

Effect of Different Tumor Types on Resting Energy Expenditure

E. W. H. M. Fredrix,¹ P. B. Soeters, E. F. M. Wouters, I. M. Deerenberg, M. F. von Meyenfeldt, and W. H. M. Saris

Departments of Human Biology [E. W. H. M. F., I. M. D., W. H. M. S.], Surgery [P. B. S., M. F. v. M.], and Pulmonary Diseases [E. F. M. W.], University of Limburg, Maastricht, The Netherlands

ABSTRACT

The purpose of this study was to investigate whether the presence of a malignant tumor influences energy metabolism of the host. Resting energy expenditure (REE) was measured in 104 gastric and colorectal (GCR) cancer patients and in 47 non-small cell lung cancer patients and was compared with REE values in 40 healthy controls. REE expressed per kilogram of fat-free mass (FFM) in lung cancer patients was elevated, in comparison with healthy controls (33.6 ± 4.6 and 29.6 ± 2.9 kcal, respectively; $P < 0.001$), in contrast to REE/FFM in GCR cancer patients, which showed no difference, compared with these controls (29.8 ± 4.3 kcal). In 47 patients with GCR cancer and in 14 patients with lung cancer, REE was also determined after tumor resection. REE in GCR cancer patients measured 1.5 years after tumor resection showed a small but significant increase. No differences were observed between GCR cancer patients with or without signs of tumor recurrence. REE in lung cancer patients with no signs of tumor recurrence measured 1 year after tumor resection had a significant decrease in REE (REE/FFM, -6.8% ; $P < 0.05$), while patients who had evidence of tumor recurrence showed no change in REE or even an increase. After curative surgery REE returned to a normal level in the lung cancer patients. These results suggest that tumor type is a major determinant of an increased energy expenditure in cancer patients.

INTRODUCTION

Weight loss is a common feature in patients with cancer. Increased EE² and decreased dietary intake have been incriminated as causative factors for the observed weight loss. Several authors have found an elevated REE in patients with malignant disease (1-5). Others have found no change (6, 7). Some of these studies, however, have been poorly controlled; data from patients were compared with data from inadequate control subjects or no control data were offered at all. It has also been suggested that different tumor types may exert different influences on REE. Dempsey *et al.* (8) determined REE in gastrointestinal cancer patients and found patients with pancreatic or hepatobiliary tumors to be predominantly hypometabolic; gastric cancer patients tended to be hypermetabolic. These conclusions were reached by comparing measured REE with that predicted from the HB formula. In only a few studies, cancer patients functioned as their own controls, by measurement of REE before and after surgical resection of the tumor (1, 4), showing evidence for an increased EE in malignancy.

The current study investigates the presence of an elevated REE in patients with GCR cancer and in patients with non-small cell lung cancer, by comparing them with healthy controls. In addition, in order to measure tumor-mediated thermogenesis, REE measurements in these cancer patients were performed before and after tumor resection.

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¹ Present address: Department of Natural Sciences, Open University, P. O. Box 2960, 6401 DL Heerlen, The Netherlands. To whom requests for reprints should be addressed.

² The abbreviations used are: EE, energy expenditure; REE, resting energy expenditure; GCR, gastric and colorectal; FFM, fat-free mass; PIBW, percentage of ideal body weight; BW, body weight; HB, Harris Benedict; PRE-REE, resting energy expenditure measured before tumor resection; POST-REE, resting energy expenditure measured after tumor resection.

MATERIALS AND METHODS

Patients with histologically proven GCR cancer and lung cancer were included in the study. All patients had newly detected tumors and no patient had undergone prior treatment.

GCR Cancer Patients. PRE-REE was measured in 104 patients. In 47 of these 104 patients, POST-REE was measured after 1.5 years (18 \pm 5 months). Fifty-seven patients were not measured. The reasons for exclusion were that these patients died ($n = 44$), refused ($n = 7$), were in a critical physical condition ($n = 5$), or were not operated upon ($n = 1$). The remaining 47 patients were categorized into a group of 32 patients in which tumor recurrence was not likely and a group of 11 patients with signs of tumor recurrence. Presence of recurrence was established by examination of medical records produced during routine follow-up on an outpatient basis. In four patients it could not be established whether they had tumor recurrence or not.

Lung Cancer Patients. PRE-REE was measured in 47 patients. In 14 of these 47 patients POST-REE was measured after 1 year (12 \pm 4 months). Thirty-three patients were not measured. The reasons for exclusion were that these patients died ($n = 26$), refused ($n = 2$), were in a critical physical condition ($n = 3$), or were not operated upon ($n = 2$). Of the remaining 14 patients, 11 patients had no detectable tumor recurrence and three patients had evidence of tumor recurrence.

REE was measured by indirect calorimetry using a ventilated hood system. Gas analyses were performed using a paramagnetic oxygen analyzer (Mijnhardt module; Bunnik, The Netherlands) and an infrared carbon dioxide analyzer (modified UG51, Mijnhardt, Bunnik, The Netherlands). Dry gases were measured and the results were converted to standard temperature and pressure. Flow through the canopy was kept constant during measurements and was adjusted to body weight of the patient (25-50 liters/min). System control and calculations were performed on a microcomputer. The equipment was calibrated at the start and at the end of every experiment. The hood consisted of clear Plexiglas and had a volume of 30 liters. REE was calculated using the abbreviated Weir formula (9).

PRE-REE in the hospital was measured between 7:00 and 9:00 a.m., after an overnight fast. POST-REE was measured on an outpatient basis. Patients visited the hospital at 9:00 a.m. They had fasted for at least 10 h and had travelled by car. REE measurements were carried out after at least 30 min of complete bed rest. On both occasions REE was measured at rest in the supine position during 30 min. In a recent study, we showed that REE in 30 healthy volunteers measured after they had spent the night in the hospital was not significantly different from REE measured after they had travelled to the hospital (10).

In addition, REE in these cancer patients was compared with REE values in a group of 40 apparently healthy controls (mean age, 65 \pm 8 years) measured according to the same procedure. These healthy controls underwent a medical examination to exclude disorders which might affect their metabolic rate, such as anemia, thyroid dysfunction, infectious disease, high blood pressure, heart failure, and chronic obstructive pulmonary disease.

FFM was estimated with the bioelectrical impedance method (BIA-101; RJL Systems, Detroit, MI) and was calculated using the formulae of Segal (11). Bioelectrical impedance was measured in only half of the GCR cancer patients, because at the start of the study no equipment was available to measure body composition.

Actual body weight was also expressed as PIBW (12). Tumor stage was assessed after review of medical records, operative reports, and pathology and radiology reports, according to the guidelines of the American Joint Committee on the Staging for Cancer for GCR cancer patients (13) and according to the guidelines of the International Union against Cancer for lung cancer patients (14).

REE was expressed in absolute terms (REE), per kilogram of body weight (REE/BW), and per kilogram of FFM (REE/FFM). Statistical analysis was performed using the Tukey pairwise multiple comparison procedure. The Mann Whitney *U* test and the Wilcoxon matched-pairs signed-ranks test were used for nonparametric statistical analyses. Further statistical procedures included Student's paired *t* test and χ^2 analysis. Results are presented as mean \pm SD, and *P* values of <0.05 were regarded as statistically significant.

RESULTS

Fifty-four men and fifty women with GCR cancer were included in the study (Table 1). Their mean age was 70 years and their mean PIBW was 99%. There were almost 4 times as many colorectal cancer patients as gastric cancer patients. Forty-three men and four women with lung cancer were included in the study. Their mean age was 66 years and their mean PIBW was 93%. PRE-REE in lung cancer patients, even when corrected for FFM, was increased, compared with GCR cancer patients or healthy controls. Males were relatively overrepresented in the lung cancer patients, compared with the control group. However, REE/FFM in male lung cancer patients was also significantly elevated, compared with male healthy controls.

The 57 GCR cancer patients who were not measured after tumor resection were older, had a lower PIBW, and had a more advanced tumor stage at the time of primary treatment than the 47 measured patients. PRE-REE was not significantly different between the two groups. POST-REE in GCR cancer patients was significantly higher than PRE-REE, no matter how it was expressed. POST-REE was significantly increased in both the 32 GCR cancer patients without tumor recurrence and the 11 GCR cancer patients with tumor recurrence (Table 2). This difference was less significant when expressed as REE/BW and was not significant for the GCR cancer patients with tumor recurrence when expressed as REE/FFM. POST-REE in GCR cancer patients after curative tumor resection was not different from REE values in healthy controls (Table 3).

A comparison between the 33 lung cancer patients that were not measured after tumor resection and the 14 measured patients showed significant differences with respect to tumor stage at the time of primary treatment. PRE-REE tended to be higher in the patients that were not measured postoperatively. POST-REE was not significantly different from PRE-REE, no matter how it was expressed. BW and FFM also showed no significant changes. However, the 11 lung cancer patients with no tumor recurrence showed a significant increase in BW and in FFM after tumor resection. Furthermore, a significant decrease in REE/BW and in REE/FFM was observed (Table 4). This was in contrast to the three lung cancer patients who had tumor recurrence. These patients all showed a decrease in BW (mean, 6.2 kg) and in FFM (mean, 3.8 kg). REE/BW was increased for all three patients, and REE/FFM was elevated for two patients (Fig. 1).

The differences in REE between lung cancer patients and GCR cancer patients or healthy controls had disappeared after surgical resection of the tumor (Table 3). After curative tumor resection POST-REE in lung cancer patients was not elevated, compared with POST-REE in GCR cancer patients or with REE in healthy controls.

DISCUSSION

It has been suggested that an increased EE contributes to the weight loss commonly seen in cancer patients. Macfie *et al.* (3)

Table 1 Patient characteristics

	GCR cancer patients (n = 104)	Lung cancer patients (n = 47)	Healthy controls (n = 40)
Age (years)	70 \pm 11 ^{a, b, c}	66 \pm 8	65 \pm 8
Sex (male/female)	54/50	43/4	18/22
Weight (kg)	65.2 \pm 11.6 ^d	65.3 \pm 11.0 ^e	72.1 \pm 12.1
FFM (kg)	45.5 \pm 8.8 ^{c, f}	49.5 \pm 8.4	51.3 \pm 9.7
PIBW (%)	99 \pm 13 ^{d, g}	93 \pm 11 ^h	105 \pm 11
Weight loss (%)	7.1 \pm 6.4	7.3 \pm 6.7	ⁱ
REE (kcal/kg of BW)	20.9 \pm 2.7 ^j	25.3 \pm 3.8 ^h	21.0 \pm 2.0
REE (kcal/kg of FFM)	29.8 \pm 4.3 ^{f, j}	33.6 \pm 4.6 ^h	29.6 \pm 2.9

^a Mean \pm SD.

^b *P* < 0.05 GCR vs. lung.

^c *P* < 0.05 GCR vs. controls.

^d *P* < 0.01 GCR vs. controls.

^e *P* < 0.01 lung vs. controls.

^f *n* = 49 patients.

^g *P* < 0.01 GCR vs. lung.

^h *P* < 0.001 lung vs. controls.

ⁱ Weight stable.

^j *P* < 0.001 GCR vs. lung.

demonstrated that REE of patients with disseminated malignancy is increased, compared with younger healthy controls. Dempsey *et al.* (8) found that approximately one third of cancer patients are hypermetabolic, one third normal, and one third hypometabolic. In their study, measured REE was compared with values predicted by the HB formula. This formula is based on measurements of REE in healthy young volunteers. Roza and Shizgal (15) suggested that this formula underpredicts REE in malnourished patients.

To assess the effect of the tumor-bearing state on REE, it is important to compare the results on cancer patients with control data. Therefore, in the current study REE of GCR and lung cancer patients was also compared with REE values of healthy controls in the same age range. The results show that lung cancer patients had an elevated REE, compared with healthy controls, in contrast to GCR cancer patients, who had a normal REE. Hansell *et al.* (16) found that REE/FFM in lung cancer patients was not significantly higher than that in GCR cancer patients. However, the number of lung cancer patients that was measured was small (*n* = 11).

In a recent study, we demonstrated that mean REE in lung cancer patients was 20% higher than predicted by the HB formula (17). Sixty % of these lung cancer patients had an elevated REE (measured REE, $\geq 115\%$ predicted REE). These results suggest that an elevated REE is an important event in the initiation of weight loss in lung cancer patients. This is also demonstrated by the result that an elevation in REE of the order found in this study can account for a weight loss of 1.5 kg/month, assuming that energy intake is unchanged.

Another way to investigate tumor-mediated thermogenesis is to measure REE in cancer patients before and after surgical resection of the tumor. Arbeit *et al.* (1) studied four patients with localized tumor, before and after tumor resection, and found that all patients had a postoperative drop in their REE. Warnold *et al.* (4) showed that after curative surgery EE returned to a normal level in one cancer patient. Bozzetti *et al.* (2) had a similar result in two cancer patients who had a good response to chemotherapy. None of these patients, however, had gastric, colorectal, or lung cancer. In the current study, lung cancer patients with no signs of tumor recurrence showed a significant decrease in POST-REE/BW and POST-REE/FFM, in contrast to lung cancer patients with evidence of tumor recurrence, who showed an increase in POST-REE/BW and POST-REE/FFM. Although the number of lung cancer patients was small, this finding is an indication that the tumor

Table 2 PRE-REE and POST-REE values in GCR cancer patients with or without signs of tumor recurrence

	Tumor recurrence (n = 11)			No tumor recurrence (n = 32)		
	PRE-REE	POST-REE	P value	PRE-REE	POST-REE	P value
Weight (kg)	65.1 ± 6.6 ^a	64.6 ± 9.6	>0.1	70.2 ± 12.2	71.9 ± 12.5	>0.1
FFM (kg)	48.9 ± 5.3 ^b	51.5 ± 6.1	0.07	50.2 ± 8.9 ^c	50.3 ± 8.2	>0.1
REE (kcal/day)	1303 ± 146	1419 ± 194	<0.05	1429 ± 254	1510 ± 275	<0.001
REE (kcal/kg of BW)	20.0 ± 1.5	22.2 ± 2.6	0.07	20.5 ± 2.1	21.1 ± 2.2	<0.05
REE (kcal/kg of FFM)	27.6 ± 1.3 ^b	28.6 ± 1.0	>0.1	28.7 ± 2.6 ^c	30.3 ± 3.6	<0.05

^a Mean values ± SD.^b n = 4 patients.^c n = 14 patients.

Table 3 REE after curative tumor resection in cancer patients, compared with controls

	GCR cancer patients (n = 32)	Lung cancer patients (n = 11)	Healthy controls (n = 40)
REE (kcal/kg of BW)	21.1 ± 2.2 ^a	22.1 ± 1.9	21.0 ± 2.0
REE (kcal/kg of FFM)	30.3 ± 3.6 ^b	30.0 ± 2.5	29.6 ± 2.9

^a Mean values ± SD; differences are not statistically significant.^b n = 27 patients.

Table 4 PRE-REE and POST-REE in non-small cell lung cancer patients with or without signs of tumor recurrence

	Tumor recurrence (n = 3)		No tumor recurrence (n = 11)		P value
	PRE-REE	POST-REE	PRE-REE	POST-REE	
Weight (kg)	73.2 ± 8.6 ^a	67.0 ± 10.8	64.9 ± 12.0	69.7 ± 10.0	<0.05
FFM (kg)	53.2 ± 2.9	49.4 ± 3.2	48.9 ± 8.4	51.3 ± 6.4	0.06
REE (kcal/day)	1626 ± 189	1616 ± 155	1558 ± 221	1536 ± 219	>0.1
REE (kcal/kg of BW)	22.2 ± 0.5	24.3 ± 1.5	24.5 ± 3.8	22.1 ± 1.9	<0.05
REE (kcal/kg of FFM)	30.5 ± 2.0	32.7 ± 1.3	32.2 ± 3.7	30.0 ± 2.5	<0.05

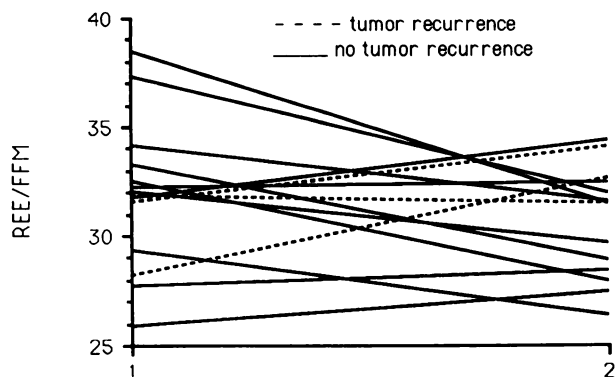
^a Mean values ± SD.

Fig. 1. REE/FFM before (1) and after (2) tumor resection in lung cancer patients with or without tumor recurrence.

itself induced the elevated REE in lung cancer patients. This is even more supported by our observation that REE values of lung cancer patients who had no signs of tumor recurrence 12 months after resection were not different from REE values in healthy controls. Eight (of 11) of the lung cancer patients with no tumor recurrence were smokers before diagnosis of their disease. Six of them stopped smoking after tumor resection and one reported smoking fewer cigarettes. The evidence concerning the effects of cigarette smoking on EE is conflicting. Hofstetter *et al.* (18) demonstrated that smoking increases 24-h EE by approximately 10%. They also found, however, that the thermogenic effect of smoking had ceased by the morning after a day of smoking. A comparison between lung cancer and GCR

cancer patients who were smokers revealed that lung cancer patients still had an elevated REE, compared with GCR cancer patients (34.2 ± 4.3 versus 31.4 ± 6.5 kcal/kg of FFM; $P < 0.05$). This suggests, therefore, that the fall in REE in lung cancer patients was the result of successful removal of the tumor rather than of cessation of smoking.

In the current study, POST-REE in GCR cancer patients increased but still not significantly different from REE in healthy controls. The observation that patients both with and without signs of tumor recurrence showed an increase in POST-REE suggests that the presence of the tumor in GCR cancer patients has no clear impact on energy metabolism, which is in agreement with the observations of Hansell *et al.* (7, 16) and Burke *et al.* (6).

In the current study the period between the two measurements was, on average, 11 months and 18 months for the lung cancer and the GCR cancer patients, respectively. We, therefore, assume that any influence on energy metabolism from the surgical procedure or subsequent radiotherapy may be ignored.

In lung cancer patients a significant correlation existed between the change in REE/FFM and the incidence of tumor recurrence ($r = 0.55$; $P < 0.05$). In addition, two (of three) patients with tumor recurrence showed a rise in REE/FFM, whereas the third patient showed a small decrease. Furthermore, seven (of 11) patients without signs of tumor recurrence showed a fall in REE/FFM, whereas the other four patients showed a (small) increase. One must assume that after an initial fall patients with tumor recurrence showed an increased REE, in two of three, to an even higher level than PRE-REE values.

We cannot explain the elevation of REE in lung cancer patients. In another study we demonstrated that there were no significant differences in tumor stage, tumor localization, pulmonary function, or smoking behavior between hypermetabolic and normometabolic lung cancer patients (17). In recent years, macrophage products capable of inducing metabolic alterations in both infectious and neoplastic diseases [cachectin (tumor necrosis factor), interleukins] have been identified (19). Starnes *et al.* (20) reported an enhanced EE in cancer patients that were administered i.v. a single dose of TNF. However, the hypothesis that some of these metabolic abnormalities in cancer cachexia are due to mediators of the immune system remains to be examined in detail.

We conclude from this study that lung cancer patients have an elevated REE, which returns to a normal level after curative surgery, while in GCR cancer patients REE is not elevated. These results suggest that tumor type is a major determinant of an increased EE in cancer patients.

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