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Fatty Acid Patterns in Gastric Mucosa of Stomach Cancer Patients

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ω6 and ω3 fatty acids are important cellular components and known to be involved in disease processes. However, few studies have focused on mucosa fatty acid in human gastric cancer. The purpose of this study was to investigate how fatty acid patterns of mucosa are altered in gastric cancer. Fatty acids were analyzed by gas chromatography and their relative compositions (%) were determined and evaluated both in mucosa total-fatty acids and in phospholipid-fatty acids in paired cancerous and non-cancerous gastric cancer tissues (n=18).

The level of arachidonic acid (20:4ω6, AA) appeared significantly higher both in phospholipid-fatty acids ($p<0.05$) and in total-fatty acids ($p<0.001$) in cancerous mucosa compared to non-cancerous mucosa. The ω6/ω3 fatty acid ratio of phospholipid-fatty acids was also significantly higher in cancerous mucosa. The higher level of AA in cancerous tissue can be partially explained by the higher ratio of 20:4ω6/20:3ω6 (desaturation index) and the lower ratio of 22:4ω6/20:4ω6 (elongation index). The change in the relative composition of arachidonic acid may influence the production of prostaglandins and related metabolites, which regulate cell differentiation and proliferation. The findings of this study with respect to fatty acid changes, especially in terms of arachidonic acid metabolism, may be of relevance in the understanding of the roles of specific fatty acids and possibly of eicosanoids in gastric cancer.

Key Words: Gastric cancer, fatty acid pattern, ω6/ω3 fatty acid ratio, arachidonic acid

INTRODUCTION

Phospholipid-fatty acids (PL-FAs) are important structural and functional components of the cell and have profound effects on membrane fluidity and cell metabolism.[1] Changes in lipid composition also alter the membrane transduction pathways of external signals and may consequently modulate the response of tumor cells to growth factors, thereby modifying the evolution of cancer.[2,3] Membrane FA composition of tumor cells results from the type of FAs available to the tumor cell, together with the specific metabolic properties of the tumor tissue, which includes alterations to enzyme pathways involved in FA uptake, activation, acylation, desaturation/elongation and oxidation.[4]

Dietary FAs can influence mucosa FAs.[5,6] In experimental animal models of mammary carcinogenesis, high dietary ω6 polyunsaturated FAs (PUFAs) were shown to stimulate mammary tumor growth, development and metastases, whereas a long chain ω3 PUFA enriched diet inhibited tumor growth.[7] Therefore, dietary long chain ω3 PUFAs seem to oppose the stimulation of tumor growth induced by ω6 FAs in the rat.[8] However, it is not known how dietary FAs influence the system. The wide range of biochemical conditions among cancer cells[9] makes it difficult to understand FA metabolism.

Despite the substantial amount of data on the role of dietary fats in cancer, few studies have focused on mucosal FA in human gastric cancer. In this research, the different FA patterns in human gastric cancer mucosa were investigated. The relative compositions (%) of FAs were analyzed both in the total mucosa and in the phospholipids in paired non-cancerous and cancerous gastric cancer tissues.

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MATERIALS AND METHODS

Subjects

Nine patients diagnosed with gastric cancer at the Yonsei Medical Center in Seoul, Korea, participated in this study. Gastric tissue, which otherwise would have been discarded, was obtained after surgical resection of the stomach (gastrectomy). Cancerous and non-cancerous (at least 10 cm away from the malignant site) gastric tissue samples weighing 2.0~3.0 g of full thickness were dissected from the tissues obtained by surgery. The tissue samples were frozen immediately in liquid nitrogen and stored at -70℃ until use. Patients characteristics are shown in Table 1.

This work was performed after obtaining approval from the Human Investigation Committee of the Yonsei University College of Medicine.

Fatty acid analysis

Preparations of the homogenates of stomach mucosal (cancerous and non-cancerous) tissues for fatty acid analyses were conducted as follows. The gastric mucosa was scraped with a scalpel, and approximately 50 mg (wet weight) of the scraped mucosa was used for analysis. Mucosal lipids were extracted using the method of Folch et al.[10] Phospholipids from the mucosa were separated by thin layer chromatography (TLC). The phospholipid portion in the silica gel was scraped off immediately after the TLC procedure and methylated, using the method of Lepage, Roy.[11] Lipid extract was obtained using the Folch method, and the fatty acid methyl esters were quantified by gas liquid chromatography (Hewlett Packard 6890A GC). For the gas chromatographic separation, we used a bonded fused-silica capillary column (Omegawax^{TM} 250). The GLC oven temperature was held at 180℃ for 5 min and increased to 210℃ in 2℃/min increments. The temperature of the injection and detector ports was maintained at 280℃. Helium was used as a carrier gas, at a flow rate 0.8 ml/min and with a split ratio of 10:1. Methyl esters of the various fatty acids were identified by comparison with GLC reference standards (#GLC-87A), Omegawax^{TM} test min (#4-8476), and PUFA- 2 (#4-7015, Supelco, Bellefonte, PA, USA). The peaks of the standard FA fractions were quantified using a Hewlett Packard 3365A series III Chemstation integrator. All GC analyses were performed in duplicate.

Statistical analysis

Results were analyzed using the SAS software package and the significance of the difference between the mean values of paired cancerous and non-cancerous gastric mucosa was tested using the paired t-test. All values were expressed as mean ± SEM.

RESULTS

Fatty acid patterns in tissue total-fatty acids (Total-FAs)

The composition of the total-fatty acid (total-FA) is shown in Table 2. The relative compo-

Table 1. Characterization of Patients with Gastric Cancer

Patient No.	Sex	Age	Height (cm)	Weight (kg)	BMI (Wt/Ht^2)	Pathology
1	M	66	150	55	24.4	Adenocarcinoma, poorly differentiated
2	M	36	168	53	18.8	Adenocarcinoma, poorly differentiated
3	M	57	163	44	16.6	Adenocarcinoma, poorly differentiated
4	M	42	168	55	19.5	Adenocarcinoma, poorly differentiated
5	M	57	167	48	17.2	Adenocarcinoma, poorly differentiated
6	M	62	167	68	24.4	Adenocarcinoma, moderately differentiated
7	M	59	164	55	20.4	Adenocarcinoma, lymphoepithelioma-like carcinoma type
8	F	68	162	61	23.2	Adenocarcinoma, poorly differentiated
9	F	68	153	58	24.8	Adenocarcinoma, well differentiated
Mean ± SEM		57 ± 1.25	1.64 ± 0.01	55 ± 0.77	20.9 ± 0.4	

Table 2. Relative Fatty Acid Composition of Total-fatty Acids in Gastric Mucosa

	Relative Composition(%)			
	Non-cancer*	Cancer*	p value	Cancer/Non-cancer
12:0	0.36 ± 0.06	0.70 ± 0.06	0.001	1.94
14:0	1.27 ± 0.25	0.96 ± 0.14		0.76
16:0	21.21 ± 0.67	20.34 ± 0.70		0.96
18:0	8.01 ± 1.02	11.08 ± 0.87	0.04	1.38
20:0	0.22 ± 0.01	0.30 ± 0.03		1.36
22:0	0.26 ± 0.04	0.41 ± 0.04	0.02	1.58
24:0	0.62 ± 0.27	0.40 ± 0.52		0.65
SFA	31.55 ± 1.03	33.96 ± 0.50	0.05	1.08
16:1 ω7	5.82 ± 0.34	3.05 ± 0.51	0.0004	0.52
18:1 ω7	2.81 ± 0.27	2.59 ± 0.24		0.92
18:1 ω9	29.23 ± 1.14	20.79 ± 1.76	0.001	0.71
20:1	0.52 ± 0.06	0.33 ± 0.07	0.05	0.63
22:1	0.15 ± 0.04	0.15 ± 0.03		1.00
24:1	0.24 ± 0.07	0.66 ± 0.09	0.002	2.75
MUFA	38.31 ± 1.54	27.56 ± 2.30	0.001	0.72
18:2 ω6	12.14 ± 0.27	12.88 ± 0.85		1.06
18:3 ω6	0.12 ± 0.03	0.08 ± 0.01		0.67
20:3 ω6	0.71 ± 0.17	1.30 ± 0.14	0.02	1.83
20:4 ω6	3.87 ± 0.37	7.69 ± 0.72	0.0005	1.99
22:4 ω6	0.37 ± 0.06	0.66 ± 0.08	0.01	1.78
22:5 ω6	0.14 ± 0.02	0.13 ± 0.01		0.93
$\sum\omega$6	19.30 ± 2.19	22.71 ± 1.54		1.18
18:3 ω3	0.29 ± 0.04	0.23 ± 0.03		0.79
20:3 ω3	0.08 ± 0.03	0.05 ± 0.01		0.63
20:5 ω3	0.77 ± 0.09	0.95 ± 0.13		1.23
22:5 ω3	0.73 ± 0.07	1.04 ± 0.08	0.01	1.42
22:6 ω3	2.91 ± 0.22	3.43 ± 0.37	0.003	1.80
$\sum\omega$3	4.78 ± 1.43	5.29 ± 0.49		1.10
PUFA	23.48 ± 0.90	28.41 ± 1.78	0.002	1.35
Others	6.06 ± 1.20	10.48 ± 1.26		
TOTAL	100.00	100.00		
$\sum\omega6/\sum\omega3$	4.70 ± 0.10	4.20 ± 0.38		

*Values are mean ± SEM.
The statistical significances between non-cancerous tissues were calculated using Student's t-test for paired data.

sitions of saturated fatty acids (SFA) ($p<0.05$) and PUFA ($p<0.05$) were significantly higher, and the monounsaturated fatty acid (MUFA, $p<0.001$) levels were lower in cancerous mucosa than in the paired non-cancerous mucosa. In particular, 16:1, 18:1 and 20:1 were significantly lower in cancerous mucosa than in non-cancerous mucosa. The higher PUFA compositions ($p<0.01$) in the total-FAs of cancerous tissue were mostly due to the longer chain PUFAs (20:3 ω6, 20:4 ω6, 22:4 ω6, 22:5 ω3, and 22:6 ω3). While the ratio of polyunsaturated fatty acids/saturated fatty acids (P/S) ratios was significantly higher in the cancerous mucosa, the ratio of $\omega6/\omega3$ was similar in the two paired groups.

Fatty acid patterns in tissue phospholipid-fatty acids (PL-FAs)

In terms of phospholipid fatty acids, 3 series fatty acids showed significantly ($p<0.05$) lower levels in cancerous mucosa than in non-cancerous tissue, although no significant differences were found in relative compositions of SFA, MUFA,

and PUFA. Among the $\omega 6$ fatty acids, arachidonic acid, the major precursor of the series II eicosanoids, was significantly higher ($p<0.01$) in the cancerous mucosa (Table 3, Fig. 1). The same result was obtained in total-FAs as in phospholipid fatty acids.

The $\omega 6/\omega 3$ FA ratio of PL-FAs was also significantly higher in cancerous mucosa ($p<0.01$) than in non-cancerous mucosa. This difference may be explained by higher levels of 20:4 $\omega 6$ and 22:5 $\omega 6$ and lower levels of 20:5 $\omega 3$ (EPA) and 22:6 $\omega 3$ (DHA) in the cancerous mucosa.

To examine to what extent desaturation mechanisms may account for the changes of fatty acid metabolism in cancerous mucosa, desaturation and elongation indices of PL-FAs were calculated (Table 4, Fig. 2). Though there was no apparent trend in desaturation or elongation indices in total-FAs, the delta-6, 5, and 4-desaturation indices calculated from the 18:3/18:2 $\omega 6$, 20:4/20:3 $\omega 6$, and 22:5/22:4 $\omega 6$ ratios, respectively, of the PL-FAs were all significantly higher and the elongation indices were all significantly lower in cancerous mucosa than in non-cancerous mucosa.

Table 3. Relative Fatty acid Composition of Phospholipid-fatty Acids in Gastric Mucosa

	Relative composition (%)			
	Non-cancer*	Cancer*	p value	Cancer/Non-cancer
12:0	0.85 ± 0.14	0.35 ± 0.09	0.009	0.41
14:0	1.34 ± 0.16	1.10 ± 0.17		0.82
16:0	29.05 ± 1.88	31.42 ± 1.42		1.08
18:0	16.60 ± 0.83	20.57 ± 0.94	0.006	1.24
20:0	0.60 ± 0.05	0.59 ± 0.04		0.98
22:0	0.85 ± 0.13	1.13 ± 0.25		1.33
24:0	0.65 ± 0.30	0.38 ± 0.07		0.58
SFA	49.72 ± 2.48	55.54 ± 1.88		1.12
16:1 $\omega 7$	0.84 ± 0.22	0.48 ± 0.16		0.57
18:1 $\omega 7$	1.02 ± 0.17	0.97 ± 0.29		0.95
18:1 $\omega 9$	3.10 ± 0.86	2.27 ± 0.58		0.73
20:1	0.39 ± 0.05	0.72 ± 0.16	0.002	1.85
22:1	1.23 ± 0.23	0.24 ± 0.05		0.20
24:1	0.46 ± 0.15	0.38 ± 0.12		0.83
MUFA	6.97 ± 1.16	5.06 ± 1.03		0.71
18:2 $\omega 6$	1.35 ± 0.25	1.48 ± 0.28		1.10
18:3 $\omega 6$	0.18 ± 0.02	0.45 ± 0.14		2.50
20:3 $\omega 6$	0.51 ± 0.08	0.32 ± 0.08		0.63
20:4 $\omega 6$	0.62 ± 0.07	1.23 ± 0.08	0.02	1.89
22:4 $\omega 6$	0.43 ± 0.09	0.50 ± 0.18		1.16
22:5 $\omega 6$	9.38 ± 1.31	11.73 ± 1.00		1.25
$\Sigma \omega 6$	12.60 ± 1.41	15.52 ± 0.98		1.23
18:3 $\omega 3$	0.18 ± 0.02	0.34 ± 0.08		1.89
20:3 $\omega 3$	0.63 ± 0.11	0.31 ± 0.07	0.04	0.49
20:5 $\omega 3$	2.66 ± 0.99	0.60 ± 0.05		0.23
22:5 $\omega 3$	0.40 ± 0.06	0.52 ± 0.15		1.30
22:6 $\omega 3$	1.49 ± 0.34	1.01 ± 0.09		0.68
$\Sigma \omega 3$	5.32 ± 0.41	2.78 ± 0.10	0.04	0.43
PUFA	17.91 ± 0.76	18.26 ± 1.06		1.02
Others	25.42 ± 1.20	21.14 ± 1.26		
TOTAL	100.00	100.00		
$\Sigma \omega 6/\Sigma \omega 3$	2.45 ± 0.73	5.57 ± 0.96	0.003	2.27

*Values are mean ± SEM.
The statistical significances between non-cancerous tissues were calculated using Student's t-test for paired data.

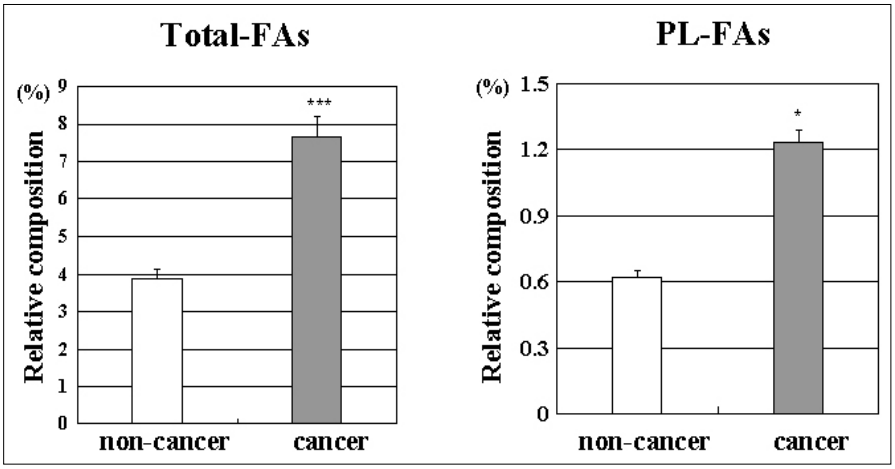

Fig. 1. Relative composition of arachidonic acid in cancerous and non-cancerous gastric mucosa. *p< 0.05, *** p<0.001. Total-FAs: total fatty acids, PL-FAs: phospholipid fatty aicds. The statistical significances between non-cancerous and cancerous tissues were calculated using Student's t-test for paired data.

Table 4. Desaturation & Elongation Index of Total-fatty Acids and Phospholipid-fatty Acids

	Total-fatty acids				Phospholipid-fatty acids			
	Non-cancer*	Cancer*	p value	Cancer /Non-cancer	Non-cancer*	Cancer*	p value	Cancer /Non-cancer
18:3ω6/18:2ω6	0.01 ± 0.001	0.01 ± 0.001		1.00	0.17 ± 0.04	0.38 ± 0.10		2.24
20:3ω6/18:3ω6	16.67 ± 1.47	20.51 ± 3.45	0.05	1.23	3.05 ± 0.62	0.92 ± 0.16	0.009	0.30
20:4ω6/20:3ω6	20.95 ± 4.92	16.19 ± 0.64		1.20	1.87 ± 0.41	5.79 ± 1.64	0.04	3.10
22:4ω6/20:4ω6	0.1 ± 0.06	0.08 ± 0.01		0.80	0.86 ± 0.33	0.44 ± 0.12		0.51
22:5ω6/22:4ω6	0.459 ± 0.02	0.21 ± 0.02	0.03	0.46	30.62 ± 6.74	51.82 ± 19.15		1.69

*Values are mean ± SEM.
The statistical significances between non-cancerous tissues were calculated using Student's t-test for paired data.

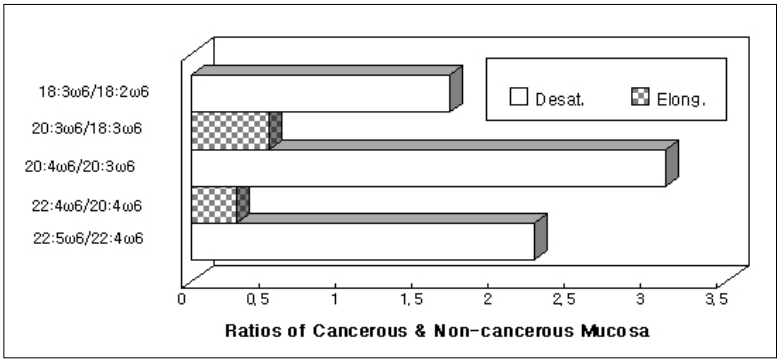

Fig. 2. Comparison between Desaturation and Elongation Index of PL-FAs in Cancerous and Non-cancerous Gastric Mucosa. Desat.: Desaturatiion, Elong.: Elongation PL-FAs: Phospholipid-fatty acids

The ratios of cancer/non-cancer values of all desaturation indices of ω6 fatty acids were remarkably higher (range 1.69~3.10) in PL-FAs than the elongation indices. There is a possibility that once desaturation from 20:3ω6 to 20:4ω6 increases, the subsequent elongation from 20:4ω6 to 22:4ω6 decreases, resulting in a larger amount of arachidonic acid (20:4ω6 AA).

DISCUSSION

The present study investigated the relative compositions (%) of FAs in both total-FAs and phospholipid (PL)-FAs in cancerous and non-cancerous gastric mucosa. The distribution pattern of fatty acids in tissues was found to broadly parallel the plasma profile[12], which may be the result of a combination of many different factors,

including biosynthesis, oxidation, esterification, turn-over rate, rate of conversion to eicosanoids, antioxidant systems and diet. This study ruled out the possibility of bias caused by different dietary FA compositions by comparing cancerous and non-cancerous mucosa in the same subjects.

In the total-FAs of cancerous mucosa, the relative compositions of SFAs were higher ($p<0.05$) and those of MUFAs (e.g. 16:1ω7, 18:1ω9) were lower ($p<0.001$) than those of non-cancerous mucosa. The fact that there was higher level of 18:0 and lower level of 16:1ω7 and 18:1ω9 in cancerous mucosa may be attributed to palmitic acid (16:0) being more converted to stearic acid (18:0) than to palmitoleic acid (16:1ω7) and stearic acid (18:0) being less converted to oleic acid (18:1 ω9).

In terms of PL-FAs, the $\omega6/\omega3$ FA ratio was significantly higher ($p<0.01$) in cancerous mucosa than in non-cancerous mucosa. This high ratio of $\omega6/\omega3$ FA was mainly due to a high level of AA and low levels of $\omega3$ fatty acids, such as 20:5ω3 (EPA) and 22:6ω3 (DHA). In a previous study[7] the results showed that high $\omega6$ FA diets stimulate mammary tumor growth and development, as well as metastases, while long chain $\omega3$ FAs or 18:3ω3 enrichment of the diet inhibits tumor growth. Erickson KL, Hubbard,[13] using a model of mammary tumor metastases, showed that mice fed $\omega6$ PUFA-rich diets showed increased in survival of metastatic cells. Other similar research has shown that dietary EPA and DHA caused increases in the low levels of EPA and decreases in the high content of AA in colon cancer mucosa and inhibited mucosa cancer cell growth[14]. According to Huang YC, et al.[15], plasma phospholipid $\omega6/\omega3$ FA ratio may be used as a nutritional compliance marker for chronic epithelial cell hyperproliferation. Among the saturated fatty acids of phospholipids, stearic acid (18:0), which was postulated to stimulate delta-5-desaturase, was found to be significantly higher in cancerous tissue.[16]

In this study, the fatty acid patterns in total fatty acids and in phospholipid-fatty acids were different. Membrane phospholipids are important reservoirs of the essential fatty acids for the body, and these may play important roles in the cell, for example they have a role in the maintenance of membrane structure and in the regulation of signal transduction.[16] Therefore, fatty acids in phospholipids may be more finely regulated in the normal physiological state, and any deviation from the normal pattern may be related to abnormal or disease states. The ratio of $\omega6/\omega3$ may provide a good example for explaining the different patterns between total-FAs and PL-FAs. Although, no change was found in the $\omega6/\omega3$ ratio of total mucosal FAs, a significant change was found in the total mucosal lipid subfraction, i.e. the phospholipid. The high level of $\omega6$ FA in cancerous tissue-PUFAs was mainly due to high AA levels, which is present in both total-FA and PL-FA. Arachidonic acid is usually incorporated into tissue PLs at carbon 2 and has to be released by the action of phospholipase A.

The AA content of the tissue is, therefore, related to the production of eicosanoids and related metabolites regulating cell differentiation and proliferation.[17,18] It has been reported that AA can directly or synergistically activate some species of protein kinase C[19,20] which affect membranes and Ca^{2+} availability, and activate cell differentiation and proliferation.[21] The higher levels of AA, especially in the PL of cancerous tissue, can be partially explained by the higher ratio of 20:4ω6/20:3ω6 (desaturation) and the lower ratio of 22:4ω6/20:4ω6 (elongation) as shown in Figure 2. It is interesting to note that changes in the specific activity of desaturase will alter the regulation of all fatty acids, because of its key role in fatty acid metabolism, and that this is particularly the case in chronic diseases, such as cancer, and cardiovascular disease.[22] The present study with gastric cancer showed that the $\omega6$-desaturation indices of PL-FAs were all higher in cancerous mucosa than in non-cancero mucosa. There is clear evidence[23] of changes in membrane fluidity in diseases, which may be either a cause or an effect of alterations of the membrane phospholipid metabolism or membrane bound enzyme activity. It can be speculated that the existence of a compensatory mechanism, which is evident in the higher levels of phospholipid-fatty acid desaturase indices in cancerous mucosa, increases the availability of PUFA for membrane fluidity regulation.

In conclusion, the findings of this study on fatty

acid changes, especially on arachidonic acid metabolism, may be of relevance to the understanding of the roles of specific fatty acids and possibly of eicosanoids in gastric cancer. Further studies are needed to differentiate the roles of fatty acids in different phospholipid fractions, such as phosphatidyl ethanolamine (PE) and phosphatidyl inositol (PI) and to clarify the roles of fatty acids, eicosanoids, and enzymes involved in the process of cancer development.

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