Evidence that long-term COX-treatment improves energy homeostasis and body composition in cancer patients with progressive cachexia

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Abstract. Cancer patients lose weight due to negative energy balance because of insufficient appetite and inappropriately high energy expenditure. Host and tumor derived cytokines and more recently eicosanoids have been held responsible as mediators. Accordingly, observations in animal experiments and short-term clinical trials in selected groups of cancer patients, have implied that cyclo-oxygenase (COX) blockade can improve host metabolism and well-being, and long-term COX-treatment of unselected groups have implied improved survival. The aim of this study was to search for evidence that long-term COX-treatment improves energy and cardiovascular homeostasis in unselected weight-losing cancer patients. A retrospective case control analysis was performed on a data-base material collected consecutively. Weight-losing untreated cancer patients had elevated resting energy expenditure compared to undernourished non-cancer patients (23.3±0.1, n=702 vs 20.9±0.3 kcal/kg/day, n=132, $p<0.001$). This difference became significantly reduced by long-term indomethacin treatment ($p<0.003$). Heart rate was correspondingly decreased, while systolic blood pressure increased following indomethacin treatment of cancer patients ($p<0.006$-0.008). Total body fat was more preserved ($p<0.005$), while lean body mass was uninfluenced by long-term indomethacin to cancer patients. All these beneficial effects were parallel to a decrease in systemic inflammation (C-reactive protein, erythrocyte sedimentation rate) in cancer patients on indomethacin ($p<0.0004$). Systemic inflammation and resting energy metabolism predicted weight loss in progressive cancer ($p<0.0001$). Our data support the concept that COX-treatment may offer beneficial metabolic effects to weight-losing cancer patients by attenuation of resting metabolism and improved appetite due to decreased systemic inflammation.

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Introduction

Mechanisms behind weight loss in patients with progressive cancer are still unclear, although elevated resting metabolism is a significant factor in some weight-losing cancer patients (1-7). Recently, we evaluated anorexia to explain weight-loss in cancer, since it is acknowledged as a significant factor behind cancer cachexia (8). Unexpectedly our results revealed that a substantial number of weight-losing cancer patients did not suffer from anorexia, accounting for changes in body weight, body composition and resting expenditure. Thus, most of the patients had elevated resting energy expenditure, although a corresponding increase in food intake was lacking to compensate for the appearing negative energy balance and for maintenance of body weight. Therefore, rather than being truly anorectic, it appeared that a substantial number of weight-losing cancer patients had lost the tight coupling between food intake and energy expenditure, as normally occurs in healthy individuals. Thus, early prevention of an appearing increased energy expenditure would attenuate progression of cachexia in cancer patients and thereby protect body composition and function. Therefore, it would be rewarding to look for evidence that provision of long-term anti-inflammatory treatment to unselected groups of cancer patients would improve energy imbalance as suggested by previous short-term studies with ibuprofen to patients with progressive gastrointestinal cancer (9,10). Accordingly, the aim of this analysis was to search for database evidence that long-term indomethacin treatment (COX1/COX-2) is associated with beneficial effects in energy homeostasis, cardiovascular activity and body composition in cohorts of unselected weight-losing cancer patients.

Materials and methods

Patients. In our database on 1332 patients we found 702 cases with cancer (age 67±12 years mean ± SD, range 30-86 years) who were subjected to measurements of nutritional state and energy metabolism in their resting state (during 1983-1999 at the Department of Surgery, Sahlgrenska University Hospital, Göteborg, Sweden). In a computer run for matched controls, 132 non-cancer patients were identified when selected according to time period (1983-1999), age

Table I. The number of cancer patients according to major clinical and histological classifications.[a]

	No.	%
Colorectal carcinoma	145	21
Pancreatic carcinoma	165	23
G-I carcinomas	190	28
Liver, biliary carcinoma	110	15
Breast carcinoma	6	<1
Head and neck carcinomas	7	<1
Lung carcinoma	3	<1
Melanoma	22	3
Kidney and urinary bladder carcinoma	10	1
Testicular carcinoma	15	2
Prostatic carcinoma	7	<1
Others[b]	22	6
Total	702	100

[a]All patients had generalized disease. [b]Unknown origin, sarcomas.

(30-86 years) and diagnosis (cancer vs non-cancer with diagnoses as shown in Table I). These non-cancer controls (age 65±11 years) had chronic gastrointestinal disease as dyspepsia or chronic pancreatitis (n=54), gastritis (n=13), inflammatory bowel disease (n=40) and miscellaneous diagnoses (hernia, claudication, etc. n=25). The non-cancer patients, who represented a larger group compared to our previous reports, had weight loss and malnutrition comparable to the cancer patients (1).

In a second computer run, weight-losing cancer patients (n=299) on repeated examinations during 1-24 months follow-up were identified. Of these, 151 cancer patients had been treated with indomethacin and 145 matched cancer patients had no indomethacin or any other NSAID treatment. Criteria for indomethacin treatment were thus palliative or adjunct to analgesics (11). Compliance to medication was validated in all subjects by interview at follow-up. All cancer patients had generalized malignant disease (stage IV) with solid tumor type, where other efficient tumor treatment was not available. Thus, current patients have had no specific tumor treatment in preceding 4-6 months to our investigations, and none of the patients received radio- or chemotherapy during remaining survival according to strict indications for such treatments at our institution. Thus, prescribed medication of indomethacin was symptomatic only, without any other systematic difference in medication. None of the patients had steroids. Pre-investigative expected survival had been deemed at least 6 months or more for all cancer patients on follow-up. On average, all patient groups had lost 8-10% of their pre-illness body weight at inclusion. Gastrointestinal tumors were predominant.

The dose of indomethacin relates to previous results on drug efficacy (11). Indomethacin treatment continued until death or until the patients were unable or unwilling to take the medication. Four patients appeared to have water retention, which was manageable by dose reduction to 25 mg x 2. No patients appeared to have clinically significant gastrointestinal bleeding due to NSAID medication. Palliative unspecific COX-treatment was thus introduced at our institution before COX-2 compounds were available, and remains a main

Table II. Resting energy expenditure at admission in consecutive cancer and non-cancer patients with progressive disease and before institution of indomethacin.

	Resting energy expenditure		
	kcal/kg/day	kcal/m^2/body surface area	kcal/kg LBM/day
Cancer	23.3±0.1[a] (702)	859±5[a] (700)	33.4±0.3 (380)
Non-cancer	20.6±0.3 (132)	775±10 (132)	34.1±0.9 (20)

Mean ± SE, number of patients within parenthesis. [a]p<0.0001 vs non-cancer.

Table III. Metabolic and circulatory activity in cancer patients treated with indomethacin during follow-up compared to cancer patients without indomethacin.

	Cancer + indomethacin	Cancer	p-value
REE (kcal/kg/day)	22.2±0.2	23.2±0.2	<0.003
REE (kcal/kg LBM/day)	32.8±0.3	32.1±0.4	ns
Carbohydrate oxidation (g/kg/day)	1.40±0.06	1.53±0.10	ns
Fat oxidation (g/kg/day)	1.39±0.04	1.33±0.05	ns
RQ (respiratory quotient)	0.80±0.006	0.80±0.005	ns
Heart rate (beats/min)	68±1	74±2	<0.006
Systolic blood pressure (mm Hg)	136±2	130±2	<0.009
Diastolic blood pressure (mm Hg)	76±1	75±1	ns

Mean ± SE. ANOVA with survival time as covariate was used for the statistical computation. Patients at risk: 1-6, 7-12, >12 months; cancer + indo: 151, 88, 60; cancer: 145, 30, 5, respectively.

Table IV. Body composition in cancer patients treated with indomethacin during follow-up compared to cancer patients without indomethacin.

	Cancer + indomethacin	Cancer	p-value
Food intake (Kcal)	1890±32	1679±49	<0.0006
Body fat (kg)	18.8±0.6	14.5±0.6	<0.005
Lean body mass (kg)	46.6±0.7	47.7±1.0	ns
Bone mineral content (g)	2563±41	2529±63	ns
Body weight (kg)	69.1±0.9	64.0±0.9	<0.05

Mean ± SE. ANOVA with survival time as covariate was used for the statistical computation. Patients at risk: 1-6, 7-12, >12 months; cancer + indo: 108, 74, 56; cancer, 40, 32, 5, respectively.

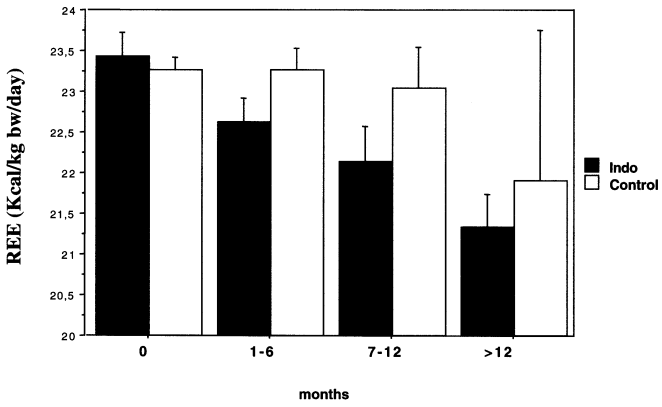

Figure 1. Resting energy expenditure in weight-losing cancer patients on indomethacin (1-24 months) compared to untreated cancer controls with survival in months as covariate; p<0.003. Patients at risk are indicated in Table III.

Table V. Biochemical tests in cancer patients treated with indomethacin during follow-up compared to cancer patients without indomethacin.

	Cancer + indomethacin	Cancer	p-value
Serum albumin (g/l)	35±0.3	37±0.5	ns
Hb (g/l)	122±1	124±1	ns
ESR (mm/h)	32±1	50±4	<0.0001
CRP (mg/l)	31±2	61±4	<0.0004
ASAT µcat/l	0.69±0.05	0.57±0.03	ns
ALAT µcat/l	0.56±0.03	0.53±0.03	ns
ALP µcat/l	7.5±0.4	6.4±0.4	ns
Bi/s µcat/l	13±1	13±1	ns
Creatinine/s (µmol/l)	104±2	95±2	<0.001

Mean ± SE. ANOVA with survival time as covariate was used for the statistical computation. Patients at risk: 1-6, 7-12, >12 months; cancer + indo: 147, 90, 69; cancer: 144, 32, 5, respectively. Hb, hemoglobin concentration; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASAT, asparate amino transferase; ALAT, alanine amino transferase; ALP, alkaline phosphatase; Bi, bilirubin.

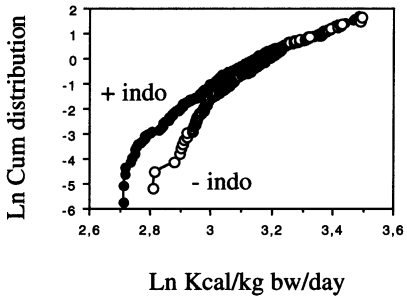

Figure 2. Cumulative distribution of REE in weight-losing cancer patients (702) treated with (151) and without (145) indomethacin during 1-24 months follow-up (p<0.04).

alternative since experimental studies suggest that some effects by indomethacin may not be entirely COX-2 mediated (12,13). Patients at risk during 1-24 months follow-up are indicated in legends to Tables III-V.

Energy expenditure. Resting energy expenditure (REE) was measured for 30-45 min in the morning after an overnight fast, 8-9 a.m. or between 10-11.30 a.m. by means of indirect calorimetry (Deltatrac, Datex, Helsinki, Finland) performed in the supine position according to standard criteria (respiratory hood technique) as described elsewhere (1,3,14).

Dietary intake. Patients had been instructed by a team dietician to complete a 4-day food record at home. The amount of all food and beverages consumed were recorded in household measures. Details and validation of the methods have been described elsewhere (8).

Antropometry. Body weight was recorded in light indoor clothing on a digital electronic scale. Habitual weight before the onset of disease was registered. Weight loss is given as per cent of habitual body weight. Body height in cm. Body composition was measured by the dual-energy X-ray absorptiometry (DEXA) as described elsewhere (15).

Blood tests as serum albumin, blood hemoglobin, erythrocyte sedimentation rate, C-reactive protein, liver function tests (ASAT, ALAT, ALP, serum bilirubin) and serum creatinine were routine hospital tests determined at the occasions of energy expenditure measurements.

Statistics. The design and analyses followed principles for case-control studies (16). Results are presented as mean ± SEM. Factorial ANOVA was used for direct group comparisons (Table II). Differences between groups over time were either tested by ANOVA with follow-up time (months) and survival (months) as covariates (Figs. 1 and 3-5), or by the Kaplan-

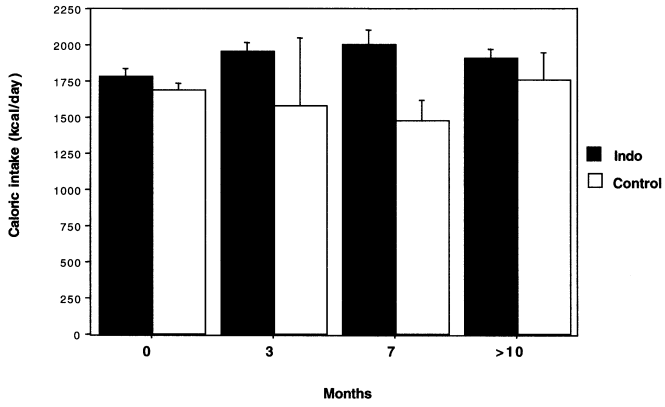

Figure 3. Daily food intake in weight-losing cancer patients on indomethacin (1-24 months) compared to untreated cancer controls with survival in months as covariate; p<0.0006. Patients at risk are indicated in Table IV.

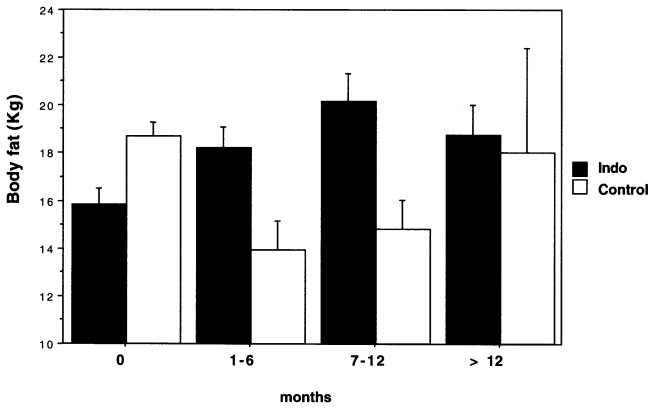

Figure 4. Whole body fat in weight-losing cancer patients on indomethacin (1-24 months) compared to untreated cancer controls with survival in months as covariate; p<0.005. Patients at risk are indicated in Table IV.

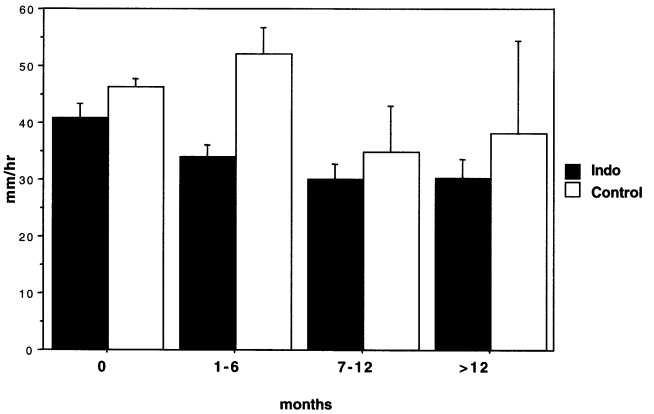

Figure 5. Erythrocyte sedimentation rate in weight-losing cancer patients on indomethacin (1-24 months) compared to untreated cancer controls with survival (months) as covariate; p<0001. Patients at risk are indicated in Table V.

Meier log-rank technique including survival calculations and by a COX proportional model (Fig. 2). Thus, all the statistical evaluations among indomethacin treated and untreated patients were based on simultaneous comparisons of all information of the patients over time. Multiple regression analysis was performed according to standard statistics (Statview® 5.0 Abacus Concepts Inc., Berkeley, CA, 1996) in cancer patients with complete sets of information. $p<0.05$ in two-tailed tests was regarded statistically significant.

Informed consent for measurements and analyses had been obtained from all patients. The Committee for Ethics at the Faculty of Medicine, Göteborg University, approved the treatment protocol.

Results

Energy expenditure in cancer versus non-cancer. Cancer patients were comparable to non-cancer patients with respect to disease duration, nutritional state and background variables based on measurements performed at inclusion, according to previous principles (1). Resting energy expenditure was higher in cancer patients compared to non-cancer patients, but this difference was not observed when resting energy expenditure was related to lean body mass, although the number of observations in non-cancer patients was small (Table II).

Cancer patients on indomethacin. Hundred and fifty-one cancer patients treated with indomethacin during 1-24 months follow-up were identified in the database, and 145 cancer patients of similar age and sex without indomethacin served as matched controls during a 1-18 months follow-up period (Table III). Cancer patients on long-term indomethacin (1-24 months) had significantly lower resting energy expenditure per kg bw compared to untreated cancer patients, particularly patients in the lower range of REE (Figs. 1 and 2). Food intake was significantly higher in indomethacin treated patients (Table IV, Fig. 3). This difference was statistically independent of follow-up time and survival as covariates ($p<0.003$-0.0006). However, no difference occurred in resting metabolism per lean body mass (kcal/kg LBM/day) among indomethacin treated and untreated cancer patients during 1-24 months follow-up (Table III). Cancer patients on indomethacin had significantly lower heart rate and increased systolic blood pressure at rest, while whole body oxidation of substrates was not altered (Table III).

Measurements of body composition with the DEXA technique revealed almost the same bone mineral content among indomethacin treated and untreated cancer patients (Table IV). This suggests that study and control groups were not skewed concerning original body surface area. Indomethacin treated patients had significantly larger body weight, during follow-up explained by more body fat (Fig. 4), while lean body mass was almost the same in the two groups (Table IV). Biochemical blood tests revealed that indomethacin treatment was not associated with abnormal liver function tests (ASAT, ALAT, ALP, Bi/s), while serum creatinine and systolic blood pressure were significantly higher in patients on indomethacin (Tables III and V). Serum albumin and blood hemoglobin concentrations were not different, while inflammatory markers as C-reactive protein

Table VI. Multiple regression analysis with weight loss (%) as dependent variable in weight-losing cancer patients (256) with a complete set of information.

	Coeff.	Std. Error	Std. Coeff.	t-value	p-value
Intercept	48.817	11.788	48.817	4.141	<0.0001
ESR	-0.035	0.026	-0.106	-1.341	0.1811
CRP	0.034	0.013	0.193	2.586	0.0103
HB	-0.103	0.040	-0.180	-2.559	0.0111
REE	-0.009	0.002	-0.249	-4.204	<0.0001
Heart rate	0.082	0.057	0.099	1.445	0.1498
RQ	-20.956	12.137	-0.103	-1.727	0.0855

The regression was significant at p<0.0002; R=0.42. REE, resting energy expenditure, kcal/day; RQ, respiratory quotient.

and erythrocyte sedimentation rate were significantly lower in patients on indomethacin (Table V, Figs. 5 and 6). There was no significant difference in survival among indomethacin treated and untreated cancer patients (data not shown).

Multivariate analyses. Multiple regression analyses were performed with weight loss (%) and resting energy expenditure (kcal/day) as dependent variables in cancer patients with complete information. These computations revealed that C-reactive protein, blood hemoglobin concentration, energy expenditure (p<0.0001), and respiratory quotient (p<0.09) were significant or borderline predictors of weight loss (%)

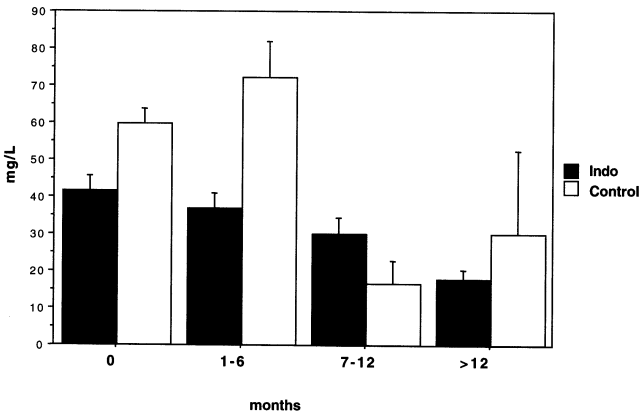

Figure 6. C-reactive protein in unselected cancer patients on indomethacin (1-24 months) compared to weight-losing cancer controls with survival as covariate; p<0.0004. Patients at risk are indicated in Table V.

(Table VI). The same modeling was also used with resting energy expenditure (REE, kcal/day) as the dependent variable. This analysis showed that lean body mass, total body fat, C-reactive protein and heart rate in the resting state explained the variance in REE in weight-losing cancer patients (Table VII), while lean body mass did not have this power when resting metabolism was expressed as kcal/kg/day (data not shown).

Bivariate regression analyses between weight loss, body fat content, lean body mass and resting energy expenditure among cancer patients with and without indomethacin showed significant correlations (r=0.40-0.50, p<0.001), which implied that indomethacin treatment had its largest impact on body fat and less so on lean tissue (data not shown). Therefore, regression analysis was performed between daily resting energy expenditure and caloric intake (Fig. 7), which indicated different relationships (slopes) between cancer patients on indomethacin compared to untreated cancer patients (p<0.05).

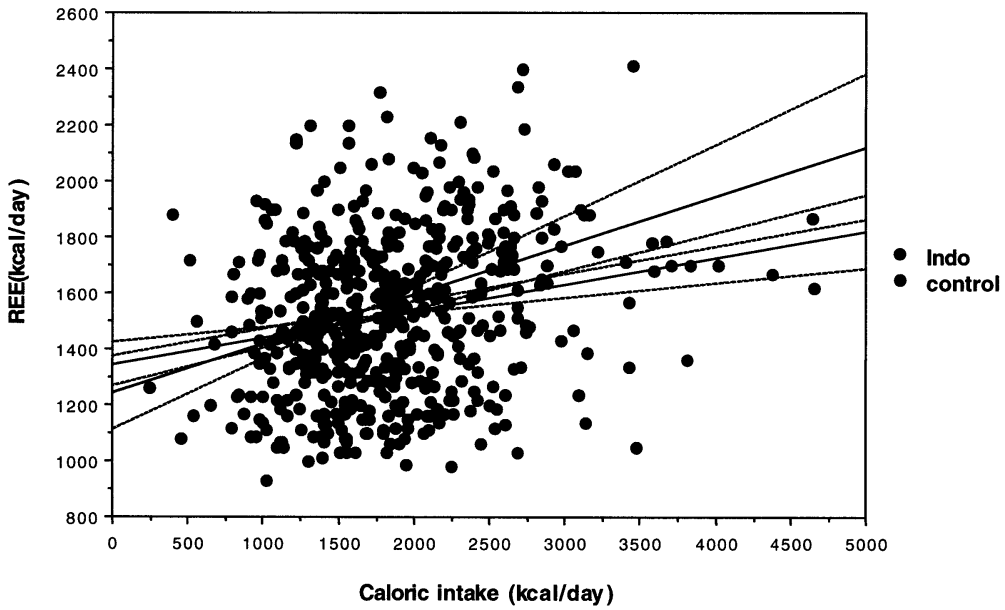

Figure 7. Relationships between resting metabolism (REE) and daily caloric intake in cancer patients with (indo) and without indomethacin (contr) (y=1345+0.095x; p<0.0001; y=1243+0.176x; p<0.001; r=0.30-0.40). The slops (solid lines) were statistically different at p<0.05.

Table VII. Multiple regression analysis with resting energy expenditure (kcal/day) as dependent variable in 157 weight-losing cancer patients with a complete set of information.

	Coeff.	Std. Error	Std. Coeff.	t-value	p-value
Intercept	-76.008	167.449	-76.008	-0.454	0.6506
ESR	-0.330	0.643	-0.030	-0.513	0.6086
CRP	0.878	0.380	0.120	2.313	0.0222
HB	0.386	0.763	0.025	0.506	0.6135
Total body fat	4.308	1.281	0.156	3.363	0.0010
LBM	21.502	1.158	0.814	18.567	<0.001
Heart rate	4.975	1.242	0.189	4.006	0.0001
Syst blood press.	0.623	0.600	0.046	1.037	0.3014

The regression was significant at $p<0.0001$; $R=0.86$. Adjusted R squared 0.73. LBM disappeared as significant when resting expenditure was expressed as kcal/kg/day.

Discussion

This study has evaluated energy expenditure in a larger cohort of cancer patients than presented in any previous report of resting metabolism in unselected weight-losing cancer patients. One of our previous investigations has suggested that anti-inflammatory treatment to cancer patients with progressive disease may prolong survival achieved by agents as either prednisolone or indomethacin, which is a non-selective COX-inhibitor (11). Of these two alternatives, indomethacin is preferred in most cases, since the catabolic effect of prednisolone on muscle and fat tissue may be limited by the use of indomethacin, as supported by the present study, since long-term indomethacin treatment had no differential effect on lean body mass in current patients. The rationale to suggest palliative treatment with COX-inhibitors in cancer is many-fold. First, these drugs are useful complements to analgetics with more central effects. Secondarily, experimental work has demonstrated that some tumors are growing less rapidly in the presence of cyclo-oxygenase inhibitors (17), and energy metabolism as well as appetite control may also be influenced (18), although it is obvious that all these effects are not universal neither in experimental tumors nor in human cancer (17,19). However, the consequences of increased cytokine expression in tumor-bearing hosts, produced either by tumor or host tissues, may be attenuated by cyclo-oxygenase inhibitors (20). Recent information also suggests that indomethacin has direct effects on tumor cells to increase apoptosis and decrease telomerase activity in some murine and human tumors (12,13), effects that may not be entirely related to COX-2 activities (unpublished data). Thus, indomethacin treatment to weight-losing cancer patients may serve beneficial in several aspects as suggested by short-term or acute provision of ibuprofen or fish-oil to patients with gastrointestinal (10) or pancreatic carcinoma (9,21).

It is controversial whether cancer cachexia is most dependent on anorexia or elevated energy expenditure in patients with progressive illness (22). Our recent information points to the possibility that elevated metabolism can be an early event in some patients in whom a tight coupling of food intake to expenditure seems to be lost (8). If so, early weight loss in some cancer patients could be a matter of negative energy balance due to either inappropriate down-regulation of energy expenditure or insufficient up-regulation of appetite in response to inflammation. A variety of speculative mechanisms could explain these uncouplings. Presently, we favor an idea that anorexia in relation to tumor disease involves prostaglandin metabolism in the central nervous system (18), following systemic activation of cytokines outside the brain. Eicosanoids may thus act in the central nervous system to control both homeostasis of temperature and other less explored neuronal activities during stress, a phenomenon that may also include control of food intake in systemic inflammation, more so than brain cytokines (18). Based on this concept, it is of interest to search for evidence that COX-treatment is metabolically beneficial to cancer patients for palliation. The most ideal situation to test this hypothesis would be to randomize weight-losing cancer patients to receive indomethacin compared to placebo treatment, as used by others in short-term treatments (2,9), but detection of alterations in body composition necessitates evaluation of patients on long-term treatment. However, we had not the possibility to adopt a randomized approach in this respect, since a previous placebo controlled study by ourselves has suggested that unspecific COX-treatment prolongs survival in some cancer patients (11) and it appeared that we had the possibility of a retrospective case-control analysis, which is objectively identical to randomized studies. A strength of case-control analyses is the informativeness usually due to relatively large number of patients compared to most experimental studies. However, a case-control analysis is highly sensitive to bias, which may create non-comparability between cases and controls.

Our cohorts of cancer patients with and without indomethacin were not significantly skewed with respect to diagnoses, tumor-stage, malnutrition or any other palliative means as provision of analgesics etc. The only obvious difference was that the majority of patients without indomethacin were recruited before 1992 and those on indomethacin after 1992. Thus, our subgroups of cancer patients were representative for the entire unselected group of patients (n=1302) being referred to our institution for palliation during the past 10-15 years. The fact that resting energy expenditure was the same in the large group of 702 cancer patients at inclusion compared to resting metabolism in the subgroup (145) of untreated patients (subjected to repeated measurements over time) also supports physiologic similarities among the subgroups (Fig. 1). However, it may be of concern that long-term clinical information on the patients who received indomethacin were derived from considerably more individuals (≈45%) compared to those without indomethacin (<10%,

Tables III-V). The most likely explanation to this is that our routines for outpatient care nowadays are more focused on long-term follow-up in all patients. However, all calculations on metabolic variables were done with survival and follow-up time as covariates, which mathematically compensates for a possible bias in this respect.

The present analysis confirms our previous observations that weight-losing cancer patients have significantly (≈11%, $p<0.001$) higher resting energy expenditure per body weight and body surface area compared to non-cancer patients who suffer from mild stress due to systemic and chronic illness leading to wasting (1,2). New information may be that resting metabolism was less different between cancer and non-cancer patients when related to lean body mass, although our previous studies on cancer have indicated higher metabolism per whole body potassium, which sometimes may reflect lean body mass (1). Thus, it remains uncertain to interpret alterations in metabolic rate in parallel to alterations in body composition (23). However, there is no contradiction between increased resting metabolism and a loss of fat compartment. On the contrary, it was most likely that increased metabolism was an integrated part of altered fat metabolism in cancer patients, since resting metabolism was significantly increased on either individual basis, per body weight or body surface area in current cancer patients at admission. Preserved body fat during indomethacin treatment, without a similar decrease in resting metabolism, may thus suggest improved fat balance by increased lipogenesis following significantly higher caloric intake.

The clinical implication of a 10% increase in resting expenditure is equivalent to a metabolic burden corresponding to chronically increased body temperature of 38˚C. Untreated thyrotoxic patients had elevated expenditures by 40±14%, which rapidly caused loss of body weight (24). Thus, previous calculations on energy metabolism have revealed that increased resting expenditure of the magnitude seen in our weight-losing cancer patients should impact on body weight during a 3-6 month period. Our recent report of rapidly increased body weight following normalization of metabolism in hyperthyroidism further supports this physiologic concept (24). It is however important to emphasize that weight-losing cancer patients suffer from a low T3-syndrome and not from elevation in thyroid hormonal activities (25). Therefore, other mechanisms explain inappropriately high metabolism in cancer disease, where both increased glucocorticoid and adrenergic activities are involved (26,27), while pain was not a common inducer (2).

In a previous study we suggested anemia as a promoter of elevated resting metabolism in progressive cancer (1,15). This suggestion was further substantiated, when we demonstrated that treatment with recombinant erythropoietin increased metabolic efficiency and normalized circulatory abnormalities as elevated heart rate, even in the presence of COX-inhibition (15). Anemia was also a predictor of weight loss in the present evaluation, and heart rate was significantly lower in patients on indomethacin. Thus, it is tempting to suggest that anti-inflammatory treatment indicated by significantly lower CRP and erythrocyte sedimentation rate attenuates systemic whole body inflammation, which counteracts effects on circulation to deliver oxygen, a phenomenon which is reflected by lower heart rates, which in part accounts for energy drain in partially starved subjects. Thus, anti-inflammatory treatment in progressive cancer may attenuate a vicious circle promoted by various cascades of cytokines and eicosanoides in part communicated by the classic hormone system. However, not all effects by anti-inflammatory treatment may be beneficial. Serum creatinine was slightly higher in indomethacin treated patients, side effects that are well-known, secondary to reduced kidney blood flow leading to significant elevation in blood pressure. Some patients may also suffer from increased gastro-intestinal bleeding and ulcers, although modern proton pump inhibitors can practically alleviate this risk. Some patients may be sensitive to water retention following NSAID treatment, but this can be compensated for by either early provision of diuretics or dose reductions of NSAID according to our own experience. It is not likely that our results are explained by water retention by indomethacin, since differences in body weight was entirely explained by body fat (Table IV).

Multiple regression analysis confirmed that weight loss in cancer patients was mathematically predicted by inflammatory markers and resting metabolism, where respiratory quotient (RQ) was a borderline factor. This supports previous observations that fat metabolism is elevated in progressive cancer (28-30), although whole body fat oxidation was not different among cancer patients with and without indometacin evaluated by indirect calorimetry. Altered fat metabolism was, however, indirectly evident by lower whole body fat in untreated cancer patients, while significant and simultaneous changes in lean body mass did not occur, which may be discrepant to a report of improved derived lean body mass following fish-oil treatment (21). Our interesting observations were also supported by the observation that whole body fat and pulse rate remained significant predictors, but not lean body mass when resting metabolism was normalized to body weight (kcal/kg/day). Bivariate analyses on weight loss, body components, resting metabolism and food intake suggested that body fat was more related to effects by indomethacin than lean tissues, and that relationships between food intake and resting metabolism showed different regressions among COX-treated and untreated cancer patients (Fig. 7). The interpretation of this observation is complex and preliminary but illustrates that indomethacin may cause a more favorable energy balance, and that each increment in food intake is accompanied by a lower increase in energy expenditure, which should favor improvements in body composition, particularly fat and carbohydrate storage. These improvements were most likely secondary to decreased systemic inflammation by indomethacin treatment.

In conclusion, this study supports previous studies that unselected weight-losing cancer patients have inappropriately high resting energy expenditure, which seems to be attenuated by COX-inhibition by provision of indomethacin, ibuprofen and fish oils (9,31). New information is that food intake may also respond to COX-treatment. The present results thus support a possibility that cancer induced anorexia involves prostaglandins as concluded from animal experiments (18). It is possible that these effects are related to decreased systemic inflammation confirmed by lower CRP and erythrocyte sedimentation rate. It is also likely that observed metabolic alterations and more preserved body composition are related

to pathways of lipid metabolism, rather than to protein metabolism and lean tissue. It remains an interesting question whether increased whole body oxidation secondarily up-regulates adrenergic and glucocorticoid activities inducing lipolysis; or whether primarily increased stress hormones following systemic inflammation induce lipolysis, which subsequently promotes oxygen consumption by stimulation of ß-oxidation in response to increased uptake of free fatty acids across visceral organs. A more direct prevention of abnormal balance in lipogenesis/lipolysis in weight-losing cancer disease should conceptually be a next logic step to take for attenuation of clinical cachexia. This hypothesis is now under test in a randomized study.

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