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Fruit and Vegetable Intakes Are Associated with Lower Risk of Breast Fibroadenomas in Chinese Women[1–3]

Zakia Coriaty Nelson,[4] Roberta M. Ray,[5] Chunyuan Wu,[5] Helge Stalsberg,[6] Peggy Porter,[5] Johanna W. Lampe,[5] Jackilen Shannon,[7] Neilann Horner,[5] Wenjin Li,[5] Wenwan Wang,[8] Yongwei Hu,[9] Daoli Gao,[8] and David B. Thomas[5]*

[4]National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, MD 20782; [5]Fred Hutchinson Cancer Research Center, Seattle, WA 98109; [6]Institute of Medical Biology, University of Tromsø, N-9035, Tromsø, Norway; [7]Oregon Health and Science University, Portland, OR 97239; [8]Department of Epidemiology, Zhong Shan Hospital Cancer Center, Shanghai 200052, China; and [9]Department of Pathology, Shi Dong Hospital, Shanghai 200438, China

Abstract

Fibroadenomas are common benign breast conditions among women and account for ~50% of breast biopsies performed. Dietary factors are known to influence benign breast conditions in the aggregate, but little is known of their association specifically with fibroadenoma. Our objective in this study was to evaluate the association between dietary and other factors and fibroadenoma risk. A case-control study, nested in a randomized trial of breast self-examination (BSE) in Chinese textile workers in Shanghai, China, was conducted between 1989 and 2000. The study sample included 327 affected women and 1070 controls. Women were administered a FFQ and a questionnaire that elicited reproductive and gynecological history and other information. Odds ratios, as estimates of relative risks, were calculated using multivariate conditional logistic regression. Significant decreasing trends in risk of fibroadenoma were observed with intake of fruits and vegetables and with number of live births, and a reduced risk was also associated with natural menopause, oral contraceptive use, and moderate exercise (walking and gardening). Increased risk of fibroadenoma was associated with heavy physical activity in one's 20s, breast cancer in a first-degree relative, and a history of prior benign breast lumps; and significant increasing trends in risk were observed with numbers of BSE per year and years of education. In conclusion, a diet rich in fruits and vegetables and the use of oral contraceptives may reduce risk of fibroadenoma. J. Nutr. 140: 1294–1301, 2010.

Introduction

Fibroadenomas are benign lesions that arise in the terminal duct lobular unit of the breast and usually present during a woman's reproductive years (1–3). They are the most common breast lesions in U.S. women <25 y of age (4) and account for 50% of all breast biopsies performed (5). In Western populations, fibroadenomas are present in 7–13% of patients examined in breast clinics (6) and ~1 in 350 women in Shanghai may be diagnosed with a fibroadenoma before the age of 60 y (7). Incidence rates in adult women decrease with age (7), particularly at menopause (8,9). Because their presence often leads to diagnostic procedures to rule out malignant disease, women with a fibroadenoma can experience considerable psychological distress, financial burden, and further health complications.

The role of diet in the etiology of fibroadenoma has not been extensively investigated. Studies of nutritional factors in relation to benign breast diseases in the aggregate that have included women with fibroadenomas have yielded inconclusive results (10–13), and 1 study reported that the risk of fibroadenoma tended to be inversely associated with the intake of β-carotene and vitamin C (14).

Several hormonal risk factors for fibroadenoma have been identified. An earlier prospective study in Shanghai demonstrated a strong decrease in risk of fibroadenoma with increasing parity (7), but results of prior studies elsewhere have been inconsistent (4,8,15–18). Increased risk has been related to estrogen replacement therapy (19–21), endogenous estrogen levels (22), premenstrual mastalgia (15), and polymorphisms in genes responsible for the production of estrogen-metabolizing enzymes (23). Cigarette smoking has antiestrogenic effects (24–28) and has been related to reduced risk (29–31) as have combined oral contraceptives (7,23), suggesting that progestins may be protective (17,32). Given these findings, dietary behaviors that decrease endogenous estrogen exposure may also be important in reducing fibroadenoma risk. We conducted the

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[3] Supplemental Table 1 is available with the online posting of this paper at jn.nutrition.org.
* To whom correspondence should be addressed. E-mail: dbthomas@fhcrc.org.

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present study to assess the role of nutritional factors in the etiology of fibroadenomas as well as to elucidate further the role of hormonal and other factors in the etiology of this condition.

Methods

Study setting and participants. This study was nested within a randomized trial of breast self-examination (BSE)[10] in the Shanghai Textile Industry Bureau (STIB) (33,34). A total of 266,064 women born between 1925 and 1958 were interviewed and enrolled into the trial between 1989 and 1991 and followed through July of 2000. All women received their primary medical care in clinics in their factory of employment. When a woman developed a breast problem, she was evaluated by a medical worker in her factory clinic and, if indicated, referred for further evaluation and treatment to 1 of 3 hospitals operated by the STIB or to other hospitals that had contractual agreements with individual factories. The histologic diagnosis was abstracted from the pathology records of all women with confirmed benign or malignant breast lesions. Histological slides of all tumors were sent to Seattle for future review.

All women who were diagnosed with histologically confirmed fibroadenoma at 1 of the 3 STIB hospitals between September 1995 and July 2000 and who had no prior or concurrent breast malignancy were eligible for this study. Of the 381 eligible women, 327 (85.9%) were interviewed. These cases were selected as part of 2 studies that also included women with fibrocystic conditions and breast cancer, 1 conducted between September 1995 and August 1997 (35) and the other between September 1997 and July 2000 (36).

Control women for the present study were also selected in conjunction with these 2 concurrent investigations. In both studies, they were randomly selected from women in the BSE trial with no breast biopsy. For each benign and malignant case enrolled in the first study, 20 potential controls of the same age were randomly selected and listed. Potential controls were contacted, starting with the first 2 names on the list, until 2 women of the same age and menstrual status as their matched case were recruited. A total of 367 controls were recruited in this manner (64% of the eligible women contacted). Controls for the cases that were enrolled in the second study were frequency matched to cases by 5-y age group and hospital affiliation of their factories at baseline. Then 703 (82%) of 862 controls selected in this manner were interviewed. In the present study, the individual matching in the first study was not retained and the cases were compared with all interviewed controls from both studies.

Validation of diagnoses. A reference pathologist reviewed slides from 158 of the 327 fibroadenomas without knowing the initial diagnosis (7): 136 (86.1%) were identified as fibroadenoma, 6 (3.8%) as "phyllodes tumor," and 16 (10.1%) as other benign breast conditions. Because of this high concordance, the diagnoses made by the pathologists in Shanghai were used for this investigation.

Data collection. Cases were interviewed in hospital clinics prior to biopsy. Controls were interviewed in their home or factory by the same team of interviewers that interviewed the cases. Informed consent was obtained from each woman prior to interview. The study was approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center and the Station for Prevention and Treatment of Cancer of the STIB, in accordance with an assurance filed with the Office for Human Research Protections of the US Department of Health and Human Services.

Information was ascertained on accepted and suspected risk factors for breast cancer, alcohol and smoking habits, and physical activity. Information on prior breast surgery was obtained from the baseline questionnaire for the BSE trial. A FFQ, based on a previously validated instrument (37,38) was used to assess the frequency of consumption of 99 types of food during adult life. Seasonality of fruits and vegetables was accounted for by asking participants to report how many months of the year they consumed each item.

Data analysis. The foods were categorized into 19 mutually exclusive groups (13). The annual frequencies of intake for the foods in each group were summed to create total values for consumption of all foods in the group. For sesame and soybean oil, the amount consumed by each participant per day was estimated by dividing the amount of each oil used by her family per day by the number of family members. Intake of fruits and vegetables was classified further into groups based on botanical taxonomy (13). A complete listing of the botanical groupings and their respective foods is in **Supplemental Table 1**.

Portion size was estimated from the median portion size reported by women in the 1992 Chinese Health and Nutrition Survey or from defined standard portion sizes from Bowes and Church (39). The nutrient composition of each food item was based on data from Chinese Food Composition Tables (40). The amount of any specific nutrient in each food was summed over all foods in the frequencies eaten to estimate total intake of specific macronutrients and micronutrients and total energy intake (based on macronutrients, cooking oils, and alcohol). Proportions of energy from fat, protein, and carbohydrates were calculated by multiplying the grams of the macronutrient consumed per day by the kJ/g (38 for fat and 17 for carbohydrates and protein) and dividing by total daily energy intake.

Dietary intakes of interest were categorized into quartiles based on the distribution of consumption in the controls. Dichotomous variables were created when too little variation precluded division into quartiles. The age-adjusted odds ratio (OR) and corresponding 95% CI associated with each variable were estimated using multivariate conditional logistic regression (41). Because controls were interviewed after their corresponding cases, all analyses were conditioned on year of interview (1995–1996, 1997, 1998–1999, 2000–2001), as well as age (<40, 40, 41, 42, 43, 44, 45–50, 51–59, 60–69 y).

Statistical models for food groups were further adjusted for total energy intake (42) and models for botanical families and nutrients were adjusted for total intake of fruits and vegetables. The significance of trends in risk with level of exposure was calculated by assigning scores to the categorized levels of exposure and treating the scores as a continuous variable in the regression models. For sample sizes smaller than 5, exact logistic regression was used to calculate OR and 95% CI estimates. Parity was included in all dietary models; it was the only nondietary factor found to be a confounder of some of the other relationships.

The associations of each food and botanical group with risk of fibroadenoma were also examined in multiple nutrient density models (42). The nutritional density was computed for each food group (food group intake/total daily energy) and entered with total daily energy, age, and parity in a multiple logistic regression model, conditioned on year of interview.

To test for multiplicative interactions, the likelihood ratio test was used to measure the difference in the deviance between a model with and without a set of interaction terms (41).

Results

General risk factors. Because the controls were selected for women with all breast conditions, including breast cancer and fibrocystic conditions as well as fibroadenomas, as expected, the fibroadenoma cases were younger than the combined control group utilized in this study (**Table 1**); 96% of the 327 cases were younger than 50 y. Compared with menstruating women of the same age, women who had gone through natural menopause were at reduced risk (**Table 2**). Too few cases were postmenopausal to adequately assess risk in relation to age at menopause. Risk decreased significantly with number of live births after adjusting for age at first live birth, but risk was not significantly associated with age at first live birth after adjusting for number of live births. After adjustment for parity, risk was not associated

[10] Abbreviations used: BSE, breast self-examination; OR, odds ratio; STIB, Shanghai Textile Industry Bureau.

TABLE 1 Age distribution of breast fibroadenoma cases and controls

	Cases		Controls	
Age, *y*	*n*	%	*n*	%
35–39	70	21.4	13	1.2
40–44	193	59.0	470	43.9
45–49	52	15.9	219	20.5
50–59	7	2.1	124	11.6
≥60	5	1.5	244	22.8
Total	327	100.0	1070	100.0

with duration of lactation. None of these associations were appreciably altered by controlling for dietary variables.

Use of oral contraceptives was significantly associated with a reduced risk. Too few women were long-term users to assess risk in relation to duration of use. We did not observe any significant trends in risk with age at menarche or numbers of miscarriages, stillbirths, or abortions, and no association was observed with outcome of first pregnancy, use of an intrauterine device, or hysterectomy (not shown). Too few women had used contraceptive injections or had an oophorectomy or tubal ligation to assess their possible influence on risk.

We did not observe any significant associations with weight or BMI (not shown). Risk was not related to overall physical activity between the ages of 20 and 49 y. However, heavy physical activity in one's 20s was significantly associated with an increased risk, and ever regularly walking and gardening, which presumably reflect more moderate and recent behavior, were associated with a reduced risk. A reduced risk was also observed in relation to running regularly [OR (95% CI) = 0.3, (0.1–1.9)] and ever smoking [OR (95% CI) = 0.6 (0.1–2.7)], but the OR estimates are based on small numbers of runners and smokers and have wide CI. No association was observed with alcohol use or spousal smoking (not shown).

Risk tended to be greater, but was not significant, in women with a first-degree female relative with breast cancer; it was unchanged after adjustment for prior benign breast lumps and practice of BSE. Risk increased with increasing educational level and this trend was not attenuated after adjustment for practice of BSE. Risk was increased in women with a history of benign breast lumps, but no trend in risk was observed with number of lumps. Risk increased with frequency of BSE. The associations with benign breast lumps and frequency of BSE remained significant after adjustment for each other and BSE was not associated with any other risk factor identified (not shown). Clinical breast examination was associated with a 50% increase in risk [OR (95% CI) = 1.5: (1.1, 2.3)]. Although strong decreasing trends in risk were observed with times since last BSE and last clinical breast examination (not shown; *P*-value for both trends < 0.001), these associations may reflect breast examinations that resulted in diagnoses that led to the participants' entry into the study.

Food groups. Because risk was somewhat higher in the lowest quartile of daily energy intake than in the other 3 quartiles (**Table 3**), we included energy intake in models that assessed risk in relation to specific food groups. There were significant decreasing trends in risk with increasing consumption of both fruits and vegetables. The results for vegetables were similar across strata of fruit intake and vice versa (not shown). Risk was not significantly associated with soy foods or other legumes,

TABLE 2 Risk of breast fibroadenomas in Chinese women in relation to general risk factors

Exposure	Cases, *n* = 327	Controls, *n* = 1070	OR[1]	95% CI	*P*-trend[2]
Menopause					
No	305	687	1.0	Reference	
Yes	22	383	0.3	0.2, 0.6	
Reason for menopause					
Natural	9	331	0.1	0.1, 0.3	
Surgical	13	50	1.5	0.6, 3.6	
Livebirths,[3] *n*					
None[4]	10	41	—	—	
1	300	713	1.0	Reference	
2	12	124	0.2	0.1, 0.5	
≥3	5	188	0.1	0.04, 0.4	<0.001[5]
Age at first live birth,[6,7] *y*					
≤24	24	273	1.0	Reference	
25–29	227	600	1.1	0.6, 2.3	
≥30	66	152	1.3	0.6, 2.8	0.54
Duration of lactation,[7] *mo*					
Never	72	188	1.0	Reference	
≤6	89	209	1.2	0.7, 2.1	
>6	156	628	1.1	0.6, 1.8	0.93
Oral contraceptive use					
Never	316	978	1.0	Reference	
Ever	11	92	0.4	0.2, 0.9	
Physical activity in twenties					
Light	89	224	1.0	Reference	
Medium	175	648	1.2	0.8, 1.9	
Heavy	64	198	1.9	1.1, 3.4	0.04
Walking					
Never	313	947	1.0	Reference	
Ever	14	122	0.3	0.1, 0.5	
Gardening					
Never	322	1,016	1.0	Reference	
Ever	5	54	0.3	0.1, 0.9	
First-degree relative with breast cancer					
Never	320	1,053	1.0	Reference	
Ever	7	17	3.2	0.8, 13.6	
Education					
Elementary school or lower	11	211	1.0	Reference	
Middle school	301	827	3.0	1.2, 7.0	
College or higher	15	31	4.1	1.2, 13.7	0.01
Prior benign breast lump[8–10]					
Never	259	1,010	1.0	Reference	
Ever	53	32	6.1	3.0, 12.6	
Frequency of BSE[10,11]					
Never	131	725	1.0	Reference	
1–6 times/y	75	137	2.0	1.2, 3.5	
7–12 times/y	113	198	3.2	2.0, 5.1	
≥13 times/y	7	7	9.0	1.4, 58.1	<0.001

[1] Adjusted for age, stratified on year of interview.
[2] Test for trend, baseline category included unless otherwise noted.
[3] Additionally adjusted for age at first live birth.
[4] Includes nulligravid women.
[5] Test for trend among exposed; baseline category excluded.
[6] Additionally adjusted for number of live births.
[7] Restricted to parous women.
[8] Additionally adjusted for practice of BSE.
[9] At administration of baseline questionnaire.
[10] Women with unknown values excluded from analyses.
[11] Additionally adjusted for prior benign breast lump.

TABLE 3 Risk of breast fibroadenomas in Chinese women in relation to energy intake and absolute intake of food groups

Exposure	Cases, *n* = 327	Controls, *n* = 1070	OR[1]	95% CI	*P*-trend
Energy intake, *kJ/d*					
<6892	98	267	1.0	Reference	
6892–7817	85	268	0.7	0.4, 1.1	
7818–8904	80	268	0.6	0.4, 1.0	
>8904	64	267	0.7	0.4, 1.2	0.12
Fruit intake, *times/y*					
<202	74	268	1.0	Reference	
202–306	85	267	0.8	0.4, 1.4	
>306 to <435	84	268	0.6	0.4, 1.2	
≥435	84	267	0.4	0.2, 0.8	0.004
Vegetable intake,[2] times/*y*					
≤538	89	268	1.0	Reference	
>538–735	81	268	0.6	0.3, 1.0	
>735–957	76	268	0.7	0.4, 1.3	
>957	81	266	0.4	0.2, 0.7	0.007
Dairy intake, *times/y*					
≤12	78	252	1.0	Reference	
>12–134	98	279	1.0	0.6, 1.7	
>134–375.3	94	267	1.2	0.7, 2.1	
>375.3	57	272	1.0	0.5, 1.9	0.75
Rice intake, *times/d*					
≥1	5	8	1.0	Reference	
2	85	378	0.4	0.05, 3.0	
3	237	684	0.6	0.1, 4.2	0.20
Other grain product intake,[3] *times/y*					
≤163	96	267	1.0	Reference	
164–284	76	259	1.0	0.6, 1.6	
285–452	87	267	1.4	0.8, 2.5	
>452	68	277	1.8	0.9, 3.4	0.06
Preserved vegetable intake, *times/y*					
≤5	66	252	1.0	Reference	
>5–16	70	275	0.5	0.3, 1.0	
17–56	80	273	0.7	0.4, 1.2	
>56	111	270	0.7	0.4, 1.1	0.29
Soy food intake,[4] *times/y*					
≤121	88	266	1.0	Reference	
>121–219	100	269	0.8	0.5, 1.4	
>219–369	74	267	0.9	0.5, 1.5	
>369	65	268	0.6	0.4, 1.1	0.14
Fermented bean curd intake					
Never	118	446	1.0	Reference	
Ever	209	624	1.1	0.7, 1.6	
Other legume intake, *times/y*					
<97.7	93	268	1.0	Reference	
97.7–137.8	83	267	0.9	0.5, 1.7	
>137.8–201.2	81	267	1.0	0.6, 1.8	
>201.2	70	268	0.6	0.3, 1.0	0.09
Red meat intake,[5] *times/y*					
≤148	62	267	1.0	Reference	
>148–220	66	259	1.0	0.5, 1.8	
>220–302	83	273	1.1	0.6, 2.1	
>302	116	271	0.9	0.5, 1.6	0.73

(Continued)

TABLE 3 *Continued*

Exposure	Cases, *n* = 327	Controls, *n* = 1070	OR[1]	95% CI	*P*-trend
Fish intake,[6] *times/y*					
≤65	68	266	1.0	Reference	
>65–116	84	327	0.9	0.5, 1.5	
>116–168	83	233	1.1	0.6, 2.0	
>168	92	244	0.9	0.5, 1.7	0.92
Cured meat and fish intake, *times/y*					
≤4	77	268	1.0	Reference	
>4–9	99	284	1.1	0.7, 1.9	
>9–16	78	254	1.4	0.8, 2.4	
>16	73	264	0.9	0.5, 1.5	0.77
Poultry intake, *times/y*					
<24	85	255	1.0	Reference	
24 to <48	83	270	0.9	0.5, 1.6	
48–64	91	287	1.0	0.6, 1.7	
>64	68	258	1.0	0.6, 1.7	0.97
Egg intake, *times/y*					
<104	69	257	1.0	Reference	
104–156	62	190	1.3	0.7, 2.3	
>156–311	108	346	1.1	0.7, 2.0	
≥312	88	277	1.6	0.9, 2.9	0.16
Shellfish intake, *times/y*					
<12	54	153	1.0	Reference	
12 to <24	80	261	0.9	0.5, 1.6	
24 to <52	75	234	1.0	0.5, 2.0	
≥52	118	422	0.7	0.4, 1.3	0.36
Sesame oil intake, *g/d*					
≤0.55	166	327	1.0	Reference	
0.56–1.10	10	115	0.5	0.2, 1.4	
1.11–1.65	119	462	0.6	0.4, 0.9	
>1.65	32	166	0.4	0.2, 0.8	0.002
Soybean oil intake, *g/d*					
>28.8	104	262	1.0	Reference	
28.8–38.4	104	301	0.9	0.6, 1.5	
38.5–49.3	54	209	1.0	0.6, 1.8	
>49.3	65	298	0.8	0.5, 1.3	0.59
Fried food intake, *times/y*					
≤33	60	263	1.0	Reference	
>33–64	60	277	0.6	0.3, 1.1	
>64–122	89	265	0.8	0.4, 1.4	
>122	118	265	0.8	0.4, 1.5	0.81
Tea intake					
Never	123	556	1.0	Reference	
Ever	204	514	0.9	0.6, 1.4	

[1] Adjusted for age, energy, and parity and stratified on year of interview.
[2] Excluding preserved vegetables, soy, legumes, powders, flavorings, and extracts.
[3] Excluding corn and rice.
[4] Excluding fermented bean curd.
[5] Excluding cured meats.
[6] Excluding cured fish.

although a reduced risk of borderline significance was observed for the highest quartiles of consumption of both of these food groups. These findings were similar for both fresh and dried products (not shown). A significant decreasing trend in risk was observed with increasing consumption of sesame oil, but not with soybean oil. There were no significant associations with any of the other food groups shown in Table 3 or with fried

TABLE 4 Risk of breast fibroadenomas in Chinese women in relation to absolute intake of botanical families of foods

Exposure, *times/y*	Cases, *n* = 327	Controls, *n* = 1070	OR[1]	95% CI	*P*-trend
Araliaceae					
No	274	861	1.0	Reference	
Yes	53	209	1.2	0.7, 2.0	
Compositae					
≤8	74	236	1.0	Reference	
9–21.2	102	294	1.2	0.7, 2.1	
21.3–56	92	253	1.0	0.5, 1.7	
>56	59	287	0.7	0.4, 1.3	0.23
Convolvaceae/Dioscoreaceae					
No	100	305	1.0	Reference	
Yes	227	765	0.8	0.5, 1.3	
Cruciferae					
<161.7	96	269	1.0	Reference	
161.8–251	87	266	1.1	0.6, 1.9	
>251–379.2	91	267	1.0	0.5, 1.8	
≥379.3	53	268	0.8	0.4, 1.7	0.60
Cucurbitaceae					
≤143	86	267	1.0	Reference	
>143–188.6	98	268	1.3	0.7, 2.4	
>188.6–243	62	267	1.0	0.5, 1.9	
>243	81	268	1.0	0.5, 2.1	0.74
Laminariaceae					
≤1	82	263	1.0	Reference	
2–6	85	224	0.7	0.4, 1.3	
7–13	63	238	1.1	0.6, 2.0	
>13	97	345	0.6	0.4, 1.0	0.14
Leguminosae					
<257	93	269	1.0	Reference	
257–381	92	266	1.4	0.8, 2.4	
382–555.1	74	267	1.0	0.6, 1.8	
≥555.2	68	268	1.0	0.5, 1.7	0.63
Liliaceae					
≤38	122	267	1.0	Reference	
39–156	96	265	0.9	0.6, 1.5	
157–370.9	65	264	1.3	0.7, 2.3	
≥371	44	274	0.5	0.3, 0.9	0.16
Nymphaeceae					
< 2	100	256	1.0	Reference	
2–3	54	239	0.6	0.3, 1.1	
>3–5	84	266	1.0	0.6, 1.8	
≥6	89	309	0.9	0.5, 1.5	0.95
Rosaceae					
≤49	67	265	1.0	Reference	
>49–99.5	81	270	1.0	0.5, 1.8	
100–188.6	98	269	0.8	0.4, 1.4	
>188.6	81	266	0.9	0.5, 1.9	0.71
Rutaceae					
≤13	78	282	1.0	Reference	
14–34.7	99	348	0.9	0.5, 1.5	
>34.7–52	57	175	0.6	0.3, 1.1	
>52	93	265	0.7	0.4, 1.2	0.13
Sapindaceae					
< 2	93	217	1.0	Reference	
2–3	107	297	0.8	0.5, 1.4	
3–5	78	285	0.7	0.4, 1.3	
≥6	49	271	0.5	0.3, 0.9	0.02

(Continued)

TABLE 4 *Continued*

Exposure, *times/y*	Cases, *n* = 327	Controls, *n* = 1070	OR[1]	95% CI	*P*-trend
Solanaceae					
≤80	110	268	1.0	Reference	
>80–127	100	264	1.0	0.6, 1.7	
>127–182	46	273	0.8	0.4, 1.5	
>182	71	265	1.3	0.7, 2.5	0.54
Umbellifereae					
<13	76	256	1.0	Reference	
13–23	91	273	1.3	0.7, 2.3	
24–39	75	274	1.4	0.8, 2.5	
>39	85	267	1.7	0.9, 3.1	0.08
Vitaceae					
<4	55	174	1.0	Reference	
4–13	87	357	1.1	0.6, 2.0	
14–25	72	229	0.8	0.4, 1.5	
≥26	113	310	1.0	0.6, 1.9	0.91
Zingiberaceae					
<208	127	264	1.0	Reference	
208–260	49	219	1.0	0.5, 1.8	
261–365	28	156	2.0	0.9, 4.2	
≥365	123	431	1.1	0.7, 1.8	0.47

[1] Adjusted for age, total fruits and vegetables, and parity, and stratified on year of interview.

foods or desserts (not shown). None of the possible relationships we observed with any of the individual food groups were found to be confounded by total intake of fruits and vegetables or by any of the nondietary factors associated with risk. No associations were observed with percentages of energy from fat, protein, or carbohydrates (not shown).

Botanical families. After adjusting for total fruit and vegetable intake, we observed reduced risks in the highest quartiles of intake of *Laminariaceae* (seaweed) and *Liliaceae* (mostly garlic and onions) and a significant decreasing linear trend in risk with intake of *Sapindaceae* (lychees) (**Table 4**). We did not observe any significant associations with any of the other botanical groups shown in the table or with *Chenopodiaceae*, *Ebenaceae*, and *Musaceae* (results not shown due to low levels of exposure). The OR estimates in Table 4 were also adjusted for total energy intake and the observed associations were not appreciably different from those presented (not shown).

The results of the multiple nutrient density models were similar to those presented above (not shown).

Micronutrients. After controlling for total fruit and vegetable intake, no significant associations were observed with total intake of vitamins E or C, total carotenoids, iron, copper, potassium, magnesium, or crude fiber (**Table 5**). Results for α-, β-, γ-, and δ-tocopherol, which are subcomponents of vitamin E, were similar to those for total vitamin E. In addition, significant associations were not observed with intake of nonbotanic sources of vitamin A, niacin, riboflavin, thiamin, zinc, manganese, and phosphorous (not shown).

Discussion

To our knowledge, this is the first report of strong decreasing trends in risk of fibroadenoma with increasing consumption of fruits and vegetables. However, the only specific botanic family

TABLE 5 Risk of breast fibroadenomas in Chinese women in relation to daily intake of specific micronutrients and minerals

Exposure	Cases, *n* = 327	Controls, *n* = 1070	OR[2]	95% CI	*P*-trend
Total vitamin E,[1] *mg α-TE/d*					
<13.9	94	268	1.0	Reference	
13.9–17.5	93	267	1.4	0.8, 2.5	
17.6–22.9	72	267	0.9	0.5, 1.6	
>22.9	68	268	1.2	0.7, 2.3	0.88
Total carotenoids, *μg/d*					
<874.0	81	267	1.0	Reference	
874.0–1138.9	94	268	1.2	0.7, 2.3	
1139.0–1450.5	70	267	0.9	0.4, 1.8	
>1450.5	82	268	0.9	0.4, 1.9	0.51
Vitamin C, *mg/d*					
<55.0	98	267	1.0	Reference	
55.0–73.4	78	268	0.5	0.3, 1.1	
73.5–96.7	86	268	0.9	0.4, 2.2	
>96.7	65	267	0.5	0.2, 1.5	0.31
Iron, *mg/d*					
<12.0	82	267	1.0	Reference	
12.0–14.5	81	268	1.2	0.6, 2.1	
14.6–17.5	81	268	1.2	0.6, 2.2	
>17.5	83	267	0.8	0.4, 1.5	0.39
Copper, *mg/d*					
<1.5	90	270	1.0	Reference	
1.5–1.8	106	267	1.4	0.8, 2.3	
1.9–2.1	68	266	1.1	0.6, 2.1	
>2.1	63	267	0.9	0.5, 1.6	0.57
Potassium, *mg/d*					
<1514.9	96	268	1.0	Reference	
1514.9–1832.2	94	267	1.4	0.7, 2.5	
1832.3–2164.3	71	268	0.8	0.4, 1.6	
>2164.3	66	267	1.0	0.5, 2.2	0.73
Magnesium, *mg/d*					
<275.9	89	267	1.0	Reference	
275.9–327.5	105	268	1.0	0.6, 1.8	
327.6–382.0	71	267	0.9	0.5, 1.7	
>382.0	62	268	0.9	0.5, 1.8	0.70
Total crude fiber, *g/d*					
<7.6	84	267	1.0	Reference	
7.6–9.6	105	268	1.3	0.7, 2.4	
6.7–11.8	73	267	1.0	0.5, 2.1	
>11.8	65	268	0.7	0.3, 1.6	0.29

[1] TE, Tocopherol equivalents.
[2] Adjusted for age, total fruits and vegetables, and parity, and stratified on year of interview.

that was significantly associated with a reduced risk was *Sapindaceae* (lychee fruit) and no associations with individual micronutrients were observed, suggesting that a dietary pattern rich in fruits and vegetables, rather than intake of 1 or more specific foods or nutrients, may reduce risk of fibroadenoma. These findings are compatible with the findings of our dietary biomarker study (43),which show no association between plasma carotenoids or vitamin C concentrations and fibroadenoma risk. The possible reduction in risk in women who consumed soy and other legumes more than once a day may be due to chance but could also indicate that the threshold of consumption necessary to observe an effect on risk was not reached by sufficient numbers of women in our study for a protective effect to be clearly observed. The inverse association between plasma isoflavone concentrations and fibroadenoma risk observed in our biomarker study (43) is consistent with the latter conclusion that there is an association but that the exposure was not captured as effectively by dietary questionnaire as it was by the objective biomarker.

No relationship between risk of fibroadenoma and fried foods, desserts, or red meat was found. However, a linear decrease in risk was significantly associated with increasing intake of sesame oil. Although this could suggest a potential protective effect of certain unsaturated fats or of antioxidants in sesame oil (44), sesame oil is consumed primarily with uncooked vegetables in China, and the observed association could also be a result of residual confounding by vegetable intake.

Although mean serving size was used to calculate intake for all of the food groups, this would bias risk estimates toward the null. This effect is probably small, because most variability in food consumption is due to frequency of intake, not portion size (42). The results of several related analyses suggest that the FFQ provided a reasonably valid assessment of consumption of soy, fruits, and vegetables and of exposure to some specific carotenoids. Soy intake, estimated from the FFQ and Chinese food tables, was positively correlated with daidzein and genistein concentrations in plasma samples collected within 1 wk of completion of the questionnaire (45); estimated fruit intake levels were correlated with plasma concentrations of α-tocopherol, β-cryptoxanthin, lycopene, α-carotene, β-carotene, retinyl palmitate, and vitamin C; and vegetable intake was correlated with plasma concentrations of γ-tocopherol, β-cryptoxanthin, and vitamin C (C. Frankenfeld, J. Lampe, J. Shannon, D. Gao, W. Li, R. Ray, C. Chen, I. King, D. Thomas, unpublished data). In addition, the intake of foods high in lycopene and high β-cryptoxanthin were positively associated plasma concentrations of lycopene and β-cryptoxanthin, respectively (unpublished data).

We have confirmed results of prior studies that risk of fibroadenoma is reduced in women who have gone through natural menopause (7,29) and who have used oral contraceptives (7,19). Although prior studies have yielded inconsistent results for parity (4,8,15–18), we also demonstrated a strong inverse relationship with increasing number of live births. Confounding by nonnutritional risk factors for fibroadenoma is unlikely to account for our results regarding nutritional factors, because we tested for confounding by all known risk factors for fibroadenoma and a broad spectrum of other potential confounding factors. Parity was the only factor found to be a confounding variable in the analyses of associations with any of the nutritional factors, and all OR estimates were accordingly adjusted for number of live births. The decline in risk of fibroadenoma with increasing parity suggests that the incidence of this disease in China may be greater in birth cohorts of women whose reproductive years included the period in which the 1-child-per-family policy was enforced than in earlier birth cohorts.

Women with prior benign breast lesions were at increased risk of fibroadenoma, which is consistent with results of previous studies that showed multiple occurrence (46) and recurrence (4,47) of this condition. Because we were not able to determine whether prior lumps were fibroadenoma or some other benign breast lesion, risk estimates in relation to prior fibroadenoma may be higher than the adjusted OR of 6.1 observed in relation to a history of all types of benign breast conditions. The significant linear trend in observed risk with frequency of BSE clearly represents increased detection, and other studies have similarly shown that BSE results in an increase in benign breast biopsies (34). However, BSE practice was not associated with any of the risk factors identified in this study and therefore confounding by BSE cannot explain any of our results.

The strong positive association with education was unchanged after adjustment for BSE and consumption of fruits and vegetables; thus, other factors associated with education may play a role in the etiology of fibroadenoma. The possible increase in risk in women with a family history of breast cancer could result from shared environmental or genetic risk factors for both conditions or reflect more complete ascertainment of family history from cases than controls. This last possibility is unlikely, because an increased risk in women with a family history of breast cancer was also observed in a cohort study conducted in this same population (7). The decrease in risk for smokers in this and other (24) studies may be a result of the reduction in estrogen levels in smokers. Given the inconsistency of the observed associations between fibroadenoma and physical exercise, further examination of the relationship is needed.

Many fibroadenomas are never clinically detected, so some women with fibroadenomas were undoubtedly classified as nondiseased in this study, introducing conservative bias into the OR estimates. Although some misclassification of exposure may have occurred due to inaccurate self-reporting, it would likely be similar for cases and controls, because the cases were not ill, and this would also tend to bias the results toward the null.

Our results suggest that risk of fibroadenoma could be reduced with a diet rich in fruits and vegetables as well as by use of oral contraceptives.

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D.B.T. and J.S. designed research; H.S., P.P, W.W., Y.H., D.G., and Q.C. conducted research; Z.C.N., R.M.R., C.W., N.H., and W.L. analyzed data; Z.C.N., J.W.L., and D.B.T. wrote the paper. D.B.T. had primary responsibility for final content. All authors read and approved the final manuscript.

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