Early Life Factors and Incidence of Proliferative Benign Breast Disease

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Abstract

Proliferative benign breast disease is a marker of increased breast cancer risk, yet little is known about its etiology. Most studies of benign breast disease have focused only on risk factors in adulthood, despite growing evidence that factors in early life influence breast cancer risk. We explored the relations of several early life factors with incidence of proliferative benign breast disease among 71,896 premenopausal women in the Nurses' Health Study II who recalled their body fatness at young ages, physical activity in adolescence, birthweight, and history of being breastfed. Between 1991 and 1997, 901 of these women were identified as having proliferative benign breast disease from a centralized pathology review. Relative risks (RR) and 95% confidence intervals (95% CI) were estimated from Cox proportional hazards models. Greater childhood body fatness (ages 5-10) was associated with decreased risk of proliferative benign breast disease; the multivariate RR (95% CI) for the most overweight compared with the most lean was 0.61 (0.44-0.86; P_{trend} < 0.0001) and remained significant after adjustment for current body mass index. Body mass index at age 18 was also inversely associated with incidence of proliferative benign breast disease, with a multivariate RR (95% CI) of 0.67 (0.52-0.88) for those who were ≥25 kg/m^2 compared with those who were <19 kg/m^2 (P_{trend} = 0.001). There were no clear associations for physical activity in adolescence, birthweight, or being breastfed. These results indicate that premenopausal women who were heavier at young ages have lower incidence of proliferative benign breast disease, consistent with previous findings for breast cancer. (Cancer Epidemiol Biomarkers Prev 2005;14(12):2889–97)

Introduction

Benign breast disease is a heterogeneous group of lesions, including a variety of tissue abnormalities that are differentially associated with breast cancer risk. Compared with women with nonproliferative lesions, who do not seem to be at increased risk of developing breast cancer, women whose biopsies show proliferative changes without atypia have 1.5- to 2-fold greater risk and those with atypical hyperplasia have 3.5- to 5-fold greater risk (1). These findings suggest that proliferative benign breast disease is a risk marker for breast cancer.

Despite the well established association of benign proliferative lesions with breast cancer risk, little is known about the etiology of benign breast disease. Results from epidemiologic studies have been inconsistent, which may be due in part to methodologic issues such as differences in control groups and lack of systematic review and classification of benign pathology (2). In addition, most studies have focused only on risk factors in adulthood, just before biopsy, which may not be the most relevant etiologic period. A risk model based on Nurses' Health Study (NHS) data has shown that women who develop benign breast disease have elevated breast cancer incidence even at very young ages and after accounting for adult risk factors, implying that inherited factors or early life events may modify risk (3). Studies of mammary gland development in rats suggest that breast tissue is most susceptible to carcinogens before the first birth, when undifferentiated cells are undergoing rapid proliferation (4, 5), and epidemiologic studies of ionizing radiation also indicate that younger age at exposure corresponds with greater breast cancer risk (6-9).

Given the evidence that early life factors are involved in the development of breast cancer (9-11), it is plausible that they also play a role in the etiology of benign breast disease, which may be a precursor marker. Two previous investigations among participants in the Nurses' Health Study II (NHS II) provide support for this hypothesis. In a prospective analysis of alcohol consumption during different periods of life, Byrne et al. observed that recent alcohol consumption was unrelated to incidence of benign breast disease, but that greater alcohol consumption between ages 18 and 22 was associated with a significant increase in risk of both proliferative and nonproliferative lesions (12). In addition, a retrospective analysis among participants who provided information on high school diet showed that intakes of vegetable fat, vitamin E, and fiber during adolescence were inversely associated with incidence of proliferative benign breast disease (13); in contrast, adult intakes of these nutrients were not associated with decreased risk (14).

These findings suggest that exposures in early life may influence risk of benign breast disease. To further investigate this hypothesis, we examined several early life factors that have been associated with breast cancer risk in previous studies, including body fatness during childhood and adolescence (15-20), physical activity during adolescence (21, 22), birthweight (23, 24), and history of being breastfed (25, 26), in relation to incidence of histologically confirmed, proliferative benign breast disease among participants in the NHS II.

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Materials and Methods

Study Design and Population. The NHS II is a prospective cohort study that began in 1989, when 116,671 female registered nurses between ages 25 and 42 completed a mailed, self-administered questionnaire about their health behaviors, lifestyle factors, and medical histories. Follow-up questionnaires have been sent to participants every two years since then to obtain updated information on risk factors and disease diagnoses. The response rate for each biennial questionnaire has been >90%. Deaths are reported by family members and the postal service, and regular searches of the computerized National Death Index are also conducted (27).

The follow-up period for this analysis was from 1991 to 1997, because biopsy specimens were collected and reviewed for incident cases of benign breast disease diagnosed during this period (described below). Participants who died (n = 38) or had a diagnosis of benign breast disease (n = 38,561) before return of the 1991 questionnaire were excluded. Women with prevalent benign breast disease were excluded because the study was originally designed to examine the relation between adult diet and incidence of benign breast disease (14), and adult diet was not assessed until 1991. The collection and review of biopsy specimens began with cases reported on the 1993 questionnaire, because dietary factors could not be assessed before diagnosis for cases reported before then; hence, prevalent cases could not be classified according to histologic category of benign breast disease. Women with a history of cancer other than nonmelanoma skin cancer (n = 960) and those with no follow-up after 1991 (n = 2,772) were also excluded, leaving 74,340 eligible participants. We included only premenopausal women (n = 71,896) in this analysis, as some studies have observed different associations of early life factors such as birthweight and body mass index (BMI) at age 18 with incidence of premenopausal and postmenopausal breast cancer (24, 28), and we had insufficient numbers of postmenopausal women for stratified analyses.

We compared women in the final analytic cohort with those who were excluded in 1991 with respect to the early life factors of interest and several other characteristics, and there were no appreciable differences (data not shown).

Assessment of Early Life Factors and Other Potential Risk Factors. Each early life factor was assessed before the beginning of follow-up and diagnosis of benign breast disease. In 1989, participants recalled their body fatness at ages 5, 10, and 20 using a nine-level figure drawing originally developed by Stunkard et al., where level 1 represents the most lean and level 9 represents the most overweight (29). We obtained an estimate of childhood body fatness by averaging each participant's figures at ages 5 and 10. Because few participants recalled their body fatness as greater than level 5 at these ages, levels 5 to 9 were combined for the analyses. Changes in body fatness between ages 5 and 10, 10 and 20, and 5 and 20 were also calculated. Weight at age 18 was reported in 1989, and current weight was reported on each of the biennial questionnaires; these were used with height, assessed in 1989, to compute BMI at age 18 and current BMI for each two-year period during follow-up in kilograms per meters squared (kg/m^2).

Must et al. evaluated the validity of remote recall of body fatness among 181 participants in the Third Harvard Growth Study (30). Height and weight were measured as part of annual examinations during childhood and adolescence and were used to calculate BMI. Participants were interviewed again more than 50 years later and asked to recall their body fatness at ages 5, 10, and 20 using the same nine-level figure drawing as in the present study. Pearson correlations between recalled body fatness and measured BMI at approximately the same ages were 0.60 for age 5, 0.70 for age 10, and 0.66 for age 20. The validity of recalled weight at age 18 was evaluated in a sample of 118 NHS II participants through review of their college entrance physical examination records; the Spearman correlation between recalled weight and recorded weight at age 18 was 0.87 (31). Among 140 participants from a similar cohort of nurses, the correlation between self-reported current weight and the average of two measurements taken by trained technicians was 0.97, and the mean difference in weights was 3.3 pounds (32).

Physical activity during adolescence was initially assessed in 1989, when participants recalled the number of months per year they engaged in strenuous physical activity (e.g., swimming, aerobics, field hockey, basketball, cycling, and running) at least twice weekly in high school and between ages 18 and 22. The response categories for each period were 0, 1 to 3, 4 to 6, 7 to 9, and 10 to 12 months per year. A measure of late adolescent activity was computed by assigning an ordinal score of 0 to 4 to participants' responses for both periods, averaging the two scores, and truncating the average to the nearest integer value (33). Physical activity during adolescence was also assessed retrospectively in 1997, at the end of the follow-up period for benign breast disease, when participants recalled the number of hours per week (from 0 to $\geq$11) they engaged in walking, moderate recreational activity, and strenuous recreational activity in grades 7 and 8, grades 9 to 12, and between ages 18 and 22. Categorical responses were converted to continuous values by assigning the midpoint of each interval, and these were summed to calculate measures of strenuous plus moderate and total activity. Participants' activity levels (strenuous, strenuous plus moderate, and total) were averaged across the three periods, and categories were created based on their distributions.

A sample of 160 participants completed the 1997 questions on physical activity again in 2000, three years after the original assessment, allowing us to examine reproducibility. The Spearman correlations for hours per week of participation in strenuous activity in grades 7 and 8, grades 9 to 12, and ages 18 to 22 were 0.63, 0.71, and 0.69, respectively; the correlations for walking were similar, although those for moderate physical activity were somewhat lower (0.37 for grades 7 and 8, 0.36 for grades 9 to 12, and 0.52 for ages 18 to 22). Averaging participants' activity levels across the three periods, the correlations between the 1997 and the 2000 assessments were 0.76 for strenuous activity, 0.70 for strenuous plus moderate activity, and 0.64 for total physical activity. The 1989 and 1997 reports of strenuous activity were also positively correlated with each other (Spearman r = 0.53 for high school and 0.50 for ages 18 to 22).

On the 1991 questionnaire, participants were asked to report their birthweight (<5.5, 5.5-6.9, 7-8.4, 8.5-9.9, and $\geq$10 pounds), and whether they were breastfed as an infant, and, if yes, for how long ($\leq$3, 4-8, and $\geq$9 months). The two highest birthweight categories were combined in the analyses due to small numbers of participants. In a validation study conducted among 538 participants in this cohort (34), the Spearman correlation between birthweight reported by women and recalled by their mothers was 0.85, and the correlation between self-reported birthweight and that obtained from state birth records was 0.74. Using mothers' reports as the gold standard, the sensitivity of participants' self-reports of being breastfed was 82% and the specificity was 86%, and the Spearman correlation between mothers' and daughters' reports of duration of being breastfed was 0.74.

Information on other potential risk factors for benign breast disease was collected at various points during the study. Date of birth, history of breast cancer in a first-degree relative (mother or sister), height, age at menarche, menstrual cycle characteristics, and alcohol consumption and smoking during adolescence were assessed on the baseline questionnaire in 1989. Menopausal status, reproductive history, oral contraceptive use, and current smoking were updated on each of the

biennial questionnaires. Adult dietary factors were assessed on semiquantitative food frequency questionnaires in 1991 and 1995, and a subset of participants also provided information on diet during adolescence by completing a supplementary questionnaire in 1998 (n = 28,563).

Case Ascertainment and Pathology Review. On each questionnaire, participants were asked if they had been diagnosed with benign breast disease and, if yes, whether the diagnosis had been confirmed by biopsy or aspiration. Among the 71,896 eligible participants, a total of 2,294 women reported a first diagnosis of biopsy-confirmed benign breast disease on the 1993, 1995, or 1997 questionnaires and were contacted to acquire permission to obtain their pathology records and specimens. Of these, 1,762 (77%) confirmed the diagnosis and granted permission, and pathology material was obtained for 1,599 women (91% of those who had given permission). Biopsy specimens were reviewed by one of four pathologists who had no knowledge of participants' exposure information, and benign lesions were classified as normal or nonproliferative, proliferative without atypia, or atypical hyperplasia according to standard criteria (1). There were 981 histologically confirmed cases of proliferative benign breast disease, with or without atypia, among women with available pathology material. Cases with histologically confirmed benign breast disease were similar to those for whom pathology material was not available in terms of early life factors and other characteristics (data not shown). After excluding women who were not premenopausal at the time of biopsy (n = 67), those whose biopsy date was after their first report of benign breast disease (n = 10), and those who reported a diagnosis of breast cancer on the same questionnaire as their first benign breast disease diagnosis (n = 3), there were a total of 901 cases of proliferative benign breast disease. Because only 65 of these cases had atypical hyperplasia, they were combined with other proliferative lesions in the analysis.

The reliability of the pathologists' classification was assessed by resubmitting a random sample of 54 specimens that had been reviewed previously to one of the other pathologists. Of the 31 specimens originally classified as proliferative (with or without atypia) in the first reading, 29 (94%) were reclassified as such in the second reading.

Statistical Analysis. Participants contributed person-time from the return date of the 1991 questionnaire until return of the 1997 questionnaire, report of benign breast disease or cancer (except nonmelanoma skin cancer), menopause, death from any cause, or loss-to-follow-up, whichever came first. Cases and person-time were assigned to the appropriate level of each early life factor and other characteristics. For time-varying covariates, such as oral contraceptive use and parity, person-time was reassigned every two years based on updated information. Participants who were missing data for one of the early life factors were excluded from analyses focusing on that factor, as were those who were missing data for covariates modeled as continuous (e.g., height, childhood body fatness, and BMI). Hazard ratios from Cox proportional hazards models with age in months and two-year questionnaire cycle as the time scale were used to estimate relative risks (RR) and 95% confidence intervals (95% CI), adjusting for potential confounders. Indicator variables were used to represent categories of early life factors, and tests for linear trend were conducted by including each early factor in a model as a continuous variable.

Because many cases of benign breast disease are asymptomatic (2), women who undergo regular breast screening are more likely to have a lesion detected. Additional factors, such as a family history of breast cancer, may also influence the likelihood of a physician ordering a tissue biopsy (35). To address this potential for bias, we conducted secondary analyses restricted to participants who reported having a mammogram or a breast examination by a clinician in the past two years and to those with no history of breast cancer in a first-degree relative.

We examined whether associations for childhood body fatness and strenuous physical activity during adolescence varied according to each other as well as parity (nulliparous, parous), oral contraceptive use (never or past <4 years, past ≥4 years or current), BMI at age 18 (<22, ≥22 kg/m^2), and current BMI (<25, ≥25 kg/m^2) by constructing stratum-specific models. Wald tests and likelihood ratio tests were also used to examine the significance of interactions.

Results

We observed 377,793 person-years of follow-up between 1991 and 1997 among the 71,896 premenopausal women in the study. Of these women, 68,725 (96%) were included in analyses of childhood body fatness, 68,989 (96%) were included in analyses of strenuous physical activity during adolescence, 56,993 (79%) were included in analyses of birthweight, and 51,490 (72%) were included in analyses of being breastfed.

Women who were heavy during childhood were heavier at birth, had earlier menarche, were more likely to smoke in adolescence and adulthood, were less likely to participate in strenuous physical activity in high school, and were more likely to be nulliparous later in life compared with those who were lean (Table 1). They were also more likely to be overweight at age 18 and in adulthood (Spearman r = 0.48 for BMI at age 18 and 0.33 for BMI in 1991). Women who frequently participated in strenuous physical activity in high school were younger, had slightly later menarche, were more likely to be heavy drinkers (≥10 g alcohol/d) between ages 18 and 22, and were less likely to be overweight at age 18 and in adulthood compared with those who never participated in strenuous activity. Participants who were heavy at birth were more likely to be breastfed, more likely to be overweight at age 18, and grew to be taller compared with those who were very light. Those who were breastfed for ≥9 months were less likely to drink heavily and to smoke during adolescence compared with those who were never breastfed.

Because the risk factors for benign breast disease are not well established, we examined associations between potential risk factors and incidence of proliferative benign breast disease among study participants to identify covariates to consider for adjustment in analyses of early life factors. First-degree family history of breast cancer, height, alcohol consumption between ages 18 and 22, and smoking between ages 15 and 19 were each weakly but positively associated with incidence of proliferative benign breast disease; in contrast, women who had been using oral contraceptives for at least four years had decreased risk compared with never users (Table 2). Although the associations of parity and age at first birth with proliferative benign breast disease differed from the known associations of these factors with breast cancer, they were still included in multivariate models for early life factors because previous studies have suggested that they may be related to risk of benign breast disease (2).

Greater childhood body fatness was associated with lower risk of proliferative benign breast disease (Table 3). The multivariate RR (95% CI) for the most overweight (level ≥5) compared with the most lean (level 1) during childhood was 0.61 (0.44-0.86; P_{trend} < 0.0001). When body fatness at ages 5, 10, and 20 were each examined separately, the multivariate RRs (95% CIs) for the most overweight compared with the most lean were 0.71 (0.53-0.96) for age 5, 0.72 (0.56-0.92) for age 10, and 0.82 (0.56-1.20) for age 20. Including childhood body fatness and body fatness at age 20 in the same model, the multivariate RRs (95% CIs) for the most overweight compared

Table 1. Characteristics of premenopausal participants in the NHS II according to early life factors

	Childhood body fatness		Strenuous activity in high school, months/y		Birthweight, pounds		Duration breastfed as infant, months	
	1	≥5	0	10-12	<5.5	≥8.5	0	≥9
No. participants	11,580	4,324	14,063	17,849	4,385	7,683	38,137	2,326
Means								
Age (y)	35.7	36.0	36.7	34.9	36.0	34.9	35.2	36.2
Adolescent vegetable fat intake (% energy)*	14.5	15.1	14.7	14.8	14.6	15.2	15.0	14.1
Age at menarche (y)	12.8	12.0	12.3	12.6	12.3	12.5	12.4	12.5
Height (inches)	64.9	65.1	64.6	65.1	64.0	66.0	64.9	64.8
BMI at age 18 (kg/m^2)	19.4	24.9	21.7	20.8	21.3	21.8	21.4	21.3
Current BMI (kg/m^2)	22.5	28.6	25.0	24.2	24.9	25.2	24.6	24.8
Age at first birth (y)†	25.7	25.8	25.9	25.8	25.9	26.0	25.9	25.8
Parity†	2.2	2.1	2.2	2.2	2.2	2.2	2.1	2.2
Percentages								
Birthweight ≥8.5 pounds	8.0	16.0	10.9	11.1	—	—	12.3	16.5
Breastfed as infant	26.0	24.9	26.4	27.7	19.4	33.4	—	—
Smoking ≥5 cigarettes/d ages 15-19	14.5	19.9	16.9	13.8	15.1	15.4	16.5	10.7
Strenuous activity 10-12 months/y in high school	29.5	18.1	—	—	25.4	26.0	25.4	28.2
BMI at age 18 ≥25 kg/m^2	2.0	37.9	14.5	6.7	10.5	14.2	10.9	10.7
Alcohol ≥10 g/d ages 18-22	22.4	26.4	19.9	28.0	21.5	26.0	25.7	16.1
Nulliparous	23.1	30.5	22.3	24.8	27.7	27.1	25.0	21.3
Current oral contraceptive user	12.0	10.5	9.0	13.1	10.9	12.8	12.7	8.9
Current smoker	12.2	17.4	10.4	12.7	12.3	10.9	12.0	9.1
Current BMI ≥30 kg/m^2	4.4	33.0	16.0	11.5	15.2	16.4	13.9	15.1
First-degree family history of breast cancer	4.8	5.2	5.4	4.6	5.0	5.1	4.8	3.6

NOTE: Unless other timeframe is noted, means and percentages refer to the distributions of characteristics among participants in 1991.
*Among participants who completed the supplementary questionnaire on adolescent diet in 1998.
†Among parous women.

with the most lean were 0.68 (0.47-0.98) for childhood body fatness and 1.01 (0.66-1.53) for body fatness at age 20. Adjustment for age at menarche, menstrual cycle characteristics, and dietary factors during adolescence or adulthood had no appreciable effect on these estimates (data not shown). Changes in body fatness between ages 5, 10, and 20 were not related to incidence of proliferative benign breast disease; women who increased two or more levels between ages 5 and 20 had a multivariate RR (95% CI) of 0.89 (0.72-1.09) compared with those with no change, adjusting for body fatness at age 5 as well as other covariates.

Greater BMI at age 18 was also associated with lower risk of proliferative benign breast disease (Table 3), with a multivariate RR (95% CI) of 0.67 (0.52-0.88) for women who were ≥25 kg/m^2 compared with those who were <19 kg/m^2 (P_{trend} = 0.001). When childhood body fatness and BMI at age 18 were mutually adjusted for one another, the multivariate RRs (95% CIs) were 0.78 (0.58-1.05; P_{trend} = 0.06) for those who were ≥25 kg/m^2 compared with those who were <19 kg/m^2 at age 18 and 0.69 (0.48-0.98; P_{trend} = 0.01) for the most overweight compared with the most lean in childhood. Current BMI was not significantly related to incidence of proliferative benign breast disease (Table 3). The multivariate RR (95% CI) was 0.84 (0.67-1.04) for those who were ≥30 kg/m^2 compared with those who were <21 kg/m^2 (P_{trend} = 0.18); it was attenuated to 0.95 (0.76-1.19) after additional adjustment for childhood body fatness (P_{trend} = 0.92).

There was a U-shaped association between strenuous physical activity during high school, based on the 1989 assessment, and incidence of proliferative benign breast disease (Table 4). The multivariate RR (95% CI) for women who participated in strenuous activity 4 to 6 months per year during high school was 0.65 (0.50-0.84) compared with those who never participated in strenuous activity. There was no apparent decrease in risk, however, with greater amounts of strenuous activity, and strenuous physical activity between ages 18 and 22 was not associated with risk. Averaging strenuous activity levels across both periods, the multivariate RR (95% CI) was 0.74 (0.61-0.89) for women who participated in 1 to 3 months per year compared with those who never participated in strenuous activity. Additional adjustment for childhood body fatness, BMI at age 18, age at menarche, and menstrual cycle characteristics had little effect on these estimates (data not shown).

A similar U-shaped association was also observed for average amount of strenuous plus moderate activity from grade 7 to age 22 based on the retrospective 1997 assessment. Compared with those who participated in <3 hours per week, women who participated in 5 to 6.9 hours of strenuous plus moderate activity per week were at lowest risk (multivariate RR, 0.73; 95% CI, 0.57-0.93), whereas those who participated in greater amounts of activity were not at decreased risk (data not shown). Women who participated in 5 to 6.9 total hours of activity per week (including walking) were also at slightly lower risk compared with those who participated in <5 hours per week (multivariate RR, 0.81; 95% CI, 0.64-1.04). Strenuous activity alone, however, was not associated with incidence of proliferative benign breast disease (data not shown).

Birthweight and being breastfed were not clearly related to incidence of proliferative benign breast disease (Table 5). The multivariate RR (95% CI) for women who weighed ≥8.5 pounds at birth compared with those who weighed between 7 and 8.4 pounds was 0.96 (0.77-1.21; P_{trend} = 0.74). Being premature or a multiple birth was not associated with incidence of proliferative benign breast disease, and exclusion of these participants did not affect the estimates for birthweight (data not shown). Although women who were breastfed for 4 to 8 months had slightly lower risk compared with those who were never breastfed (multivariate RR, 0.78; 95% CI, 0.59-1.04), those who were breastfed for ≥9 months were not at decreased risk (P_{trend} = 0.40). The multivariate RR (95% CI) for women who were ever breastfed compared with those who were never breastfed was 0.93 (0.78-1.11). Additional adjustment for childhood body fatness and attained height, which are indicators of growth and potential intermediate factors, had no appreciable effect on the estimates for

birthweight or being breastfed. We also examined whether the association for birthweight was modified by childhood body fatness or height, but we did not observe significant interactions with either of these factors (data not shown).

The observed associations for body fatness, physical activity, birthweight, and being breastfed were similar when the population was restricted to women who had regular screening during the follow-up period and to women with no first-degree family history of breast cancer (data not shown). The inverse association for childhood body fatness was stronger among never and past, short-term oral contraceptive users (multivariate RR, 0.48; 95% CI, 0.30-0.77, for the most overweight compared with the most lean) than among current and past users of long duration (multivariate RR, 0.89; 95% CI, 0.55-1.45), and a test for interaction was marginally significant (P = 0.10). The inverse trend for childhood body fatness was also somewhat more apparent among those who were lean at age 18 than among those who were heavy (P for interaction = 0.09). The estimates for strenuous physical activity did not vary considerably according to any of the factors examined, and none of the interactions were statistically significant (data not shown).

Discussion

In this study, we observed a significant inverse association between childhood body fatness and incidence of proliferative benign breast disease in premenopausal women, with approximately 40% lower risk for the most overweight compared with the most lean. The reduction in risk was greater for body fatness at ages 5 and 10 than at age 20 and remained apparent after adjustment for later BMI, suggesting that adiposity at young ages, perhaps even before puberty, may have an independent effect on risk. BMI at age 18 was also inversely associated with incidence, with approximately 30% lower risk for those who were ≥25 kg/m^2 at age 18 compared with those who were <19 kg/m^2. The association for childhood body fatness was stronger than for BMI at age 18 when they were mutually adjusted for each other, indicating that childhood or early adolescence may be the most relevant period. Current BMI was not significantly associated with incidence of proliferative benign breast disease, providing further support for this hypothesis.

Although several studies have indicated a possible protective effect of adiposity in adulthood (2, 36-38), we are not aware of any previous investigations of childhood body fatness in relation to incidence of benign breast disease. However, greater body fatness during childhood and adolescence has been associated with decreased incidence of premenopausal as well as postmenopausal breast cancer in several studies (15-20, 39, 40). In one of these studies, greater body size during adolescence was associated with reduced risk of premenopausal breast cancer, but weight gain after age 20 was only associated with reduced risk of early-stage and low-grade (not late-stage or high-grade) breast cancer (39). Furthermore, a recent analysis in the NHS II found a stronger inverse association of childhood body fatness with premenopausal breast cancer than either BMI at age 18 or current BMI (20). Given that proliferative benign breast disease is a risk marker for breast cancer, our results are consistent with these previous findings.

Several biological mechanisms have been proposed to explain the inverse association between body fatness at young ages and breast cancer incidence, and similar pathways may be

Table 2. RRs of NHS II incident proliferative benign breast disease according to potential risk factors among 71,896 premenopausal participants, 1991-1997

	Cases (N = 901)*	Age-adjusted RR (95% CI)†	Multivariate RR (95% CI)‡
Height, inches			
<63	155	1.0 (Reference)	1.0 (Reference)
63-64	244	1.10 (0.90-1.35)	1.09 (0.89-1.34)
65-66	238	1.05 (0.86-1.29)	1.03 (0.84-1.26)
67-68	185	1.21 (0.98-1.50)	1.17 (0.94-1.45)
≥69	78	1.21 (0.92-1.58)	1.17 (0.89-1.53)
First-degree family history of breast cancer			
No	844	1.0 (Reference)	1.0 (Reference)
Yes	57	1.31 (1.00-1.71)	1.30 (1.00-1.71)
Alcohol consumption, g/d, ages 18-22			
0	208	1.0 (Reference)	1.0 (Reference)
0.1-1.4	204	1.22 (1.00-1.48)	1.23 (1.01-1.50)
1.5-4.9	80	1.21 (0.93-1.57)	1.23 (0.95-1.60)
5-9.9	196	1.28 (1.05-1.56)	1.31 (1.07-1.60)
≥10	209	1.22 (1.01-1.49)	1.25 (1.02-1.54)
Cigarette smoking, cigarettes/d, ages 15-19			
0	679	1.0 (Reference)	1.0 (Reference)
1-4	59	0.95 (0.72-1.23)	0.91 (0.69-1.19)
≥5	163	1.22 (1.03-1.45)	1.15 (0.96-1.37)
Recency and duration of oral contraceptive use			
Never	127	1.0 (Reference)	1.0 (Reference)
Past <4 y	392	1.26 (1.03-1.54)	1.18 (0.96-1.44)
Past ≥4 y	306	1.09 (0.88-1.34)	0.99 (0.80-1.23)
Current <4 y	17	1.41 (0.85-2.36)	1.37 (0.82-2.28)
Current ≥4 y	35	0.60 (0.41-0.87)	0.55 (0.37-0.80)
Parity and age at first birth			
Nulliparous	171	1.0 (Reference)	1.0 (Reference)
1-2 pregnancies, first birth at age <25	174	1.40 (1.13-1.74)	1.34 (1.08-1.66)
1-2 pregnancies, first birth at age 25-29	208	1.11 (0.91-1.36)	1.06 (0.87-1.31)
1-2 pregnancies, first birth at age ≥30	110	0.90 (0.71-1.15)	0.85 (0.67-1.09)
≥3 pregnancies, first birth at age <25	123	1.12 (0.88-1.41)	1.05 (0.83-1.33)
≥3 pregnancies, first birth at age 25-29	80	0.85 (0.65-1.11)	0.78 (0.59-1.02)
≥3 pregnancies, first birth at age ≥ 30	20	1.12 (0.70-1.78)	1.03 (0.65-1.65)

*Total number of cases for some risk factors is less than 901 due to missing data.
†All RRs from Cox model with age in months and two-year questionnaire cycle as time scale.
‡Adjusted for BMI at age 18 (<19, 19-20.4, 20.5-21.9, 22-24.9, ≥25 kg/m^2) and other variables in table.

Table 3. RRs of incident proliferative benign breast disease according to body fatness at different ages among 68,725 premenopausal NHS II participants, 1991-1997

	Childhood body fatness					
	1 (Most lean)	1.5-2	2.5-3	3.5-4.5	≥5 (Most overweight)	P_{trend}
Cases (N = 866)	177	284	196	166	43	
Person-years	59,810	111,604	92,086	75,497	22,521	
Age-adjusted RR (95% CI)*	1.0 (Reference)	0.89 (0.74-1.08)	0.74 (0.60-0.90)	0.75 (0.61-0.93)	0.63 (0.45-0.88)	0.0002
Multivariate RR (95% CI)†	1.0 (Reference)	0.89 (0.74-1.08)	0.73 (0.60-0.90)	0.74 (0.60-0.91)	0.61 (0.44-0.86)	<0.0001
+ BMI at age 18‡	1.0 (Reference)	0.91 (0.75-1.10)	0.77 (0.62-0.95)	0.81 (0.64-1.01)	0.69 (0.48-0.98)	0.01
+ Current BMI‡	1.0 (Reference)	0.89 (0.74-1.08)	0.73 (0.60-0.90)	0.74 (0.59-0.92)	0.61 (0.44-0.87)	0.0003
	BMI at age 18, kg/m^2 (median)					
	<19 (18.2)	19-20.4 (19.7)	20.5-21.9 (21.2)	22-24.9 (23.2)	≥25 (27.4)	P_{trend}
Cases	211	238	196	147	74	
Person-years	75,173	93,005	84,359	70,055	38,926	
Age-adjusted RR (95% CI)*	1.0 (Reference)	0.91 (0.76-1.10)	0.83 (0.68-1.01)	0.75 (0.61-0.93)	0.68 (0.52-0.89)	0.001
Multivariate RR (95% CI)†	1.0 (Reference)	0.91 (0.75-1.09)	0.83 (0.68-1.01)	0.74 (0.60-0.92)	0.67 (0.52-0.88)	0.001
+ Childhood body fatness‡	1.0 (Reference)	0.94 (0.78-1.14)	0.89 (0.73-1.10)	0.83 (0.66-1.04)	0.78 (0.58-1.05)	0.06
	Current BMI, kg/m^2 (median in 1991)					
	<21 (19.9)	21-22.9 (22.0)	23-24.9 (23.9)	25-29.9 (26.7)	≥30 (34.0)	P_{trend}
Cases	206	184	138	189	149	
Person-years	80,979	78,692	63,292	79,063	59,492	
Age-adjusted RR (95% CI)*	1.0 (Reference)	0.87 (0.72-1.07)	0.80 (0.65-1.00)	0.85 (0.70-1.04)	0.86 (0.69-1.06)	0.28
Multivariate RR (95% CI)†	1.0 (Reference)	0.88 (0.72-1.07)	0.80 (0.65-1.00)	0.84 (0.69-1.03)	0.84 (0.67-1.04)	0.18
+ Childhood body fatness‡	1.0 (Reference)	0.90 (0.74-1.10)	0.84 (0.68-1.05)	0.91 (0.74-1.11)	0.95 (0.76-1.19)	0.92

*All RRs from Cox model with age in months and two-year questionnaire cycle as time scale.
†Adjusted for height (continuous), first-degree family history of breast cancer (yes, no), alcohol consumption (g/d) between ages 18 and 22 (0, 0.1-1.4, 1.5-4.9, 5.0-9.9, ≥10), cigarette smoking (cigarettes/d) between ages 15 and 19 (0, 1-4, ≥5), recency and duration of oral contraceptive use (never, past <4 years, past ≥4 years, current <4 years, current ≥4 years), and parity and age at first birth (nulliparous; 1-2 pregnancies, first birth at age <25; 1-2 pregnancies, first birth at age 25-29; 1-2 pregnancies, first birth at age ≥30; ≥3 pregnancies, first birth at age <25; ≥3 pregnancies, first birth at age 25-29; ≥3 pregnancies, first birth at age ≥30).
‡Adjusted for above variables plus BMI at age 18, current BMI, or childhood body fatness, each modeled as continuous.

involved with proliferative benign breast disease. Despite having earlier menarche, more overweight girls may experience a slower rate of pubertal growth (41), which could lead to decreased risk (17, 19). Body fatness at young ages may also influence concentrations of sex hormones. Obesity in preadolescent and adolescent girls has been associated with higher basal insulin levels, increased androgen production in the ovary, decreased plasma levels of sex hormone-binding globulin, and increases in free (unbound) testosterone and estradiol (42-44); these hormonal changes have been linked to metabolic features of polycystic ovary syndrome and increased frequency of anovulatory cycles (43, 45). In addition, experimental studies in rats suggest that early estrogen exposure may induce differentiation of immature breast cells as well as stimulate epithelial growth (46, 47). Higher levels of estrogens may be protective in the breasts of young girls, which are less likely to contain malignant cells, but harmful in older women, whose breasts are more likely to have acquired transformed cells.

The observed associations of physical activity during adolescence with incidence of proliferative benign breast disease were inconsistent and do not have a clear biological explanation. Although women who participated in intermediate levels of activity were at lower risk compared with those who participated in very low levels of activity, there was no apparent risk reduction for higher levels of activity. This association was evident for strenuous activity during high school based on the 1989 assessment, whereas it was only observed for strenuous plus moderate and total activity (not strenuous activity alone) based on the 1997 assessment. Strenuous and moderate physical activity at young ages are hypothesized to lower risk of premenopausal breast cancer by delaying menarche, inducing secondary amenorrhea, and reducing the frequency of ovulatory cycles, thus decreasing cumulative exposure to ovarian hormones (48). These mechanisms would be expected to produce a monotonic inverse association, but they would not explain the U-shaped association observed in this study. The association also was not substantially affected by adjustment for childhood body fatness or BMI at age 18, which are inversely associated with levels of physical activity, nor did it seem to be modified by these factors.

Although several case-control studies have observed inverse associations of physical activity during adolescence or lifetime physical activity with breast cancer risk (49), a prospective study that examined strenuous activity during high school and between ages 18 and 22 in relation to incidence of premenopausal breast cancer in this population did not find any such association (33); another large prospective cohort study conducted in Norway and Sweden also found no protective effect for physical activity at age 14 (50). To our knowledge, only one other investigation has considered the association between physical activity during adolescence and early adulthood and risk of benign breast disease. This was a cross-sectional survey of over 5,000 college and university alumnae, which reported a lower prevalence of benign diseases of the breast as well as breast cancer among former college athletes compared with nonathletes (51, 52). However, the definition of benign breast disease in this study was based only on self-report, preventing classification by histologic subtype. Several previous studies have examined recent physical activity in relation to incidence of benign breast disease, but they have not shown any consistent associations (53-55).

The lack of a consistent association for physical activity during adolescence in this study as well as the previous study of breast cancer among NHS II participants could be due to misclassification of participants' activity levels and attenuation of the RR estimates. Although we observed fairly high reproducibility correlations for activity levels recalled by

Table 4. RRs of incident proliferative benign breast disease according to frequency of participation in strenuous physical activity during adolescence (reported in 1989) among 68,989 premenopausal NHS II participants, 1991-1997

	Strenuous physical activity, months/y					
	0	1-3	4-6	7-9	10-12	P_{trend}
High school						
Cases (N = 863)	205	178	83	151	246	
Person-years	73,635	71,336	50,513	73,476	93,973	
Age-adjusted RR (95% CI)*	1.0 (Reference)	0.98 (0.80-1.20)	0.67 (0.52-0.86)	0.81 (0.66-1.00)	1.06 (0.88-1.28)	0.89
Multivariate RR (95% CI)†	1.0 (Reference)	0.97 (0.79-1.19)	0.65 (0.50-0.84)	0.81 (0.65-1.00)	1.05 (0.87-1.26)	0.95
+ Childhood body fatness ‡	1.0 (Reference)	0.96 (0.78-1.17)	0.64 (0.50-0.83)	0.80 (0.64-0.98)	1.01 (0.84-1.22)	0.81
Ages 18-22						
Cases	262	269	143	89	100	
Person-years	93,380	115,125	65,455	44,424	44,549	
Age-adjusted RR (95% CI)*	1.0 (Reference)	0.91 (0.77-1.08)	0.89 (0.73-1.10)	0.83 (0.65-1.06)	0.93 (0.74-1.17)	0.30
Multivariate RR (95% CI)†	1.0 (Reference)	0.91 (0.76-1.08)	0.89 (0.73-1.10)	0.84 (0.65-1.07)	0.95 (0.75-1.20)	0.40
+ Childhood body fatness ‡	1.0 (Reference)	0.90 (0.76-1.07)	0.88 (0.72-1.08)	0.82 (0.64-1.05)	0.93 (0.73-1.17)	0.29
Average, late adolescence						
Cases	245	188	211	140	79	
Person-years	82,896	93,293	90,479	63,852	32,413	
Age-adjusted RR (95% CI)*	1.0 (Reference)	0.74 (0.61-0.90)	0.89 (0.74-1.07)	0.85 (0.69-1.04)	0.94 (0.73-1.21)	0.78
Multivariate RR (95% CI)†	1.0 (Reference)	0.74 (0.61-0.89)	0.88 (0.73-1.06)	0.84 (0.68-1.04)	0.95 (0.74-1.23)	0.83
+ Childhood body fatness ‡	1.0 (Reference)	0.73 (0.60-0.88)	0.87 (0.72-1.05)	0.82 (0.67-1.02)	0.92 (0.71-1.20)	0.62

*All RRs from Cox model with age in months and two-year questionnaire cycle as time scale.
†Adjusted for height (continuous), first-degree family history of breast cancer (yes, no), alcohol consumption (g/d) between ages 18 and 22 (0, 0.1-1.4, 1.5-4.9, 5.0-9.9, ≥10), cigarette smoking (cigarettes/d) between ages 15 and 19 (0, 1-4, ≥5), recency and duration of oral contraceptive use (never, past <4 years, past ≥4 years, current <4 years, current ≥4 years), and parity and age at first birth (nulliparous; 1-2 pregnancies, first birth at age <25; 1-2 pregnancies, first birth at age 25-29; 1-2 pregnancies, first birth at age ≥30; ≥3 pregnancies, first birth at age <25; ≥3 pregnancies, first birth at age 25-29; ≥3 pregnancies, first birth at age ≥30).
‡Adjusted for above variables plus childhood body fatness modeled as continuous.

participants who completed the assessment in both 1997 and 2000, we were not able to examine validity because we had no record of true activity levels during adolescence. Both recalls could be poor measures of actual activity levels although they are highly correlated with each another, given that the time interval between the two recalls was much less than the amount of time since adolescence. Another potential concern is that we observed high correlations between activity levels for different ages that were recalled at the same time, either in 1997 or in 2000. This could indicate that activity levels track closely over time; however, it could also indicate that recall is not sufficiently accurate to distinguish activity levels for different periods.

Despite these issues, the validity of recall of other exposures during adolescence (e.g., BMI and dietary factors) has been shown in this cohort (31, 56), and we would expect recall of physical activity for the same period to have similar accuracy. There were only weak correlations between recent physical activity and recalled activity during adolescence, suggesting that recent physical activity does not have a strong influence on recall of past activity. Furthermore, several other studies in which adult women have recalled their activity levels during adolescence have observed significant inverse associations with breast cancer risk (21, 22, 57, 58), indicating that the amount of misclassification was not extreme enough to obscure the observed associations.

Table 5. RRs of incident proliferative benign breast disease according to birthweight and duration breastfed as an infant among premenopausal NHS II participants, 1991-1997

	Birthweight, pounds				
	<5.5	5.5-6.9	7.0-8.4	≥8.5	P_{trend}
Cases (N = 757)	66	222	372	97	
Person-years	23,080	92,325	148,181	41,281	
Age-adjusted RR (95% CI)*	1.11 (0.85-1.44)	0.96 (0.81-1.13)	1.0 (Reference)	0.96 (0.77-1.21)	0.70
Multivariate RR (95% CI)†	1.10 (0.85-1.43)	0.95 (0.81-1.12)	1.0 (Reference)	0.96 (0.77-1.21)	0.74
+ Childhood body fatness‡	1.08 (0.83-1.40)	0.94 (0.79-1.11)	1.0 (Reference)	0.99 (0.79-1.23)	>0.99
+ Height‡	1.13 (0.87-1.47)	0.97 (0.82-1.15)	1.0 (Reference)	0.95 (0.76-1.19)	0.51
	Duration breastfed as an infant, months				
	0	≤3	4-8	≥9	P_{trend}
Cases (N = 686)	519	79	55	33	
Person-years	204,503	31,132	27,874	12,437	
Age-adjusted RR (95% CI)*	1.0 (Reference)	0.99 (0.78-1.26)	0.77 (0.58-1.02)	0.98 (0.69-1.39)	0.25
Multivariate RR (95% CI)†	1.0 (Reference)	1.02 (0.80-1.30)	0.78 (0.59-1.04)	1.04 (0.73-1.48)	0.40
+ Childhood body fatness‡	1.0 (Reference)	1.02 (0.81-1.30)	0.78 (0.59-1.04)	1.04 (0.73-1.48)	0.40
+ Height‡	1.0 (Reference)	1.02 (0.80-1.29)	0.78 (0.59-1.03)	1.04 (0.73-1.48)	0.39

NOTE: Includes 56,993 participants with information on birthweight and 51,490 with information on duration breastfed.
*All RRs from Cox model with age in months and two-year questionnaire cycle as time scale.
† Adjusted for first-degree family history of breast cancer (yes, no), alcohol consumption (g/d) between ages 18 and 22 (0, 0.1-1.4, 1.5-4.9, 5.0-9.9, ≥10), cigarette smoking (cigarettes/d) between ages 15 and 19 (0, 1-4, ≥5), recency and duration of oral contraceptive use (never, past <4 years, past ≥4 years, current <4 years, current ≥4 years), and parity and age at first birth (nulliparous; 1-2 pregnancies, first birth at age <25; 1-2 pregnancies, first birth at age 25-29; 1-2 pregnancies, first birth at age ≥30; ≥3 pregnancies, first birth at age <25; ≥3 pregnancies, first birth at age 25-29; ≥3 pregnancies, first birth at age ≥30).
‡ Adjusted for above variables plus childhood body fatness or height, each modeled as continuous.

Another possibility is that there was insufficient variability in adolescent activity among participants to detect an association. In the case-control study that found the strongest association between lifetime physical activity and breast cancer risk, the highest activity category was ≥3.8 hours per week (21), which would have included the vast majority of women in our cohort. If even very low levels of activity can reduce risk, the relatively high levels in this population could have obscured an association.

To our knowledge, no other studies have examined whether birthweight or being breastfed are related to incidence of proliferative benign breast disease. Many studies, including one in this population (23), have shown positive or J-shaped associations of birthweight with breast cancer risk (10). In addition, several recent studies have examined whether birthweight is associated with adult mammographic density, although their results are inconsistent (59-61). Greater birthweight may reflect higher concentrations of maternal estrogens during pregnancy (62, 63) or may be an indicator of more rapid fetal growth (64). In contrast, several studies have observed decreased risk of breast cancer for women who were breastfed as infants (10), although this was not apparent among NHS II participants (65). Infants who are breastfed may experience slower postnatal growth (66-68), and exposure to gonadotropin-releasing hormone and other hormones in breast milk may suppress premature development of the reproductive organs (69). In this study, however, neither birthweight nor being breastfed was associated with incidence of proliferative benign breast disease. These factors are reported with a high degree of accuracy by women in this population (34), making it unlikely that misclassification could be the primary explanation. However, if the true associations are very weak, even a small degree of misclassification could account for null findings. It is also possible that these associations could be modified by other factors, such as childhood growth, but we had limited power to examine interactions.

Because benign breast disease encompasses a variety of lesions that are differentially associated with breast cancer risk (1), the collection of tissue biopsy specimens and the confirmation of cases based on a uniform, centralized pathology review is a major advantage of this study. In addition, our focus on proliferative lesions is justified given that proliferative benign breast disease is the relevant marker of breast cancer risk and may represent an intermediate stage on the pathway from normal breast tissue to breast cancer. The prospective nature of the study is another strength, because it minimizes the possibility that a diagnosis of benign breast disease could affect recall of early life factors. We were also able to control for several potential risk factors for benign breast disease and breast cancer. The similarity between the age-adjusted and multivariate RRs suggests that there was little confounding of the early life factors of interest by adult risk factors in these data, which may be relevant for other studies with less information on adult risk factors. However, a limitation of this study is that some degree of misclassification is unavoidable, given that all of the early life factors were recalled many years after they occurred. Another limitation is that atypical hyperplasia, which is associated with the greatest increase in breast cancer risk and may be a precursor lesion (1), could not be examined as a separate outcome due to the small number of cases.

In summary, these data indicate that greater body fatness during childhood and adolescence may reduce incidence of proliferative benign breast disease among premenopausal women, independently of later BMI. This inverse association is consistent with previous findings for breast cancer, and future studies should focus on elucidating the biological mechanisms that would explain these associations. Our findings do not provide strong evidence for associations of physical activity during adolescence, birthweight, and being breastfed with incidence of proliferative benign breast disease, although these should be examined in other populations to confirm our findings.

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