ORIGINAL

Comparison of Measured Resting Energy Expenditure between Cancer Patients and Non-Cancer Controls

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ABSTRACT *Background and purpose.* Resting energy expenditure (REE) is generally known to be increased in cancer patients, contributing to the development of malnutrition and cachexia. The objective of this study is to compare the difference in measured REE between cancer patients and non-cancer controls. *Methods*. A cross-sectional study was conducted from January to April 2018 to compare the REE between cancer patients and non-cancer controls. A total of 25 patients diagnosed with colorectal cancer and 19 non-cancer controls were recruited using purposive sampling method. Data collection included socio-demographic characteristics, anthropometric measurements, dietary data and REE measured by the Fitmate GS Indirect Calorimetry instrument. Statistical analyses used were independent sample T-test and one-way Analysis of Covariates (ANCOVA) to compare the difference in measured REE between the two groups. *Results*. There was no significant difference in measured REE (p=0.053) and REE/kilogram of Fat-Free Mass (REE/kg FFM) [p=0.372] between cancer and control groups. The one-way ANCOVA showed that there is no significant difference in measured REE (p=0.100) between cancer and control groups after controlling for the covariate of fat-free mass. Similar observation was also found in REE/kg FFM between the two groups after controlling for age (p=0.486). Unaltered REE found in colorectal cancer patients as compared to control group with strong confounding factors such as age and FFM controlled implicates the importance of a more reasonable and individualised approach in dietetics practice when caloric load is administered to cancer patients, as opposed to a conventional approach of supplying a caloric surplus beyond maintenance level.
Keywords: Resting energy expenditure (REE), cancer, indirect calorimetry.

INTRODUCTION

Cancer is a global epidemic, causing around 8.8 million deaths in 2015 according to World Health Organization (WHO) (1). It is a fourth leading cause of death in Malaysia according to Malaysian National Cancer Registry (MNCR). A total of 64,275 cancer deaths had been reported over the year of 2007 to 2011. The overall cancer incidence peaks at a total of 103,507 new cases from 2007 to 2011 (2). Cancer is a collection of genetic diseases characterised by uncontrolled cell growth, in which the cancerous cells exhibit genetic alterations such as DNA mutations. These genetic changes affect how the cells function and behave. Through their genetically altered functionality and physiology, cancerous cells form a mass of tissue called tumour, which invade and destroy other body parts through a process called metastasis.

Resting energy expenditure (REE) is the amount of energy required to sustain basal metabolism for a 24-hour period at rest (3). REE comprises the largest proportion of human energy output, accounting up to 60-75% of total daily energy expenditure (TDEE) (4). REE is reported to be abnormally altered in cancer patients. Depending on the type of cancer, patients were shown to exhibit either normal or increased REE values. Hypermetabolic activity as in increased REE contributes to weight loss through the creation of negative energy balance and progressive tissue wasting, which is a defining characteristic of malnutrition observed in 30 to 80% of cancer patients (5). REE alteration plays a significant role in accelerating weight loss, which then subsequently progresses the development of malnutrition and cachexia. Malnutrition and cachexia are poor prognostic factors for cancer patients, and studies have

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shown that it is a risk factor for negative outcomes, treatment response and quality of life (6). Furthermore, primary cause of deaths in cancer patients was suggested to be due to imbalances in nutrition metabolism (7). Ironically, despite the negative health outcome implicated and the benefits of nutritional intervention, malnutrition is often neglected in clinical settings (8). This demands an understanding of REE changes to facilitate the delivery of an optimal nutritional intervention. Determining the discrepancies of REE between cancer patients and non-cancer controls will allow us to administer an appropriate caloric load, to rectify the nutritional status in cancer patients without risk of underfeeding or overfeeding (9).

REE difference in cancer patients remains uncertain and unclear due to various methodological flaws such as heterogeneity in cancer type among studies. Also, most relevant scientific studies were not conducted locally. Therefore, we aim to compare the differences in REE between cancer patients and non-cancer controls for a better guidance of evidence-based practice by dietitians in improving the nutritional status of cancer patients.

METHODS

Study design

This study was a cross sectional study conducted from January to April 2018 among cancer patients and non-cancer controls. The study site was the Surgical Outpatient Department of the State Hospital of Negeri Sembilan. Ethical approval was obtained from the International Medical University Joint-Committee on Research and Ethics [IMU-BDN I-2017 -13] and from the National Medical Research Registry, Ministry of Health Malaysia (NMRR-17-3166-39347). Informed consent was obtained from all study participants before enrolment, consistent with the Helsinki Declaration and the guidelines of the institutional review committee.

Power and sample size

The sample size was calculated based on published data on REE in cancer patients (Khor SM, 2011) (10). A standard deviation of 178 for REE in cancer patients was used at 80% power with a type I error of 5% (α=5%) alongside with a detectable difference of 15, the estimated sample size is 31 per group taking into consideration of 10% drop-out.

Participants

Purposive sampling method was used to select study participants. Participants will be pre-screened by the attending surgeon for eligibility as per appointment to the surgical outpatient clinic, having fulfilled all the inclusion criteria and presenting none of the exclusion criteria. Participants were provided with the information sheet and explained by the research team regarding the study and written consent was obtained upon agreement to join the study. Participants were recruited if they were cancer patients and non-cancer controls, age 20 years old and above. For cancer patients, the inclusion criterion was the diagnosis of colorectal cancer. Participants were excluded if they were having severe endocrine abnormalities such as hypothyroidism or hyperthyroidism, using high-dose steroid medication, with presence of inflammatory diseases other than cancer or infection, and presence of oedema or ascites. Pregnant and breastfeeding women, smokers, individuals with diabetes or HIV, kidney, liver, heart or lung disease and individuals who have experienced trauma or burn were excluded. Cancer patients who underwent surgery one month or anticancer treatment such as chemotherapy before the study participation were also excluded. These exclusion criteria were set based on their independent effects on energy expenditure.

Measurements

A self-administered questionnaire was designed to collect socio-demographic profile of the participants. It included gender, ethnicity, age, occupation, marital status, smoking status, education level, household monthly income and medical history.

For dietary assessment, the research team interviewed the participants on a 7-day dietary history to evaluate usual dietary intake. A structured interview method consisting of questions was used to prompt for the habitual intake of foods from food groups and frequency of consumption per week. Nutripro Software was then used to analyse the energy and macronutrient intake. A mean of energy and nutrient intake were recorded.

Weight was measured using a digital weighing scale (Tanita, Japan) and height was measured using a stadiometer (SECA, Hamburg, Germany). BMI was then calculated using the obtained weight and height measurements. BMI was classified according to the Asian Pacific cut-off criteria for adults and recorded. The body fat percentage of participant was measured using bioelectrical impedance analysis machine (OMRON Karada, Omron Healthcare, Japan). Fat-free mass (FFM) was calculated with subtracting the calculated fat mass from body fat percentage using the formula of FFM= Body weight (kg) – [Body fat percentage (%) x Body weight (kg)]. All measurements were taken two times and an average of the two readings was obtained and recorded.

REE was measured using Fitmate GS Indirect Calorimetry. Participant was informed to relax and lie down on a bed. They were requested not to sleep or talk during the analysis to avoid interference with normal breathing. The Fitmate Indirect Calorimetry was first calibrated and the blower unit was turned on. The first phase of REE measurement was initiated by placing the hood with veil on the patient's head. The veil was safely enclosed over the patient to minimise air leakage. After 5 minutes of default test phase, the data acquired was discarded. The data collected during the first phase was to ensure accuracy. Then, the actual data acquisition phase commenced for 10 minutes. Flow rate of the pump was required to be monitored so it achieves a FeO2 between 19.50% and 20.25% by adjustments with the flow selector. After a default 15 minutes of data acquisition phase, the test was ended. The hood was removed from the patient and the blower unit was turned off. REE was expressed in REE (kcal) and REE/kg FFM (kcal/kg).

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics 24. Descriptive statistics were used to describe the baseline data. The parametric data were presented as mean±SD, where comparisons between groups were done using independent sample T-test for continuous variables. The non-parametric data were presented as median±IQR, where comparisons between groups were done using Mann-Whitney U test. Pearson's chi-squared tests were used for comparison between

groups for categorical data. The mean difference of measured REE (kcal) and REE/kg FFM (kcal/kg) between cancer patients and non-cancer controls were compared using independent sample T-test. The mean difference of measured REE (kcal) controlling covariate of FFM between cancer patients and non-cancer controls and REE/kg FFM controlling covariate of age between groups were analysed using one-way ANCOVA. All p values of less than 0.05 were statistically significant.

RESULTS

Twenty-five patients with colorectal cancer and nineteen control subjects were recruited in this study. Out of all the cancer patients, 22 of them have undergone tumour resection surgery, after which they are following up for check-up and palliative care, whereas the other 3 of them have not undergone any tumour resection. Table 1 shows the socio-demographic characteristics of 25 colorectal cancer patients and 19 control subjects. Independent sample t-test showed significant mean differences in age (65.4±10.4 vs 45.0±12.4, $p<0.001$) and in height (155.0±9.1cm vs 160.5±8.2cm, $p<0.05$) between cancer and control group. Mean age of cancer patients was significantly older than the mean age of control subjects, and the mean height of cancer subjects was significantly shorter than that of the control subjects. In terms of REE and REE/kg FFM, there was no significant difference in measured REE (1188±314 kcal/day vs 1372±287 kcal/day, $p>0.05$) and REE/kg FFM (28.7±7.9 kcal/kg/day vs 30.6±5.8 kcal/kg/day, $p>0.05$) between cancer and control group. Pearson's chi-squared test also showed no statistically significant association for gender and ethnicity with cancer.

As for the comparison of energy and macronutrient intake between cancer and control group, Mann-Whitney U test showed a significant difference in fat intake between cancer and control group (46±26 g/day vs 59±23 g/day, $p<0.05$). The control group had significantly higher fat intake than the cancer group. There was no significant difference in calories intake, carbohydrate intake and protein intake between cancer and control group.

Fat-free mass (FFM) is a strong determinant for REE in both genders (11). FFM is a heterogeneous component with higher metabolic activity than fat mass, as skeletal muscle mass and liver mass have been reported to significantly contribute to REE. In view of this, FFM has been proposed to overtake body weight as an adjustment factor in the determination of REE (12,13). Table 2 shows a one-way ANCOVA conducted to compare the difference in measured REE between cancer and control group whilst controlling for FFM. Levene's test, normality test, and homogeneity of regression were checked, and assumptions were met. Yet, there was no significant difference of measured REE between cancer and control group, after controlling for FFM ($p=0.100$).

Age was significantly different between cancer and control group ($p<0.001$) in this study. According to Elia et al, aging is associated with a progressive decline in REE of 1-2% per decade after 20 years of age. This decline is closely related to a reduction of fat-free mass (14). The one-way ANCOVA comparing the difference in REE/kg FFM between cancer and control whilst controlling for age (Table 3) shows no significant result ($p=0.486$).

Table 1. Baseline data

Parameter	**Cancer (n=25)**	**Control (n=19)**	***P* value**
Gender, Male : Female	11:14	8:11	0.900[b]
Ethnicity, Malay : Chinese	12:13	4:15	0.066[b]
	Mean ± SD		
Age, year	65.4±10.4	45.0±12.4	0.000[a]
Weight, kg	62.0±12.5	69.4±16.9	0.099[a]
Height, cm	155.0±9.1	160.5±8.2	0.048[a]
BMI, kg/m^2	25.7±4.1	26.9±5.6	0.412[a]
FFM, kg	42.8±10.9	46.3±12.0	0.320[a]
mREE, kcal/day	1188±314	1372±287	0.053[a]
REE/kg FFM, kcal/day/kg	28.7±7.9	30.6±5.8	0.372[a]
	Median ± IQR		
Calories intake, kcal/day	1294 ± 482	1308 ± 406	0.678[c]
Carbohydrate intake, g/day	176 ± 102	148 ± 79	0.084[c]
Protein intake, g/day	55 ± 29	60 ± 25	0.546[c]
Fat intake, g/day	46 ± 26	59 ± 23	0.030[c]

[a] *Independent sample t test*
[b] *Pearson Chi-Square test*
[c] *Mann-Whitney U Test*
REE: Resting Energy Expenditure; FFM: Fat free mass

Table 2. Comparison of measured REE between cancer and control group with and without adjustment of FFM using ANCOVA

	n	Mean	Mean difference	*P* value
Cancer	25	1188±314	-157.910	0.053 [a]
Control	19	1372±287		
Cancer	25	1208(1100, 1316)[b]	-116.325	0.100[c]
Control	19	1346(1222, 1470)[b]		

Data are expressed as mean ± SD unless specified otherwise
[a] *Independent sample T test*
[b] *Mean (Lower Boundary, Upper Boundary)*
[c] *ANCOVA applied (adjustment for FFM)*

Table 3. Comparison of REE/kg FFM between cancer and control group with and without adjustment of age using ANCOVA

	n	Mean	Mean difference	*P* value
Cancer	25	28.7±7.9	-1.95	0.372 [a]
Control	19	30.6±5.8		
Cancer	25	30.3(26.5, 30.0)[b]	-1.20 (-3.7, 7.7)[d]	0.486[c]
Control	19	28.3(24.0, 32.6)[b]		

Data are expressed as mean ± SD unless specified otherwise
[a] *Independent sample t test*
[b] *Mean (Lower Boundary, Upper Boundary)*
[c] *ANCOVA applied (adjustment for FFM)*
[d] *Mean difference (Lower Boundary, Upper Boundary)*

DÍSCUSSION

Resting Energy Expenditure

Earlier studies reported that cancer patients had significantly increased REE and untreated leukaemia patients had been reported to exhibit elevated basal metabolism (15,16). However, recent studies have shown that actual energy expenditure of cancers were not accurately captured and inconsistent findings had been reported in a meta-analysis investigating changes of REE in cancer patients (17,18). There is an unresolved uncertainty due to discrepancy of results, which is a gap to be filled. Furthermore, very limited studies and information are currently available with regards to REE status in Malaysian colorectal cancer patients.

In this study, no significant difference was found in measured REE between cancer and control group. This finding is in agreement with a large-scale study by Cao et al featuring over 714 cancer patients and 642 controls (19) as well as other studies by Baidi et al, Fredrix et al, Ceolin Alves et al, Dempsey et al and Nixon et al (10,20,21-23). Fat-free mass consumes more energy at rest than their non-metabolically active counterparts such as adipose tissue. It is an important confounding variable that needs to be adjusted for in measurement of REE (24). Hence, for a more meaningful comparison of REE between individuals, expression of REE per kilogram FFM allows us to discover metabolic rate proportional to FFM and to eliminate this confounding variable. Upon adjusted expression of REE for FFM, the result of this study showed no significant difference of REE/kg FFM between cancer and control group.

Using one-way ANCOVA controlling for the covariate of FFM, no significant difference in measured REE between cancer and control group was observed. Since FFM is positively correlated with REE with statistical significance ($p<0.001$), a lack of significant difference in REE after adjustment for FFM indicated that there was no elevated energy expenditure proportional to FFM in the presence of colorectal cancer. This result again, agrees with the study of Cao et al, which observed no significant difference in REE/kg FFM for colorectal cancer group, the homogeneous type of cancer subjects recruited in this study (19). In the study of Cao et al, no significant difference was observed in measured REE between different types of cancer and control group. Upon adjustment for FFM, significant differences of REE/kg FFM were observed between other types of cancer such as esophageal cancer, pancreatic cancer, gastric cancer and control group but no significant difference in REE/kg FFM was observed between colorectal cancer and control group. This implicated that adjustment for FFM is indicated for a correct interpretation of REE changes in different types of cancer, as logically reasoned by the effect of independent effects of FFM on REE.

Furthermore, Cao et al (19) also indicated that no elevated energy expenditure per kg FFM was present in colorectal cancer patients. Nonetheless, this was in conflict with the study finding of Baidi et al and Reeves et al, which found that significant difference in REE/kg FFM was observed between cancer and control after adjustment for FFM (10,25). Discrepancy in findings can be attributed to the heterogeneous feature of cancer group in the studies of Baidi et al and Reeves et al, which

included solid tumours of different cancer types and leukaemia patients. Considering REE was not altered upon adjustment for confounder and FFM was not significantly different from control in the presence of colorectal cancer, interpretation of these results implicates that REE is not uniformly elevated in all cancer patients, providing convincing support that REE experiences different degree of abnormal alteration in different clinical disease characteristic in cancer, as coherently suggested by the study of Fredrix et al which reported that the type of tumour plays an important determining factor of REE changes in cancer patients (20). Hansell et al reported in a study that in cancers with different type of tumour, different effect on fat-free mass was incurred and hence REE changes differed (26). Considering how energy metabolism alterations can be affected by FFM and differ from one type of cancer to another due to numerous factors affecting metabolic alteration in cancer (17), important considerations about the results presented in these studies involve controlling for homogeneity in clinical characteristics of cancer such as type of cancer as recommended by the study finding of Hansell et al and progression of disease and adjustment for significant confounding variable (26). As such, results generated from these studies also lack power to validly demonstrate a clear picture of the changes in REE of colorectal cancer patients.

Judging from a perspective for practicality from this study, the colorectal cancer patients in this study featured 88% (n=22) tumour-resected subjects who were in follow-up palliative care. Hence, results obtained may be less accurate or bear less meaningful generalisability for patients who are not under palliative care but facing a more aggressive or advanced stage of colorectal cancer as studies have repeatedly shown that presence of tumour, aggression as in metastases and stages of cancer may experience significantly elevated REE or metabolic rate (27-29).

Dietary intake

In our study, 88% (n=22) of the colorectal cancer subjects underwent surgical resection of tumour and were in routine follow-up care. Hence, an increased need for thoughtful nutrition care approach is implicated as a systematic review reported that adherence to quality nutrition is inversely associated with overall mortality in cancer survivors (30).

In our study, mean energy, carbohydrate and protein intake were assessed and no significant differences were found between cancer and control group. However, significant difference was observed in fat intake between cancer and control group. The healthy control group consumed significantly higher fat intake than the cancer group. This result does not agree with the cross-sectional study of Kim et al which reported that no significant difference was observed in total fat intake between colorectal cancer patients and healthy controls. The mean fat intake of cancer and control group were 46g and 58g, which amounts to 32% and 40% of total energy intake respectively. Fats intake in healthy control group exceeded the upper limit of 35% total energy intake for fats set by RNI 2017 Malaysia (31) High diet quality index and healthy pattern of diet as defined in low intake of high fat foods were reported to be associated with a reduced risk of mortality in cancer survivors, whereas Western dietary pattern as defined by high fat intake was associated with higher risk of mortality in colorectal cancer survivor (30). Moreover, Meyerhardt et al reported in a study that colorectal patients who scored high for Western dietary pattern, who is characterized by high fat intake, refined grains, red and processed meat had 3-fold risk of cancer recurrence (32). The integrated interpretation of these differing studies indicates that a more prudent nutrition education post treatment in cancer patients would be an increase in energy and protein intake without corresponding increase in fat content or use of processed meats.

Limitation

There was limitations in this study as the sample size of colorectal cancer patients was small, which imposes technical limitation on statistical analysis in reducing power to detect differences that may, in fact, exist, and may not be representative of colorectal cancer patients, which is prerequisite for generalisability of results. As a result, the validity of the study was undermined, and extrapolation of results to other colorectal cancer patients have lacked in validity as well. Hence, a study with larger sample size should be used in the future.

In conclusion, colorectal cancer patients showed no significant difference in measured REE as compared to healthy, normal controls. Even after adjustment and control for FFM, no significant difference was observed in the REE/kg FFM between cancer and control group. Considering the limitations of our study, a study matched for socio-demographics, with a larger sample size and homogeneous feature of cancer clinical characteristics is implicated to validate the findings from this study and as well as providing clearer picture on the effect of cancer on REE. As cancer is most popularly believed to elevate REE, and together in reference with studies showing that excessive caloric prescription for cancer patients are detrimental and deleterious (33,34); clearly, unaltered REE in colorectal cancer patients implicates the importance of a more reasonable and individualised approach in dietetics practice when caloric load is being administered. A one-size-fit-all model of nutrition care is ill advised. Furthermore, in post-treatment cancer patients, nutrition education may prove to be of significant usefulness as dietary intake are associated with recurrence or survival in cancer survivors.

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