Eur J Cancer Clin Oncol, Vol. 23, No. 4, pp. 407–410, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00
Pergamon Journals Ltd.

Comparison of Mammary Adipose Fatty Acid Composition in Japanese and American Breast Cancer Patients

P. HILL and E.L. WYNDER*

American Health Foundation, 320 East 43rd Street, New York, New York 10017, U.S.A.

Abstract—*In a comparative study of the fatty acid composition of pre- and postmenopausal Japanese and Caucasian breast cancer patients, a higher concentration of linoleic acid, the obligate precursor of arachidonic acid and its metabolites including prostaglandins, was significantly higher in postmenopausal Caucasian vs. Japanese patients. Comparable levels of linoleic acid occurred in premenopausal patients.*

Results indicate that a difference in linoleic acid metabolism occurs in postmenopausal Caucasian but not Japanese patients and suggest dietary modification could be beneficial in this high risk group.

INTRODUCTION

EPIDEMIOLOGICAL studies have linked the consumption of fat in Western Societies with increased risk of breast cancer [1] and with decreased relapse-free survival time, particularly in postmenopausal women [2, 3].

The fatty acid composition of a diet is reflected in the fatty acid composition of adipose tissue [4] which is similar in men and women [5] and in different locations of the body [6]. It is, therefore, of interest if the higher risk of breast cancer in Caucasian vs. Japanese women could be associated in part with differences in fatty acid metabolism in relation to oestrogen and prostaglandin metabolism in mammary adipose tissue.

In experimental animals, polyunsaturated fatty acids (PUFA) have been reported to modify mammary tumourigenesis by (1) inhibition of intercellular communication [7]; (2) aberrant prostaglandin production [8]; and (3) by their cocarcinogenic action [9].

Since PUFA are obligate precursors of prostaglandins, diet induced changes in fatty acid metabolism could be related to high concentrations of prostaglandins reported in mammary tumours in experimental animals [10] and man [11] and could concomitantly alter the immune response [12].

Accordingly, we have compared the fatty acid composition of mammary adipose tissue in Caucasian women with breast cancer with Japanese women with breast cancer who have a lower incidence and longer relapse-free survival time [13]. Concomitantly, we determined the fatty acid composition of mammary adipose tissue from premenopausal Caucasian women who died from causes other than breast cancer, to determine whether specific differences occur in the fatty acid composition of mammary adipose tissue of breast cancer patients.

METHODS

Mammary adipose tissue was obtained during mastectomy from pre- and postmenopausal Japanese and American patients. Healthy tissue was dissected from the mammary mass on ice and then frozen in tubes in acetone dry-ice. Samples were sent air mail in freezing containers to Valhalla, New York. Duplicate 0.5 g pieces were homogenized in ice cold ethanol–ether and the soluble fraction removed, and the residue re-extracted. The combined soluble fractions were evaporated to small volume and the fatty acids transesterified with percholic acid and methanol as described previously [14]. Samples were also obtained at autopsy in seven women, while needle biopsy of abdomen and hip adipose tissue were taken from Japanese men and treated as above.

Gas chromatographic analysis of the methyl esters was carried out on a 6 ft, 3.5 mm i.d. column,

Accepted 22 August 1986.
*To whom correspondence should be addressed.

Table 1. Fatty acid composition of adipose tissue in pre- and postmenopausal Japanese and American women with breast cancer

Fatty acid* C:O	Adipose tissue Patients Japanese Pre (16)†	Japanese Post (12)	American Pre (18)	American Post (5)	Control‡ (7)
14:0	2.7 ± 0.1§	3.3 ± 0.4	4.1 ± 0.4	5.2 ± 1.0	2.5 ± 0.2
16:0	24.4 ± 0.8	22.0 ± 1.	23.7 ± 1.2	16.5 ± 0.8†	24.8 ± 0.5
16:1	3.9 ± 0.5	3.8 ± 1.0	3.0 ± 0.4	5.2 ± 1.4	5.0 ± 0.8
18:0	4.0 ± 0.4	2.0 ± 0.3	6.1 ± 0.4	9.1 ± 0.1¶	4.7 ± 0.5
18:1	44.0 ± 1.2	45.0 ± 1.4	45.0 ± 2.7	32.8 ± 0.7‖	44.0 ± 1.1
18:2	17.0 ± 1.3	18.9 ± 1.2	16.4 ± 2.0	26.6 ± 0.9¶	15.8 ± 1.1

* C = Chain length; O = number of double bonds. Only major constituents included. 13% FA less than C. 14.0.
† Number of subjects per group. Pre = premenopausal; Post = postmenopausal.
‡ Obtained autopsy.
§ Mean ± S.E.
¶ $P \leq 0.01$ Significant increase in postmenopausal Caucasian vs. Japanese women patients.
‖ $P < 0.01$ significant decrease in postmenopausal Caucasian vs. Japanese patients.

containing 15% ethylene glycol succinate on Anachrom ABS 80/100 mesh operated at a constant temperature. Methyl esters were identified by comparing retention times with mixtures of methyl esters of known composition supplied by Applied Science Laboratories Inc., State College, Pennsylvania. The area of each peak on the chromatograph was expressed as a percentage of the total area of the fatty acids. This method gives a 95% recovery with intra- and interassay variation of less than 10%. A statistical differences between groups were determined by Student's *t*-test.

RESULTS

As shown in Table 1, the fatty acid composition of mammary adipose tissue from premenopausal Caucasian and Japanese patients were similar. The fatty acid composition of adipose tissue obtained at autopsy from Caucasian patients whose deaths were unrelated to breast cancer were also similar.

In postmenopausal and premenopausal Japanese patients, the fatty acid composition of adipose tissue were the same, but in postmenopausal Caucasian vs. Japanese patients a significant increase in linoleic acid (18 : 2) palmitic acid (18 : 0) and a significant decrease in stearic (16 : 0) and oleic (18 : 1) acids was observed.

DISCUSSION

In view of the lower mortality in postmenopausal Japanese compared to Caucasian women with breast cancer, the lower linoleic and higher oleic acid concentration in the former is of etiological interest.

Japanese subjects over the last 30 years have progressively increased their fat intake and concomitantly decreased the P/S ratio of their diet [15]. Interestingly, when Asian subjects, normally eating a diet containing a high linoleic acid content, are fed an American diet a marked decrease occurred in adipose linoleic acid [16]. In Caucasians, the linoleic acid contents of adipose tissue ranges from 7 to 12% with values as high as 26.2% in Seventh Day Adventist vegetarians [6]. However, despite the recent increase in PUFA in young American women and the increased daily fat intake and decrease in PUFA in Japanese women, the long chain fatty acid composition is markedly different [17]. The content of *n*-3, PUFA in Japanese subjects who used to eat 4 times the amount of fish eaten by Americans has decreased; a significant change since *n*-3 PUFA may decrease the growth of mammary tumors in experimental carcinogenesis [18].

Since a high concentration of prostaglandins in breast tumours is associated with an increased invasiveness [19] and decreased survival [18] changes in linoleic acid metabolism form an important factor in increasing tumour incidence [20]. In addition, the lower breast cancer mortality rate in Greece and Spain, countries with a high intake of monoenes (oleic, palmitoleic acids), support the conclusion that the composition of dietary fatty acids play a major role in the development of breast cancer.

Apart from differences in dietary patterns with age [21], differences in diet induced changes in the biological activity of oestrogens [22, 23] and their effect on the oxidation of fatty acid esters of oestradiol [24] and prostaglandins [11] in mammary adipose tissue may explain why diet-related changes are evident mainly in postmenopausal patients. Since the fatty acid content, including linoleic acid, of mammary tissue from women who died from causes unrelated to breast cancer was similar to that in premenopausal breast cancer patients, we suggest that the different adipose fatty acid composition induced by tumours [25] in postmenopausal

American patients may reflect adverse changes in linoleic acid metabolism associated with different growth factors related to hormonal dysfunction and dietary patterns. Comparison on the fatty acid composition of mammary adipose tissue of Caucasian and Japanese patients suggest that a higher polyunsaturated to monounsaturated fatty acid ratio is associated with an increased risk of this disease.

This study stresses the importance of the current dietary intervention studies in the treatment of postmenopausal patients.

REFERENCES

1. Wynder EL, Hirayama T. Comparative epidemiology of cancers in the United States and Japan. *Prev Med* 1977, **6**, 567–594.
2. Gregorio DI, Emrich LJ, Graham S, Marshall JR, Nemoto T. Dietary fat consumption and survival among women with breast cancer. *JNCI* 1985, **75**, 37–41.
3. Mulvihill MN, Posner J, Gotsis W, Saevitz J, Feinberg M. Effect of dietary habits and lipids on prognosis in breast cancer. *European Congress, Diet and Tumor Carcinogenesis. Abst.* 66, Aarhus, Denmark, 1985, June 19–21.
4. Field CJ, Clandinin MT. Modulation of adipose tissue fat composition by diet: a review. *Nutr Res* 1984, **4**, 743–755.
5. Heffernan AGA. Fatty acid composition of adipose tissue in normal and abnormal subjects. *Am J Clin Nutr* 1964, **15**, 5–10.
6. Hirsch J. Fatty acid patterns in human adipose tissue. *Handbook of Physiology*, Chapt. 17, Sect. 5, 1962, 181–189.
7. Stamford IF, Berstock DA, Bennett A. Early breast cancer death correlates with tumor prostaglandins in post- but not pre- menopausal women. London, Intl Assoc of Breast Cancer Research. Abst. 3–16, March, 24–28, 1985.
7. Aylsworth CF, Jone CY, Trosko JE, Meites J, Welsch CW. Promotion of 7,12-dimethylbenz[a]anthracene-induced mammary tumourigenesis by high dietary fat in the rat: possible role of intercellular communication. *JNCI* 1984, **72**, 637–645.
8. Dao RL, Chan PC. Effect of duration of high fat intake on enhancement of mammary carcinogenesis. *JNCI* 1983, **71**, 201–205.
9. Cohen LA, Thompson DO, Maeura Y, Choi K, Blank ME, Rose DP. Dietary fat and mammary cancer I. Modifying effects of different dietary fats on *N*-nitrosomethylurea induced rat mammary tumorigenesis. *JNCI* (in press).
10. Karmali R, Thaler HT, Cohen LA. Prostaglandin concentrations and prostaglandin synthesis activity in *N*-nitrosomethylurea-induced rat mammary adenocarcinoma. *Eur J Cancer Clin Oncol* 1983, **19**, 817–823.
11. Watson J, Chuah SY. Prostaglandins, steroids and human mammary cancer. *Eur J Cancer Clin Oncol* 1985, **21**, 1051–1055.
12. Chandra RK. Cell-mediated immunity in nutrition inbalance. *Fed Proc* 1980, **39**, 3088–3092.
13. Morrison AS, Black MM, MacMahon B, *et al.* Some international differences in histology and survival in breast cancer. *Int J Cancer* 1973, **11**, 261–267.
14. Hill P, Reddy BS, Wynder EL. Effects of unsaturated fats and cholesterol in serum and fecal lipids. *J Am Dietetic Assoc* 1975, **75**, 414–420.
15. Ueshima K, Asakura S. Time trend of fat intake among Japanese, 1956–1980. *Japan J Public Health* 1984, **31**, 325–330.
16. Scott RF, Lee KT, Kim DN, Morrison ES, Goodale F. Fatty aids of serum and adipose tissue in six groups eating natural diet containing 7–40 per cent fat. *Am J Clin Nutr* 1964, **14**, 280–290.
17. Kagawa Y. Impact of Westernization on the nutrition of Japanese: changes in physique, cancer, longevity and centenarians. *Prev Med* 1978, **7**, 205–217.
18. Jurkowski JJ, Cave WT. Dietary effects of an *n*-3 polyunsaturated lipid (Menhaden oil) on the growth and membrane composition of rat mammary tumours. *Proc Am Assoc Cancer Res* 1984, **210**, Abst. 832.
19. Rolland PH, Martin PM, Jacquemier J, Rolland AM, Toga M. Prostaglandin in human breast cancer. Evidence suggesting that an elevated prostaglandin production is a marker of high metastatic potential for neoplastic cells. *JNCI* 1980, **64**, 1061–1070.
20. Chan PC, Ferguson KA, Dao TL. Effects of different dietary fats on mammary carcinogenesis. *Cancer Res* 1984, **43**, 1079–1083.
21. Advanced data selected findings of food consumption profiles in white and black persons. 1–74 years of age in the United States, 1971–74. U.S. Dept HEW. Pub No V21, 1978.
22. Anderson KE, Kappas A, Conney AH, Bradlow HL, Fishman J. The influence of dietary protein and carbohydrate on oxidative biotransformations of estradiol in normal subjects. *J Clin Endocrinol Metab* 1984, **59**, 103–107.
23. Goldin BR, Adlercreutz H, Gorbach SI, *et al.* Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N Engl J Med* 1982, **307**, 1542–47.

24. Hershcope RJ, Bradlow HL, Fishman J, Swaneck GE, Larner JM, Hochberg RB. Metabolism of estradiol fatty acid esters in man. *J Clin Endocrinol Metab* 1985, **61**, 1971–1075.
25. Kitada S, Hays EF, Mead JF. A lipid-mobilising factor in serum of tumour-bearing mice. *Lipids* 1981, **15**, 168–174.