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Biomarkers of Dietary Exposure Are Associated with Lower Risk of Breast Fibroadenomas in Chinese Women[1,2]

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Abstract

Fibroadenomas are the most common benign breast condition among women and account for up to 50% of all breast biopsies being performed. Although considered a benign condition, fibroadenomas utilize substantial resources for management and treatment to rule out potential malignancies. Dietary factors may influence benign fibrocystic breast conditions, but little is known of their association with fibroadenomas. We examined possible associations between a broad spectrum of circulating biomarkers of dietary intake and risk of fibroadenomas. Participants were women in a breast self-examination trial in Shanghai, China who were diagnosed with fibroadenomas (n = 258) and 1035 controls. Conditional logistic regression was used to estimate adjusted odds ratios (OR) and 95% CI. Isoflavone concentrations were inversely associated with risk of fibroadenomas. Adjusted OR (95% CI) for the highest versus the lowest quartile of plasma concentration were 0.36 (0.16–0.79; P-trend < 0.001) for daidzein and 0.39 (0.19–0.84; P-trend = 0.010) for genistein. We also observed inverse associations between higher percentages of the RBC (n-3) fatty acids, eicosapentaenoic acid (EPA) ([0.38 (0.19–0.77); P-trend = 0.007] and docosapentaenoic acid (DPA) [0.32 (0.15–0.70); P-trend = 0.024], and fibroadenoma risk. Circulating concentrations of carotenoids, vitamin C, retinol, and ferritin were not associated with fibroadenoma risk. The inverse associations between plasma isoflavone concentrations and RBC EPA and DPA and fibroadenoma risk suggest that higher intakes of soy foods and fatty fish may lower the risk of fibroadenomas. J. Nutr. 140: 1302–1310, 2010.

Introduction

Fibroadenomas are characterized by an overgrowth of fibrous tissue with epithelial elements and present as firm, smooth, and mobile rubbery breast masses that are usually painless (1). Fibroadenomas are the most common benign breast lumps in women <25 y of age and they account for 50% of all breast biopsies performed (2). The process of evaluation and management has an enormous impact on the cost of health care and causes physiological and psychological stress to the patient (3–5). After reaching young adulthood, incidence rates decrease with age and fibroadenomas are rarely found in women after menopause (6,7).

Fibroadenomas are considered a benign disease (8,9), although several studies have found an increase in breast cancer risk among women with fibroadenomas compared with unaffected women of similar age (10–13). Low parity (6,14), older age at first live birth (15), and a history of previous benign breast lesions have been associated with an increased risk of fibroadenomas. Use of oral contraceptives (16) and cigarette smoking (17) have been associated with reduced risk. Studies of nutritional factors in relation to benign breast diseases in the aggregate, which have included women with fibroadenomas, have yielded inconclusive results (14,18–21).

In a study of Australian women, Yu et al. (14) reported that the risk of fibroadenomas tended to be inversely associated with the intake of β-carotene and vitamin C as estimated from a FFQ. The use of biomarkers that reflect not only dietary intake but also effects of absorption, metabolism, and excretion may be more informative than self-reported dietary intake alone in characterizing exposure at the tissue level. In the current study, we investigated possible associations between plasma concentrations of isoflavones, carotenoids, retinol, vitamin C, and ferritin, as well as RBC fatty acids, and fibroadenoma risk in a case-control study in Shanghai, China. We further explored the

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relationship between different ratios of RBC fatty acids and fibroadenoma risk.

Materials and Methods

Study setting and recruitment. This study is a nested-case control study of women who were recruited from a previously described randomized trial of breast self-examination (BSE)[9] in Shanghai, China (22). Participants in the BSE trial were employees of the Shanghai Textile Industry Bureau born between 1925 and 1958. Women were interviewed and enrolled into the trial between 1989 and 1991 and were followed for occurrences of benign or malignant breast conditions through July 2000.

We provide a detailed description of case and control selection for the present study in a companion paper (23). Briefly, this study included women who, in addition to being in the BSE trial, were reinterviewed for 2 studies of benign and malignant breast conditions conducted from September 1995 to July 2000. At the time of this reinterview, participants were asked to donate a blood sample, which was the source of the biologic specimens for this study.

Case selection. Eligible cases were women who were diagnosed with histologically confirmed fibroadenomas between September 1995 and July 2000 and who had no prior or concurrent breast malignancy. For 296 (90.0%) of the 327 interviewed women, nonfasting blood samples for analysis of the biomarkers were available. From these 296 women, we further excluded 38 women for whom the date of blood draw was >30 d before or 2 wk after the date of diagnosis or >30 d from the date of interview. Thus, 258 women with fibroadenomas were included in the study.

Control selection. Control women were randomly selected from women in the BSE trial with no breast biopsy. For each benign (i.e. fibroadenoma and other fibrocystic breast condition) and malignant (i.e. breast cancer) case that was diagnosed between September 1995 and August 1997, 2 controls were selected by matching on age and menstrual status, but the matching was not retained and all controls selected in this manner were included in the present study. Controls for the remaining cases were frequency matched to cases by 5-y age group and hospital affiliation of their factories at baseline. Of the 1070 interviewed controls, 1041 women had a nonfasting blood sample for the analyses of biomarkers. Five women were excluded because their date of blood draw was >30 d from the date of the in-person interview.

To be eligible for inclusion in the analyses, cases and controls had to have at least 1 biomarker measured. These criteria were met by all participants, except for 1 control woman, yielding a final sample of 258 women with fibroadenomas and 1035 control women.

The Institutional Review Boards of the Fred Hutchinson Cancer Research Center and the Station for Prevention and Treatment of Cancer in the Shanghai Textile Industry Bureau approved the study in accordance with the assurance of the Office for Human Research Protection of the U.S. Department of Health and Human Services. Informed consent was obtained from each woman before the interview.

Validation of diagnoses. A reference pathologist reviewed slides from a subset of the cases. Of the 158 fibroadenomas diagnosed by a pathologist in Shanghai, 136 (86.1%) were identified by the reference pathologist as fibroadenomas. Six (3.8%) of the fibroadenomas were classified by the reference pathologist as phyllodes tumor and the remaining 16 (10.1%) were classified as other benign breast conditions. Because of this high concordance, no further slide review was undertaken for this study and the diagnoses made by the pathologist in Shanghai were used for this investigation.

Plasma daidzein and genistein. The methods used to measure plasma daidzein and genistein concentrations have been described in detail previously (23). Two different methods were used. Initially, the liquid chromatography (LC)-Coularray method was used. Later, we switched to a LC-MS method to improve assay efficiency and precision of the sample measurements (23). Comparison of the 2 methods showed that mean serum daidzein concentrations were higher when analyzed by LC-Coularray compared with LC-MS, but mean serum genistein concentrations were similar in the 2 methods (23). Samples from 62 women with fibroadenomas and 62 controls were analyzed by the LC-Coularray method. Samples from 193 women with fibroadenomas and 741 controls were analyzed by LC-MS. For both methods, daidzein and genistein concentrations of <1 μg/L (3.9 and 3.7 nmol/L, respectively) were considered below the limit of quantitation and were assigned the midpoint value of 0.5 μg/L (1.9 and 1.8 nmol/L).

Plasma vitamin C. Vitamin C concentrations were measured on frozen plasma samples that were preserved prior to freezing with a solution of meta phosphoric acid/dithiothreitol (final concentration: 3.6% meta phosphoric acid, 4.86 mmol/L dithiothreitol). After thawing, samples were centrifuged for 10 min at 4°C and 2368 $\times$ *g* to remove precipitate and produce a clear supernatant. Ascorbic acid was oxidized to dehydroascorbic acid (DHAA) by ascorbic acid oxidase. DHAA is converted to the quinoxolone derivative by a reaction with *O*-phenylenediamine at pH 6.5. The *O*-phenylenediamine-DHAA absorbs at 340 nm and this absorbance is directly proportional to the ascorbic acid concentration in the sample. A 5-point standard curve was included in every run. Linearity of the assay was 5.7–170 μmol/L. Two in-house quality controls were assayed at the beginning and the end of each run. The intra-assay CV were 6.3 and 1.3%. and the inter-assay CV were 8.1 and 5.0% at 44.3 and 93.7 μmol/L, respectively.

Plasma carotenoids. The extraction of analytes from plasma, the quality control parameters, and the HPLC methods were previously published (25,26). Briefly, hexane extract of serum injected onto a 3-μm C-18 Spherisorb ODS-2 HPLC column was eluted with an isocratic solvent consisting of 73% acetonitrile, 12% tetrahydrofuran, 8% methanol, 7% water, 0.025% ammonium acetate, and 0.05% diethylamine by volume at a flow rate of 1.2 mL/min. Detection limits for analytes were as follows: 476 nmol/L for lutein, zeaxanthin, β-cryptoxanthin, and lycopene, 452 nmol/L for α-carotene and β-carotene, and 325 nmol/L for retinol. The HPLC system was a fully automated Hewlett Packard 1050 system that included quaternary pumps, electronic degasser, insulating column housing, automatic sampler, diode array detector, and software to control the system and perform data management. The CV for pooled quality control samples for all analytes were $\leq$10%.

RBC fatty acids. We previously described in detail the method to analyze RBC fatty acids (27). RBC were processed to extract lipid and produce FAME, which were separated by GC and detected using a flame ionization detector. The accuracy of the chromatographic system was monitored with commercial standards (GLC-87, NIH-D, and NIH_F; Nu Check). Fatty acid composition is reported as a weight percentage of the total RBC fatty acids.

Plasma ferritin. Plasma ferritin was measured by a 2-site immunoradiometric technique using a commercially available reagent kit, DPC Coat-A-Count Ferritin IRMA. Plasma samples, BioRad Laboratories controls, and 7 levels of standards were analyzed in duplicate (28).

Data analysis. Frequencies of demographic and reproductive characteristics in the cases and controls were compared. Percentages among cases were standardized to the age distribution of the controls using the indirect method of adjustment (29). For the fatty acids, we created ratios of fatty acids including (n-3):(n-6) fatty acid ratios, and the (n-7) and (n-9) fatty acid saturation indices (SI). The SI represent ratios of the 2 most common SFA in tissues and monounsaturated fatty acids that are direct metabolites of these SFA (30,31). The (n-7) fatty acid SI was the ratio of palmitic acid:palmitoleic acid and the (n-9) fatty acid SI was the ratio of stearic acid:oleic acid. Biomarker variables were categorized into quartiles according to their distribution among all controls. Conditional logistic regression models were used to calculate odds ratios (OR) and

[9] Abbreviations used: BSE, breast self-examination; DPA, docosapentaenoic acid; DHAA, dehydroascorbic acid; EPA, eicosapentaenoic acid; LC, liquid chromatography; OR, odds ratio; SI, saturation index.

TABLE 1 Characteristics of fibroadenoma cases and control women in Shanghai, China

	Cases, n = 258	Controls, n = 1035
Age, *y*	*n (%)*	
35–39	52 (22.3)[1]	13 (1.3)
40–44	157 (58.8)	460 (44.4)
45–49	38 (15.2)	217 (21.0)
50–59	6 (2.0)	122 (11.8)
≥60	5 (1.7)	223 (21.6)
Live births, *n*		
0	10 (2.6)	37 (3.6)
1	234 (70.6)	700 (67.9)
2	9 (5.3)	119 (11.5)
≥3	5 (21.5)	175 (17.0)
Age at first live birth,[2] *y*		
≤24	13 (23.9)	193 (20.4)
25–29	170 (52.0)	579 (61.2)
≥30	55 (24.1)	174 (18.4)
Duration of breast-feeding,[2] *mo*		
Never	58 (22.9)	183 (18.4)
≤6	74 (19.2)	205 (20.6)
7–12	99 (32.3)	355 (35.7)
13–24	12 (4.4)	111 (11.2)
≥25	5 (21.3)	140 (14.1)
Duration of oral contraceptive use, *y*		
0	250 (98.3)	945 (91.4)
≤1	6 (1.2)	34 (3.3)
≥1	2 (0.6)	55 (5.3)
Age at first menstrual period, *y*		
≤13	36 (18.5)	150 (14.6)
14	66 (19.6)	198 (19.3)
15	49 (18.4)	198 (19.3)
16	39 (22.8)	216 (21.0)
≥17	66 (20.8)	266 (25.9)
Menopausal status		
No	240 (66.6)	674 (65.1)
Yes	18 (33.4)	361 (34.9)
Prior breast lump		
Never	183 (96.8)	987 (96.8)
Ever	67 (3.2)	32 (3.7)
BSE, *n/y*		
Never to 1	111 (41.8)	709 (69.0)
2–5	36 (10.1)	93 (9.1)
6–12	102 (45.5)	219 (21.3)
≥13	4 (2.6)	7 (0.7)
BMI, *kg/m²*		
≤20	87 (22.1)	195 (18.8)
21–25	259 (56.4)	607 (58.7)
≥26	23 (21.5)	233 (22.5)
Education level		
≤Elementary	11 (22.8)	195 (18.9)
Middle school	235 (68.6)	810 (78.3)
≥College	12 (8.7)	29 (2.8)
Family history of breast cancer		
No	253 (97.2)	1019 (98.5)
Yes	5 (2.8)	16 (1.6)
Smoking		
No	255 (99.2)	1011 (97.7)
Yes	3 (0.8)	24 (2.3)
Daily energy intake, *kJ/d*		
<6908	80 (23.6)	260 (25.1)
6908–7828	70 (30.1)	259 (25.0)
7828–8908	61 (23.3)	257 (24.8)
>8908	47 (23.0)	259 (25.0)
Alcohol intake, *g ethanol/y*		
0	232 (87.2)	914 (88.3)
10–110	16 (4.3)	31 (3.0)
≥120	10 (8.6)	90 (8.7)

[1] Indirect age-adjusted percentages based on age distribution of the controls.
[2] Among women with a live birth.

95% CI, with the lowest quartile serving as reference group. All models were adjusted for age, using 5-y age categories. To control for possible changes in dietary habits, and because blood draws from controls tended to have been taken at a later date than those from the cases, the models were stratified by year of blood draw (1995–1996, 1997, 1998–1999, 2000–2001). For the isoflavone analyses, models were further adjusted for the plasma isoflavone analysis method.

We evaluated potential confounding by adding each variable related to fibroadenomas, or suspected a priori to be related to fibroadenomas, to the age-adjusted model individually and we compared the full model with and without the covariate. Potential confounders considered were age at first birth, the number of live births, total duration of lactation, years of oral contraceptive use, age at first menstrual period, menopausal status, prior breast lump, number of times BSE performed per year, BMI, and education. For parsimony in model construction, covariates that changed the estimate of OR over 10% were included in the final model (32). Only prior breast lump changed the estimates appreciably and was therefore included in the final model (yes/no categories).

Tests for trends were carried out by entering the categorical variable as a continuous parameter in the regression models. Pearson's correlation coefficient was used to determine collinearity between the biomarkers. Results are presented for 2-sided tests based on a nominal significance level of $P = 0.05$. In addition, we readjusted the P-values by applying Bonferroni's corrections for the number of simultaneous tests conducted within each category of analyte (i.e. isoflavones, carotenoids, and RBC fatty acids). Analyses were carried out using SAS statistical software (SAS Institute).

Results

The fibroadenoma cases tended to be younger than the control women; 96% of cases were younger than 50 y of age at time of diagnosis compared with 67% of the controls (**Table 1**). This was expected, because the control women were selected to serve as controls for cases of all breast conditions, including breast cancer, fibrocystic conditions, and fibroadenomas. As described in our companion paper (23), fewer women with fibroadenomas than control women reported use of oral contraceptives. In addition, the cases, compared with the controls, tended to be younger at menarche, had higher education levels, were older at first live birth, and reported more BSE per year than the controls.

The adjusted OR (95% CI) for risk of fibroadenomas were inversely associated with both daidzein [0.36 (0.16–0.79) for the highest vs. lowest quartile; P-trend < 0.001] and genistein concentrations [0.39 (0.19–0.84) for the highest vs. lowest quartile; P-trend = 0.01] (**Table 2**). Among the carotenoids, only plasma α-carotene was associated with fibroadenoma risk [1.72 (0.87–3.37) for the highest vs. lowest quartile; P-trend = 0.018]. There were no significant associations with any of the other carotenoids, retinol, vitamin C, or ferritin.

TABLE 2 Risk of fibroadenomas in relation to quartiles of plasma isoflavone, carotenoid, vitamin C, and ferritin concentrations among women in Shanghai, China[1]

	Quartiles of biomarker concentrations				
	1	2	3	4	*P*-trend
Isoflavones, *nmol/L*					
Daidzein					
Cases/controls, *n/n*	100/239	61/238	41/240	36/238	
Quartiles cutoff points	<27	27–73	73–166	>166	
OR (95% CI)[2]	1.00	0.82 (0.41–1.66)	0.27 (0.13–0.58)	0.36 (0.16–0.79)	<0.001[3]
Genistein					
Cases/controls, *n/n*	91/246	64/244	52/245	44/246	
Quartiles cutoff points	<35	35–118	118–284	>284	
OR (95% CI)	1.00	0.44 (0.22–0.86)	0.42 (0.22–0.84)	0.39 (0.19–0.84)	0.010[3]
Carotenoids, μ*mol/L*					
α-carotene					
Cases/controls, *n/n*	52/257	59/262	66/259	81/255	
Quartiles cutoff points	<0.0317	0.0317–0.0400	0.0400–0.0522	>0.0522	
OR (95% CI)	1.00	0.96 (0.49–1.86)	1.35 (0.70–2.62)	1.72 (0.87–3.37)	0.018[4]
β -carotene					
Cases/controls, *n/n*	64–257	69/258	75/259	50/259	
Quartiles cutoff points	<0.3800	0.3800–0.5476	0.5476–0.7525	>0.7525	
OR (95% CI)	1.00	1.04 (0.55–1.96)	2.02 (1.07–3.84)	1.13 (0.59–2.18)	0.30
Total lycopene					
Cases/controls, *n/n*	41/253	86/261	61/262	70/257	
Quartiles cutoff points	<0.1356	0.1356–0.1993	0.1993–0.3129	>0.3129	
OR (95% CI)	1.00	1.62 (0.84–3.14)	1.37 (0.68–2.77)	1.77 (0.91–3.46)	0.17
Trans-lycopene					
Cases/controls, *n/n*	47/246	87/285	58/243	66/259	
Quartiles cutoff points	<0.0522	0.0522–0.0857	0.0857–0.1583	>0.1583	
OR (95% CI)	1.00	1.27 (0.67–2.41)	1.35 (0.67–2.74)	1.45 (0.75–2.78)	0.28
Lutein and zeaxanthin					
Cases/controls, *n/n*	57/260	82/263	56/250	63/260	
Quartiles cutoff points	<0.4605	0.4605–0.6205	0.6205–0.8156	>0.8156	
OR (95% CI)	1.00	1.39 (0.74–2.65)	0.85 (0.43–1.65)	0.96 (0.48–1.90)	0.50
Lutein					
Cases/controls, *n/n*	68/263	78–253	60/258	52/259	
Quartiles cutoff points	<0.4061	0.4061–0.5344	0.5344–0.6855	>0.6855	
OR (95% CI)	1.00	1.59 (0.84–2.99)	0.85 (0.45–1.62)	0.85 (0.44–1.67)	0.32
Zeaxanthin					
Cases/controls, *n/n*	58/268	56/249	72/255	72/261	
Quartiles cutoff points	<0.0563	0.0563–0.0791	0.0791–0.1160	>0.1160	
OR (95% CI)	1.00	1.05 (0.53–2.07)	0.82 (0.42–1.58)	0.77 (0.39–1.49)	0.33
β-cryptoxanthin					
Cases/controls, *n/n*	55/251	69/264	78/262	56/256	
Quartiles cutoff points	<0.1013	0.1013–0.1719	0.1719–0.3365	>0.3365	
OR (95% CI)	1.00	1.23 (0.63–2.40)	1.27 (0.66–2.47)	0.70 (0.36–1.37)	0.30
Total carotenoids					
Cases/controls, *n/n*	63/259	69/257	66/258	60/259	
Quartiles cutoff points	<1.364	1.364–1.751	1.751–2.249	>2.249	
OR (95% CI)	1.00	1.41 (0.73–2.72)	1.35 (0.70–2.63)	1.18 (0.61–2.27)	0.70
Retinol, μ*mol/L*					
Cases/controls, *n/n*	72/260	78/258	66/257	42/257	
Quartiles cutoff points	<1.187	1.187–1.393	1.393–1.658	>1.658	
OR (95% CI)	1.00	1.21 (0.67–2.18)	1.05 (0.55–1.98)	1.57 (0.77–3.17)	0.33
Vitamin C, 10^2 μ*mol/L*					
Cases/controls, *n/n*	76/259	48/255	56/267	72/253	
Quartiles cutoff points	<0.28	0.28–0.42	0.42–0.55	>0.55	
OR (95% CI)	1.00	0.75 (0.38–1.47)	0.59 (0.31–1.14)	0.98 (0.53–1.81)	0.86

(Continued)

TABLE 2 *Continued*

	Quartiles of biomarker concentrations				
	1	2	3	4	*P*-trend
Ferritin, *pmol/L*					
Cases/controls, *n/n*	90/258	72/259	66/259	30/259	
Quartiles cutoff points	<43	43–103	103–229	>229	
OR (95% CI)	1.00	0.94 (0.52–1.69)	1.01 (0.56–1.81)	1.37 (0.58–3.26)	0.63

[1] All analyses were stratified by year of blood draw (1995–1996, 1997, 1998–1999, and 2000–2001) with conditional logistic regression.
[2] Adjusted for age and prior breast lump (yes/no). Isoflavone analyses additionally adjusted for analysis method.
[3] Significant at $P < 0.025$ after Bonferroni's adjustment for 2 isoflavone tests.
[4] NS ($P \geq 0.006$) after Bonferroni's adjustment for 9 carotenoid tests.

We present adjusted OR for risk of fibroadenomas in relation to quartiles of fatty acids as percentages of total fatty acids in the RBC membrane (**Table 3**). Palmitic and stearic acids, the principal SFA in RBC, were not associated with risk of fibroadenomas. We observed an inverse association between higher percentages of eicosapentaenoic acid (EPA) [OR (95% CI) = 0.38 (0.19–0.77) for the highest vs. the lowest quartile; *P*-trend = 0.007] and docosapentaenoic acid (DPA) [OR (95% CI) = 0.32 (0.15–0.70) for the highest vs. the lowest quartile; *P*-trend = 0.024] and fibroadenoma risk but no significant association with total (n-3) fatty acids. Risk tended to decrease with increasing total PUFA percentages, although the OR for the 3 highest quartiles were quite similar, suggesting a possible threshold effect [0.51 (0.24–1.05) for the highest vs. the lowest quartile; *P*-trend = 0.052]. Risk also tended to decrease with increasing values of the (n-7) fatty acid SI (*P*-trend = 0.011). This inverse association was driven primarily by variations in risk associated with concentrations of palmitoleic acid (SI denominator) rather than by changes in risk associated with concentrations of palmitic acid (SI numerator). All other RBC fatty acids measured showed no significant association with fibroadenoma risk.

Discussion

To our knowledge, no prior study has assessed risk of fibroadenomas in relation to a broad panel of circulating biomarkers of dietary exposure. According to Dupont and Page (8), fibroadenomas are classified as a nonproliferative breast condition. As such, we can compare our data more generally with dietary studies of nonproliferative breast conditions acknowledging, however, that risk factors for various types of nonproliferative breast conditions may differ. In this nested case-control study in Shanghai, China, risk of fibroadenomas decreased significantly with increasing concentrations of daidzein and genistein. RBC percentages of EPA, DPA, and total PUFA also were inversely associated with fibroadenoma risk.

In a prior study conducted in the same population as this one, we observed decreasing trends in risk with increasing soy food intake for proliferative fibrocystic conditions but not for nonproliferative fibrocystic conditions (21,33). In contrast, plasma isoflavone concentrations were significantly inversely associated with the risk of nonproliferative fibrocystic breast conditions, suggesting that other aspects of isoflavone availability and overall exposure, beyond reported intake, need to be considered (34). More consistent findings are reported for the inverse association between soy intake (35) and biomarkers of soy exposure (36,37) and breast cancer risk in Asian populations. Possible mechanisms for the inverse association between breast disease, soy intake, and isoflavones are based on the capacity of isoflavones to modulate endogenous hormones, known risk factors for both benign and malignant breast disease (21), and to affect breast tissue development (38). The inverse association between plasma isoflavones and fibroadenomas in our study is consistent with other studies that suggest that earlier life exposure to isoflavones may influence normal structural changes in the breast in later life (39–41).

Prior studies of fat intake and types of fat as risk factors for fibroadenomas and proliferative fibrocystic breast conditions have yielded inconsistent results (18,19,39,42). A case-control study in Australia found no evidence for an association between dietary fat intake and fibroadenoma risk (14). In our study of dietary intake, sesame oil consumption was inversely related to fibrocystic breast conditions (33). Sesame oil contains a high percentage of PUFA, especially (n-6) fatty acids, and is a rich source of the lignan sesamol (43). However, we found no association between RBC (n-6) fatty acids and fibroadenoma risk. In the previous study, we did find a decreasing trend in risk of nonproliferative fibrocystic breast conditions with increasing RBC EPA (43), and in the present study, RBC percentages of EPA and DPA were associated with lower fibroadenoma risk. Fatty fish and fish oil are the richest sources of EPA, and foods that contain EPA also contain its metabolic derivative, DPA (45). Consumption of seafood is high in Shanghai (46) and the findings in this study may reflect dietary fish consumption in this population. To our knowledge, this is the first report of an inverse association between DPA and risk of fibroadenomas. In humans, DPA can be formed by means of the elongation of EPA. The rapid retroconversion of DPA to EPA in human blood also suggests the possibility that DPA could serve as a storage pool for EPA (47). This may explain the association we observe with DPA in this study.

Studies on breast cancer risk (27,30,31) have also suggested that the ratios of RBC fatty acids may be of greater importance than individual fatty acids. Previously, and consistent with our findings here, we found that the (n-7) fatty acid SI was also inversely associated with nonproliferative and proliferative fibrocystic breast conditions (44). This ratio may indirectly reflect the activity of $\Delta 9$-desaturase, because palmitoleic acid is preliminarily produced through desaturation of palmitic acid by $\Delta 9$-desaturase. Because the inverse association was due to lower concentrations of RBC palmitoleic acid, this finding suggests a role for reduced activity of $\Delta 9$-desaturase.

In Western populations, plasma carotenoids and vitamin C are proposed biomarkers of fruit and vegetable intake (48,49); however, in this Chinese population, plasma carotenoid concentrations were associated with total fruit, but not total vegetable, intake (C. Frankenfeld, J. Lampe, J. Shannon, D.

TABLE 3 Risk of fibroadenomas in relation to quartiles of RBC fatty acid percentages among women in Shanghai, China[1]

	Quartiles of RBC fatty acid percentages				
	1	2	3	4	*P*-trend
Palmitic acid (16:0)					
Cases/controls, *n/n*	47/257	64/256	73/256	71/256	
Quartiles cutoff points	<18.15	18.15–18.69	18.69–19.27	>19.27	
OR (95% CI)[2]	1.00	0.61 (0.29–1.30)	0.63 (0.30–1.30)	0.82 (0.39–1.71)	0.85
Stearic acid (18:0)					
Cases/controls, *n/n*	19/257	30/256	92/255	114/257	
Quartiles cutoff points	<13.33	13.33–14.03	14.03–14.60	>14.60	
OR (95% CI)	1.00	1.35 (0.52–3.53)	2.27 (0.94–5.52)	1.52 (0.63–3.65)	0.47
Palmitoleic acid [16:1(n-7)]					
Cases/controls, *n/n*	56/257	85/255	87/256	27/257	
Quartiles cutoff points	<0.13	0.13–0.17	0.17–0.24	>0.24	
OR (95% CI)	1.00	1.71 (0.93–3.17)	4.00 (2.11–7.58)	1.15 (0.52–2.56)	0.023[3]
Oleic acid [18:1(n-9)]					
Cases/controls, *n/n*	114/256	85/257	32/255	24/257	
Quartiles cutoff points	<9.81	9.81–10.38	10.38–11.01	>11.01	
OR (95% CI)	1.00	1.12 (0.65–1.94)	0.67 (0.34–1.28)	0.96 (0.43–2.13)	0.50
Vaccenic acid [18:1(n-7)]					
Cases/controls, *n/n*	69/257	81/256	59/256	46/256	
Quartiles cutoff points	<0.85	0.85–0.93	0.93–1.01	>1.01	
OR (95% CI)	1.00	0.84 (0.46–1.56)	0.78 (0.40–1.50)	0.78 (0.40–1.52)	0.43
Linolenic acid [18:2(n-6)]					
Cases/controls, *n/n*	59/256	88/256	75/256	33/257	
Quartiles cutoff points	<10.20	10.20–11.41	11.41–13.64	>13.64	
OR (95% CI)	1.00	0.85 (0.45–1.58)	0.99 (0.51–1.91)	0.65 (0.29–1.47)	0.50
γ-Linolenic acid [18:3(n-6)]					
Cases/controls, *n/n*	101/257	72/255	48/256	34/257	
Quartiles cutoff points	<0.05	0.05–0.07	0.07–0.09	>0.09	
OR (95% CI)	1.00	1.04 (0.60–1.82)	0.60 (0.31–1.16)	1.00 (0.47–2.15)	0.49
α-Linolenic acid [18:3(n-3)]					
Cases/controls, *n/n*	75/257	84/256	78/255	18/257	
Quartiles cutoff points	<0.18	0.18–0.23	0.23–0.32	>0.32	
OR (95% CI)	1.00	1.91 (1.06–3.43)	1.94 (1.04–3.62)	0.60 (0.24–1.47)	0.79
Arachidonic acid [20:4(n-6)]					
Cases/controls, *n/n*	59/256	63/256	81/256	52/257	
Quartiles cutoff points	<11.44	11.44–12.18	12.18–12.92	>12.92	
OR (95% CI)	1.00	0.74 (0.39–1.40)	0.93 (0.49–1.76)	0.61 (0.31–1.21)	0.28
EPA [20:5(n-3)]					
Cases/controls, *n/n*	95/257	68/255	62/256	30/257	
Quartiles cutoff points	<0.46	0.46–0.56	0.56–0.69	>0.69	
OR (95% CI)	1.00	0.79 (0.43–1.45)	0.64 (0.35–1.17)	0.38 (0.19–0.77)	0.007[3]
Erucic acid [22:1(n-9)]					
Cases/controls, *n/n*	71/256	113/257	50/255	21/257	
Quartiles cutoff points	<0.13	0.13–0.22	0.22–0.44	>0.44	
OR (95% CI)	1.00	1.55 (0.88–2.75)	1.51 (0.76–3.01)	0.54 (0.23–1.25)	0.49
DPA [22:5(n-3)]					
Cases/controls, *n/n*	61/257	97/256	70/255	27/257	
Quartiles cutoff points	<1.63	1.63–1.85	1.85–2.09	>2.09	
OR (95% CI)	1.00	1.00 (0.53–1.88)	1.29 (0.66–2.55)	0.32 (0.15–0.70)	0.024[3]
Docosahexaenoic acid [22:6(n-3)]					
Cases/controls, *n/n*	45/257	60/255	76/257	74/256	
Quartiles cutoff points	<4.42	4.42–4.90	4.90–5.47	>5.47	
OR (95% CI)	1.00	0.93 (0.46–1.88)	1.25 (0.64–2.42)	1.06 (0.54–2.06)	0.68
Σ MUFA[4]					
Cases/controls, *n/n*	104/256	94/257	37/256	20/256	
Quartiles cutoff points	<17.22	17.22–18.78	18.78–20.90	>20.90	
OR (95% CI)	1.00	1.53 (0.88–2.64)	1.75 (0.86–3.57)	1.27 (0.55–2.95)	0.24

(Continued)

TABLE 3 *Continued*

	Quartiles of RBC fatty acid percentages				
	1	2	3	4	*P*-trend
Σ PUFA[5]					
Cases/controls, *n/n*	82/257	67/256	72/255	34/257	
Quartiles cutoff points	<34.65	34.65–35.68	35.68–36.97	>36.97	
OR (95% CI)	1.00	0.55 (0.29–1.01)	0.57 (0.31–1.06)	0.51 (0.24–1.05)	0.052
Σ (n-6) FA[6]					
Cases/controls, *n/n*	65/256	72/256	86/257	32/256	
Quartiles cutoff points	<26.62	26.62–27.80	27.80–29.49	>29.49	
OR (95% CI)	1.00	0.58 (0.31–1.07)	0.84 (0.46–1.55)	0.61 (0.28–1.32)	0.38
Σ (n-3) FA[7]					
Cases/controls, *n/n*	58/256	67/256	79/256	51/257	
Quartiles cutoff points	<7.07	7.07–7.65	7.65–8.37	>8.37	
OR (95% CI)	1.00	0.95 (0.49–1.84)	1.34 (0.70–2.57)	0.63 (0.32–1.24)	0.35
(n-3):(n-6)					
Cases/controls, *n/n*	44/257	69/255	84/256	58/257	
Quartiles cutoff points	<0.24	0.24–0.27	0.27–0.31	>0.31	
OR (95% CI)	1.00	1.15 (0.57–2.30)	1.89 (0.97–3.70)	0.93 (0.47–1.87)	0.84
(n-9) SI[8]					
Cases/controls, *n/n*	18/257	32/255	69/257	136/256	
Quartiles cutoff points	<1.23	1.23–1.35	1.35–1.47	>1.47	
OR (95% CI)	1.00	0.53 (0.20–1.38)	1.33 (0.55–3.22)	1.03 (0.43–2.48)	0.28
(n-7) SI[9]					
Cases/controls, *n/n*	28/256	84/256	83/256	60/257	
Quartiles cutoff points	<77.67	77.67–112.30	112.30–141.54	>141.54	
OR (95% CI)	1.00	3.22 (1.44–7.24)	1.34 (0.60–2.98)	0.77 (0.34–1.72)	0.011[3]

[1] All analyses were stratified by year of interview with conditional logistic regression.
[2] Adjusted for age and prior breast lumps (yes/no).
[3] NS ($P \geq 0.0025$) after Bonferroni's adjustment for 20 RBC fatty acid tests.
[4] 14:1 + 16:1(n−9) + 16:1(n−7) + 17:1(n−9) + 18:1(n−8) + 18:1(n−7) + 22:1(n −9) + 24:1(n−9). MUFA, monounsaturated fatty acid.
[5] (n−3) PUFA + (n−6) PUFA.
[6] 18:2(n−6) + 18:3(n−6) + 20:2(n−6) + 20:3(n−6) + 20:4(n−6) + 22:2(n−6) + 22:4(n-6).
[7] 18:3(n−3) + 20:3(n−3) + 20:5(n−3) + 22:5(n−3) + 22:6(n−3).
[8] 18:0/18:1(n-9).
[9] 16:0/16:1(n-7).

Gao, W. Li, R. Ray, C. Chen, I. King, D. Thomas, unpublished data). We found no associations between the plasma concentrations of the carotenoids and vitamin C and fibroadenoma risk, except for a higher risk associated with plasma α-carotene concentrations. Previously, we found that higher consumption of fruit and vegetables, but not vitamin C and total carotenoids, was associated with lower risk of fibroadenomas (23) and of nonproliferative fibrocystic breast conditions (21,33). In a case-control study in Australia, estimated vitamin C intake was inversely associated with risk of fibroadenomas (14). One small case-control study conducted in India reported that 10 fibroadenoma patients had significantly lower mean plasma vitamin C concentrations compared with controls (50). Taken together, our data suggest that vitamin C and the carotenoids we investigated do not account for the possible protective effect of fruits and vegetables in relation to risk of fibroadenomas.

There are several proposed biological mechanisms for possible effects of iron in induction and promotion of carcinogenesis (51). Some of these may also apply to nonproliferative conditions. We previously reported that women with higher plasma ferritin levels had a higher risk of nonproliferative fibrocystic breast conditions (28); however, the association between plasma ferritin and risk of fibroadenomas was not significant ($P = 0.63$).

This study has several strengths. It is a population-based study conducted in 1502 women, nested within a large, well-defined cohort. We evaluated the effect of dietary exposure using different biomarkers, with a wide range of concentrations. Measurements of biomarkers do not depend on recall and take into account effects of absorption, bioavailability, influences of microbiota, and excretion (52). Furthermore, limitations of food composition tables are avoided.

Possible limitations influencing the interpretation of these results include the case-control design of the study. In a case-control study, an observed association may be a result of disease status rather than a factor in the cause of the disease. In this study, every effort was made to draw blood samples at or near the time of diagnosis. Because fibroadenomas are not a condition that alters appetite or makes women ill, changes in diet in women with fibroadenomas are unlikely. Misclassification of diagnosis is a potential problem in studies of fibroadenomas, because some fibroadenomas go undetected and may regress with time (53). To the extent that this occurred in the controls, results would be biased toward the null. The use of 2 different isoflavone assays was not ideal. However, we analyzed 88% of the samples by LC-MS, we adjusted for assay type in the statistical model, and our exclusion of samples run by LC-Coularray did not alter the overall findings; this suggests that the

impact of this potential limitation is probably minor. Plasma and RBC biomarkers may be limited as biomarkers of dietary intake, because they also reflect human and bacterial processing, which may attenuate the correct classification. Finally, we performed numerous statistical analyses with several biomarkers, which increases the possibility that the associations we found reflect chance. After Bonferroni's adjustment, only the associations of daidzein and genistein concentrations with risk of fibroadenomas remained significant at $P < 0.05$.

In conclusion, we observed inverse associations between fibroadenoma risk and plasma isoflavone concentrations and RBC EPA and DPA. Our results provide support for a protective effect of soy foods and fatty fish and suggest that the ratios of fatty acids may also play an important role in fibroadenoma development. More prospective studies are needed to further characterize the relationships between these dietary constituents, their related biomarkers, and risk of fibroadenomas.

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J.S., D.B.T., J.W.L. designed research; C.C., I.B.K., D.G., Y.H., C.W., and W.L. conducted research; K.W. provided essential reagents; S.C.D., R.B., and R.M.R. performed statistical analysis; S.C.D., J.W.L, R.M.R, and J.S. wrote the paper. J.W.L., R.M.R., and D.B.T. had primary responsibility for final content. All authors read and approved the final manuscript.

Literature Cited

1. Greenberg R, Skornick Y, Kaplan O. Management of breast fibroadenomas. J Gen Intern Med. 1998;13:640–5.
2. Schuerch C III, Rosen PP, Hirota T, Itabashi M, Yamamoto H, Kinne DW, Beattie EJ Jr. A pathologic study of benign breast diseases in Tokyo and New York. Cancer. 1982;50:1899–903.
3. Cunningham LL, Andrykowski MA, Wilson JF, McGrath PC, Sloan DA, Kenady DE. Physical symptoms, distress, and breast cancer risk perceptions in women with benign breast problems. Health Psychol. 1998;17:371–5.
4. Hislop TG, Elwood JM. Risk factors for benign breast disease: a 30-year cohort study. Can Med Assoc J. 1981;124:283–91.
5. Chang DS, McGrath MH. Management of benign tumors of the adolescent breast. Plast Reconstr Surg. 2007;120:13e–9e.
6. Coriaty Nelson Z, Ray RM, Gao DL, Thomas DB. Risk factors for fibroadenoma in a cohort of female textile workers in Shanghai, China. Am J Epidemiol. 2002;156:599–605.
7. Cole P, Mark Elwood J, Kaplan SD. Incidence rates and risk factors of benign breast neoplasms. Am J Epidemiol. 1978;108:112–20.
8. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med. 1985;312:146–51.
9. Carter BA, Page DL, Schuyler P, Parl FF, Simpson JF, Jensen RA, Dupont WD. No elevation in long-term breast carcinoma risk for women with fibroadenomas that contain atypical hyperplasia. Cancer. 2001;92:30–6.
10. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr, Rados MS, Schuyler PA. Long-term risk of breast cancer in women with fibroadenoma. N Engl J Med. 1994;331:10–5.
11. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, Vierkant RA, Maloney SD, Pankratz VS, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353:229–37.
12. Wang J, Costantino JP, Tan-Chiu E, Wickerham DL, Paik S, Wolmark N. Lower-category benign breast disease and the risk of invasive breast cancer. J Natl Cancer Inst. 2004;96:616–20.
13. Dorjgochoo T, Deming SL, Gao YT, Lu W, Zheng Y, Ruan Z, Zheng W, Shu XO. History of benign breast disease and risk of breast cancer among women in China: a case-control study. Cancer Causes Control. 2008; 19:819–28.
14. Yu H, Rohan TE, Cook MG, Howe GR, Miller AB. Risk factors for fibroadenoma: a case-control study in Australia. Am J Epidemiol. 1992;135:247–58.
15. Sartwell PE, Arthes FG, Tonascia JA. Benign and malignant breast tumours: epidemiological similarities. Int J Epidemiol. 1978;7:217–21.
16. Brinton LA, Vessey MP, Flavel R, Yeates D. Risk factors for benign breast disease. Am J Epidemiol. 1981;113:203–14.
17. Berkowitz GS, Canny PF, Vivolsi VA, Merino MJ, O'Connor TZ, Kelsey JL. Cigarette smoking and benign breast disease. J Epidemiol Community Health. 1985;39:308–13.
18. Webb PM, Byrne C, Schnitt SJ, Connolly JL, Jacobs TW, Baer HJ, Willett WC, Colditz GA. A prospective study of diet and benign breast disease. Cancer Epidemiol Biomarkers Prev. 2004;13:1106–13.
19. Rohan TE, Cook MG, Potter JD, McMichael AJ. A case-control study of diet and benign proliferative epithelial disorders of the breast. Cancer Res. 1990;50:3176–81.
20. Lubin F, Wax Y, Ron E, Black M, Chetrit A, Rosen N, Alfandary E, Modan B. Nutritional factors associated with benign breast disease etiology: a case-control study. Am J Clin Nutr. 1989;50:551–6.
21. Wu C, Ray RM, Lin MG, Gao DL, Horner NK, Nelson ZC, Lampe JW, Hu YW, Shannon J, et al. A case-control study of risk factors for fibrocystic breast conditions: Shanghai Nutrition and Breast Disease Study, China, 1995–2000. Am J Epidemiol. 2004;160:945–60.
22. Thomas DB, Gao DL, Ray RM, Wang WW, Allison CJ, Chen FL, Porter P, Hu YW, Zhao GL, et al. Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst. 2002;94:1445–57.
23. Coriaty Nelson Z, Ray RM, Wu C, Stalsberg H, Porter P, Lampe JW, Shannon J, Homer N, Li W, et al. Fruit and vegetable intakes are associated with lower risk of breast fibroadenomas in Chinese women. J Nutr. 2010;1294–1301.
24. Frankenfeld CL, Lampe JW, Shannon J, Gao DL, Ray RM, Prunty J, Kalhorn TF, Wähälä K, Patterson RE, et al. Frequency of soy food consumption and serum isoflavone concentrations among Chinese women in Shanghai. Public Health Nutr. 2004;7:765–72.
25. Kalman DA, Goodman GE, Omenn GS, Bellamy G, Rollins B. Micronutrient assay for cancer prevention clinical trials: serum retinol, retinyl palmitate, alpha-carotene, and beta-carotene with the use of high-performance liquid chromatography. J Natl Cancer Inst. 1987;79:975–82.
26. Zhang C, Williams MA, Sanchez SE, King IB, Ware-Jauregui S, Larrabure G, Bazul V, Leisenring WM. Plasma concentrations of carotenoids, retinol and tocopherols in preeclamptic and normotensive pregnant women. Am J Epidemiol. 2001;153:572–80.
27. Shannon J, King IB, Moshofsky R, Lampe JW, Gao DL, Ray RM, Thomas DB. Erythrocyte fatty acids and breast cancer risk: a case-control study in Shanghai, China. Am J Clin Nutr. 2007;85:1090–7.
28. Moore AB, Shannon J, Chen C, Lampe JW, Ray RM, Lewis SK, Lin MG, Stalsberg H, Thomas DB. Dietary and stored iron as predictors of breast cancer risk: a case control study in Shanghai. Int J Cancer. 2009;125:1110–7.
29. Szklo M, Nieto FJ. Epidemiology: beyond the basics. Gaithersburg (MD): Aspen Publishers Inc., 2000.
30. Chajes V, Hulten K, Van Kappel AL, Winkvist A, Kaaks R, Hallmans G, Lenner P, Riboli E. Fatty-acid composition in serum phospholipids and risk of breast cancer: an incident case-control study in Sweden. Int J Cancer. 1999;83:585–90.
31. Pala V, Krogh V, Muti P, Chajes V, Riboli E, Micheli A, Saadatian M, Sieri S, Berrino F. Erythrocyte membrane fatty acids and subsequent breast cancer: a prospective Italian study. J Natl Cancer Inst. 2001;93:1088–95.
32. Breslow NE. Statistics in epidemiology: the case-control study. J Am Stat Assoc. 1996;91:14–28.
33. Li W, Ray RM, Lampe JW, Lin MG, Gao DL, Wu C, Nelson ZC, Fitzgibbons ED, Horner N, et al. Dietary and other risk factors in women having fibrocystic breast conditions with and without concurrent breast cancer: a nested case-control study in Shanghai, China. Int J Cancer. 2005;115:981–93.
34. Lampe JW, Nishino Y, Ray RM, Wu C, Li W, Lin MG, Gao DL, Hu Y, Shannon J, et al. Plasma isoflavones and fibrocystic breast conditions and breast cancer among women in Shanghai, China. Cancer Epidemiol Biomarkers Prev. 2007;16:2579–86.

35. Wu AH, Yu MC, Tseng CC, Pike MC. Epidemiology of soy exposures and breast cancer risk. Br J Cancer. 2008;98:9–14.
36. Iwasaki M, Inoue M, Otani T, Sasazuki S, Kurahashi N, Miura T, Yamamoto S, Tsugane S. Plasma isoflavone level and subsequent risk of breast cancer among Japanese women: a nested case-control study from the Japan Public Health Center-based prospective study group. J Clin Oncol. 2008;26:1677–83.
37. Dai Q, Franke AA, Jin F, Shu XO, Hebert JR, Custer LJ, Cheng J, Gao YT, Zheng W. Urinary excretion of phytoestrogens and risk of breast cancer among Chinese women in Shanghai. Cancer Epidemiol Biomarkers Prev. 2002;11:815–21.
38. Warri A, Saarinen NM, Makela S, Hilakivi-Clarke L. The role of early life genistein exposures in modifying breast cancer risk. Br J Cancer. 2008;98:1485–93.
39. Baer HJ, Schnitt SJ, Connolly JL, Byrne C, Willett WC, Rosner B, Colditz GA. Early life factors and incidence of proliferative benign breast disease. Cancer Epidemiol Biomarkers Prev. 2005;14:2889–97.
40. Byrne C, Webb PM, Jacobs TW, Peiro G, Schnitt SJ, Connolly JL, Willett WC, Colditz GA. Alcohol consumption and incidence of benign breast disease. Cancer Epidemiol Biomarkers Prev. 2002;11:1369–74.
41. Wu AH, Koh WP, Wang R, Lee HP, Yu MC. Soy intake and breast cancer risk in Singapore Chinese Health Study. Br J Cancer. 2008;99: 196–200.
42. Rohan TE, Jain M, Miller AB. A case-cohort study of diet and risk of benign proliferative epithelial disorders of the breast (Canada). Cancer Causes Control. 1998;9:19–27.
43. Jan KC, Ho CT, Hwang LS. Bioavailability and tissue distribution of sesamol in rat. J Agric Food Chem. 2008;56:7032–7.
44. Shannon J, King IB, Lampe JW, Gao DL, Ray RM, Lin MG, Stalsberg H, Thomas DB. Erythrocyte fatty acids and risk of proliferative and nonproliferative fibrocystic disease in women in Shanghai. Am J Clin Nutr. 2009;89:265–76.
45. Whelan J, Rust C. Innovative dietary sources of n-3 fatty acids. Annu Rev Nutr. 2006;26:75–103.
46. Satia JA, Patterson RE, Herrero R, Jin F, Dai Q, King IB, Chen C, Kristal AR, Prentice RL, et al. Study of diet, biomarkers and cancer risk in the United States, China and Costa Rica. Int J Cancer. 1999;82:28–32.
47. Benistant C, Achard F, Ben Slama S, Lagarde M. Docosapentaenoic acid (22:5,n-3): metabolism and effect on prostacyclin production in endothelial cells. Prostaglandins Leukot Essent Fatty Acids. 1996;55: 287–92.
48. Pollard J, Wild CP, White KL, Greenwood DC, Cade JE, Kirk SF. Comparison of plasma biomarkers with dietary assessment methods for fruit and vegetable intake. Eur J Clin Nutr. 2003;57:988–98.
49. Campbell DR, Gross MD, Martini MC, Grandits GA, Slavin JL, Potter JD. Plasma carotenoids as biomarkers of vegetable and fruit intake. Cancer Epidemiol Biomarkers Prev. 1994;3:493–500.
50. Kumaraguruparan R, Subapriya R, Kabalimoorthy J, Nagini S. Antioxidant profile in the circulation of patients with fibroadenoma and adenocarcinoma of the breast. Clin Biochem. 2002;35:275–9.
51. Kabat GC, Rohan TE. Does excess iron play a role in breast carcinogenesis? An unresolved hypothesis. Cancer Causes Control. 2007;18:1047–53.
52. Jenab M, Slimani N, Bictash M, Ferrari P, Bingham SA. Biomarkers in nutritional epidemiology: applications, needs and new horizons. Hum Genet. 2009;125:507–25.
53. Takei H, Iino Y, Horiguchi J, Maemura M, Yokoe T, Koibuchi Y, Oyama T, Ohwada S, Morishita Y. Natural history of fibroadenomas based on the correlation between size and patient age. Jpn J Clin Oncol. 1999;29:8–10.