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Research Article

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Dietary Fat Intake During Adolescence and Breast Density Among Young Women

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Abstract

Background: Lack of association between fat intake and breast cancer risk in cohort studies might be attributed to the disregard of temporal effects during adolescence when breasts develop and are particularly sensitive to stimuli. We prospectively examined associations between adolescent fat intakes and breast density.

Method: Among 177 women who participated in the Dietary Intervention Study in Children, dietary intakes at ages 10–18 years were assessed on five occasions by 24-hour recalls and averaged. We calculated geometric mean and 95% confidence intervals for MRI-measured breast density at ages 25–29 years across quartiles of fat intake using linear mixed-effect regression.

Results: Comparing women in the extreme quartiles of adolescent fat intakes, percent dense breast volume (%DBV) was positively associated with saturated fat (mean = 16.4% vs. 21.5%; $P_{trend} < 0.001$). Conversely, %DBV was inversely associated with monounsaturated fat (25.0% vs. 15.8%; $P_{trend} < 0.001$) and the ratio of polyunsaturated fat to saturated fat (P/S ratio; 19.1% vs. 14.3%; $P_{trend} < 0.001$). When examining intake by pubertal stages, %DBV was inversely associated with intake of polyunsaturated fat (20.8% vs. 16.4%; $P_{trend} = 0.04$), long-chain omega-3 fat (17.8% vs. 15.8%; $P_{trend} < 0.001$), and P/S ratio (22.5% vs. 16.1%; $P_{trend} < 0.001$) before menarche, but not after. These associations observed with %DBV were consistently observed with absolute dense breast volume but not with absolute nondense breast volume.

Conclusions: In our study, adolescent intakes of higher saturated fat and lower mono- and polyunsaturated fat are associated with higher breast density measured approximately 15 years later.

Impact: The fat subtype composition in adolescent diet may be important in early breast cancer prevention. *Cancer Epidemiol Biomarkers Prev; 25(6); 918–26. ©2016 AACR.*

Introduction

Although studied extensively, the association between diet and breast cancer remains unsettled. In pooled analyses of eight prospective cohort studies (1) and randomized controlled trials (2, 3), little association was observed between total and subtypes of fat intakes during adulthood and breast cancer risk, despite positive associations observed in ecologic (4, 5) and animal studies (6). Associations with the risk of breast cancer subtypes also have been inconsistent (7, 8). However, breast tissue is most sensitive to stimuli during adolescence (9), when breasts develop and undergo structural changes (10–12). Little is known whether early-life fat intake affects breast development or morphology, which may, in part, mediate breast cancer risk later in life.

Breast density is a measure of the relative amount of glandular and stromal tissue in the breasts, and is a strong risk factor for breast cancer (13, 14). Dietary fat intake was reported to affect endogenous hormones (15, 16), which regulates ductal morphogenesis during puberty (12). Pubertal high-fat diets in rats altered cellular proliferation and breast tissue composition (17, 18), and induced abnormal breast lesions (18, 19). The few studies that examined associations of early-life fat intake with breast density reported null results (20, 21). Still, these studies were limited by recall of diet in the distant past, and no investigation of fat subtypes and pubertal stages. In the Dietary Intervention Study in Children (DISC), children with elevated levels of blood cholesterol who were randomized to a reduced fat diet for 7 years had similar breast density in their 20s to children randomized to the control group who consumed usual diets (22), though variation in fat intake between groups was modest.

Therefore, utilizing adolescent dietary data collected repeatedly in the DISC trial (23, 24) and breast density measured by magnetic resonance imaging (MRI) at age 25–29 years in the DISC06 Follow-Up Study (22, 25), we expanded our initial analyses and prospectively evaluated associations between breast density and reported total and subtypes of fat intakes during adolescence and at specific pubertal stages.

Materials and Methods

Study population

DISC was a two-armed, multicenter, randomized controlled clinical trial to evaluate the efficacy and safety of a lipid-lowering diet in children with elevated low-density lipoprotein cholesterol

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(LDL-C; refs. 26, 27). Between 1988 and 1990, healthy, prepubertal, 8- to 10-year-old girls ($N = 301$) and boys ($N = 362$) with elevated LDL-C were randomized to a reduced-fat diet intervention or a usual-care control group in six clinical centers until 1997 (27). Between 2006 and 2008, the DISC06 Follow-Up Study was conducted among female DISC participants ages 25–29 years to assess the long-term effect of the diet intervention during childhood and adolescence on breast cancer–related biomarkers (22). Assent from participants and informed consent from parents or guardians were obtained prior to randomization and informed consent was obtained from participants before the DISC06 Follow-Up Study. The institutional review boards at participating centers approved original and follow-up DISC protocols.

Of 260 women who participated in the DISC06 Follow-Up Study, women who were pregnant or breastfeeding within 12 weeks before the follow-up visit ($N = 30$), had breast augmentation or reduction surgery ($N = 16$), had unacceptable or missing breast density data ($N = 32$), or were without dietary data during the DISC trial ($N = 5$) were excluded. Consequently, this analysis includes 177 women.

Data collection

Participants completed questionnaires on demographics, lifestyle, physical activity, medication use, and reproductive, menstrual, and medical history at baseline and at follow-up visits in the DISC trial and the DISC06 Follow-Up Study. Height and weight were measured (25). Childhood BMI z-score was calculated on the basis of Centers for Disease Control and Prevention 2000 Growth Charts (28). In DISC06, whole-body percent fat was estimated by dual energy X-ray absorptiometry (25). During the DISC trial, sexual maturation was evaluated annually by ascertaining onset of menses and conducting a physical examination including Tanner staging (29).

Diet at baseline, year 1, 3, and 5 and last visits during the DISC trial and at DISC06 follow-up visits was assessed via three nonconsecutive 24-hour dietary recalls obtained on two weekdays and one weekend day over two weeks (30, 31). Trained, certified nutritionists conducted face-to-face interviews during clinic visits and two subsequent recalls were obtained via telephone. Parents provided additional details, if needed. Nutrition Coordinating Center at the University of Minnesota estimated nutrient intake from 24-hour recalls using their food and nutrient database (version 20). Nutrient intakes from recalls were averaged to estimate usual dietary intake. Records with implausible energy intakes (<600 kcal/day or >3,500 kcal/day; $N = 7$) were set to missing (32). Energy intakes from each type of fat or protein were divided by total energy intake to calculate percent energy from those nutrients. The correlations between 24-hour recalls and dietary records collected on a subset of participants were 0.73 for total fat, 0.64 for saturated fat, 0.78 for monounsaturated fat, and 0.64 for polyunsaturated fat (33).

Breast density was measured by noncontrast MRI (22), because MRI avoids radiation exposure, and provides three-dimensional volumetric measurements of breast composition that is reported by some to be more predictive of breast cancer risk (34) and is also not impaired by high breast density typical of young women. Even so, percent breast density measured by MRI is highly correlated with mammographic measurements ($r > 0.75$; refs. 35, 36). Breasts were imaged with a whole-body 1.5 Tesla or higher field-strength MRI scanner with a dedicated breast-imaging radiofrequency coil. All MRI image data were processed by Dr. C. Klifa (University of California, San Francisco, San Francisco, CA), who identified chest wall–breast tissue boundary and skin surface, and separated breast fibroglandular and fatty tissue via automated fuzzy C-means method (37). MRI technologists were trained to recognize and correct failures. Each DISC clinic was certified after obtaining acceptable images from three volunteers.

We measured total breast volume and absolute dense breast fibroglandular volume (ADBV) for each breast. Absolute nondense breast volume (ANDBV) was estimated by subtracting ADBV from total breast volume. Percent dense breast volume (%DBV) was calculated as the ratio of ADBV to total breast volume. Breast density measures for both breasts were averaged for analysis.

Statistical analyses

Our primary exposure was long-term fat intake during adolescence estimated by averaging reported intakes (38) over the course of the DISC trial. We also estimated fat intakes separately by menarche status as breasts' susceptibility to stimuli might vary during pubertal transition (10, 39–41). Specifically, we averaged fat intakes from age 10 years, the approximate age of onset of breast development (42, 43), to the last DISC trial visit (median age = 16.6 years) to estimate overall adolescent intake, from age 10 years to the onset of menarche to estimate premenarcheal intake, and thereafter to the last DISC trial visit to estimate postmenarcheal intake.

%DBV, ADBV, and ANDBV values were log-transformed to approximate normality. We imputed missing values of whole-body percent fat ($N = 6$) using values from a prediction model that included adult BMI as an independent variable; this process was repeated 25 times to create 25 multiply imputed datasets. The correlation coefficient between imputed whole-body percent fat and adult BMI ranged from 0.74 to 0.99 across the imputed datasets, which compared favorably to a correlation of 0.82 based on actual data. In each imputed dataset, the geometric mean and the 95% confidence interval for %DBV, ADBV, and ANDBV were calculated across fat intake quartiles using linear mixed-effects regression models with robust SEs. To adjust for potential confounders known to be associated with breast cancer risk, breast density, and fat intake (1, 25, 44), fully adjusted multivariable models included the following predictors, race, education, childhood BMI z-score, adulthood whole-body percent fat, duration of hormone use, number of live births, smoking status, and intakes of total calories, protein, fiber, and alcohol as fixed effects; clinic was included as a random effect; other types of fat were simultaneously adjusted for in analyses of specific types of fat (38). Trends across quartile medians modeled as continuous variables were tested using the Wald test statistic. Interactions of fat intake by intervention assignment, hormone use, and whole-body percent fat were tested in the model including cross-product terms. Results from the fully adjusted multivariable model in each imputed dataset were pooled using Rubin's rule (45).

Analyses were conducted by STATA (version 13.0). All tests were two-sided and done at the 0.05 level of significance.

Results

In our analyses of 177 women, the mean percent energy from total and major subtypes of fat intakes during adolescence at age 10–18 years were 29.7% for total fat, 10.8% for saturated fat,

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10.9% for monounsaturated fat, and 5.8% for polyunsaturated fat (Table 1). In the DISC06 Follow-Up Study when breast density was measured, participants' mean age was 27.2 years and their mean BMI was 25.4 kg/m^2. The majority of women were White (91%) and nulliparous (72%), had attended at least college (91%), and ever used hormonal contraceptives (94%). The median of breast density measures (interquartile ranges) were 24.3% (9.7%–41.2%) for %DBV, 93.6 cm^3 (50.0–140.3 cm^3) for ADBV, and 299.2 cm^3 (157.8–484.9 cm^3) for ANDBV. Fat intakes at the DISC06 follow-up visit are shown in Supplementary Table S1.

Table 1. Study population characteristics at the DISC06 follow-up visit

Characteristics	*N*	Mean ± SD
Age, y	177	27.2 ± 1.0
BMI	177	25.4 ± 5.4
Physical activity (Mets-hrs/week)	177	309.4 ± 54.5
Age at menarche, y	177	12.9 ± 1.2
Duration of hormonal contraceptive use, y[a]	166	5.6 ± 3.5
Dietary intake during adolescence		
Total energy intake (kcal/day)	177	1,611.2 ± 350.8
Percentage of energy from		
Total fat (%)	177	29.7 ± 4.8
Saturated fat (%)	177	10.8 ± 2.2
Monounsaturated fat (%)	177	10.9 ± 1.9
Polyunsaturated fat (%)	177	5.8 ± 1.3
Long-chain omega-3 fat (%)	177	0.04 ± 0.06
Linoleic acid (%)	177	5.2 ± 1.2

	N	Percentage
Race		
White	161	91%
Non-white	16	9%
Education		
Some college	43	24%
Bachelor's degree	93	53%
Graduate degree	24	14%
Other[b]	17	9%
Number of live births		
0	127	72%
≥1	50	28%
Family history of breast cancer		
No	167	97%
Yes	6	3%
Hormonal contraceptive use		
Never	11	6%
Former	62	35%
Current	104	59%
Smoking status		
Never	97	55%
Former	38	21%
Current	42	24%
Alcohol consumption		
Never/former	16	9%
Current, <3 per week	67	38%
Current, 3–<6 per week	33	19%
Current, 6–<10 per week	40	22%
Current, ≥10 per week	21	12%
Treatment assignment		
Intervention	86	49%
Usual care	91	51%

Breast density measures	*N*	Median (IQR)
Percent dense breast volume (%)	177	24.3 (9.7–42.5)
Absolute dense breast volume (cm^3)	177	93.6 (50.0–140.3)
Absolute nondense breast volume (cm^3)	177	299.2 (157.8–484.9)

Abbreviations: BMI, body mass index; IQR, interquartile range.

[a]Mean duration of hormonal use was calculated among past and current hormone users.

[b]Other education includes education until 8–11 years, completion of high school and vocational or technical school.

We present results only from the fully adjusted multivariable model because associations of fat intakes with breast density measures were similar from the simpler model adjusting for adult whole body percent fat, treatment assignment, and intake of total energy and protein (data not shown). Intake of saturated fat was significantly positively, whereas monounsaturated fat and the ratio of polyunsaturated fat to saturated fat (P/S ratio) were significantly inversely associated with %DBV (all $P_{trend} < 0.001$; Table 2). Comparing women in the extreme quartiles of each fat subtype or P/S ratio (Q1–Q4), the multivariable-adjusted mean %DBV increased from 16.4% to 21.5% for saturated fat, while it decreased from 25.0% to 15.8% for monounsaturated fat and from 19.1% to 14.3% for the P/S ratio.

When we examined intakes before and after menarche (refs. 10, 39–41; Table 2), premenarcheal, but not postmenarcheal, intakes of polyunsaturated fat ($P_{trend} = 0.04$) and long-chain omega-3 fat ($P_{trend} < 0.001$) and the P/S ratio ($P_{trend} < 0.001$) were significantly inversely associated with %DBV. The multivariable-adjusted mean %DBV decreased from 20.8% to 16.4% for polyunsaturated fat, from 17.8% to 15.8% for long-chain omega-3 fat, and from 22.5% to 16.1% for the P/S ratio when comparing women in the lowest and the highest quartiles for each fat. Total fat and linoleic acid intakes during adolescence or during pre- or postmenarche periods were not associated with %DBV.

Because variation of fat intakes and the P/S ratio was relatively modest, particularly among women in the lower quartiles, we conducted sensitivity analyses categorizing fat intakes and the P/S ratio into tertiles to improve contrasts (data not shown). The linear inverse trend with %DBV became clearer. For example, the multivariable-adjusted mean %DBV decreased monotonically from 20.9% to 18.4% and 17.0% for monounsaturated fat and from 21.8% to 18.6% and 16.2% for the P/S ratio with increasing tertiles.

Additional adjustment for adult fat intakes or restricting analyses to nulliparous women did not change results substantially (data not shown). Treatment assignment, whole-body percent fat, and hormone use did not statistically significantly modify associations between total or subtypes of fat intakes and %DBV (all $P_{interaction} \geq 0.11$).

When examining associations separately for individual components of breast tissue that compose %DBV (Tables 3 and 4), the associations observed with %DBV were generally seen with ADBV, although results for polyunsaturated fat were not significant. Comparing extreme quartiles (Q1–Q4) of each subtype of fat intake or the P/S ratio, the multivariable-adjusted mean ADBV increased from 65.6 cm^3 to 97.4 cm^3 for saturated fat ($P_{trend} = 0.03$), whereas it decreased from 105.4 cm^3 to 69.0 cm^3 for monounsaturated fat ($P_{trend} = 0.05$) as well as for premenarcheal long-chain omega-3 fat (from 76.6 cm^3 to 65.5 cm^3; $P_{trend} < 0.001$) and P/S ratio (from 85.1 cm^3 to 71.8 cm^3; $P_{trend} < 0.002$). In contrast, ANDBV was significantly positively associated with premenarcheal intakes of polyunsaturated fat ($P_{trend} = 0.01$), linoleic acid ($P_{trend} = 0.02$), and the P/S ratio ($P_{trend} < 0.001$). The multivariable-adjusted mean ANDBV increased from 260.8 cm^3 to 324.1 cm^3 for polyunsaturated

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Table 2. Multivariable[a] adjusted geometric mean and 95% confidence interval (95% CI) of percent dense breast volume (%DBV) according to quartiles of intakes of total and subtypes of fat during adolescence

	All periods ($N = 177$)		By menarcheal status			
			Before menarche ($N = 160$)		After menarche ($N = 163$)	
Quartiles of intake	Median intake, % kcal	%DBV mean (95% CI)	Median intake, % kcal	%DBV mean (95% CI)	Median intake, % kcal	%DBV mean (95% CI)
Total fat						
Q1	24.4	21.4 (20.0–23.0)	24.6	17.1 (14.9–19.7)	22.5	16.6 (14.0–19.7)
Q2	28.0	16.8 (14.1–20.0)	29.5	22.7 (19.0–27.2)	27.2	19.3 (17.6–21.2)
Q3	31.3	18.4 (15.5–21.8)	33.1	18.1 (13.6–24.2)	30.3	17.4 (14.8–20.5)
Q4	35.3	18.6 (14.5–23.9)	37.4	16.5 (12.7–21.4)	35.4	20.7 (16.9–25.4)
P_{trend}[b]		0.50		0.61		0.22
Saturated fat						
Q1	8.2	16.4 (14.1–19.0)	8.5	16.2 (14.0–18.8)	7.6	18.4 (17.2–19.6)
Q2	10.0	17.7 (16.8–18.6)	10.4	17.1 (14.2–20.7)	9.6	16.8 (13.2–21.4)
Q3	11.6	19.9 (16.7–23.6)	12.1	20.4 (17.5–23.8)	11.3	17.9 (12.8–25.0)
Q4	13.4	21.5 (16.6–27.8)	14.1	20.5 (15.5–27.3)	13.3	21.1 (16.2–27.4)
P_{trend}[b]		<0.001		0.22		0.37
Monounsaturated fat						
Q1	8.8	25.0 (18.3–34.1)	9.1	18.7 (14.3–24.6)	8.0	19.4 (10.6–35.5)
Q2	10.4	16.8 (13.5–20.8)	10.9	18.9 (15.2–23.4)	9.7	20.4 (15.8–26.2)
Q3	11.5	18.6 (13.2–26.4)	12.2	17.3 (12.8–23.4)	11.4	17.0 (12.3–23.5)
Q4	13.2	15.8 (13.3–18.8)	14.2	19.0 (15.9–22.7)	13.3	17.3 (13.0–23.0)
P_{trend}[b]		<0.001		0.88		0.74
Polyunsaturated fat						
Q1	4.3	21.4 (18.3–25.1)	4.1	20.8 (17.0–25.5)	4.1	17.2 (14.7–20.1)
Q2	5.2	18.6 (14.3–24.2)	5.2	20.4 (18.5–22.3)	5.0	18.7 (15.0–23.3)
Q3	6.1	17.5 (12.7–24.0)	6.3	16.7 (13.6–20.6)	6.0	19.0 (16.6–21.7)
Q4	7.3	17.6 (16.0–19.4)	7.9	16.4 (13.3–20.4)	7.6	19.0 (15.0–24.1)
P_{trend}[b]		0.28		0.04		0.67
Long-chain omega-3 fat						
Q1	0.007	20.9 (17.4–25.0)	0.005	17.8 (13.8–22.8)	0.004	17.9 (16.0–20.0)
Q2	0.01	20.8 (16.9–25.5)	0.01	21.0 (17.6–25.1)	0.01	18.1 (14.2–23.2)
Q3	0.03	17.7 (14.5–21.6)	0.03	19.8 (15.1–25.9)	0.02	17.8 (15.4–20.5)
Q4	0.08	15.7 (11.2–22.0)	0.09	15.8 (14.2–17.5)	0.09	20.2 (15.9–25.6)
P_{trend}[b]		0.24		<0.001		0.45
Linoleic acid						
Q1	3.8	21.2 (18.6–24.2)	3.7	20.3 (16.1–25.4)	3.51	20.3 (16.1–25.4)
Q2	4.7	17.7 (13.5–23.3)	4.6	19.6 (17.2–22.3)	4.52	19.6 (17.2–22.3)
Q3	5.5	17.4 (14.0–21.8)	5.6	18.0 (16.4–19.8)	5.36	18.0 (16.4–19.8)
Q4	6.7	18.7 (16.3–21.5)	7.1	16.3 (12.7–20.8)	6.74	16.3 (12.7–20.8)
P_{trend}[b]		0.48		0.14		0.14
P/S ratio						
Q1	0.4	19.1 (15.8–23.1)	0.3	22.5 (17.6–28.8)	0.4	17.6 (15.9–19.6)
Q2	0.5	22.1 (17.3–28.2)	0.5	20.3 (16.2–25.6)	0.5	22.4 (18.8–26.6)
Q3	0.6	20.4 (17.3–24.1)	0.6	15.8 (12.8–19.5)	0.6	18.3 (14.7–22.9)
Q4	0.8	14.3 (11.5–17.7)	0.8	16.1 (12.9–20.1)	0.8	16.0 (12.8–19.9)
P_{trend}[b]		<0.001		<0.001		0.12

[a]Geometric means and 95% CI are estimated from linear mixed effects models including clinic as a random effect and including treatment group (diet intervention group and usual care-control group), childhood BMI *z*-score, current adult percent body fat from dual energy X-ray absorptiometry (%, continuous), number of live births (0 and >0), duration of hormone use (years, continuous), race (White and non-White), education (bachelor's degree, graduate school and other), status of smoking (never, former, and current), alcohol consumption (never/former, <3 drinks/week, 3–<6 drinks/week, 6–<10 drinks/week, ≥10 drinks/week), total energy intake (kcal/day, continuous), fiber intake (g/day, continuous), and percent of energy from protein (%, continuous) as fixed effects; in analyses of specific types of fat, percent of energy from saturated fat (%, continuous), polyunsaturated fat (%, continuous), and monounsaturated fats (%, continuous) were mutually adjusted for each another.

[b]P_{trend} was conducted by modeling the quartile medians of intakes of each fat as a continuous term in linear mixed effects models and calculating the Wald test statistic.

fat, from 280.2 cm^3 to 320.0 cm^3 for linoleic acid, and from 241.2 cm^3 to 313.7 cm^3 for the P/S ratio between the extreme quartiles.

Discussion

In this prospective analysis, adolescent total fat intake was not significantly associated with %DBV, ADBV, or ANDBV. However, adolescent intake of saturated fat was significantly positively associated, while monounsaturated fat was significantly inversely associated with %DBV and ADBV but not with ANDBV. When examining intakes by pubertal stages, premenarcheal intakes of polyunsaturated fat and long-chain omega-3 fat, and the P/S ratio were significantly inversely associated with %DBV. Intake of long-chain omega-3 fat also was significantly inversely associated with ADBV, whereas polyunsaturated fat was significantly positively associated with ANDBV. The P/S ratio was significantly inversely associated with ADBV and positively with ANDBV. No postmenarcheal fat intakes were associated with %DBV, ADBV, or ANDBV.

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Table 3. Multivariable[a] adjusted geometric mean and 95% confidence interval (95% CI) of absolute dense breast volume (ADBV) (cm^3) according to quartiles of total and subtypes of fat intake during adolescence

	All periods ($N = 177$)		By menarcheal status			
			Before menarche ($N = 160$)		After menarche ($N = 163$)	
Quartiles of intake	Median intake, % kcal	ADBV mean (95% CI)	Median intake, % kcal	ADBV mean (95% CI)	Median intake, % kcal	ADBV mean (95% CI)
Total fat						
Q1	24.4	89.3 (73.5–108.7)	24.6	71.7 (59.9–85.7)	22.5	69.0 (49.7–95.9)
Q2	28.0	63.1 (52.0–76.5)	29.5	90.4 (76.7–106.5)	27.2	78.4 (70.8–86.8)
Q3	31.3	81.8 (69.3–96.7)	33.1	80.8 (64.8–100.8)	30.3	78.2 (62.2–98.2)
Q4	35.3	84.3 (65.5–108.6)	37.4	69.5 (50.6–95.6)	35.4	90.5 (74.5–109.8)
P_{trend}[b]		0.82		0.67		0.19
Saturated fat						
Q1	8.2	65.6 (45.8–94.1)	8.5	67.5 (59.4–76.7)	7.6	74.9 (54.5–103.0)
Q2	10.0	72.0 (66.4–78.1)	10.4	67.4 (53.9–84.3)	9.6	78.3 (63.9–96.0)
Q3	11.6	85.1 (71.3–101.5)	12.1	87.1 (80.6–94.1)	11.3	71.1 (47.9–105.8)
Q4	13.4	97.4 (73.5–129.0)	14.1	91.9 (65.4–129.3)	13.3	91.8 (69.6–120.7)
P_{trend}[b]		0.03		0.08		0.45
Monounsaturated fat						
Q1	8.8	104.5 (76.7–142.4)	9.1	81.6 (70.2–94.9)	8.0	71.7 (34.9–147.4)
Q2	10.4	66.4 (58.2–75.9)	10.9	76.7 (60.4–97.4)	9.7	84.4 (67.5–105.7)
Q3	11.5	80.9 (57.6–113.6)	12.2	76.6 (52.0–112.7)	11.4	75.9 (52.1–110.6)
Q4	13.2	69.0 (57.4–82.9)	14.2	76.0 (60.4–95.5)	13.3	83.1 (56.1–123.0)
P_{trend}[b]		0.05		0.71		0.82
Polyunsaturated fat						
Q1	4.3	86.5 (75.8–98.9)	4.1	85.1 (78.3–92.5)	4.1	69.3 (55.6–86.4)
Q2	5.2	76.9 (54.5–108.4)	5.2	80.2 (67.7–95.0)	5.0	81.7 (65.1–102.6)
Q3	6.1	68.9 (44.0–108.0)	6.3	71.3 (56.5–90.0)	6.0	84.5 (63.4–112.6)
Q4	7.3	84.9 (70.8–101.7)	7.9	74.8 (54.8–102.0)	7.6	79.7 (59.5–106.9)
P_{trend}[b]		0.93		0.36		0.73
Long-chain omega-3 fat						
Q1	0.007	89.3 (76.2–104.7)	0.005	76.6 (62.5–93.7)	0.004	71.4 (56.4–90.4)
Q2	0.01	81.9 (65.5–102.3)	0.01	87.7 (68.5–112.2)	0.01	77.0 (54.3–109.1)
Q3	0.03	76.6 (59.1–99.3)	0.03	82.8 (62.4–109.9)	0.02	79.2 (58.9–106.5)
Q4	0.08	69.4 (46.0–104.6)	0.09	65.5 (54.9–78.2)	0.09	87.8 (59.0–130.6)
P_{trend}[b]		0.35		<0.001		0.53
Linoleic acid						
Q1	3.8	83.0 (73.9–93.3)	3.7	86.8 (78.7–95.7)	3.51	78.0 (64.2–94.8)
Q2	4.7	72.7 (54.0–97.9)	4.6	72.1 (57.7–90.2)	4.52	74.8 (57.4–97.5)
Q3	5.5	74.3 (54.6–102.9)	5.6	79.9 (67.9–94.0)	5.36	84.0 (66.1–106.8)
Q4	6.7	85.2 (68.6–105.8)	7.1	72.8 (53.4–99.2)	6.74	77.8 (58.3–103.7)
P_{trend}[b]		0.68	0.40	0.40		0.92
P/S ratio						
Q1	0.4	76.6 (62.6–93.8)	0.3	85.1 (64.9–111.5)	0.4	71.1 (62.7–80.7)
Q2	0.5	96.5 (66.8–139.2)	0.5	88.2 (69.5–111.8)	0.5	100.7 (73.7–137.6)
Q3	0.6	82.2 (66.4–101.8)	0.6	67.6 (48.9–93.5)	0.6	73.4 (52.7–102.2)
Q4	0.8	64.2 (49.8–82.8)	0.8	71.8 (58.5–88.1)	0.8	72.4 (54.3–96.5)
P_{trend}[b]		0.19		<0.001		0.54

[a]Geometric means and 95% CI are estimated from linear mixed effects models including clinic as a random effect and including treatment group (diet intervention group and usual care-control group), childhood BMI z-score, current adult percent body fat from dual energy X-ray absorptiometry (%, continuous), number of live births (0 and >0), duration of hormone use (years, continuous), race (White and non-White), education (bachelor's degree, graduate school and other), status of smoking (never, former, and current), alcohol consumption (never/former, <3 drinks/week, 3–<6 drinks/week, 6–<10 drinks/week, ≥10 drinks/week), total energy intake (kcal/day, continuous), fiber intake (g/day, continuous), and percent of energy from protein (%, continuous) as fixed effects; in analyses of specific types of fat, percent of energy from saturated fat (%, continuous), polyunsaturated fat (%, continuous), and monounsaturated fats (%, continuous) were mutually adjusted for each another.

[b]P_{trend} was conducted by modeling the quartile medians of intakes of each fat as a continuous term in linear mixed effects models and calculating the Wald test statistic.

The null association we observed between total fat intake and %DBV is largely consistent with previous evidence. Of eight cross-sectional studies of adult women (46–53), total fat intake was not associated with breast density in six (46, 47, 50–53), whereas two found significant positive associations (48, 49). Similarly, high-fat food consumption during childhood was not associated with breast density in adulthood (20, 21). In two (22, 54) of three randomized controlled trials (22, 54, 55), women assigned to a low-fat diet in adolescence (22) or midlife (54) had similar breast density to women assigned to a usual diet, although another found a significant difference in breast density (55).

Nonetheless, fatty acids have unique chemical and biophysical properties (56, 57) and varying physiologic functions (58–61). Examining only total fat intakes may mask specific effects of each subtype of fat on breasts. Indeed, in our data, saturated fat and unsaturated fat intakes, such as mono- and polyunsaturated fat, particularly from long-chain omega-3 fat, had opposing associations with %DBV. Our significant positive association of saturated fat with %DBV is consistent with three studies (46, 48, 62),

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Table 4. Multivariable[a] adjusted geometric mean and 95% confidence interval (95% CI) of absolute nondense breast volume (ANDBV) (cm^3) according to quartiles of total and subtypes of fat intake during adolescence

	All periods ($N = 177$)		By menarcheal status			
			Before menarche ($N = 160$)		After menarche ($N = 163$)	
Quartiles of intake	Median intake, % kcal	ANDBV mean (95% CI)	Median intake, % kcal	ANDBV mean (95% CI)	Median intake, % kcal	ANDBV mean (95% CI)
Total fat						
Q1	24.4	271.0 (226.5–324.4)	24.6	276.1 (222.9–341.9)	22.5	293.5 (240.5–358.1)
Q2	28.0	242.9 (242.9–301.2)	29.5	267.4 (245.2–291.6)	27.2	275.4 (233.9–324.4)
Q3	31.3	288.0 (240.9–344.4)	33.1	305.2 (254.7–365.6)	30.3	301.9 (257.5–354.0)
Q4	35.3	326.6 (257.1–414.8)	37.4	312.1 (256.1–380.5)	35.4	298.5 (253.4–351.6)
P_{trend}[b]		0.25		0.33		0.80
Saturated fat						
Q1	8.2	297.1 (232.5–379.7)	8.5	288.3 (259.4–320.3)	7.6	288.1 (219.5–378.1)
Q2	10.0	274.5 (252.2–298.6)	10.4	282.8 (211.9–377.4)	9.6	318.4 (261.0–388.3)
Q3	11.6	281.5 (230.2–344.2)	12.1	281.9 (253.7–313.2)	11.3	270.9 (235.0–312.4)
Q4	13.4	299.7 (265.0–339.1)	14.1	306.0 (276.2–339.0)	13.3	293.1 (259.3–331.3)
P_{trend}[b]		0.78		0.55		0.80
Monounsaturated fat						
Q1	8.8	267.1 (215.2–331.4)	9.1	283.1 (208.2–385.0)	8.0	247.7 (187.7–326.7)
Q2	10.4	268.5 (217.0–332.2)	10.9	289.5 (260.5–321.8)	9.7	280.6 (241.6–325.8)
Q3	11.5	301.2 (267.4–339.3)	12.2	311.2 (269.5–359.3)	11.4	303.3 (252.2–364.7)
Q4	13.2	319.4 (270.3–377.4)	14.2	275.6 (250.3–303.5)	13.3	346.8 (293.7–409.7)
P_{trend}[b]		0.24		0.66		0.10
Polyunsaturated fat						
Q1	4.3	274.8 (242.3–311.7)	4.1	260.8 (217.4–312.9)	4.1	289.2 (260.7–320.8)
Q2	5.2	275.1 (249.6–303.1)	5.2	271.7 (236.9–311.5)	5.0	303.7 (270.6–340.7)
Q3	6.1	278.6 (226.6–342.5)	6.3	306.3 (263.0–356.6)	6.0	302.2 (267.7–341.2)
Q4	7.3	327.3 (254.7–420.8)	7.9	324.1 (291.8–359.8)	7.6	274.0 (218.0–344.3)
P_{trend}[b]		0.30		0.01		0.49
Long-chain omega-3 fat						
Q1	0.007	297.8 (262.0–338.6)	0.005	297.9 (269.1–329.7)	0.004	281.3 (246.1–321.5)
Q2	0.01	276.6 (233.3–328.1)	0.01	278.6 (260.5–297.9)	0.01	289.1 (262.8–318.0)
Q3	0.03	300.5 (245.9–367.2)	0.03	289.4 (232.4–360.4)	0.02	327.0 (288.2–371.0)
Q4	0.08	277.9 (217.2–355.6)	0.09	292.8 (248.2–345.4)	0.09	273.4 (217.5–343.6)
P_{trend}[b]		0.75		0.87		0.55
Linoleic acid						
Q1	3.8	275.1 (249.3–303.5)	3.7	280.2 (222.3–353.0)	3.51	296.9 (274.3–321.4)
Q2	4.7	276.7 (256.3–298.8)	4.6	249.0 (208.6–297.3)	4.52	292.6 (251.5–340.5)
Q3	5.5	295.8 (233.5–374.6)	5.6	315.0 (276.5–358.8)	5.36	293.8 (240.2–359.4)
Q4	6.7	306.1 (235.7–397.6)	7.1	320.0 (284.7–359.7)	6.74	285.0 (220.7–368.1)
P_{trend}[b]		0.48	0.40	0.02		0.78
P/S ratio						
Q1	0.4	280.2 (254.8–308.1)	0.3	241.2 (222.4–261.5)	0.4	274.3 (254.3–296.0)
Q2	0.5	272.5 (219.9–337.7)	0.5	304.3 (253.3–365.6)	0.5	297.0 (251.4–350.8)
Q3	0.6	284.9 (252.8–321.0)	0.6	305.5 (265.7–351.2)	0.6	287.5 (239.6–345.0)
Q4	0.8	316.8 (281.4–354.7)	0.8	313.7 (285.3–344.9)	0.8	311.3 (240.0–403.7)
P_{trend}[b]		0.07		<0.001		0.42

[a]Geometric means and 95% CI are estimated from linear mixed effects models including clinic as a random effect and including treatment group (diet intervention group and usual care-control group), childhood BMI *z*-score, current adult percent body fat from dual energy X-ray absorptiometry (%, continuous), number of live births (0 and >0), duration of hormone use (years, continuous), race (White and non-White), education (bachelor's degree, graduate school and other), status of smoking (never, former, and current), alcohol consumption (never/former, <3 drinks/week, 3–<6 drinks/week, 6–<10 drinks/week, ≥10 drinks/week), total energy intake (kcal/day, continuous), fiber intake (g/day, continuous), and percent of energy from protein (%, continuous) as fixed effects; in analyses of specific types of fat, percent of energy from saturated fat (%, continuous), polyunsaturated fat (%, continuous), and monounsaturated fats (%, continuous) were mutually adjusted for each another.

[b]P_{trend} was conducted by modeling the quartile medians of intakes of each fat as a continuous term in linear mixed effects models and calculating the Wald test statistic.

although others have reported no associations (47, 50, 52) or significant inverse associations (53). Contrary to the inverse associations, we observed with unsaturated fat intake, most studies of adult women found no significant association between breast density and intakes of monounsaturated fat (47, 48, 50, 53, 62), polyunsaturated fat (46–48, 50, 53), or omega-3 fat (48), while one found significant positive association with monounsaturated fat (49).

The stronger associations observed for specific subtypes of fat in our study, compared with previous studies of adult women, might be attributed to the early-life dietary assessment. Adolescence is a critical period when mammary ducts elongate and branch (10). These structural changes accompany rapid proliferation of undifferentiated cells, which may render breasts particularly vulnerable to any effects of fat. The degree of saturation in fatty acids influences fluidity and structure of cell membranes, which affects cell receptors, membrane transporters, and cellular signaling pathways (56, 57, 63). Increasing saturated fat while decreasing monounsaturated fat and polyunsaturated fat, and particularly omega-3 fat, were shown to promote proliferation, insulin

resistance, and inflammation, and to depress cellular responses to DNA damage and apoptosis (60, 61, 64–67). The P/S ratio was also inversely associated with estrogens that promote ductal growth and proliferation (68, 69). The opposing associations of saturated and unsaturated fats we observed with %DBV may reflect different roles of these fats in formation and maintenance of breast tissue.

Early-life timing when fat would most influence breast morphology is unknown. Nonetheless, breast maturation during adolescence consists of a sequence of physical changes, in which ductal outgrowth is followed by accumulation of breast fat (10). Recent studies underscore earlier prolonged exposures at the time of breasts' ductal expansion, regarding early breast cancer initiation (39, 40, 70). In prospective analyses, an earlier age at thelarche (onset of breast development; ref. 39), a longer interval between thelarche and menarche (39), and higher premenarcheal adrenal hormone levels (40) were significantly associated with higher breast density (40) and increased breast cancer risk (39). In this first analysis, examining fat intakes before and after menarche with %DBV, stronger associations observed between %DBV and polyunsaturated fat and omega-3 fat intakes before menarche, but not after, align with previous evidence (39, 40, 70). However, the significant associations of saturated and monounsaturated fat intakes with %DBV in our data were from cumulative intakes during both pre- and postmenarche periods. Further investigation is warranted to examine whether our results reflect true fat-induced dynamics occurring with breast maturation.

With regard to whether our findings can be translated to later breast cancer risk, it is worth noting that significant associations observed between subtypes of fat and %DBV were generally also seen with ADBV. ADBV reflects fibroglandular tissue amount, which comprises highly proliferative structures like mammary ducts where most tumors arise. Indeed, ADBV was more strongly associated with breast cancer risk than %DBV in a recent cohort study (34). Our significant results for ADBV may indicate that fat intake alters breast tissue composition during adolescence and potentially could influence later breast cancer risk.

Our study has some limitations. We could not examine associations with the main food sources of saturated fat (e.g., cheese, milk, meat) and unsaturated fats (e.g., fish, nuts, seeds; refs. 71–75) or methods used to prepare food (76), because individual foods and cooking methods data are not available. We had limited intake variations for total and subtypes of fat. Nonetheless, percent energy range for each fat type in our study was comparable with national data for girls of a similar age (30). Significant inverse associations observed for unsaturated fats and the P/S ratio with %DBV was nonlinear, possibly due to modest intake variations in lower quartiles; for example, median daily percent energy intakes from long-chain omega-3 fat were 0.01% and 0.03% in second quartile and third quartile, respectively, while the corresponding value in the highest quartile was 0.09%. We had adequate power to detect modest associations of total fat, saturated fat, monounsaturated fat, polyunsaturated fat and linoleic acid intakes during adolescence with breast density measures, but power was more limited for omega-3 fatty acids and the P:S ratio. Although analyses and interpretation were conducted cautiously with consideration of prior findings and biologic relevance (77), concern remains about multiple testing. Our results could be due to chance and warrant replication in a separate cohort. Unknown residual confounding cannot be ruled out; however, we comprehensively adjusted for the known possible confounders associated with both breast density and intake of fat such as number of live births, duration of hormonal contraceptive use, educational attainment, smoking status and alcohol consumption in our full multivariable model. Similar results between simpler and fully adjusted models suggest little confounding by known covariates.

Nevertheless, this is the first comprehensive prospective analysis that examined the long-term effect of adolescent fat intakes on breast density, measured approximately 15 years later. The prospective design minimized recall bias of early life diet. With multiple diet assessments, we estimated fat intakes at specific pubertal stages, as well as long-term intake during adolescence; averaging intake also dampened potential random measurement errors. MRI-measured breast density is more accurate than mammography for dense breasts typical of young women. We measured breast density at ages 25–29 years, which might be the most relevant marker to assess the effect of adolescent fat intake on breasts, because it precedes natural involution of breast tissue that occurs with aging, and decreases breast density (78). We adjusted for both childhood and adulthood potential confounders.

In conclusion, we observed that types of dietary fat during adolescence were associated with adult breast density. Higher intakes of saturated fats and lower intakes of unsaturated fats were associated with higher %DBV and ADBV, whereas higher intakes of unsaturated fats were associated with lower ANDBV. These findings emphasize fat subtype composition in adolescent diets in determining breast's morphologic characteristics and support early risk accumulation of breast cancer. Further cohort studies are warranted to replicate our findings, validate whether they are independent of other components in food sources for fat, and identify underlying mechanisms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: S. Jung
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.G. Snetselaar, L. Van Horn
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Jung, O. Goloubeva, L. Van Horn, J.F. Dorgan
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Klifa, J.F. Dorgan
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References

1. Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, et al. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer 2001;92:767–74.
2. Martin LJ, Li Q, Melnichouk O, Greenberg C, Minkin S, Hislop G, et al. A randomized trial of dietary intervention for breast cancer prevention. Cancer Res 2011;71:123–33.
3. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:629–42.
4. Hursting SD, Thornquist M, Henderson MM. Types of dietary fat and the incidence of cancer at five sites. Prev Med 1990;19:242–53.
5. Prentice RL, Sheppard L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. Cancer Causes Control 1990;1:81–97.
6. Freedman LS, Clifford C, Messina M. Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: a review. Cancer Res 1990;50:5710–9.
7. Park SY, Kolonel LN, Henderson BE, Wilkens LR. Dietary fat and breast cancer in postmenopausal women according to ethnicity and hormone receptor status: the Multiethnic Cohort Study. Cancer Prev Res 2012; 5:216–28.
8. Sieri S, Chiodini P, Agnoli C, Pala V, Berrino F, Trichopoulou A, et al. Dietary fat intake and development of specific breast cancer subtypes. J Natl Cancer Inst 2014;106:pii: dju068.
9. Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. Radiat Res 2003;160:707–17.
10. Javed A, Lteif A. Development of the human breast. Semin Plast Surg 2013;27:5–12.
11. Russo IH, Russo J. Pregnancy-induced changes in breast cancer risk. J Mammary Gland Biol Neoplasia 2011;16:221–33.
12. Sternlicht MD. Key stages in mammary gland development: the cues that regulate ductal branching morphogenesis. Breast Cancer Res 2006;8:201.
13. Pettersson A, Graff RE, Ursin G, Santos Silva ID, McCormack V, Baglietto L, et al. Mammographic density phenotypes and risk of breast cancer: a meta-analysis. J Natl Cancer Inst 2014;106: pii: dju078.
14. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1159–69.
15. Forman MR. Changes in dietary fat and fiber and serum hormone concentrations: nutritional strategies for breast cancer prevention over the life course. J Nutr 2007;137:170s–4s.
16. Kaklamani VG, Linos A, Kaklamani E, Markaki I, Koumantaki Y, Mantzoros CS. Dietary fat and carbohydrates are independently associated with circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 concentrations in healthy adults. J Clin Oncol 1999;17:3291–8.
17. Olson LK, Tan Y, Zhao Y, Aupperlee MD, Haslam SZ. Pubertal exposure to high fat diet causes mouse strain-dependent alterations in mammary gland development and estrogen responsiveness. Int J Obes 2010; 34:1415–26.
18. Woolcott CG, Koga K, Conroy SM, Byrne C, Nagata C, Ursin G, et al. Mammographic density, parity and age at first birth, and risk of breast cancer: an analysis of four case–control studies. Breast Cancer Res Treat 2012;132:1163–71.
19. Zhao Y, Tan YS, Aupperlee MD, Langohr IM, Kirk EL, Troester MA, et al. Pubertal high fat diet: effects on mammary cancer development. Breast Cancer Res 2013;15:R100.
20. Sellers TA, Vachon CM, Pankratz VS, Janney CA, Fredericksen Z, Brandt KR, et al. Association of childhood and adolescent anthropometric factors, physical activity, and diet with adult mammographic breast density. Am J Epidemiol 2007;166:456–64.
21. Mishra GD, dos Santos Silva I, McNaughton SA, Stephen A, Kuh D. Energy intake and dietary patterns in childhood and throughout adulthood and mammographic density: results from a British prospective cohort. Cancer Causes Control 2011;22:227–35.
22. Dorgan JF, Liu L, Klifa C, Hylton N, Shepherd JA, Stanczyk FZ, et al. Adolescent diet and subsequent serum hormones, breast density, and bone mineral density in young women: results of the Dietary Intervention Study in Children follow-up study. Cancer Epidemiol Biomarkers Prev 2010; 19:1545–56.
23. Dorgan JF, Hunsberger SA, McMahon RP, Kwiterovich POJr, Lauer RM, Van Horn L, et al. Diet and sex hormones in girls: findings from a randomized controlled clinical trial. J Natl Cancer Inst 2003;95:132–41.
24. Dorgan JF, Liu L, Barton BA, Deshmukh S, Snetselaar LG, Van Horn L, et al. Adolescent diet and metabolic syndrome in young women: results of the Dietary Intervention Study in Children (DISC) follow-up study. J Clin Endocrinol Metab 2011;96:E1999–2008.
25. Dorgan JF, Klifa C, Shepherd JA, Egleston BL, Kwiterovich PO, Himes JH, et al. Height, adiposity and body fat distribution and breast density in young women. Breast Cancer Res 2012;14:R107.
26. The Writing Group for the DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). JAMA 1995;273:1429–35.
27. DISC Collaborative Research Group. Dietary intervention study in children (DISC) with elevated low-density-lipoprotein cholesterol. Design and baseline characteristics. Ann Epidemiol 1993;3:393–402.
28. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 2002:1–190.
29. Tanner JM. Growth at adolescence. 2nd ed. Oxford, United Kingdom: Blackwell Scientific; 1962.
30. van Horn LV, Stumbo P, Moag-Stahlberg A, Obarzanek E, Hartmuller VW, Farris RP, et al. The Dietary Intervention Study in Children (DISC): dietary assessment methods for 8- to 10-year-olds. J Am Diet Assoc 1993;93:1396–403.
31. Jones JA, Hartman TJ, Klifa CS, Coffman DL, Mitchell DC, Vernarelli JA, et al. Dietary energy density is positively associated with breast density among young women. J Acad Nutr Diet 2015;115:353–9.
32. Farvid MS, Eliassen AH, Cho E, Chen WY, Willett WC. Adolescent and early adulthood dietary carbohydrate quantity and quality in relation to breast cancer risk. Cancer Epidemiol Biomarkers Prev 2015; 24:1111–20.
33. Van Horn LV, Gernhofer N, Moag-Stahlberg A, Farris R, Hartmuller G, Lasser VI, et al. Dietary assessment in children using electronic methods: telephones and tape recorders. J Am Diet Assoc 1990;90:412–6.
34. Shepherd JA, Kerlikowske K, Ma L, Duewer F, Fan B, Wang J, et al. Volume of mammographic density and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2011;20:1473–82.
35. Wei J, Chan HP, Helvie MA, Roubidoux MA, Sahiner B, Hadjiiski LM, et al. Correlation between mammographic density and volumetric fibroglandular tissue estimated on breast MR images. Med Phys 2004;31:933–42.
36. Thompson DJ, Leach MO, Kwan-Lim G, Gayther SA, Ramus SJ, Warsi I, et al. Assessing the usefulness of a novel MRI-based breast density estimation algorithm in a cohort of women at high genetic risk of breast cancer: the UK MARIBS study. Breast Cancer Res 2009;11:R80.
37. Klifa C, Carballido-Gamio J, Wilmes L, Laprie A, Lobo C, Demicco E, et al. Quantification of breast tissue index from MR data using fuzzy clustering. Conf Proc IEEE Eng Med Biol Soc 2004;3:1667–70.
38. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–40.
39. Bodicoat DH, Schoemaker MJ, Jones ME, McFadden E, Griffin J, Ashworth A, et al. Timing of pubertal stages and breast cancer risk: the Breakthrough Generations Study. Breast Cancer Res 2014;16:R18.
40. Jung S, Egleston BL, Chandler DW, Van Horn L, Hylton NM, Klifa CC, et al. Adolescent endogenous sex hormones and breast density in early adulthood. Breast Cancer Res 2015;17:77.
41. Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol Biomarkers Prev 1995;4:567–71.
42. Biro FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, et al. Onset of breast development in a longitudinal cohort. Pediatrics 2013;132:1019–27.
43. Euling SY, Herman-Giddens ME, Lee PA, Selevan SG, Juul A, Sorensen TI, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. Pediatrics 2008;121Suppl 3:S172–91.

44. Dorgan JF, Klifa C, Deshmukh S, Egleston BL, Shepherd JA, Kwiterovich POJr, et al. Menstrual and reproductive characteristics and breast density in young women. Cancer Causes Control 2013;24:1973–83.
45. Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY: Wiley; 1987.
46. Brisson J, Verreault R, Morrison AS, Tennina S, Meyer F. Diet, mammographic features of breast tissue, and breast cancer risk. Am J Epidemiol 1989;130:14–24.
47. Masala G, Ambrogetti D, Assedi M, Giorgi D, Del Turco MR, Palli D. Dietary and lifestyle determinants of mammographic breast density. A longitudinal study in a Mediterranean population. Int J Cancer 2006;118:1782–9.
48. Nagata C, Matsubara T, Fujita H, Nagao Y, Shibuya C, Kashiki Y, et al. Associations of mammographic density with dietary factors in Japanese women. Cancer Epidemiol Biomarkers Prev 2005;14:2877–80.
49. Nordevang E, Azavedo E, Svane G, Nilsson B, Holm LE. Dietary habits and mammographic patterns in patients with breast cancer. Breast Cancer Res Treat 1993;26:207–15.
50. Qureshi SA, Couto E, Hilsen M, Hofvind S, Wu AH, Ursin G. Mammographic density and intake of selected nutrients and vitamins in Norwegian women. Nutr Cancer 2011;63:1011–20.
51. Sala E, Warren R, Duffy S, Welch A, Luben R, Day N. High risk mammographic parenchymal patterns and diet: a case-control study. Br J Cancer 2000;83:121–6.
52. Tseng M, Byrne C, Evers KA, Daly MB. Dietary intake and breast density in high-risk women: a cross-sectional study. Breast Cancer Res 2007;9:R72.
53. Vachon CM, Kushi LH, Cerhan JR, Kuni CC, Sellers TA. Association of diet and mammographic breast density in the Minnesota breast cancer family cohort. Cancer Epidemiol Biomarkers Prev 2000;9:151–60.
54. Martin LJ, Greenberg CV, Kriukov V, Minkin S, Jenkins DJ, Yaffe M, et al. Effect of a low-fat, high-carbohydrate dietary intervention on change in mammographic density over menopause. Breast Cancer Res Treat 2009;113:163–72.
55. Boyd NF, Greenberg C, Lockwood G, Little L, Martin L, Byng J, et al. Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: results from a randomized trial. Canadian Diet and Breast Cancer Prevention Study Group. J Natl Cancer Inst 1997;89:488–96.
56. Tvrzicka E, Kremmyda LS, Stankova B, Zak A. Fatty acids as biocompounds: their role in human metabolism, health and disease–a review. Part 1: classification, dietary sources and biological functions. Biomed Pap Med Fac Univ Palacky Olomouc Czech 2011;155:117–30.
57. Kremmyda LS, Tvrzicka E, Stankova B, Zak A. Fatty acids as biocompounds: their role in human metabolism, health and disease: a review. Part 2: fatty acid physiological roles and applications in human health and disease. Biomed Pap Med Fac Univ Palacky Olomouc Czech 2011;155:195–218.
58. MacLennan MB, Clarke SE, Perez K, Wood GA, Muller WJ, Kang JX, et al. Mammary tumor development is directly inhibited by lifelong n-3 polyunsaturated fatty acids. J Nutr Biochem 2013;24:388–95.
59. Zheng JS, Hu XJ, Zhao YM, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ 2013;346:f3706.
60. Fabian CJ, Kimler BF, Hursting SD. Omega-3 fatty acids for breast cancer prevention and survivorship. Breast Cancer Res 2015;17:62.
61. MacLennan M, Ma DW. Role of dietary fatty acids in mammary gland development and breast cancer. Breast Cancer Res 2010;12:211.
62. Knight JA, Martin LJ, Greenberg CV, Lockwood GA, Byng JW, Yaffe MJ, et al. Macronutrient intake and change in mammographic density at menopause: results from a randomized trial. Cancer Epidemiol Biomarkers Prev 1999;8:123–8.
63. Corsetto PA, Cremona A, Montorfano G, Jovenitti IE, Orsini F, Arosio P, et al. Chemical-physical changes in cell membrane microdomains of breast cancer cells after omega-3 PUFA incorporation. Cell Biochem Biophys 2012;64:45–59.
64. Menendez JA, Vellon L, Colomer R, Lupu R. Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu (erbB-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab (Herceptin) in breast cancer cells with Her-2/neu oncogene amplification. Ann Oncol 2005;16:359–71.
65. Escrich E, Solanas M, Moral R, Escrich R. Modulatory effects and molecular mechanisms of olive oil and other dietary lipids in breast cancer. Curr Pharm Des 2011;17:813–30.
66. Riccardi G, Giacco R, Rivellese AA. Dietary fat, insulin sensitivity and the metabolic syndrome. Clin Nutr 2004;23:447–56.
67. Muka T, Kiefte-de Jong JC, Hofman A, Dehghan A, Rivadeneira F, Franco OH. Polyunsaturated Fatty acids and serum C-reactive protein: the Rotterdam study. Am J Epidemiol 2015;181:846–56.
68. Dorgan JF, Reichman ME, Judd JT, Brown C, Longcope C, Schatzkin A, et al. Relation of energy, fat, and fiber intakes to plasma concentrations of estrogens and androgens in premenopausal women. Am J Clin Nutr 1996;64:25–31.
69. Sloth B, Due A, Larsen TM, Holst JJ, Heding A, Astrup A. The effect of a high-MUFA, low-glycaemic index diet and a low-fat diet on appetite and glucose metabolism during a 6-month weight maintenance period. Br J Nutr 2009;101:1846–58.
70. Novotny R, Daida Y, Morimoto Y, Shepherd J, Maskarinec G. Puberty, body fat, and breast density in girls of several ethnic groups. Am J Hum Biol 2011;23:359–65.
71. Bao Y, Han J, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, et al. Association of nut consumption with total and cause-specific mortality. N Engl J Med 2013;369:2001–11.
72. Inoue-Choi M, Sinha R, Gierach GL, Ward MH. Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP Diet and Health Study. Int J Cancer 2016;138:1609–18.
73. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ERIII, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA 2005;294:2455–64.
74. Keast DR, Fulgoni VLIII, Nicklas TA, O'Neil CE. Food sources of energy and nutrients among children in the United States: National Health and Nutrition Examination Survey 2003–2006. Nutrients 2013;5:283–301.
75. Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC. Premenopausal dietary fat in relation to pre- and post-menopausal breast cancer. Breast Cancer Res Treat 2014;145:255–65.
76. Slattery ML, Potter JD, Duncan DM, Berry TD. Dietary fats and colon cancer: assessment of risk associated with specific fatty acids. Int J Cancer 1997;73:670–7.
77. Gyorffy B, Gyorffy A, Tulassay Z. [The problem of multiple testing and solutions for genome-wide studies]. Orv Hetil 2005;146:559–63.
78. Milanese TR, Hartmann LC, Sellers TA, Frost MH, Vierkant RA, Maloney SD, et al. Age-related lobular involution and risk of breast cancer. J Natl Cancer Inst 2006;98:1600–7.

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