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Plasma Phosphatidylcholines Fatty Acids in Men with Squamous Cell Esophageal Cancer: Chemoradiotherapy Improves Abnormal Profile

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDG 1 **Milada Zemanová***
CDF 2 **Marek Vecka***
AEG 1 **Luboš Petruželka**
BCF 2 **Barbora Staňková**
DEF 2 **Aleš Žák**
ADE 2 **Miroslav Zeman***

1 Department of Oncology, 1st Faculty of Medicine of Charles University in Prague and General University Hospital, Prague, Czech Republic
2 4th Department of Internal Medicine, 1st Faculty of Medicine of Charles University in Prague and General University Hospital, Prague, Czech Republic

* These authors contributed equally to the article

Corresponding Author: Milada Zemanova, e-mail: milada.zemanova@vfn.cz

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Background: Abnormal metabolism of fatty acids (FA) is considered to play a role in human cancers, including esophageal cancer (EC). Nevertheless, there have been only a few studies dealing with the influence of the chemotherapy or radiotherapy on the plasma FA profiles. In this work we compared FA in plasma phosphatidylcholine (PC) of the patients with squamous EC and healthy subjects and investigated changes in the FA spectrum during neoadjuvant chemoradiotherapy (CRT).

Material/Methods: Forty-two men with squamous EC were compared with age-matched healthy controls. The EC group was subjected to concurrent neoadjuvant CRT. We analyzed FA in plasma PC before and after CRT.

Results: The EC group was characterized by increased levels of both saturated and monounsaturated FA, associated with an increased index of SCD1 (stearoyl-CoA desaturase-1). Moreover, decreased levels of linoleic acid and total polyunsaturated FA (PUFA) n-6 were found in EC patients. The CRT was accompanied by increased docosahexaenoic acid and total PUFA n-3 content in plasma PC, concurrently with the decrease of estimated activity of SCD1.

Conclusions: We found that patients with EC had altered FA profile in plasma PC, which could be related to abnormal FA metabolism in cancer (e.g., altered synthesis *de novo*, β-oxidation, desaturation, and elongation). The described changes in FA profiles during CRT could be involved in favorable functioning of CRT. Further studies investigating the plasma FA compositions and their changes due to CRT in EC patients are warranted.

MeSH Keywords: **Chemoradiotherapy • Esophageal Neoplasms • Fatty Acids • Phosphatidylcholines • Stearoyl-CoA Desaturase**

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Background

Esophageal cancer rates have risen dramatically in recent decades. Worldwide, esophageal cancer is the eighth most common malignancy and the sixth most common cause of cancer-related death; chance for long-term survival is only about 10% [1]. In the Czech Republic, the yearly incidence of esophageal cancer is about 550 cases [2]. Several risk factors of esophageal carcinoma have been recognized; alcohol drinking, smoking, and the temperature of ingested fluids play a main role in squamous cell esophageal cancer (SCEC), while reflux esophagitis in the case of esophageal adenocarcinoma (EAC) [3]. The indices of nutritional status may influence risk of development and prognosis of esophageal cancer [4,5]. The role of fats in SCEC and EAC remains controversial [2,6,7–9]. Fatty acid composition in various lipid classes may serve as an epidemiological tool to examine the association of dietary patterns and the development of pathological states such as esophageal cancer. FA profiles in cholesteryl esters, total phospholipids, and phosphatidylcholines reflect not only FA dietary intake, but also synthesis of saturated FA, their desaturation and elongation, and both enzymatic (β-oxidation) and non-enzymatic (lipoperoxidation) degradation [10]. In malignant states, the metabolism of FA is significantly changed (for review see [11]) towards increased *de novo* synthesis, elongation, and desaturation processes. Higher turnover of fatty acid chains also has a profound effect on levels of dietary long-chain polyunsaturated fatty acids (PUFA), which are important precursors of many compounds with anti-cancer effects. Interestingly, exogenous PUFA may be associated with prevention of some cancers [12]. Data on serum FA composition in esophageal cancer are very scarce. A small study in 22 patients with esophageal cancer found decreased levels of linoleic acid (LA) and increased of levels of palmitic acid (PA) in plasma phospholipids in comparison with healthy subjects [13]. In a metabolomic study using high-performance liquid chromatography-mass spectrometry (LC-MS) methods, plasma myristic, linolenic acid, and linoleic acid were lower in EAC patients compared to healthy controls [14]. A recent work by Guo et al. (2014) found activation of *de novo* lipogenesis in 6 different types of cancer (breast, lung, colorectal, esophageal, gastric, and thyroid cancer) [15]. Increased lipogenesis *de novo* is accompanied by increased activity of stearoyl-CoA desaturase-1 (SCD-1), which catalyzes desaturation of palmitic acid (16: 0) to palmitoleic acid (16: 1 n-7) and stearic acid (18: 0) to oleic acid (18: 1 n-9). Higher content of monounsaturated fatty acid (FA) in membranes of cancer cells significantly affects membrane dynamics and modulates the uptake and efficacy of chemotherapeutics [16]. Only a few studies have investigated the influence of cancer chemotherapy or radiotherapy on the plasma FA profiles, with inconsistent results [17–19]. The aim of the present study was to compare the spectrum of FA in plasma PC (which accounts for most plasma phospholipids) in esophageal cancer patients with that of healthy subjects. Recent studies have shown that adverse metabolism of phosphatidylcholines can play a role in pathogenesis of different cancers [20,21]. The secondary aim was to investigate the changes in FA spectrum during neoadjuvant CRT.

Material and Methods

Subjects

Forty-two men (mean age of 58.0±7.4 years; mean ±SD) with squamous cell esophageal cancer (EC group) were investigated and compared with a control group consisting of 42 age-matched healthy control subjects. After signing informed consent, the cancer patients were subjected to a multimodal regimen of concurrent neoadjuvant CRT followed by surgery. Patients had histologically-proven squamous cell carcinoma of the esophagus, with resectable tumors in the stage II or III of the disease as defined by the TNM classification of malignant tumors, Fifth Edition, of the International Union against Cancer [22]. The control group consisted of apparently healthy volunteers from medical staff of the 1st Faculty of Medicine. The study protocol was approved by the Joint Ethics Committee of the General University Hospital and the 1st Faculty of Medicine, Charles University in Prague.

No subjects had been treated with hypolipidemic medications or supplemented by polyunsaturated fatty acids and/or antioxidants.

Treatment protocol

The neoadjuvant chemoradiotherapy (CRT) protocol has been described in detail elsewhere [23]. Briefly, CRT consisted of 2 cycles of chemotherapy with carboplatin at AUC 6 or cisplatin at 80 mg/m^2 on days 1 and 22 from the start of treatment. Continuous infusion of 5-fluorouracil was administered on days 1–42 at 200 mg/m^2/day. Paclitaxel 200 mg/m^2 by 3-h infusion on day 1 and 22 was a part of the combination in some patients. Radiotherapy was delivered from day 1 concurrently, 1.8 Gy per fraction, 5 fractions per week, total dose 45 Gy in 25 fractions. RT dose was increased to 50.4–56.8 Gy if a contraindication to surgery occurred during the treatment course. Surgery was performed 4–6 weeks after CRT unless it was contraindicated or refused by the patient. After surgery or definitive CRT, patients were followed up without further adjuvant therapy.

Laboratory analyses

Blood collection was performed before the start of CRT (Baseline) and after ending the treatment. Blood samples

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Table 1. Relevant fatty acids in the patients with esophageal cancer and controls.

	Healthy subjects (n=42)	Esophageal cancer (n=42)	P value[g]
14: 0[a]	0.26±0.07[b]	0.22±0.07[h]	NS
16: 0	29.61±1.28	31.67±1.69	<0.001
16: 1n-7	0.49±0.24	0.81±0.44	<0.001
18: 0	13.56±1.07	13.60±1.58	NS
18: 1n-9	9.99±1.68	12.31±2.22	0.005
18: 2n-6	23.59±2.39	19.49±2.67	<0.001
18: 3n-3	0.20±0.07	0.22±0.08	NS
18: 3n-6	0.08±0.03	0.09±0.06	NS
20: 3n-6	2.89±0.42	2.81±0.63	NS
20: 4n-6	11.31±1.68	10.47±2.14	NS
20: 5n-3	0.96±0.44	0.72±0.44	NS
22: 6n-3	3.44±0.88	3.34±0.97	NS
Σ SFA	43.49±1.15	45.51±2.03	<0.001
Σ MUFA	12.25±1.94	15.37±2.76	0.002
Σ PUFA n-6	38.73±1.94	33.92±3.32	<0.001
Σ PUFA n-3	5.53±1.23	5.17±1.11	NS
n-6/n-3 ratio	7.398±1.932	6.844±1.549	NS
D9D 16[c]	0.016±0.008	0.025±0.014	0.001
D9D 18[d]	0.748±0.185	0.923±0.239	0.002
D6D+E[e]	0.124±0.025	0.147± 0.041	0.004
D5Df	3.986±0.777	3.941±1.267	NS

[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%); 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. [c] 16: 1n-7/16: 0 – Δ9 desaturase; [d] 18: 1n-9/18: 0 – Δ9 desaturase; [e] 20: 3n-6/18: 2n-6 – Δ6 desaturase+elongase; [f] 20: 4n-6/20: 3n-6 – Δ5 desaturase; [g] statistical analysis – ANCOVA *(with BMI as covariate)*; [h] data in this column are baseline values before treatment; D9D=SCD1.

were collected after overnight fasting. The routine biochemical tests were performed on automatic analyzers according to standard methods. The FA composition of plasma PC was determined by gas chromatography [24]. Desaturase activities were estimated using product/precursor ratios of respective FA (see Tables 1 and 2 for details).

Statistical analyses

For statistical analysis, STATISTICA® statistical software for Windows (StatSoft, Tulsa, U.S.A.) was used. We used the *t* test and Wilcoxon test, as appropriate, for comparison of continuous variables, while the chi-square test was used for comparison of categorical variables. The tests for comparison of the EC *vs.* the control group were adjusted for body mass index (BMI) (applying ANCOVA test). The statistical significance was defined as P<0.05.

Results

Basic clinical and biochemical parameters of the patients with esophageal cancer and control group are presented in Table 3. As expected, the patients significantly differed from controls in BMI (23.5±4.2 *vs.* 26.9±3.9 kg/m^2, p<0.001), albumin (40.4±4.6 *vs.* 46.5±2.5 g/l, p<0.001), and C-reactive protein (CRP) [6.75 *vs.* 3.2 (median), p=0.014]. There were no significant differences between groups in the concentrations of total plasma

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Table 2. Changes of plasma phosphatidylcholine fatty acids of esophageal cancer patients during chemoradiotherapy.

	Before CRT	After CRT	P value[h]
14: 0[a]	0.22±0.07[b]	0.21±0.08	NS
16: 0	31.67±1.69	31.02±1.87	NS
16: 1n-7	0.81±0.44	0.70±0.40	0.015
18: 0	13.60±1.58	13.66±1.76	NS
18: 1n-9	12.31±2.22	11.61±2.18	NS
18: 2n-6	19.49±2.67	19.26±3.25	NS
18: 3n-3	0.22±0.08	0.20±0.08	NS
18: 3n-6	0.09±0.06	0.07±0.04	NS
20: 3n-6	2.80±0.63	3.02±0.81	NS
20: 4n-6	10.47±2.14	11.08±2.32	0.036
20: 5n-3	0.72±0.44	0.69±0.24	NS
22: 6n-3	3.34±0.97	4.02±0.91	0.001
Σ SFA	45.51±2.03	44.95±2.41	NS
Σ MFA	15.37±2.76	14.73±2.79	NS
Σ PUFA n-6	33.92±3.32	33.76±5.90	NS
Σ PUFA n-3	5.17±1.11	5.72±0.99	0.038
n-6/n-3 ratio	6.844±1.549	6.13±1.515	NS
D9D 16[c]	0.025±0.014	0.022±0.013	0.009
D9D 18[d]	0.923±0.239	0.874±0.244	NS
D6D[e]	0.005±0.004	0.004±0.002	NS
D6D+E[f]	0.147±0.041	0.163±0.057	NS
D5D[g]	3.941±1.267	3.827±1.350	NS

[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%); 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. [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; [h] Wilcoxon paired test; D9D=SCD1; CRT – chemoradiotherapy.

cholesterol, triacylglycerols (TAG), and glucose. The plasma FA profile in PC is demonstrated in Table 1. The patients with EC were characterized by lower levels of linoleic acid (18: 2n-6, LA) (–17%, p<0.001) and sum (Σ) of n-6 PUFA in PC (–12%, p<0.001). This decrease was accompanied by an increase in levels of palmitic acid (16: 0, PA) (+7%, p <0.001), palmitoleic acid (16: 1n-7, POA) (+29%, p<0.001), oleic acid (18: 1 n-9, OA) (+19%, p<0.01), and both sum of saturated FA (ΣSFA) (+4.6%, p<0.001) and sum of monoenoic FA (ΣMFA) (+20%, p<0.01). When we observed estimated activities of desaturases, we found that patients had EC elevated index of SCD1 (e.g., Δ-9 desaturase, D9D) for both stearic (18: 0) (+19%, p<0.05) and palmitic (16: 0) (+64%, p<0.001) acids and we have also observed the significant increase in activity index for Δ-6 desaturase (D6D) (+16%, p<0.01). Index of activity for Δ-5 desaturase (D5D) did not differ significantly between groups.

Table 4, shows changes in basic clinical and laboratory parameters of EC patients during the CRT. We observed significant trends to lower BMI (–5%, p<0.001), and albumin (–16%, p<0.02). On the contrary, we did not see any changes in concentrations of glucose and plasma lipids. Table 2 shows the changes in plasma PC fatty acids during the CRT. We observed a significant decrease of the proportion of POA (–14%, p<0.02), an increase in arachidonic acid (AA) (+5%, p<0.05) and docosahexaenoic acid (DHA) (+18%, p<0.001), Σ n-3 PUFA (+9%, p<0.05), and a significant decrease in the index of SCD1 activity (16: 1/16: 0) (–12%, p<0.01)

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Table 3. Basic demographic and clinical data of the patients and control group.

	Healthy subjects (n=42)	Esophageal cancer (n=42)	P value
Age (years)[a]	58.3±8.1	58.0±7.3	NS
Smokers (ratio)	14/42	38/42	<0.001[b]
BMI (kg·m^{-2})	26.9±3.9	23.5±4.2	<0.001[c]
Albumin (g/l)	46.5±2.5	40.4±4.6	<0.001
Cholesterol (mmol/l)	5.14±0.82	4.94±1.01	NS
Triacylglycerols (mmol/l)	1.16±0.47	1.36±0.68	NS
Glucose (mmol/l)	5.37±0.89	5.42±0.97	NS
CRP (mg/l)	3.2 [2.1; 5.9][d]	6.75 [2.78; 13.58]	0.014

[a] Data are presented as mean ±S.D.; [b] χ^2 test; [c] Wilcoxon test; [d] median [interquartile range-Q1;Q3]; BMI – body mass index = weight(kg)/[(height(m)]^2; CRP – C-reactive protein.

Table 4. Changes of clinical and laboratory parameters of esophageal cancer patients during chemoradiotherapy.

	Before CRT	After CRT	P value
BMI (kg·m^{-2})	23.5±4.2[a]	22.4±3.9	<0.001[b]
Albumin (g/l)	40.4±2.5	38.9±6.3	0.014
Cholesterol (mmol/l)	4.94±1.01	4.85±1.15	NS
Triacylglycerols (mmol/l)	1.36±0.68	1.48±0.51	NS
Glucose (mmol/l)	5.42±0.97	5.48±0.90	NS
CRP (mg/l)	6.75 [2.78; 13.58][c]	10.90 [3.0; 28.0]	NS[d]

[a] Data are presented as mean ±S.D.; [b] paired t-test; [c] median [interquartile range-Q1;Q3]; [d] Wilcoxon paired test; BMI – body mass index = weight(kg)/[(height(m)]^2; CRP – C-reactive protein.

Discussion

In the presented observational pilot study, we found significant differences between the FA profile in plasma PC in the group of men with squamous cell esophageal cancer and age-matched healthy men. Moreover, we also observed significant changes in plasma PC fatty acid concentrations after ending the CRT.

Fatty acids in plasma phosphatidylcholine in esophageal cancer

In the patients with EC, we found increased content of ΣMFA in plasma PC due to higher contents of both POA (16: 1n-7) and OA (18: 1n-9). The increased proportion of PA (16: 0) and that of ΣSFA was observed in the EC group as well. Concurrently, we found decreased proportions of LA (18: 2n-6) in plasma PC in EC patients. The patients with EC were characterized by increased indexes of D9D for both palmitate (16: 0) and stearate (18: 0). Increased synthesis of FA *de novo* and accelerated formation of monogenic FA (MFA) from saturated FA (SFA) is a common feature of growing tumors. The activities of both fatty acid synthase (FAS), which catalyzes synthesis of palmitic acid from acetyl-CoA, and malonyl-CoA and SCD1, catalyzing conversion palmitic acid to palmitoleic and stearic acid (18: 0) to oleic acid, take part in these processes. Both FAS and SCD1 activities support cancer cell growth and survival, as it was found in breast and endometrial cancer [25]. It was suggested that the FAS expression is of functional importance in human esophageal tumorigenesis, and that inhibiting FAS might be applied to treat esophageal cancer [26].

In our EC group, both 16: 1 n-7/16: 0 and 18: 1 n-9/18: 0 ratios were higher, thus suggesting higher activity of SCD1. This is consistent with the finding of Li et al. in 1994 [27], who reported increased desaturase mRNA SCD1 levels in human colonic and esophageal carcinomas. In an earlier study we found higher estimated D9D activity for both palmitate and stearate in patients with pancreatic cancer [28], suggesting a therapeutic role for SCD1 inhibitors. In an experimental study, the downregulation of SCD1 in lung carcinoma cells delayed and limited tumor growth; the activity of SCD1 was correlated with the rate of cell proliferation and invasiveness of tumor cells [29]. In our patients with squamous carcinoma of the esophagus, we found lower levels of LA and Σ n-6 PUFA in plasma PC in comparison

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with controls. In 2002, Zuijdgeest-van Leeuwen et al. [13] found lower levels of n-6 and n-3 FA in plasma phospholipids in patients with newly diagnosed pancreatic non-small cell lung cancer and stomach/esophageal cancer compared to normal healthy controls. The causes of the lower level of PUFA in plasma lipids in patients with cancer are not clear. It is known that the level of FA in plasma lipid is influenced by dietary lipid content in randomly selected middle-aged adults, including those with chronic illnesses [30] and in healthy volunteers [31]. However, in patients with advanced cancer, Pratt et al. (2002) [17] found significantly decreased total plasma phospholipids concentration and linoleic and alpha-linolenic acid proportion, which were not dependent on intake of total fat and calories.

A lower level of PUFA n-6 can be caused by cigarette smoking or excessive alcohol intake [32], which are established risk factors for esophageal cancer [33]. Moreover, plasma profile of PUFAs is influenced by both genetic factors and sex [34,35]. Decreased levels of LA (18: 2n-6) and total n-6 PUFAs in plasma PC of EC patients could also be caused by increased oxidative stress [36]. Oxidative stress plays an important role in the pathogenesis of various cancer types, including esophageal cancer [37]. We did not analyze the parameters of oxidative stress in this study. The decreased level of PUFA in cancer patients can be connected with the stage of the disease and the applied treatment. Recently, Murphy et al. (2012) [38] found that patients with advanced lung cancer compared to those with early-stage lung cancer had significantly lower levels of total phospholipid FA. Interestingly, patients who did not complete chemotherapy due to toxicity or disease progression had progressive loss of total phospholipid FA, stearic acid, linoleic acid, and sum of n-6 fatty acids; in contrast, those who completed chemotherapy maintained stable FA levels for at least 1 month following completion of chemotherapy [38].

Another important finding of this study was significantly increased estimated activity of D6D in our patients with EC. The potential pathogenetic role of higher activity of D6D during carcinogenesis has been shown in several experimental studies. In 2012, He et al. [39] found that the activity of D6D was upregulated during melanoma and lung cancer growth in mice, whereas the inhibition of D6D prevents tumor growth. Inhibition of D6D in experimental conditions hindered the growth of human colorectal carcinoma cells [40]. The breast carcinoma tissues, particularly those of the estrogen receptor-negative genotype have enhanced synthesis of AA, higher activity of D6D, and higher levels of prostaglandin E2 [41].

Changes in plasma phosphatidylcholine fatty acid composition after chemoradiotherapy

The changes in plasma PC profile after CRT are shown in Table 2. We have observed lower POA levels and decreased level of SCD1 activity index, whereas the contents of PUFA n-3 (especially DHA) and AA (20: 4n-6) were higher.

The literature on the effect of CRT on FA profiles in plasma lipid classes is scant. One study described depletion of PUFA during chemotherapy (5-fluorouracil, Adriamycin, and cyclophosphamide) in advanced breast cancer [17]. In contrast, in the study in which 25 breast cancer patients on anthracycline-based chemotherapy for metastases were dietary supplemented, Bougnoux et al. (2009) [42] found that this treatment did not prevent enrichment of plasma phospholipids with a highly unsaturated FA and that high levels can be sustained for at least 4 months of treatment. Because we used platinum and 5-FU based chemotherapy and concomitant RT in this study, it is difficult to distinguish the effect of the chemotherapy and radiotherapy on the observed changes of FA profiles in plasma PC. Interestingly, FA profiles in patients with squamous carcinoma of the esophagus after CRT were similar to FA profiles in control individuals. Moreover, the DHA level after CRT exceeded even the control values. The decreased SCD1 activity index could be also considered as a beneficial effect of CRT.

To the best of our knowledge, this study is the first to describe increased levels of DHA and PUFA n-3 in plasma PC in connection with cancer treatment using CRT. After CRT treatment, we did not find any changes in activity indices for D5D or D6D. The increased content of PUFA n-3 during CRT was caused mainly by higher levels of DHA but not eicosapentaenoic acid (EPA). Apart from the influence of CRT, other factors have to be considered, such as the intensity of β-oxidation, DHA retro-conversion efficiency to EPA [43], the presence of allele ε4 for *APOE* [44], and the total content and quality of dietary fat [45]. It was recently found that cisplatin in adult C57Bl/6J male mice caused a decrease in the lipogenic enzymes FAS and SCD1 in liver, white adipose tissue (WAT), and muscle; concurrently, cisplatin increased lipolysis in WAT and β-oxidation in liver and WAT [46]. This finding supports the hypothesis that the CRT used in our study can, at least partly, participate in altering the plasma PC fatty acid profile of EC patients.

These observed higher levels of PUFA n-3 in plasma PC in patients with EC could have practical consequences. It was suggested that certain PUFAs have tumoricidal action and are capable of enhancing the cytotoxic action of anticancer drugs, specifically on drug-resistant cells, by promoting drug uptake and reducing its efflux [47]. Moreover, "combination therapy" of DHA and cytostatic drugs may reduce endogenous antioxidant tumor cell defenses, and increase drug uptake [48]. Interestingly, DHA and EPA do not sensitize non-tumor tissues to anticancer drugs, which suggest that the effect of these lipids is tumor-specific [49].

The strengths of the present study are the description of FA profile in plasma PC for the group of patients with squamous

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cell esophageal cancer This has only been reported once before, in a very small group of patients. Furthermore, the present study is the first to describe increased levels of PUFA n-3 in plasma PC after platinum-based CRT. The major drawbacks of this study are the lack of data for parameters of oxidative stress and for the content of fat in the diet.

Conclusions

Patients with EC in our study were characterized by significantly altered profile of plasma PC fatty acids – there were increased levels of both saturated and monounsaturated FA. The index of estimated activity of SCD1 was increased as well. Moreover, lower levels of LA and total PUFA n-6 were found in plasma PC of EC patients. The differences in FA profiles in esophageal cancer support the hypothesis that dietary supplementation could be important in this disease. The chemoradiotherapy was accompanied by increased DHA and total PUFA n-3 content of plasma PC, concurrently with decreased estimated activity of SCD1. With respect to the importance of these factors in the onset and development of cancer, the described changes in FA profiles during CRT could be involved in favorable functioning of CRT. Further studies investigating the plasma fatty acid compositions and their changes due to chemoradiotherapy in esophageal cancer patients are warranted.

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