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Effects of Spontaneous Physical Exercise on Experimental Cancer Anorexia and Cachexia

Peter L.-E. Daneryd, Larsolof R. Hafström and Ingvar H. Karlberg

The aim of this study was to evaluate whether spontaneous physical exercise can modify cancer anorexia and cachexia in tumour-bearing rats. Two transplantable experimental tumours were evaluated. Tumour-bearing Wistar Furth rats fed *ad libitum* and with free access to a running wheel had a delayed onset of anorexia compared with their non-exercised tumour-bearing controls, retained normal behaviour and were able to run the same daily distance as non-tumour controls until the onset of cachexia. Exercise resulted in a decreased carcass wet weight and lipid stores but in an increased carcass dry weight in the tumour-bearing animals. Despite increased food intake, physical exercise resulted in a reduced final tumour weight without any change in water content. Skeletal and cardiac muscle tissue did not show any difference in water content but there was an increased RNA/protein quotient in the exercising tumour-bearing animals. Thus the deleterious alterations induced by the malignancy on tumour host metabolism are not inevitable but can be modified by spontaneous physical exercise.
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INTRODUCTION

EARLY EXPERIMENTAL studies showed beneficial effects of physical exercise on tumour growth [1–3] but effects on tumour host metabolism were not evaluated. It is not known whether the effects of physical exercise on tumour host metabolism are primary metabolic events, or secondary to an effect on tumour growth itself. Superimposed on these effects is the changed motor activity that has been noted in experimental tumour models [4]. Experimental studies of the effect of physical exercise on metabolism often include forced exercise to standardise the experiment and the amount of activity [5]. This might increase stress with subsequent neuroendocrine changes compared with spontaneous activity. Promotion of experimental tumour growth as a result of stress has been described [6, 7], as have adverse effects on skeletal muscle metabolism in man [8] and in rodents [9, 10].

In view of the possibly negative side-effects of forced physical activity on the metabolism of the tumour host and/or the tumour

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growth, it is important to study the effects of spontaneous physical exercise. This was done with an experimental model in which tumour-bearing and control rats had free access to a treadmill. The aim of the study was to evaluate whether spontaneous physical exercise delays the onset and reduces the extent of cancer anorexia and cachexia. Whether tumour growth could be influenced by spontaneous physical exercise was also investigated.

MATERIALS AND METHODS

Female Wistar Furth rats were used. All experiments were done in growing animals, which were matched in study and control groups by body weight. The animals were divided into four groups in each experiment: tumour-bearing exercising animals (TBE), tumour-bearing sedentary animals (TBS), non-tumour-bearing exercising animals (CE) and non-tumour-bearing sedentary animals (CS). After adaption in separate cages, implantation or sham operation was performed under ether anaesthesia with a trocar. The animals in each tumour group were implanted with a transplantable Leydig cell tumour (LTW) or with a transplantable nitrosoguanidine-induced adenocarcinoma (NGW) subcutaneously in each flank [11, 12]. The tumours neither metastasise nor penetrate adjacent tissues. 2 × 1.0 mm^3 of viable tumour tissue was implanted while controls received the same volume of saline.

The experiments were done according to three different protocols: (1) implantation or sham operation with LTW after 4 days of adaption to the cages and killing 32 days later (LTW 32); (2) the same as (1), but implantation was done after an "adaption/training" period of 24 days (LTW 56); and (3) implantation or sham operation with NGW after 4 days of adaption to the cages and killing 24 days later (NGW). The animals allocated to exercise in each experiment were individually housed in cages open to a freely-moving non-motorised running wheel with a diameter of 33 cm. The other animals were individually housed in standard cages with approximately the same area and volume. All animals had free access to a balanced diet (EWOS—ALAB) and tap water. the room temperature was 22 (s.o.1)°C and the light/dark cycle was 12/12 h. Body weight and food intake were recorded every fourth day and calculated per day while distance run (expressed as revolutions of the wheel) was recorded daily. This experimental model was approved of by the Ethical Committee of the University of Göteborg.

On day 24 or 32, respectively, after tumour implantation, all animals were sacrificed. They were anaesthetised with sodium pentobarbital intraperitoneally (50 mg/kg) before being killed. The tumours were dissected free, measured and weighed. In animals where body composition was not measured, the gastrocnemius muscles were dissected free; the left muscle was immediately frozen in liquid N_2 while the right muscle was weighed dry. The heart was dissected free, weighed and one portion was immediately frozen in liquid N_2 while another portion was weighed dry. The liver and the spleen were dissected free, weighed and samples were weighed dry.

Body composition was measured as described [13]. The animals were killed and the tumours were dissected free. The viscera were exposed. The entire animal and the tumour were weighed. The gastrointestinal tract was not opened, to include the gastrointestinal content in the whole-body pool of substrates. The animals and the tumours were dried at 80°C to constant weight. Dry weight was measured and the water content was calculated. The carcass (the animal minus the tumour) and the tumours were subjected to extraction of lipids which were measured by weighing. Lipids were extracted sequentially in chloroform/methanol (1/1), in ethanol/acetone (1/1) and finally in pure ether. Different lipid fractions were pooled and the organic solvents were removed by drying under N_2. Fat-free dry weight was assumed to be proportional to tissue proteins [14].

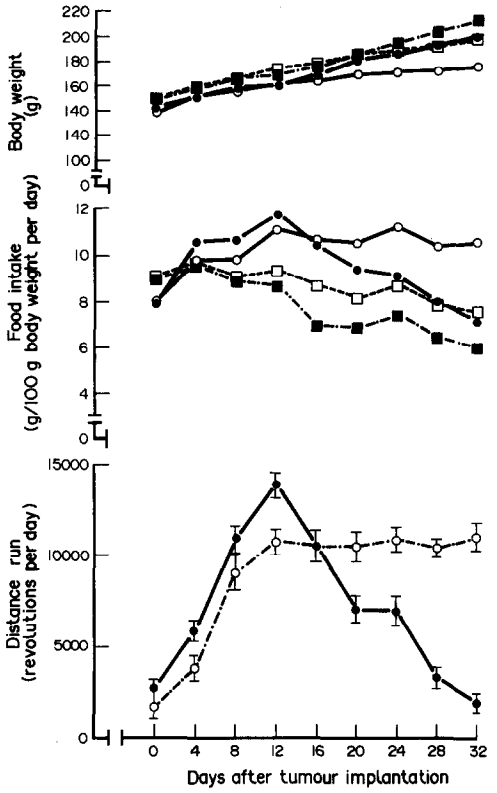

Fig. 1. Body weight, food intake and running distance in protocol LTW 32. 10 rats per group. ● = TBE, ○ = CE, ■ = TBS and □ = CS.

The protein content was assayed according to Lowry *et al.* [15] and the RNA content was measured with the method originally described by Schmidt and Thannhauser [16] and modified by Munro and Fleck [17].

All variables were analysed as multivariate data. Analysis of variance (ANOVA) factorial measurement and the Mann–Whitney *U* test were used.

RESULTS

Body weight

In protocols LTW 32 and NGW there were no differences between the TBE and TBS groups in total body weight, or total body weight minus tumour weight, throughout the experiment. There was a significant difference between the CE and CS group from day 12 after implantation in both LTW protocols. In protocol LTW 56 (i.e. the animals were trained before tumour implantation) both body weight and body weight minus the tumour weight in the TBE group showed a significantly reduced increase compared with the TBS group (Figs 1–3 and Table 1).

Food intake

In all experiments, both groups of exercising animals had a significantly increased food intake compared with sedentary controls after the 4th day of the experiment (Figs 1–3). The

TBE animals had a significantly increased food intake until day 28 in all experiments (i.e. until the onset of late cachexia). These rats even had almost the same or an increased food intake per day compared with the CS group until the onset of late cachexia and the cumulated food intake remained significantly increased compared with the TS rats throughout the experiment (Figs 1–3).

Organ weights and water content

TBE animals in the LTW 32 and the NGW experiments maintained their cardiac mass compared with their sedentary controls (Table 2). The opposite was found for cardiac mass with the LTW 56 protocol. Liver and spleen weights were increased in the tumour-bearing animals in all experiments but this increase was smaller in the LTW 56 experiments. Water content in cardiac or skeletal muscle were significantly different between the groups in the LTW 56 experiments only.

Body composition

Total body weight minus tumour weight at the end of the experiments was lower in both groups of tumour-bearing animals compared with total body weight in non-tumour-bearers and the lowest values were recorded for TBE rats (Table 1). The dry body weight in the TBE animals was lower compared with that of the TBS animals (Table 3). There was also a tendency towards a lower lipid content in the TBE animals and the carcass weight minus the lipid content was higher compared with the TBS controls. The dry body weight minus the lipid content in the TBE rats at the end of the experiment was not statistically different from that of the CE animals, while there was a difference between the sedentary tumour-bearers and the exercising non-tumour-bearers.

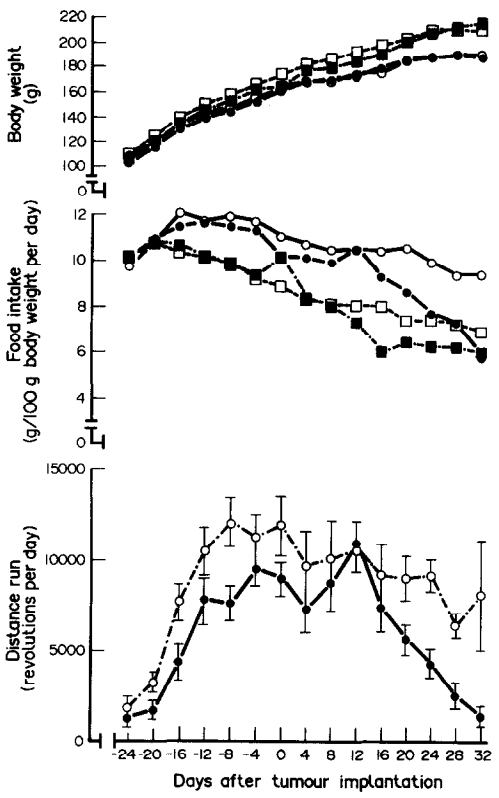

Fig. 2. Body weight, food intake and running distance in protocol LTW 56.

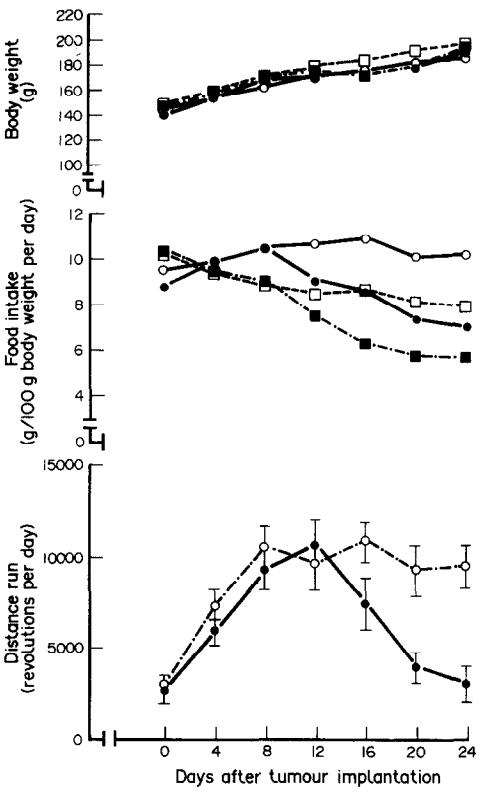

Fig. 3. Body weight, food intake and running distance in protocol NGW.

Tumour weight

Lower tumour weights relative to body weight were recorded in the exercising groups in all experiments but a statistically significant difference was reached only in the LTW 32 experiments (Table 4). The water content of the tumours was not different between the groups.

Physical activity and behaviour

The distance run is shown in Figs 1–3. Each revolution of wheel is equivalent to approximately 1 m. There were wide

Table 1. Carcass weight

Protocol	Group	Total body weight − tumour weight (g)
LTW 32	TBE	184.1 (3.4)
	TBS	191.5 (4.8)
	CE	179.1 (2.9)*
	CS	201.2 (3.2)
LTW 56	TBE	178.3 (5.5)†‡
	TBS	199.8 (5.3)
	CE	191.8 (4.8)
	CS	212.1 (3.7)
NGW	TBE	169.3 (3.0)†
	TBS	168.7 (2.6)
	CE	193.1 (4.5)
	CS	199.4 (3.8)

10 rats per group.
Significant difference between group within protocol, $P < 0.05$. * CE vs. CS, † TBE vs. CS and ‡ TBE vs. TBS.

Table 2. Organ weights relative to body weight, and water content

Protocol	Group	Liver		Spleen		Heart		Skeletal muscle
		Wet weight/total body weight (%)	Water content (%)	Wet weight/total body weight (%)	Water content (%)	Wet weight/total body weight (%)	Water content (%)	Water content (%)
LTW 32	TBE (n=6)	5.4 (0.1)*†	73.5 (0.6)*	0.44 (0.02)*†	77.9 (0.3)	0.44 (0.01)†‖	77.6 (0.7)	77.1 (0.1)
	TBS (n=5)	5.5 (0.2)‡§	72.0 (0.9)	0.41 (0.01)‡§	77.6 (0.5)	0.39 (0.01)‡	77.4 (0.5)	76.9 (0.8)
	CE (n=6)	4.2 (0.1)	70.3 (0.5)	0.25 (0.01)	77.1 (0.3)	0.46 (0.01)¶	76.3 (0.8)	76.0 (0.4)
	CS (n=5)	4.2 (0.1)	70.4 (0.8)	0.27 (0.01)	76.9 (0.4)	0.38 (0.01)	75.3 (0.9)	75.9 (0.6)
LTW 56	TBE (n=5)	4.6 (0.1)*†	70.1 (1.1)‖	0.41 (0.01)*†	78.6 (0.5)†	0.41 (0.01)†	80.9 (2.8)*	76.9 (0.5)*†
	TBS (n=5)	4.9 (0.2)‡§	72.8 (0.7)‡§	0.41 (0.03)‡§	77.9 (0.4)§	0.41 (0.03)	78.4 (0.9)	76.3 (0.1)‡§
	CE (n=5)	4.0 (0.1)¶	69.6 (0.4)	0.41 (0.01)	77.2 (0.7)	0.41 (0.01)¶	77.0 (0.3)	75.7 (0.4)
	CS (n=5)	3.7 (0.1)	69.3 (0.7)	0.36 (0.01)	75.7 (0.7)	0.36 (0.01)	76.8 (0.4)	74.7 (0.2)
NGW	TBE (n=5)	4.9 (0.1)*†	73.9 (2.2)	0.62 (0.05)*†	77.3 (0.8)‖	0.36 (0.01)*	78.6 (0.6)	77.1 (0.8)
	TBS (n=5)	5.0 (0.1)‡§	70.0 (3.1)	0.70 (0.07)‡§	79.7 (1.1)‡	0.34 (0.01)‡§	78.0 (0.4)	76.1 (0.6)
	CE (n=5)	3.7 (0.1)	70.9 (0.5)	0.24 (0.01)	77.3 (0.2)¶	0.41 (0.01)¶	77.7 (0.1)	76.5 (0.5)
	CS (n=5)	3.8 (0.1)	72.8 (0.7)	0.25 (0.01)	78.4 (0.3)	0.37 (0.01)	77.8 (0.3)	76.4 (0.7)

Significant difference between groups within protocol, $P < 0.05$. * TBE vs. CE, † TBE vs. CS, ‡ TBS vs. CE, § TBS vs. CS, ‖ TBE vs. TBS and ¶ CE vs. CS.

variations within the groups, but each animal showed only minor variations from one period to another. With the LTW 32 and NGW protocols, there was a significant difference between the groups from day 16 onwards, but this difference was not seen until day 20 in the animals trained before tumour implantation (LTW 56). A constant finding in the LTW 32 experiments was an unexpected and early increase in distance run daily (and cumulated) in the first part of the experiment for TBE compared with CE rats. This overshoot was not found in the LTW 56 or the NGW experiments. Throughout the experiments, 80% or more of the distance was run during the dark cycle. Another finding was a clear difference in grooming behaviour and gross appearance between the exercising animals and their respective control groups after 8–12 days of exercise. In view of the increased food intake as early as the 4th day of the experiment, subtle changes in behaviour might be detected much earlier. These differences in behaviour between the TBE and the TBS animals remained until the onset of late cachexia (i.e. approximately the last 4 days of the experiments).

Table 3. Body composition in protocol LTW 32

Group	Total body weight − tumour weight (g)	Lipid content (g)	Dry weight (g)	Dry weight − lipid content (g)
TBE	130 (11)	4.6 (0.8)	35.2 (3.5)	30.6 (2.9)
TBS	114 (11)*†	5.1 (0.9)	32.7 (3.5)†	27.6 (2.6)*
CE	146 (3)	6.0 (0.5)	41.0 (1.0)‡	35.0 (1.2)
CS	156 (5)	6.9 (0.9)	48.0 (3.3)	41.1 (4.1)

5 rats per group.
Significant difference between groups, $P < 0.05$: * TBS vs. CE, † TBS vs. CS and ‡ CE vs. CS.

Table 4. Tumour weight relative to body weight

Protocol	Group	Weight/total body weight (− tumour) (%)
LTW 32	TBE	11.1 (2.0)*
	TBS	17.7 (1.6)
LTW 56	TBE	5.7 (0.8)
	TBS	8.9 (1.6)
NGW	TBE	14.0 (2.7)
	TBS	21.5 (5.1)

10 rats per group.
Significant difference: TBE vs. TBS, $P < 0.05$.

Protein and RNA content

The RNA/protein quotient was increased in skeletal muscle from TBE animals compared with their sedentary controls (Table 5). The same was found in cardiac tissue, except in the NGW experiments. In addition to an increase in the RNA content this increased quotient was due to a slightly decreased protein content in some of the animals (data not shown).

DISCUSSION

Physical activity may be an important contributing factor in many types of cancer such as colon [18, 19] and breast cancer [20]. Our experimental model was different from most of the animal models previously described, which usually included forced exercise to standardise the procedure. This difference might be important, since stress has been related to both the cell-mediated [6, 21] and the humoral immune system [22]. An increase in tumour frequency and progression has been reported in stressed animals [6], which contrasts with studies showing beneficial effects of physical exercise in such conditions [1–3, 5, 23]. Furthermore, forced exercise may have negative effects on skeletal muscle metabolism [8–10] and this effect may be added

Table 5. RNA/protein quotients

Protocol	Group	Skeletal muscle RNA/protein (mg/g)		Heart RNA/protein (mg/g)	
LTW 32	TBE	7.7	(1.9)*	17.8	(1.4)*‡
	TBS	6.1	(0.6)	12.7	(0.6)
	CE	16.7	(2.5)	23.1	(1.1)
	CS	14.7	(1.2)	12.0	(1.0)
LTW 56	TBE	10.8	(0.5)‡	15.3	(1.3)
	TBS	7.3	(0.8)	13.3	(1.1)
	CE	12.6	(1.6)	13.9	(1.0)
	CS	8.5	(0.7)	11.5	(0.7)
NGW	TBE	14.2	(1.6)†‡	12.6	(0.6)
	TBS	4.2	(0.7)	13.7	(1.4)
	CE	17.6	(4.4)	12.8	(0.5)
	CS	9.0	(0.6)	19.8	(1.7)

5 rats per group.
Significant difference between groups within protocol, $P < 0.05$;
* TBE vs. CE, † TBE vs. CS and ‡ TBE vs. TBS.

to the negative effects of the tumour on tumour host metabolism [24, 25]. This might be important, as one of the most prominent findings in the tumour host metabolism is extensive wasting of skeletal muscle [25]. With a semi-voluntary work load, Norton *et al.* demonstrated uniform hypertrophy in skeletal muscle from tenotomised limbs in tumour-bearing and non-tumour-bearing rats, which indicates the possibility of preserving skeletal muscle mass [26]. These animals had to stand on their operated hind-limbs to reach the water bottle and therefore some stress cannot be ruled out. Furthermore, anorexia and level of activity were not recorded. With forced exercise, Deuster *et al.* found an increased rate of protein synthesis and a decreased rate of protein degradation in skeletal muscle in tumour-bearing animals [5]. These results are in some aspects in accord with our findings despite different protocols.

In our study all animals allowed spontaneous physical exercise showed a relatively constant running distance from one day to another after a few days of adaption (Figs 1–3). Thus the training was fairly standardised since the results were similar for both types of transplantable tumour and with two types of training. The results differ from those of Deuster *et al.* [5] in some important aspects: (1) exercised tumour-bearing animals consumed equal amounts of food or even more compared with sedentary controls until the onset of late cachexia; (2) there was no significant difference between the tumour-bearing groups in total body weight during the experiment; and (3) the tumour-bearing animals ran the same distance as their non-tumour-bearing controls until the onset of cachexia. A constant finding in the experiments with the LTW tumour without training before implantation was the overshoot in the distance that was run by the tumour-bearing animals compared with their non-tumour controls during the first third of the experiment. This finding has not been described before. The reason for this increase in distance run may be an early change in the neuroendocrine response associated with malignancy. Some of the differences between the models might depend on differences between male and female rats. Deuster *et al.* studied male rats during exercise while we studied female rats. Differences between the sexes during physical exercise have been evaluated by Applegate *et al.* [27] and Tokuyama *et al.* [28]. There are differences between the sexes in the behaviour associated with physical exercise, but the importance is difficult to evaluate since the results from different protocols are contradictory.

The experiments with tumour implantation after training for 24 days were done to establish whether training would make the tumour-bearers better able to withstand the negative effects of the tumour on the host metabolism. Total body weight, distance run and food intake showed a similar pattern as in the other experiments but the exercised tumour-bearers were not able to preserve their body mass to the same extent compared with their sedentary controls in the other experiments. These results are unexpected since epidemiological studies in man [18–20] and experimental studies in rodents [1–3] have shown a negative effect for carcinogenesis and several experimental studies (including this study) have shown beneficial effects on tumour host metabolism from physical exercise [5, 24, 26].

Do the metabolic demands associated with physical exercise counteract those associated with the tumour? In the present study, food intake was significantly increased in the tumour-bearing exercised animals until the last 4 days in the LTW experiments, but remained significantly different throughout the experiment in the NGW series. In each protocol a significant difference remained for cumulated food intake between exercised and sedentary controls. Furthermore total body weights of the exercising animals were slightly lower (but not significantly different) throughout the experiments. These results indicate that in the first half of the experiments (i.e. until tumour weight had reached a few grams) the anabolic effects of physical exercise had priority. This beneficial effect was gradually reversed in parallel to tumour growth, and in the last part of the experiments it was evident that the negative metabolic effects of tumour growth had priority. The early beneficial effects of physical exercise are underlined by the fact that the exercising tumour bearers were able to run despite tumour growth and their behaviour and gross appearance were more like the exercising non-tumour-bearers than the sedentary tumour-bearing controls.

The predominant feature of cancer cachexia is a progressive wasting of skeletal and cardiac muscle [24, 25, 29]. During exercise and for some time after, protein synthesis is decreased and protein degradation is increased [8–10] and at some point following exercise these effects are reversed, causing increased muscle mass. The time course of these events is unclear but the intensity and frequency of training are critical [8]. In our pilot studies (unpublished) we found a maintained content of RNA but decreased protein content in skeletal muscle in exercising tumour-bearing animals compared with sedentary tumour bearers with final cachexia. These findings contradict the present results in which cachexia was not so severe. The increased RNA/protein quotients were due to an increase in RNA content and/or a slight decrease in protein content, which indicates possible increased protein turnover. In more severe cachexia, the significantly decreased protein content in skeletal muscle might reflect an inability to meet the demands of protein breakdown for fuel substrate in combination with the influence of the tumour on the host metabolism. This might finally cause an even more extreme degree of cachexia in exercising animals.

Our findings on body composition indicate the possibility of preserving body mass in the tumour-bearing animals subjected to exercise. Since protein is the dominant portion of the carcass weight, the increased dry carcass weight in the exercising tumour-bearing group reflected an important ability to delay

the onset of more dramatic cachexia. The reduced lipid content in the exercising groups was consistent with previous findings in animal models [27].

The relative tumour weights were reduced in the exercised animals in all series but a significant difference was reached only in the LTW 32 series. Several studies have shown that substrate availability is the most important factor for tumour growth [29–31]. Efforts to improve the nutritional status of the tumour host always include the risk of "feeding the tumour" [32]. Therefore, our findings were remarkable since food intake was increased without subsequent increase in tumour growth in most of our experiments. However, in previous experiments in which animals were followed to late and severe cachexia, this difference disappeared during the last few days and the exercised animals had an increased relative tumour burden instead. This finding indicates a beneficial effect of physical exercise on tumour host metabolism until a certain stage in the tumour progress had been reached.

The clinical implication of these experiments is difficult to delineate until a more detailed evaluation of tumour host metabolism has been done in an experimental setting. Our findings indicated that spontaneous physical exercise might be beneficial until a certain stage in the progressive disease has been reached, but after this point exercise might cause more harm than good.

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