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Plasma Fatty Acid Composition in Patients with Pancreatic Cancer: Correlations to Clinical Parameters

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Pancreatic cancer (PC) ranks as the fourth cause of cancer-related deaths in the Czech Republic. Evidence exists that deregulation of fatty acid (FA) metabolism is connected with some malignancies; therefore, we decided to analyze FA profile in plasma lipid classes in patients with PC with relation to tumor staging, nutritional status, and survival. The study included 84 patients (47 males, 37 females) with PC and 68 controls (36 males, 32 females). FA patterns were analyzed in plasma lipid classes by gas-chromatography. We observed increased proportion of total monounsaturated FA (MUFA) in PC group in all plasma lipid classes. These changes were connected with increased Δ9-desaturase (SCD1) and Δ5-desaturase indices. Correlations of dihomo-γ-linolenic acid (DHGLA) with these variables were opposite. Longer survival of patients was connected with higher content of EPA, DHA, and with lower SCD1 index, respectively. Plasma phospholipid proportions of α-linolenic acid, DHGLA, EPA, and n-3 polyunsaturated fatty acids displayed negative trend with tumor staging. Plasma lipid FA pattern in PC patients resulted from decreased dietary fat intake and increased de novo synthesis of FA with transformation into MUFA. Changes in FA profile implicated some pathophysiological mechanisms responsible for disturbed FA metabolism in PC and importance of appropriate nutritional support.

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INTRODUCTION

Pancreatic cancer (PC) is one of the most fatal human malignancies. It ranks as the fourth cause of cancer-related deaths in the United States (1) as well as in the Czech Republic (2). Its incidence varies worldwide with high rates in the United States, Canada, Australia, and Europe. In the Czech Republic, the incidence reached 18.9 per 100,000 inhabitants in men (18.6 in women) in 2009 (2).

Besides age, genetic risk factors, preexisting diseases (chronic pancreatitis, diabetes mellitus, obesity, and other insulin resistance states), several lifestyle and environmental factors have been reported to contribute to the development of PC (3–9). Cigarette smoking, the most well-established environmental risk factor, increases the risk of PC by 25%–30%; 9% is related to diabetes mellitus and 3% to heavy alcohol consumption (8). Dietary factors are supposed to contribute to the risk of PC by 20% (10–12).

There is growing evidence that the deregulation of fatty acid (FA) metabolism is connected with some malignancies similar to cardiovascular disease, metabolic and nutritional disease (such as obesity, diabetes mellitus, and other insulin resistance states) (13). FA composition in plasma phospholipids (PL) and cholesteryl esters (CE) reflects both dietary intake of FA over a 6-wk to 3-mo period as well as endogenous FA metabolism (synthesis of FA de novo, β-oxidation, enzymatic desaturation and elongation, conversion of polyunsaturated FA to eicosanoids, and lipoperoxidation) (14). The de novo biosynthesis of FA is induced in several types of malignant tumors by overexpression of FA synthase (FAS) and stearoyl-CoA desaturase (SCD1). FAS plays a role only in the liver and adipose tissue (15,16) in

healthy subjects, whereas tumor-induced expression and activities of FAS and SCD1 help to sustain the malignant phenotype, survival, and proliferation of cancer cells (16,17).

Several studies proved the association of risk for PC with total fat (18) and saturated FA (18–20) intake. When the saturated and monounsaturated FA were replaced with polyunsaturated FA (PUFA), the risk for PC decreased in obese individuals (21). High intake of n-6 PUFA, especially linoleic acid (LA; 18:2n-6), and the elevated ratio of n-6 PUFA to n-3 PUFA also increased the risk for alimentary tract tumors (colorectal carcinoma, pancreas) and breast and prostate cancer (22). Beneficial effects of n-3 PUFA (ratio n-6 PUFA/n-3 PUFA, respectively) in the risk and progression of several carcinoma were reported in epidemiological studies (22,23). In general, n-6 PUFA enhances tumor growth by supporting tumor proliferation, invasiveness, metastases formation, and apoptosis as well as the reaction of the organism (inflammation, immune responses, and angiogenesis) whereas n-3 PUFA opposes these effects (24).

The aim of the study was to analyze the profile of FA in the main plasma lipid classes: PL, CE, and triacylglycerols (TAG) in relation to tumor staging, nutritional status, and survival in the patients with PC.

MATERIALS AND METHODS

Subjects

The study included 84 patients (47 males/37 females) with PC and mean age of 64.7 ± 9.5 years (mean ± SD) and 68 control subjects (36 males/32 females) with a mean age of 59.3 ± 8.0. The study protocol was approved by the Joint Ethical Committee of the General University Hospital and the 1st Faculty of Medicine, Charles University in Prague. Written informed consent was obtained from each study participant.

The PC group was recruited from the consecutive patients hospitalized at the 4th Department of Internal Medicine between the years of 2008 and 2011. The control group was recruited from the medical staff of the institution and from outpatients with functional gastrointestinal disorders. Both groups of subjects were examined clinically, including an assessment of basic anthropometrical data using standard methods (25). The percentage of body fat was estimated according to the Durnin and Womersley method (26). The 7-day dietary intake was calculated from dietary record using NutriMaster SE software, as described earlier (27). Malnutrition was categorized into the mild, moderate, and severe form according to the Nutritional Risk Index (NRI) (28). The NRI was calculated according to formula: NRI = (1.519 * albumin + 0.417 * current body weight/usual body weight * 100) and the classification was as follows: normal nutrition: NRI > 100; mild malnutrition: NRI, 97.5–100; moderate malnutrition: NRI, 83.0–97.4; severe malnutrition: NRI < 83.0.

The homeostasis model assessment (HOMA) method was used as an index of insulin resistance (IR) (29). Diagnosis of PC was confirmed histologically in all of the patients (based on histological examination of pancreatic resection or endoscopic ultrasonography-guided aspiration cytology). PC staging was performed according to the TNM system and Union Internationale Contre le Cancer with the American Joint Committee on Cancer (UICC/AJCC 2003) (30). Blood samples were taken after 12 h of fasting. Routine biochemical and hematological analyses were performed immediately; samples for special analyses were stored at −80°C until use.

Laboratory Analyses

The routine biochemical parameters were analyzed by conventional methods on automatic analyzers according to standard procedures. The FA patterns in plasma PL, CE, and TAG were analyzed by gas chromatography (31). The molar percentages of FA were used for estimation of desaturase indices, which were calculated as the appropriate product/substrate ratio (see Tables 3 and 4 for details). These can serve as surrogate marker for the activities of the respective enzymes (32). Concentrations of conjugated dienes in precipitated LDL (CD-LDL) were determined spectrophotometrically (33).

Statistical Analysis

The data were processed with STATISTICA® statistical software for Windows. As the patients with PC were older than controls ($P < 0.001$, t-test), other variables were adjusted for age in the case of comparison between the PC vs. control group. The variables were log transformed where appropriate (non-Gaussian distribution of data). For the analyses within the PC group, we used nonparametric tests. $P < 0.05$ was considered to be statistically significant.

RESULTS

Demographic and clinical data of the patients are presented in Table 1. The patients with PC were older ($P < 0.001$, unpaired t-test with estimated variances) than controls and therefore further statistical analyses were performed after the adjustment for age when these 2 groups were compared. The PC group had a lower body mass index (BMI) and body weight. The decrease in weight is caused mainly by adipose tissue loss without changes in its centripetal distribution, as the waist circumference and waist-to-hip ratio remained similar. Nevertheless, the PC group had a higher ratio for subscapularis/triceps skinfold. Patients with PC had, in comparison with control group, the lower intake of total energy (CON vs. PC, 2240 ± 460 vs. 1560 ± 610, mean ± SD in Kcal/day, $P < 0.05$), lower relative intake of fat (CON vs. PC, 35 ± 8 vs. 25 ± 14, mean ± SD in % of total energy intake, NS), lower relative intake of protein (CON vs. PC, 20 ± 7 vs. 14 ± 8, mean ± SD in % of total energy intake, NS), and higher relative intake of saccharides (CON vs. PC, 45 ± 9 vs. 61 ± 18, mean ± SD in % of total energy intake, NS). Moreover, we found decrease in animal fat consumption, but differences were not statistically significant (CON vs. PC, 35 ± 17 vs. 22 ± 12, mean ± SD in g/day), probably because of high variance of variables. The patients with PC had also lower levels

TABLE 1
Demographic and clinical characteristics of studied groups

Characteristic	Control group	Pancreatic cancer	Stage II	Stage III	Stage IV	*P* (trend)[e]
Number of subjects (male/female)	36/32	47/37[b/ N.S.]	7/6	19/17	21/13[b/ N.S.]	
Age at diagnosis (yr)	59.3 ± 8.0[a]	64.7 ± 9.5[c/***]	66.6 (64.8–72.2)[f]	64.6 (56.8–71.8)	63.7 (59.1–70.1)	NS
Duration of symptoms (mo)	n.a.	5.3 ± 6.8	3.5 (2.3–7.5)	3.0 (1.0–6.0)	3.5 (2.0–6.0)	NS
Smoking status[g]						
Nonsmokers	38	24	9	5	10	
Exsmokers	11	28	1	16	11	
Smokers	19	30[b/**]	3	14	12[b/**]	
Diabetes mellitus[g]						
Absent	68	42	7	19	16	
Present <3 yr		23	1	7	15	
Present >3 yr		17	3	10	3[b/*]	
Body mass index (kg/m^2)	27.3 ± 5.4	24.7 ± 4.9**	25.3 (23.0–27.9)	25.1 (20.5–27.5)	23.6 (20.8–27.1)	NS
Nutritional risk index	113 ± 4	96 ± 11**	107 (95–110)	98 (92–103)	98 (86–101)	0.014↓
Fat mass (kg)	21.4 ± 11.5	16.3 ± 7.8*	18.7 (13.6–22.9)	17.0 (11.9–24.1)	13.4 (7.3–17.9)	0.007↓
Lean body mass (kg)	58.9 ± 14.7	53.9 ± 12.7	54.5 (45.7–59.9)	53.0 (45.1–60.7)	53.0 (43.3–61.7)	NS
Midarm circumference (cm)	30.2 ± 3.7	26.6 ± 3.6***	27.3 (26.1–28.4)	27.0 (24.0–29.5)	26.5 (24.5–28.5)	NS
Midarm muscle circumference (cm)	23.4 ± 3.6	22.6 ± 3.4	22.2 (20.6–25.0)	21.7 (20.2–24.8)	23.1 (20.0–24.3)	NS
Waist circumference (cm)	93.6 ± 13.5	92.5 ± 13.9	90 (85–105)	90 (82–101)	93 (85–100)	NS
Waist-to-hip circumference ratio	0.94 ± 0.08	0.95 ± 0.09	0.94 (0.89–1.02)	0.94 (0.88–1.00)	0.96 (0.91–1.01)	NS
Subscapularis to triceps skinfold ratio	1.34 ± 0.64	1.77 ± 0.95***	1.28 (1.01–2.18)	1.53 (1.18–1.97)	1.58 (1.25–2.00)	NS
Weight loss (kg/previous 3 mo)	−0.1 ± 1.1	11.5 ± 8.7***	6.3 (1.2–10.0)	9.4 (6.0–19.0)	14.5 (7.0–16.5)	0.022↑

Fat mass was calculated from % of fat mass (according to Durnin and Womersley). BMI, body mass index = weight(kg)/[(height(m)]^2; MAMC, midarm muscle circumference) = midarm circumference (cm) – 3.141 * triceps skinfold (cm), nutritional risk score = 1.519 x albumin (g/l) + 41.7 x (current weight / normal weight).

[a]Data are presented as mean ± SD.

[b]Chi-square test (with Yates' correction where appropriate).

[c]Unpaired *t*-test.

[d]Analysis of covariance with age as a covariate.

[e]Jonckheere-Terpstra test for ordered alternatives (↓ = decreasing, ↑ = increasing trend).

[f]The data are in the median (25th–75th percentile) format.

[g]The respective sums may not add to 84 because of missing data.

*$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.

TABLE 2
Biochemical characteristics of studied groups

Characteristic	Control group	Pancreatic cancer	stage II	stage III	stage IV	P(trend)[c]
Albumin (g/l)	46.7 ± 2.7[a]	40.4 ± 5.9[c***]	45.1 (38.6–46.8)[b]	41.6 (37.5–45.1)	40.3 (34.7–43.2)	0.016↓
Prealbumin (g/l)	0.25 ± 0.05	0.18 ± 0.08[c***]	0.21 (0.15–0.25)	0.19 (0.16–0.23)	0.14 (0.08–0.19)	0.001↓
CRP (mg/l)	5.5 ± 7.1	31.7 ± 38.2[c***]	12.7 (7.5–18.9)	8.1 (3.7–17.2)	36.7 (12.5–83.7)	0.005↑
Cholinesterase (μkat/l)	144 ± 30	104 ± 36[c***]	106 (91–153)	112 (88–140)	85 (65–113)	0.004↓
CA 19-9 (kU/l)	9 (6–14)[a]	273 (52–4514)[c***]	210 (29–662)	315 (51–2283)	256 (54–9178)	NS
CA 72-4 (kU/l)	1.5 (1.0–4.5)	3.1 (1.7–13.5)[c***]	2.2 (1.2–3.2)	2.1 (1.6–8.1)	9.1 (2.8–36.6)	0.001↑
CEA (μg/l)	0.6 (0.5–1.4)	3.8 (1.7–9.5)[c***]	2.3 (1.2–3.9)	2.4 (1.4–5.9)	6.5 (3.1–33.3)	0.001↑
Glucose (mmol/l)	5.18 ± 0.56	7.58 ± 3.17[c***]	6.10 (5.10–6.90)	7.40 (5.70–10.10)	6.44 (5.60–8.10)	NS
Insulin (mIU/l)	7.7 (5.4–13.3)	7.1 (4.6–11.1)	8.82 (7.41–12.34)	5.82 (4.44–11.96)	6.98 (4.44–10.70)	NS
HOMA-IR (ratio)	2.40 ± 1.74	3.49 ± 4.42	3.19 (2.15–4.36)	2.05 (1.28–4.96)	2.01 (1.14–3.14)	NS
LDL-CD (μmol/l)	48.7 ± 17.4	57.4 ± 26.9	43.8 (35.9–49.9)	53.0 (42.9–60.8)	55.6 (46.0–67.5)	0.043↑
Total cholesterol (mmol/l)	5.42 ± 1.01	5.43 ± 2.34	5.29 (4.23–6.62)	4.99 (4.11–5.98)	4.78 (3.70–5.65)	NS
LDL-cholesterol (mmol/l)	3.32 ± 0.81	3.59 ± 2.25	2.88 (2.29–5.28)	3.15 (2.44–3.83)	3.07 (2.13–3.99)	NS
HDL-cholesterol (mmol/l)	1.57 ± 0.38	0.94 ± 0.34 [c***]	1.06 (0.81–1.41)	0.97 (0.79–1.18)	0.90 (0.66–1.18)	NS
Triacylglycerols (mmol/l)	1.1 (0.8–1.4)	1.7 (1.2–2.1)[c***]	1.67 (1.33–2.56)	1.58 (1.12–2.18)	1.69 (1.38–1.97)	NS
FFA (mmol/l)	0.54 ± 0.24	0.75 ± 0.43[c**]	0.66 (0.51–0.85)	0.80 (0.49–0.89)	0.57 (0.40–0.98)	NS
apo A-I (g/l)	1.51 ± 0.29	0.93 ± 0.32[c***]	1.10 (0.90–1.48)	0.90 (0.73–1.10)	0.91 (0.64–1.09)	NS
apo B (g/l)	1.02 ± 0.25	1.27 ± 0.53[c**]	1.04 (0.88–1.66)	1.11 (0.92–1.45)	1.19 (0.91–1.37)	NS

CD, conjugated diene in precipitated LDL; CEA, carcinoembryonal antigen; CA, carbohydrate antigen; apo, apolipoprotein; FFA, free fatty acids; HOMA-IR, homeostasis model assessment of insulin resistance = glucose (mmol/l) * insulin (mUI/l)/22.5.

[a]Values are expressed as mean ± SD or [b]median (25th–75th percentile).

[c]Analysis of covariance with age as a covariate; Jonckheere-Terpstra test for ordered alternatives (↓ = decreasing, ↑ = increasing trend).

[d]The data are in the median (25th–75th percentile) format.

$^{*}P < 0.05$. $^{**}P < 0.01$. $^{***}P < 0.001$.

of visceral proteins (albumin, prealbumin, cholinesterase) and increased concentrations of CRP and tumor markers: CA 19-9, CA 72-4, and carcinoembryonal antigen (Table 2).

In 40 patients from the PC group, DM2 was present in more than half of the cases (57%) lasting less than 3 yr. We found higher levels of plasma glucose in the PC group. HOMA-IR index and concentrations of insulin and C-peptide were similar in both groups. Analyses of parameters of lipid metabolism in the PC group revealed elevated TAG, free FA and apo B, as well as a lower concentration of apo A-I. No differences were noted in the values of TC, HDL-C, LDL-C and conjugated dienes in LDL particles (Table 2). There were no links of plasma lipid (lipoproteins, respectively) parameters to the stages of PC.

The plasma fatty acid profile in main lipid classes (PL, TAG, and CE) is shown in Table 3. The patients with PC had a decreased sum (Σ) of n-6 PUFA in PL and CE, which was accompanied with an increase in the sum of monoenoic fatty acids (MUFA) in PL, CE as well as TAG together with a decreased content of Σn-3 PUFA in PL and TAG. As for individual fatty acid composition in the PC group, we observed elevations of palmitoleic acid (POA; 16:1n-7) in both PL and CE, oleic (OA; 18:1n-9) in PL only, and CE and TAG and vaccenic (VA; 18:1n-7) acids in both PL and CE. On the contrary, lower contributions to the total FA sum were proved for LA in PL and CE, α-linolenic (ALA; 18:3n-3) in all lipid classes, whereas a drop in eicosapentaenoic acid (EPA; 20:5n-3) was seen in PC and TAG. The changes in the activities of delta desaturases (DD), estimated as the (product/substrate) ratio of respective fatty acids, are presented in Table 3. We proved a raised activity index of SCD1 for both stearic (18:0) and palmitic (16:0) acids, which was significant in PL and TAG (in CE only SCD1 for 18:0). The consistent result is the increase in activity index for delta 5 desaturase (D5D), demonstrable in all lipid classes, whereas a decrease of D6D activity index was seen only in TAG.

In Table 4, the trends between PC staging and composition of FA in plasma PL are presented. A negative trend was detected between the concentration of ALA, DHGLA, EPA, PUFA n-3 and PC staging (all $P < 0.05$). We did not observe any consistent changes in FA profiles between the subgroups of PC divided according to the presence/absence of DM (data not shown). In

TABLE 3
Fatty acid profiles in plasma main lipid classes

	Phospholipids		Triacylglycerols		Cholesteryl esters	
Fatty acid	CON	PC	CON	PC	CON	PC
16:0[a]	29.70 ± 1.20[b]	33.05 ± 2.93***	26.73 ± 3.30	26.80 ± 2.10	10.26 ± 2.00	10.24 ± 2.70
16:1n-7	0.49 ± 0.15	0.69 ± 0.35***	3.30 ± 1.01	3.42 ± 1.03	2.93 ± 0.99	3.69 ± 1.36**
18:0	13.58 ± 1.10	11.77 ± 1.61***	3.44 ± 0.83	2.78 ± 0.74***	0.64 ± 0.29	0.65 ± 0.33
18:1n-9	10.05 ± 1.13	12.15 ± 2.21***	40.35 ± 4.72	42.96 ± 2.89***	19.40 ± 2.60	21.46 ± 2.89***
18:1n-7	1.47 ± 0.22	1.92 ± 0.36***	2.47 ± 0.40	2.62 ± 0.35	1.19 ± 0.33	1.47 ± 0.32***
18:2n-6	23.09 ± 2.24	19.43 ± 3.07***	16.16 ± 4.95	15.02 ± 2.57	56.58 ± 4.32	51.24 ± 4.98***
18:3n-6	0.08 ± 0.03	0.07 ± 0.04*	0.29 ± 0.14	0.19 ± 0.10***	0.69 ± 0.31	0.68 ± 0.36
18:3n-3	0.20 ± 0.07	0.13 ± 0.04***	0.84 ± 0.34	0.57 ± 0.20***	0.52 ± 0.17	0.38 ± 0.12***
20:3n-6	3.07 ± 0.70	2.77 ± 0.87*	0.31 ± 0.17	0.28 ± 0.15	0.65 ± 0.17	0.69 ± 0.17
20:4n-6	11.37 ± 1.54	11.62 ± 2.81	1.51 ± 0.69	1.50 ± 0.52	5.42 ± 2.38	7.47 ± 3.18***
20:5n-3	1.07 ± 0.61	0.55 ± 0.26***	0.22 ± 0.19	0.12 ± 0.06***	0.28 ± 0.24	0.27 ± 0.18
22:6n-3	3.48 ± 0.86	3.59 ± 1.05	0.63 ± 0.61	0.51 ± 0.22	0.17 ± 0.12	0.30 ± 0.19***
ΣSFA	43.62 ± 0.98	45.10 ± 2.82**	32.11 ± 4.29	31.06 ± 2.41	11.65 ± 2.08	11.69 ± 2.61
ΣMUFA	12.25 ± 1.26	15.03 ± 2.71***	47.14 ± 4.96	49.95 ± 3.15***	23.92 ± 3.39	27.15 ± 3.68***
ΣPUFA n-6	38.46 ± 1.69	34.74 ± 3.84***	18.73 ± 5.48	17.46 ± 2.78	63.44 ± 4.91	60.18 ± 5.37**
ΣPUFA n-3	5.67 ± 1.35	5.12 ± 1.37*	2.02 ± 1.04	1.53 ± 0.44***	0.99 ± 0.46	0.99 ± 0.39
D9D-16[c]	0.017 ± 0.005	0.021 ± 0.009**	0.124 ± 0.037	0.128 ± 0.037	0.293 ± 0.098	0.390 ± 0.174***
D9D-18[d]	0.746 ± 0.120	1.065 ± 0.332***	12.52 ± 3.65	16.35 ± 4.14***	33.06 ± 8.54	39.58 ± 15.56**
D6D n-6[e]	0.004 ± 0.002	0.004 ± 0.002	0.018 ± 0.007	0.013 ± 0.008***	0.012 ± 0.006	0.014 ± 0.008
D6DE n-6[f]	0.135 ± 0.039	0.146 ± 0.052	0.020 ± 0.010	0.019 ± 0.010	0.012 ± 0.004	0.014 ± 0.004**
D5D n-6[g]	3.87 ± 0.96	4.55 ± 1.69**	5.02 ± 1.36	5.99 ± 2.16***	8.39 ± 3.60	11.49 ± 5.76***

Statistical analysis was performed with analysis of covariance (with age as covariate). Σ, sum; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA n-6, polyunsaturated fatty acids of n-6 family; PUFA n-3, polyunsaturated fatty acids of n-3 family. Only relevant fatty acids are presented.

[a]Shorthand notation of fatty acids—number of carbon atoms: number of double bonds, n = number of carbon atoms from methyl end to the nearest double bond.

[b]The data are presented as a mean ± SD (mol%).

[c]16:1n-7/16:0, Δ9 desaturase.

[d]18:1n-9/18:0, Δ9 desaturase.

[e]18:3n-6/18:2n-6, Δ6 desaturase.

[f]20:3n-6/18:2n-6, Δ6 desaturase+elongase.

[g]20:4n-6/20:3n-6, Δ5 desaturase.

*$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.

the PC group, proportion of MUFA and SCD1 index correlated negatively with cholinesterase (r = −0.551 and r = −0.483, both $P < 0.001$, Spearman rank order coefficients), albumin (r = −0.579 and r = −0.476, both $P < 0.001$), prealbumin (r = −0.333 and r = −0.223, both $P < 0.01$) and positively with CRP level (r = 0.197 and r = 0.225, both p < 0.05). Correlations of dihomo-γ-linolenic acid (DHGLA) with these variables were opposite (with cholinesterase r = 0.473, albumin r = 0.499, prealbumin r = 0.375, and with CRP r = −0.407, albumin r = 0.499, and with prealbumin 0.375, all $P < 0.001$).

The preliminary results indicate that better prognosis (survival >100 days at the time of the diagnosis) is in our patients with PC connected with higher content of EPA (0.49 ± 0.17 vs. 0.61 ± 0.32 mol%, $P = 0.05$; <100 days vs. >100 days, $n = 70$, unpaired t-test), DHA (3.30 ± 1.00 vs. 3.83 ± 1.13 mol%, $P = 0.04$) as well as lower SCD1 index (1.18 ± 0.41 vs.1.01 ± 0.28, $P = 0.05$) in plasma PL. These 2 subgroups did not differ in tumor staging and presence of severe/moderate malnutrition. Moreover, the SCD1 index in phospholipids is negatively correlated with time of the survival in PC patients ($n = 70$, Spearman rank coefficient = −0.356, $P < 0.01$).

DISCUSSION

It is known that PC belongs to the tumors with the highest incidence of malnutrition, which is induced by diminished food intake and higher resting energy expenditure (34). Significant depletion of adipose tissue represents a hallmark of metabolic

TABLE 4
Tumor stage and plasma phospholipids fatty acids

Fatty acid	Stage II	Stage III	Stage IV	*P* (trend)[b]
16:0	33.12 (31.64–33.66) [a]	32.75 (31.09–34.13)	33.04 (32.14–34.74)	NS
16:1n-7	0.61 (0.51–0.82)	0.60 (0.48–0.78)	0.56 (0.47–0.82)	NS
18:0	12.08 (11.14–12.48)	11.68 (10.59–13.04)	11.72 (10.92–12.88)	NS
18:1n-9	11.97 (10.36–13.23)	11.61 (10.88–13.52)	12.05 (10.61–13.00)	NS
18:1n-7	1.99 (1.68–2.18)	1.87 (1.65–2.15)	1.93 (1.70–2.05)	NS
18:2n-6	19.18 (16.67–21.94)	19.61 (18.28–21.89)	19.61 (18.14–20.83)	NS
18:3n-6	0.05 (0.05–0.06)	0.07 (0.05–0.09)	0.07 (0.04–0.10)	NS
18:3n-3	0.13 (0.11–0.16)	0.13 (0.10–0.15)	0.11 (0.09–0.14)	0.029↓
20:3n-6	2.72 (2.30–3.46)	2.95 (2.38–3.52)	2.40 (1.94–3.10)	0.033↓
20:4n-6	11.11 (9.19–14.51)	11.67 (9.92–12.70)	12.40 (10.07–13.76)	NS
20:5n-3	0.66 (0.44–0.76)	0.53 (0.40–0.70)	0.45 (0.37–0.62)	0.026↓
22:5n-3	0.92 (0.78–1.17)	0.92 (0.67–1.01)	0.78 (0.70–1.03)	NS
22:6n–3	3.80 (3.18–4.83)	3.48 (2.89–4.22)	3.49 (2.78–4.30)	NS
ΣSFA	44.83 (44.15–45.66)	44.56 (43.73–45.23)	45.16 (44.03–46.12)	NS
ΣMUFA	14.50 (13.22–16.20)	14.33 (13.38–16.27)	14.58 (12.78–15.93)	NS
ΣPUFA n-6	35.71 (32.90–36.80)	36.08 (33.47–37.09)	35.37 (33.30–36.53)	NS
ΣPUFA n-3	5.53 (4.88–6.38)	5.25 (4.22–5.92)	4.86 (3.97–5.78)	0.050↓
D9D-16[a]	0.018 (0.016–0.025)	0.019 (0.015–0.024)	0.017 (0.014–0.025)	NS
D9D-18[b]	0.970 (0.901–1.045)	0.976 (0.900–1.125)	1.034 (0.883–1.135)	NS
D6D n-6[c]	0.002 (0.002–0.003)	0.004 (0.002–0.005)	0.003 (0.002–0.005)	NS
D6DE n-6[d]	0.142 (0.109–0.199)	0.153 (0.119–0.177)	0.115 (0.098–0.165)	0.021↓
D5D n-6[e]	4.56 (3.26–5.55)	3.79 (3.08–4.95)	4.57 (3.68–6.95)	0.045↑

Σ, sum; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA n-6, polyunsaturated fatty acids of n-6 family; PUFA n-3, polyunsaturated fatty acids of n-3 family. Only relevant fatty acids are presented.

[a]The data are in the median (25th–75th percentile) format. 16:1n-7/16:0, Δ9 desaturase.

[b]Jonckheere-Terpstra test (↓ = decreasing, ↑ = increasing trend). 18:1n-9/18:0, Δ9 desaturase.

[c]18:3n-6/18:2n-6, Δ6 desaturase.

[d]20:3n-6/18:2n-6, Δ6 desaturase + elongase.

[e]20:4n-6/20:3n-6, Δ5 desaturase.

changes associated with cancer as well as with cancer cachexia. It was demonstrated that loss of body fat occurs before losing protein mass. Furthermore, it has been shown that adipose tissue depletion starts from the trunk followed by adipose tissue in lower and upper extremities (35). Anthropometric data found in our PC patients (decreased BMI without changes in lean body mass and midarm muscle circumference, decreased fat mass, and increased subscapularis to triceps skinfold ration) are consistent with these findings (35,36). The presence of cancer and/or cancer cachexia is associated with lipid metabolism changes that include reduction of fat mass, increased lipolysis and fatty acid oxidation connected with decreased lipogenesis. Observed changes of increased concentrations of TAG, FFA, apo B, accompanied with a decrease in HDL-C and apo A-I are consistent with cancer-induced dyslipidemia. Increased levels of hormone sensitive lipase mRNA and enzyme, which were detected in cancer patients led to increased hydrolysis of TAG and FFA turnover. Cancer-related dyslipidemia (hyperTAG, hyper apo B, hypo HDL-C, and hypo apo A-I) found in some cancers (colorectal, breast, endometrial, and pancreatic) (37–39) is similar to atherogenic dyslipidemia specific for metabolic syndrome (MS). Interestingly, both obese (40) and cancer cachectic (41) patients have increased intramyocellular lipid content, which may be related to the changes in energy balance. Fouladiun et al. found that body fat was lost more rapidly than lean tissue in progressive cancer cachexia, a phenomenon that was related highly to alterations in the levels of circulating hormones (insulin, leptin, ghrelin) and food intake (42).

We observed decreased levels of LA, ALA, and EPA in the PC group. With regard to the fact that the patients with PC did not exhibit increased concentrations of conjugated dienes in LDL particles, a marker of lipoperoxidation (43), it can be concluded that the observed decreased proportions of LA, ALA, and EPA are not caused by the systemic oxidative stress and/or lipoperoxidation but more likely by lowered dietary intake of these FA. The decreased LA, ALA, and EPA content can be also induced by malabsorption (44), which is highly probable in PC, and cigarette smoking as well as alcohol consumption (45).

Pratt et al. (46) reported in patients with advanced cancer a low content of total essential fatty acids, as well as decrease of ALA and LA in plasma PL regardless of total caloric or total fat intake. The effect of genetic and gender background on the fatty acid profile also cannot be excluded (47,48). Closer examination of the correlations between PUFA content and weight loss (mainly resulting from fat loss) revealed only a negative relationship with DHGLA. The lack of these correlations with essential fatty acids is not clear; the data about FA content in the fat tissue in cancer patients is scarce. In a study of patients with colorectal carcinoma published by Neoptolemos (49), it was found that in the healthy individuals, the adipose tissue LA content correlated well with the respective content in erythrocytes, whereas in the cancer group the correlation was missing. Another study described the negative relationship of dietary intake of animal fat with the PUFA/saturated fatty acids (SFA) ratio and C18 PUFA content in adipose tissue in endometrial cancer (50).

An important and consistent finding of this study is the increased composition of the $\sum$ of MUFA, because of elevated proportions of POA (16:1n-7), OA (18:1n-9), and VA (18:1n-7). The patients with PC were shown to have increased activities of desaturation of palmitate (16:0) and stearate (18:0), which implicate the increased activity of SCD1 (e.g., Δ9-desaturase activity) as well as D5D [e.g., fatty acid desaturase-1 (FADS1)]. The enzyme SCD1, which is, under physiological state, predominantly expressed in the liver, catalyzes the synthesis of monounsaturated long-chain FA from fatty acid acyl-CoA. The preferred substrates for SCD1 are stearoyl (18:0), and palmitoleyl (16:0) CoA, which are converted to oleolyl-CoA (18:1n-9) and palmitoleoyl-CoA (16:1n-7).

Increased activity of SCD1 is usually observed in various cancers. Aggressively growing tumors are characterized by an elevated synthesis of FA de novo and accelerated transformation of SFA to MFA, which is combined with synthetic (FAS) and desaturation (SCD1) activities. FAS is a multifunctional enzymatic complex that synthesizes palmitic acid (C16:0) from acetyl-CoA and malonyl-CoA.

SCD1, the isoform that is expressed in the liver, is an enzyme synthesizing MUFA: POA (16:1n-7) and OA (18:1n-9) from palmitic (C16:0) and stearic acids (18:0). POA and OA are key substrates for the formation of complex lipids (e.g., PL, CE, TG and waxes) (17). Increased content of POA was in several studies linked to higher level of lipogenesis (51). Activities of SCD1, which closely correlated with the OA/SA ratio, were found to be higher in several types of tumors (52). In our PC group, a higher OA/SA ratio was found that implicated a higher activity of SCD1 in these patients. Moreover, in all lipid classes analyzed, there was also higher content of vaccenic acid (18:1n-7), which is the known to be elongation product POA (16:1n-7). Our results are consistent with a study describing an increased ratio of 18:1 to SA (18:1n-9 + 18:1n-7/18:0) in patients with PC (53). FAS as well as SCD1 has elevated activities in cancer cells, where the de novo synthesis is important for cell membrane synthesis, membrane remodeling, and proliferation (15,17,54). In states with an absolute and relative lack of PUFA (n-6 and/or n-3), SCD1 is necessary for maintenance of cellular lipid homeostasis, because it keeps the synthesis of MUFA that is essential for complex lipid formation (17). Selective inhibition of SCD1 with cerulenin (natural mycotoxine) shortens the lifespan of human cancer cells (54). An experimental model of hepatocellular carcinoma in rats and mice has proven a higher expression of SCD1 (55). Women with a decreased ratio of MUFA in plasma phospholipids (as a surrogate marker of SCD1 activity) who were supposed to have a lower activity of SCD1, revealed decreased risk for breast cancer (56). In this study, we also analyzed the relationship of FA and tumor staging of PC; however, we did not find significant changes for the content of MUFA as well as SCD1 indices. Nevertheless, we observed trends for a decreased content of PUFA n-3, ALA, EPA, and DHGLA with an increased burden of disease. The lower content of plasma PUFA n-3 was found in some types of cancer (53) with its further loss pointing at a worse prognosis (57).

In the PC group, we proved higher SCD1 and D5D indices as well as both desaturation activity indices of palmitate (16:1-7/16:0) and stearate (18:1n-9/18:0). In an earlier study with metabolic syndrome patients, we found only higher desaturation index of palmitate (16:1-7/16:0), together with higher D6D and lower D5D indices (47). Because stearate is preferred to palmitate as a substrate of SCD1 this finding could be explained by dilution of products: POA (16:1-7) and OA (18:1n-9) by dietary fatty acids. Dietary lipids contain only small amounts of POA, whereas OA is the most abundant dietary FA. This finding could be explained by decreased intake of dietary lipids in the patients with PC. Therefore, the phenomenon of dilution of products (POA, OA) could not operate in the PC patients. As compared to MS, we did not find decreased activity of D6D. Increased activities of D6D have been ascribed to hyperinsulinemia and increased BMI and generally considered as a characteristic feature of IR. On the other hand, decreased D5D activities, an important feature of MS, was shown not to be dependent on BMI and on physical activity (32).

Our previous results indicated that in PC, the condition connected with high inflammatory response and low concentrations of the inhibitor of SCD1, leptin (58), the inhibition of SCD-1 concomitantly with anti-inflammatory intervention could be possible therapeutic strategy, as it was suggested for MS (59). Both the experimental animal studies and clinical data proved the protective effects of n-3 PUFA in prostate, breast, and colorectal cancer (60,61). We have observed the positive relationship of EPA and DHGLA (20:3n-6), on one hand, and the concentrations of visceral proteins and cholinesterase on the other, suggesting the beneficial effects of these FA on the protein metabolism.

In newly referred patients with nonsmall cell lung cancer, intervention with fish oil compared with standard of care led to increased or maintained muscle mass. Moreover, an increasing concentration of EPA positively correlated with

muscle gain (62). In patients with advanced PC, supplementation with n-3 PUFA led to weight gain, an increase in LBM, and changes in plasma EPA correlated positively with changes in body weight and LBM (63). EPA may support the anabolic potential of muscle acting against the insensitivity of skeletal muscle of cancer patients to insulin (64). Supplementation with EPA could attenuate muscle degradation by decreasing the expression of proteasome subunits, which are elevated in cancer cachexia (31), or by downregulating the acute-phase response.

High levels of CRP in the PC group point to the advanced stages of the disease with the invasions to the lymphatic nodes and peritoneum. The negative correlations of CRP with DPA (C22:5n-3) and DHGLA (C20:3n-6) implicate the therapeutic potential of these PUFA. The correlation of DHGLA exhibits a significant negative trend, which is dependent of the degree of malnutrition.

The limitations of the study include the estimation of the activities of desaturases with the help of substrate/product ratio, because the activities were not analyzed from the tissue biopsy because of ethical reasons. On the other hand, the literature data advocate the usage of the ratios in the PL lipid class. We also did not observe any patient at stage I. The number of the patients in the subgroups of PC was low, but sufficient for determining the effect according to the power analyses. Moreover, according to our knowledge, the study has included the highest number of the patients suffering from pancreatic ductal adenocarcinoma with determined FA profile in PL lipid class so far.

CONCLUSION

In conclusion, a specific plasma esters FA profile in patients with PC was described. In comparison with control subjects, patients with PC revealed increased concentrations of monounsaturated FA. These changes were associated with increased index of SCD1. Moreover, decreased concentrations of LA, ALA, and EPA were found in plasma lipid esters of PC patients, and these changes are probably caused by a lower intake of dietary fat. Positive correlations between levels of visceral proteins and concentrations of EPA and DHGLA were found. On the contrary, these FA negatively correlated with concentration of CRP. Index of SCD-1 in PL correlated negatively with survival time of the patients. Moreover, longer survival of the patients was connected with higher content of EPA, DHA, and with lower index of SCD-1 activity, respectively. Proportions of PUFA n-3 displayed a negative trend with tumor staging, whereas the positive trends of MUFA, SCD1, and on the degree of malnutrition as well as the negative trend of DHGLA content to the extent of malnutrition were found. The changes in FA profile implicate pathophysiological mechanisms responsible for disturbed FA metabolism in cancer patients and indicate the importance of appropriate nutritional support.

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