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EPIDEMIOLOGY

Dietary intake from birth through adolescence in relation to risk of benign breast disease in young women

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Abstract

Purpose Nutritional factors during different periods in life impact breast cancer risk. Because benign breast disease (BBD) is a well-established risk factor for breast cancer, we investigated childhood nutrition from birth through age 14 year and subsequent BBD.

Methods A prospective cohort study of 9031 females, 9–15 year at baseline, completed questionnaires (including heights, weights) annually from 1996 to 2001, in 2003, 2005, 2007, 2010, 2013 and 2014. In 1996, mothers reported infant feeding practices during their daughters first year of life. Beginning in 1996, participants completed annual food frequency questionnaires. In 2005, participants (18 year+) began reporting whether they had ever been diagnosed with biopsy-confirmed BBD (N = 173 cases). Multivariable logistic regression models estimated associations between childhood nutrition and BBD, adjusted for maternal breast disease and childhood body size factors.

Results Although no infant nutrition factors were associated with biopsy-confirmed BBD, certain adolescent dietary factors were. A multivariable model simultaneously included the most important diet and body size factors from different age periods: higher BBD risk was associated with greater age 10 year consumption of animal (non-dairy, energy-adjusted) fat (OR 2.27, $p < .02$, top vs. bottom quartiles) and with lower 14 year consumption of nuts/peanut butter (OR 0.60, $p = .033$, top vs. bottom quartiles).

Conclusion Greater intake of animal (non-dairy) fat at 10 year and lower intake of nuts/peanut butter at 14 year were independently associated with higher BBD risk. These dietary factors appeared to operate on BBD risk independent of childhood growth (gestational weight gain, childhood BMI and height, adolescent height growth velocity), young adult height and BMI, and family history.

Keywords Infant nutrition · Childhood diet · Adolescent diet · Alcohol · Pre-malignant · Benign breast disease

Introduction

Substantial evidence implicates the period before a woman's first full term pregnancy, when mammary gland cells are undergoing rapid proliferation, as a critical time for exposures that may increase her lifetime risk for breast cancer [1]. Some childhood and adolescent exposures confer a greater risk than adult exposures in breast cancer development, [2–5] so prevention efforts must begin early [6]. Both animal and human studies suggest mechanisms whereby in utero, childhood and adolescent exposures influence cancer risk in women [7–9].

Understanding how modifiable factors during early life contribute to breast cancer risk in later life is a public health priority. Diet from early life through adolescence is potentially highly modifiable, and there is growing evidence that this contributes to breast cancer risk. Intake of soy foods during childhood [10] and adolescence [11] were associated with lower breast cancer risk in Asian migrants to the US and in Asian women, but not in Western countries. Among Icelandic women, higher fish consumption during adolescence was associated with lower risk of breast cancer [12]. In Nurses Health Study II (NHSII) women, greater

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total and animal fat consumption, [13] but less fiber [14] and fruits, [15] were associated with increased premenopausal breast cancer risk. No significant associations were found with adolescent intakes of whole grain foods [16] or carbohydrate quantity and quality [17]. Analyses of Canadian women found that higher adolescent intakes of dietary fiber, vegetable protein, vegetable fat, and nuts were associated with lower breast cancer risk, even after controlling for adult intakes [18].

Because benign breast disease (BBD), even without atypia, is a well-established risk factor for breast cancer, [19, 20] the investigation of dietary exposures in girls and their subsequent development of BBD may provide insight into the etiology of breast cancer and present possible new strategies for prevention. A previous investigation of fetal/infant factors, in which nurses (NHSII, then aged 27–44) self-reported whether (and for how long) they had been breast fed as infants, found no association between having been breast fed and proliferative BBD [21]. However, adolescent intakes of vegetable fat and fiber were inversely associated with risk, [22] as were nuts and dietary fiber, [23] though another analysis found no association of adolescent fat or micronutrient intakes with proliferative BBD [24]. Total milk intake during high school was associated with higher risk, [25] as was adolescent alcohol intake [26]. Analyses of girls in the Growing Up Today Study (GUTS) found no associations between infant feeding practices [27] or adolescent intakes of milk and dairy foods [28] and risk of biopsy-confirmed BBD in young women, though adolescent consumption of vegetable protein, vegetable fat, and peanut butter and nuts were all associated with lower BBD risk [29]. In this same cohort, girls (when 16–23 years) with higher alcoholic beverage consumption had increased risk for BBD [30].

Longitudinal data from GUTS females facilitate the investigation of relationships between nutritional factors (from infancy through adolescence) and childhood growth and adult body size. This provides the background for our primary interest, to understand the early life antecedents of breast cancer risk, by estimating associations between infant/childhood nutrition and BBD in young women, while adjusting for family history of breast disease and body size factors from various periods of childhood that are most strongly associated with BBD [31]. These updated analyses are performed on $N = 173$ cases, while our previous investigations were each performed on between $N = 67$ and $N = 142$ cases.

Materials and methods

Study population

The Growing Up Today Study (founding PI, Dr. Colditz) includes 9031 girls from all 50 states who are daughters of NHSII participants [32]. The study was approved by the Institutional Review Board at Brigham and Women's Hospital. Mothers provided informed consent, and their 9–15 year old daughters assented by completing baseline questionnaires in 1996. The cohort returned questionnaires annually (by mail or Internet) from 1996 through 2001, then in 2003, 2005, 2007, 2010, 2013, and 2014. The response rate to one or more follow-ups after baseline has been 97%. Most study participants are white/non-Hispanic (95%).

Benign breast disease

The 2005, 2007, 2010, 2013, and 2014 surveys inquired "Has a health care provider ever diagnosed you as having Benign Breast Disease?" and, if yes, whether it had been "Confirmed by breast biopsy". A total of 7362 females (when 18–32 year) reported whether a health care provider ever, or never, diagnosed them with BBD ($n = 385$ said yes), and if any diagnosis had been confirmed by breast biopsy ($n = 173$). After excluding six girls whose mothers reported childhood cancer in their daughters, 6971 females who returned surveys during this period but never reported any BBD diagnosis provide the non-cases for these analyses of biopsy-confirmed BBD.

Most of these 173 BBD cases were likely diagnosed because participants (or their physicians) found a clinically palpable mass, which was then biopsied, since participants were too young to be undergoing routine screening mammography. The most common type of BBD occurring in adolescents and young women is fibroadenoma, which accounts for nearly 70% of benign breast lesions; the remaining types are primarily cysts and fibrocystic changes [33]. A validation study conducted in 621 NHSII women confirmed the accuracy (95%) of self-reported biopsy-confirmed BBD [34].

Early life nutritional factors

In 1996 the mothers answered a series of questions regarding feeding their infant daughters, all born during the previous decade, including "Did you feed this child breast-milk or infant formula during the first 6 months of life?". Other questions regarded her infant daughter's age when breast feeding stopped, type of formula most often used, and ages when her daughter began infant formula, cow's milk and solid foods.

The validity of maternal recall of breast feeding is strongly supported ($r = 0.95$) by a study that compared maternal recall, 8–9 years after childbirth, of breast-feeding duration with prospectively collected data [35]. Because our early life data were recalled, as soon as 9 years after childbirth, by mothers who were all nurses, we expect our data to have a high degree of validity.

Dietary intakes of older children and adolescents

Our self-administered semi-quantitative food frequency questionnaire (FFQ), designed specifically for older children and adolescents, has good validity and reproducibility for children ages 9–18 years [36]. A meta-analysis of the validity of FFQ for adolescents showed good overall correlation with food records and 24 h recalls.[37]

Our FFQ inquired about the usual frequency of past-year intakes of a wide variety of foods. Included were questions about white and chocolate milk, cheese, and yogurt; we combined the white and chocolate milk intakes to get servings/day of dairy milk (soy milk excluded). Children also reported the fat content of milk they usually drink (whole, 2%, 1%, skim). We combined reports of peanut butter sandwiches with (small bags of) peanuts and nuts. We further derived total fruit intakes and also combined intakes of apples/bananas/grapes that appeared protective in a recent breast cancer study; [15] we also derived total fruit juice (orange, apple). Other foods investigated included total vegetables (white potatoes excluded), green leafy vegetables, yellow orange vegetables, legumes, eggs, fish, white potatoes/bread/fries, and olive oil use. Our surveys inquired about drinking, during a typical week over the past year, of beer, wine, wine coolers, and liquor. Vegetable fat and protein, dairy fat and protein, animal (non-dairy) fat and protein, carbohydrates, fiber and total energy were calculated based upon all reported food and beverage intakes. Our analyses use energy-adjusted (residual-method) nutrients. Total daily energy intakes below 500 kcal or greater than 5,000 kcal were considered implausible and set to missing.

Here we use FFQ's from the 1996, 1997, and 1998 surveys to obtain dietary data at age 10 year (if age 10 year not available, using closest report from age 9.0 to 11.99 year) and at age 14 year (if age 14 year not available, then using closest report from age 13.0 to 15.99 year). The number of girls with age 10 data ($N=4454$) is a subset of our full cohort because many of our participants were too old at baseline (up to age 15 year). A total of $N=5677$ girls provided dietary data at age 14 year, a subset of our full cohort because the youngest at baseline (as young as 9 year) were not age 14 year within the 1996–1998 follow-up window.

Other variables

We computed ages (to the month) from dates of questionnaire return and birth. Our early surveys annually asked the girls "Have you started having menstrual periods?" and "If yes, age when periods began". Later surveys asked if the participants were, or had recently been, pregnant. The derivation of childhood body size measures [gestational weight gain, age 10 height, age 10 BMI, adolescent peak height growth velocity (PHV)] was described previously [31]. Participants' mothers provided information regarding their own diagnoses of breast cancer and biopsy-confirmed BBD.

Statistical analysis

Because body size in girls may be a result of dietary factors earlier in life, and both childhood body size and diet have been reported to be associated with risks of BBD and breast cancer, we first used linear regression models to investigate associations between infant nutrition and body size at age 10 year and subsequent growth to adulthood. Similar models investigated the possible effects of age 10 year diet on body size/growth from age 10 year to adulthood, and age 14 year diet on adult height and BMI.

The outcome for our primary analyses was biopsy-confirmed BBD. Logistic regression models, estimated using SAS, [38] provided odds ratios (OR) and 95% confidence intervals (CI). All multivariable models adjusted for girl's age (to the month) at cohort initiation in 1996, maternal history of breast cancer, maternal history of BBD, and those childhood body size factors we found most important (for BBD risk) in our previous work on this cohort: gestational weight gain, height at 10 year, BMI at 10 year, and adolescent peak height growth velocity (PHV) [31]. We initially fit a model separately to each dietary variable from each period of life, whether infancy, age 10 year, or age 14 year. Age 10 year and 14 year are individually important because they represent dietary exposures before and after adolescent height growth, typically completed by 14 year. A final model included the seven adjustment factors along with those dietary factors from infancy through adolescence that were most strongly associated with BBD risk. Models were fit using categorical versions of each dietary variable to investigate nonlinear associations.

Results

Eighty-two percent of our females returned at least one survey (2005–2014) containing questions about BBD. Comparing childhood data of these participants with the 18% who returned none of those surveys, we found only very small differences. The included girls were slightly younger (< 5 weeks) at baseline than those not included, but age 10 year height, weight and BMI were similar between the two groups. Among earliest life factors, those included and omitted from the disease analyses had similar maternal gestational weight gain. The two groups were fed similar infant formula types, but the included were more likely to have been breast fed and longer (by 12 days). Regarding age 10 year diet, the included girls consumed significantly more milk (0.15 serving/day), yogurt (0.03 serving/day), legumes (0.02 serving/day), green leafy vegetables (0.04 servings/

day), but intakes of cheese, eggs, fruits, juice, yellow/orange vegetables, peanut butter/nuts, fish, white potatoes/bread/fries, total energy, and olive oil use did not differ. At age 14 year, only consumption of milk and yogurt differed between groups. These small differences are unlikely to be a source of bias in our investigation of BBD risk factors.

Table 1 presents means or percentages, within tertile of BMI at 10 year, of dietary exposure variables and other important characteristics. Girls with highest BMI at 10 year had stopped breast feeding and began infant formula at younger ages. (Supplemental Table S1 presents analyses of BMI at 10 year with each infant and age 10 year dietary factor, many statistically significant.) Girls with highest BMI at 10 year also had slower adolescent peak height growth velocities and earlier ages at peak velocity and menarche. The thinnest 10 year-olds were more likely (than heavier 10 year-olds) to receive a diagnosis of BBD during follow-up through 2014 (Table 1).

Because adult height, influenced both by genes and diet from infancy through adolescence, is related to lifetime risk of breast cancer and BBD, Table 2 presents means (or percentages) within adult height tertiles. Female infants who were breast fed longer appeared to become taller women. Ten-year-old and fourteen-year-old girls who drank more dairy milk and consumed more total dairy protein became taller women (also see Supplemental Tables S1 and S2). The tallest women had more cases of BBD (3%) than the shortest women (2%) (Table 2). The many significant relationships (Supplement) between infant/childhood diet and later body size demonstrate the importance of adjusting for childhood body size in our models relating childhood diet to BBD.

Table 3 presents the estimated association of each childhood diet variable, from infancy, at age 10 year and at 14 year (each in a separate model), with BBD risk in young women. As in our earlier work [27] but now with 22% more cases, there were no significant associations between infant nutrition and risk of BBD (Table 3). Regarding intakes of specific foods at 10 year, there were no significant findings, though some energy-adjusted nutrients were associated with risk. The strongest finding was that BBD risk was positively associated with animal (non-dairy) fat consumption (OR 2.33 for top vs. bottom quartile, $p = .01$). Evidence also pointed to animal (non-dairy) protein (OR 2.08, $p = .04$) and carbohydrates (OR 0.45, $p = .048$), both highly correlated ($r = +0.79$ and $r = -0.62$, respectively) with animal (non-dairy) fat.

For age 14 year diet (Table 3), our strongest finding was that greater consumption of nuts/peanut butter (OR .59 top vs bottom quartile, $p = .027$) is associated with lower BBD risk. Our finding that moderate (OR 0.64, $p = .04$, middle vs. bottom), but not high (OR 0.95, $p = .85$, top vs. bottom quartiles), intakes of apples, bananas and grapes were associated with lower BBD risk, is intriguing. The age-adjusted (but not multivariable) model of total dietary fiber (OR 0.56, $p = .03$; not shown) at 14 year suggests an inverse association with BBD risk. Finally, though most girls were not yet drinking alcohol at 14 year, those who reported ≥ 1 drink/week were at marginally increased BBD risk (OR 1.88 compared to non-drinkers, $p = .097$, Table 3).

From the models in Table 3, we conclude that only a small number of childhood dietary factors were associated with BBD in young women. From infancy, we found no significant dietary associations, but age 10 year animal (non-dairy) fat consumption was most strongly (positively) associated with risk, and at age 14 year consumption of peanut butter and nuts was most strongly (inversely) associated. To simultaneously investigate these strongest dietary factors, we entered them into a single multivariable model (Table 4). Animal (non-dairy) fat at 10 year continued to be associated with increased risk (OR 2.27, $p = .016$; top vs bottom quartile) and consumption of peanut butter and nuts at 14 year was still associated with reduced risk (OR 0.60, $p = .033$). In a final model (not shown) further adjusted for adult height and BMI at 18 year, the significant associations of animal fat at 10 year and peanut butter/nuts at 14 year persist, as do gestational weight gain, age 10 height and adolescent peak height velocity, confirming the importance of childhood and adolescent factors on BBD risk.

Discussion

In this prospective investigation of nutrition from infancy to adolescence, adjusted for key childhood body size variables [31] and family history, girls' higher consumption of animal (non-dairy) fat at 10 year and lower nut/peanut butter consumption at 14 year were independently related to higher risk of biopsy-confirmed BBD as young women. Our analyses suggest that these childhood dietary factors operate directly on BBD risk rather than through body size pathways, such as peak height growth velocity, which retain their own independent associations with risk. This is important because diet in early life could be modified to influence later risk of BBD, independent of growth and body size which are more determined by genetic factors.

This work differs from our previously published manuscripts on this cohort in several ways. First, we now have more biopsy-confirmed BBD cases (22% more than our most recent paper). Second, our linear regression models (Supplement) investigate associations between nutrition from birth through age 14 year and subsequent childhood growth and development. Third, the multivariable BBD model in Table 4 simultaneously includes the strongest dietary factors from different age periods, adjusted for family history and important childhood body size measures [31]. And fourth, we further adjusted our most important childhood factors (in

Table 1 Characteristics of girls in the Growing Up Today Study, according to tertile of body mass index at age 10 year

	Body fatness (BMI) tertile at age 10 year		
	< 16.5 kg/m^2	16.5–18.98 kg/m^2	> 18.98 kg/m^2
No. of girls	1486	1480	1488
Exact age (year) for 10 year data	10.72	10.86	10.89
Infant diet			
Cow's milk (age began, mo.)	11.61	11.73	11.53
Breast feeding (age stopped, mo.)	5.68	5.94	5.48
Formula (age began, mo.)	2.91	2.94	2.64
Solid food (age began, mo)	5.10	5.16	4.98
Type of formula			
Cow milk	75%	74%	74%
Soybean	24%	25%	25%
Breast or bottle (1st 6mo)			
Breast only	29%	33%	27%
Both	58%	55%	60%
Formula only	13%	12%	13%
Age 10 year foods			
Dairy milk (glasses/day)	1.99	1.89	1.85
Soy milk (glasses/day)	0.010	.003	.002
Tofu (servings/day)	0.006	.005	.004
Yogurt (cups/day)	0.11	0.13	0.12
cheese (slices/day)	0.52	0.54	0.53
Eggs (per day)	0.11	0.11	0.12
Total fruit (servings/day)	1.12	1.14	1.09
Apples, bananas, grapes	0.56	0.58	0.54
Fruit juice (glasses/day)	0.79	0.79	0.76
Total vegetables (servings/day)	1.18	1.16	1.15
Green leafy vegetables	0.41	0.41	0.41
Yellow/orange Vegetables	0.40	0.38	0.37
Legumes	0.14	0.14	0.14
Peanut butter sandwiches and small bags of nuts (per day)	0.21	0.20	0.18
Fish (servings/day)	0.11	0.10	0.10
White potatoes, bread, fries	1.06	0.99	1.06
Olive oil	22%	24%	20%
Age 10 year nutrients (gm/day)[a]			
Animal (non-dairy) protein	25.3	25.6	25.7
Dairy protein	27.9	28.1	28.1
Vegetable protein	24.7	24.6	24.4
Animal (non-dairy) fat	16.6	16.5	17.0
Dairy fat	18.2	17.8	17.1
Vegetable fat	35.6	35.2	35.3
Total carbohydrates	280.2	282.4	283.0
Total fiber	16.2	16.3	16.2
Total calories (kcal/day)	2074	2020	1963
Body size at 10 year			
BMI at 10 year (kg/m^2)	15.20	17.67	21.84
Height at 10 year (in)	56.2	57.1	58.0
Weight at 10 year (lb)	68.4	82.3	105.0
Physical activity 10 year (h/day)	1.30	1.33	1.25
Body size: adolescence to adulthood			
PHV (in/year)	3.43	3.40	3.36

Table 1 (continued)

	Body fatness (BMI) tertile at age 10 year		
	< 16.5 kg/m^2	16.5–18.98 kg/m^2	> 18.98 kg/m^2
Peak age (year)	12.0	11.85	11.76
Age at menarche (year)	13.3	12.8	12.4
Adult height (in)	65.3	65.2	65.2
Weight at 18 year (lb)	123.4	133.3	154.5
BMI at 18 year (kg/m^2)	20.3	22.00	25.48
Height growth (in) 10–18 year	10.0	8.9	8.0
Weight change (lb) 10–18 year	57.8	54.3	53.2
BMI change 10–18 year	5.4	4.7	4.0
Breast disease			
GUTS BBD (young adulthood)	2.35%	1.77%	1.93%
Maternal BC	4.6%	5.9%	5.7%
Maternal BBD	18.5%	18.8%	15.8%
Maternal BC and BBD	1.01%	1.35%	1.48%

Girls ($N = 4454$) were born between 1985 and 1987. Shown above are Mean or % within each tertile

[a]Nutrients are energy-adjusted (residual method)

Table 4) for adult height and BMI at 18 year, finding that the estimated effects of these childhood factors persisted.

Our multivariable analyses of BBD are important because there are many associations, shown here (Supplement) and by others, among the nutrition and body size factors and growth from early life and through adolescence. When childhood growth is more rapid, it is hypothesized that there is less time for repair of DNA damage caused by exposures to carcinogenic factors and thus greater likelihood that permanent DNA damage will lead to cancer [6]. Whether the most rapid growth itself, and how it may impact DNA damage and repair, [6] or related factors (nutritional, hormones) that promote growth are cancer initiators/promoters warrants further investigation, but our results suggest that rapid height growth and certain dietary factors independently impact BBD risk.

Our findings are consistent with earlier work (NHSII) reporting no association between proliferative BBD in premenopausal women and having been breast fed, [21] or with childhood dairy and milk consumption [22]. Also consistent with our results were NHSII findings that adolescent animal fat was positively associated [22] and adolescent nut intake was inversely associated with proliferative BBD [22, 23]. In that cohort, adolescent alcohol intake was associated with higher BBD risk, [26] consistent with our earlier work on drinking at age 16 year and older [30] and our suggestive ($p < .10$) finding here of the risk of drinking as young as 14 year.

Our findings are sometimes, but not always, consistent with published associations between childhood diet and breast cancer [13, 14, 18]. In addition to investigating an intermediate disease outcome (BBD) rather than the final disease, our still young cohort was born more recently than women in breast cancer studies. Furthermore, some inconsistencies in the literature may reflect different pathways to disease.

Regarding possible mechanisms, total dietary fat intakes during childhood may influence circulating levels of plasma sex steroid hormones and insulin-like growth factor, [39, 40] which have been associated with BBD and breast cancer risk. Among our 10-year-old girls, animal (non-dairy) fat intake was approximately 24% of their total fat intake, while dairy fat intake was 25%, and the remainder (51%) was from vegetables, but only animal (non-dairy) fat was associated with BBD. Regarding mechanisms for nuts at 14 year, our food frequency question did not specify types of nuts but there is evidence that walnuts contain bioactive molecules (alpha-linolenic acid and phytosterols) that affect mammary epithelial cells [41]. Tree nuts and peanuts are rich in unsaturated fatty acids and other bioactive compounds that produce a broad range of metabolic benefits [42, 43].

Because premenopausal breast density, like BBD, is a risk factor for breast cancer, [19, 44] certain aspects of childhood/adolescent diet might instead impact breast density; unfortunately, we do not yet have mammographic density information on our participants. In NHSII women, adolescent animal fat intake [45] was positively associated with breast density, but adolescent fiber intake was not [46]. In another cohort, higher adolescent saturated fat intakes were associated with higher breast density 15 years later [47]. A third cohort observed an inverse association between adiposity at 10 years and breast density in premenopausal women [48].

The longitudinal design of this investigation comprises its major strength. Infant nutrition was reported by mothers as soon as 9 years after childbirth, far earlier than many other studies utilizing recalled pregnancy/infant data, and

Table 2 Characteristics of girls in the Growing Up Today Study, according to tertile of adult height

	Adult height tertile		
	< 63.9 inches	63.9–66.45 inches	> 66.45 inches
No. of girls	2191	2991	2713
Infant diet			
Cow's milk (age began, mo.)	11.58	11.57	11.52
Breast feeding (age stopped, mo.)	5.63	5.82	6.04
Formula (age began, mo.)	2.83	2.89	2.95
Solid food (age began, mo)	5.05	5.12	5.03
Type of formula			
Cow milk	74%	77%	78%
Soybean	25%	23%	21%
Breast or bottle (1st 6 mos)			
Breast only	31%	32%	34%
Both	56%	56%	55%
Formula only	13%	12%	11%
Age 10 year foods			
Dairy milk (glasses/day)	1.86	1.91	2.04
Soy milk (glasses/day)	.003	.005	.006
Tofu (servings/day)	.008	.005	.004
Yogurt (cups/day)	0.12	0.13	0.13
Cheese (slices/day	0.52	0.54	0.55
Eggs (per day)	0.11	0.11	0.12
Total fruit (servings/day)	1.12	1.09	1.16
Apples, bananas, grapes	0.56	0.55	0.59
Fruit juice (glasses/day)	0.79	0.76	0.81
Total vegetables (servings/day)	1.20	1.13	1.22
Green leafy vegetables	0.41	0.40	0.43
Yellow/orange vegetables	0.40	0.37	0.40
legumes	0.14	0.14	0.15
Peanut butter sandwiches and small bags of nuts (per day)	0.19	0.19	0.20
Fish (servings/day)	0.11	0.10	0.10
White potatoes, bread, fries	1.10	1.01	1.03
Olive oil	23%	21%	22%
Age 10 nutrients (gm/day)[a]			
Animal (non-dairy) protein	26.07	25.24	25.4
Dairy protein	27.26	28.53	29.1
Vegetable protein	24.70	24.64	24.5
Animal (non-dairy) fat	16.86	16.5	16.6
Dairy fat	17.7	17.8	17.8
Vegetable fat	35.3	35.5	34.8
Total carbohydrates	281.9	281.3	282.2
Total fiber	16.19	16.2	16.4
Total calories (kcal/day)	2040	1988	2044
Age 14 year foods			
Dairy milk (glasses/day)	1.53	1.68	1.86
Soy milk (glasses/day)	.003	.007	.002
Tofu (servings/day)	.011	.009	.009
Yogurt (cups/day)	0.13	0.13	0.14
Cheese (slices/day)	0.53	0.55	0.59
Eggs (per day)	0.09	0.10	0.12

Table 2 (continued)

	Adult height tertile		
	< 63.9 inches	63.9–66.45 inches	> 66.45 inches
Total fruit (servings/day)	1.10	1.12	1.19
Apples, bananas, grapes	0.51	0.53	0.57
Fruit juice (glasses/day)	0.83	0.80	0.89
Total vegetables (servings/day)	1.24	1.23	1.30
Green leafy vegetables	0.47	0.48	0.51
Yellow/orange vegetables	0.36	0.35	0.38
Legumes	0.14	015	0.15
Peanut butter sandwiches and small bags of nuts (per day)	0.15	0.16	0.16
Fish (servings/day)	0.10	0.10	0.10
White potatoes, bread, fries	1.06	1.08	1.17
Olive oil	18%	15%	15%
Alcohol (drinks/day)	0.019	0.014	0.019
Age 14 nutrients (gm/day)[a]			
Animal (non-dairy) protein	25.7	25.3	25.3
Dairy protein	25.0	26.4	27.3
Vegetable protein	24.0	24.2	23.8
Animal (non-dairy) fat	15.3	15.1	15.3
Dairy fat	16.0	16.3	16.3
Vegetable fat	33.5	33.7	33.2
Total carbohydrates	280.8	279.6	279.8
Total fiber	15.5	15.6	15.5
Total calories (kcal/day)	1940	1974	2063
Body Size at 10 year			
BMI (kg/m^2)	18.19	18.23	18.25
Height (inches)	54.97	57.03	59.24
Weight (lb)	78.87	84.87	91.81
Physical activity (hrs/day)	1.26	1.29	1.33
Body size: adolescence to adulthood			
PHV (in/year)	3.24	3.27	3.19
Peak Age (year)	12.19	12.23	12.45
Age at Menarche (year)	12.65	12.82	13.04
BMI at 14 year (kg/m^2)	20.88	20.84	20.7
Height at 14 year (in)	61.51	64.09	66.8
Adult Height (in)	62.11	65.1	68.3
Weight at 18 year (lb)	124.52	135.8	149.3
BMI at 18 year (kg/m^2)	22.69	22.55	22.44
Height growth (in) 10–18 year	7.81	8.84	10.08
Weight change (lb) 10-18 year	48.53	54.51	61.65
BMI change 10–18 year	4.83	4.69	4.56
Breast disease			
GUTS BBD (young adulthood)	2.0%	2.2%	3.0%
Maternal BC	5.2%	5.5%	5.2%
Maternal BBD	19.0%	19.2%	18.0%
Maternal BC and BBD	1.6%	1.5%	1.2%

Girls ($N = 7895$) were born between 1980 and 1987. Shown above are Mean or % within each tertile

[a]Nutrients are energy-adjusted (residual method)

Table 3 Risk of biopsy-confirmed benign breast disease (BBD) related to dietary factors from infancy through adolescence in females from the Growing Up Today Study (7144 girls, 173 BBD cases), born 1980–1987

	Categorical exposure models				
	OR (p)	OR (p)	OR (p)	OR (p)	OR (p)
Infant diet					
Breast or bottle	Breast only	More breast	Both equally	More formula	Only formula
	1.00 (ref)	0.97 (.88)	1.17 (.61)	0.96 (.87)	0.83 (.50)
Breast feeding (age stop)	<1 mo/never	1–3 mo	4–6 mo	7–9 mo	>9 mo
	0.94 (.82)	1.21 (.43)	1.16 (.51)	1.24 (.35)	1.00 (ref)
Formula (age began)	<1 mo	1–3 mo	4–6 mo	7–9 mo	Never
	1.00 (ref)	1.14 (.52)	0.86 (.58)	1.41 (.19)	1.05 (.83)
Cow's milk (age began, mo.)		4–6 mo	7–9 mo	10–12 mo	>12 mo/never
		1.08 (.86)	1.20 (.47)	1.12 (.53)	1.00 (ref)
Solid food (age began)		1–3 mo	4–6 mo	7–9 mo	>9 mo
		1.00 (ref)	0.89 (.58)	0.77 (.35)	1.10 (.82)
Type of formula		Cow Milk	Soybean	Other	
		1.00 (ref)	0.89 (.60)	0.74 (.77)	
	BBD status		Categorical exposure models		
	Never	Case			
	Serv/day	Serv/day	Bottom 25%	Middle 50%	Top 25%
	Mean	Mean	Referent	OR (p)	OR (p)
Age 10 year foods					
Dairy milk	1.94	1.86	1.00	1.05 (.87)	0.78 (.50)
Yogurt	0.12	0.12	1.00	1.19 (.53)	1.06 (.84)
Cheese	0.53	0.57	1.00	1.64 (.14)	1.89 (.09)
Eggs	0.11	0.13	1.00	1.14 (.65)	1.65 (.20)
Total fruit	1.12	1.16	1.00	1.01 (.99)	1.18 (.62)
Apples, bananas, grapes	0.57	0.60	1.00	1.16 (.62)	1.11 (.77)
Fruit juice	0.79	0.76	1.00	1.02 (.95)	1.02 (.95)
Total vegetables	1.18	1.25	1.00	1.29 (.41)	1.18 (.65)
Green leafy vegetables	0.42	0.40	1.00	1.09 (.78)	1.49 (.21)
Yellow orange vegs	0.39	0.41	1.00	1.09 (.78)	1.33 (.41)
Legumes	0.14	0.15	1.00	0.96 (.88)	1.29 (.44)
Peanut butter and nuts	0.20	0.18	1.00	1.80 (.08)	1.20 (.64)
Fish[b]	0.11	0.12	1.00	0.99 (.98)	1.38 (.41)
White pots, bread, fries	1.04	1.15	1.00	1.22 (.54)	1.68 (.14)
Olive oil[c]	22%	22%	1.00	1.04 (.91)	0.95 (.91)
Age 10 year nutrients[a]					
Animal (non-dairy) prot	25.5	28.7	1.00	1.47 (.25)	2.08 (.04)
Dairy protein	28.3	27.4	1.00	1.07 (.83)	0.83 (.60)
Vegetable protein	24.7	25.3	1.00	1.73 (.11)	1.95 (.07)
Animal (non-dairy) fat	16.6	18.7	1.00	1.27 (.47)	2.33 (.01)
Dairy fat	17.7	17.1	1.00	0.88 (.67)	0.97 (.93)
Vegetable fat	35.2	35.3	1.00	1.02 (.93)	0.69 (.30)
Total carbohydrates	282	276	1.00	1.07 (.79)	0.45 (.049)
Total fiber	16.3	16.5	1.00	1.25 (.47)	1.36 (.38)
Total calories	2017	2028	1.00	1.13 (.69)	1.13 (.73)
Age 14 year foods					
Dairy milk	1.71	1.69	1.00	0.65 (.051)	0.75 (.25)
Yogurt	0.14	0.14	1.00	1.02 (.94)	0.93 (.76)

Table 3 (continued)

	BBD status		Categorical exposure models		
	Never	Case			
	Serv/day	Serv/day	Bottom 25%	Middle 50%	Top 25%
	Mean	Mean	Referent	OR (p)	OR (p)
Cheese	0.56	0.52	1.00	1.23 (.36)	0.88 (.65)
Eggs	0.10	0.11	1.00	0.86 (.51)	1.18 (.47)
Total fruit	1.14	1.10	1.00	0.92 (.70)	1.01 (.96)
Apple, banana, grape	0.54	0.52	1.00	0.64 (.04)	0.95 (.85)
Fruit juice	0.85	0.86	1.00	1.24 (.38)	1.11 (.69)
Total vegetables	1.26	1.24	1.00	1.11 (.66)	1.18 (.54)
Green leafy vegetables	0.49	0.52	1.00	0.76 (.25)	1.10 (.71)
Yellow orange vegs	0.37	0.32	1.00	0.95 (.81)	0.73 (.27)
Legumes	0.15	0.14	1.00	1.09 (.68)	0.84 (.54)
Peanut butter and nuts	0.16	0.13	1.00	0.66 (.06)	0.59 (.03)
Fish[b]	0.10	0.13	1.00	1.54 (.07)	1.63 (.11)
White pots, bread, fries	1.10	0.94	1.00	0.95 (.81)	0.64 (.11)
Olive oil[c]	16%	12%	1.00	1.02 (.95)	0.49 (.12)
Alcohol[d]	0.017	0.035	1.00	1.34 (.53)	1.88 (.097)
Age 14 year nutrients[a]					
Animal (non-dairy) prot	25.3	26.8	1.00	0.81 (.37)	1.15 (.59)
Dairy protein	26.5	26.0	1.00	1.02 (.93)	0.95 (.84)
Vegetable protein	24.0	23.2	1.00	0.72 (.14)	0.72 (.21)
Animal (non-dairy) fat	15.2	15.6	1.00	0.76 (.23)	1.17 (.54)
Dairy fat	16.2	16.3	1.00	0.90 (.66)	1.09 (.75)
Vegetable fat	33.4	32.5	1.00	0.79 (.28)	0.70 (.18)
Total carbohydrates	280	281	1.00	0.90 (.64)	0.98 (.95)
Total fiber	15.6	15.1	1.00	0.74 (.17)	0.60 (.06)
Total calories	1996	1972	1.00	0.90 (.65)	0.89 (.65)

Multivariable models include (only) the dietary factor shown, along with age, maternal history of breast cancer, maternal history of BBD, gestational weight gain, height at 10 year, BMI at 10 year, and PHV, which are the most important independent body size facts previously noted in this cohort [31]. Age 10 year physical activity was not included because it was not an important BBD risk factor in these girls ($p > 0.52$)

[a]Nutrients are energy-adjusted (residual method); gm/day

[b]Fish categories: servings < 1/wk, 1/wk to < 2/wk, and ≥ 2/wk

[c]Olive oil Categories: For means, shown are percentages reporting any Olive Oil use. For Categorical Exposure Models: No Olive oil (referent), Olive oil with other oils, and Only Olive oil

[d]Alcohol Categories: servings/day None, < 1/wk, and ≥ 1/wk

long before the reporting (beginning in 2005) of BBD by their daughters. In our large cohort of girls from all over the USA, diet was reported in real time. Any misclassifications due to errors in maternal reporting of early life nutrition or childhood reports of intakes are likely non-differential with respect to subsequent BBD, though these errors may attenuate estimated associations. Though all models controlled for a series of potential confounders in multivariable-adjusted models, some residual and unmeasured confounding may remain, and we cannot exclude the possibility of incomplete adjustment or confounding through variables not considered. Because our participants are daughters of nurses, this reduces confounding by socioeconomic and other unmeasured factors, while enhancing the accuracy of the data. Although our cohort is not representative of US females, the comparison of risks within our cohort should still be valid and generalizable [49]. However, the racial/ethnic makeup of our cohort (95% white/non-Hispanic) hinders race/ethnic-group-specific analyses and generalization to other races/ethnicities.

Concluding, we assessed the relationship between biopsy-confirmed BBD in young women and nutrition from infancy through adolescence, a period critical for the development of breast cancer. Based upon girls born in the 1980′s, we found evidence that two dietary factors had independent (of each other) associations with

Table 4 Risk of biopsy-confirmed benign breast disease (BBD) related to body size and dietary factors from infancy through adolescence in females from the Growing Up Today Study (7144 girls, 173 BBD cases), born 1980–1987

	Categorical exposures model			
	OR (p)	OR (p)	OR (p)	P^b_{trend}
Maternal BBD	No	Yes		
	1.00 (ref)	1.84 (.0004)		
Maternal BC	No	Yes		
	1.00 (ref)	2.20 (.0015)		
Gestational weight gain	< 20 lbs	≥ 20 to 35 lbs	› 35 lbs	
	1.00 (ref)	0.57 (.02)	0.61 (.07)	0.26
BMI at 10 year (kg/m^2)	Bottom 25%	Middle 50%	Top 25%	
	1.00 (ref)	0.81 (.36)	0.62 (.10)	0.078
Height at 10 year (in)	Bottom 25%	Middle 50%	Top 25%	
	1.00 (ref)	4.31 (.001)	3.64 (.01)	0.01
Peak height velocity	Bottom 25%	Middle 50%	Top 25%	
	1.00 (ref)	1.85 (.049)	2.31 (.014)	0.018
Animal (non-dairy) fat[a] intake at 10 year	Bottom 25%	Middle 50%	Top 25%	
	1.00 (ref)	1.28 (.46)	2.27 (.016)	0.007
Peanut butter & bags of nuts at 14 year	Bottom 25%	Middle 50%	Top 25%	
	1.00 (ref)	0.67 (.068)	0.60 (.033)	0.099

Body size factors were previously found [31] to be most strongly associated with BBD, while dietary factors were those found most important in Table 3 Multivariable Models

[a]At age 10 year, the major contributors to animal (non-dairy) fat intake were beef or lamb as a main dish, and pork, ribs, or ham as a main dish

[b]Tests for trend (P_t) were performed by using the median exposure value, within each category, as a continuous variable

biopsy-confirmed BBD: consumption of animal (non-dairy) fat at 10 year was associated with higher risk, while consumption of nuts and peanut butter at 14 year was associated with lower risk. Of equal significance, childhood body size measures continued to be important in our multivariable models, indicating that childhood body size and nutrition independently impact BBD risk in young women. Because our number of cases was relatively small, and because some dietary exposures may have longer latency periods, continued follow-up of this cohort will be critical to re-assess these results as new cases of BBD, and eventually cases of breast cancer, are diagnosed.

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Author contributions CB and GC conceived and designed the study and prepared the initial draft. CB, RT, WW, BR, AF, and GC contributed to data collection efforts over multiple years. CB performed the analyses. CB, RT, WW, BR, MH, AT, AF, and GC contributed to the interpretation of the data and revision of the manuscript.

Data availability The corresponding author (Dr. Berkey) declares that she has full access to all the data and final responsibility for the decision to submit this work for publication.

Compliance with ethical standards

Conflicts of interest Dr. Frazier serves on the clinical advisory board for Decibel Therapeutics (not related to this manuscript). The remaining authors declare that they have no conflict of interest.

Ethical approval All procedures were in accordance with the ethical standards of Brigham & Women's Hospital, and with the 1964 Helsinki Declaration.

Informed consent Informed consent was obtained from all individual participants included in this study.

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