Energy Balance and Body Composition in Cancer Patients

Ingrid Warnold, Kent Lundholm, and Tore Scherstén

Institute of Clinical Nutrition [I. W.] and Department of Surgery [K. L., T. S.], Sahlgrenska Sjukhuset, University of Göteborg, Göteborg, Sweden

ABSTRACT

Energy balance and body composition were studied in 10 cancer patients to investigate the interrelationship between energy expenditure and energy intake in the development of cancer cachexia. These data were compared to the findings in control patients of similar age with diseases affecting physical activities to about the same extent. The measurements of energy expenditure and intake were repeated when possible during progression of the malignant disease. Body composition in a larger group of cancer patients (n = 29) was compared to data from a group of healthy subjects within the same age range (n = 164). The cancer patients were below normal in body weight and body cell mass. Body fat was reduced in women with cancer. Energy intake (mean, 1270 kcal/day), although varying greatly, was not significantly different from the intake in the controls (mean, 1470 kcal/day). Both the daily energy expenditure (mean, 2020 kcal/24 hr) and the resting metabolic rate (mean, 1630 kcal/24 hr) were significantly greater in the cancer patients than they were in the controls (mean, 1420 and 1170 kcal/24 hr, respectively). Parallel to exacerbation of the disease and reduced energy intake, the energy expenditure and the resting metabolic rate increased in relation to body cell mass in two patients. After curative surgery both intake and expenditure of energy returned to normal levels in one patient. For a more accurate interpretation of the higher daily energy expenditure and resting metabolic rate found in the cancer patients, the influences of body weight, body cell mass, and height were ruled out. The results suggest that one of the reasons for the development of cancer cachexia is an increasing resting metabolic rate and daily energy expenditure.

INTRODUCTION

Rapid weight loss in patients with cancer has mostly been attributed to a decreased energy intake due to loss of appetite (22). However, an increased energy expenditure in tumor-bearing animals has been observed (11, 19). There has been disagreement as to whether an increasing energy expenditure is paralleled by an increasing tumor mass (16) or is initiated before any rapid tumor growth occurs (11, 19). In human cancer patients an increased basal metabolic rate has been reported (14, 25).

The aims of this study were to determine body composition and to examine whether the weight reduction in cancer patients is predominantly coupled to an elevated energy expenditure or to a decreased energy intake.

MATERIALS AND METHODS

 Patients. The study comprised 10 patients (mean age, 65 years; range, 51 to 75) with various types of malignant tumors. Table 1 lists the diagnoses and other pertinent clinical data on the patients. None of the patients was febrile during the study. Normal liver tests were defined as follows: serum bilirubin, 3.4 to 21 μmol/liter; alkaline phosphatase, <5 μkat/liter; aspartate aminotransferase, <0.7 μkat/liter; and alanine aminotransferase, <0.7 μkat/liter. Besides the laboratory tests the following investigations were performed: X-ray of the lungs and the skeletal system and, in most patients, aortography.

None of the patients had apparent loss of body fluids. Most of the patients were explored surgically. The degree of tumor spread was judged from preoperative examinations and the finding at operation. Histological grading of the tumor cells was performed in all patients.

The following inclusion criteria for appropriate controls were used: hospitalization for at least 4 weeks, low grade of physical activity, no clinical and laboratory evidence of malignant disease, and age comparable with the cancer patients.

Nine patients (mean age, 70 years; range, 45 to 87), treated for hemiparesis, column fracture, and rheumatoid arthritis, fulfilled these criteria. The patients' informed consent to participate in the study was obtained.

 Body Composition. Body composition was measured in a larger group of cancer patients (19 women and 10 men), including the 10 patients selected for energy balance measurements. The clinical data of these 19 additional patients have been reported previously (13). The BCM was calculated from total body potassium (15) determined in a whole-body counter (20). Total body water was measured by an isotope dilution technique with tritiated water as tracer (12). From body weight, total body water, and BCM, the BF was calculated as described by Berg and Isaksson (3). The body composition of the cancer patients was compared to data obtained with identical techniques from a group of healthy men and women within the same age range. The body composition in the controls was estimated from body height, body weight, and age as described by Ellis et al. (7).

Energy Expenditure. The energy expenditure was calculated from continuous heart rate recordings during 4 to 6 days and nights and from individual relationships between oxygen consumption and heart rate determined as described previously (23). This method was considered to be...
Table 1

Age, anthropometric data, BCM, extracellular water, BF, and diagnosis of patients when admitted to hospital

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Body wt (kg)</th>
<th>Body composition (kg)</th>
<th>Hemoglobin concentration in blood (g/liter)</th>
<th>Liver serum tests</th>
<th>Grade of differentiation</th>
<th>Tumor spread</th>
</tr>
</thead>
<tbody>
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<td>Men:</td>
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<tr>
<td>1</td>
<td>72</td>
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<td>0.98</td>
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<td>12.2</td>
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<tr>
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<td>16.1</td>
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<td>4</td>
<td>51</td>
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<td>0.89</td>
<td>26.9</td>
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<td>5</td>
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<td>55.5</td>
<td>164</td>
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<td>48.1</td>
<td>164</td>
<td>0.77</td>
<td>20.2</td>
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<td>48.0</td>
<td>152</td>
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<td>21.3</td>
<td>20.9</td>
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<td>0.93</td>
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<td>13.9</td>
<td>11.7</td>
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<table>
<thead>
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<th>a Actual weight/desirable weight (25).</th>
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<td>b ECW, extracellular water.</td>
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the only feasible one since it does not disturb the patient or influence his level of activity. The calibration lines were based on simultaneous measurements of oxygen consumption and heart rate during habitual activities such as lying, sitting, and walking. In some patients measurements were possible only during lying and sitting. The oxygen content of the expired air was analyzed in a paramagnetic oxygen analyzer (Beckman OM-11), and the energy expenditure was calculated according to the method of Weir (27).

The resting metabolic rate was measured after an overnight fast before the patients had been out of bed in the morning.

Energy Intake. The food intake was recorded during the periods when energy expenditure was measured. The intake records were mostly made by the patients themselves, but in some patients this was not considered reliable and weighing of the servings and returns were then performed by a dietitian. The energy and protein intake was calculated from the recipes by use of conventional food tables (1). The energy intake was also estimated from 4-day dietary recordings in Patients 3 and 7 when they were living at home.

Urine Analyses. Daily collections were performed during all periods of energy intake and expenditure measurements. The daily urinary nitrogen excretion was determined according to the Technicon Autoanalyzer Method N-3B, and the daily urinary creatinine excretion was determined according to the method of Bonsnes and Tonssky (4).

Statistical Methods. Wilcoxon's test for 2 samples and for pair differences was used (28) except where otherwise stated. Pitman's nonparametric permutation test was used (6) for comparisons of energy expenditure and resting metabolic rate between the cancer patients and the controls. Height, body weight, and BCM were used as background variables. For determination of the p values, the Edgeworth expansion was used. The material was divided into categories according to 1 background variable (BCM, body weight, and height) at a time. Within each of these categories, the Pitman test variable was determined, and the results from the different categories were pooled for a summarizing test.

RESULTS

In the cancer patients subjected to energy balance measurements, the mean weight index, 0.95 (range, 0.77 to 1.18), was not significantly different from the mean observed in the controls, 0.96 (range, 0.74 to 1.23) (Table 1). The cancer patient (No. 2) who was overweight had lost 26 kg the year before the study.

The absolute values of body weight, BCM, and BF (women only) in the larger group of cancer patients (n = 29) were significantly lower than they were in healthy subjects (n = 164), whereas height was not significantly different (Table 2). The BF of the men with cancer was, however, not different from that of the healthy males. The same differences from normal body composition found in the larger group of cancer patients were also observed in the 10 cancer patients subjected to energy balance measurements. In percentage of body weight, the extracellular water was above normal in the women with cancer. BF was above normal in Patient 9 although the patient had lost 22 kg during the preceding 6 months (see Table 1).

The BCM changes are shown in Chart 1 for the 6 patients in whom the measurements were repeated. In most of them a decrease was observed.

The mean creatinine excretion/24 hr was not significantly different between the cancer patients in whom energy balance was studied (6.8 mmol; range, 3.9 to 11.1) and the controls (5.4 mmol; range, 3.4 to 8.0).

The individual calibration equations for calculation of energy expenditure are given in Table 3. In 1 patient (No. 4), the slope of the calibration line was significantly decreased at the second calibration performed 32 weeks later.
This change can be ascribed at least partly to low motor activity because of progression of the disease. In Patient 9 the heart rate was monitored for a second period 5 weeks after the first measurement, but a second calibration was impossible due to nausea.

The daily energy intake and expenditure and the energy balance are shown in Table 4. In 6 of 16 recordings (38%), the daily energy intake was below 1000 kcal, and in 4 of 16 (25%) the intake exceeded 2000 kcal. The daily energy intake in Patient 3 increased from 1390 to 2290 kcal within 1 month after successful surgical removal of a 4.5-kg tumor, as indicated by a 4-day dietary record, and the intake was also high (2270 kcal) during a follow-up study at the hospital 20 weeks after the operation. The total energy intake in Patient 4 (Period a) was high (3200 kcal/day) during i.v. hyperalimentation (40 kcal/kg of body weight, given as glucose (800 kcal), amino acids (400 kcal), and fat (Intralipid) (2000 kcal)). The energy intake in Patient 7 was high during the first 2 periods (2250 and 2160 kcal/day) and during two 4-day records performed at home (2640 and 1920 kcal/day) within 2 months after the second period of hospital stay. Due to nausea the energy intake decreased further between Periods c and d, and thereafter no oral intake was possible. A continuous infusion of 1500 kcal/day was therefore necessary.

The mean daily energy intake was 1270 kcal in 9 of the cancer patients during their initial period of hospital stay (Patient 4 was omitted) and 1470 kcal in the controls (Chart 2). The variation was much greater in the cancer patients (range, 580 to 2250 kcal/day) than it was in controls (range, 1210 to 1860 kcal/day). No significant difference was found between the groups. When the last measured energy intake in the cancer patients was considered, there was still no difference in energy intake between the groups.

The daily energy expenditure was above 1500 kcal in all cancer patients and above 2000 kcal during 6 (38%) determinations (Table 4). The energy expenditure was high in Patient 3 (3330 kcal/24 hr) when measured before surgical removal of the tumor. The energy expenditure in Patient 4 was also high (2510 kcal/day) during i.v. hyperalimentation (Period a). An increasing energy expenditure was observed in Patients 7 and 9 during progression of the disease.

As is shown in Chart 3, the mean daily energy expenditure in the cancer patients during the initial period of hospital stay was 2020 kcal (range, 1530 to 3330 kcal/24 hr), which was 42% higher (p < 0.01) than that in the control patients, who expended 1420 kcal (range, 1230 to 1680 kcal/24 hr).

Exceedingly large negative energy balances were measured in 7 of the patients during the first period of hospital stay (Table 4). Patient 8 was in energy balance due to a low energy expenditure. A large positive energy balance (1140 kcal/day) was observed in Patient 4 during hyperalimentation in spite of an elevated energy expenditure. During the first 2 determinations, Patient 7 was in positive energy balance, but during the subsequent 2 periods a negative energy balance was observed. A large negative energy balance (~1940 kcal/day) was determined in Patient 3 before surgery, and this negative energy balance became positive (+80 kcal/day) 20 weeks after successful removal of the tumor.
The resting metabolic rate was higher (p < 0.01) in the cancer patients during the initial period of hospital stay (mean, 1630 kcal; range, 1090 to 2490 kcal/24 hr) than it was in the control group (mean, 1170 kcal; range, 1010 to 1370 kcal/24 hr) (Chart 4).

The daily energy expenditure and the resting metabolic rate were compared between the cancer patients and the controls with the use of Pitman’s permutation test (6). A positive correlation was found between daily energy expenditure and both body weight and height within the cancer patients (p < 0.05), as well as between the resting metabolic rate and body weight (p < 0.01), body height (p < 0.05), and BCM (p < 0.01). Within the control group a positive correlation was found between energy expenditure and BCM (p < 0.05) and between resting metabolic rate and body height (p < 0.05). When the influences of body weight, height, and BCM were eliminated, both the energy expenditure and the resting metabolic rate were higher in the cancer patients compared to the controls.

The energy expenditure and the resting metabolic rate in relation to BCM as well as the daily energy intake are shown in Chart 5 for 4 of the patients who were studied on more than 1 occasion. The energy expenditure and resting metabolic rate were higher than normal in Patient 3 when studied before successful surgical removal of a 4.5-kg tumor (Period a). Measurements performed 20 weeks after the operation (Period b) showed normal energy expenditure per kg of BCM. During hyperalimentation in Patient 4 (Period a), the daily energy expenditure and the resting metabolic rate were above normal, but they returned to the normal range at a later phase of the disease (Period b). A parallel increase in energy expenditure and resting metabolic rate was demonstrated in Patients 7 and 9 during progression of the...
Energy Balance in Cancer Patients

Chart 2. Energy intake in the cancer patients during initial hospital stay and in the control patients (mean values are indicated).

Energy intake (kcal/day)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>2000</td>
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<tr>
<td>1500</td>
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<td>1000</td>
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<td>500</td>
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</table>

Chart 3. Energy expenditure in the cancer patients during initial hospital stay and in the control patients (mean values are indicated).

Energy expenditure (kcal/24 hr)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>3000</td>
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<td>2500</td>
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<td>2000</td>
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<td>1500</td>
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</table>

Chart 4. Resting metabolic rate in the cancer patients during initial hospital stay and in the controls (mean values are indicated).

Resting metabolic rate (kcal/24 hr)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Control</th>
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<tbody>
<tr>
<td>2000</td>
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<td>1500</td>
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<td>1000</td>
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</table>

Chart 5. Daily energy expenditure (●) and resting metabolic rate (▵) in relation to BCM, as well as daily energy intake (●, oral intake; ○, total intake), with changes in the malignant disease in 2 men (Patients 3 and 4) and in 2 women (Patients 7 and 9). Shaded area, mean ± S.E. in the control group.

malignant disease. The energy intake decreased in Patients 4 (no parenteral support was given during Period b), 7, and 9 during progression of the disease, while an increased energy intake was observed in Patient 3 after the successful surgery.

In 4 of 16 measurements in the 10 cancer patients (25%), the urinary nitrogen excretion exceeded the intake (Chart 6). When fecal and dermal losses (estimated to be 1 g each) were also considered, 7 of 16 measurements (44%) indicated losses larger than intakes. In Patients 4, 7, and 9, the balance became more negative during progression of the disease, while in Patient 3 a negative balance changed into

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DISCUSSION

These results show significantly altered body composition and energy balance in cancer patients as compared with controls. The cancer specificity of these changes can be questioned. The cancer patients were hospitalized most of the time during the study, and their physical activity was low. To minimize the risk of misinterpretations because of these and similar factors, the control patients for the energy balance studies were selected from patients hospitalized because of diseases affecting physical activity to about the same extent. Energy expenditure was measured by a method based on heart rate recordings. In a recent evaluation of this method, it was found to provide accurate and reproducible estimates of energy expenditure both in sedentary and in active patients (25), which is in agreement with previous reports (5, 8).

A low BCM was observed in all cancer patients. The cell mass was calculated from total body potassium, and consequently the tumor potassium was also included in the determinations. There was no means of separating the tumor potassium from the body potassium of the host. This indicated that the host was even more depleted than the BCM indicated. During slow progression of the malignant disease, an adaptive response sometimes occurred, resulting in a preserved BCM (e.g., Patients 7 and 8), while a depletion could be seen during acute exacerbation (e.g., Patients 9 and 10).

The energy expenditure in the cancer patients was high. Obviously, body weight must exert an influence on energy expenditure, at least during physical activity. A positive relationship has also been proposed between daily energy expenditure and total active metabolic mass (2, 10). Furthermore, a positive relationship has been demonstrated between basal metabolic rate and total body potassium (26). As the energy expenditure per unit of vital organs (e.g., heart, kidney, liver, and brain) is larger than that per unit of skeletal muscles, both the control patients and our cancer patients should show about the same energy expenditure or resting metabolic rate. This might lead to the conclusion that the tumor per se had a high energy turnover or that the tumor initiated increased metabolism in the host.

Moreover, studies on rats showed that the increased energy expenditure could not be accounted for by tumor growth only (11, 19). The great differences observed between the cancer patients and the control group make it probable that the tumor initiated elevated metabolism in the host.

To interpret accurately the higher daily energy expenditure and the resting metabolic rate in the cancer patients, we ruled out the influences of body weight, BCM, and height. The statistical test (6) allowed us to state with certainty that both the daily energy expenditure and the resting metabolic rate were higher in our cancer patients than they were in the control patients. As the physical activity was low in both groups, the resting metabolic rate accounted for the greatest part of the discrepancies.

The large variation in energy intake observed in the cancer patients was due to nausea in some patients, while other patients still showed unaffected appetite. During the development of the disease, all patients showed a decreasing energy intake, while an increase was demonstrated in 1 patient after successful removal of the tumor. The energy intake was not statistically different between the cancer group and the control group. Although the intake decreased in the cancer patients during progression of the disease, it was still not less than that in the controls and in other groups of disabled patients (24).

Parallel to an exacerbation of the disease and a reduced energy intake, the energy expenditure and the resting metabolic rate increased in relation to BCM in 2 of the patients (Nos. 7 and 9), thus showing no adaptive responses to the semistarvation such as were found in healthy subjects (9). After elective surgery both intake and expenditure of energy returned to normal levels in 1 patient (No. 3), indicating that the metabolic changes were reversible. A noteworthy finding was the extremely high energy expenditure (3330 kcal) observed before surgery in spite of a low level of physical activity. The reversed changes found in Patient 4 during progression of the disease were probably

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due to hyperalimentation during the initial measurement. Increased energy expenditure has been demonstrated after a single dose of protein and carbohydrate (18). Moreover, only slight increases in body weight and BCM were observed during the hyperalimentation.

The increased energy expenditure found in 2 patients (Nos. 7 and 9) was paralleled by an increasingly negative nitrogen balance, and the opposite was true after resection of the tumor in 1 patient (No. 3). A gradually decreasing nitrogen excretion has been found during semistarvation of healthy subjects (9), but no such adaptive response was observed in our cancer patients.

The results of this study suggest that 1 of the reasons for the development of cancer cachexia is an increasing resting metabolic rate and daily energy expenditure, even when the influences of body weight, body height, and BCM are ruled out. As pointed out by Morrison (17), the central problem is why the host fails to meet the increased expenditure by increased caloric intake.

REFERENCES

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