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Adipose tissue and the effects of fat and calories on breast tumorigenesis in rats

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A high fat diet fed ad libitum *will promote breast tumorigenesis in rats while caloric restriction of the same high fat diet counteracts this promotional effect. The present study examined the effects of dietary fat and calorie intake on adipose tissue weight and fatty acid composition and on tumor incidence and development. The sites of adipose tissue chosen were the mammary fat pad, representing adipose tissue in the immediate location of the studied tumor, and the abdominal fat depot which in humans has been associated with an increased risk of breast cancer. High (20% corn oil) and low (5% corn oil) fat test diets were offered ad libitum and at 40% restriction levels. In agreement with prior studies, caloric restriction of both high and low fat diets led to marked decreases in tumor incidence (63 to 68% versus 21%), tumor burden (1.84 to 2.05 versus 0.37 to 0.43 tumors/rat), and tumor weight (7.1 to 11.9 versus 1.4 to 2.2 g) at the time of sacrifice (133 days post-DMBA). While final body weights were reduced in proportion to the level of caloric restriction (290 to 291 g versus 184 to 201 g), abdominal fat (8.8 to 9.2 versus 0.9 to 1.6 g), and mammary fat weights (3.1 to 4.1 versus 0.7 to 2.0 g) were reduced markedly in association with the decrease in tumorigenesis. While both tumor and mammary fat were enriched with linoleate reflecting the fatty acid composition of dietary fat, the ratio of arachidonic acid to linoleic acid was higher in tumor tissue than in surrounding normal mammary tissue in both the phospholipid (0.78 versus 0.18) and neutral lipid fractions (0.22 versus 0.03). These observations are consistent with the concept that increases in fat tissue mass in abdominal and mammary fat depots may mediate some of the promotional effects of high fat and high calorie diets. Restriction of dietary fat and calories to reduce body fat and strategies to modify the composition of stored lipids in fat depots may offer nutritional approaches to breast cancer prevention and treatment.* (J. Nutr. Biochem. 6:667–672, 1995.)

Keywords: DMBA; breast cancer; rat; fatty acids; adipose tissue; mammary gland

Introduction

In ad libitum fed rats, a high fat diet is associated with a significantly higher incidence and burden of DMBA-induced mammary tumors.[1] Caloric restriction[2–4] counteracts the promotional effects of high fat diets, and graded levels of restriction reduce tumorigenesis in a dose-response fashion.[5] The mechanisms by which fat and calories interact to potentiate tumorigenesis are not established. Both increased calories and increased dietary fat intake as a percentage of total energy intake have been proposed to mediate the promotional effects of a high fat diet fed ad libitum. Tumor incidence and development has been shown to increase in ad libitum fed animals receiving a low fat diet compared with calorically restricted animals maintained on a high fat diet and consuming considerably more dietary fat.[3,4,6] Thus, ad libitum feeding and increased energy intake are critical factors in the promotion of tumorigenesis in animals fed either high or low fat diets ad libitum.[7,8]

Dietary fats high in linoleic acid (18:2, n-6) such as corn

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oil have been shown to enhance the growth of mammary tumors.[9–11] Suggested mechanisms for this effect include alterations in membrane function, prostaglandin synthesis, local hormonal signals, and effects on immune function.[12,13] Prostaglandins, synthesized from arachidonic acid (20:4, n-6), have been found to be elevated in various tumors.[14,15] The epithelial parenchymal cells of rat mammary gland are surrounded by stromal adipose tissue. It has been shown that normal mammary epithelial cells cannot grow and proliferate outside the stromal microenvironment. Further, the invasion of adjacent normal tissue by tumor cells has been shown to involve the cell surface membrane components of the stroma and require intercellular contact.[16] Phospholipids, which are the major lipid constituents of the cell membrane, may be important in cell signaling, growth factor receptor availability, and tumor growth.[17] Diet can significantly alter the fatty acid composition of cell membranes, including phospholipids and other fractions that may influence the growth of neoplastic cells.

The present study examined the effects of dietary fat and calorie intake on adipose tissue weight and fatty acid composition and on tumor incidence and development. The sites of adipose tissue chosen were the mammary fat pad, representing adipose tissue in the immediate location of the studied tumor and the abdominal fat depot which in humans has been associated with an increased risk of breast cancer. High (20% corn oil) and low (5% corn oil) fat test diets were offered ad libitum and at 40% restriction levels.

Methods and materials

Seventy-six outbred female Sprague–Dawley rats were purchased from Simonsen Laboratories (Gilroy, CA, USA) at weaning. The animals were housed individually in standard stainless steel cages with wire mesh floors and maintained on 24 hr lighting cycle of 12 hr light and 12 hr dark.

All animals were fed a 5% corn oil diet ad libitum from the time of arrival on day 21 until day 62, i.e., 1 week after each rat received a single dose of 5 mg of dimethylbenzanthracene (DMBA) intragastrically dissolved in 1 mL of sesame oil. One week post-DMBA administration, the rats were weighed and distributed among the four diet treatment groups so that each group had similar mean body weight. Rats were maintained on their respective diets for 133 days. *Figure 1* depicts a schematic presentation of the experimental design. Rats in groups 1 and 3 (n = 19) received a 5% (low fat; LF) and a 20% (high fat; HF) corn coil diet, respectively, ad libitum, and their food intakes were determined every 3 days. Rats in groups 2 (low-fat restricted; LFR) and 4 (high-fat restricted; HFR) (n = 19 each) were energy restricted and received 60% of the mean daily energy intakes of rats in groups 1 and 2, respectively. Composition of the test diets is described in *Table 1*. The low fat ad libitum and low-fat restricted diets were isocaloric to the high fat ad libitum and high-fat restricted diets, respectively. The vitamin and mineral mixes as well as methionine and choline were adjusted to the level of caloric

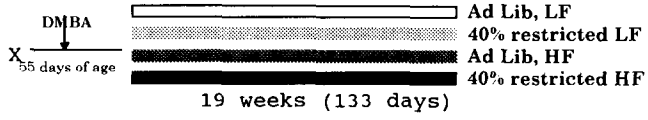

Figure 1 Experimental design.

Table 1 Composition of diets*

Ingredient	5% corn oil (LF)		20% corn oil (HF)	
	Ad libitum	Restricted	Ad libitum	Restricted
Casein	22	22	22	22
Corn oil	5	5	20	20
Sucrose	58	58	58	43
Celufil	10	10	10	10
AIN mineralst	3.5	6.0	3.5	6.0
AIN vitaminst	1.0	1.7	1.0	1.7
D-L methionine	0.3	0.5	0.3	0.5
Choline bitartrate	0.2	0.3	0.2	0.3

*All ingredients in g/100 g of diet.
†AIN, American Institute of Nutrition.

restriction to assure that the intake of these essential nutrients was not reduced with caloric restriction. In addition, all animals were palpated weekly for the occurrence of tumors.

The following measurements were made at the time of sacrifice: body weight; abdominal fat weight, determined by removing the mesenteric fat from the small and large intestines; mammary fat weight including connective tissue dissected free from the thoracic wall and pooled for each animal; tumor incidence, i.e., number of animals with tumors; and tumor weight and tumor burden (total weight of tumors per tumor bearing animal).

Fatty acid profiles of the mammary tumors and mammary glands was determined in rats of low-fat and high-fat ad libitum fed groups. The lipids were extracted from the tissues, by the method of Radin.[18] Briefly, 60 to 70 mg of tissue was homogenized in hexane-isopropanol (3:2, vol/vol). The clear extract containing virtually all the tissue lipids was divided into two parts and dried under nitrogen. To determine the fatty acid profile of the total tissue, one part of the extracted lipids was converted to methyl esters by direct transesterification using the method of LePage.[19]

The second portion of the lipid extract was fractionated into neutral and phospholipid by column chromatography using silica Sep-Pak columns.[20] Briefly, the dried sample of lipid in 2 mL of chloroform was placed on top of prewashed packing. The sample was followed by nine column volumes of chloroform. The eluate was collected as the neutral lipid fraction. This was followed by another 3 vol of chloroform to wash the column followed by 6 column vol of 1% acetic acid in methanol which eluted the phospholipids. The fractionation was carried out on a prepacked Sep-Pak column containing 2 g of adsorbent. The collected fractions were dried under nitrogen and lipids were transesterified by the method of LePage.

Fatty acid methyl esters were analyzed on a Hewlett-Packard (Palo Alto, CA, USA) 5830 gas chromatograph, using a 6 × ⅛ (OD), SP-2330 (68% cyano propyl silicone, polar) on 100/200 mesh SUPELCOPORT stainless steel column (Supelco Inc., Bellefonte, PA, USA). Chromatographic temperatures and conditions were: injector, 240°C; detector, 240°C; and column oven program, 100°C to 220°C, at 2°C/min. Identification of methyl esters was established by comparison of retention times with known standards (Nu-Chek-Prep, Elysian, MN, USA). Quantitative analyses were made from the peak areas determined by an electronic integrator.

Since preliminary data analysis did not show any significant difference between the fatty acid composition of mammary or tumor tissues taken from animals fed the 5 or 20% corn oil diet,

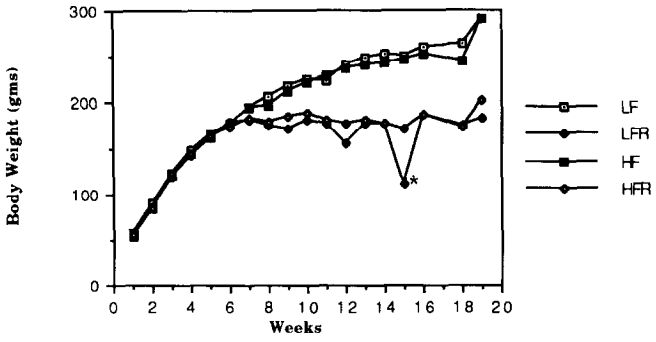

Figure 2 Changes in body weight in different groups during the 19 week post-DMBA administration feeding period.

tissues from animals were pooled in both 5 and 20% corn oil diet groups for subsequent analyses.

Statistical analysis was carried ou using analysis of variance via a SAS-BMDP package. The differences among groups was tested by analysis of variance and the Scheffe's multiple comparison procedure which was used for pair-wise comparisons. The differences among fatty acid composition between tumor and mammary gland was tested using student's *t*-test. Exact Chi-square test and two-way analysis of variance (ANOVA), was used to examine interactive effects of calories and fat on tumor number per group.

Results

The growth rates by treatment group are shown in *Figure 2*. Mean body weights were similar for the two ad libitum fed groups as well as for the two diet-restricted groups. The decrease in the mean body weights in the LFR group at week 15 may be attributed to the error made in the weighing of the number of animals in that week. The data were calculated as an average including the incorrect measurements taken. Thus the loss and gain in body weight in the LFR group during week 15 and 16 cannot be attributed to the LFR diet.

Tumors were observed in all four groups after DMBA administration. Animals fed a high-fat ad libitum diet had the highest number of tumors followed by those fed a low-fat diet ad libitum, HFR, and LFR diets. The number of tumors per group was similar for the low-fat and high-fat groups at either the ad libitum or the restricted feeding levels (*Figure 3*). However, energy restriction was associated with a highly significant increase in the total tumor number per group. Tumor incidence, tumor burden, and tumor weight per tumor burdened rat values are shown in *Table 2*. Tumor incidence and tumor burden were both significantly higher in the ad libitum fed compared with the calorically restricted groups. No effect of percent fat in the diet on tumor incidence or development was noted in either of the two ad libitum fed or the two calorically restricted groups.

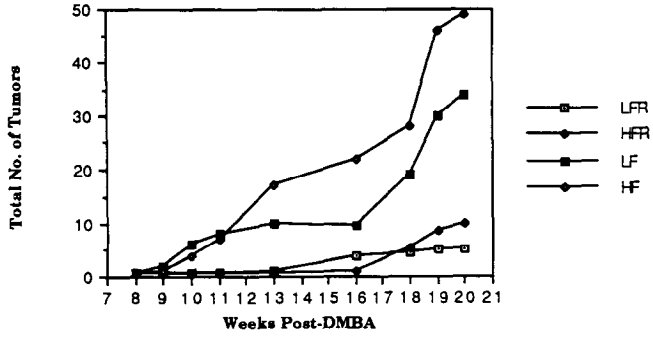

Figure 3 Total number of tumors in different diet groups during the 19 week post-DMBA administration feeding period.

Table 2 Tumor incidence, tumor burden, and tumor weight by diet treatment

Diet group	# of tumor bearing rats	Incidence (%)	Tumor burden (# of tumors/ rat)	Tumor weight per tumor burdened rat
LF	12/19	63	2.05 ± 0.43[a]	7.1 ± 3.6[a]
LFR	4/19	21	0.37 ± 0.16[b]	2.2 ± 0.8[b]
HF	13/19	68	1.84 ± 0.32[a]	11.9 ± 4.4[a]
HFR	4/19	21	0.42 ± 0.16[b]	1.4 ± 0.1[b]

Data are mean ± SE.
[a,b]Different superscripts denote a statistically significant difference at $P < 0.05$ (Scheffe's multiple comparison test).

Final body weights, mean daily energy intakes, and weights of the mammary fat pads and abdominal fat depots are shown in *Table 3*. There was a clear effect of energy restriction on reducing both abdominal and mammary fat depots. Energy restriction on either diet resulted in a greater proportionate decline in abdominal as compared with mammary fat weight.

The lipids of the mammary gland and tumor tissue showed a significant difference in their content of linoleic acid (18:2, n-6) and arachidonic acid (20:4, n-6) as shown in *Table 4*. The ratio of total arachidonic acid to linoleic acid was higher in tumor tissue than the mammary gland (1.36 versus 0.03). The percent of unknown peaks in the tumor were more than the mammary gland; however, none of the unknown peaks in the tumor tissue accounted for more than 1% of the total tumor fatty acid content.

To determine whether this difference merely reflected a difference in tissue contents of membrane-associated phospholipid and neutral lipid (largely intracellular), the amounts of the neutral lipid (NL) and phospholipids (PL) fractions in the tissues and the fatty acid profiles of the

Table 3 Final body weights, mean daily food intake, and weight of abdominal and mammary fat depots by diet treatment

Diet group	Final body weight (g)	Daily food intake (KCal)	Abdomen fat (g)	Mammary fat (g)
LF	291 ± 6[a]	55.4 ± 2.2[a]	8.8 ± 1.3[a]	3.1 ± 0.5[a]
LFR	184 ± 7[b]	34.6 ± 1.6[b]	0.9 ± 0.2[b]	0.7 ± 0.2[b]
HF	290 ± 10[a]	59.7 ± 2.3[a]	9.2 ± 1.1[a]	4.1 ± 0.8[a]
HFR	201 ± 4[b]	37.0 ± 1.7[b]	1.6 ± 2.2[b]	2.0 ± 0.4[a]

Data are mean ± SE.
[a,b]Different superscripts denote a statistically significant difference at $P < 0.05$ (Scheffe's multiple comparison test).

Table 4 Percentage distribution of fatty acids in total lipids of rat mammary gland and mammary tumor tissue

Fatty acid	Mammary gland (% fatty acid)	Mammary tumor (% fatty acid)
14:0	0.90 ± 0.43*	2.07 ± 3.17
16:0	17.55 ± 3.50	22.86 ± 2.39
16:1 (n-7)	3.92 ± 2.59	1.99 ± 0.92
18:0	11.03 ± 12.76	13.38 ± 3.31
18:1 (n-9)	22.38 ± 10.65	19.54 ± 4.05
18:2 (n-6)	37.84 ± 10.25	8.04 ± 3.75†
18:3 (n-3)	0.28 ± 0.01	trace‡
20:0	0.43 ± 0.11	0.29 ± 0.37
20:1 (n-9)	0.67 ± 0.17	0.19 ± 0.12
20:2 (n-6)	0.34 ± 0.19	0.42 ± 0.25
20:3 (n-6)	0.29 ± 0.01	0.49 ± 0.24
20:4 (n-6)	1.21 ± 0.14	10.95 ± 3.50†
24:0	0.21 ± 0.14	1.77 ± 0.97
24:1	0.33 ± 0.09	3.60 ± 1.53
22:6 (n-3)	0.09 ± 0.03	0.38 ± 0.18
Unknown	2.80 ± 1.13	9.11 ± 2.95

*Mean ± SD.
†Significantly different $P < 0.05$.
‡Trace: fatty acid <0.1%.

separate fractions were quantified as shown in *Table 5*. Palmitic acid (16:0), oleic acid (18:1, n-9), and linoleic acid were the predominant fatty acids in both mammary and tumor NL and PL fractions. Further, the NL in both tissue types contained a higher percentage of linoleic acid (18:2, n-6), oleic acid (18:1, n-9), and palmitic acid (16:0). The ratio of arachidonic acid to linoleic acid in the neutral lipid was much higher in tumor tissue than mammary gland (0.22 versus 0.03). In contrast, the phospholipid fraction of both the tissue types showed an increase in the percentage of arachidonic acid. Greater amounts of 16:0, 18:0, 20:4 (n-6), but less 14:0, 16:1 (n-7), 18:1 (n-9), and 18:2 (n-6) were noted with PL compared with NL in both tissue types. Nevertheless, the ratio of arachidonic acid to linoleic acid was again higher in tumor than mammary gland phospholipid fraction (0.78 versus 0.18).

Discussion

In humans, high-fat diets are associated with increased body fat, including intra-abdominal fat which is associated with hyperinsulinemia and metabolic changes promoting dyslipidemia, hypertension, and diabetes mellitus. Recently, increased intra-abdominal fat in women has been associated with an increased risk of breast cancer. Transplantable breast tumor cell lines can only be successfully implanted subcutaneously in areas which contain adipose tissue.

While increased body fat is associated with increased fat and calorie intake, studies over the last decade have demonstrated that adipose tissue is not metabolically uniform. Different metabolic and endocrine profiles are associated with regional differences in fat distribution.[21–23] A recent case-control study in a carefully matched group of 40 breast cancer patients demonstrated a significant association of increased intra-abdominal fat with breast cancer.[24] Intra-abdominal fat accumulation is associated with increased circulating androgens, insulin, and with increased risks for hypertension, diabetes, and heart disease.[21–23] Moreover, such patients have increased circulating free estradiol levels compared with patients with lower body fat providing a rationale for increased breast cancer promotion.[23]

Both fat content of the diet (percent of total calories as fat) and total caloric intake have been implicated in nutritional promotion of carcinogen-induced breast tumors.[3–8] In some studies, total energy intake appeared to be critical for expression of the tumorigenic effects of high fat diets, since energy restriction, even at moderate levels (12%), could

Table 5 Fatty acid profile of neutral lipid and phospholipid fractions of rat mammary gland and mammary tumor tissue*

	Neutral lipid		Phospholipid	
Fatty acid	Mammary gland (% fatty acid)	Tumor (% fatty acid)	Mammary gland (% fatty acid)	Tumor (% fatty acid)
14:0	0.8 ± 0.26†	1.07 ± 0.49	0.84 ± 0.37	0.5 ± 0.01
16:0	17.8 ± 2.35	20.9 ± 1.51	22.41 ± 1.76	25.7 ± 3.03
16:1 (n-7)	3.4 ± 1.56	3.65 ± 2.65	3.32 ± 1.22	1.95 ± 0.07
18:0	2.73 ± 0.06	6.2 ± 2.43	10.86 ± 5.03	12.6 ± 3.18
18:1 (n-9)	34.17 ± 4.13	29.82 ± 4.48	27.79 ± 8.97	23.73 ± 3.79
18:2 (n-6)	35.87 ± 8.17[a]	25.03 ± 3.68[b]	23.01 ± 2.7[b]	11.95 ± 5.33[a]
18:3 (n-3)	0.36 ± 0.21	0.15 ± 0.06	trace[b]	trace
20:0	0.47 ± 0.11	0.23 ± 0.12	0.45 ± 0.21	trace
20:1 (n-9)	0.9 ± 0.53	0.45 ± 0.40	0.37 ± 0.46	trace
20:2 (n-6)	0.4 ± 0.1	0.45 ± 0.13	0.13 ± 0.05	trace
20:3 (n-6)	0.33 ± 0.15	0.47 ± 0.10	0.79 ± 0.34	0.95 ± 0.62
20:4 (n-6)	0.96 ± 0.29[a]	5.63 ± 1.39[b]	4.05 ± 2.02[b]	9.38 ± 3.26[a]
24:0	0.13 ± 0.05	0.75 ± 1.10	2.35 ± 1.34	2.23 ± 0.70
24:1	0.37 ± 0.06	1.10 ± 0.71	1.25 ± 0.65	4.11 ± 0.72
22:6 (n-3)	0.07 ± 0.05	0.18 ± 0.05	0.08 ± 0.02	0.20 ± 0.01
Unknown	1.19 ± 0.26	3.91 ± 1.47	2.69 ± 1.99	7.63 ± 3.90

*Fatty acid analysis was carried out on pooled fractions from mammary gland and tumors of six animals.
†Mean ± SD.
[b]Trace: fatty acid <0.1%.
[a,b]Different numerical superscripts denote a statistically significant difference at $P < 0.05$ (Student's *t*-test).

antagonize these effects.[4,8,23] In studies reporting similar ad libitum energy intakes of high- and low-fat diets, conflicting results have been reported regarding enhancement of mammary tumor development. Some investigators find significant effects of dietary fat content on tumor promotion,[4,6] while others report only a minor effect.[3] These different results may reflect differences in experimental design relative to total energy intakes and the levels of energy retention which occur on low-fat and high-fat diets. In only one study was there an attempt made to determine directly the relationship between tumor development induced by a high-fat diet and energy retention associated with its consumption.[6] Greater energy retention was associated with increased tumorigenesis only when total energy intake was relatively high under ad libitum feeding conditions.[6]

As reported previously by others,[2–8,25] we observed a large diminution of DMBA-induced tumorigenesis by energy restriction. At 60% of normal intake, tumor incidence and burden as well as tumor weight per affected animal were reduced significantly compared with those observed under conditions of ad libitum intake (*Table 2*). Also consistent with data in the literature, under conditions of caloric restriction there was no difference observed in tumorigenesis when rats were fed high (20% wt/wt) or low (5% wt/wt) fat diets.[4]

Dietary fat is utilized with a higher metabolic efficiency than carbohydrate,[26] and consequently we anticipated larger abdominal and mammary fat depots in the rats fed isocaloric high-fat diets. However, there was only a small increase in adiposity in this group (*Table 3*). The reason is not clearly apparent, but since carcass analysis was not performed all adipose tissue depots were not measured in this study. Therefore, it is possible that additional fat was deposited subcutaneously.

It is noteworthy that under the ad libitum feeding conditions, there was no statistically significant effect of dietary fat content on tumorigenesis (*Table 2*). This may be explained by the fact that total energy intakes and adipose tissue accumulation on both the high- and low-fat ad libitum diets tended to be relatively high. According to Ip et al.[27] a propotional increase of mammary tumorigenesis is observed in the range of 3.5 to 4.4% of linoleic acid intake. A further increase of linoleic acid intake from 4.4 to 11.4% leads to a plateau in tumor incidence and tumor yield. Under these conditions even the low-fat diet group may have fulfilled the requirement for linoleic acid for enhancement of mammary tumorigenesis. Using the same strain and age of rats as in the current study, Welsch and co-workers observed a significant enhancing effect of the high-fat over the low-fat diet on DMBA-induced tumor incidence and growth when the two diets were consumed ad libitum at equal energy intakes.[4] However, in our study both groups of ad libitum fed rats consumed on average about 15 to 20% more energy than the animals studied by Welsch et al.[4] which may have obscured differences between the low- and high-fat diet groups.

Interestingly, energy restriction caused a greater relative reduction in abdominal as compared with the mammary fat weight on either test diet (*Table 3*). Abdominal fat thus appears to be more responsive to caloric restriction than mammary fat. This observation may be important in designing human intervention studies where intra-abdominal fat may have important effects on the levels of a number of hormones that could promote tumorigenesis (e.g., percent free estradiol, insulin, IGF-I).

The normal mammary epithelial cells cannot grow and proliferate outside a surrounding fatty stroma.[28] The fatty acid compositions of the stromal fatty tissues can be altered by feeding varying amounts of polyunsaturated fatty acid in the diet.[29] The high percentage of linoleic acid observed in the neutral lipids of mammary gland probably resulted from storage of linoleic acid from corn oil in the diet.

Furthermore, arachidonate levels were higher and linoleate levels were lower in tumor tissue compared with normal mammary gland. Similar differences in fatty acid composition between mammary gland and tumors have been reported by others.[30,31] In addition, Tan et al.[32] also reported an increased ratio of arachidonate to linoleate in both the neutral and phospholipid fractions of mammary tumor tissue compared with normal mammary gland in agreement with our observation.

The fatty acid composition of tumor neutral lipid was more reflective of dietary fatty acid intake than was tumor phospholipid fatty acid composition. This is not surprising because neutral lipid is composed primarily of storage triglycerides, which are derived from dietary triglyceride.[33] However, phospholipid is primarily associated with cell membranes, which tend to have a more constant composition. Tumor tissue phospholipid contained an increased percentage of arachidonic acid compared with the surrounding normal mammary tissue. Arachidonic acid, which is acylated in the membrane phospholipid cells is derived mainly from dietary linoleate with the conversion to arachidonate taking place in the liver.[34] Thus, while tumor tissue is capable of de novo arachidonate synthesis from linoleate, the activity and concentration of the required elongase and desaturase enzymes are extremely low. For this reason, much of the lipid utilized by the growing tumor is likely to come from the host and mechanism for mediating a transfer to tumor tissue must exist.[35]

The specific pool releasing arachidonic acid for prostaglandin synthesis has not been established. Some investigators have suggested that the arachidonic acid source may not be a phospholipid, but may be the free fatty acid fraction within the tumor cell[36] while others have found a positive correlation between phospholipid arachidonate and prostaglandin biosynthesis.[37] Phosphatidylinositol has been suggested as the primary source of released arachidonic acid[37] since it has a high turnover rate.[38]

Recent experiments have shown significant tumor growth inhibition in rats fed a marine oil–enriched diet high in omega-3 fatty acids.[39] Eicosapentanoic acid and docosahexaenoic acid present in fish oils may compete with arachidonic acid for enzymatic sites involved in prostaglandin synthesis[40] and may partially antagonize the overproduction of prostaglandins from omega-6 series fatty acids such as linoleic acid. Thus changes in the fatty acid composition of mammary fat and tumor tissue may affect tumor growth.

The relatively higher percentage of arachidonic acid observed in the tumor tissue phospholipid fraction may reflect both increased dietary intake of linoleate and enhanced activation of cellular signaling systems which can alter mem-

brane composition. Further, this enhanced availability of precursor fatty acids due to linoleate feeding may lead to elevation in tumor prostaglandin levels and inhibition of specific aspects of immune function to facilitate tumor growth.

Body fat is strongly correlated with dietary fat intake in epidemiologic studies of populations. The present study strongly suggests that body fat depots both in the breast and abdomen may be important correlates of excess fat and caloric intake which should be quantitated in human studies of nutrition intervention for breast cancer prevention.

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