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Subcutaneous, omentum and tumor fatty acid composition, and serum insulin status in patients with benign or cancerous ovarian or endometrial tumors. Do tumors preferentially utilize polyunsaturated fatty acids?

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Abstract

The relationships between the fatty acid composition of cancerous endometrium and ovary, and peripheral adipose tissues were studied in Israeli Jewish women, and are presented together since no differences were shown between them. The results suggest a mobilization of linoleic acid from subcutaneous and omental depots and its incorporation into tumors accompanied by a high degree of desaturation. High blood insulin concentrations characterized patients with stage I and II disease, and low concentrations characterized patients with advanced degrees of malignancy. © 1997 Elsevier Science Ireland Ltd. All rights reserved

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1. Introduction

Cellular fatty acid composition may affect physical properties such as membrane fluidity, permeability, metabolic functions including transport systems, receptor binding, the activities of many cellular enzymes, eicosanoid production, motility and metastatic potential [1–5]. All of these properties are strongly influenced by polyunsaturated fatty acids (PUFA). Thus, the following have been reported. (a) PUFA incorporated in tumor cell membranes affect anti cancer therapy [6]. (b) n-6 linoleic fatty acid (LA) increases fluidity and enhances cell motility [5]. (c) LA and arachidonic fatty acids (AA) enhance protein kinase C, a key enzyme in the regulation of cell proliferation and function in a number of normal and tumor cells types [7], thereby increasing human cancer cell adhesion to extracellular matrix components [8] and enhancing the tumor metastatic potential [9]. (d) Normal cells enriched with LA had an increased number of insulin receptors with a decreased receptor affinity [10]. The same may occur in tumor cells, without affecting receptor affinity [11]. (e) LA pro-

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Table 1

Subcutaneous fatty acid (FA) composition from patients with cancerous (CA), benign (BE) ovarian or endometrial tumors and non-cancerous subjects (NC)

	Cancerous patients ($n = 45$)[a]	Benign or healthy subjects[a,b]	BE/CA ratio
Saturated FA			
14:0	0.08 ± 0.02	0.07 ± 0.03	88
16:0	21.60 ± 2.3	19.87 ± 0.8	92
18:0	5.50 ± 2.2	5.28 ± 1.1	96
24:0	0.25 ± 0.04	0.17 ± 0.02	68**
Total saturated FA	27.43 ± 2.8	25.39 ± 1.2	93
Monounsaturated FA			
16:1	4.47 ± 1.4	4.20 ± 1.2	94
18:1	40.26 ± 1.2	41.87 + 1.3	104
Total mono-unsaturated FA	44.73 ± 1.6	46.07 ± 1.5	103
Polyunsaturated FA			
18:2 n-6	20.50 ± 4.2	26.44 ± 1.6	129**
18:3 n-6	1.27 ± 0.5	1.28 ± 0.7	101
20:3 n-6	0.35 ± 0.09	0.15 ± 0.03	43**
20:4 n-6	0.38 ± 0.1	0.23 ± 0.02	61**
Total n-6	22.50 ± 3.1	28.10 ± 1.8	125**
18:3 n-3	0.95 ± 0.6	0.91 ± 0.5	96
20:5 n-3	0.39 ± 0.1	0.18 ± 0.1	48
22:6 n-3	0.19 ± 0.02	0.12 ± 0.08	65
Total n-3	1.53 ± 0.8	1.21 ± 0.9	70
16:0/16:1	4.83 ± 1.7	4.73 ± 1.3	98
18:0/18:1	0.136 ± 0.08	0.126 ± 0.09	92
18:2/20:4	53.94 ± 30.6	114.956 ± 18.6	213**
20:3/20:4	0.94 ± 0.13	0.65 ± 0.12	47**
n-6/n-3	14.70 ± 4.26	23.22 ± 2.1	180**
Saturated/unsaturated FA	0.39 ± 0.02	0.336 ± 0.01	86**

[a]Data are mean ± SD, expressed as % of total area: variation among measures was less than 2%.
[b]BE, $n = 21$; NC, $n = 15$.

vides structural and functional essential FA for dividing cells and serves as a precursor for eicosanoid metabolites of A4. Among these are prostaglandins which enhance tumor development, have immunosuppressing effects [12,13] and may be involved in angiogenic activity [14]. According to fatty acid analyses of subcutaneous adipose tissue, which reflects the intake of essential PUFA, the Israeli Jewish population has the highest dietary LA n-6 PUFA in the world. Several different studies yielded mean LA content ranging from 22.1% of total FA in 1986 [15] to 27.2% in 1994 [16]. In USA, where the intake of LA has been increasing progressively over the past decades, the LA content of adipose tissue has reached 16% [17], compared to less than 10% in most northern European countries, 12–14% in Germany, Italy and The Netherlands and 16.7% in Belgium [18].

Insulin status is another factor to be considered in the dietary/cancer complex. This is because high levels of insulin have been observed in cancerous tumors and in their adjacent adipose tissue [16,19] and hyperinsulinemia appears to be a common feature

Table 2

Omentum fatty acid (FA) composition from patients with cancerous (CA) or benign (BE) ovarian or endometrial tumors

	CA patients ($n = 45$)[a]	BE patients ($n = 21$)[a]	BE/CA ratio
Saturated FA			
14:0	0.11 ± 0.02	0.12 ± 0.02	111
16:0	19.86 ± 1.2	18.46 ± 0.9	93
18:0	4.16 ± 1.6	4.74 ± 1.2	114
24:0	0.22 ± 0.02	0.13 ± 0.02	63
Total saturated FA	24.35 ± 1.8	23.47 ± 1.3	95
Monounsaturated FA			
16:1	4.43 ± 1.2	4.17 ± 1.1	106
18:1	41.18 ± 3.6	41.40 ± 1.2	100
Total mono-unsaturated FA	45.61 ± 3.8	45.57 ± 1.4	101
Polyunsaturated FA			
18:2 n-6	24.19 ± 2.1	27.33 ± 0.8	113**
18:3 n-6	1.42 ± 0.8	1.29 ± 0.5	91
20:3 n-6	0.26 ± 0.07	0.15 ± 0.01	57**
20:4 n-6	0.36 ± 0.06	0.21 ± 0.02	58**
Total n-6	26.23 ± 2.4.	28.98 ± 1.5	112
18:3 n-3	1.02 ± 0.2	1.14 ± 0.8	112
20:5 n-3	0.37 ± 0.2	0.31 ± 0.1	86
22:6 n-3	0.32 ± 0.2	0.25 + 0.05	78
Total n-3	1.71 ± 0.8	1.70 ± 0.9	95
16:0/16:1	4.48 ± 1.6	4.42 ± 1.4	100
18:0/18:1	0.10 ± 0.09	0.114 ± 0.08	115
18:2/20:4	67.19 ± 24.8	130.14 ± 21.6	194**
20:3/20:4	0.72 ± 0.11	0.714 ± 0.13	99
n-6/n-3	15.34 ± 2.6	17.04 ± 3.1	118
Saturated/unsaturated FA	0.33 ± 0.1	0.30 ± 0.01	93

[a]Data are mean ± SD, expressed as % of total area: variation among measures was less than 2%.
**$P < 0.05$

in certain tumors [20–22]. Furthermore, many reports have emphasized the involvement of insulin in various processes associated with tumor cell proliferation and metabolism such as DNA synthesis [23], cell mitosis and growth [24] and eicosanoid formation by enhancing phospholipase AZ activity [25]. Also, dietary LA may augment insulin secretion [26]. This study forms part of an ongoing investigation on diet and insulin involvement in cancer and reinforces the results presented in our previous report [16,22].

2. Materials and methods

2.1. Patients, blood and tissue samples

Our study population comprised 45 patients suffering from ovarian and endometrial cancer tumors (CT), stages I–IV, undergoing laparotomy for possible surgical treatment and 21 patients undergoing laparotomy for benign tumors (BT). Biopsies of ovary and endometrium, subcutaneous and abdominal adipose tissue were obtained from all of these patients and of subcutaneous adipose tissue from 15 patients undergoing surgery for non-cancerous conditions. All samples were kept frozen at −20°C. Fasting venous blood was taken from CT and BT patients before and after surgery and from 23 healthy subjects.

2.2. Blood insulin concentrations

Serum insulin concentrations were determined by a double-antibody radioimmunoassay using ^{125}I-labelled human insulin (Pharmacia Diagnosis AB, Uppsala, Sweden).

2.3. Tumor and adipose tissue fat insulin and fatty acid composition

Tumor and adipose tissue fat insulin concentration, after weighing and homogenization (using a glass Potter homogenizer), sonification and centrifugation, was determined as in serum. Tissue fatty acid composition, approximately 0.5 g tissue in 5 ml methanol + 0.05% butylated hydroxytoluene, was stored at −20°C. Lipids were extracted with diethylether, dried under nitrogen and transmethylated by the method of MacGree and Allen [27]. Fatty acid analysis of the methyl esters was performed with a Perkin-Elmer Auto System Gas Cromatograph fitted with a 565 GLC column (1.85 m × 4 mm i.d.; Tracor, Inc., TX), filled with 10% SP-2330 on 100/120 Chromosorb in WAW 1-1851. The oven temperature was maintained at 18°C for 2 min and then raised to 23°C at a rate of 5°C/min. Peaks were identified by comparing their retention times with known standards (Supelco, Inc., Bellefonte, PA).

Table 3

Fatty acid (FA) composition of ovary (OV) and endometrial (EN), cancerous (CA) or benign (BE) ovarian tumors

	CA tumors[a,b]	BE tumours[a,c]	BE/CA ratio
Saturated FA			
14:0	0.10 ± 0.08	0.12 ± 0.06	120
16:0	21.91 ± 1.9	24.76 ± 2.9	113
18:0	8.25 ± 3.6	15.90 ± 1.8	193**
24:0	0.70 ± 0.2	0.86 ± 0.08	123
Total saturated FA	30.96 ± 3.8.	41.64 ± 3.9	135**
Monounsaturated FA			
16:1	3.25 ± 1.0	1.65 ± 0.5	51**
18:1	34.06 ± 8.8	23.16 ± 1.5	688**
Total mono-unsaturated FA	37.31 ± 0.9.5.	24.81 ± 1.9	66**
Polyunsaturated FA			
18:2 n-6	19.68 ± 6.6	9.84 + 2.7	50**
18:3 n-6	0.82 ± 0.2	0.49 ± 0.1	60**
20:3 n-6	1.74 ± 0.3	2.31 ± 0.2	133**
20:4 n-6	4.13 ± 4.8	13.71 ± 1.2	332**
Total n-6	26.37 ± 7.2	26.35 ± 3.6	100
18:3 n-3	0.96 ± 0.3	0.50 ± 0.1	53**
20:5 n-3	0.25 ± 0.05	0.36 ± 0.04	144**
22:6 n-3	0.75 ± 0.3	0.57 ± 0.2	77
Total n-3	0.96 ± 0.3	1.43 ± 0.2	74**
16:0/16:1	6.741 ± 4.5	15.00 + 3.4	221**
18:0/18:1	0.242 ± 0.2	0.686 ± 0.2	285**
18:2/20:4	4.765 ± 3.5	0.717 ± 0.4	0.15**
20:3/20:4	0.421 ± 0.1	0.168 ± 0.1	0.40**
n-6/n-3	13.45 ± 2.4	18.43 ± 2.0	135**
Saturated/ unsaturated FA	0.471 ± 0.2	0.807 ± 0.1	169**

[a]Data are mean ± SD, expressed as % of total area: variation among measures was less than 2%.
[b]OV stages I and II, n = 12; OV stage III, n = 14; EN stages I and II, n = 8; EN stages I and IV, n = 11.
[c]OV, n = 10; EN, n = 11.
**$P < 0.05$.

Table 4

Mean fasting serum insulin values of healthy subjects and patients (PA) with benign or cancerous ovarian or endometrial tumor

	Mean (μU/ml)
Healthy non-obese[a] subjects (n = 23)	6.56 ± 1.4[b]
Benign tumor patients (n = 21)	
15 non-obese PA	7.82 ± 2.1[b]
6 obese PA	14.14 ± 3.8[c]
Cancerous ovary and endometrium patients	
Stages I and II (n = 19)	
9 non-obese PA	19.25 ± 2.9[d]
11 obese PA	29.44 ± 6.1[e]
Stages III and IV (n = 23)	
9 non-obese PA	8.62 ± 7.1[b]
14 obese PA	14.58 ± 12.9[c]

[a]Obese, BMI>27.

[b,c,d,e]Different letters represent statistically significant differences, $P < 0.05$.

2.4. Statistical analysis

Statistical analysis was performed using paired t-tests, at significance level of $P < 0.05$.

3. Results

Omentum and especially the subcutaneous adipose tissues in CT patients exhibit opposite trends to benign ones (Tables 1 and 2), i.e. higher saturation index: 27.43 and 24.35%. of total FA in CT subcutaneous, respectively, vs. 25.39 and 23.47% in BT. However, the most evident differences in these tissues are the lower content of LA 18:2 in CT, 20.50 and 24.19% vs. 26.44 and 27.33%, and the significantly lower 18:2/20:4 ratio, 53.94 and 67.19 vs. 114.95 and 130.42 in BT. There is a notably high variability in the data obtained from the cancerous tissues themselves (Table 3). Despite this, there are some common characteristics in endometrial and ovarian tumors at all different stages of malignancy. Compared with ovarian or endometrial benign tumors, the cancerous ones had less saturated 16:0, 18:0 and 24:0 FA (presenting 30.96 as saturation index vs. 41.64), more 16:1, 18:1 FA (with a total of 37.31 monounsaturated FA vs. 24.81%), and significantly higher amounts of 18:2 LA (19.68 vs. 9.84%). Noteworthy is the low content of 20:4 n-6 in CT: 4.13 vs. 13.71%. Despite this, one may suppose that enzymatic actions are normal considering the amounts of 18:3 and 20:3 n-6 FA.

In the case of blood insulin (Table 4), significantly higher insulin values were found in non-obese CT at stages I and II and obese at all stages of disease (19.25, 29.44 and 14.58 μU/ml, respectively), and normal values, 8.62 μU/ml, in non-obese in the last stages. In comparison, normal non-obese subjects presented 6.56 μU/ml, BT non-obese 7.82 and obese ones 14.14 μU/ml.

4. Discussion

Fatty acid constituents in subcutaneous adipose tissue [15,16] and cholesterol esters [28] reflect the dietary fat intake, and are strong evidence for the high dietary LA of the Israeli Jewish population, including our cancer patients.

In comparison to healthy subjects, cancer patients (CP) had lower amounts of monounsaturated and PUFA and especially LA in the subcutaneous (20.50% LA vs. 26.44%) and omental adipose tissue (24.19 vs. 27.33%, Tables 1 and 2). Similar features have been shown also in cholesterol esters of patients from different types of cancer, leading Zureik et al., [29] to suggest that these patients had a lower intake of PUFA and an inverse association between intake of these FA and risk of death from cancer. An opposite trend characterized the tumor's fatty acid composition in comparison to benign tissues (Table 3), such as: a decreased saturation index, (30.96 vs. 41.64% of total FA), higher monounsaturated FA content (37.21 vs. 24.81%), a very high amount of LA n-6 (19.68 vs. 9.84%) and a very low AA n-6 (4.13 vs. 13.71%). This data may point to the following. (a) Mobilization of LA from peripheral adipose tissues and its incorporation into tumor's adipose tissues. This assumption merits further investigation, since these tissues exhibit specifically different fatty acid profiles. (b) Enhanced activity of the delta 9 desaturase enzyme, as reported by Wood et al. [30] in red cells from patients with various types of cancer, causing desaturation of 16:0 to 16:1 and stearic (18:0) to oleic acid (18:1). The high LA content in tumor cells is of special interest because, according to Taraboletty et. al. [5], it increases fluidity and enhances cell motility, activates protein kinase C [7] and enhances tumor metastatic potential [9]. One may postulate that the very high

Table 5

Mean incidence of endometrium and ovarian cancer in Israel (rates per 100000)

	Israeli-born			Migrants Europe and Asia			Migrants Africa and Asia			Non-Jews		
	1960	1989	1989/1960	1960	1989	1989/1960	1960	1989	1989/1960	1960	1989	1989/1960
Endometrium	7.9	14.3	1.81	10.7	11.1	1.04	4.6	7.1	1.54	2.6	6.8	2.61
Ovary	7.3	17.9	2.45	15.3	14.4	0.94	4.3	7.9	1.83	2.7	4.5	1.66

Sources: Israel Cancer Registry, Cancer in Israel, Facts and Figures, 1989. State of Israel, Ministry of Health, Department of Epidemiology, Jerusalem, 1993.

18:2/20:4 n-6 ratio present in tumor tissues from CP may be a sign of (a) decreased activity of the delta 6 desaturase elongase and delta 5 desaturase enzymes, as reported in insulin- or non-insulin-dependent diabetes mellitus patients [31–33]; (b) presence of high amounts of n-3 FA which inhibit competitively the n-6 FA pathway [34]; (c) increased lipid peroxidation. However, these assumptions are compatible with the considerable amounts of 18:3 and 20:3 n-6 FA observed in the cancer cells, the low concentrations of n-3 FA in benign and cancerous tissues as well (Table 3), and the fact that reduced peroxidation is a feature in rapidly growing cells. In addition, hyperinsulinemia does not affect insulin action in tumor cells [11], but on the contrary, in diabetic patients' tissues or even in normal tissues in CP. Therefore, it may be more acceptable to attribute the very low amount of the AA to its increased metabolism, via the lipoxygenase and cyclooxygenase pathways, to produce higher concentrations of eicosanoids, as shown by Fulton [35] and Hubbard et al. [36] in mammary tumors, and suggested by Chaudry et al. [37] for malignant prostatic tumor. This hypothesis is also reinforced by the fact that the mobilization and availability of 20:4 to eicosanoid formation are regulated by phospholipase A2 whose activity is enhanced by insulin [25], levels of which were high in CP (Table 4).

In this study, as in our previous study [16], obese and non-obese CP at stages I and II had pronounced hyperinsulinemia as compared to BT (19.25 vs. 7.82 μU/ml in non-obese patients, and 29.44 vs. 14.44 μU/ml in obese ones) and considerable amounts of insulin in cancerous tissue [16]. It is not clear why insulin levels return to normal in CP stages I and II after surgery [16], and why there are lower insulin concentrations at stages III and IV (8.62 μU/ml in non-obese patients and 14.58 μU/ml in obese ones). In addition to genetic failure, hyperinsulinemia may be caused by a combination of several factors such as: (a) impaired insulin metabolism as seen in obesity; (b) high consumption of LA [26]; (c) insulin secretion by insulin/secreting tumors [21]; and (d) enhanced secretion of insulin by pancreatic B cells induced by the tumor, presumably via some messenger [38]. Furthermore, hyperinsulinemia may lead to insulin resistance in normal cells and confer to cancer ones serious advantages. Insulin/cancer relationships merit investigation, especially because hyperinsulinemia and perhaps insulin resistance appear to be, in addition to its presence in ovarian and endometrial cancers, also a common factor in other types of human malignancy such as breast, lung, colon, and stomach [16,20,22].

The essentiality of insulin in cancer becomes apparent from studies performed with diabetic animals [38,39], and its involvement in cancer processes such as cell proliferation, DNA synthesis, cell mitosis and growth were extensively reported in several studies [23,24] and reviewed by Yam [21].

Table 5 presents the higher incidence of endometrium and ovarian cancer in all ethnic Israeli Jews in comparison to non-Jewish women. Incidence of both tumors is influenced by dietary fats [40,41]. Therefore, one may ask to what extent is the Israeli diet involved in this malignancy, especially because the non-Jewish diet include high intake of olive oil. In contrast to animal studies, studies in human have found little evidence of any association between intake of PUFA or vegetable fat and risk of cancer [42,43]. The findings of this study may point to an important role for vegetable oils in the development of ovary and endometrium neoplasia. This reinforces the concept that a high intake of LA may have deleterious effect as suggested in the USA, where breast

cancer mortality and LA intake have risen significantly in the past years [44].

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