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Original article

Measurement of resting energy expenditure and its accuracy in women with breast cancer

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SUMMARY

Background & aims: Breast cancer (BC) is frequently linked with obesity, metabolic syndrome, and sarcopenia. Therefore, measuring or accurately estimating resting energy expenditure (REE) is crucial for tailoring nutritional needs, managing weight and prevent under- or over-nutrition. We aimed to measure and compare REE between women with BC and a matched control group. Moreover, the prediction accuracy of selected formulas was evaluated.
Methods: Women aged ≥18 years with newly diagnosis of BC (stage 0-III) and body mass index (BMI) ≤ 30 kg/m^2 were included in this cross-sectional analysis. Anthropometry, indirect calorimetry, and bioelectrical impedance analysis (BIA) were performed. Patients with BC data were compared to healthy women with similar age and BMI range. Measured REE (mREE) was compared against 15 predictive equations. Agreement between methods was evaluated using Bland-Altman analysis.
Results: We included 106 women with BC (age 49.9 ± 11.1 years and BMI 24.5 ± 2.8 kg/m^2) and 75 women as control group. There were no differences in age, anthropometry, and BIA variables between groups, except for percentage fat mass. Measured REE values, alone and adjusted for fat-free mass (FFM) and age, were higher in patients with BC compared to controls (+4.3 % and +6.1 %, respectively). Regarding REE prediction, most of the selected equations underestimated mREE. Precision varied widely, with the two Marra equations showing the highest agreement (73 % and 74.5 %) along with the Müller equation (74 %), however, the wide limit of agreement range indicates substantial variability.
Conclusions: Women with early-stage BC exhibited higher mREE compared to controls, albeit its clinical significance is unknown. None of the selected predictive equations provided accurate and precise REE estimates in this group. Although the Marra equation displayed the highest agreement, further studies are needed to evaluate REE variability and its prediction in women with BC.

1. Introduction

Breast cancer (BC) remains one of the most prevalent cancers among women worldwide. However, in the last few decades, effective screening practices, and the development of advanced treatment options have contributed to remarkable improvements in survival rates [1,2]. Extended life expectancy in patients with BC and survivors has been associated with increased risks of developing short- and/or long-term disease complications. In particular, chemotherapy-related side effects such as fatigue, pain, anorexia, nausea, and neurological disturbances can persist after completing treatment, resulting in an increased risk of developing malnutrition, characterized by alterations in body weight and compartments, with detrimental effects on clinical outcomes, quality of life and prognosis [1,3–5].

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One of the most critical aspects of managing malnutrition (i.e., both under- and over-nutrition) is the achievement of energy balance, which is determined by the ratio between energy intake and total energy expenditure (TEE). Resting energy expenditure (REE), the largest component of TEE, plays a key role in determining energy needs [6]. Several studies have observed variations in REE in patients with cancer, which may be influenced by tumour location, size, and stage [1,7–10], as well as other factors such as types, modalities and duration of treatment [11].

Indirect calorimetry (IC) is the criterion method for measuring REE, but it may not always be available or practical in clinical settings [12–14]. As such, in healthy populations, REE can be estimated by predictive equations [15–18], whereas their use might be unsuitable in patients with cancer [1,11] due to unfavourable changes in body composition, such as fat-free mass (FFM) loss and/or fat mass (FM) gain [1,3,4,11,19], which differently contribute to energy expenditure over the disease course. Currently, an increasing number of studies and systematic reviews have pointed out that patients with BC and survivors are at risk for developing obesity, especially after chemotherapy [5,20–22], impacting negatively on recurrence and mortality. Although measuring REE can provide an overview of metabolic changes experienced by patients during disease, only a few numbers of studies have been performed in patients with BC and survivors. These studies, taken alone [23–26] or in comparison with a matched healthy group [27–30] have provided contrasting results [23,26]. For instance, REE was reported to be similar between patients with BC and controls [28,29], and increased or decreased by others, when adjusted for FFM [27] or due to adjuvant [26] or neo-adjuvant [30] chemotherapy. Conversely, the accuracy of using predictive formulas to estimate REE in these patients has been relatively unexplored [26,28]. To date, only some predictive equations, mostly the Harris-Benedict (HB) formula, have been used [26,28–30]. Importantly, there is still a need for the development of a population-based equation.

In view of the available evidence, the accurate assessment of REE is crucial for meeting the nutritional demands of patients with BC and avoiding under- or over-nutrition. Therefore, the primary objective of this study was to measure and compare REE in women with newly diagnosed BC and contrast it against a healthy control group. Additionally, the study evaluated the prediction accuracy of REE (pREE) at both group (bias) and individual levels (precision) using established equations in patients with BC to explore the best fit.

2. Methods

This is a secondary analysis of a lifestyle intervention study in which measured REE (mREE) data were collected at baseline from a group of patients with early diagnosis of BC, candidates for surgery and adjuvant/neoadjuvant therapy. Women were consecutively recruited at the Oncology Unit of the Department of Clinical Medicine and Surgery, Federico II University, Naples (Italy) from September 2018 to June 2021, as part of a randomized controlled trial assessing the effect of a targeted dietary intervention on weight change and quality of life (data unpublished).

Inclusion criteria were a) pre-and postmenopausal women; b) age $\geq$18 years; c) early diagnosis of BC (stage I-III); d) body mass index (BMI) > 18.5 and $\leq$ 30 kg/m^2; and d) available medical history. Exclusion criteria were as follows: metastasis, BMI >30 kg/m^2 and the presence of severe clinical conditions, as previously described [4]. The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the local Ethics Committee of Federico II University (Prot. n. 280/17). All patients gave their informed consent to participate in the study.

The first visit was scheduled and consisted of collecting data about nutritional status, including anthropometric measures, body composition and REE. The above-mentioned measurements were performed early in the morning after a fasting period of 8–10 h according to standardized conditions (abstention from alcohol, smoking, and vigorous physical activity for 24 h prior to the assessment).

To compare mREE between patients with BC and healthy subjects, a group of women having similar age and BMI, without a cancer diagnosis or other related conditions known to affect REE, were randomly selected from our database. These included Caucasian adults, aged $\geq$18 years with a BMI between 18.5 and 30 kg/m^2, who served as control group, as previously reported [4,31].

2.1. Anthropometric measurements

Body weight and stature were measured by the same operator following standard procedures according to Lohman et al. [32]. Body weight was measured to the nearest 0.1 kg using a platform beam scale and stature to the nearest 0.5 cm using a stadiometer (Seca 709; Seca, Hamburg, Germany). The patients wore light clothes and no shoes. Both measures were used to calculate BMI (weight in kilograms divided by stature in meters squared).

2.2. Body composition assessment

Body composition was estimated by bioelectrical impedance analysis (BIA), using a phase-sensitive device (Human Im Plus II - DS Medica-Milan, Italy). Before starting the measurement, patients were asked to remain in supine position for 10–15 min, with upper and lower limbs slightly abducted at 30 and 45°, respectively, to avoid any contact between the extremities and the trunk. A standard tetra-polar technique was used. Measuring electrodes were placed on the anterior surface of the wrist and the ankle, and injecting electrodes on the dorsal surface of the hand and the foot [33]. Before each test, the device was calibrated using a standard control circuit with known impedance (Z) and reactance (supplied by the manufacturer). The test–retest coefficient of variation (CV) of the measurements (in eight individuals) was always less than 3 %. Impedance and phase angle (PhA) were measured at 50 kHz on the nondominant side of the body. Bioimpedance index (BI-index) was calculated as the ratio stature^2/Z (cm^2/ohm). Fat-free mass and FM were estimated using the predictive equations developed by Sun [34].

2.3. Measurement of resting energy expenditure

Resting energy expenditure was measured by IC [35] using a canopy system, V max29 (Sensor Medics, Anaheim, CA, USA). The instrument was routinely checked by burning ethanol to assess the accuracy of RQ measurement (Table S1); the observed RQ was 0.669 ± 0.008 compared to an expected value of 0.667 and an acceptable range of 0.640–0.690 [36]. Oxygen and carbon dioxide analysers were calibrated on the test day using nitrogen and standardized gases (mixtures of nitrogen, carbon dioxide, and oxygen). The flowmeter was calibrated using a syringe of known volume (3 L).

Measurement conditions for IC were defined following the suggestions made by Compher et al. [37] and Fullmer et al. [38]. REE was assessed in a thermo-neutral condition (22°C-25 °C) after an overnight fast and, in women having menstrual cycle, during the follicular phase to avoid any potential effects. Participants lay down on a bed in a quiet environment for a 15-minute adaptation period. Afterward, oxygen consumption and carbon dioxide production were measured for 45 min, discarding the first 5 min. Only steady-

state periods of measurement were selected according to the procedures for the ventilated hood system (<5 % CV). Also, the inter-day CV (as determined in 10 subjects on subsequent days) was always less than 4 %. The flow throughout the canopy was modified in order to maintain the CO_2 between 0.6 and 0.8 %. Energy expenditure was calculated using the abbreviated Weir formula, neglecting protein oxidation [39].

Data were excluded from analysis if the respiratory quotient (RQ) was outside the expected range (0.71–0.90) and when mREE was ±3 standard deviations outside the mean REE.

2.4. Prediction of resting energy expenditure

Several selected predictive formulas to estimate REE, with and without body composition variables, were used for patients with BC: the HB [17], FAO/WHO/UNU [40], Schofield [18], Owen [41,42], Huang [43], Mifflin [44], Müller [45], Cunningham [46] and Wang [47] equations. In addition, the Marra equations [15], recently developed by our group, and characterized by PhA and BI-index in the formula, plus another equation specifically developed for patients with cancer by Souza-Singer et al. [8] were selected for REE prediction. All the included formulas are presented in Table S2.

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS (version 28, Chicago, IL, USA). All data are presented as mean ± standard deviation (SD), unless otherwise specified, and significance was defined as $p < 0.05$. The Kolmogorov–Smirnov test and the Shapiro–Wilk test were used to examine whether variables were normally distributed. Unpaired t-test and the Mann Whitney U-test were used for continuous and non-continuous variables to determine differences between two groups. Since more than half of patients ($n = 65$) started their treatments before measuring REE, they were also grouped by treatment timing (treatment vs. no treatment) and compared to controls. Analysis of variance (ANOVA) was used to compare variables between subgroups and controls, and Tukey *post hoc* tests were made when the omnibus test was statistically significant. Pearson's linear correlation was applied to evaluate associations between variables (mREE and age, weight, height, BMI, FFM, FM, PhA, BI-index). Then, to explore determinants of mREE in patients with BC and controls, a stepwise linear regression analysis was applied using mREE, as dependent variable, and age, weight, height, BMI, FFM, FM, PhA and BI-index as independent variables. Moreover, disease stage, menopausal status and treatment timing were added as further variables in patients with BC. Multicollinearity was checked among independent variables to avoid any misinterpretation of the results.

General linear model was used to adjust mREE for FFM, as mREE without this adjustment can be misleading due to unaccounted variations in body composition [48]. Since age can also potentially affect mREE values, it was included as an additional covariate in the model.

Bias, calculated as average difference between pREE minus mREE, and percent bias were used as a measure of group-level accuracy. In particular, percent bias was acceptable if within ±5 % [49,50]. The percentage of patients with a pREE within ±10 % of mREE was used as a primary determinant of individual-level accuracy (i.e., precision). Values lower than 90 % represent underpredictions of mREE, whereas values higher than 110 % indicate overpredictions of mREE. In addition, limits of agreement (LOA), represented by bias ± 1.96 SD were used to describe individual accuracy, based on the Bland-Altman analysis [51]. Finally, the root mean squared error (RMSE) was used to define the prediction obtained with this model.

3. Results

One hundred and twenty-two women with a diagnosis of BC, candidates for surgery and adjuvant/ neo-adjuvant therapy, were recruited to participate in the original study. A total of 106 women were included in this cross-sectional analysis of mREE data collected at baseline since 11 declined to undergo REE measurement, and 5 had RQ values outside the reference range. Patients had a mean age of 49.9 ± 11.1 years (range 28–78 years, with 19 % of subjects over 60 years) and an average BMI of 24.5 ± 2.8 kg/m^2 (range 19.1–30 kg/m^2, 43 % were classified as overweight).

As described in Table 1, most patients had stages I-II BC, and many were post-menopausal, which was pharmacologically induced in 43 % of them. Regarding surgery, quadrantectomy and mastectomy were performed respectively in 57.7 % and 16 % of patients, while in 25 % of them was not performed yet. Since 65 out 106 patients had already started their cancer treatment when REE was measured, 28 % of patients were in neoadjuvant and 72 % in adjuvant therapy, mostly chemotherapy.

3.1. Comparison of anthropometric measurements and BIA variables between patients with BC and controls

As mentioned above, a group of 75 healthy women having similar age and BMI of patients were selected to serve as a control group. Age, anthropometric characteristics, and BIA variables are presented in Table 2 for patients with BC and controls. As expected, no differences were observed for age and BMI between groups. Similarly, FFM, FM (kg) and PhA did not significantly differ, whereas FM (%) and BI-index were slightly higher in patients with BC than in controls.

3.2. Comparison of mREE, RQ and mREE adjusted for FFM and age between patients with BC and controls

Absolute mREE and its value adjusted for FFM and age (mREE *adj* FFM, age) were slightly increased in patients with BC compared to controls (mREE: 1391 ± 158 vs. 1333 ± 171 kcal/d, $p = 0.020$; mREE *adj* FFM, age: 1401 ± 12.9 kcal/d vs. 1319 ± 15.3 kcal/d; $p = 0.001$), while no difference was observed for RQ between the two groups

Table 1
Clinical characteristics of 106 BC patients.

Stage of disease	n	(%)
0	3	2.8
I	44	41.5
II	43	40.63
III	14	13.2
Not known	2	1.9
Menopause		
No	10	9.4
Yes	50	47.2
Induced	46	43.4
Surgery		
Yes		
- Quadrantectomy	61	57.5
- Mastectomy	17	16
Not performed yet	26	24.5
Not known	2	1.9
Ongoing treatment		
No	41	38.7
Yes	65	61.3
Type of ongoing treatment		
Neoadjuvant	18	27.7
Adjuvant		
- Chemotherapy	40	61.5
- Hormone therapy	7	10.8

Data are expressed as number (n) and percentage (%).

Table 2
Anthropometric measurements, BIA variables and MREE in BC patients and controls.

		Breast Cancer (N = 106)	Control group (N = 75)	*p-value*
Age	years	49.9 ± 11.1	48.0 ± 10.1	0.245
Body weight	kg	63.1 ± 7.3	63.6 ± 12.2	0.775
Stature	cm	161 ± 7	161 ± 6	0.551
BMI	kg/m^2	24.5 ± 2.8	24.4 ± 4.1	0.808
FFM	kg	42.6 ± 3.8	43.6 ± 4.9	0.099
FM	kg	20.6 ± 5.0	19.9 ± 8.7	0.523
FM	%	32.2 ± 5.1	30.0 ± 8.2	*0.030*
BI	cm^2/ohm	44.5 ± 5.2	46.4 ± 6.3	*0.026*
PhA	degrees	5.58 ± 0.56	5.63 ± 0.65	0.613
mREE	kcal/d	1391 ± 158	1333 ± 171	*0.020*
mREE *adj* FFM, age	kcal/d[a]	1401 ± 12.9	1319 ± 15.3	*0.001*
RQ		0.85 ± 0.05	0.84 ± 0.05	0.071

Data are expressed as mean ± standard deviation. Adj = adjusted; BI = bioimpedance index; BMI = body mass index; d: day; FM = fat mass; FFM = fat-free mass; PhA = phase angle; mREE = measured resting energy expenditure; RQ: respiratory quotient.
[a] Mean values are adjusted for FFM and age.

(Table 2). As expected, mREE was strongly correlated to FFM in patients with BC and controls ($R^2 = 0.423$, $p < 0.001$, $R^2 = 0.299$, $p < 0.001$; respectively) as presented in Figure S1.

As further analysis, we investigated potential predictors of mREE in both groups. A multiple regression analysis was performed, showing that FFM ($\beta = 0.654$, $p < 0.001$), emerged as the main determinant of mREE in this cohort of patients with BC. Conversely, FFM ($\beta = 0.517$, $p < 0.001$) and PhA ($\beta = 0.311$, $p = 0.001$) were the main predictors of mREE in the control group.

3.3. Effects of treatment timing on mREE

According to their medical records, 65 out of 106 patients underwent REE measurement when they had just started pharmacological treatment. Therefore, we performed a sub-analysis evaluating the effect of treatment timing on mREE and mREE *adj* FFM and age in patients with BC, treatment (T) *versus* no treatment (NT), in comparison with controls, considering differences in BIA variables among the three groups as well (Table 3).

Findings showed no difference in mREE between patients with BC who had just started therapy compared to those who had not, even after adjusting values for BC stage ($p = 0.385$) and treatment type, i.e., adjuvant vs. neo-adjuvant therapy ($p = 0.410$). While mREE was overall increased in both groups of patients compared to controls, but it was statistically higher solely in the T group compared to controls (1399 ± 155 kcal/d vs. 1333 ± 171 kcal/d vs. $p = 0.048$; respectively). Still, mREE *adj* FFM and age meaningfully differed between patients with BC and controls, resulting in higher values for patients with BC, unrelated to their treatment status, as shown in Table 3. Regarding BIA variables and body composition, patients in the NT group showed greater FM% and BI-index compared to controls ($p = 0.027$; $p = 0.041$, respectively).

3.4. Prediction accuracy of REE in patients with BC

Group level accuracy was estimated in patients with BC by bias, percent bias, and RMSE, whereas individual-level accuracy (precision) was assessed by the percentage of participants with a PREE within ±10 % of mREE and the Bland-Altman analysis.

Data are presented for each of the selected equations in Table 4. Overall, formulas tended to underestimate REE in this sample, except for two [18,40] as shown in Fig. 1. Percent bias within ±5 % was found for the following anthropometric-based equations: HB (−4.2 %), FAO/WHO/UNU (3.2 %), Owen (−3.2 %) and Marra (−1.6 %). Whilst, when BIA variables were included in the formula, the Müller (FFM) (−3.8 %), Wang (FFM) (−4.2 %), and Marra (PhA) (−2.2 %) equations showed the lowest values.

In terms of accuracy at individual level, the highest values were observed with formulas by HB (71 %), Marra (73 %), Müller (FFM) (74 %) and Marra (PhA) (74.5 %) (Fig. 2). However, when looking at the Bland-Altman analysis, although it was found that several plots were within the LOA area (Fig. 3), the absolute LOA ranged from 29 % to 41 % (478–604 kcal/d), suggesting a large variation at individual level.

4. Discussion

This is the largest study that explored REE in patients with BC and compared to a control group. Overall, findings revealed that

Table 3
Comparison of BIA variables and mREE between patients with BC who were or not under treatment versus controls.

		Breast Cancer			Control group	
		NT (N = 41)	T (N = 65)	*p*[a]	(N = 75)	*p*[b]
mREE	kcal/d	1379 ± 164	1399 ± 155	0.523	1333 ± 171	0.05 §
mREE *adj* $_{FFM, age}$	kcal/d*	1405 ± 20.4	1401 ± 16.1	0.886	1317 ± 15	0.001*
RQ		0.84 ± 0.05	0.86 ± 0.06	0.163	0.84 ± 0.06	0.08
FFM	kg	42.1 ± 3.9	42.8 ± 3.9	0.378	43.6 ± 4.9	0.19
FM	kg	21.4 ± 5.0	20.0 ± 5.0	0.179	19.9 ± 8.7	0.49
FM	%	33.3 ± 4.6	31.4 ± 5.1	0.062	30.0 ± 8.2	0.03°
BI	cm^2/ohm	43.7 ± 5.3	44.9 ± 6.3	0.235	46.4 ± 6.3	0.05°
PhA	degrees	5.65 ± 0.55	5.54 ± 0.57	0.342	5.63 ± 0.65	0.59

Data are expressed as mean ± standard deviation unless mREE FFM, age (Mean ± standard error). Adj = adjusted; BI = bioimpedance index; d: day; FM = fat mass; FFM = fat-free mass; NT = no treatment; PhA = phase angle; mREE = measured resting energy expenditure; RQ: respiratory quotient; T = treatment.
*Mean values are adjusted for FFM and age using an ANCOVA test with post-hoc analysis.
[a] Un-paired T test between NT and T.
[b] ANOVA test among T, NT and controls with significant values between: (§) T vs. controls; (°) NT vs. controls and (*) T and NT vs. controls.

Table 4
Predicted REE, bias, limits of agreement, accuracy and root mean square error in 106 patients with BC.

REE predictive equations	pREE	Bias[a]	Percent Bias	LOA	Absolute LOA	Minimum negative error	Maximum positive error	Accuracy ‡	RMSE
	kcal/d	kcal/d	%	%	%	%	%	%	kcal/d
Equations including anthropometry									
HB	1322 ± 98*	−69 ± 126	−4.2 ± 8.9	−21.6, 13.2	34.9	−24.1	24.8	70.8	112
FAO/WHO/UNU	1424 ± 108*	33 ± 142	3.2 ± 10.4	−17.2, 23.6	40.8	−19.5	41.1	63.2	119
Schofield	1475 ± 80*	83 ± 134	7.0 ± 10.2	−13.0,27.0	40.0	−16.6	46.0	58.5	132
Owen	1332 ± 53*	−59 ± 141	−3.2 ± 9.6	−22.0,15.6	37.6	−26.4	31.7	67.0	118
Huang	1262 ± 93*	−129 ± 130	−8.6 ± 8.6	−25.5,8.3	33.7	−27.4	23.2	53.8	147
Mifflin	1228 ± 125*	−164 ± 132	−11.2 ± 8.8	−28.4,6.0	34.5	−30.6	15.4	41.5	176
Muller	1309 ± 92*	−83 ± 127	−5.2 ± 8.6	−22.1,11.7	33.7	−25.6	24.7	68.9	118
Marra	1358 ± 108*	−33 ± 131	−1.6 ± 9.3	−19.8,16.6	36.5	−21.6	32.3	72.6	108
Equations including FFM, FM, BI and PhA									
Cunningham	1290 ± 90*	−102 ± 122	−6.6 ± 8.0	−22.3,9.1	31.4	−23.8	18.4	65.1	123
Owen	1173 ± 75*	−219 ± 123	−15.0 ± 7.3	−29.3,-0.7	28.6	−30.6	7.6	25.5	220
Mifflin	1282 ± 74*	−110 ± 123	−7.1 ± 8.1	−23.0,8.8	31.8	−24.8	18.4	62.3	229
Muller	1326 ± 69*	−65 ± 128	−3.8 ± 8.7	−20.9,13.3	34.2	−25.3	26.7	73.6	110
Marra[b]	1350 ± 108*	−41 ± 122	−2.2 ± 8.5	−18.9,14.5	33.4	−20.3	24.6	74.5	101
Wang	1322 ± 81*	−69 ± 122	−4.2 ± 8.3	−20.5,12.1	32.6	−22.0	21.7	67.9	108
Souza-Singer	1228 ± 50*	−163 ± 154	−10.7 ± 9.8	−29.9,8.5	38.4	−30.4	13.5	41.5	181

Data from pREE, bias and percent bias are expressed as mean ± standard deviation. BI (bioimpedance index); d (day); FFM (fat free mass); FM (fat mass); mREE (measured REE); LOA (limits of agreement); PhA (phase angle); pREE (predicted REE) REE (resting energy expenditure), RMSE (root mean squared error).
Average MREE by indirect calorimetry = 1391 ± 158 kcal/d.
*$p < 0.05$ measured versus predicted mREE.
[b] Including bioimpedance index (BI) and phase angle (PhA).
[a] Mean difference between predicted and measured REE; ‡The percentage of patients predicted by predictive equations within 10 % of the measured value.

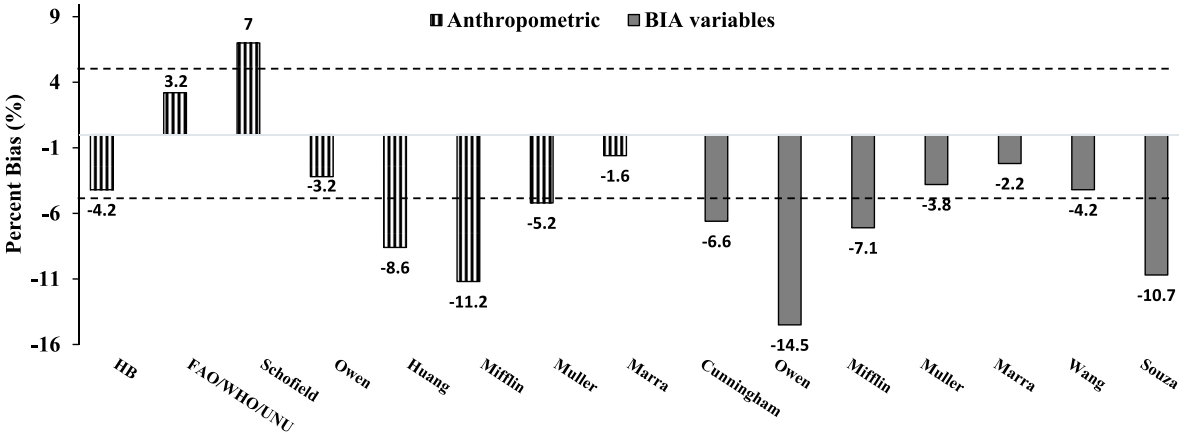

Fig. 1. Percent bias using equations with and without BIA variables in patients with BC.

mREE, both in absolute value and adjusted for FFM and age, was slightly higher in patients with BC than in controls, although the difference was small (+4.3 % and +6.1 %, respectively). Fat-free mass was the strongest determinant of mREE in both groups. Regarding accuracy prediction, we observed a general tendency towards underestimation of REE in patients with BC. The least percent bias was found for the HB, FAO/WHO/UNU, Owen, Marra, Marra (PhA) and Müller (FFM). The Marra equations (~73 %, 74.5 %), followed by the HB (71 %) and Müller (FFM) formulas (74 %), yielded the highest precision (i.e., accuracy ± 10 %).

Broadly, patients with cancer are at an elevated risk of developing malnutrition for countless reasons, including age, disease stage, complications, and type of treatment [1,3–5]. Resting energy expenditure is the largest and most measured component of TEE and can be affected by several factors such as inflammation status and changes in body composition [11]. As a result, accurately measuring or predicting REE might be crucial to meet and/or monitor the energy needs of patients over the course of the disease. Data from previous systematic reviews have found that patients with BC and survivors often experienced weight gain, which is one of the most common side effects of chemotherapy [5,25]. Although the exact mechanism has not yet been completely established [26], it is likely that increases in FM coupled with decreases or maintenance in FFM can negatively influence REE [4,52–54].

The role of REE in modulating energy balance in patients with BC and survivors is still unclear because the data are highly heterogeneous (patients' characteristics, treatment type, and study design). In the present study, mREE was slightly increased (+4.3 %) in patients with early diagnosis of BC compared to controls, even though it was not meaningfully from a clinical point of view. Similarly, a recent study showed that REE measured before starting any treatments, was +11 % greater in patients with BC compared to controls [30]. Whereas no differences were observed by previous studies [27–29]. Our findings were quite unexpected, as 90 % of the patients were menopausal (with 43 % experiencing induced menopause), which typically leads to a reduction of REE due to its

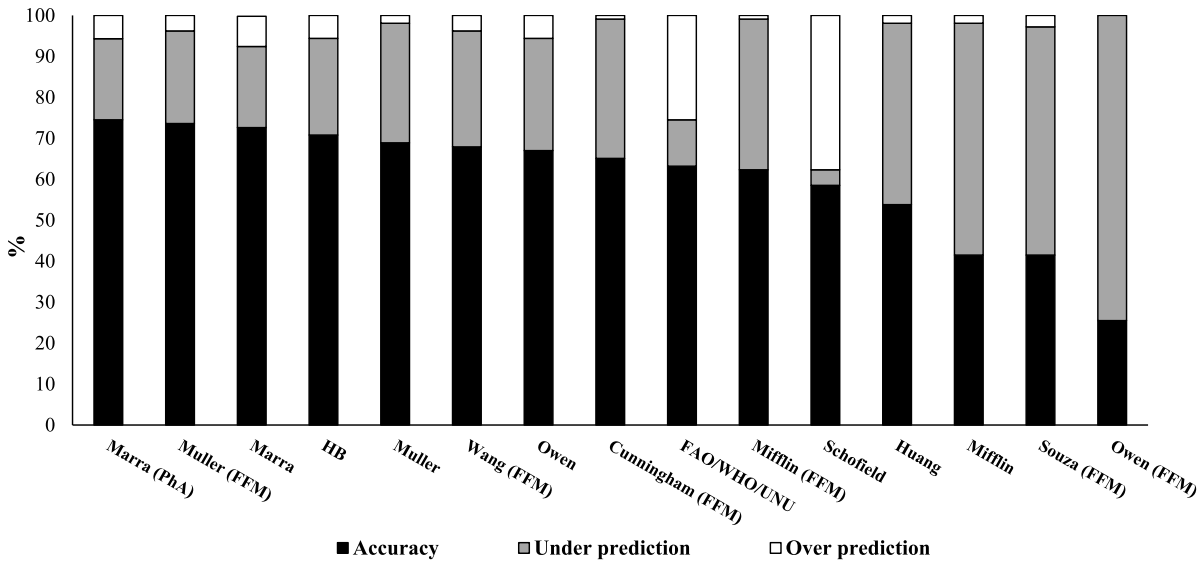

Fig. 2. Prediction accuracy for mREE within ±10 % in patients with BC.

effects on body composition [55]. However, it remains unclear if the pharmacological suppression of sex hormones in premenopausal women has the same impact on REE as naturally-occurring menopause, at least in the short term [55]. This uncertainty might have minimised the likelihood of changes in mREE at this early stage. Unfortunately, previous studies did not investigate the effect of menopausal status [27–29], preventing us from providing further comparisons.

Likewise, heterogenous findings on mREE emerged from various prospective studies conducted solely in patients with BC, where mREE was assessed before, during and at the end of the treatment (mostly adjuvant chemotherapy) [23–26,29] as well as in the follow-ups [26], highlighting discrepancies across the studies. Some reported unchanged mREE values between pre- and post-treatment after 12 weeks [24,25,30], while others observed an increase [23] or decrease [26] in mREE values from baseline to the end of the therapy (after 6 months). Interestingly, Harvie et al. [26] showed that mREE returned to pre-chemotherapy values after 1 year. Inconsistencies in mREE changes observed so far might be explained by type and timing of treatment, population characteristics and limited sample sizes. In the present study, our baseline mREE values showed no significant differences between patients who had started the first cycles of therapy (mainly chemotherapy) and those who had not, since mREE was quite similar, even after adjustment for stage, menopause and treatment type. On the other hand, absolute mREE was different between patients and controls, but it was statistically significant solely in the T group, suggesting that absolute mREE might be increased at the beginning of treatment, or in any case, before any apparent alterations in FFM emerged [29]. Also, we observed a trend in age variation among the three groups, since both patients in the T group and controls were slightly younger than those in the NT group (NT: 52.2 ± 10.2 years; T: 48.4 ± 11.4 years; C: 48.0 ± 10.1 years; $p = 0.11$). Indeed, when absolute values were adjusted for FFM and age both groups of patients differed from controls. Interestingly, the increase in mREE observed in patients with early diagnosis of BC might be hypothetically linked to the crosstalk between sympathetic nervous system (SNS), which is also involved in the regulation of energy expenditure, and BC, as highlighted by a recent review focusing on tumour progression [56]. The authors pointed out that sympathetic activation, induced by disease-related stress and/or by tumour itself, increases the local release of catecholamines from the tumour site, leading to an overactivation of adrenergic receptors and enhancing tumour growth [56]. The specific mechanisms involved in the link between SNS and BC have not been sufficiently explored so far [56]. While there are evidence about the role of SNS in the regulation of energy expenditure by β-adrenergic stimulation, which elicits an increase in metabolic rate (i.e., thermogenesis) [57], whereas a complete β-adrenergic blockade induces an acute reduction in REE in healthy adults [57,58], highlighting the function of SNS in supporting small REE variations [57]. However, this aspect needs to be further explored in patients with BC. Therefore, even though a difference in mREE of less than 100 kcal might be not relevant from a clinical point of view at the beginning, it is important to note that if this difference persists over time, it could become more clinically significant and contribute to consistent weight changes.

Weight gain may often occur in patients with BC over time [23,24,26], albeit not always statistically significant [25], and is generally characterized by a significant increase in total FM [23,25,26] or percent FM [24,25] and a reduced [24,26] or unchanged FFM [29,30]. Since FFM is considered the largest contributor of REE and is frequently impaired in patients with cancer [4], we initially adjusted mREE values for FFM in both groups, then we added age as a further covariate in the model, being another crucial determinant of REE. We found that mREE *adj* FFM and age was still higher (+6 %) in patients with BC compared to controls. By exploring the relationship between mREE and FFM in both groups, we observed a greater increase in mREE in patients with BC than in controls, especially for FFM values above 40 kg. Notably, we used the proper adjustment approach, as simply dividing REE by FFM is incorrect as explained elsewhere [59]. As such, modalities used for adjusting mREE for FFM varied; three previous studies showed a higher mREE/kg of FFM (mREE/FFM) [27,29,30], with significantly greater values in post-menopausal BC survivors as well as in patients with BC when compared to the control group (BC: 36.1 ± 2.22 vs. C: 33.0 ± 4.3; $p = 0.015$; BC: 33 ± 3 vs. C: 31 ± 3; $p = 0.031$; BC: 34.4 ± 4.8 vs. C: 31.0 ± 3.0; $p < 0.001$, respectively), whereas Zuconi et al. [28], did not find any differences either in mREE *adj* for FFM or in mREE/FFM ratio.

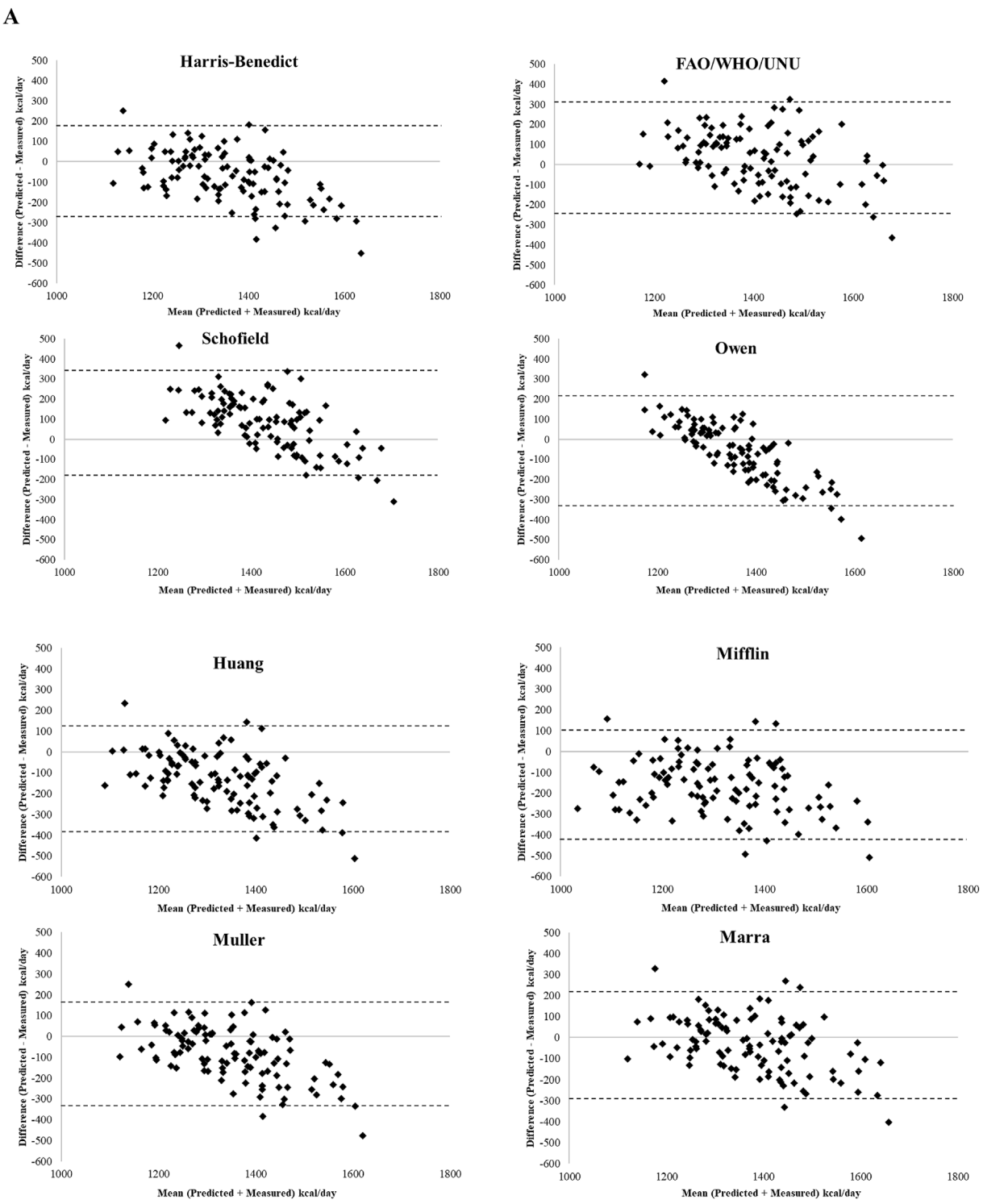

Fig. 3. Bland–Altman plots between differences and mean pREE-mREE using anthropometric - (A) and BIA - (B) based equations.

Besides FFM, which did not differ between groups, the percent of FM was found to be slightly higher in our sample of patients with BC than in controls, even though half of them were at the beginning of treatment. Notably, neither of the previous studies [27–30] that compared patients with BC or survivors to controls reported any statistical difference in percent FM at baseline, although all of them showed the same trend characterized by higher percent FM values in patients with BC compared to controls [27,28,30]. It is likely that our results might be influenced by the high percentage of patients (71 %) who resulted inactive at baseline, according to the International Physical Activity Questionnaire (IPAQ) – short form. In addition, most of them were in menopause, naturally or

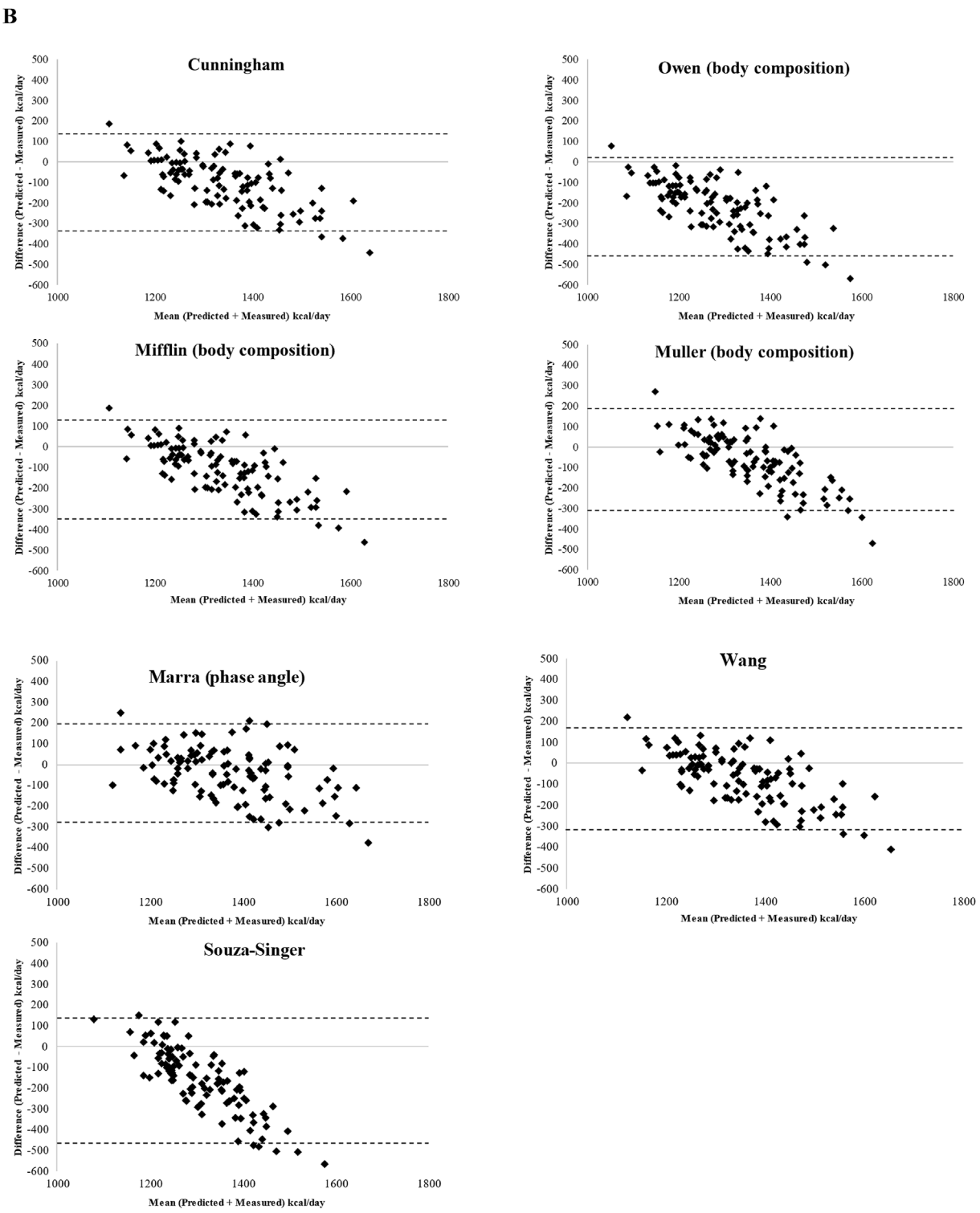

Fig. 3. (*continued*).

pharmacologically induced, potentially affecting FM. Therefore, differences in tools adopted (BIA or Bod pod or DXA), sample size ($n \leq 20$ subjects) and patient's characteristics (i.e., BMI above 25 kg/m^2 [27,28], large body weight variations [27] and menopausal status) might have contributed to dissimilarities in percent FM found across the studies.

Regarding accuracy prediction, the current literature lacks comprehensive data, and highlights inaccuracies in REE estimation in patients with cancer [1,26,28,60]. Two recent studies assessing REE prediction in a mixed cancer population, mostly with gastrointestinal tract cancer [1] and BC [60], indicated poor accuracy across all equations considered, with a high degree of variability and overall REE underestimation. Similarly, we observed a wide variation in pREE with the equations we used, resulting in an overall tendency toward underestimation. Surprisingly, some equations, with and without BIA variables, yielded acceptable REE

predictions (percent bias ± 5 %) at the population level. Likewise, accuracy within ±10 % (i.e., precision) was close to ~75 % for some equations [15,45] in contrast to earlier findings [26,28]. However, the wide LOA range (around 500 kcal/d) indicates a substantial variability in REE prediction at the individual level.

The high variability of REE prediction and the inaccuracy of some equations, including the one specifically developed for patients with cancer, can have multiple reasons. First, the equations commonly used for predicting REE were obtained from healthy subjects, generally not affected by malnutrition and/or metabolic abnormalities, which typically occur in patients with cancer [11]. In addition, most studies investigating the accuracy of REE prediction in patients with cancer have been performed using small samples and a limited number of equations [26,28]. Last but not least, disease-specific equations could theoretically ensure better predictive accuracy, but this is not always true [1]. Indeed, the poor accuracy of REE observed in this study by using the equation developed by Souza-Singer et al. [8], mostly depends on differences between our sample and the one used for developing the equations, characterized by patients with advanced head-neck cancer and severe malnourishment.

It is widely accepted that IC is the recommend method to measure REE in clinical practice, but due to its limitations, it is often required the utilization of specific equations. In the present study, some of the most adopted equations provide accurate REE prediction (i.e., percent bias within±5 %) in patients with early-stage BC, suggesting the use of predictive equations as viable alternatives at a group level. On individual-level, pREE was found to be within 10 % of mREE in ~75 % of patients using the Marra and the Muller equations [15,45], however, it is crucial to consider that prediction remains inaccurate for about 25 % of women, mostly depending on subjects' characteristics; therefore, the use of the equations should be carefully evaluated on a case-by-case basis.

4.1. Strength and limitations

The present study has several strengths. First, the data from mREE were derived from a large sample size, compared with those obtained by previous studies (n < 20), which is homogeneous in terms of BMI, disease stage, and treatments. Second, to our knowledge, this is the first study to assess numerous predictive formulas to estimate REE in BC population, considering both anthropometric- and BIA-based equations, including one using raw BIA variables, such as BI-index and PhA.

Nevertheless, some limitations of this study need to be acknowledged. The exclusion of patients with obesity (BMI ≥30) from our study limits the generalizability of our results. However, this decision, rooted in ethical considerations, was made during the design of the primary study. Recognizing that weight gain is a common side effect of cancer treatment, we chose not to randomize women with obesity to a non-intensive dietary intervention without the assurance of consistent dietitian support. Nevertheless, our findings can serve as a foundation for future research, which can expand on our work by including a more diverse sample in terms of body weight and relative BMI. Body composition was not assessed by criterion techniques such as dual-energy x-ray absorptiometry and although BIA is widely used in clinical setting and has its merit, hydration abnormalities and the use of non-specific equations (to predict body composition) may have impacted our analysis/findings. Moreover, menopausal status observed in 90 % of women (hormonally induced in 43 % of them) might have prevented us from seeing a consistent effect or difference of menopause on REE, at least in the short term, highlighting a need for future studies. Last, but not least, data was collected to a single time point, mostly at the beginning of BC diagnosis, providing a partial notion of potential metabolic changes that occur during cancer.

5. Conclusions

In conclusion, the present study showed that patients with early-stage BC exhibited higher mREE values than controls, even after adjusting for FFM and age. The clinical meaningfulness of this difference remains to be determined. Despite some equations displayed acceptable group-level accuracy, none yielded accurate and precise REE estimates within on individual-basis. Therefore, further studies are needed to evaluate mREE and potential new prediction equations should be developed and tested for patients with BC. These should consider differences in age and BMI, and potential changes occurring during the trajectory of the disease.

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Author contributions

Iolanda Cioffi: Conceptualization, Methodology, Data curation, Writing - Original draft preparation, Writing - Reviewing and Editing. Olivia Di Vincenzo: Writing - Original draft preparation, Writing - Reviewing and Editing. Delia Morlino: Investigation. Bruna Ramos da Silva: Writing - Reviewing and Editing. Carla M. Prado: Writing - Reviewing and Editing. Lidia Santarpia: Visualization. Luca Scalfi: Visualization. Mario Giuliano: Visualization. Carmine De Angelis: Visualization. Fabrizio Pasanisi: Visualization. Grazia Arpino: Visualization. Maurizio Marra: Conceptualization, Methodology, Formal analysis.

Conflict of interest

Authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.09.037.

References

[1] Purcell SA, Elliott SA, Baracos VE, Chu QSC, Sawyer MB, Mourtzakis M, et al. Accuracy of resting energy expenditure predictive equations in patients with cancer. Nutr Clin Pract 2019;34:922–34. https://doi.org/10.1002/ncp.10374.
[2] Purcell SA, Melanson EL, Afghahi A, Borges VF, Sinelli I, Cornier M-A. The effects of resistance exercise on appetite sensations, appetite related hormones and energy intake in hormone receptor-positive breast cancer survivors. Appetite 2023;182:106426. https://doi.org/10.1016/j.appet.2022.106426.
[3] Morlino D, Cioffi I, Marra M, Di Vincenzo O, Scalfi L, Pasanisi F. Bioelectrical phase angle in patients with breast cancer: a systematic review. Cancers 2022;14:2002. https://doi.org/10.3390/cancers14082002.
[4] Morlino D, Marra M, Cioffi I, Santarpia L, De Placido P, Giuliano M, et al. Prevalence of sarcopenia in women with breast cancer. Nutrients 2022;14:1839. https://doi.org/10.3390/nu14091839.
[5] Trestini I, Carbognin L, Monteverdi S, Zanelli S, De Toma A, Bonaiuto C, et al. Clinical implication of changes in body composition and weight in patients

with early-stage and metastatic breast cancer. Crit Rev Oncol Hematol 2018;129:54–66. https://doi.org/10.1016/j.critrevonc.2018.06.011.
[6] Heymsfield SB, Smith B, Dahle J, Kennedy S, Fearnbach N, Thomas DM, et al. Resting energy expenditure: from cellular to whole-body level, a mechanistic historical perspective. Obesity 2021;29:500–11. https://doi.org/10.1002/oby.23090.
[7] Cao D, Wu G, Zhang B, Quan Y, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr 2010;29:72–7. https://doi.org/10.1016/j.clnu.2009.07.001.
[8] 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. https://doi.org/10.1016/j.nut.2017.12.006.
[9] Ravasco P, Monteiro-Grillo I, Camilo M. Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest 2007;25:308–14. https://doi.org/10.1080/07357900701208873.
[10] Nguyen TYV, Batterham MJ, Edwards C. Comparison of resting energy expenditure between cancer subjects and healthy controls: a meta-analysis. Nutr Cancer 2016;68:374–87. https://doi.org/10.1080/01635581.2016.1153667.
[11] Purcell SA, Elliott SA, Kroenke CH, Sawyer MB, Prado CM. Impact of body weight and body composition on ovarian cancer prognosis. Curr Oncol Rep 2016;18:8. https://doi.org/10.1007/s11912-015-0488-3.
[12] Marra M, Cioffi I, Sammarco R, Santarpia L, Contaldo F, Scalfi L, et al. Are raw BIA variables useful for predicting resting energy expenditure in adults with obesity? Nutrients 2019;11:216. https://doi.org/10.3390/nu11020216.
[13] Cioffi I, Marra M, Pasanisi F, Scalfi L. Prediction of resting energy expenditure in healthy older adults: a systematic review. Clin Nutr 2021;40:3094–103. https://doi.org/10.1016/j.clnu.2020.11.027.
[14] Marra M, Cioffi I, Morlino D, Vincenzo OD, Pagano MC, Imperatore N, et al. New predictive equations for estimating resting energy expenditure in adults with crohn's disease. J Parenter Enter Nutr 2020;44:1021–8. https://doi.org/10.1002/jpen.1790.
[15] Marra M, Sammarco R, Cioffi I, Morlino D, Di Vincenzo O, Speranza E, et al. New predictive equations for estimating resting energy expenditure in subjects with normal weight and overweight. Nutrition 2021;84:111105. https://doi.org/10.1016/j.nut.2020.111105.
[16] Marra M, Di Vincenzo O, Cioffi I, Sammarco R, Morlino D, Scalfi L. Resting energy expenditure in elite athletes: development of new predictive equations based on anthropometric variables and bioelectrical impedance analysis derived phase angle. J Int Soc Sports Nutr 2021;18:68. https://doi.org/10.1186/s12970-021-00465-x.
[17] Harris JA, Benedict FG. A biometric study of human basal metabolism. Proc Natl Acad Sci U S A 1918;4:370–3. https://doi.org/10.1073/pnas.4.12.370.
[18] Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39(Suppl 1):5–41.
[19] McNeil J. Energy balance in cancer survivors at risk of weight gain: a review. Eur J Nutr 2023;62:17–50. https://doi.org/10.1007/s00394-022-02975-z.
[20] 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;65:1495–501. https://doi.org/10.1093/ajcn/65.5.1495.
[21] 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;19:2381–9. https://doi.org/10.1200/JCO.2001.19.9.2381.
[22] Ekenga CC, Wang X, Pérez M, Schootman M, Jeffe DB. A prospective study of weight gain in women diagnosed with early-stage invasive breast cancer, ductal carcinoma in situ, and women without breast cancer. J Womens Health (Larchmt) 2020;29:524–33. https://doi.org/10.1089/jwh.2018.7638.
[23] Del Rio G, Zironi S, Valeriani L, Menozzi R, Bondi M, Bertolini M, et al. Weight gain in women with breast cancer treated with adjuvant cyclophosphomide, methotrexate and 5-fluorouracil. Analysis of resting energy expenditure and body composition. Breast Cancer Res Treat 2002;73:267–73. https://doi.org/10.1023/a:1015892714162.
[24] Kutynec CL, McCargar L, Barr SI, Hislop TG. Energy balance in women with breast cancer during adjuvant treatment. J Am Diet Assoc 1999;99:1222–7. https://doi.org/10.1016/s0002-8223(99)00301-6.
[25] 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;30:95–100. https://doi.org/10.1097/01.NCC.0000265004.64440.5f.
[26] Harvie MN, Campbell IT, Baildam A, Howell A. Energy balance in early breast cancer patients receiving adjuvant chemotherapy. Breast Cancer Res Treat 2004;83:201–10. https://doi.org/10.1023/B:BREA.0000014037.48744.fa.
[27] Madzima TA, Deaterly CD. Body composition, metabolism, and inflammation in breast cancer survivors and healthy age-matched controls: a cross-sectional analysis. Int J Exerc Sci 2020;13:1108–19.
[28] Zuconi CP, Ceolin Alves AL, Toulson Davisson Correia MI. Energy expenditure in women with breast cancer. Nutrition 2015;31:556–9. https://doi.org/10.1016/j.nut.2014.05.009.
[29] Van Soom T, Tjalma W, Van Daele U, Gebruers N, van Breda E. Resting energy expenditure, body composition, and metabolic alterations in breast cancer survivors vs. healthy controls: a cross-sectional study. BMC Wom Health 2024;24:117. https://doi.org/10.1186/s12905-024-02900-y.
[30] Van Soom T, Tjalma W, Papadimitriou K, Gebruers N, van Breda E. The effects of chemotherapy on resting energy expenditure, body composition, and cancer-related fatigue in women with breast cancer: a prospective cohort study. Cancer Metabol 2023;11:21. https://doi.org/10.1186/s40170-023-00322-2.
[31] Cioffi I, Marra M, Imperatore N, Pagano MC, Santarpia L, Alfonsi L, et al. Assessment of bioelectrical phase angle as a predictor of nutritional status in patients with Crohn's disease: a cross sectional study. Clin Nutr 2020;39:1564–71. https://doi.org/10.1016/j.clnu.2019.06.023.
[32] Lohman TG, Roche AF, Martorell L. Anthropometric standardization reference manual. Human. 1940-Roche. Alex F 1988. 1921. n.d.
[33] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr 2004;23:1430–53. https://doi.org/10.1016/j.clnu.2004.09.012.
[34] Sun G, French CR, Martin GR, Younghusband B, Green RC, Xie Y-G, et al. Comparison of multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for assessment of percentage body fat in a large, healthy population. Am J Clin Nutr 2005;81:74–8. https://doi.org/10.1093/ajcn/81.1.74.
[35] Elia M, Livesey G. Theory and validity of indirect calorimetry during net lipid synthesis. Am J Clin Nutr 1988;47:591–607. https://doi.org/10.1093/ajcn/47.4.591.
[36] Delsoglio M, Dupertuis YM, Oshima T, van der Plas M, Pichard C. Evaluation of the accuracy and precision of a new generation indirect calorimeter in canopy dilution mode. Clin Nutr 2020;39:1927–34. https://doi.org/10.1016/j.clnu.2019.08.017.
[37] Compher C, Frankenfield D, Keim N, Roth-Yousey L, Evidence Analysis Working Group. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc 2006;106:881–903. https://doi.org/10.1016/j.jada.2006.02.009.
[38] Fullmer S, Benson-Davies S, Earthman CP, Frankenfield DC, Gradwell E, Lee PSP, 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;115:1417–1446.e2. https://doi.org/10.1016/j.jand.2015.04.003.
[39] Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. Nutrition 1949;6:213–21. 1990.
[40] Energy and protein requirements. Report of a joint FAO/WHO/UNU expert consultation. World Health Organ Tech Rep Ser 1985;724:1–206.
[41] 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;46:875–85. https://doi.org/10.1093/ajcn/46.6.875.
[42] 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;44:1–19. https://doi.org/10.1093/ajcn/44.1.1.
[43] Huang K-C, Kormas N, Steinbeck K, Loughnan G, Caterson ID. Resting metabolic rate in severely obese diabetic and nondiabetic subjects. Obes Res 2004;12:840–5. https://doi.org/10.1038/oby.2004.101.
[44] 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;51:241–7. https://doi.org/10.1093/ajcn/51.2.241.
[45] 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;80:1379–90. https://doi.org/10.1093/ajcn/80.5.1379.
[46] Cunningham JJ. A reanalysis of the factors influencing basal metabolic rate in normal adults. Am J Clin Nutr 1980;33:2372–4. https://doi.org/10.1093/ajcn/33.11.2372.
[47] 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:E539–45. https://doi.org/10.1152/ajpendo.2000.279.3.E539.
[48] 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;70:1230–8. https://doi.org/10.1038/ejcn.2016.96.
[49] Frankenfield DC, Rowe WA, Smith JS, Cooney RN. Validation of several established equations for resting metabolic rate in obese and nonobese people. J Am Diet Assoc 2003;103:1152–9. https://doi.org/10.1016/s0002-8223(03)00982-9.
[50] 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;105:775–89. https://doi.org/10.1016/j.jada.2005.02.005.
[51] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.
[52] Thomson ZO, Reeves MM. Can weight gain be prevented in women receiving treatment for breast cancer? A systematic review of intervention studies. Obes Rev 2017;18:1364–73. https://doi.org/10.1111/obr.12591.
[53] Pedersen B, Delmar C, Lörincz T, Falkmer U, Grønkjær M. Investigating changes in weight and body composition among women in adjuvant

treatment for breast cancer: a scoping review. Cancer Nurs 2019;42:91–105. https://doi.org/10.1097/NCC.0000000000000590.
[54] Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. CA A Cancer J Clin 2017;67:378–97. https://doi.org/10.3322/caac.21405.
[55] Day DS, Gozansky WS, Van Pelt RE, Schwartz RS, Kohrt WM. Sex hormone suppression reduces resting energy expenditure and {beta}-adrenergic support of resting energy expenditure. J Clin Endocrinol Metab 2005;90:3312–7. https://doi.org/10.1210/jc.2004-1344.
[56] Hu J, Chen W, Shen L, Chen Z, Huang J. Crosstalk between the peripheral nervous system and breast cancer influences tumor progression. Biochim Biophys Acta Rev Cancer 2022;1877:188828. https://doi.org/10.1016/j.bbcan.2022.188828.
[57] Monroe MB, Seals DR, Shapiro LF, Bell C, Johnson D, Parker Jones P. Direct evidence for tonic sympathetic support of resting metabolic rate in healthy adult humans. Am J Physiol Endocrinol Metab 2001;280:E740–4. https://doi.org/10.1152/ajpendo.2001.280.5.E740.
[58] Saad MF, Alger SA, Zurlo F, Young JB, Bogardus C, Ravussin E. Ethnic differences in sympathetic nervous system-mediated energy expenditure. Am J Physiol 1991;261:E789–94. https://doi.org/10.1152/ajpendo.1991.261.6.E789.
[59] Carneiro IP, Elliott SA, Siervo M, Padwal R, Bertoli S, Battezzati A, et al. Is obesity associated with altered energy expenditure? Adv Nutr 2016;7:476–87. https://doi.org/10.3945/an.115.008755.
[60] Da Silva BR, Pagano AP, Kirkham AA, Gonzalez MC, Haykowsky MJ, Joy AA, et al. Evaluating predictive equations for energy requirements throughout breast cancer trajectory: a comparative study. Clin Nutr 2024. https://doi.org/10.1016/j.clnu.2024.07.032. S0261561424002590.