery at Sahlgrenska University Hospital (Gothenburg, Sweden) (Study 1) or the Cross Cancer Institute (Study 2). This is the first study to examine inflammation, body composition, and stage as determinants of individual REE change during cancer treatment. This has been accepted for publication as a full-length article in Clinical Nutrition (submitted on August 30, 2018, accepted December 26, 2018). Co-authors were as follows: Dr. Ola Wallengren, Dr. Vickie E. Baracos, Dr. Kent Lundholm, Dr. Britt-Marie Iresjö, Dr. Quincy S.C. Chu, Dr. Sunita Ghosh and Dr. Carla M. Prado.

I was responsible carrying out data analysis and interpretation and drafting the first version of the chapter/manuscript; I did not directly collect any patient data (~60% total proportion of contribution to research and writing). Data from Study 1 was provided from collaborators in Sweden (Professor Kent Lundhom, Dr. Ola Wallengren, and Dr. Britt-Marie Iresjö) and data from Study 2 was previously collected by individuals other than me at the Cross Cancer Institute. In addition to my role, collaborator contributions were as follows: Dr. Vickie Baracos and Dr. Carla Prado contributed to the acquisition of data in Study 2; Dr. Kent Lundholm and Dr. Britt-Marie Iresjö contributed to the acquisition of data in Study 1; all authors contributed to the analysis and interpretation of the data and revising the manuscript for intellectual content.

6.2 Abstract

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. 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. One-hundred and nine patients were included at baseline (59.6% male; 67 ± 12 years; body mass index 24.1 ± 4.3 kg/m^2); 49 had follow-up data (61.2% male; 65 ± 12 years; body mass index 25.4 ± 4.3 kg/m^2), 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 (17.3 ± 4.2 mg/dL, $p<0.001$) and stage (81.3 ± 38.7, $p=0.042$) predicted REE change in multivariate analysis, controlling for age, FFM change, and days between visits (R^2: 0.417 ± 88.2, $p<0.001$). In conclusion, 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.

6.3 Introduction

Resting energy expenditure (REE, the largest component of total energy expenditure) 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 FFM) is a major determinant of REE in healthy populations, substantial changes in FFM could affect REE in these patients. Furthermore, systemic inflammation is also positively 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 which increase REE (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 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. It was hypothesized that REE at follow-up would not be different than REE at baseline, given the findings from Maguire *et al*. (13) and Ravasco *et al*. (2, 11). Despite average null changes in REE, it was hypothesized that FFM change, inflammation (C-reactive protein, CRP) change, and stage (III or IV) would independently predict REE change in individual patients because 1) FFM is a major determinant of REE (14, 15), 2) inflammatory cytokines positively associate with REE (2), and 3) metastases increase REE through increased tumor burden (5).

6.4 Methods

6.4.1 Participants

This is a unique analysis of data collected as part of two previously published studies (16, 17). 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 (18), insulin (19), erythropoietin for anemia (20, 21), dietary counseling, and nutritional support (22). 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 453 days (interquartile range [IQR]: 303 - 742 days).

Data from Study 2 (17, 23) 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 183 days (IQR: 104 – 320 days). Informed consent was collected from all participants in both studies, in line with the Declaration of Helsinki.

6.4.2 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 a LUNAR DPX-L dual X-ray absorptiometry (Scanexport Medical, Helsingborg, Sweden). The extended research mode of the LUNAR-DPX-L software (version 1.31, Scanexport Medical) was used.

In Study 2, body weight was assessed using a SECA 766 digital scale (Hanover, MD, USA) and height was assessed using a QuickMedical Heightronic digital stadiometer (Northbend, WA, USA). Body composition was measured by a LUNAR Prodigy High Speed Digital Fan Beam Densitometer with enCORE 9.20 software. Body mass index (BMI, kg/m^2) for all patients was calculated and categorized according to the World Health Organization (24).

6.4.3 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 (25). The Weir equation (26) was used to calculate REE and respiratory quotient was calculated as the ratio of CO_2 volume to O_2 volume. A rest period of 30 minutes before REE was conducted in each study. Study 1 measured gas exchange from 30 minutes (after the first 3 minutes were discarded) and Study 2 collected a minimum of 15 minutes 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 REE (1). REE change was expressed in absolute terms and as percentage change/100 days (percent change/days between visits x 100) to account for follow-up heterogeneity between and within studies.

6.4.4 Biochemical Assessments

CRP 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). CRP values were converted from mg/L to mg/dL by multiplying the former value by 0.1 before inclusion in any statistical analyses.

6.4.5 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 $p \leq 0.05$ 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; in the case of non-normally distributed variables, Mann-Whitney U-test was used.

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. 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), α 0.05, β 0.90, and six independent variables. Study number 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 in each model was also investigated, but only included if significance was reached.

6.5 Results

6.5.1 Baseline

A total of 109 patients had baseline data available, **Table 6.1**. 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).

In univariate analysis, age, sex, height, body weight, stage, FM, FFM, and CRP were significant predictors of REE, **Table 6.2**. In stepwise regression, age, FFM, and CRP explained 68.9% of the variability in REE. All other variables were not significant predictors of REE in multivariate analyses. When only patients with stage IV cancer were assessed, similar results were observed with age, sex, height, body weight, FM, FFM, and CRP significant in univariate analysis, and age, FFM, and CRP generating the strongest predictive model in multivariate analysis, **Table 6.3**.

6.5.2 Change over Time

Follow-up data was available for 49 patients, **Table 6.4**. No differences in REE change were observed between those taking intervention medications in Study 1 compared to those who did not take these medications; patients were therefore grouped for analysis. Change in body weight, FM, FFM, CRP, or REE were not different between males and females and results are

hence presented with both sexes combined for this analysis. Study 1 median follow-up time was approximately four months (126 days, IQR: 118 - 136 days) and study 2 median follow-up was approximately two months (64 days, IQR: 56 - 77 days).

Overall, absolute REE increased by 35 kcal/day (1559 ± 240 to 1594 ± 268 kcal/day, p=0.026), **Table 6.4**. FFM (50.2 ± 10.0 to 50.9 ± 9.1 kg, p=0.037) and CRP (0.8, IQR: 0.3 – 2.3 to 1.0 IQR: 0.5 – 4.6 mg/dL, p=0.049) also increased. 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, **Figure 6.1**.

Results of the linear regression for predictors of REE change are shown in **Table 6.5**. In univariate analysis only stage, CRP at follow-up, and CRP change were significant predictors of REE change. Stage and CRP change remained significant predictive factors when controlling for study, days between visits, age, and FFM change, **Table 6.5.** Results were similar when trunk lean soft tissue change was used instead of FFM (data not shown). Results were similar when indomethacin treatment (n=14) was included as a covariate (R^2: 0.467; standard error of the estimate: 86.5; CRP change: 17.1 [95% confidence interval: 8.8, 25.5], p<0.001; stage: 87.1 [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.

6.6 Discussion and Conclusions

This study is the first to collectively assess changes in REE, body composition, and inflammation in individuals with colorectal cancer. We found that age, FFM 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 FFM change.

In healthy adults, FFM is a significant predictor of REE (27). Decreases in FFM explain approximately 60% of decrease in REE observed with age (28), but other age-related factors affect REE independently of FFM (29). FFM and age were therefore expected to predict REE in our sample at baseline. Although it was anticipated that FFM change would be a significant predictor of REE change, this was not observed in our data. Notably, FFM 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, FFM alterations might change in oppositional proportion to inflammatory alterations; namely, skeletal muscle (a large portion of FFM) atrophy is associated with inflammatory cytokines (30). It is therefore possible that the impact of body composition alterations is obscured in the face of high systemic inflammation, although further research is needed. According to the findings presented here, FFM is a useful determinant of REE at a single timepoint, but cannot detect tumor burden or metastases, which – along with inflammation – impacts 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) (31). Although change in REE 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 kcal/day 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% (32); 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 (33, 34). The same concept can be applied to energy balance where variation in REE and total energy expenditure change and the predictors of such 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 (18, 35) and may predict survival (36, 37) in various cancer types. The

presence of a tumor induces a chronic inflammatory response associated with the production of T helper 1 cytokines (38) and an ensuing 'energy appeal reaction' consumes glucose from the liver, protein from muscle, and lipids from fat tissue, perpetuating high energy expenditure (1, 39). Other clinical conditions might also elicit increased inflammation and concomitant increased REE. For example, in individuals with chronic kidney disease, a similar linear regression analyses revealed REE increase of approximately 23 - 27 kcal/day per unit increase in CRP in mg/dL (40, 41). This change in REE per unit increase in CRP is slightly higher than that of the present sample (β 17.3 ± 4.2 kcal/day increase per 1 unit increase in CRP in mg/dL). However, both studies reported high CRP concentrations (defined as ≥0.5 mg/dL) in around 40% of patients where as 76.1% (n=83) patients in the present study had CRP values above this cut-off at baseline. There was also a wide range of CRP values at baseline (0.1 – 30.0 mg/dL) and CRP change (-6.1 to 16.8 mg/dL) in the present sample, which might contribute to these apparent lower coefficients. The relationship between inflammation and REE might therefore differ in cancer according to overall levels of inflammation at baseline and how these change longitudinally, although more research is needed in this regard. REE change in relation to CRP change in multivariate models is lacking in other populations, but our data suggest that dramatic changes in CRP could indicate underlying metabolic changes that might affect energy metabolism, irrespective of FFM alterations. Notably, however, CRP change in univariate and multivariate analyses only explained approximately 30% and 40% of the variation in REE change, respectively. A large proportion of REE change is left unexplained and might relate to error in the measurement methods (i.e. 3 - 8% intra-individual coefficient of variation for metabolic carts [25]; 5.2% analytic variation and 42.2% within-subject variation in CRP measurements [42]), metabolic adaptations related to chronically low dietary intake, or changes in hormonal/endocrine status (i.e. thyroid hormones [43], insulin resistance [44]). Therefore, although inflammation is an explanatory variable in REE change, a large portion of the variability in REE is unexplained and should be explored in future studies.

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 to 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) (45), 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 (31, 46). 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, stage IV disease predicts REE increase, the impact and extent of site of metastases is unknown.

Since REE is the largest component of TEE, any perturbations in REE might impact energy requirements. However, REE changes should be assessed in the context of overall energy balance, which is especially true in the face of relatively small average REE change observed here (35 kcal/day increase). Alterations in REE may not substantially impact total energy needs since physical activity levels may also shift. Some have suggested that physical activity is diminished in cancer (47). Accurate methods to measure free-living total energy expenditure such as doubly labeled water have only been utilized in advanced cancer patients who were cachectic (i.e. high rates of weight loss and inflammation) (48, 49). Exploring REE and total energy expenditure in the context of colorectal cancer will guide future energy recommendations, perhaps based on body weight or composition, inflammation, physical activity, and disease stage, an area we are actively pursuing (50). Similarly, energy intake varies substantially among individuals with cancer and might be noticeably diminished by hundreds of calories (51-53), especially in later stages of disease. Understanding the magnitude of alterations in REE is particularly relevant since REE rarely relates to weight change in studies of cancer

cachexia (54), meaning that changes in total energy expenditure and energy intake are more important in modulating body weight than REE assessments in isolation.

REE changes in relation to energy balance should be considered in interventions aimed at mitigating or reversing weight loss or the development of cachexia. For example, REE might decrease (with concomitant increase is FFM) in response to an anti-inflammatory agent in individuals with advanced gynecological cancer (55). In individuals with unresectable pancreatic cancer, a nutrition supplement enriched with anti-inflammatory eicosapentaenoic acid did not change REE over an 8-week period, but TEE and physical activity increased during this time (48), suggesting that inflammation may modulate TEE through changes in physical activity. However, indomethacin treatment was not related to REE or REE change in our analysis. Identifying groups of individuals who could benefit from anti-inflammatory medication or nutritional supplements and how this might impact energy requirements should be explored in more depth.

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 (%REE change/100 days) and the primary statistical analyses (linear regression with days between measurements as an independent variable). Between-study heterogeneity is inherent in data aggregation and must be considered as a potential source of error within the present study. In particular, we noted differences between studies in CRP at baseline and follow-up and respiratory quotient at follow-up, which might have introduced error in our analyses. To partially control for these differences, findings for REE change were similar when study (1 or 2) was included as a covariate in the linear regression analysis. Individuals with cachexia are at risk for developing insulin resistance (56) which may predict higher REE, at least in healthy adults (44). While glucose and insulin were not available in the present analysis, these indices should be considered in future studies of energy metabolism in cancer.

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 total energy expenditure will shed light on the relevant and over-looked area of energy needs in cancer.

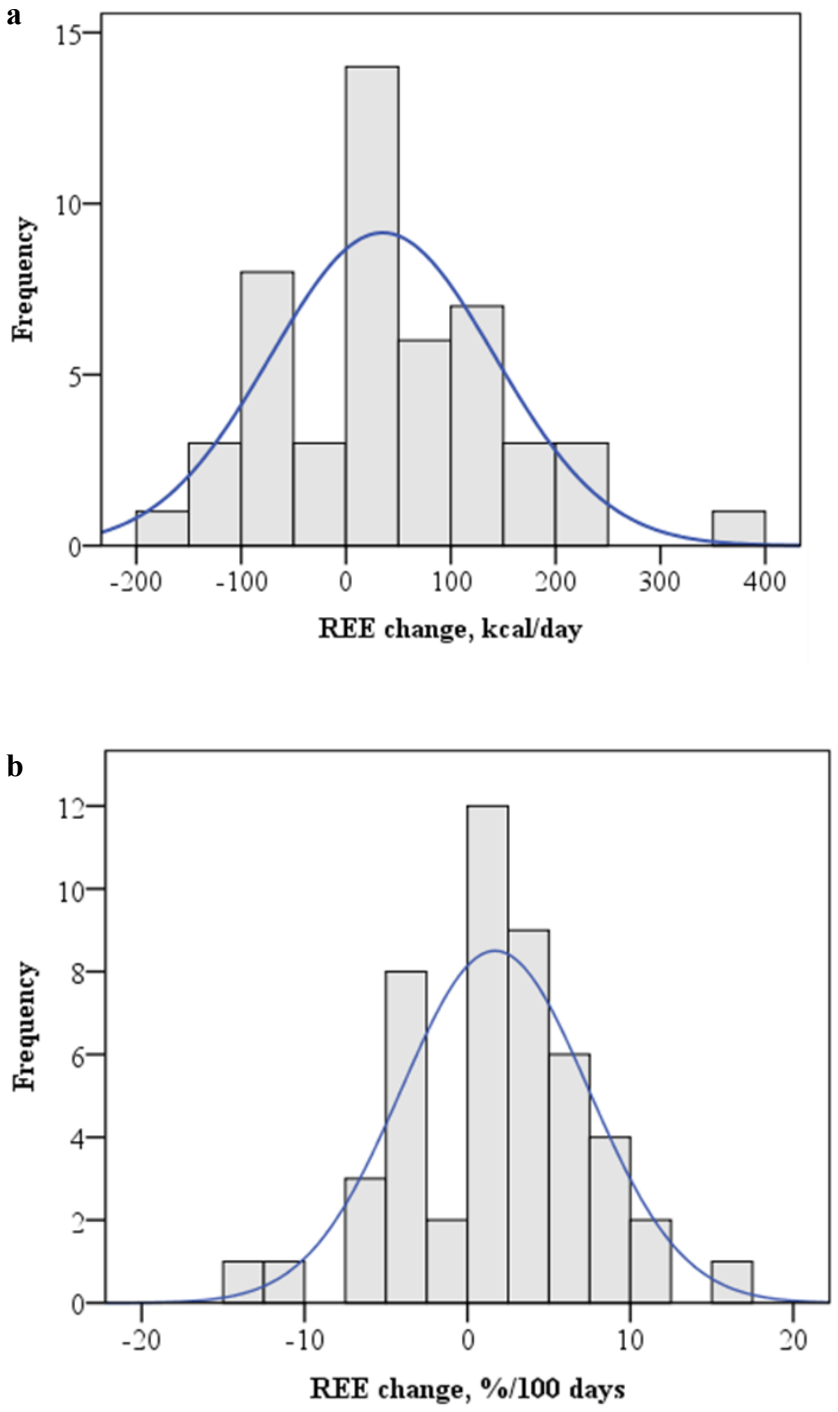


Figure 6.1 Variability in resting energy expenditure (REE) change, expressed as (a) kcal/day and (b) percent change/100 days. Change ranged from -156 to 370 kcal/day or -13.0 to 15.7%/100 days.

Table 6.1 Demographic, anthropometric, and metabolic characteristics of patients with colorectal cancer at baseline (n=109)

	Entire sample (n=109)	Males (n=65)	Females (n=44)	p-value
Age, y	67.5 (59.6, 76.9)	67.0 (60.3, 75.9)	67.5 (58.2, 79.0)	0.583
Body weight, kg	71.0 ± 15.3	77.3 ± 14.2	61.1 ± 11.7	<0.001
Body mass index, kg/m^2	24.1 ± 4.3	24.9 ± 4.2	23.1 ± 4.2	0.033
Fat-free mass, kg	49.6 ± 10.2	56.3 ± 7.1	39.7 ± 3.8	<0.001
Fat-free mass index, kg/m^2	16.7 ± 2.3	18.1 ± 1.9	14.8 ± 1.2	<0.001
Fat mass, kg	20.5 ± 9.2	20.2 ± 8.9	20.9 ± 9.6	0.706
Fat mass index, kg/m^2	7.0 ± 3.2	6.5 ± 2.8	7.8 ± 3.5	0.036
C-reactive protein, mg/dL[a]	1.5 (0.5, 4.0)	1.4 (0.5, 3.7)	1.8 (0.5, 4.7)	0.668
Measured REE, kcal/day	1555 ± 257	1674 ± 229	1380 ± 187	<0.001
Respiratory quotient	0.79 ± 0.06	0.80 ± 0.06	0.77 ± 0.06	0.043

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
[a]n=105; n=63 males; n=42 females

Table 6.2 Regression analysis of predictors of resting energy expenditure in patients with stage III and IV colorectal cancer at baseline (n=109)

Univariate analysis					
	Coefficient	**95% CI**	**p-value**	**R^2**	**SE**
Age, years	-7.7	-11.6, -3.7	<0.001	0.126	2.0
Sex	294.3	211.7, 376.8	<0.001	0.318	41.7
Height, cm	19.1	14.7, 23.4	<0.001	0.416	2.2
Weight	10.2	7.7, 12.8	<0.001	0.373	1.3
Stage[b]	135.8	6.2, 265.3	0.040	0.039	65.3
Fat mass, kg	6.4	1.2, 11.7	0.016	0.053	2.6
Fat-free mass, kg	18.5	15.1, 21.7	<0.001	0.532	1.7
C-reactive protein, mg/dL	11.5	2.3, 20.7	0.015	0.056	4.7
Multivariate analysis					
	Coefficient	**95% CI**	**p-value**	**R^2**	**SE**
Step 1			<0.001	0.527	176.8
Fat-free mass, kg	18.1	14.7, 21.4	<0.001		
Step 2[c]			<0.001	0.624	158.5
Fat-free mass, kg	18.9	15.8, 21.8	<0.001		
C-reactive protein, mg/dL	15.2	9.3, 21.0	<0.001		
Step 3[c]			<0.001	0.689	144.7
Fat-free mass, kg	18.3	15.5, 21.1	<0.001		
C-reactive protein, mg/dL	13.6	8.2, 19.0	<0.001		
Age, y	-5.5	-7.9, -3.1	<0.001		

CI: confidence interval; SE: standard error of the coefficient in univariate analysis or standard error of the estimate in multivariate models.
[a]compared to females, [b]compared to stage III, [c]n=105

Table 6.3 Regression analysis of predictors of resting energy expenditure in patients with stage IV colorectal cancer at baseline (n=91)

Univariate analysis					
	Coefficient	**95% CI**	**p-value**	**R^2**	**SE**
Age, years	-7.6	-11.9, -3.2	0.001	0.118	2.2
Sex[a]	290.2	191.5, 388.8	<0.001	0.277	49.6
Height, cm	20.7	15.6, 25.7	<0.001	0.428	2.5
Weight	10.2	7.3, 13.1	<0.001	0.351	1.5
Fat mass, kg	6.4	0.6, 12.1	0.031	0.051	2.9
Fat-free mass, kg	19.3	15.4, 23.1	<0.001	0.527	1.9
C-reactive protein, mg/dL[b]	10.8	0.9, 20.8	0.033	0.052	4.9
Multivariate analysis					
	Coefficient	**95% CI**	**p-value**	**R^2**	**SE**
Step 1			<0.001	0.527	181.6
Fat-free mass, kg	19.3	15.4, 23.1	<0.001		
Step 2[b]			<0.001	0.608	164.4
Fat-free mass, kg	19.5	16.0, 23.0	<0.001		
C-reactive protein, mg/dL	1.4	0.8, 2.1	<0.001		
Step 3[b]			<0.001	0.678	150.0
Fat-free mass, kg	19.1	15.9, 22.3	<0.001		
C-reactive protein, mg/dL	1.3	6.9, 18.7	<0.001		
Age, y	-5.7	-8.4, -3.1	<0.001		

CI: confidence interval; SE: standard error of the coefficient in univariate analysis or standard error of the estimate in multivariate models.
[a]compared to females, [b]n=88

Table 6.4 Demographic, anthropometric, and metabolic characteristics of patients with colorectal cancer at baseline and follow-up (n=49)

	Baseline	Follow-up	p-value
Age, y	64.9 ± 12.0	65.2 ± 12.1	<0.001
Body weight, kg	74.4 ± 14.6	75.0 ± 14.7	0.129
Body mass index, kg/m^2	25.4 ± 4.1	25.5 ± 4.1	0.463
Fat-free mass, kg	50.2 ± 10.0	50.9 ± 9.1	0.037
Fat-free mass index, kg/m^2	16.9 ± 2.2	17.1 ± 2.2	0.057
Fat mass, kg	23.1 ± 8.7	23.1 ± 9.5	1.000
Fat mass index, kg/m^2	7.9 ± 3.1	7.9 ± 3.3	0.816
C-reactive protein, mg/dL[a]	0.8 (0.3, 2.3)	1.0 (0.5, 4.6)	0.049
Measured REE, kcal	1559 ± 240	1594 ± 268	0.026
Respiratory quotient	0.79 ± 0.67	0.80 ± 0.05	0.440

Presented as mean ± standard deviation for normally distributed variables or median (interquartile range) for differences that are non-normally distributed (C-reactive protein).
REE: resting energy expenditure
[a]n=47 at baseline and n=48 at follow-up

Table 6.5 Linear regression analysis showing the determinants of resting energy expenditure change in patients with colorectal cancer (n=46)

Univariate analysis					
	Coefficient	**95% CI**	**p-value**	**R^2**	**SE**
Age, years	-0.7	-3.3, 1.8	0.568	0.007	1.3
Sex[a]	-3.4	-67.1, 60.3	0.915	<0.001	31.6
Height, cm	-0.3	-4.1, 3.5	0.873	0.001	1.9
Weight	-0.9	-3.1, 1.2	0.390	0.016	1.1
Stage[b]	87.5	2.6, 172.3	0.044	0.084	42.2
Baseline fat mass, kg	-1.3	-4.9, 2.3	0.455	0.012	1.8
Baseline fat-free mass, kg	-0.7	-3.8, 2.4	0.658	0.004	1.6
Baseline CRP, mg/dL	0.2	-7.3, 7.6	0.965	<0.001	0.4
Follow-up fat mass, kg	-1.6	-4.9, 1.6	0.320	0.021	1.6
Follow-up fat-free mass, kg	-0.5	-3.8, 2.7	0.744	0.002	1.6
Follow-up CRP, mg/dL	0.7	0.2, 1.3	0.010	0.135	0.3
Fat mass change, kg	-5.6	-17.8, 6.5	0.353	0.024	6.0
Fat-free mass change, kg	4.2	-10.1, 18.5	0.554	0.007	7.1
CRP change, mg/dL	1.9	1.1, 2.6	<0.001	0.342	0.4
Multivariate analysis					
	Coefficient	**95% CI**	**p-value**	**R^2**	**SEE**
Model			0.001	0.433	88.0
FFM change, kg	0.2	-12.3, 12.7	0.975		
CRP change, mg/dL	17.3	8.8, 25.8	<0.001		
Age, y	0.4	-2.1, 2.8	0.762		
Stage[a]	89.0	9.5, 168.4	0.029		
Days between visits	-0.1	-1.0, 0.9	0.895		
Study[b]	-50.7	-146.5, 45.0	0.291		

CI: Confidence interval; CRP: C-reactive protein; FFM: Fat-free mass; SEE: standard error of the estimate

[a]compared to stage III; [b]compared to study 1

6.7 References

1. Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr. 2016;70(11):1230-8.
2. Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? Cancer J. 2007;13(6):392-8.
3. Fouladiun M, Korner U, Bosaeus I, Daneryd P, Hyltander A, Lundholm KG. Body composition and time course changes in regional distribution of fat and lean tissue in unselected cancer patients on palliative care--correlations with food intake, metabolism, exercise capacity, and hormones. Cancer. 2005;103(10):2189-98.
4. Friesen DE, Baracos VE, Tuszynski JA. Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia. Theor Biol Med Model. 2015;12(1):17.
5. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr. 2009;89(4):1173-9.
6. Nguyen TYV, Batterham MJ, Edwards C. Comparison of resting energy expenditure between cancer subjects and healthy controls: A meta-analysis. Nutr Cancer. 2016;68(3):374-87.
7. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. Cancer incidence and mortality worldwide: IARC CancerBase No. 11 Lyon, France: World Health Organization 2012.
8. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, 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(12):1539-47.
9. Langius JA, Kruizenga HM, Uitdehaag BM, Langendijk JA, Doornaert P, Leemans CR, et al. Resting energy expenditure in head and neck cancer patients before and during radiotherapy. Clin Nutr. 2012;31(4):549-54.
10. Harvie MN, Campbell IT, Thatcher N, Baildam A. Changes in body composition in men and women with advanced nonsmall cell lung cancer (NSCLC) undergoing chemotherapy. J Hum Nutr Diet. 2003;16(5):323-6.
11. Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest. 2007;25(5):308-14.

12. Heymsfield SB, Thomas D, Bosy-Westphal A, Shen W, Peterson CM, Muller MJ. Evolving concepts on adjusting human resting energy expenditure measurements for body size. Obes Rev. 2012;13(11):1001-14.
13. Maguire R, McMillan DC, Wallace AM, McArdle C. A longitudinal study of leptin and appetite, resting energy expenditure and body fat mass in weight-stable cancer patients. Cytokine. 2002;20(4):174-7.
14. Heymsfield SB, Gallagher D, Kotler DP, Wang Z, Allison DB, Heshka S. Body-size dependence of resting energy expenditure can be attributed to nonenergetic homogeneity of fat-free mass. Am J Physiol Endocrinol Metab. 2002;282(1):E132-8.
15. Gallagher D, Belmonte D, Deurenberg P, Wang Z, Krasnow N, Pi-Sunyer FX, et al. Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass. Am J Physiol. 1998;275(2 Pt 1):E249-58.
16. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer. 2013;21(6):1569-77.
17. Prado CMM, Mourtzakis M, Baracos V, Reiman T, Sawyer MB, McCargar LJ. Overweight and obese patients with solid tumors may have sarcopenia, poor prognosis and early features of cachexia. Int J Body Compos Res. 2010;8(1):7-15.
18. Lundholm K, Daneryd P, Korner U, Hyltander A, Bosaeus I. Evidence that long-term COX-treatment improves energy homeostasis and body composition in cancer patients with progressive cachexia. Int J Oncol. 2004;24(3):505-12.
19. Lundholm K, Korner U, Gunnebo L, Sixt-Ammilon P, Fouladiun M, Daneryd P, et al. Insulin treatment in cancer cachexia: effects on survival, metabolism, and physical functioning. Clin Cancer Res. 2007;13(9):2699-706.
20. Daneryd P, Svanberg E, Korner U, Lindholm E, Sandstrom R, Brevinge H, et al. Protection of metabolic and exercise capacity in unselected weight-losing cancer patients following treatment with recombinant erythropoietin: a randomized prospective study. Cancer Res. 1998;58(23):5374-9.

21. Lindholm E, Daneryd P, Korner U, Hyltander A, Fouladiun M, Lundholm K. Effects of recombinant erythropoietin in palliative treatment of unselected cancer patients. Clin Cancer Res. 2004;10(20):6855-64.
22. Lundholm K, Daneryd P, Bosaeus I, Korner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: Effects on survival, metabolism, and function. Cancer. 2004;100(9):1967-77.
23. Prado CM, Lieffers JR, Bergsten G, Mourtzakis M, Baracos VE, Reiman T, et al. Dietary patterns of patients with advanced lung or colorectal cancer. Can J Diet Pract Res. 2012;73(4):e298-303.
24. World Health Organization Consultation. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. WHO Technical Report Series: 894. Geneva, Switzerland 2000;894:1-253.
25. Cooper JA, Watras AC, O'Brien MJ, Luke A, Dobratz JR, Earthman CP, et al. Assessing validity and reliability of resting metabolic rate in six gas analysis systems. J Am Diet Assoc. 2009;109(1):128-32.
26. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1-2):1-9.
27. Wang Z, Heshka S, Gallagher D, Boozer CN, Kotler DP, Heymsfield SB. Resting energy expenditure-fat-free mass relationship: new insights provided by body composition modeling. Am J Physiol Endocrinol Metab. 2000;279(3):E539-45.
28. Geisler C, Braun W, Pourhassan M, Schweitzer L, Glüer C-C, Bosy-Westphal A, et al. Age-dependent changes in resting energy expenditure (REE): Insights from detailed body composition analysis in normal and overweight healthy caucasians. Nutrients. 2016;8(6):322.
29. Manini TM. Energy expenditure and aging. Ageing Res Rev. 2010;9(1):1-26.
30. Burckart K, Beca S, Urban RJ, Sheffield-Moore M. Pathogenesis of muscle wasting in cancer cachexia: Targeted anabolic and anticatabolic therapies. Curr Opin Clin Nutr Metab Care. 2010;13(4):410-6.
31. Fredrix EW, Soeters PB, Rouflart MJ, von Meyenfeldt MF, Saris WH. Resting energy expenditure in patients with newly detected gastric and colorectal cancers. Am J Clin Nutr. 1991;53(5):1318-22.

32. Adriaens MP, Schoffelen PF, Westerterp KR. Intra-individual variation of basal metabolic rate and the influence of daily habitual physical activity before testing. Br J Nutr. 2003;90(2):419-23.
33. de Roos B, Brennan L. Personalised interventions—a precision approach for the next generation of dietary intervention studies. Nutrients. 2017;9(8):847.
34. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015;163(5):1079-94.
35. Scott HR, McMillan DC, Watson WS, Milroy R, McArdle CS. Longitudinal study of resting energy expenditure, body cell mass and the inflammatory response in male patients with non-small cell lung cancer. Lung Cancer. 2001;32(3):307-12.
36. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care. 2009;12(3):223-6.
37. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88(1):218-30.
38. Gordon JN, Green SR, Goggin PM. Cancer cachexia. QJM. 2005;98(11):779-88.
39. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10(2):90-9.
40. Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. Am J Clin Nutr. 2005;82(4):801-5.
41. Kamimura MA, Draibe SA, Avesani CM, Canziani ME, Colugnati FA, Cuppari L. Resting energy expenditure and its determinants in hemodialysis patients. Eur J Clin Nutr. 2007;61(3):362-7.
42. Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin Chem. 1997;43(1):52-8.
43. Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. Thyroid. 2008;18(2):141-4.

44. Drabsch T, Holzapfel C, Stecher L, Petzold J, Skurk T, Hauner H. Associations between C-reactive protein, insulin sensitivity, and resting metabolic rate in adults: A mediator analysis. Front Endocrinol (Lausanne). 2018;9:556-.
45. Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN, editors. Energy Metabolism: Tissue Determinants and Cellular Coeollaries. New York: Raven Press; 1992. p. 61-80.
46. Hansell DT, Davies JW, Burns HJ. Effects of hepatic metastases on resting energy expenditure in patients with colorectal cancer. Br J Surg. 1986;73(8):659-62.
47. Irwin ML, Crumley D, McTiernan A, Bernstein L, Baumgartner R, Gilliland FD, et al. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. Cancer. 2003;97(7):1746-57.
48. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996-1002.
49. Skipworth RJ, Stene GB, Dahele M, Hendry PO, Small AC, Blum D, et al. Patient-focused endpoints in advanced cancer: criterion-based validation of accelerometer-based activity monitoring. Clin Nutr. 2011;30(6):812-21.
50. clinicaltrials.gov. Identifier: NCT03131921. Resting Energy Expenditure in Cancer - Associations With Body Composition, Dietary Intake, and Exercise Habits Bethesda, MD: National Library of Medicine; 2017 [updated May 3, 2017. Accessed February 2, 2018].
51. Bosaeus I, Daneryd P, Lundholm K. Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. J Nutr. 2002;132(11 Suppl):3465s-6s.
52. Nasrah R, Kanbalian M, Van Der Borch C, Swinton N, Wing S, Jagoe RT. Defining the role of dietary intake in determining weight change in patients with cancer cachexia. Clin Nutr. 2018;37(1):235-41.
53. Kubrak C, Olson K, Jha N, Scrimger R, Parliament M, McCargar L, et al. Clinical determinants of weight loss in patients receiving radiation and chemoirradiation for head and neck cancer: a prospective longitudinal view. Head Neck. 2013;35(5):695-703.

54. Blum D, Omlin A, Baracos VE, Solheim TS, Tan BH, Stone P, et al. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. Crit Rev Oncol Hematol. 2011;80(1):114-44.
55. Maccio A, Madeddu C, Gramignano G, Mulas C, Floris C, Sanna E, et al. A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life. Gynecol Oncol. 2012;124(3):417-25.
56. Dev R, Bruera E, Dalal S. Insulin resistance and body composition in cancer patients. Ann Oncol. 2018;29(suppl_2):ii18-ii26.

Chapter 7 Total Energy Expenditure in Relation to Body Composition, Physical Activity, and Current Energy Recommendations in Patients with Colorectal Cancer

7.1 Preface

This analysis measured total energy expenditure (TEE) using doubly labeled water in 21 patients with stage II-IV colorectal cancer (CRC), recruited from the Cross Cancer Institute. This is the first study to characterize TEE in primarily early stage CRC and one of only four other studies that have assessed TEE in cancer. A version of Chapter 7 is being prepared for submission to the Journal of Cachexia Sarcopenia and Muscle with the following co-authors: Dr. Sarah A. Elliott, Dr. Peter J. Walter, Dr. Tom Preston, Dr. Hongyi Cai, Dr. Richard J.E. Skipworth, Dr. Michael B. Sawyer, and Dr. Carla M. Prado.

This was part of a larger study which I designed in collaboration with my supervisor, Dr. Carla Prado. I was responsible for collecting, analyzing and interpreting data and creation of the initial chapter/manuscript. I administered the doubly labelled water and collected and processed the biological samples, but isotope enrichments were ultimately assessed using mass spectrometry by Dr. Peter J. Walter and Dr. Hongyi Cai at the National Institutes of Health. I was responsible for obtaining all other measurements mentioned in the following chapter (~80% proportion of contribution to research and writing). Other collaborator contributions were as follows: Dr. Sarah A. Elliott, Dr. Peter J. Walter, and Dr. Tom Preston helped guide the doubly labeled water protocol; all collaborators have contributed to data interpretation and manuscript revision.

7.2 Abstract

Preventing and mitigating muscle loss is essential for improved prognosis. Muscle mass maintenance and accretion requires consumption of sufficient calories. Accurate energy recommendations hinge on the characterization of total energy expenditure (TEE), which associates with body composition and physical activity in healthy populations. However, TEE data in patients with cancer is scarce (especially in those with earlier cancer stages), precluding an understanding of energy requirements. The objective of the current research was to cross-sectionally characterize TEE in patients with colorectal cancer (CRC) in relation to body composition and physical activity levels (PAL) and to compare measured TEE to cancer-specific energy intake recommendations. It was hypothesized that TEE would differ according to body mass, body composition and PAL and current energy recommendations would have poor individual-level accuracy. Patients with newly-diagnosed CRC had resting energy expenditure (REE) measured by indirect calorimetry and TEE by doubly labeled water. Hypermetabolism was defined as REE > 110% predicted from the Mifflin St.-Jeor equation. Body composition was assessed via dual X-ray absorptiometry. Physical activity was determined as the ratio TEE:REE (PAL) and residual activity energy expenditure (RAEE). TEE was compared to energy recommendations of 25-30 kcal/day and dietary reference intakes (DRI) using Bland-Altman analyses. Patients were stratified according to median body mass index (BMI), PAL, and sex-specific fat mass (FM) to fat-free mass (FFM) ratio (FM:FFM). Twenty-one patients (M:F 14:7; BMI: 28.3±4.9kg/m^2, age: 57±12years) were included. Most (n=20) had stage II-III disease; 1 had stage IV. Approximately half (n=11) were hypermetabolic; TEE was not different in those with hypermetabolism and REE was not correlated to TEE. TEE was 2473±499 kcal/day (range: 1562 - 3622 kcal/day), or 29.7±6.3 kcal/kg body weight (range: 20.4 - 48.5 kcal/kg). Average PAL was 1.43 ± 0.27. Energy recommendation of 25 kcal/kg underestimated TEE (-12.6 ± 16.5%, P = 0.002); all energy recommendations had wide limits of agreement (smallest was DRI: -21.2 to 29.3%). Patients with higher BMI and FM:FFM had higher bias using kcal/kg recommendations; bias from several recommendations was frequently lower in patients with higher PAL and RAEE. In conclusion, TEE variability was not reflected in energy recommendations and error was influenced by body weight, body composition, and physical activity.

7.3 Introduction

Characterizing total energy expenditure (TEE) is essential for the provision of sufficient dietary energy to support energy balance. Maintaining and synthesizing skeletal muscle in negative energy balance (i.e. during weight loss) is difficult, if not unattainable, even in highly trained athletes (1). Understanding energy balance is especially relevant for individuals with cancer since body weight and body composition changes (i.e. loss of skeletal muscle or fat-free mass, FFM) are common and detrimental to prognosis (2-4). Conversely, weight gain during cancer treatment may not confer a survival advantage in some circumstances (2), might worsen pre-existing comorbidities, and increase secondary disease risk in patients with obesity (5, 6).

In oncology, most of our understanding of energy expenditure comes from studies of resting energy expenditure (REE). However, REE might be affected by changes in body composition, systemic inflammation or tumor burden and may not correlate to TEE (7). Since the ratio of TEE to REE is indicative of physical activity level (PAL), absence of a relationship between REE and TEE indicates that variable physical activity (rather than REE) might impact TEE.

To date, only four reports on measured TEE in cancer have been published, with measures made in free-living patients using objective and accurate techniques such as doubly labeled water (DLW) or bicarbonate-urea (7-10). The majority of patients in these previous studies had advanced disease (7) or severe weight loss (i.e. 19% of pre-illness body weight) (8). However, this might represent a small proportion of patients with certain types of cancer. For example, colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world (11); improvements in screening practices, lower incidence of risk factors, and effective treatments options has led to a higher proportion of cancer cases diagnosed at earlier stages (12), where severe weight loss is less common (13). These patients also have a high prevalence of obesity and may gain body weight during curative-intent treatment (14). Furthermore, low and loss of muscle (3, 15) (and therefore FFM) occur independently of body weight alterations in individuals with earlier-stage colorectal cancer and negatively impact survival (3, 16). The dietary energy required to prevent and treat loss of body weight and skeletal muscle is unknown. Similarly, the potential impact of body composition on TEE has not been characterized.

Due the paucity of data characterizing TEE in patients with cancer, current internationally-accepted oncology energy intake recommendations from the European Society of Clinical Nutrition and Metabolism are based on an estimate of 25-30 kcal/kg body weight with a call for further research (17). However, basing recommendations on body weight alone would likely overestimate energy requirements in individuals with obesity and underestimate it in those with low body weight (18). Furthermore, such recommendations do not consider body composition, physical activity, cancer type, or disease stage, which might impact TEE.

The objectives of the current study were to compare TEE to current energy recommendations and to characterize TEE in relation to body weight, body composition, and physical activity. Exploratory objectives included assessing relationships between energy expenditure, physical activity, and body composition and the potential impact of these variables on several patient-centered and treatment-related parameters. It was hypothesized that current energy recommendations would have poor individual-level accuracy, given findings regarding REE presented in Chapter 3 and by others (19). It was also hypothesized that TEE would differ according to body mass, body composition, and PAL categories, since these variables are the primary determinants of TEE in healthy populations (20).

7.4 Methods

7.4.1 Participants

This analysis is part of a larger cross-sectional study measuring energy expenditure, body composition, physical activity and dietary intake in patients with cancer (21). Patients with stage II-IV CRC were recruited from the Cross Cancer Institute in Edmonton, Alberta, Canada. This study was approved by the Health Research Ethics Board of Alberta and informed consent was obtained from all patients prior to study assessments. Inclusion criteria were recent cancer diagnosis, aged 18 - 90 years, and able to communicate freely in English. Exclusion criteria included anti-cancer therapy or surgery within the past four weeks, confinement to a wheelchair, medications or conditions that might affect body composition or metabolism (steroids, hormone replacement, unstable thyroid disease), inability to breathe under the calorimetry hood for 30 minutes, pregnancy, or breastfeeding. All measurements were completed within (before or after) two weeks of starting anti-cancer therapy, where applicable.

7.4.2 Patient-Reported Measures

Patients completed the Patient-Generated Subjective Global Assessment (PG-SGA) – short form (22), which consists of four sections: weight (score range: 0 - 5), food intake (score range: 0 - 4) symptoms (score range: 0 - 24), and activities and function (score range: 0 - 3). Lower scores indicate better results in each section. The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire – C30 (version 3.0) (23) was also completed; only overall quality of life score (range: 1 - 7) was used in this analysis, with higher scores representing better quality of life. The International Physical Activity Questionnaire – Long Form (IPAQ)(24) was used to measure subjective physical activity; continuous values from the IPAQ were expressed as metabolic equivalencies of tasks (MET) minutes/week.

7.4.3 Anthropometry and Body Composition

Height and weight were measured using a Health-O-Meter Professional digital scale with height rod (McCook, IL, USA; model number: 597KL) with shoes and heavy clothing removed. One-month and six-month previous weight change percent was collected from the PG-SGA. Body mass index (BMI) was calculated [weight (kg)/ height (m^2)] and classified according to the World Health Organization's cut-points (25).

Body composition was assessed by dual X-ray absorptiometry (Lunar iDXA, GE Healthcare, Chicago, IL; Encore 2001 software version 13.60) within a median of 9 ± 3 days of energy expenditure assessments. Fat mass (FM) and FFM were expressed adjusting for height in m^2 (fat mass index, FMI, and fat-free mass index, FFMI) and as a ratio of each together (FM:FFM), to represent metabolic load and capacity (26). Percent body fat was also reported. Appendicular skeletal muscle index (ASMI) was calculated as the sum of lean soft tissue from limbs divided by height (kg/m^2), with low ASMI defined as <5.45 kg/m^2 for females and <7.26 kg/m^2 for males (13, 22). Similarly, FFMI <15 kg/m^2 for females and <16 kg/m^2 for males were used to define "myopenia" (27) for exploratory purposes.

7.4.4 Resting Energy Expenditure

A metabolic cart with ventilated hood system (VMax^{TM} Spectra 29N, Nutritional Assessment Instrument; Sensor-Medics, Yorba Linda, CA, USA) was used to measure REE. This particular system is considered one of the most accurate metabolic carts (28) and has been used as a gold standard in previous studies (29, 30). Volume and air flow were calibrated prior to each measurement using a three-liter syringe. Although a burn test was not conducted, gas

analysers were calibrated before each test with standard gas concentrations of 20.95% oxygen (O_2) and 0.03% carbon dioxide (CO_2). Fraction of expired carbon dioxide was kept between 0.75 and 0.80 for as much time as possible. Breath samples were collected for a minimum 30 minutes and only steady state data (variations in volume of O_2 and CO_2 of $\leq$ 10% over five consecutive minutes) was used to calculate REE according to the abbreviated Weir equation (31). No steady state data was collected in the first ten minutes of testing and a minimum of 10 minutes of steady state data was needed for REE calculation. Respiratory quotient was calculated as the ratio between carbon dioxide produced and oxygen consumed (CO_2/O_2). Measured REE was compared to predicted REE for the sole purpose of identifying high or low REE, or hyper- or hypo-metabolism, respectively. The Mifflin St.-Jeor equation was used for predicted REE since it has been shown to have the least amount of individual variability among 24 other anthropometric and body composition-based equations (Chapter 3).

7.4.5 Total Energy Expenditure

The DLW method was used to determine TEE over 14 days (primary endpoint of the study). Stock doses were formulated using 10 atom% oxygen 18 (^{18}O) and 99.9 atom% deuterium (^{2}H) based on 1g/kg ^{18}O and 0.1 g/kg ^{2}H of body weight per patient. A single baseline urine sample was collected before dosing (pre-dose). Patients drank the dose with a straw followed by ~50mL tap water to rinse the dose cup; actual dose was therefore assumed to be the same as the dose given. All patients were asked to collect a urine sample 4.5 and 6 hours after dosing and 1-2 times/day for the following 13 days. Only urine samples from pre-dose, 4.5 and 6 hours post-dose, days 3, 7, and 14 were used in the analyses.

Measurement of $^{2}H_2$ and ^{18}O isotope enrichments from stock doses and urine samples were analyzed by using a dual inlet chromium reduction and continuous flow isotope ratio mass spectrometer at the National Institutes of Health (Bethesda, MD, USA). Natural logarithms of ^{2}H and ^{18}O enrichments were regressed against time, with slopes of regression lines representing rates of ^{2}H and ^{18}O loss from body water (k_H and k_O, respectively). ^{2}H and ^{18}O dilution spaces (N_H and N_O, respectively) were determined by dividing administered isotopes (in moles) by the intercepts. Total body water was then calculated as (32, 33):

Total body water = 0.5 x ($N_O/c_O + N_H/c_H$)

Where c_H and c_O were the ^2H and ^{18}O pool sizes relative to total body water. To account for some isotopes entering organic pools, non-aqueous c_H was assumed to be 1.041 and c_O was assumed to be 1.007. The isotope fractionation for ^2H leaving the body as water vapor is 0.946 times the true rate of water it equilibrates with and the fractionation factor for ^{18}O leaving the body as CO_2 is 1.038 times the true rate of carbon dioxide production (34). We assumed breath was saturated with water vapor and non-sweat skin water vapour loss was proportional to exposed skin surface; therefore the simplified equation from the International Atomic Energy Agency (34) was used to calculated CO_2 as follows:

CO_2 (moles) = 0.455 x total body water ($c_O k_O - c_H k_H$)

CO_2 was used in the modified Weir equation (31) to calculate TEE as:

TEE (kcal/day) = 22.4 x (1.1 x CO_2 + 3.9 x O_2)

where O_2 (in liters/day) was calculated by:

O_2 = CO_2 ÷ food quotient

Calculation of food quotients (35) in the present study indicated average food quotient of 0.86 ± 0.03. However, this was calculated from 24-hour dietary recalls (data not presented), which are inaccurate for long-term dietary assessment. As such, food quotient was assumed to be 0.86 for all subjects, representative of a typical diet on a population level (36). Measuring respiratory quotient or predicting respiratory quotient from the composition of the diet will result in small TEE errors not exceeding ± 2% (35).

Quality control measures to screen for unacceptable estimates included confirming the following for each patient: ^{18}O enrichment/intercept >0.08, linear fit of ^2H and ^{18}O slopes, k_O/k_H 1.1 - 1.7, similar residuals of predicted and measured ^2H and ^{18}O, and N_H/N_O 1.0 - 1.7. One patient provided urine samples for isotope analysis on days 11 and 17 and both were assessed.

Another patient underwent unexpected surgery on day 5 and had 4 days of samples; since all quality control measures outlined above were met (including k_O/k_H =1.315 and N_H/N_O = 1.050) and our results were similar with and without this patient, the data was kept in the final analyses.

TEE was expressed as kcal/day and kcal/kg body weight. Predicted TEE was calculated as 25 kcal/kg and 30 kcal/kg body weight based on internationally-accepted clinical oncology guidelines (17) and from Dietary Reference Intakes (DRI), using the overweight and obese specific equation where appropriate (37). For exploratory purposes, IPAQ categories were used to determine physical activity categories for the DRI TEE equation as follows: sedentary: IPAQ category 1, low active: IPAQ category 2, active: IPAQ category 3.

7.4.6 Physical Activity

PAL was determined as the ratio between TEE and REE. The thermic effect of food was not considered in this calculation, as it was not measured in this study. Since PAL is a ratio method and subject to bias as the regression intercept is not zero (38) (or could be indicative of a non-linear relationship), activity was also expressed as residual activity-related energy expenditure (RAEE)(39). This was calculated as the residual from TEE (dependent) and REE (independent), with positive values being associated with higher-than-average physical activity and negative numbers being associated with lower-than-average physical activity (expressed in kcal/day).

Patients were asked to wear ActiCal accelerometers (Phillips Respironics, Bend, OR, USA) during the 14-day collection period on the right hip. A 15-second epoch length was used. Patients were also asked to keep a record of wear times, including time awoken in the morning and time to bed in the evening. A valid day of monitoring was defined as ≥12 hours of wear time (40). Only patients with at least four valid days of accelerometer monitoring were included (41). TEE calculations from ActiCal was also compared to measured TEE.

7.4.7 Medical Variables

At the time of assessment, patients were scheduled to begin either radiation, chemotherapy, combined radiation and chemotherapy, or surveillance. For exploratory purposes, the association between energy expenditure and body composition measures with alterations in treatment were described. Treatment alterations included treatment delays, dose reductions, or dose discontinuations; any occurrence of these were coded as a treatment alteration (“0” or “1”).

Prospective weight change over treatment or surveillance was also acquired from medical records and expressed as %weight change/100 days to account for varying follow-up appointment dates.

7.4.8 Statistical Analysis

All data was assessed using SPSS software, version 24 (IBM Corp., Armonk, NY, USA), with the threshold for significance set at $p \leq 0.05$. Normality in variables was determined using the Shapiro-Wilk test; non-normally distributed variables were reported as median and interquartile range (IQR). Effect size for post-hoc sample size analysis was calculated using TEE data at baseline from an ongoing clinical trial in a similar population (42). An effect size of 0.73 and α 0.05 yielded a power of 0.89 to detect differences between measured versus predicted TEE from the DRI equation using two-tailed paired samples t-test.

Pearson correlation coefficients or Spearman's rank-order correlation (for non-parametric variables) described relationships between variables. BMI and PAL were split by the sample median and FM:FFM was split by sex-specific sample median to explore differences in energy expenditure. Paired t-tests assessed differences in parameters within individuals. Independent samples t-tests or Mann-Whitney U-test (when dependent variables were non-normally distributed for each group of the independent variable) determined differences between patient groups stratified by sex, previous radiotherapy (yes or no), % REE from predicted, ASMI, PAL median, RAEE (negative versus positive residuals), BMI median, sex-specific FM:FFM median, or TEE. Bland-Altman analyses were used to assess the agreement between measured and predicted TEE from current equations and ActiCal-derived TEE. Bias, or the mean difference between predicted and measured values indicates group-level agreement. Limits of agreement, or bias ± two standard deviations indicates agreement for each individual. Bias and limits of agreement were expressed as percent to account for body size and individual energy expenditure. Proportional bias was quantified by Pearson correlation coefficient between mean of measured and predicted TEE and bias were used to determine if there were trends in the magnitude of bias with increasing TEE.

7.5 Results

Patients

A total of 21 patients (14 male, 7 female) were included in the study, with 20 completing body composition and accelerometer measurements. Patient characteristics are presented in **Table 7.1**. Only one patient had stage IV disease and was not an outlier in terms of energy expenditure or body composition measurements. All other patients had stage II (n=3, 14.3%) or stage III (n=17, 80.1%) disease and most individuals were overweight (n=8, 38.1%) or obese (n=8, 38.1%). Average previous one-month weight change was -1.5% ± 3.4% (range: -7.9% to 4.9%) and previous six-month weight change was -5.3% ± 5.1% (range: -20.0% to 0%), with no differences in weight loss between sexes. Seven patients had weight loss >5% in the past 6 months. Four patients had undergone neoadjuvant combined radiotherapy and chemotherapy (>1 month prior to study inclusion), with two having colon cancer and two having rectal cancer. There were no differences in anthropometric, demographic, energy expenditure, or body composition variables between those who had received or not received radiotherapy. Most (n=17) patients had undergone surgery for early stage disease; these individuals were still considered as patients with cancer since adjuvant therapy was part of the prospective treatment plan to completely eradicate the cancer. Most (n=10, 47.6%) were scheduled to undergo adjuvant chemotherapy with folinic acid, fluorouracil, and oxaliplatin, with remaining patients scheduled to begin neoadjuvant radiochemotherapy (n=8, 38.1%), neoadjuvant short-course radiotherapy (n=2, 9.5%), or surveillance (n=1, 4.8%).

Patient-reported measures

Most patients had low scores for all PG-SGA boxes, indicating good subjective nutritional status and physical function. Most (n=11, 52.4%) scored 0 for weight change. All patients scored 0 (n=9, 42.9%) or 1 (n=12, 57.1%) for food intake. Symptom score was variable (range 0 - 6), with most (n=13, 61.9%) indicating no symptoms. Within activities and function, most patients indicated they were “normal with no limitations” (n=10, 47.6%) or “not my normal self, but able to be up and about with fairly normal activities” (n=9, 42.9%), with two (9.5%) selecting “able to do little activity and spend most of the day in bed or chair”. Median global quality of life score was 5.5 (IQR: 4.5 - 6.0) on a scale of 1 to 7. Self reported physical activity from IPAQ was highly variable: median walking MET-minutes/week was 693 (IQR: 396 - 2871) and median moderate activity was 900 MET-minutes/week (IQR: 300 - 1875). Most (n=17,

81.0%) did not report vigorous activity. Median total MET-minutes/week was 1955 (IQR 1265 - 5724).

Anthropometrics and body composition

Anthropometric and body composition variables are presented in **Table 7.1**. As expected, FFM and FFMI were lower in females; however, there were no differences in FM or FMI between sexes. Median BMI was 28.7 kg/m^2 and median FM:FFM was 0.44 in males and 0.63 in females.

Energy expenditure description

All measures of TEE from DLW met quality control estimates. Average tracer elimination rate (k_O/k_H) from DLW was normal (1.281 ± 0.050) and $^2H_2$:^{18}O distribution volume (N_H/N_O) was 1.036 ± 0.018. Males had higher REE and TEE, but not PAL, **Table 7.1**. Average respiratory quotient was 0.80 ± 0.05. Group median REE was 1698 kcal/day (IQR: 1146 - 2009 kcal/day; mean ± standard deviation: 1764 ± 415 kcal/day), which was higher than the Mifflin St.-Jeor prediction (median [IQR]: 1545 [1411 - 1817], p=0.001). Approximately half (n=11, 52.4%) of patients had measured REE >110% of predicted (suggestive of hypermetabolism) and none had measured REE <90% of predicted (suggestive of hypometabolism). Patients with REE > 110% predicted had lower PAL (1.31 vs. 1.56, p=0.024) and RAEE (-179 vs. 196 kcal/day from the regression line, p=0.022). However, percent REE bias was not correlated to TEE in kcal/day or kcal/kg/day and there were no differences in TEE, percent one-month or six-month weight change between groups; in other words, higher REE compared to predicted was associated with lower physical activity but did not impact total energy requirements or weight change.

TEE was 2473 ± 499 kcal/day or 29.7 ± 6.3 kcal/kg body weight. These values were highly variable ranging from 1562 to 3622 kcal/day or 20.4 to 48.5 kcal/kg body weight. Males had higher absolute TEE than females (males: 2646 ± 490 vs. females: 2127 ± 313 kcal/day, p=0.020) although TEE in kcal/kg body weight and PAL were not different between sexes, **Table 7.1**. Approximately half (n=12, 57.1%) of patients fell within 25-30 kcal/kg body weight, **Figure 7.1**. Average PAL was 1.43 ± 0.27 and was also variable, ranging from 1.04 to 2.16.

Relationships between energy expenditure variables and age, body weight, FM, and FFM are shown in **Table 7.2**. REE and TEE were positively correlated to body weight and FFM, with

higher correlations observed with FFM compared to body weight. PAL and RAEE were not related to any variable. Four patients had low ASMI (all male) and two of these had weight loss >2% in the previous 6 months (i.e. cachectic [43]). There were no differences in any anthropometric, energy expenditure, or physical activity variables between individuals with low versus normal ASMI; these results were the same when only males were assessed. Similarly, only one patient had FFMI below pre-defined cut-off values, precluding any further comparison.

Agreement with energy requirement equations

Predicted TEE was correlated with measured TEE in all equations (r: 0.548 - 0.826, p: 0.010 - <0.001). Predicted TEE with 25 kcal/kg was significantly lower than measured TEE (2128 ± 459 vs. 2473 ± 499 kcal/day, p=0.002), but all other equations were not different on a group level, **Table 7.3**. However, all equations had wide limits of agreement; for example, even the equation with the smallest limits of agreement (DRI with measured PAL) under-predicted by up to 22.5% below (484 kcal/day) to 22.7 % above (468 kcal/day) measured TEE, **Figures 7.2a-e**. Using assumed PAL from IPAQ categories did not improve the predictive ability and produced the widest limits of agreement (-33.5 to 50.2%, or -742 to 1060 kcal/day). No proportional bias was apparent in any equation.

Body weight, FM, and FM:FFM were positively correlated to percent bias using 25 kcal/kg and 30 kcal/kg, **Table 7.4**. PAL and RAEE were negatively correlated to percent bias from 25 kcal/kg, 30 kcal/kg, DRI with assumed PAL, and ActiCal TEE. Average percent bias using 25 kcal/kg and 30 kcal/kg was lower (i.e. underestimation) in those with BMI and FM:FFM below the medians (BMI median: 28.29 kg/m^2; FM:FFM median: males: 0.44, females: 0.63), **Figures 7.3a** and **7.3b**. Bias was frequently lower in those with higher PAL and RAEE, **Figures 7.3c and 7.3d.** Patients with TEE > 30 kcal/kg (n=7) had lower BMI (24.1 vs. 30.4 kg/m^2, p<0.001), higher PAL (1.67 vs. 1.31, p=0.001), and higher RAEE (0.78 vs. -0.39, p=0.006). REE bias from Mifflin St.-Jeor equations was not related to bias from TEE equations.

Activity patterns

Average wear time of the ActiCal devices was 12 ± 3 days, with 20 patients having ≥ 4 days of wear time and at least one weekend (2 days) available. Average step count was 5,101 ± 2,547 steps/day with a range of 1,470 to 10,823 steps/day. Total IPAQ score was not correlated

to any measure of energy expenditure and no other correlations between activity and body composition, physical function, or quality of life was observed.

Clinical parameters

Average weight change during treatment was -2.4 ± 5.2%/100 days and was not associated with any energy expenditure, body composition, or physical activity measures. Of patients who underwent treatment (n=20), 13 (65%) experienced a change in treatment plan such as dose reductions (n=9), delays (n=5), or discontinuations (n=4). The composite score of any treatment alteration was not related to any anthropometric, body composition, or energy expenditure variables.

7.6 Discussion

To our knowledge, this study is the first to measure TEE in free living conditions in patients with primarily earlier stage cancer. TEE and PAL were higher than previously reported (8, 9) and were greatly variable, which is not reflected in current oncology or general population recommendations (17, 37). Additionally, discrepancies between measured versus predicted TEE were influenced by body weight, body composition, and physical activity.

As screening and treatment modalities continue to improve, it is expected that more patients will be diagnosed at earlier stages of cancer with longer expected survival; therefore, understanding differences in energy requirements between earlier stage non-cachectic patients and those with advanced disease and severe weight loss is important for optimal nutritional care. However, our current knowledge base relies primarily on patients with cachexia and/or advanced disease, which might be unrepresentative of many patients with CRC (13, 44). The largest study to date that objectively measured TEE using DLW included 24 cachectic patients with advanced pancreatic cancer with an average BMI of 20 kg/m^2 and 19% pre-illness weight loss (8). Average REE was higher and TEE was lower than predicted and average PAL was 1.24 at baseline (8). Others have reported overall low PAL (9) and TEE (7) and that structured exercise can increase TEE (10) in sample sizes ranging from four to eight patients with various cancer types. Average PAL of our sample was 1.43 ± 0.27, which is higher than previously reported in oncology (8, 9); this value corresponds to a “low active” lifestyle (37) and is slightly lower than reported in healthy individuals (PAL 1.6) (45). Compared to previous research (7, 8), patients in the current sample had generally earlier stage disease, less weight loss, lower incidence of low ASMI and

low FFMI. Notably, CRC is associated with lower incidence of weight/loss cachexia compared to other cancer types (e.g. pancreatic, lung, gastric cancer) (44). Most individuals in this study also had adequate physical function and PAL was highly variable. In advanced, cachectic patients, higher REE and lower TEE may indicate an adaptive response to narrow the gap between TEE and reduced energy intake or a reflection of low physical activity secondary to the disease and its associated side effects (8), which may not occur in earlier stage CRC. Our findings are novel and suggest that energy metabolism - and therefore energy requirements - differs greatly according to cancer site and stage. Further exploration of the determinants of TEE and PAL according to cancer site and stage is warranted.

We found that energy recommendations based on body weight alone were poor assessments of actual energy requirements (assumed to be equal to TEE), with individual differences ranging from -1613 kcal/day (or 48.5%) underprediction with 25 kcal/kg body weight/day to 968 kcal/day (or 46.9%) overprediction with 30 kcal/kg body weight/day. The recommendation of 25 kcal/kg/day was significantly lower on a group level, suggesting this is an inappropriate approach to estimate energy requirements in these patients. Although DRI energy requirement predictions with measured PAL had the smallest limits of agreement, individual error was still high. Additionally, a small proportion of energy requirement predictions fell within 10% of measured TEE, ranging from 33.3% using 25 kcal/kg/day to 47.6% using DRI with measured PAL and DRI with assumed PAL. This proportion is smaller than previous reports in healthy adults (62.9 - 85.7%) (46, 47), suggesting that cancer impacts TEE in ways not captured by current energy recommendations.

Inaccuracies in energy recommendations appear to be related to body weight, body composition, and physical activity. Since obesity is a risk factor for several cancers (including CRC) (48, 49), a large number of individuals have obesity at diagnosis (50). Indeed, our sample had a large proportion of individuals with obesity and percent body fat was high in both sexes. However, low FFM is apparent at diagnosis in patients with CRC, independent of body weight and FM, and is not a condition exclusive to advanced cancer (3). Indeed, we found that bias using body weight-based equations was positively related to body weight and composition (i.e. higher body weight, FM, and higher FM:FFM related to over-prediction) and negatively related to physical activity (i.e. higher physical activity related to under-prediction). Interestingly, REE

bias as a measure of abnormal metabolism was not related to TEE. While previous research suggests that TEE might be lower in the presence of high REE (8), this was not true for all individuals in the current study and assuming an altered TEE based on REE alone might introduce substantial bias in energy recommendations. Therefore, equations that incorporate body composition and physical activity and developed from oncology populations would likely be more accurate, although further research on the feasibility and accuracy of such approaches is needed.

Physical activity is highly variable in healthy individuals and can significantly impact TEE (45). In the present study, PAL variability was similar than that of healthy adults (45). One individual had a PAL corresponding to a "very active" lifestyle (37)(PAL: 2.16); this individual reported working a job requiring moderate physical labor (electrician/handyman) and had the highest percent of time spent in moderate activity of all participants (20%, from ActiCal data). This value is therefore likely reflective of this individual's habitual activity, although such a high value may not sustainable in individuals during chemotherapy. We found average step count was slightly higher than previously reported in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy (51). It was anticipated that TEE and physical activity measures would be related to quality of life (52); however, this was not the case, although this might be due to the small sample (not the primary research question) and lack of follow-up after treatment initiation. According to our data, it appears that physical activity also greatly impacted energy requirements in these patients and was the most variable component of TEE. However, subjective measures of physical activity (IPAQ) did not improve estimation of energy requirements and were not related to any physical or clinical measure. This is likely because physical activity is often over-reported (53) or under-reported (54) and is therefore a poor reflection of actual physical activity engagement. Since physical activity is feasible, safe, and beneficial for patients with cancer (55-57) and impacts energy requirements, improved techniques for capturing this modality are needed.

Although this study did not include direct measures of inflammation such as C-reactive protein, interleukins 1 or 6, or tumor necrosis factor-α, REE has been shown to associate with these indices in cancer (58, 59). However, the potential causative effects of inflammation on PAL has not been elucidated in cancer. For example, inflammation is associated with higher

fatigue (60), and could indirectly and unconsciously reduce PAL. Conversely, physical activity is negatively correlated with inflammatory markers in healthy populations (61, 62) and structured exercise reduces inflammation and fatigue in cancer (60). Future investigations should investigate the relationship between inflammation and REE, PAL, and TEE.

While this is the largest exploratory study of TEE in earlier stage cancer and CRC using several accurate techniques, there are limitations. Firstly, DLW measures TEE over a span of only two weeks. The impact of anti-cancer therapy (and associated side effects), body composition changes, or disease progression on TEE and physical activity patterns cannot be assumed. Our findings may only be applied to patients early in the treatment trajectory since only one timepoint was investigated. Furthermore, REE was measured with a metabolic cart, which might underestimate REE compared to whole-body calorimetry units (63). However, metabolic carts are the most widely used methodology in the current literature and our results can therefore be compared to similar studies. Overall results would also likely be similar in terms of TEE and PAL variability if REE had been measured using a whole-body calorimetry unit as methodological discrepancy is presumably systematic.

There are also several assumptions of the doubly labelled water method that should be considered in the interpretation of these results. Food quotient was assumed rather than measured, given the inaccuracies of dietary recall and in line with the majority of outpatient studies of energy expenditure, which also assume food quotients of 0.85 or 0.86. Extreme perturbations in the carbohydrate content of the diet influence the accuracy of CO_2 production rates used in the calculation of TEE. However, the magnitude of this potential bias likely amounts to a TEE difference of about 30-60 kcal/day and may only be significant when comparing TEE between ketogenic and normal diets (64). Review of 24-hour dietary recalls completed on the first day of DLW dosing in the present study indicated that no patient was following a ketogenic diet (data not presented). However, the popularity of these diets continues to increase and the potential for therapeutic benefit might become more apparent in cancer (65); therefore, ketosis should be considered in future studies utilizing DLW. Finally, body composition was not measured at the end of the two-week DLW protocol, and we therefore cannot conclude that body composition was stable. However, tools to measure body composition such as dual energy X-ray absorptiometry are not sensitive enough to detect body composition

changes over short time spans and rely on several assumptions when used to estimate energy balance (66). Therefore, short-term energy balance must be assumed.

In conclusion, TEE and measures of physical activity are highly variable in patients with CRC, which is not apparent in current energy recommendations. Differences between measured and predicted TEE are related to body weight, body composition, and physical activity. Future research should therefore characterize the feasibility and impact of incorporating these variables in the estimation of energy requirements for these patients.

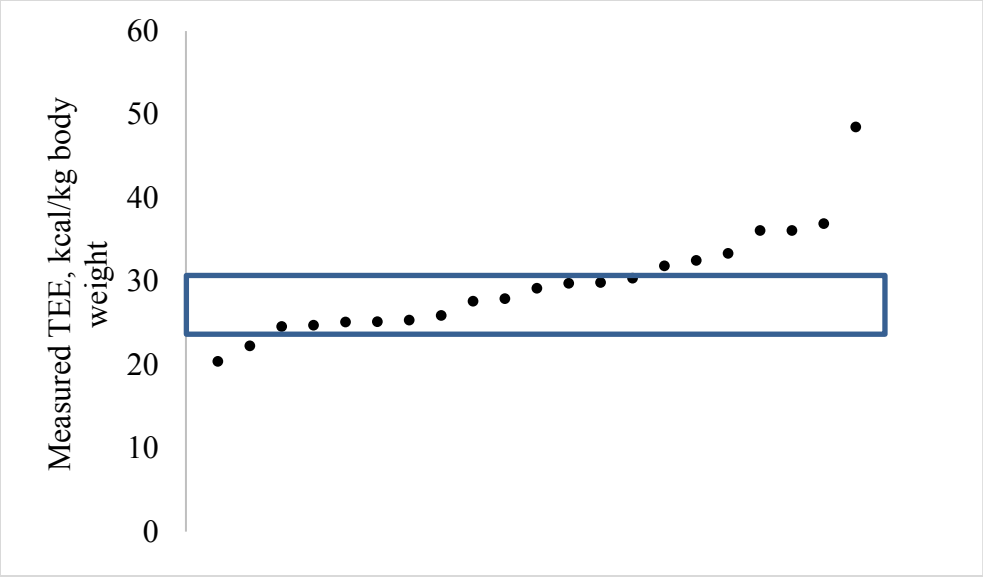
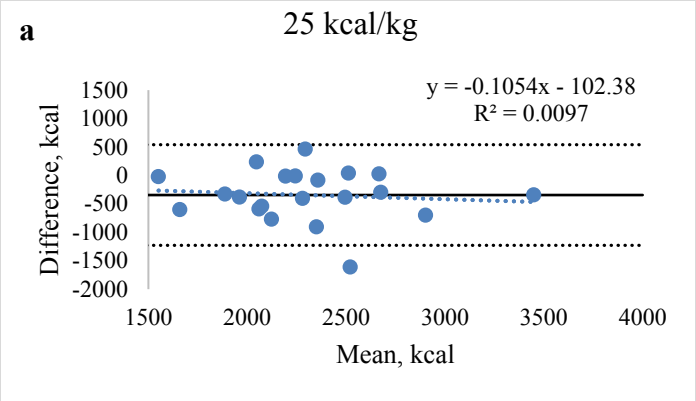
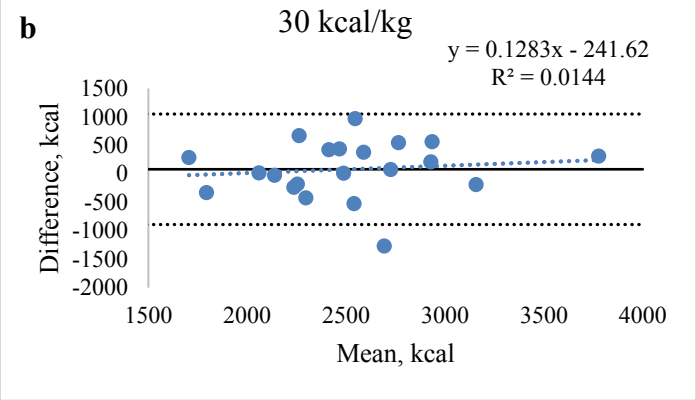
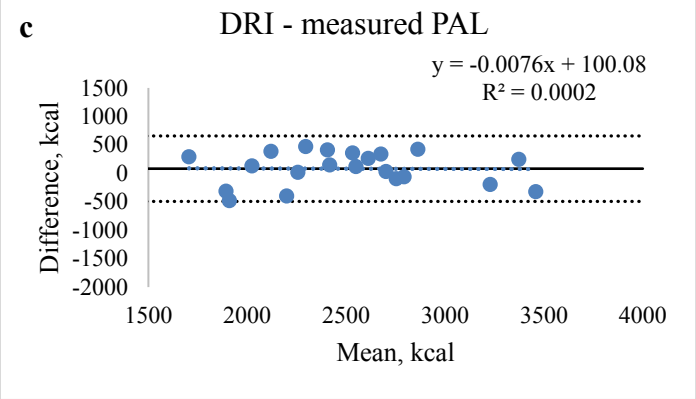
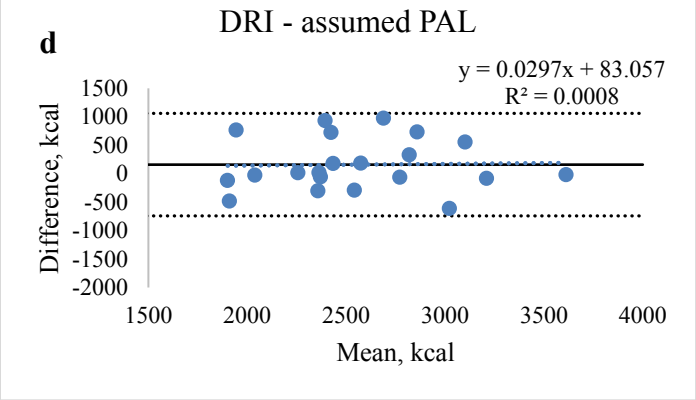


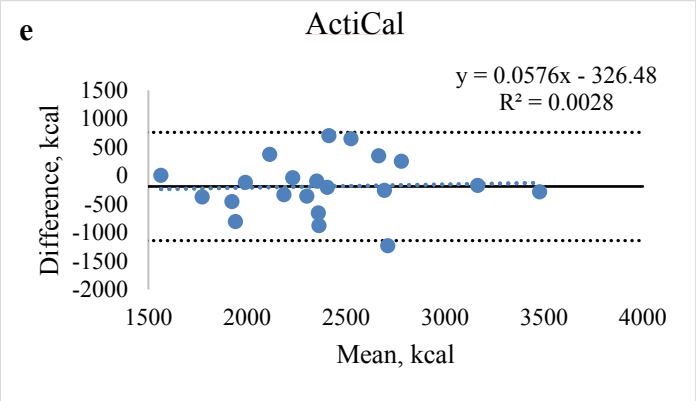
Figure 7.1 Range of measured total energy expenditure (TEE) in kcal/kg body weight in 21 patients with colorectal cancer. Each point is a patient. The blue box represents current recommendations of 25-30 kcal/kg body weight.


a
25 kcal/kg
y = -0.1054x - 102.38
R² = 0.0097
Difference, kcal
1500
1000
500
0
-500
-1000
-1500
-2000
1500
2000
2500
3000
3500
4000
Mean, kcal

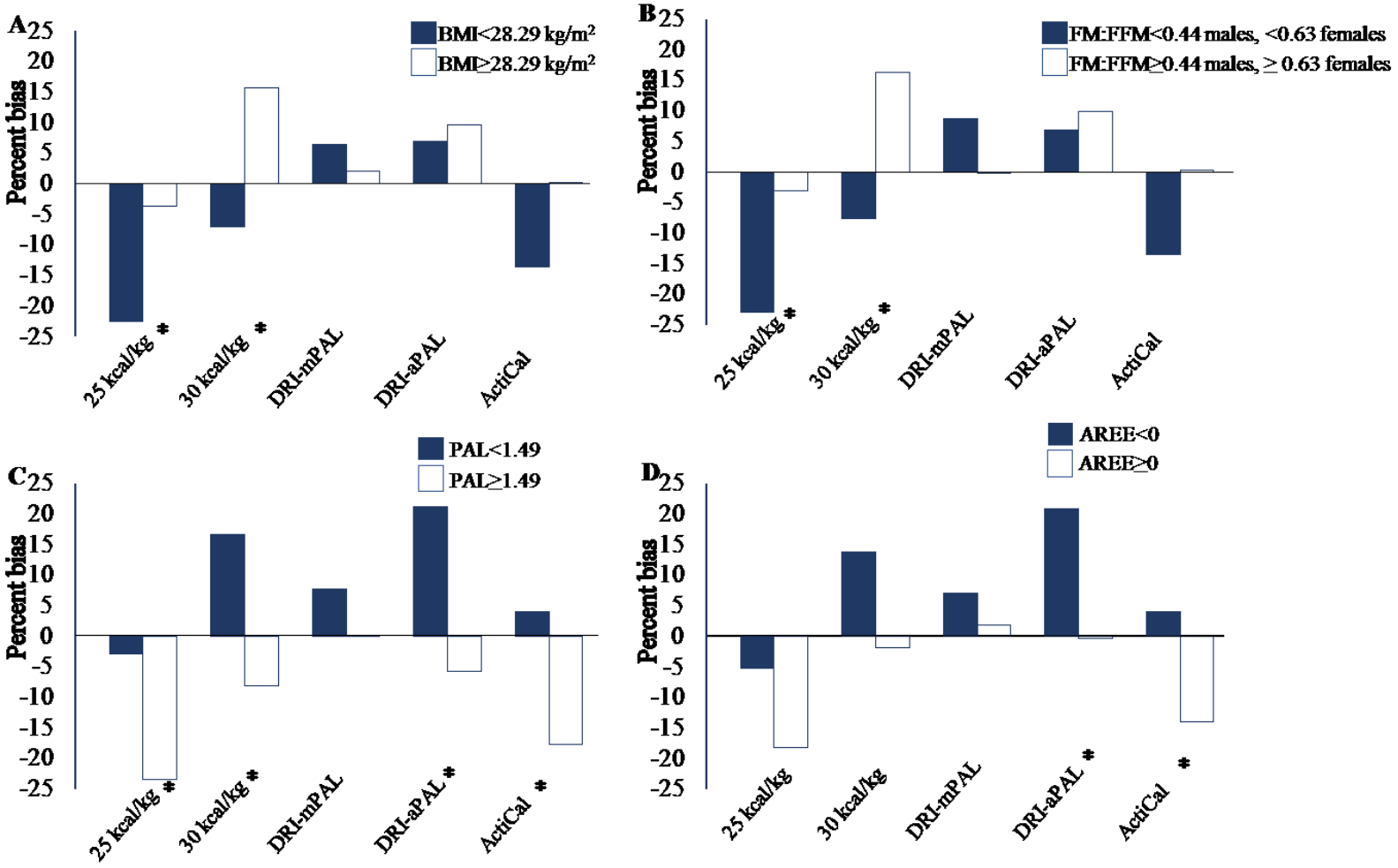

b
30 kcal/kg
y = 0.1283x - 241.62
R² = 0.0144
Difference, kcal
1500
1000
500
0
-500
-1000
-1500
-2000
1500
2000
2500
3000
3500
4000
Mean, kcal


c
DRI - measured PAL
y = -0.0076x + 100.08
R² = 0.0002
Difference, kcal
1500
1000
500
0
-500
-1000
-1500
-2000
1500
2000
2500
3000
3500
4000
Mean, kcal


d
DRI - assumed PAL
y = 0.0297x + 83.057
R² = 0.0008
Difference, kcal
1500
1000
500
0
-500
-1000
-1500
-2000
1500
2000
2500
3000
3500
4000
Mean, kcal



Figures 7.2a-e Bland-Altman plots of measured versus predicted total energy expenditure (TEE) in 21 patients with colorectal cancer. The middle solid line represents bias (mean difference between measured and predicted energy expenditure) and the two dotted lines represent the 95% limits of agreement (bias ± 2 standard deviations). DRI: dietary reference intakes; PAL: physical activity level, measured as TEE:resting energy expenditure. DRI was calculated using measured PAL and estimated from a subjective questionnaire. DRI: Dietary Reference Intake. PAL: Physical activity level



Figures 7.3 a-d Percent bias of measured versus predicted total energy expenditure according to (a) median of body mass index (BMI), (b) fat mass:fat-free mass (FM:FFM), (c) physical activity level (PAL), and (d) residual activity-related energy expenditure (RAEE). *p≤0.05, independent samples t-test. DRI, dietary reference intake; mPAL, measured physical activity level; aPAL, assumed PAL from subjective questionnaire.

Table 7.1 Characteristics of patients with colorectal cancer (n=21)

	Total (n=21)[1]	Males (n=14)	Females (n=7)	*P* value
Age, years	57 ± 12 (34 – 73)	55 ± 13 (34 – 72)	59 ± 13 (40 – 73)	0.582
Body weight, kg	85.1 ± 18.4 (54.3 – 131.1)	91.5 ± 17.3 (68.6 – 131.1)	72.5 ± 14.0 (54.3 – 92.6)	0.021
Body mass index, kg/m^2	28.3 ± 4.9 (20.9 – 39.5)	29.2 ± 4.9 (20.9 – 39.5)	26.7 ± 4.9 (22.0 – 35.0)	0.294
Fat mass, kg	28.8 ± 12.3 (9.9 – 59.8)	29.5 ± 13.8 (9.9 – 59.8)	27.6 ± 9.6 (16.5 – 41.4)	0.754
Fat mass index, kg/m^2	9.6 ± 3.8 (3.1 – 18.0)	9.3 ± 13.8 (3.1 – 18.0)	10.1 ± 3.4 (6.3 – 15.1)	0.651
Percent fat	32.9 ± 8.7 (14.7 – 45.6)	30.6 ± 9.1 (14.7 – 45.6)	37.3 ± 6.3 (27.6 – 44.4)	0.101
Fat-free mass, kg	56.3 ± 10.7 (37.6 – 74.1)	62.6 ± 6.8 (48.1 – 74.1)	44.6 ± 5.1 (37.6 – 51.8)	<0.001
Fat-free mass index, kg/m^2	18.6 ± 2.4 (14.1 – 22.2)	19.8 ± 1.8 (16.5 – 22.2)	16.5 ± 1.9 (14.1 – 19.8)	0.001
Fat mass:fat-free mass	0.51 ± 0.19 (0.17 – 0.84)	0.46 ± 0.19 (0.17 – 0.84)	0.61 ± 0.16 (0.38 – 0.80)	0.102
Appendicular skeletal muscle, kg	24.4 ± 6.4 (16.2 – 42.6)	27.5 ± 5.6 (20.3 – 42.6)	18.5 ± 2.1 (16.2 – 21.4)	0.001
Appendicular skeletal muscle index, kg/m^2	7.9 ± 1.5 (5.7 – 12.3)	8.5 ± 1.5 (6.9 – 12.3)	6.9 ± 0.9 (5.7 – 8.4)	0.018
Resting energy expenditure, kcal/day	1698 (IQR: 1446 – 2009)	1841 (IQR: 1668 – 2077)	1423 (IQR: 1388 – 1500)	<0.001
Respiratory quotient	0.80 ± 0.05 (0.73 – 0.93)	0.81 ± 0.05 (0.73 – 0.93)	0.79 ± 0.03 (0.74 – 0.82)	0.393
TEE, kcal/day	2473 ± 499 (1562 – 3622)	2646 ± 490 (1929 – 3622)	2127 ± 313 (1562 – 2509)	0.020
TEE, kcal/kg body weight	29.7 ± 6.3 (20.4 – 48.5)	29.7 ± 7.1 (20.4 – 48.5)	29.8 ± 4.8 (25.1 – 36.1)	0.952
Measured physical activity level	1.43 ± 0.27 (1.04 – 2.16)	1.40 ± 0.29 (1.04 – 2.16)	1.49 ± 0.22 (1.04 – 1.76)	0.463

Presented as mean ± and standard deviation (range) or median (interquartile [IQR] range) for non-normality between groups. Physical activity level=total energy expenditure:resting energy expenditure. TEE=total energy expenditure. All differences tested using independent samples t-test except in the case of non-normality wherein Mann-Whitney U-test was utilized.
[1]n=20 total and n=13 males with body composition measurements

Table 7.2 Correlations between energy expenditure variables and age, body weight, fat mass, and fat-free mass (n=21).

	Age	Weight	FM	FFM	FM:FFM
Resting energy expenditure†	-0.353	0.729***	0.388	0.873***	-0.029
Total energy expenditure	-0.382	0.558**	0.350	0.658**	0.025
Physical activity level	0.163	-0.366	-0.396	-0.255	-0.273
RAEE	0.083	0.050	-0.093	0.213	-0.197

*p<0.05, **p<0.01, ***p<0.001, Pearson correlation. †Spearman's rank-order correlation
RAEE: residual activity-related energy expenditure; FM:FFM: fat mass:fat-free mass

Table 7.3 Agreement between measured total energy expenditure (TEE) and energy requirement equations (n=21)

	Mean ± SD	Percent bias, mean ± SD	Proportional bias		LOA, %	Absolute LOA, %	Min. difference, %	Max. difference, %	Within 10% measured TEE, n (%)
			r	*P*					
Measured TEE	2473 ± 499								
25 kcal/kg	2128 ± 459*	-12.6 ± 16.5	-0.099	0.670	-45.1, 19.8	64.9	-48.5	22.4	7 (33.3)
30 kcal/kg	2554 ± 551	4.8 ± 19.9	0.120	0.604	-34.1, 43.8	77.8	-38.2	46.9	8 (38.1)
DRI – measured PAL	2554 ± 495	4.1 ± 12.9	-0.012	0.958	-21.2, 29.3	50.5	-22.5	22.7	10 (47.6)
DRI – assumed PAL	2632 ± 510	8.3 ± 21.4	0.029	0.901	-33.5, 50.2	83.8	-22.5	48.9	10 (47.6)
ActiCal	2359 ± 549	-4.6 ± 19.5	0.125	0.600	-42.7, 33.6	76.3	-35.1	43.3	9 (42.9)

DRI: dietary reference intake; PAL: physical activity level; SD: standard deviation; LOA: limits of agreement; *p≤0.05 difference between measured and predicted TEE via paired samples t-test. Proportional bias determined as Pearson correlation between bias and mean of measured and predicted TEE.

Table 7.4 Correlation of equation percent bias with patient characteristics (n=21)

	Age	Weight	FM	FFM	FM:FFM	PAL	AREE
25 kcal/kg	0.133	0.509*	0.586**	0.285	0.507*	-0.767***	-0.722***
30 kcal/kg	0.133	0.509*	0.586**	0.285	0.507*	-0.767***	-0.722***
DRI – measured PAL	-0.240	-0.008	-0.225	0.245	-0.410	-0.344	-0.384
DRI – assumed PAL	-0.194	0.187	0.084	0.290	-0.085	-0.791***	-0.760***
ActiCal	-0.107	0.478*	0.429	0.380	0.297	-0.631**	-0.587**

*p<0.05, **p<0.01, ***p<0.001, Pearson correlation

PAL: physical activity level; FM: fat mass; FFM: fat-free mass; AREE: residual activity-related energy expenditure;

7.7 References

1. Helms ER, Zinn C, Rowlands DS, Brown SR. A systematic review of dietary protein during caloric restriction in resistance trained lean athletes: a case for higher intakes. Int J Sport Nutr Exerc Metab. 2014;24(2):127-38.
2. Meyerhardt JA, Kroenke CH, Prado CM, Kwan ML, Castillo A, Weltzien E, et al. Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente Northern California population. Cancer Epidemiol Biomarkers Prev. 2017;26(1):30-7.
3. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the obesity paradox: The association between body composition and colorectal cancer survival (C-SCANS Study). Cancer Epidemiol Biomarkers Prev. 2017;26(7):1008-15.
4. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107(6):931-6.
5. Ross SA, Dzida G, Vora J, Khunti K, Kaiser M, Ligthelm RJ. Impact of weight gain on outcomes in type 2 diabetes. Curr Med Res Opin. 2011;27(7):1431-8.
6. Demark-Wahnefried W, Campbell K, Hayes SC. Weight management and its role in breast cancer rehabilitation. Cancer. 2012;118(8 Suppl):2277-87.
7. Skipworth RJ, Stene GB, Dahele M, Hendry PO, Small AC, Blum D, et al. Patient-focused endpoints in advanced cancer: criterion-based validation of accelerometer-based activity monitoring. Clin Nutr. 2011;30(6):812-21.
8. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996-1002.
9. Gibney E, Elia M, Jebb SA, Murgatroyd P, Jennings G. Total energy expenditure in patients with small-cell lung cancer: results of a validated study using the bicarbonate-urea method. Metabolism. 1997;46(12):1412-7.

10. Hayes S, Davies PS, Parker T, Bashford J. Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme. Bone Marrow Transplant. 2003;31(5):331-8.
11. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
12. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-93.
13. Fox KM, Brooks JM, Gandra SR, Markus R, Chiou C-F. Estimation of cachexia among cancer catients based on four definitions. J Oncol. 2009;2009.
14. Winkels RM, Snetselaar T, Adriaans A, van Warmerdam LJC, Vreugdenhil A, Slooter GD, et al. Changes in body weight in patients with colorectal cancer treated with surgery and adjuvant chemotherapy: an observational study. Cancer Treatment and Research Communications. 2016;9:111-5.
15. Brown JC, Caan BJ, Meyerhardt JA, Weltzien E, Xiao J, Cespedes Feliciano EM, et al. The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I-III colorectal cancer: a population-based cohort study (C-SCANS). J Cachexia Sarcopenia Muscle. 2018;9(4):664-72.
16. Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? Am J Clin Nutr. 2013;98(4):1012-9.
17. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr.2016;36(1):11-48.
18. Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. Proc Nutr Soc. 2016:1-11.
19. Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition. 2006;22(6):609-15.
20. Westerterp KR. Control of energy expenditure in humans. Eur J Clin Nutr. 2016;71:340.

21. clinicaltrials.gov. Identifier: NCT03131921. Resting Energy Expenditure in Cancer - Associations With Body Composition, Dietary Intake, and Exercise Habits Bethesda, MD: National Library of Medicine; 2017 [updated May 3, 2017 Accessed February 2, 2018].
22. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.
23. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
24. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381-95.
25. World Health Organization Consultation. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. WHO Technical Report Series: 894. Geneva, Switzerland 2000;894:1-253.
26. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: A critical appraisal of the current evidence. Clin Nutr. 2012;31(5):583-601.
27. Fearon K, Evans WJ, Anker SD. Myopenia—a new universal term for muscle wasting. Journal of Cachexia, Sarcopenia and Muscle. 2011;2(1):1-3.
28. Cooper JA, Watras AC, O'Brien MJ, Luke A, Dobratz JR, Earthman CP, et al. Assessing validity and reliability of resting metabolic rate in six gas analysis systems. J Am Diet Assoc. 2009;109(1):128-32.
29. Woo P, Murthy G, Wong C, Hursh B, Chanoine J-P, Elango R. Assessing resting energy expenditure in overweight and obese adolescents in a clinical setting: validity of a handheld indirect calorimeter. Pediatr Res. 2016;81:51.
30. Reeves MM, Capra S, Bauer J, Davies PS, Battistutta D. Clinical accuracy of the MedGem indirect calorimeter for measuring resting energy expenditure in cancer patients. Eur J Clin Nutr. 2005;59(4):603-10.
31. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1-2):1-9.

32. Racette SB, Schoeller DA, Luke AH, Shay K, Hnilicka J, Kushner RF. Relative dilution spaces of 2H- and 18O-labeled water in humans. Am J Physiol. 1994;267(4 Pt 1):E585-90.
33. Speakman JR, Nair KS, Goran MI. Revised equations for calculating CO2 production from doubly labeled water in humans. Am J Physiol. 1993;264(6 Pt 1):E912-7.
34. International Atomic Energy Agency. Assessment of Body Composition and Total Energy Expenditure in Humans Using Stable Isotope Techniques. IAEA Human Health Series No. 3. Vienna, Austria, 2009.
35. Black AE, Prentice AM, Coward WA. Use of food quotients to predict respiratory quotients for the doubly-labelled water method of measuring energy expenditure. Hum Nutr Clin Nutr. 1986;40(5):381-91.
36. Prentice AM. The doubly-labelled water method for measuring energy expenditure: technical recommendations for use in humans Vienna: International Atomic Energy Agency, 1990.
37. Institute of Medicine of the National Academics, Food and Nutrition Board. Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington D.C. United States, 2005.
38. Allison DB, Paultre F, Goran MI, Poehlman ET, Heymsfield SB. Statistical considerations regarding the use of ratios to adjust data. Int J Obes Relat Metab Disord. 1995;19(9):644-52.
39. Most J, Vallo PM, Gilmore LA, St Amant M, Hsia DS, Altazan AD, et al. Energy expenditure in pregnant women with obesity does not support energy intake recommendations. Obesity. 2018;26(6):992-9.
40. Herrmann SD, Barreira TV, Kang M, Ainsworth BE. Impact of accelerometer wear time on physical activity data: a NHANES semisimulation data approach. Br J Sports Med. 2014;48(3):278-82.
41. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc. 2008;40(1):181-8.
42. Clinicaltrials.gov. Identifier: NCT02788955 Protein Recommendations to Increase Muscle (PRIMe) Bethesda, MD2017 [cited 2017 May 5]. Available from: https://clinicaltrials.gov/ct2/show/NCT02788955.

43. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-95.
44. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491-7.
45. Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. Eur J Clin Nutr. 1996;50(2):72-92.
46. Ndahimana D, Lee SH, Kim YJ, Son HR, Ishikawa-Takata K, Park J, et al. Accuracy of dietary reference intake predictive equation for estimated energy requirements in female tennis athletes and non-athlete college students: comparison with the doubly labeled water method. Nutr Res Pract. 2017;11(1):51-6.
47. Kim E-K, Kim J-H, Kim M-H, Ndahimana D, Yean S-E, Yoon J-S, et al. Validation of dietary reference intake equations for estimating energy requirements in Korean adults by using the doubly labeled water method. Nutr Res Pract. 2017;11(4):300-6.
48. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569-78.
49. Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013;8(1):e53916.
50. Kroenke CH, Neugebauer R, Meyerhardt J, Prado CM, Weltzien E, Kwan ML, et al. Analysis of body mass index and mortality in patients with colorectal cancer using causal diagrams. JAMA Oncol. 2016;2(9):1137-45.
51. Loughney L, West MA, Dimitrov BD, Kemp GJ, Grocott MPW, Jack S. Physical activity levels in locally advanced rectal cancer patients following neoadjuvant chemoradiotherapy and an exercise training programme before surgery: a pilot study. Perioper Med. 2017;6:3.
52. Dahele M, Skipworth RJ, Wall L, Voss A, Preston T, Fearon KC. Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. J Pain Symptom Manage. 2007;33(6):676-85.

53. Lewis LS, Hernon J, Clark A, Saxton JM. Validation of the IPAQ against different accelerometer cut-points in older cancer survivors and adults at risk of cancer. J Aging Phys Act. 2018;26(1):34-40.
54. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act. 2008;5:56.
55. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409-26.
56. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev. 2017;52:91-104.
57. Barbaric M, Brooks E, Moore L, Cheifetz O. Effects of physical activity on cancer survival: a systematic review. Physiother Can. 2010;62(1):25-34.
58. Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? Cancer J. 2007;13(6):392-8.
59. Johnson G, Salle A, Lorimier G, Laccourreye L, Enon B, Blin V, et al. Cancer cachexia: measured and predicted resting energy expenditures for nutritional needs evaluation. Nutrition. 2008;24(5):443-50.
60. LaVoy EC, Fagundes CP, Dantzer R. Exercise, inflammation, and fatigue in cancer survivors. Exerc Immunol Rev. 2016;22:82-93.
61. Lavoie ME, Rabasa-Lhoret R, Doucet É, Mignault D, Messier L, Bastard JP, et al. Association between physical activity energy expenditure and inflammatory markers in sedentary overweight and obese women. Int J Obes. 2010;34:1387.
62. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology. 2002;13(5):561-8.
63. Rising R, Whyte K, Albu J, Pi-Sunyer X. Evaluation of a new whole room indirect calorimeter specific for measurement of resting metabolic rate. Nutr Metab (Lond). 2015;12(1):46.

64. Hall KD, Guo J, Chen KY, Leibel RL, Reitman ML, Rosenbaum M, et al. Challenges of measuring energy expenditure differences between diets varying in carbohydrate using doubly labeled water. Pre-print. bioRxiv. 2018:403931. Accessed January 22, 2019.
65. Oliveira CLP, Mattingly S, Schirrmacher R, Sawyer MB, Fine EJ, Prado CM. A nutritional perspective of ketogenic diet in cancer: a narrative review. J Acad Nutr Diet. 2018;118(4):668-88.
66. Pourhassan M, Schautz B, Braun W, Gluer CC, Bosy-Westphal A, Muller MJ. Impact of body-composition methodology on the composition of weight loss and weight gain. Eur J Clin Nutr. 2013;67(5):446-54.

Chapter 8: Conclusions and Discussion

8.1 Introduction

Energy expenditure forms the basis of all dietary recommendations and both resting energy expenditure (REE) and total energy expenditure (TEE) might be altered in the presence of a tumor. I aimed to characterize energy expenditure in patients with solid tumors and colorectal cancer (CRC). In Chapter 3, I hypothesized that 1) REE equations would be accurate on a group level but not on an individual level; 2) equation accuracy would differ according to body weight and cancer stage; and 3) equation inaccuracy from body-weight based equations would relate to age, weight, fat mass (FM) and fat-free mass (FFM). Several equations had bias considerably outside error range expected from intra-individual metabolic cart variation alone (1), and all equations had high individual error. Biases in almost all equations trended more towards over-prediction of REE in patients with stage IV disease and were not impacted by body weight. Age was positively correlated with REE bias and FM was negatively correlated with REE bias in body composition-based equations; however no other correlations were apparent. In Chapter 4 I hypothesized and also demonstrated that REE cannot be accurately measured in individuals with solid tumors with a portable indirect calorimeter. In Chapter 5 I utilized a sample of patients with stage II-IV CRC to test the hypotheses that body weight, height, age, sex, cancer stage, lean soft tissue, and fat mass (the latter of which were calculated from computerized-tomography image-derived values of skeletal muscle and adipose tissue) would independently predict REE. All variables *except* cancer stage predicted REE, contrary to the hypothesis. In Chapter 6 I hypothesized that average REE would not change over time in patients with stage III-IV CRC but FFM change, inflammation (C-reactive protein, CRP) change, and stage (III or IV) would independently predict change in REE. REE increased over time and a wide variability in REE change was observed after controlling for differing follow-up times. CRP change and cancer stage predicted REE change. Lastly, TEE in patients with stage II-IV CRC was investigated in relation to body composition, physical activity, and current energy intake recommendations in Chapter 7. I hypothesized that overall mean energy intake recommendations would not be different than measured TEE, but that a wide variation in individual-level agreement would be observed and that TEE would differ according to body mass index (BMI), FM:FFM ratio, and physical activity (PAL) classes. Overall mean energy intake recommendations were not different

than measured TEE, but highly erroneous estimations were observed on an individual level. Furthermore, patients with TEE >30 kcal/kg/day had lower average BMI and FM:FFM ratio and higher PAL.

Collectively, these results can be used to inform future evidence-based nutrition guidelines for patients with cancer and have the potential to change the dietetic care that these individuals receive. A summary schematic of the energy expenditure research findings is presented in **Figure 8.1**. The following sections will discuss the implications and limitations of the present findings and provide suggestions for future research.

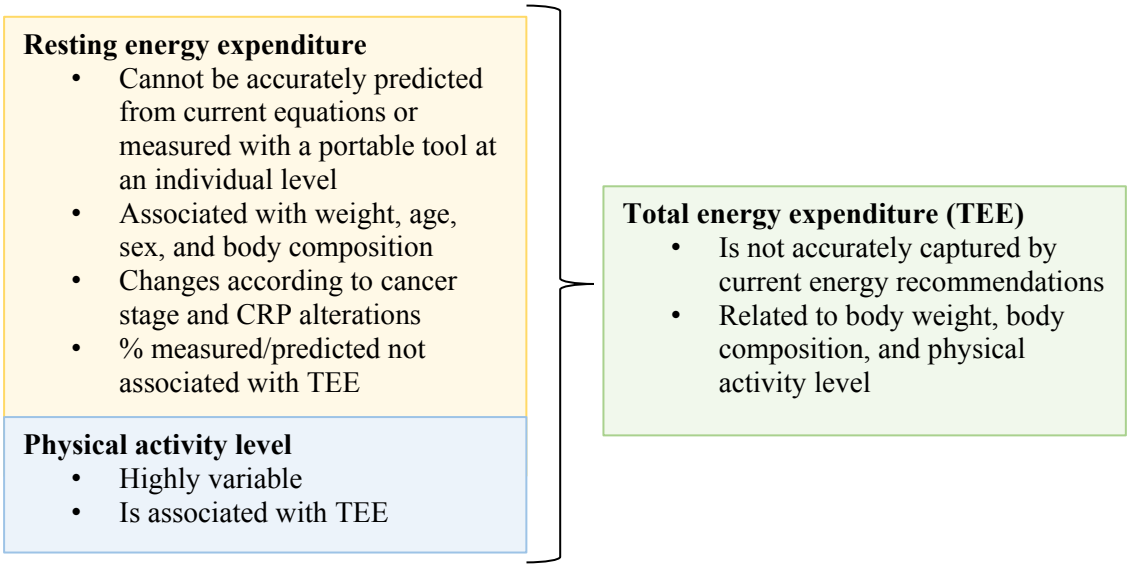


Figure 8.1 Summary of main thesis findings. CRP: C-reactive protein

8.2 Inaccuracies in Measuring Resting Energy Expenditure

Dietetic practice relies on individual quantification of energy requirements. REE individual assessments were commonly erroneous; such equations should therefore not be recommended for use in individual assessment of energy requirements. Large discrepancies between measured and predicted REE could have significant negative implications if such equations are used as an estimation of energy requirements. Underestimation might lead to weight loss while overestimation might contribute to weight gain. Body weight might also change frequently and rapidly in individuals with cancer. For example, in patients with CRC undergoing surgery with curative intent, body weight decreased in the perioperative period and increased during adjuvant chemotherapy (2.9 ± 5.8 kg) and during oncological follow-up (2.2 ± 6.6 kg) (2). Weight loss is

also more common in those with metastatic disease (3), hence the need for improved early nutritional interventions in these individuals. Importantly, weight loss is a negative prognostic factor for survival when all tumor types are combined, regardless of BMI (4). In CRC specifically, weight loss after diagnosis is associated with increased cancer-specific and overall mortality compared to weight-stable patients (5). Furthermore, weight gain might not confer a survival advantage (5) in some instances (i.e. comorbidities associated with obesity) and prevention of increased FM might therefore be beneficial. Hence, understanding and anticipating energy requirements is an important endeavor to prevent reduced survival associated with weight loss, while also avoiding unnecessary weight gain.

Inaccurately estimating energy expenditure might also hinder the effectiveness of interventions. For example, nutrition and exercise interventions are often aimed at improving clinical outcomes such as maintenance of skeletal muscle mass and/or physical function with the expectation that higher muscle mass will associate with lower risk of treatment toxicity and longer survival. However, such efforts are likely to fail in the face of insufficient dietary intake since sustained periods of negative energy balance are associated with decreased protein turnover rates (6), thereby impacting skeletal muscle retention and gain. Understanding energy balance is therefore important for designing effective clinical trials.

Theoretically, variables that might impact the accuracy of prediction equations include age, body weight, and body composition. We found that age and FM were frequently associated with equation error (Chapter 3). Most equations might not account for the decline in REE observed with age that occur independently of FFM loss (7). In addition, the degree of adiposity affects the relationship between FM and REE; specifically, the contribution of FM to REE has been shown to decrease sharply at high levels of percent body fat (>40%) (8). In other words, the relationship between FM and REE is not linear, as assumed by predictive equations. Age and FM should be used in equations, especially in populations with high prevalence of older age and in individuals with obesity.

Given that REE equations are inaccurate in individuals with cancer, measured REE is a better method to assess energy metabolism. However, in Chapter 4 I reported that error from a portable and accessible REE measurement tool were larger than common prediction equations, despite the use of a ventilated hood (similar to a metabolic cart). Error from such devices likely

reflects the absence of carbon dioxide (CO_2) measurement, which is especially important in conditions such as cancer where carbohydrate and fat metabolism (and therefore oxygen production and CO_2 consumption) are altered (9). The benefits of portability, lesser degree of technical expertise required, and greater cost effectiveness of this device might therefore be negated in light of large individual inaccuracies. Development and validation of improved portable tools to assess REE in clinical setting are needed. For example, the inclusion of CO_2 measurements from portable indirect calorimeters - such as the new Q-NRG calorimeter (COSMED, Chicago, IL, USA) - might offer an easier solution to acquiring accurate REE values. Alternatively, measuring REE from metabolic carts in patients at risk for weight loss might also be a sensible option, given the negative impact of weight loss on prognosis.

8.3 Determinants of Resting Energy Expenditure

Given the clear adverse impact of negative energy balance on prognosis, it is imperative to assess and anticipate mechanisms of altered REE in cancer and describe how this evolves throughout disease trajectory. Findings from Chapters 5 and 6 are herein discussed within this context.

Close to diagnosis, the predictors of REE in individuals with stage II-IV CRC are similar to that of healthy adults (Chapter 5). However, most patients with metastatic disease will develop cachexia, a multi-factorial, severe wasting syndrome that cannot be fully reversed by nutritional support alone (10). In addition to several endocrine and central nervous system alterations (11), cachexia is associated with increased lipolysis (50 ± 30% above normal rates), proteolysis (40 ± 10%), and gluconeogenesis via the Cori Cycle (300 ± 100%) (12). Consequences of such inefficient metabolic cycling coupled with mathematical modeling of tumor size suggest the energetic demand of the tumor itself impacts REE in the range of 100 to 1400 kcal/day (13). Tumor metabolism and consumption of energy fuels is specific; for example, a certain type of colon cancer cell (WiDr) demonstrates a preferentially higher rate of glucose consumption than lactate consumption compared to cervical cancer, glioblastoma, or glioma cell lines (14). Although this suggests histological tumor type influences metabolism, whether this translates to whole-body energy expenditure is unknown. To date, mathematical models for tumor burden (12, 13) and longitudinal analysis of metastatic disease (15) have shed light on the evolution of REE of the tumor in cancer cachexia. Furthermore, higher increase of metastatic sites over time

has been associated with higher rates of weight loss (3). Research presented in this thesis has added to this line of investigation since cancer stage (as a marker of more advanced disease and higher tumor burden) and inflammation were found to be significantly associated with REE change over time (Chapter 6). Taken together, these findings suggest REE evolution relates to tumor burden and early nutrition and exercise interventions aimed at anticipating and preventing such changes are warranted. However, to date, there is no accurate and clinically-accessible method of assessing individual changes in REE associated with tumor burden. A novel possibility of characterizing REE in light of tumor metabolism includes utilizing [18]F-flourodeoxyglucose uptake, which is a measure of glucose uptake from presumed tumors used for diagnostic purposes (expressed in mmol glucose uptake/gram of tissue). Combining repeated scans with estimated tumor size may represent an avenue for assessing tumor burden in clinical settings; however, the accuracy and efficacy of such techniques in relation to REE and TEE are speculative.

Another metabolic alteration that might occur in individuals with cancer is that of increased systemic inflammation. Inflammation could impact REE through alterations in the hypothalamic-pituitary axis, dysautonomia, oxidative stress, subdued muscle protein synthesis, and/or increased muscle proteolysis (16, 17) or might be a sign of more aggressive cancer (which could be associated with higher REE) (18, 19). A recent analysis has suggested that hypermetabolism (defined as measured REE from a portable indirect calorimeter > 10% than REE predicted by the Harris-Benedict equation) is highly prevalent in patients with newly diagnosed caner (49%) and is associated with higher prevalence of weight loss, poor performance status, and lower nutrition risk index (a formula that considers albumin and weight loss) (20). Hypermetabolic patients also had higher average CRP values compared to patients without hypermetabolism. However, this population primarily consisted of patients with metastatic disease (n=263, 67%) and/or genitourinary cancer (n=109, 28%), which differs from patient samples studied throughout this thesis. Nevertheless, our findings in Chapter 6 suggest that changes in CRP associate with changes in REE. A limitation of assessing inflammation is that biological indicators of inflammatory status are not readily available outside of research settings. Neutrophil:lymphocyte ratio as a marker of immune system activation is available in medical records, and relates to survival in individuals with CRC (21). However, the mechanisms

by which neutrophil:lymphocyte and CRP increase within the body differs. More specifically, neutrophils activate several pro-angiogenic factors to support tumor growth (i.e. increased vascular endothelial growth factor) and lymphocytes are part of the immune response aimed to destroy tumor cells (22). CRP is an acute phase protein regulated by several cytokines (i.e. interleukin-6, tumor necrosis factor-α) (22). It is reasonable to speculate that these inflammatory markers might have differing relationships with whole-body metabolism, with neutrophil:lymphocyte ratio indicating tumor aggressiveness and disease progression arising from the tumor microenvironment, and CRP representing systemic inflammation that directly impacts processes leading to increased REE (discussed in Chapter 2). Neutrophil:lymphocyte ratio has not been previously assessed as a determinant of REE in other populations. Further analysis of the role of biological markers on energy balance and continued exploration of accurate and clinically viable ways of identifying chronic inflammation in relation to REE without added patient burden should continue to be investigated.

8.4 Total Energy Expenditure: A Crucial Indicator of Energy Metabolism and Requirements

While REE might be altered in patients with cancer as described in this thesis, dietary energy requirements ultimately relate to TEE. Our understanding of TEE to date has been primarily informed by a study in patients with advanced pancreatic cancer with overall low PAL (32). In fact, current guidelines from the European Society for Clinical Nutrition and Metabolism on energy requirements (33) describe REE as being frequently elevated despite lower than predicted TEE. Estimated TEE between 25-30 kcal/day is therefore currently assumed based on the supposition that TEE does not differ substantially from healthy subjects. This recommendation was informed by the aforementioned study in patients with pancreatic cancer (32), combined with those from Gibney *et al.* (34) which included eight patients with unresectable small cell lung cancer (discussed in more depth in Chapter 2). The recommendations also used data from studies which assume that activity monitors accurately measure TEE (35, 36), which may be an invalid assumption (37). The results presented in Chapter 7 add to the small body of literature investigating TEE and found that such recommendations cannot be used for individual energy intake recommendations. Furthermore, "abnormal" REE was not correlated to TEE (previously corroborated by Skipworth *et al*. [38]) and TEE was not different when patients were grouped by higher versus lower REE. A high

variability in PAL was observed, and TEE differed according to PAL categories, as expected. These results collectively suggest that in patients with primarily earlier stage CRC, PAL variability could be more important in determining energy requirements rather than universal PAL. Estimating energy requirements should therefore no longer assume that all individuals with cancer are sedentary, and that PAL should be considered when designing individualized diets. Furthermore, understanding *both* REE and TEE (and inherently PAL) is vital since these measurements should theoretically influence different outcomes. For example, elevated REE might predict treatment toxicity (39), while TEE and PAL might relate to quality of life (32). Characterization of these entities across the disease trajectory – including diagnosis, treatment, and survivorship – and their potential use for clinical trial design, warrants future investigation.

Our data of TEE should be put into context of REE and energy intake. For example, liver metastases may only increase REE by approximately 150 kcal/day on average (15). However, average TEE in individuals with pancreatic cancer was around 170 kcal/day *lower* than predicted from (Schofield equation [40] multiplied by 1.5) (32). Large energy balance perturbations are more likely to occur from changes in PAL or energy intake. For example, 150 kcal/day is equivalent to approximately 35 minutes of walking 2.5 miles/hour on a solid, flat surface (metabolic equivalency of task = 2.5)(41), assuming body weight is 85.1 kg (average observed in Chapter 7). In terms of energy intake, a small snack would impact energy intake in the range of 150 kcal/day. Therefore, while REE might be altered in cancer, the relative changes in this value are likely smaller than energy balance alterations that are subject to behavioral alterations. Error in current energy expenditure estimations should also be considered in context of each other. Error in TEE estimates (Chapter 7) were substantially larger than error in REE estimates (Chapter 3) and were worsened by assuming PAL from patient recall. To put this in context, the Mifflin St. Jeor equation produced limits of agreement ranging from -21.7 to 11.3% (-394 to 203 kcal/day), while the Dietary Reference Intake equation with assumed PAL generated limits of agreement ranging from -33.3 to 50.8% (-736 to 1074 kcal/day). Energy intake recommendations based on such error would undoubtedly contribute to unwanted weight change. It is therefore imperative that future research identifies more clinically viable tools to estimate PAL and how these relate to total energy requirements.

Structured exercise (a constituent of PAL) during cancer treatment is related to improved physical function, lower treatment toxicity, and longer survival (42). Current guidelines also support exercise in individuals with cancer (43), which presumably might impact PAL. Chapter 7 highlights the wide variability in PAL close to cancer diagnosis and suggests that PAL is a primary driver of TEE and therefore energy requirements. Understanding the impact of exercise interventions on PAL and subsequent energy requirements across disease trajectory therefore represents an area of further research need. It can also be hypothesized that the relationship between energy expenditure and energy intake might be altered in cancer. In healthy adults, REE predicts energy intake (44), but higher REE is not always associated with higher energy intake in cancer (20, 45). Further elucidation of the multifaceted interactions between TEE, PAL, energy intake, body composition, and clinical outcomes in cancer are needed to answer the complex questions within this research area.

TEE estimation error was associated with body weight, body composition, and PAL. Results from this study also indicate that TEE and PAL are specific to cancer type and stage, since TEE and PAL were much lower in patients with pancreatic cancer, previously reported (32). This raises the question of how to better estimate TEE in clinical settings. The utility of easily-accessible online calculators developed from large samples of healthy adults such as those put forth by Pennington Biomedical Research Center (46) or National Institutes of Health (47) to predict weight loss would be beneficial in anticipating energy balance alterations in cancer. However, the development of such calculators requires large sample sizes to account for the heterogeneity in energy balance change over time and to support the sophisticated mathematical modeling undertaken to develop these tools. There are also several assumptions associated with these calculations (48, 49) and the efficacy of implementing these in dietetic practice in patients with cancer should be investigated. Nevertheless, it is expected that this thesis can someday be used develop improved energy balance equations.

8.5 Limitations

This research is highly novel and has shed light on several aspects of energy metabolism in patients with cancer. However, some limitations must be considered, in addition to those mentioned in Chapters 3 - 7. Firstly, all REE measurements were assessed with a metabolic cart, which might underestimate REE as measured by more sensitive techniques such as whole-body

calorimetry units that can also measure REE (in addition to TEE, thermic effect of food, exercise energy expenditure, and sleep energy expenditure). For example, the Vmax Encore 2900 (Sensor-Medics, Yorba Linda, CA, USA) produced REE values 195 kcal/day lower than that of a whole body calorimetry unit in healthy subjects ($p<0.001$) (50). Data from our ongoing study (51) suggest that the Vmax 29N produces REE values that are on average 168 ± 88 kcal/day lower than our whole-body calorimetry unit, although this is not significantly different ($p=0.292$). Nevertheless, results presented in this thesis can be compared to previous research in the field of energy metabolism, which almost invariably utilize metabolic carts. In addition, only the study presented in Chapter 6 was designed to assess changes in energy metabolism over time. The applicability of REE or TEE equations across time (i.e. after treatment) can therefore not be assumed. Chapters 5, 6, and 7 present data on patients with CRC only; thus, findings should only be applied to patients with CRC. Chapters 4, 5, and 6, consist of data from different cohorts of patients. While this was controlled for in several analyses and the populations were similar, it is plausible that some error might have been introduced. In addition, the study measuring TEE did not collect longer-term measurements of dietary intake or sensitive markers of body composition changes directly before and after DLW assessments; no conclusions regarding energy balance can be made. Thermic effect of food (TEF) was assumed to be 10%, in line with most previous research in the field in which PAL reflects the ratio between TEE and REE. Alterations in the number of calories consumed or macronutrient distribution of the diet would impact TEF. However, TEE assessments presented in Chapter 7 were designed to collect as much information as possible to answer the research questions while minimizing patient burden. Further elucidation of macronutrient metabolism and TEF in relation to TEE are warranted.

8.6 Translation and Future Directions

Understanding energy expenditure in terms of energy balance regulation is key for clinical translation and to direct future research aimed at improving nutritional care. There is accumulating evidence to suggest that long-term energy intake and TEE are rather tightly controlled in states of energy balance in healthy adults. In fact, mathematical modeling suggests that to maintain body weight within 1 kg over several years requires that long-term average energy intake must be accurate within about 22 kcal/day (52). The research presented in Chapter 7 suggests an interesting scientific paradigm might be present in patients with cancer. Namely,

many individuals with cancer will develop nutrition impact symptoms in relation to the cancer or treatment and might consequently have low energy intake (this is especially true in advanced stages of disease) (53, 54). Weight loss is highly prevalent in cancer and our data suggests that some individuals can maintain relatively high TEE and PAL, at least close to diagnosis. Such patterns of TEE and PAL might be indicative of the independent or performance allocation models of energy expenditure, wherein exercise would increase TEE in an additive manner or that REE increase reflects an increased capacity to mobilize energy stores, respectively (55, 56). Future research that characterizes PAL and TEE in relation to energy intake will shed light on dietary requirements in individuals with cancer.

Findings in Chapter 3, 4, and 7 highlight that current clinically viable methods of estimating REE and TEE are not accurate on an individual level (which is more important than group agreement in dietetic practice). Given the negative impact weight loss has on survival in cancer (4), understanding effective methods to prevent and mitigate energy balance changes should be a priority for future investigations and research practices. Consideration of energy requirements according to BMI classes might be a feasible starting place since patients have measures of height and weight recorded in medical records. In addition, improved energy recommendations are needed, but should be continually followed up with clinical translation practices. More specifically, characterizing the barriers and facilitators of behavior change should be determined concurrently with the advent of evidence-based dietary recommendations.

8.7 Conclusion

The major findings of this research were that REE and TEE (and consequently PAL) were highly variable in patients in cancer, which was not captured by current predictive equations, portable tools, or energy recommendations. Furthermore, body composition is a major determinant of REE at one timepoint and factors such as inflammation and cancer stage impact the progression of REE across time. This research highlights individual variation in energy metabolism in patients with cancer. These findings will contribute to the formation of evidence-based dietary recommendations, considering disease stage, cancer type, body weight, body composition, and/or physical activity, with the ultimate goal of improving cancer care.

8.8 References

1. Bader N, Bosy-Westphal A, Dilba B, Muller MJ. Intra- and interindividual variability of resting energy expenditure in healthy male subjects - biological and methodological variability of resting energy expenditure. Br J Nutr. 2005;94(5):843-9.
2. Winkels RM, Snetselaar T, Adriaans A, van Warmerdam LJC, Vreugdenhil A, Slooter GD, et al. Changes in body weight in patients with colorectal cancer treated with surgery and adjuvant chemotherapy: An observational study. Cancer Treatment and Research Communications. 2016;9:111-5.
3. Shiono M, Huang K, Downey RJ, Consul N, Villanueva N, Beck K, et al. An analysis of the relationship between metastases and cachexia in lung cancer patients. Cancer Med. 2016;5(9):2641-8.
4. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015;33(1):90-9.
5. Meyerhardt JA, Kroenke CH, Prado CM, Kwan ML, Castillo A, Weltzien E, et al. Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente Northern California population. Cancer Epidemiol Biomarkers Prev. 2017;26(1):30-7.
6. Carbone JW, McClung JP, Pasiakos SM. Skeletal muscle responses to negative energy balance: effects of dietary protein. Adv Nutr. 2012;3(2):119-26.
7. Manini TM. Energy expenditure and aging. Ageing Res Rev. 2010;9(1):1-26.
8. Bosy-Westphal A, Müller MJ, Boschmann M, Klaus S, Kreymann G, Lührmann PM, et al. Grade of adiposity affects the impact of fat mass on resting energy expenditure in women. Br J Nutr. 2008;101(4):474-7.
9. Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr. 2010;29(1):72-7.
10. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-95.
11. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105.

12. Hall KD, Baracos VE. Computational modeling of cancer cachexia. Curr Opin Clin Nutr Metab Care. 2008;11(3):214-21.
13. Friesen DE, Baracos VE, Tuszynski JA. Modeling the energetic cost of cancer as a result of altered energy metabolism: Implications for cachexia. Theor Biol Med Model. 2015;12(1):17.
14. Mendoza-Juez B, Martinez-Gonzalez A, Calvo GF, Perez-Garcia VM. A mathematical model for the glucose-lactate metabolism of in vitro cancer cells. Bull Math Biol. 2012;74(5):1125-42.
15. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr. 2009;89(4):1173-9.
16. Baracos VE. Metabolism and physiology. In: Del Fabbro E, Baracos V, Demark-Wahnefried W, Bowling T, Hopkinson JB, Bruera E, editors. Nutrition and the Cancer Patient. Oxford, United Kingdom: Oxford University Press; 2010. p. 7-18
17. Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr. 2016;70(11):1230-8.
18. Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? Cancer J. 2007;13(6):392-8.
19. Guo J, Chen S, Chen Y, Li S, Xu D. Combination of CRP and NLR: a better predictor of postoperative survival in patients with gastric cancer. Cancer Manag Res. 2018;10:315-21.
20. Vazeille C, Jouinot A, Durand JP, Neveux N, Boudou-Rouquette P, Huillard O, et al. Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. Am J Clin Nutr. 2017;105(5):1139-47.
21. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer. 2011;104:1288.
22. Mao M, Wei X, Sheng H, Chi P, Liu Y, Huang X, et al. C-reactive protein/albumin and neutrophil/lymphocyte ratios and their combination predict overall survival in patients with gastric cancer. Oncol Lett. 2017;14(6):7417-24.

23. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. J Am Diet Assoc. 2005;105(5):775-89.
24. Weijs PJ, Vansant GA. Validity of predictive equations for resting energy expenditure in Belgian normal weight to morbid obese women. Clin Nutr. 2010;29(3):347-51.
25. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332(10):621-8.
26. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. Cell Metab. 2018;27(4):805-15 e4.
27. Muller MJ, Enderle J, Pourhassan M, Braun W, Eggeling B, Lagerpusch M, et al. Metabolic adaptation to caloric restriction and subsequent refeeding: the Minnesota Starvation Experiment revisited. Am J Clin Nutr. 2015;102(4):807-19.
28. Siervo M, Faber P, Lara J, Gibney ER, Milne E, Ritz P, et al. Imposed rate and extent of weight loss in obese men and adaptive changes in resting and total energy expenditure. Metabolism. 2015;64(8):896-904.
29. Most J, Vallo PM, Gilmore LA, St Amant M, Hsia DS, Altazan AD, et al. Energy expenditure in pregnant women with obesity does not support energy intake recommendations. Obesity. 2018;26(6):992-9.
30. Bosy-Westphal A, Braun W, Schautz B, Muller MJ. Issues in characterizing resting energy expenditure in obesity and after weight loss. Front Physiol. 2013;4:47.
31. Ostendorf DM, Melanson EL, Caldwell AE, Creasy SA, Pan Z, MacLean PS, et al. No consistent evidence of a disproportionately low resting energy expenditure in long-term successful weight-loss maintainers. Am J Clin Nutr. 2018;108(4):658-66.
32. Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996-1002.
33. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr.2016;6(1):11-48.

34. Gibney E, Elia M, Jebb SA, Murgatroyd P, Jennings G. Total energy expenditure in patients with small-cell lung cancer: results of a validated study using the bicarbonate-urea method. Metabolism. 1997;46(12):1412-7.
35. Cereda E, Turrini M, Ciapanna D, Marbello L, Pietrobelli A, Corradi E. Assessing energy expenditure in cancer patients: a pilot validation of a new wearable device. JPEN J Parenter Enteral Nutr. 2007;31(6):502-7.
36. Bencini L, Di Leo A, Pozzessere D, Bozzetti F. Total energy expenditure in patients with advanced solid tumors: a preliminary report. Nutritional Therapy & Metabolism. 2008;26(1):45-7.
37. Johannsen DL, Calabro MA, Stewart J, Franke W, Rood JC, Welk GJ. Accuracy of armband monitors for measuring daily energy expenditure in healthy adults. Med Sci Sports Exerc. 2010;42(11):2134-40.
38. Skipworth RJ, Stene GB, Dahele M, Hendry PO, Small AC, Blum D, et al. Patient-focused endpoints in advanced cancer: criterion-based validation of accelerometer-based activity monitoring. Clin Nutr. 2011;30(6):812-21.
39. Jouinot A, Vazeille C, Durand JP, Huillard O, Boudou-Rouquette P, Coriat R, et al. Resting energy expenditure in the risk assessment of anticancer treatments. Clin Nutr. 2018;37(2):558-65.
40. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39 Suppl 1:5-41.
41. Ainsworth BE HW, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-81.
42. Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A systematic review of exercise systematic reviews in the cancer literature (2005-2017). PM R. 2017;9(9S2):S347-S84.
43. Segal R, Zwaal C, Green E, Tomasone JR, Loblaw A, Petrella T, et al. Exercise for people with cancer: a clinical practice guideline. Curr Oncol. 2017;24(1):40-6.
44. McNeil J, Lamothe G, Cameron JD, Riou ME, Cadieux S, Lafreniere J, et al. Investigating predictors of eating: is resting metabolic rate really the strongest proxy of energy intake? Am J Clin Nutr. 2017;106(5):1206-12.

45. Bosaeus I, Daneryd P, Lundholm K. Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. J Nutr. 2002;132(11 Suppl):3465s-6s.
46. Pennington Biomedical Research Center. Weight loss predictor [Accessed October 31, 2018]. Available from: https://www.pbrc.edu/research-and-faculty/calculators/weight-loss-predictor/.
47. National Institutes of Health Body Weight Planner [Accessed Oct 31, 2018]. Available from: https://www.niddk.nih.gov/bwp
48. Thomas DM, Martin CK, Heymsfield S, Redman LM, Schoeller DA, Levine JA. A simple model predicting individual weight change in humans. J Biol Dyn. 2011;5(6):579-99.
49. Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL, et al. Quantification of the effect of energy imbalance on bodyweight. Lancet. 2011;378(9793):826-37.
50. Rising R, Whyte K, Albu J, Pi-Sunyer X. Evaluation of a new whole room indirect calorimeter specific for measurement of resting metabolic rate. Nutr Metab (Lond). 2015;12(1):46.
51. clinicaltrials.gov. Identifier: NCT03131921. Resting Energy Expenditure in Cancer - Associations With Body Composition, Dietary Intake, and Exercise Habits Bethesda, MD: National Library of Medicine; 2017 [updated May 3, 2017February 2, 2018].
52. Chow CC, Hall KD. Short and long-term energy intake patterns and their implications for human body weight regulation. Physiol Behav. 2014;134:60-5.
53. Omlin A, Blum D, Wierecky J, Haile SR, Ottery FD, Strasser F. Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions, a case–control study. J Cachex Sarcopenia Muscle. 2013;4(1):55-61.
54. Kubrak C, Olson K, Jha N, Scrimger R, Parliament M, McCargar L, et al. Clinical determinants of weight loss in patients receiving radiation and chemoirradiation for head and neck cancer: a prospective longitudinal view. Head Neck. 2013;35(5):695-703.
55. Mathot KJ, Dingemanse NJ. Energetics and behavior: unrequited needs and new directions. Trends Ecol Evol. 2015;30(4):199-206.
56. Melanson EL. The effect of exercise on non-exercise physical activity and sedentary behavior in adults. Obes Rev. 2017;18 Suppl 1:40-9.

Alphabetical Bibliography

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-c30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

Achamrah N, Jesus P, Grigioni S, Rimbert A, Petit A, Dechelotte P, et al. Validity of predictive equations for resting energy expenditure developed for obese patients: impact of body composition method. Nutrients. 2018;10(1).

Adriaens MP, Schoffelen PF, Westerterp KR. Intra-individual variation of basal metabolic rate and the influence of daily habitual physical activity before testing. Br J Nutr. 2003;90(2):419-23.

Ainsworth BE HW, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and met values. Med Sci Sports Exerc. 2011;43(8):1575-81.

Allison DB, Paultre F, Goran MI, Poehlman ET, Heymsfield SB. Statistical considerations regarding the use of ratios to adjust data. Int J Obes Relat Metab Disord. 1995;19(9):644-52.

Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2016;36(1):11-48.

Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.

Bader N, Bosy-Westphal A, Dilba B, Muller MJ. Intra- and interindividual variability of resting energy expenditure in healthy male subjects - biological and methodological variability of resting energy expenditure. Br J Nutr. 2005;94(5):843-9.

Baracos VE. Metabolism and physiology. In: Del Fabbro E, Baracos V, Demark-Wahnefried W, Bowling T, Hopkinson JB, Bruera E, editors. Nutrition and the Cancer Patient. Oxford, United Kingdom: Oxford University Press; 2010. p. 7-18.

Baracos VE, Arribas L. Sarcopenic obesity: Hidden muscle wasting and its impact for survival and complications of cancer therapy. Ann Oncol. 2018;29(suppl_2):ii1-ii9.

Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105.

Barbaric M, Brooks E, Moore L, Cheifetz O. Effects of physical activity on cancer survival: A systematic review. Physiother Can. 2010;62(1):25-34.

Barber MD, McMillan DC, Preston T, Ross JA, Fearon KC. Metabolic response to feeding in weight-losing pancreatic cancer patients and its modulation by a fish-oil-enriched nutritional supplement. Clin Sci (Lond). 2000;98(4):389-99.

Bauer J, Reeves MM, Capra S. The agreement between measured and predicted resting energy expenditure in patients with pancreatic cancer: A pilot study. JOP. 2004;5(1):32-40.

Becker Veronese CB, Guerra LT, Souza Grigolleti S, Vargas J, Pereira da Rosa AR, Pinto Kruel CD. Basal energy expenditure measured by indirect calorimetry in patients with squamous cell carcinoma of the esophagus. Nutricion hospitalaria. 2013;28(1):142-7.

Bencini L, Di Leo A, Pozzessere D, Bozzetti F. Total energy expenditure in patients with advanced solid tumors: A preliminary report. Nutritional Therapy & Metabolism. 2008;26(1):45-7.

Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: An analysis of 574 doubly-labelled water measurements. Eur J Clin Nutr. 1996;50(2):72-92.

Black AE, Prentice AM, Coward WA. Use of food quotients to predict respiratory quotients for the doubly-labelled water method of measuring energy expenditure. Hum Nutr Clin Nutr. 1986;40(5):381-91.

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.

Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, den Braver NR, Berkhof J, Langius JA, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. J Clin Oncol. 2016;34(12):1339-44.

Blum D, Omlin A, Baracos VE, Solheim TS, Tan BH, Stone P, et al. Cancer cachexia: A systematic literature review of items and domains associated with involuntary weight loss in cancer. Crit Rev Oncol Hematol. 2011;80(1):114-44.

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992;101(6):1644-55.

Boothby WM, Berkson J, Dunn HL. Studies of the energy of metabolism of normal individuals: A standard for basal metabolism, with a nomogram for clinical application. Am J Physiol. 1936;116(2):468-84.

Boothby WM, Sandiford RB. Nomographic charts for the calculation of the metabolic rate by the gasometer method. Boston Med Surg J. 1921;185(12):337-54.

Bosaeus I, Daneryd P, Lundholm K. Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. J Nutr. 2002;132(11 Suppl):3465s-6s.

Bosaeus I, Daneryd P, Svanberg E, Lundholm K. Dietary intake and resting energy expenditure in relation to weight loss in unselected cancer patients. Int J Cancer. 2001;93(3):380-3.

Bosy-Westphal A, Braun W, Schautz B, Müller MJ. Issues in characterizing resting energy expenditure in obesity and after weight loss. Front Physiol. 2013;4:47.

Bosy-Westphal A, Müller MJ, Boschmann M, Klaus S, Kreymann G, Lührmann PM, et al. Grade of adiposity affects the impact of fat mass on resting energy expenditure in women. Br J Nutr. 2008;101(4):474-7.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

Broderick JM, Ryan J, O'Donnell DM, Hussey J. A guide to assessing physical activity using accelerometry in cancer patients. Support Care Cancer. 2014;22(4):1121-30.

Brown JC, Caan BJ, Meyerhardt JA, Weltzien E, Xiao J, Cespedes Feliciano EM, et al. The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I-III colorectal cancer: A population-based cohort study (C-SCANS). J Cachexia Sarcopenia Muscle. 2018;9(4):664-72.

Buchowski MS, Choi L, Majchrzak KM, Acra S, Matthews CE, Chen KY. Seasonal changes in amount and patterns of physical activity in women. J Phys Act Health. 2009;6(2):252-61.

Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: an individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev. 2017;52:91-104.

Burckart K, Beca S, Urban RJ, Sheffield-Moore M. Pathogenesis of muscle wasting in cancer cachexia: targeted anabolic and anticatabolic therapies. Curr Opin Clin Nutr Metab Care. 2010;13(4):410-6.

Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS study). Cancer Epidemiol Biomarkers Prev. 2017;26(7):1008-15.

Campbell KL, Lane K, Martin AD, Gelmon KA, McKenzie DC. Resting energy expenditure and body mass changes in women during adjuvant chemotherapy for breast cancer. Cancer Nurs. 2007;30(2):95-100.

Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2018. Toronto, ON: Canadian Cancer Society, 2018. Available at: cancer.ca/Canadian-Cancer-Statistics-2018-EN (accessed [September 2018])

Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr. 2010;29(1):72-7.

Carbone JW, McClung JP, Pasiakos SM. Skeletal muscle responses to negative energy balance: effects of dietary protein. Adv Nutr. 2012;3(2):119-26.

Carneiro IP, Elliott SA, Siervo M, Padwal R, Bertoli S, Battezzati A, et al. Is obesity associated with altered energy expenditure? Adv Nutr. 2016;7(3):476-87.

Ceolin Alves AL, Zuconi CP, Correia MI. Energy expenditure in patients with esophageal, gastric, and colorectal cancer. JPEN J Parenter Enteral Nutr. 2016;40(4):499-506.

Cereda E, Turrini M, Ciapanna D, Marbello L, Pietrobelli A, Corradi E. Assessing energy expenditure in cancer patients: a pilot validation of a new wearable device. JPEN J Parenter Enteral Nutr. 2007;31(6):502-7.

Chen WJ, Chung YC. Energy expenditure in patients with hepatocellular carcinoma. Cancer. 1994;73(3):590-5.

Chow CC, Hall KD. Short and long-term energy intake patterns and their implications for human body weight regulation. Physiol Behav. 2014;134:60-5.

Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer. 2011;104:1288.

Clinicaltrials.gov. Identifier: Nct02788955 Protein recommendations to increase muscle (PRIMe) Bethesda, MD2017 [accessed May 5, 2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT02788955.

Clinicaltrials.gov. Identifier: Nct03131921. Resting energy expenditure in cancer - associations with body composition, dietary intake, and exercise habits Bethesda, MD: National Library of Medicine; 2017 [updated May 3, 2017, accessed February 2, 2018].

Compher C, Frankenfield D, Keim N, Roth-Yousey L. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc. 2006;106(6):881-903.

Cooper JA, Watras AC, O'Brien MJ, Luke A, Dobratz JR, Earthman CP, et al. Assessing validity and reliability of resting metabolic rate in six gas analysis systems. J Am Diet Assoc. 2009;109(1):128-32.

Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381-95.

Cunningham JJ. Body composition as a determinant of energy expenditure: a synthetic review and a proposed general prediction equation. Am J Clin Nutr. 1991;54(6):963-9.

Cypess AM, Weiner LS, Roberts-Toler C, Franquet Elia E, Kessler SH, Kahn PA, et al. Activation of human brown adipose tissue by a beta3-adrenergic receptor agonist. Cell Metab. 2015;21(1):33-8.

Dahele M, Skipworth RJ, Wall L, Voss A, Preston T, Fearon KC. Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. J Pain Symptom Manage. 2007;33(6):676-85.

Daneryd P, Svanberg E, Korner U, Lindholm E, Sandstrom R, Brevinge H, et al. Protection of metabolic and exercise capacity in unselected weight-losing cancer patients following treatment with recombinant erythropoietin: A randomized prospective study. Cancer Res. 1998;58(23):5374-9.

de Oliveira C, Weir S, Rangrej J, Krahn MD, Mittmann N, Hoch JS, et al. The economic burden of cancer care in Canada: A population-based cost study. CMAJ Open. 2018;6(1):E1-E10.

de Roos B, Brennan L. Personalised interventions—a precision approach for the next generation of dietary intervention studies. Nutrients. 2017;9(8):847.

Deans DA, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. Br J Cancer. 2009;100(1):63-9.

DeLany JP, Kelley DE, Hames KC, Jakicic JM, Goodpaster BH. High energy expenditure masks low physical activity in obesity. Int J Obes (Lond). 2013;37(7):1006-11.

Demark-Wahnefried W, Campbell K, Hayes SC. Weight management and its role in breast cancer rehabilitation. Cancer. 2012;118(8 0):10.1002/cncr.27466.

Demark-Wahnefried W, Hars V, Conaway MR, Havlin K, Rimer BK, McElveen G, et al. Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. Am J Clin Nutr. 1997;65(5):1495-501.

Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, et al. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol. 2001;19(9):2381-9.

Dev R, Bruera E, Dalal S. Insulin resistance and body composition in cancer patients. Ann Oncol. 2018;29(suppl_2):ii18-ii26.

Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern cooperative oncology group. Am J Med. 1980;69(4):491-7.

Donahoo WT, Levine JA, Melanson EL. Variability in energy expenditure and its components. Curr Opin Clin Nutr Metab Care. 2004;7(6):599-605.

Drabsch T, Holzapfel C, Stecher L, Petzold J, Skurk T, Hauner H. Associations between C-reactive protein, insulin sensitivity, and resting metabolic rate in adults: a mediator analysis. Front Endocrinol (Lausanne). 2018;9:556-.

Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. JPEN J Parenter Enteral Nutr. 2015;39(7):787-822.

Ebadi M, Mazurak VC. Evidence and mechanisms of fat depletion in cancer. Nutrients. 2014;6(11):5280-97.

Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN, editors. Energy metabolism: Tissue determinants and cellular coeollaries. New York: Raven Press; 1992. p. 61-80.

Elia M, Ritz P, Stubbs RJ. Total energy expenditure in the elderly. Eur J Clin Nutr. 2000;54 Suppl 3:S92-103.

Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg. 1994;219(4):325-31.

Food and Agricultural Organization, World Health Organization, and United Nations University. Human Energy Requirements. Report of a joint FAO/WHO/UNU expert consultation. Rome, Italy: 2001. [accessed September 2018]. Available at: http://www.fao.org/3/a-y5686e.pdf

Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10(2):90-9.

Fearon K, Evans WJ, Anker SD. Myopenia - a new universal term for muscle wasting. J Cachexia Sarcopenia Muscle. 2011;2(1):1-3.

Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol. 2011;12(5):489-95.

Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: Mediators, signaling, and metabolic pathways. Cell Metab. 2012;16(2):153-66.

Fenninger LD, Mider GB. Energy and nitrogen metabolism in cancer. Adv Cancer Res. 1954;2:229-53.

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. Cancer incidence and mortality worldwide: IARC Cancerbase no. 11 Lyon, France: World Health Organization 2012.

Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology. 2002;13(5):561-8.

Fouladiun M, Korner U, Bosaeus I, Daneryd P, Hyltander A, Lundholm KG. Body composition and time course changes in regional distribution of fat and lean tissue in unselected cancer patients on palliative care--correlations with food intake, metabolism, exercise capacity, and hormones. Cancer. 2005;103(10):2189-98.

Fox KM, Brooks JM, Gandra SR, Markus R, Chiou C-F. Estimation of cachexia among cancer patients based on four definitions. J Oncol. 2009;2009.

Frankenfield D. Energy expenditure and protein requirements after traumatic injury. Nutr Clin Pract. 2006;21(5):430-7.

Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. J Am Diet Assoc. 2005;105(5):775-89.

Frankenfield DC. Bias and accuracy of resting metabolic rate equations in non-obese and obese adults. Clin Nutr. 2013;32(6):976-82.

Freake HC. Uncoupling proteins: Beyond brown adipose tissue. Nutr Rev. 1998;56(6):185-9.

Fredrix EW, Soeters PB, Rouflart MJ, von Meyenfeldt MF, Saris WH. Resting energy expenditure in patients with newly detected gastric and colorectal cancers. Am J Clin Nutr. 1991;53(5):1318-22.

Friesen DE, Baracos VE, Tuszynski JA. Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia. Theor Biol Med Model. 2015;12(1):17.

Fullmer S, Benson-Davies S, Earthman CP, Frankenfield DC, Gradwell E, Lee PS, et al. Evidence analysis library review of best practices for performing indirect calorimetry in healthy and non-critically ill individuals. J Acad Nutr Diet. 2015;115(9):1417-46 e2.

Gallagher D, Allen A, Wang Z, Heymsfield SB, Krasnow N. Smaller organ tissue mass in the elderly fails to explain lower resting metabolic rate. Ann N Y Acad Sci. 2006;904(1):449-55.

Gallagher D, Belmonte D, Deurenberg P, Wang Z, Krasnow N, Pi-Sunyer FX, et al. Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass. Am J Physiol. 1998;275(2 Pt 1):E249-58.

Garby L, Lammert O. Within-subjects between-days-and-weeks variation in energy expenditure at rest. Hum Nutr Clin Nutr. 1984;38(5):395-7.

Garcia-Peris P, Lozano MA, Velasco C, de La Cuerda C, Iriondo T, Breton I, et al. Prospective study of resting energy expenditure changes in head and neck cancer patients treated with chemoradiotherapy measured by indirect calorimetry. Nutrition. 2005;21(11-12):1107-12.

Geisler C, Braun W, Pourhassan M, Schweitzer L, Glüer C-C, Bosy-Westphal A, et al. Age-dependent changes in resting energy expenditure (REE): insights from detailed body composition analysis in normal and overweight healthy Caucasians. Nutrients. 2016;8(6):322.

Gibney E, Elia M, Jebb SA, Murgatroyd P, Jennings G. Total energy expenditure in patients with small-cell lung cancer: results of a validated study using the bicarbonate-urea method. Metabolism. 1997;46(12):1412-7.

Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: New insights provided by body composition. Am J Clin Nutr. 2014;99(5):999-1005.

Gordon JN, Green SR, Goggin PM. Cancer cachexia. QJM. 2005;98(11):779-88.

Grossberg AJ, Scarlett JM, Marks DL. Hypothalamic mechanisms in cachexia. Physiol Behav. 2010;100(5):478-89.

Guo J, Chen S, Chen Y, Li S, Xu D. Combination of CRP and NLR: a better predictor of postoperative survival in patients with gastric cancer. Cancer Manag Res. 2018;10:315-21.

Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88(1):218-30.

Hall KD, Baracos VE. Computational modeling of cancer cachexia. Curr Opin Clin Nutr Metab Care. 2008;11(3):214-21.

Hall KD, Guo J, Chen KY, Leibel RL, Reitman ML, Rosenbaum M, et al. Challenges of measuring energy expenditure differences between diets varying in carbohydrate using doubly labeled water. Pre-print. bioRxiv. 2018:403931. Accessed January 22, 2019.

Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL, et al. Quantification of the effect of energy imbalance on bodyweight. Lancet. 2011;378(9793):826-37.

Hansell DT, Davies JW, Burns HJ. Effects of hepatic metastases on resting energy expenditure in patients with colorectal cancer. Br J Surg. 1986;73(8):659-62.

Hansell DT, Davies JW, Burns HJ. The effects on resting energy expenditure of different tumor types. Cancer. 1986;58(8):1739-44.

Harris JA, Benedict FG. A biometric study of human basal metabolism. Proc Natl Acad Sci U.S.A. 1918;4(12):370-3.

Harvie MN, Campbell IT, Baildam A, Howell A. Energy balance in early breast cancer patients receiving adjuvant chemotherapy. Breast Cancer Res Treat. 2004;83(3):201-10.

Harvie MN, Campbell IT, Thatcher N, Baildam A. Changes in body composition in men and women with advanced nonsmall cell lung cancer (NSCLC) undergoing chemotherapy. J Hum Nutr Diet. 2003;16(5):323-6.

Haugen HA, Chan L-N, Li F. Indirect calorimetry: a practical guide for clinicians. Nutr Clin Pract. 2007;22(4):377-88.

Hayes S, Davies PS, Parker T, Bashford J. Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme. Bone Marrow Transplant. 2003;31(5):331-8.

Helms ER, Zinn C, Rowlands DS, Brown SR. A systematic review of dietary protein during caloric restriction in resistance trained lean athletes: A case for higher intakes. Int J Sport Nutr Exerc Metab. 2014;24(2):127-38.

Henry CJ. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr. 2005;8(7A):1133-52.

Herrmann SD, Barreira TV, Kang M, Ainsworth BE. Impact of accelerometer wear time on physical activity data: a NHANES semi-simulation data approach. Br J Sports Med. 2014;48(3):278-82.

Heymsfield SB. Measurements of energy balance. Acta Diabetol. 2003;40 Suppl 1:S117-21.

Heymsfield SB, Gallagher D, Kotler DP, Wang Z, Allison DB, Heshka S. Body-size dependence of resting energy expenditure can be attributed to nonenergetic homogeneity of fat-free mass. Am J Physiol Endocrinol Metab. 2002;282(1):E132-8.

Heymsfield SB, Thomas D, Bosy-Westphal A, Shen W, Peterson CM, Muller MJ. Evolving concepts on adjusting human resting energy expenditure measurements for body size. Obes Rev. 2012;13(11):1001-14.

Hill RJ, Cleghorn GJ, Withers GD, Lewindon PJ, Ee LC, Connor F, et al. Resting energy expenditure in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2007;45(3):342-6.

Hipskind P, Glass C, Charlton D, Nowak D, Dasarathy S. Do handheld calorimeters have a role in assessment of nutrition needs in hospitalized patients? A systematic review of literature. Nutr Clin Pract. 2011;26(4):426-33.

Huang KC, Kormas N, Steinbeck K, Loughnan G, Caterson ID. Resting metabolic rate in severely obese diabetic and nondiabetic subjects. Obes Res. 2004;12(5):840-5.

Institute of Medicine of the National Academics, Food and Nutrition Board. Dietary reference Intakes for Energy, Carbohydrates, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington D.C., United States, 2005.

International Agency for Research on Cancer. World Health Organization. World Cancer Report 2014. Lyon, France: 2014.

International Atomic Energy Agency. Assessment of body composition and total energy expenditure in humans using stable isotope techniques. IAEA Human Health Series No. 3. Vienna, Austria, 2009.

Irving CJ, Eggett DL, Fullmer S. Comparing steady state to time interval and non–steady state measurements of resting metabolic rate. Nutr Clin Pract. 2016;32(1):77-83.

Irwin ML, Crumley D, McTiernan A, Bernstein L, Baumgartner R, Gilliland FD, et al. Physical activity levels before and after a diagnosis of breast carcinoma: The health, eating, activity, and lifestyle (HEAL) study. Cancer. 2003;97(7):1746-57.

Itoi A, Yamada Y, Yokoyama K, Adachi T, Kimura M. Validity of predictive equations for resting metabolic rate in healthy older adults. Clin Nutr ESPEN. 2017;22:64-70.

Jatoi A, Daly BD, Hughes VA, Dallal GE, Kehayias J, Roubenoff R. Do patients with nonmetastatic non-small cell lung cancer demonstrate altered resting energy expenditure? Ann Thorac Surg. 2001;72(2):348-51.

Javed F, He Q, Davidson LE, Thornton JC, Albu J, Boxt L, et al. Brain and high metabolic rate organ mass: Contributions to resting energy expenditure beyond fat-free mass. Am J Clin Nutr. 2010;91(4):907-12.

Jebb SA, Osborne RJ, Dixon AK, Bleehen NM, Elia M. Measurements of resting energy expenditure and body composition before and after treatment of small cell lung cancer. Ann Oncol. 1994;5(10):915-9.

Jesus P, Achamrah N, Grigioni S, Charles J, Rimbert A, Folope V, et al. Validity of predictive equations for resting energy expenditure according to the body mass index in a population of 1726 patients followed in a nutrition unit. Clin Nutr. 2015;34(3):529-35.

Jochem C, Leitzmann M. Obesity and colorectal cancer: recent results. Cancer Res. 2016;208:17-41.

Johannsen DL, Calabro MA, Stewart J, Franke W, Rood JC, Welk GJ. Accuracy of armband monitors for measuring daily energy expenditure in healthy adults. Med Sci Sports Exerc. 2010;42(11):2134-40.

Johnson G, Salle A, Lorimier G, Laccourreye L, Enon B, Blin V, et al. Cancer cachexia: measured and predicted resting energy expenditures for nutritional needs evaluation. Nutrition. 2008;24(5):443-50.

Johnson M, Meltz K, Hart K, Schmudlach M, Clarkson L, Borman K. Validity of the ActiCal activity monitor for assessing steps and energy expenditure during walking. J Sports Sci. 2015;33(8):769-76.

Johnstone AM, Rance KA, Murison SD, Duncan JS, Speakman JR. Additional anthropometric measures may improve the predictability of basal metabolic rate in adult subjects. Eur J Clin Nutr. 2006;60(12):1437-44.

Joosen AM, Gielen M, Vlietinck R, Westerterp KR. Genetic analysis of physical activity in twins. Am J Clin Nutr. 2005;82(6):1253-9.

Jouinot A, Vazeille C, Durand JP, Huillard O, Boudou-Rouquette P, Coriat R, et al. Resting energy expenditure in the risk assessment of anticancer treatments. Clin Nutr. 2018;37(2):558-65.

Kamimura MA, Draibe SA, Avesani CM, Canziani ME, Colugnati FA, Cuppari L. Resting energy expenditure and its determinants in hemodialysis patients. Eur J Clin Nutr. 2007;61(3):362-7.

Keys A, Brozek J, Henschel A, Michelson O, Taylor HL. The Biology of Human Starvation: University of Minnesota Press; Minneapolis, Minnesota. 1950.

Khor SM, Mohd BB. Assessing the resting energy expenditure of cancer patients in the Penang general hospital. Malays J Nutr. 2011;17(1):43-53.

Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. Thyroid. 2008;18(2):141-4.

Kim E-K, Kim J-H, Kim M-H, Ndahimana D, Yean S-E, Yoon J-S, et al. Validation of dietary reference intake equations for estimating energy requirements in Korean adults by using the doubly labeled water method. Nutr Res Pract. 2017;11(4):300-6.

Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE, et al. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature. 2014;513(7516):100-4.

Knox LS, Crosby LO, Feurer ID, Buzby GP, Miller CL, Mullen JL. Energy expenditure in malnourished cancer patients. Ann Surg. 1983;197(2):152-62.

Kocarnik JM, Hua X, Hardikar S, Robinson J, Lindor NM, Win AK, et al. Long-term weight loss after colorectal cancer diagnosis is associated with lower survival: the colon cancer family registry. Cancer. 2017;123(23):4701-8.

Korber J, Pricelius S, Heidrich M, Muller MJ. Increased lipid utilization in weight losing and weight stable cancer patients with normal body weight. Eur J Clin Nutr. 1999;53(9):740-5.

Korth O, Bosy-Westphal A, Zschoche P, Gluer CC, Heller M, Muller MJ. Influence of methods used in body composition analysis on the prediction of resting energy expenditure. Eur J Clin Nutr. 2007;61(5):582-9.

Kroenke CH, Neugebauer R, Meyerhardt J, Prado CM, Weltzien E, Kwan ML, et al. Analysis of body mass index and mortality in patients with colorectal cancer using causal diagrams. JAMA Oncol. 2016;2(9):1137-45.

Kubrak C, Olson K, Jha N, Scrimger R, Parliament M, McCargar L, et al. Clinical determinants of weight loss in patients receiving radiation and chemo-irradiation for head and neck cancer: a prospective longitudinal view. Head Neck. 2013;35(5):695-703.

Kutynec CL, McCargar L, Barr SI, Hislop TG. Energy balance in women with breast cancer during adjuvant treatment. J Am Diet Assoc. 1999;99(10):1222-7.

Kyle UG, Genton L, Hans D, Karsegard L, Slosman DO, Pichard C. Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. Eur J Clin Nutr. 2001;55(8):663-72.

Lam YY, Ravussin E. Analysis of energy metabolism in humans: a review of methodologies. Molecular Metabolism. 2016;5(11):1057-71.

Langius JA, Kruizenga HM, Uitdehaag BM, Langendijk JA, Doornaert P, Leemans CR, et al. Resting energy expenditure in head and neck cancer patients before and during radiotherapy. Clin Nutr. 2012;31(4):549-54.

Later W, Bosy-Westphal A, Kossel E, Gluer CC, Heller M, Muller MJ. Is the 1975 reference man still a suitable reference? Eur J Clin Nutr. 2010;64(10):1035-42.

Lavoie ME, Rabasa-Lhoret R, Doucet É, Mignault D, Messier L, Bastard JP, et al. Association between physical activity energy expenditure and inflammatory markers in sedentary overweight and obese women. Int J Obes. 2010;34:1387.

LaVoy EC, Fagundes CP, Dantzer R. Exercise, inflammation, and fatigue in cancer survivors. Exerc Immunol Rev. 2016;22:82-93.

Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332(10):621-8.

Levine JA. Non-exercise activity thermogenesis (NEAT). Best Pract Res Clin Endocrinol Metab. 2002;16(4):679-702.

Levine JA. Measurement of energy expenditure. Public Health Nutr. 2005;8(7a):1123-32.

Levine JA, Eberhardt NL, Jensen MD. Role of non-exercise activity thermogenesis in resistance to fat gain in humans. Science. 1999;283(5399):212-4.

Lewis LS, Hernon J, Clark A, Saxton JM. Validation of the IPAQ against different accelerometer cut-points in older cancer survivors and adults at risk of cancer. J Aging Phys Act. 2018;26(1):34-40.

Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107(6):931-6.

Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr. 2009;89(4):1173-9.

Lindholm E, Daneryd P, Korner U, Hyltander A, Fouladiun M, Lundholm K. Effects of recombinant erythropoietin in palliative treatment of unselected cancer patients. Clin Cancer Res. 2004;10(20):6855-64.

Loughney L, West MA, Dimitrov BD, Kemp GJ, Grocott MPW, Jack S. Physical activity levels in locally advanced rectal cancer patients following neoadjuvant chemoradiotherapy and an exercise training programme before surgery: a pilot study. Periop Med. 2017;6:3.

Lundholm K, Daneryd P, Bosaeus I, Korner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: effects on survival, metabolism, and function. Cancer. 2004;100(9):1967-77.

Lundholm K, Daneryd P, Korner U, Hyltander A, Bosaeus I. Evidence that long-term COX-treatment improves energy homeostasis and body composition in cancer patients with progressive cachexia. Int J Oncol. 2004;24(3):505-12.

Lundholm K, Edstrom S, Karlberg I, Ekman L, Schersten T. Glucose turnover, gluconeogenesis from glycerol, and estimation of net glucose cycling in cancer patients. Cancer. 1982;50(6):1142-50.

Lundholm K, Korner U, Gunnebo L, Sixt-Ammilon P, Fouladiun M, Daneryd P, et al. Insulin treatment in cancer cachexia: effects on survival, metabolism, and physical functioning. Clin Cancer Res. 2007;13(9):2699-706.

Lupinsky L, Singer P, Theilla M, Grinev M, Hirsh R, Lev S, et al. Comparison between two metabolic monitors in the measurement of resting energy expenditure and oxygen consumption in diabetic and non-diabetic ambulatory and hospitalized patients. Nutrition. 2015;31(1):176-9.

Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013;8(1):e53916.

Maccio A, Madeddu C, Gramignano G, Mulas C, Floris C, Sanna E, et al. A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life. Gynecol Oncol. 2012;124(3):417-25.

Macy EM, Hayes TE, Tracy RP. Variability in the measurement of c-reactive protein in healthy subjects: Implications for reference intervals and epidemiological applications. Clin Chem. 1997;43(1):52-8.

Maguire R, McMillan DC, Wallace AM, McArdle C. A longitudinal study of leptin and appetite, resting energy expenditure and body fat mass in weight-stable cancer patients. Cytokine. 2002;20(4):174-7.

Manini TM. Energy expenditure and aging. Ageing Res Rev. 2010;9(1):1-26.

Mao M, Wei X, Sheng H, Chi P, Liu Y, Huang X, et al. C-reactive protein/albumin and neutrophil/lymphocyte ratios and their combination predict overall survival in patients with gastric cancer. Oncol Lett. 2017;14(6):7417-24.

Marra M, Cioffi I, Sammarco R, Montagnese C, Naccarato M, Amato V, et al. Prediction and evaluation of resting energy expenditure in a large group of obese outpatients. Int J Obes (Lond). 2017;41(5):697-705.

Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, 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(12):1539-47.

Martin L, Kubrak C. How much does reduced food intake contribute to cancer-associated weight loss? Curr Opin Support Palliat Care. 2018:12(4):410-9.

Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015;33(1):90-9.

Mathot KJ, Dingemanse NJ. Energetics and behavior: unrequited needs and new directions. Trends Ecol Evol. 2015;30(4):199-206.

McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care. 2009;12(3):223-6.

McNeil J, Lamothe G, Cameron JD, Riou ME, Cadieux S, Lafreniere J, et al. Investigating predictors of eating: is resting metabolic rate really the strongest proxy of energy intake? Am J Clin Nutr. 2017;106(5):1206-12.

Meijer EP, Westerterp KR, Verstappen FT. Effect of exercise training on total daily physical activity in elderly humans. Eur J Appl Physiol Occup Physiol. 1999;80(1):16-21.

Melanson EL. The effect of exercise on non-exercise physical activity and sedentary behavior in adults. Obes Rev. 2017;18 Suppl 1:40-9.

Mendoza-Juez B, Martinez-Gonzalez A, Calvo GF, Perez-Garcia VM. A mathematical model for the glucose-lactate metabolism of in vitro cancer cells. Bull Math Biol. 2012;74(5):1125-42.

Meyerhardt JA, Kroenke CH, Prado CM, Kwan ML, Castillo A, Weltzien E, et al. Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente Northern California population. Cancer Epidemiol Biomarkers Prev. 2017;26(1):30-7.

Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241-7.

Miles CW, Wong NP, Rumpler WV, Conway J. Effect of circadian variation in energy expenditure, within-subject variation and weight reduction on thermic effect of food. Eur J Clin Nutr. 1993;47(4):274-84.

Morrison SA, Petri RM, Hunter HL, Raju D, Gower B. Comparison of the Lunar Prodigy and iDXA dual-energy x-ray absorptiometers for assessing total and regional body composition. J Clin Densitom. 2016;19(3):290-7.

Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer. 2004;90(5):996-1002.

Most J, Vallo PM, Gilmore LA, St Amant M, Hsia DS, Altazan AD, et al. Energy expenditure in pregnant women with obesity does not support energy intake recommendations. Obesity. 2018;26(6):992-9.

Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.

Müller MJ, Bosy-Westphal A, Klaus S, Kreymann G, Lührmann PM, Neuhäuser-Berthold M, et al. World Health Organization equations have shortcomings for predicting resting energy expenditure in persons from a modern, affluent population: generation of a new reference standard from a retrospective analysis of a German database of resting energy expenditure. Am J Clin Nutr. 2004;80(5):1379-90.

Muller MJ, Enderle J, Pourhassan M, Braun W, Eggeling B, Lagerpusch M, et al. Metabolic adaptation to caloric restriction and subsequent refeeding: the Minnesota Starvation Experiment revisited. Am J Clin Nutr. 2015;102(4):807-19.

Nasrah R, Kanbalian M, Van Der Borch C, Swinton N, Wing S, Jagoe RT. Defining the role of dietary intake in determining weight change in patients with cancer cachexia. Clin Nutr. 2018;37(1):235-41.

National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases. Body weight planner [Oct 31, 2018]. Available from: https://www.niddk.nih.gov/bwp.

Ndahimana D, Lee SH, Kim YJ, Son HR, Ishikawa-Takata K, Park J, et al. Accuracy of Dietary Reference Intake predictive equation for estimated energy requirements in female tennis athletes and non-athlete college students: comparison with the doubly labeled water method. Nutr Res Pract. 2017;11(1):51-6.

Nguyen TYV, Batterham MJ, Edwards C. Comparison of resting energy expenditure between cancer subjects and healthy controls: a meta-analysis. Nutr Cancer. 2016;68(3):374-87.

Nieman DC, Austin MD, Benezra L, Pearce S, McInnis T, Unick J, et al. Validation of Cosmed's FitMate in measuring oxygen consumption and estimating resting metabolic rate. Res Sports Med. 2006;14(2):89-96.

Nixon DW, Kutner M, Heymsfield S, Foltz AT, Carty C, Seitz S, et al. Resting energy expenditure in lung and colon cancer. Metabolism. 1988;37(11):1059-64.

O'Driscoll R, Turicchi J, Beaulieu K, Scott S, Matu J, Deighton K, et al. How well do activity monitors estimate energy expenditure? a systematic review and meta-analysis of the validity of current technologies. Br J Sports Med. 2018:bjsports-2018-099643.

Okamoto H, Sasaki M, Johtatsu T, Kurihara M, Iwakawa H, Akabane M, et al. Resting energy expenditure and nutritional status in patients undergoing transthoracic esophagectomy for esophageal cancer. J Clin Biochem Nutr. 2011;49(3):169-73.

Oliveira CLP, Mattingly S, Schirrmacher R, Sawyer MB, Fine EJ, Prado CM. A nutritional perspective of ketogenic diet in cancer: a narrative review. J Acad Nutr Diet. 2018;118(4):668-88.

Omlin A, Blum D, Wierecky J, Haile SR, Ottery FD, Strasser F. Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions, a case–control study. J Cachexia Sarcopenia Muscle. 2013;4(1):55-61.

Orava J, Nuutila P, Lidell ME, Oikonen V, Noponen T, Viljanen T, et al. Different metabolic responses of human brown adipose tissue to activation by cold and insulin. Cell Metab. 2011;14(2):272-9.

Ostendorf DM, Melanson EL, Caldwell AE, Creasy SA, Pan Z, MacLean PS, et al. No consistent evidence of a disproportionately low resting energy expenditure in long-term successful weight-loss maintainers. Am J Clin Nutr. 2018;108(4):658-66.

Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.

Owen OE, Kavle E, Owen RS, Polansky M, Caprio S, Mozzoli MA, et al. A reappraisal of caloric requirements in healthy women. Am J Clin Nutr. 1986;44(1):1-19.

Park YS, Park DJ, Lee Y, Park KB, Min S-H, Ahn S-H, et al. Prognostic roles of perioperative body mass index and weight loss in the long-term survival of gastric cancer patients. Cancer Epidemiol Biomarkers Prev 2018;27(8):955-62.

Pennington Biomedical Research Center. Weight loss predictor [Accessed October 31, 2018]. Available from: https://www.pbrc.edu/research-and-faculty/calculators/weight-loss-predictor/.

Perusse L, Tremblay A, Leblanc C, Bouchard C. Genetic and environmental influences on level of habitual physical activity and exercise participation. Am J Epidemiol. 1989;129(5):1012-22.

Petruzzelli M, Schweiger M, Schreiber R, Campos-Olivas R, Tsoli M, Allen J, et al. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. Cell Metab. 2014;20(3):433-47.

Pirat A, Tucker AM, Taylor KA, Jinnah R, Finch CG, Canada TD, et al. Comparison of measured versus predicted energy requirements in critically ill cancer patients. Respir Care. 2009;54(4):487-94.

Pourhassan M, Schautz B, Braun W, Gluer CC, Bosy-Westphal A, Muller MJ. Impact of body-composition methodology on the composition of weight loss and weight gain. Eur J Clin Nutr. 2013;67(5):446-54.

Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. Proc Nutr Soc. 2016:1-11.

Prado CM, Gonzalez MC, Heymsfield SB. Body composition phenotypes and obesity paradox. Curr Opin Clin Nutr Metab Care. 2015;18(6):535-51.

Prado CM, Lieffers JR, Bergsten G, Mourtzakis M, Baracos VE, Reiman T, et al. Dietary patterns of patients with advanced lung or colorectal cancer. Can J Diet Pract Res. 2012;73(4):e298-303.

Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35.

Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? Am J Clin Nutr. 2013;98(4):1012-9.

Prado CM, Siervo M, Mire E, Heymsfield SB, Stephan BC, Broyles S, et al. A population-based approach to define body-composition phenotypes. Am J Clin Nutr. 2014;99(6):1369-77.

Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr. 2012;31(5):583-601.

Prado CMM, Mourtzakis M, Baracos V, Reiman T, Sawyer MB, McCargar LJ. Overweight and obese patients with solid tumors may have sarcopenia, poor prognosis and early features of cachexia. Int J Body Compos Res. 2010;8(1):7-15.

Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act. 2008;5:56.

Purcell SA, Elliott SA, Baracos VE, Chu QSC, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr. 2016;70(11):1230-8.

Purcell SA ES, Ryan AM, Sawyer MB, Prado CM. Accuracy of a portable indirect calorimeter for measuring resting energy expenditure in individuals with cancer. JPEN J Parenter Enteral Nutr. 2019;43(1):145-151.

Racette SB, Schoeller DA, Luke AH, Shay K, Hnilicka J, Kushner RF. Relative dilution spaces of 2H- and 18O-labeled water in humans. Am J Physiol. 1994;267(4 Pt 1):E585-90.

Ræder H, Kværner AS, Henriksen C, Florholmen G, Henriksen HB, Bøhn SK, et al. Validity of bioelectrical impedance analysis in estimation of fat-free mass in colorectal cancer patients. Clin Nutr. 2018;37(1):292-300.

Ravasco P. Aspects of taste and compliance in patients with cancer. Eur J Oncol Nurs. 2005;9 Suppl 2:S84-91.

Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest. 2007;25(5):308-14.

Ravasco P, Monteiro-Grillo I, Camilo M. How relevant are cytokines in colorectal cancer wasting? Cancer J. 2007;13(6):392-8.

Ravussin E, Bogardus C. Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization. Am J Clin Nutr. 1989;49(5 Suppl):968-75.

Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WGH, et al. Reduced rate of energy expenditure as a risk factor for body-weight gain. N Engl J Med. 1988;318(8):467-72.

Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. Cell Metab. 2018;27(4):805-15 e4.

Reeves MM, Battistutta D, Capra S, Bauer J, Davies PS. Resting energy expenditure in patients with solid tumors undergoing anticancer therapy. Nutrition. 2006;22(6):609-15.

Reeves MM, Capra S. Predicting energy requirements in the clinical setting: are current methods evidence based? Nutr Rev. 2003;61(4):143-51.

Reeves MM, Capra S, Bauer J, Davies PS, Battistutta D. Clinical accuracy of the MedGem indirect calorimeter for measuring resting energy expenditure in cancer patients. Eur J Clin Nutr. 2005;59(4):603-10.

Reis C, Liberman S, Pompeo AC, Srougi M, Halpern A, Filho WJ. Body composition alterations, energy expenditure and fat oxidation in elderly males suffering from prostate cancer, pre and post orchiectomy. Clinics (Sao Paulo). 2009;64(8):781-4.

Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569-78.

Rising R, Whyte K, Albu J, Pi-Sunyer X. Evaluation of a new whole room indirect calorimeter specific for measurement of resting metabolic rate. Nutr Metab (Lond). 2015;12(1):46.

Romu T, Vavruch C, Dahlqvist-Leinhard O, Tallberg J, Dahlström N, Persson A, et al. A randomized trial of cold-exposure on energy expenditure and supraclavicular brown adipose tissue volume in humans. Metabolism. 2016;65(6):926-34.

Ross SA, Dzida G, Vora J, Khunti K, Kaiser M, Ligthelm RJ. Impact of weight gain on outcomes in Type 2 diabetes. Curr Med Res Opin. 2011;27(7):1431-8.

Rubenbauer JR, Johannsen DL, Baier SM, Litchfield R, Flakoll PJ. The use of a handheld calorimetry unit to estimate energy expenditure during different physiological conditions. JPEN J Parenter Enteral Nutr. 2006;30(3):246-50.

Ryan AM, Power DG, Daly L, Cushen SJ, Ni Bhuachalla E, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. Proc Nutr Soc. 2016;75(2):199-211.

Schiessel DL, Baracos VE. Barriers to cancer nutrition therapy: excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. Proc Nutr Soc. 2018;77(4):394-402.

Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409-26.

Schoeller DA. Measurement of energy expenditure in free-living humans by using doubly labeled water. J Nutr. 1988;118(11):1278-89.

Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. J Appl Physiol Respir Environ Exerc Physiol. 1982;53(4):955-9.

Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39 Suppl 1:5-41.

Schwartz A, Kuk JL, Lamothe G, Doucet E. Greater than predicted decrease in resting energy expenditure and weight loss: results from a systematic review. Obesity. 2012;20(11):2307-10.

Scott HR, McMillan DC, Watson WS, Milroy R, McArdle CS. Longitudinal study of resting energy expenditure, body cell mass and the inflammatory response in male patients with non-small cell lung cancer. Lung Cancer. 2001;32(3):307-12.

Segal R, Zwaal C, Green E, Tomasone JR, Loblaw A, Petrella T, et al. Exercise for people with cancer: a clinical practice guideline. Curr Oncol. 2017;24(1):40-6.

Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333-8.

Shiono M, Huang K, Downey RJ, Consul N, Villanueva N, Beck K, et al. An analysis of the relationship between metastases and cachexia in lung cancer patients. Cancer Med. 2016;5(9):2641-8.

Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-93.

Siervo M, Bertoli S, Battezzati A, Wells JC, Lara J, Ferraris C, et al. Accuracy of predictive equations for the measurement of resting energy expenditure in older subjects. Clin Nutr. 2014;33(4):613-9.

Siervo M, Faber P, Lara J, Gibney ER, Milne E, Ritz P, et al. Imposed rate and extent of weight loss in obese men and adaptive changes in resting and total energy expenditure. Metabolism. 2015;64(8):896-904.

Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. Head Neck. 2007;29(10):893-900.

Simons JP, Schols AM, Buurman WA, Wouters EF. Weight loss and low body cell mass in males with lung cancer: Relationship with systemic inflammation, acute-phase response, resting energy expenditure, and catabolic and anabolic hormones. Clin Sci (Lond). 1999;97(2):215-23.

Skipworth RJ, Stene GB, Dahele M, Hendry PO, Small AC, Blum D, et al. Patient-focused endpoints in advanced cancer: criterion-based validation of accelerometer-based activity monitoring. Clin Nutr. 2011;30(6):812-21.

Souza MTP, Singer P, Ozorio GA, Rosa VM, Alves MMF, Mendoza López RV, et al. Resting energy expenditure and body composition in patients with head and neck cancer: an observational study leading to a new predictive equation. Nutrition. 2018;51-52:60-5.

Speakman JR, Nair KS, Goran MI. Revised equations for calculating CO2 production from doubly labeled water in humans. Am J Physiol. 1993;264(6 Pt 1):E912-7.

Speakman JR, Selman C. Physical activity and resting metabolic rate. Proc Nutr Soc. 2003;62(3):621-34.

Speakman JR, Westerterp KR. Associations between energy demands, physical activity, and body composition in adult humans between 18 and 96 y of age. Am J Clin Nutr. 2010;92(4):826-34.

Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv. 2010;4(2):87-100.

Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol. 2018;9:754.

Staal-van den Brekel AJ, Dentener MA, Schols AM, Buurman WA, Wouters EF. Increased resting energy expenditure and weight loss are related to a systemic inflammatory response in lung cancer patients. J Clin Oncol. 1995;13(10):2600-5.

Stewart CL, Goody CM, Branson R. Comparison of two systems of measuring energy expenditure. JPEN J Parenter Enteral Nutr. 2005;29(3):212-7.

Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A systematic review of exercise systematic reviews in the cancer literature (2005-2017). PM R. 2017;9(9S2):S347-S84.

Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med. 2010;267(6):543-60.

Tappy L. Metabolic consequences of overfeeding in humans. Curr Opin Clin Nutr Metab Care. 2004;7(6):623-8.

Taylor HL, Keys A. Adaptation to caloric restriction. Science. 1950;112(2904):215-8.

Thomas DM, Martin CK, Heymsfield S, Redman LM, Schoeller DA, Levine JA. A simple model predicting individual weight change in humans. J Biol Dyn. 2011;5(6):579-99.

Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, Birdsell L, et al. The association of nutritional assessment criteria with health-related quality of life in patients with advanced colorectal carcinoma. Eur J Cancer Care (Engl). 2012;21(4):505-16.

Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the united states measured by accelerometer. Med Sci Sports Exerc. 2008;40(1):181-8.

Trutschnigg B, Kilgour RD, Morais JA, Lucar E, Hornby L, Molla H, et al. Metabolic, nutritional and inflammatory characteristics in elderly women with advanced cancer. J Geriatr Oncol. 2013;4(2):183-9.

Tschop MH, Speakman JR, Arch JR, Auwerx J, Bruning JC, Chan L, et al. A guide to analysis of mouse energy metabolism. Nat Methods. 2011;9(1):57-63.

United States Department of Health and Human Services. National Institutes of Health. National Cancer Institute. Cancer Statistics [April 27, 2018]. Available from: https://www.cancer.gov/about-cancer/understanding/statistics.

Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. Am J Clin Nutr. 2005;82(4):801-5.

Vaisman N, Lusthaus M, Niv E, Santo E, Shacham-Shmueli E, Geva R, et al. Effect of tumor load on energy expenditure in patients with pancreatic cancer. Pancreas. 2012;41(2):230-2.

Vandarakis D, Salacinski AJ, Broeder CE. A comparison of Cosmed metabolic systems for the determination of resting metabolic rate. Res Sports Med. 2013;21(2):187-94.

Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324(5930):1029-33.

Vazeille C, Jouinot A, Durand JP, Neveux N, Boudou-Rouquette P, Huillard O, et al. Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. Am J Clin Nutr. 2017;105(5):1139-47.

Vermaete N, Wolter P, Verhoef G, Gosselink R. Physical activity and physical fitness in lymphoma patients before, during, and after chemotherapy: a prospective longitudinal study. Ann Hematol. 2014;93(3):411-24.

Viggiani MT, Lorusso O, Natalizio F, Principi M, Di Leo A, Barone M. Influence of chemotherapy on total energy expenditure in patients with gastrointestinal cancer: a pilot study. Nutrition. 2017;42:7-11.

Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: Relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer. 2013;21(6):1569-77.

Walsh D, Nelson KA. Autonomic nervous system dysfunction in advanced cancer. Support Care Cancer. 2002;10(7):523-8.

Wang Z, Heshka S, Gallagher D, Boozer CN, Kotler DP, Heymsfield SB. Resting energy expenditure-fat-free mass relationship: new insights provided by body composition modeling. Am J Physiol Endocrinol Metab. 2000;279(3):E539-45.

Wang Z, Heshka S, Heymsfield SB, Shen W, Gallagher D. A cellular-level approach to predicting resting energy expenditure across the adult years. Am J Clin Nutr. 2005;81(4):799-806.

Weijs PJ, Vansant GA. Validity of predictive equations for resting energy expenditure in Belgian normal weight to morbid obese women. Clin Nutr. 2010;29(3):347-51.

Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1-2):1-9.

Wells JC, Williams JE, Haroun D, Fewtrell MS, Colantuoni A, Siervo M. Aggregate predictions improve accuracy when calculating metabolic variables used to guide treatment. Am J Clin Nutr. 2009;89(2):491-9.

Westerterp KR. Diet induced thermogenesis. Nutr Metab (Lond). 2004;1(5).

Westerterp KR. Physical activity and physical activity induced energy expenditure in humans: measurement, determinants, and effects. Front Physiol. 2013;4:90.

Westerterp KR. Control of energy expenditure in humans. Eur J Clin Nutr. 2016;71:340.

Westerterp KR. Exercise, energy expenditure and energy balance, as measured with doubly labelled water. Proc Nutr Soc. 2018;77(1):4-10.

Weston PM, King RF, Goode AW, Williams NS. Diet-induced thermogenesis in patients with gastrointestinal cancer cachexia. Clin Sci (Lond). 1989;77(2):133-8.

Weyer C, Walford RL, Harper IT, Milner M, MacCallum T, Tataranni PA, et al. Energy metabolism after 2 y of energy restriction: The Biosphere 2 Experiment. Am J Clin Nutr. 2000;72(4):946-53.

Winkels RM, Snetselaar T, Adriaans A, van Warmerdam LJC, Vreugdenhil A, Slooter GD, et al. Changes in body weight in patients with colorectal cancer treated with surgery and adjuvant

chemotherapy: an observational study. Cancer Treatment and Research Communications. 2016;9:111-5.

Woo P, Murthy G, Wong C, Hursh B, Chanoine J-P, Elango R. Assessing resting energy expenditure in overweight and obese adolescents in a clinical setting: validity of a handheld indirect calorimeter. Pediatr Res. 2016;81:51.

World Health Organization Consultation. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. WHO Technical Report Series: 894. Geneva, Switzerland 2000;894:1-253.

Wu J, Huang C, Xiao H, Tang Q, Cai W. Weight loss and resting energy expenditure in male patients with newly diagnosed esophageal cancer. Nutrition. 2013;29(11-12):1310-4.

Xiao J, Caan BJ, Weltzien E, Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. J Cachexia Sarcopenia Muscle. 2018;9(4):654-63.

Xu WP, Cao DX, Lin ZM, Wu GH, Chen L, Zhang JP, et al. Analysis of energy utilization and body composition in kidney, bladder, and adrenal cancer patients. Urol Oncol. 2012;30(5):711-8.

Yee-Moon Wang A, Man-Mei Sea M, Tang N, Sanderson JE, Lui S-F, Kam-Tao Li P, et al. Resting energy expenditure and subsequent mortality risk in peritoneal dialysis patients. J Am Soc Nephrol. 2004;15(12):3134-43.

Yoneshiro T, Aita S, Matsushita M, Kayahara T, Kameya T, Kawai Y, et al. Recruited brown adipose tissue as an anti-obesity agent in humans. J Clin Invest. 2013;123(8):3404-8.

Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015;163(5):1079-94.

Zuconi CP, Ceolin Alves AL, Toulson Davisson Correia MI. Energy expenditure in women with breast cancer. Nutrition. 2015;31(4):556-9.