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Prospective Study of Growth and Development in Older Girls and Risk of Benign Breast Disease in Young Women

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Abstract

BACKGROUND—In adult women with retrospective data, childhood adiposity, pubertal growth and development were associated with benign breast disease (BBD) and/or breast cancer. We prospectively evaluate these childhood/adolescent characteristics and BBD risk.

METHODS—The Growing Up Today Study (GUTS) includes females, 9–15yrs in 1996, who completed annual questionnaires through 2001, then 2003, 2005 and 2007. Participants annually/biennially provided information regarding menarche, and height and weight from which we derived body mass index (BMI, kg/m^2). Peak height growth velocity (PHV, cm/yr) was estimated from longitudinal data. On 2005–2007 surveys, 6899 females (18–27yrs) reported whether a health care provider ever diagnosed BBD (n=147), and if confirmed by biopsy (n=67). Logistic models investigated risk factors adjusted for age, alcohol, pregnancy, and maternal history.

RESULTS—More childhood adiposity (OR=0.91/(kg/m^2), p=.04) and shorter adult height (OR=0.93/inch shorter, p=.07) were associated with lower risk of biopsy-confirmed BBD. Girls with most rapid height growth were at increased risk (OR=2.12, p=.09) relative to those with slowest growth. Age at menarche was not associated (OR=1.11/yr, p=0.32), nor was adult BMI (adjusted for childhood BMI: OR=1.01/(kg/m^2), p=.98); larger BMI increases (childhood to adulthood) were not protective (OR=+1.04/(kg/m^2), p=0.37). Among girls with maternal breast cancer, those with more rapid growth had higher risk (OR=1.47/(cm/yr), p=.02). All estimates are age-adjusted.

CONCLUSION—Increased BBD risk (likely translating into elevated breast cancer risk) was observed in thinner girls, girls with most rapid growth, and taller women. Contrary to expectations, later menarche age was not protective against BBD, consistent with studies finding BBD cases are not protected against breast cancer by later menarche.

Keywords

adolescents; pre-teens; age at menarche; height; weight; BMI; height growth spurt; peak growth velocity; BBD; breast cancer

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Multiple lines of evidence point to the period in life prior to a woman's first pregnancy, when mammary gland cells are undergoing rapid proliferation, as a critical time for carcinogenic exposures that may increase her lifetime risk of breast cancer.[1] Human studies indicated that childhood and adolescent exposures can be more critical than exposures from adulthood in the development of breast cancer.[2–4] Several suggested that more rapid childhood height growth may be a factor in the development of cancer, and especially breast cancer in women.[5–7] In particular, our own work has linked more rapid peak height growth, earlier menarche, being thinner at ages 5 and 10 years, and being taller in adulthood to elevated risk for breast cancer.[5]

Benign breast disease (BBD) is well established as a risk factor for breast cancer.[8] The investigation of adolescent exposures and BBD may provide insight into the etiology of breast cancer and possible avenues for prevention. We recently reported a strong association between adolescent consumption of alcoholic beverages and risk of BBD in young women.[9] Alcohol consumption by adult women is one of few preventable factors known to increase breast cancer risk.[10]

Using data from a prospective cohort of children initiated when they were 9–15 years old, with follow-up data available to age 27, we investigated whether several growth, pubertal and developmental factors that occur during older childhood and adolescence are associated with BBD in young women. We focus on factors that we previously showed, in retrospective analyses, to be associated with risk of breast cancer.[5]

MATERIALS AND METHODS

Study Population

Established in 1996, the Growing Up Today Study (GUTS) includes 9037 girls from all 50 states who are daughters of Nurses' Health Study II (NHSII) participants.[11] The study, approved by Institutional Review Boards at Harvard School of Public Health and Brigham and Women's Hospital, is described elsewhere.[12] Mothers provided informed consent, and their daughters assented by completing baseline questionnaires. The cohort returned follow-up questionnaires annually (by mail or Internet) from 1996 through 2001, followed by surveys in 2003, 2005 and 2007. The girls' response rate to one or more follow-ups after baseline was 97%. A total of 77% (n=6927) returned the 2005 and/or 2007 (through December 2008) surveys inquiring about BBD. A total of 6899 females provided information on BBD; excluded were 8 girls whose mothers reported their daughter had been diagnosed with childhood cancer.

Benign Breast Disease

The 2005 and 2007 surveys asked "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 6752 females who responded that they had never been diagnosed with BBD provide the non-cases for these analyses. Another 147 females reported that they had been given a diagnosis of BBD, though not all were confirmed by biopsy. Among these cases are 67 females who reported that their BBD diagnoses were confirmed by breast biopsy; these include 27 with biopsy-confirmed BBD reported in both 2005 and 2007, another 29 with confirmed BBD only in 2007 (some returned no 2005 survey), and 11 with confirmed BBD reported in 2005 (but no 2007 survey). These 67 cases and 6752 non-cases provided the data for analyses of biopsy-confirmed BBD, but some analyses also used all 147 reported cases of BBD.

Questionnaires did not ask for date of diagnosis. Most BBD cases were likely diagnosed because participants (or their physicians) found a clinically palpable mass, since they were

too young to be undergoing routine screening mammography. Details from a validation study, regarding self-reports by women of biopsy-confirmed BBD, were reported previously.[13]

Risk Factors from Older Childhood and Adolescence

Age at Menarche—Our surveys annually asked the girls "Have you started having menstrual periods?" and "If yes, age when periods began".

Height and Weight—Children reported their heights and weights on each survey. Our questionnaire provided specific measuring instructions but suggested that they seek assistance; their mothers biennially self-report their own weights for NHSII.[11] An analysis of NHANES III adolescents indicated high validity for self-reported height (correlation r=0.82) and weight (r=0.90).[14] We assessed relative weight status by computing body mass index (BMI= weight/height^2, (kg/m^2)). The validity of self-reported BMI was demonstrated by National Longitudinal Study of Adolescent Health analyses that found high correlation (r=0.92) between BMI computed from measured values and from self-reports by youth in grades 7–12.[15]

Baseline BMI was obtained in 1996 from measurements at ages 9 to 15yrs. To represent body fatness at age 10, that we used in a prior study of breast cancer in another cohort,[5] we utilized the CDC BMI charts.[16] From each girl's baseline BMI, we subtracted the CDC age-specific (to the month) 50%ile BMI to obtain a BMI deviation; we then added to her deviation the median BMI of the 10-year old girls in our cohort. Adult height and adult BMI were assessed from the 2005 and 2007 surveys, when participants were between ages 18 and 27; adult BMI was of interest due to concerns that overweight and obesity may reduce the likelihood of a BBD diagnosis because of greater difficulty detecting a mass in a fatter breast.

Peak Height Growth Velocity (PHV)—From the serial heights on a girl, we computed a series of annualized height growth increments, $HT_t - HT_{t-1}$ divided by the time interval (in years, to the month) between adjacent survey return dates. Whenever an annual survey or height was missing, and when surveys were biennial (2001, 2003, 2005), we computed annualized height growth from surveys two years apart. Girls who, at baseline, had already begun their menstrual periods (34%) were past peak growth, so we cannot estimate peak velocity from their heights; they are omitted from analyses of peak growth velocity. For each girl who was pre-menarchal at baseline, we inspected her annualized growth increments and designated the largest her peak height growth velocity (PHV; cm/yr). These were used in an earlier investigation of dairy food consumption and height growth.[17] In the current analysis of 6899 females with BBD information, 4519 were pre-menarchal at baseline, and 3926 of them provided an estimated PHV.

Other Variables—At baseline, participants reported their race/ethnic group by marking all (of six) options that applied. We computed ages (to month) from dates of questionnaire return and birth. On several surveys (1999, 2003, 2005) the females reported whether they had ever been pregnant. Cumulative alcohol intake was derived from alcohol reported on the 2000, 2001 and 2003 surveys.[9] Participants' mothers provided information regarding their own diagnoses of breast cancer and biopsy-confirmed BBD.

Statistical Analyses

We compared, using baseline/1996 data, females who are in these analyses (returned 2005 and/or 2007 surveys) with those not included. Because we did not have information regarding when cases were diagnosed, the outcome for our analyses was prevalent BBD.

Logistic regression models, estimated using SAS,[18] provided odds ratios (OR) and 95% confidence intervals (CI) for each risk factor. Because age was related to each female's chance of being diagnosed with BBD during follow-up, we adjusted all models for exact age (to the month) at baseline. [Baseline age was more important than adult age (when BBD surveys returned) and follow-up time since baseline, both of which were non-significant (p=0.63 and p=0.55) when included in models with baseline age.] Univariate (age-adjusted) models tested hypotheses that childhood body fatness, age at menarche, adult height, adult BMI, and PHV are associated with BBD risk. We estimated multivariate models as well, in which these factors appear together along with additional adjustment factors. Because adolescent alcohol consumption significantly increased BBD risk in this cohort, multivariate models include it.[9] Because there is a transient increase in risk of breast cancer following pregnancy,[19] we also adjust for pregnancy history. Multivariate models further include maternal history of BBD and breast cancer; among women with biopsy-confirmed BBD, a positive family history increased breast cancer risk by 50%.[20]

Age-adjusted and multivariate models use continuous versions of hypothesized risk factors. These factors are analyzed in other models as categorical variables, in which the categories are (when possible) from our earlier paper on these factors and breast cancer.[5] For adult height and PHV, the categories are identical to those used earlier. For age at menarche, the categories are identical except that ages 15yr+ are pooled with the 14yr group. For BMI variables, we use quintiles.

We also investigate risk factors separately among females with, and without, a maternal history of BBD and/or breast cancer.

RESULTS

BBD responses were obtained from 6899 females, who provided 67 biopsy-confirmed BBD cases and 6752 non-cases for these analyses. Most GUTS females are white/non-Hispanic (95%), as are most BBD cases. One case reported "other" race, one case reported being both white and American Indian or Alaskan native, and another did not complete the race question.

Baseline (1996) data of females who returned the 2005 and/or 2007 surveys (77% of the original cohort) are compared with those who returned neither survey and thus had no BBD information to contribute to these analyses. At baseline, the included girls were slightly younger (6 weeks) than those not analyzed here, they reached menarche 6 weeks later, and their mean PHV was 0.57cm greater (all $p<0.05$). However, they were similar at baseline in BMI and height. Thus, we may be missing older participants who were diagnosed with BBD, or some girls with earlier menarche or slower peak growth. Our slightly reduced range of exposures on these variables may reduce our ability to detect associations.

Table 1 shows means of variables in our analyses, separately by BBD status. Biopsy-confirmed cases were, at baseline, about 7 months older and a half BMI (0.54 kg/m^2) slimmer. Cases' mean age at menarche was 2 months later, and as young women they were thinner and taller than non-cases. Cases and non-cases had similar mean peak height growth velocity (PHV). Multivariate analyses of these risk factors adjusted for alcohol, pregnancy history, and maternal history of disease (Table 1); cases drank more alcohol (age-adjusted OR=1.64/(daily drink), p=.01), more of them had been pregnant at least once (OR=1.14, p=.80), and more had a maternal history of BBD (OR=1.59, p=.096), or breast cancer (OR=1.94, p=.20).

Table 2 presents the mean and standard deviation for each risk factor, along with its distribution among the categories used in logistic models. The GUTS mean age at menarche

(12.85yr) is similar to an earlier cohort in which menarche was reported in real time (12.8yr).[21] And the GUTS mean PHV of 8.58 cm/yr (Table 2) is comparable to means from several earlier female cohorts, in which the PHVs were derived from heights measured by study personnel rather than self-reported by participants.[21–23]

Age-adjusted and multivariate models appear in Table 3. For each risk factor, we present models estimated using all 147 reported cases of BBD, followed by models estimated using the 67 biopsy-confirmed cases. Comments below refer to univariate (age-adjusted) models of biopsy-confirmed cases, unless stated otherwise.

The general trend for age at menarche was opposite what we expected, with all models hinting at either no association or greater risk of BBD for later age at menarche (Table 3). Taller women (OR=1.61 for ≥67 inches vs ≤62 inches) appear to have elevated BBD risk, and there was a marginally significant linear trend (OR=1.08/inch, p=.07; Table 3).

There was an inverse association between childhood BMI and BBD risk (OR=0.91 per kg/m^2, p<.04; Table 3). Girls in the top two quintiles of body fatness appeared to have substantially reduced risk relative to girls in the bottom 3 quintiles (OR=0.46, CI=.26–.81, p=.007). Adult BMI also appeared to be inversely associated with BBD risk, but the association was weaker (OR=0.95/(kg/m^2), p=.14) than for childhood BMI (Table 3).

Girls with most rapid peak height growth (PHV =≥8.9cm/yr) were at increased risk for biopsy-confirmed BBD (OR=2.12, p=.09) relative to those whose peak growth was slowest (Table 3). When all 147 reported BBD cases were analyzed, girls growing most rapidly had significantly increased risk (OR=1.88, p=.04; Table 3). [In a separate analysis on all girls, including those who were no longer growing at baseline, we used the same model that we used earlier[5] to obtain predicted PHVs (from age at menarche, childhood adiposity, and adult height) in a cohort that did not have childhood height data; GUTS girls with higher predicted PHVs had significantly greater risk of biopsy-confirmed BBD (middle 30% relative to bottom 40%, OR=1.86, p<0.05, and the top 30% compared to bottom 40%, OR=1.95, p=0.03).]

Conclusions from multivariate models are generally consistent with those from age-adjusted models (Table 3). The primary exception is, because childhood BMI is highly correlated with adult BMI (r=0.70), the multivariate-adjusted risk for adult BMI is null (OR=1.00/(kg/m^2), p=.98).

Even though childhood BMI appeared protective, larger increases in BMI from childhood to adulthood were not (OR=1.04/(kg/m^2), p=0.37; adjusted for baseline age and mean of baseline and adult BMIs). Because childhood BMI is inversely associated with physical activity,[12] we additionally adjusted this model for childhood physical activity (hours/day; derived from 1996 through 2001 surveys). Our BMI conclusions persisted: for childhood BMI, OR=0.92/(kg/m^2) (p<.05), and for increases in BMI from baseline to adulthood, OR=1.04/(kg/m^2) (p=.42).

Girls with later age at menarche tend to have lower peak height velocities (r=−0.12). We further fit a model including those 2 factors and baseline age; PHV was the stronger predictor of biopsy-confirmed BBD (OR =2.09 for fastest growing girls relative to slowest, p=0.09, whereas all p>0.16 for age at menarche (modelled continuously, or categorically). Analyzing all reported BBD cases, PHV remained the stronger predictor of BBD (OR=1.84, p<.05, for fastest growing girls, whereas all p>.64 for age at menarche variables).

We also estimated age-adjusted risks for continuous factors, separately for females with, and without, a maternal history of disease (BBD or breast cancer), but added caution is

warranted due to smaller samples in sub-analyses (Table 4). Among those without a maternal history of disease, being heavier as children and in early adulthood (18–27yr) was associated with reduced risk of BBD, while taller adult height increased risk. Age at menarche, though not significant, had opposite effects in maternal-history groups, with an apparent protective effect only among those with a maternal history (Table 4). Interestingly, among those with a maternal history of BBD or breast cancer, PHV was significantly associated with risk (OR=1.19/cm, p=.006). When we further studied females with maternal history of breast cancer, disregarding maternal BBD status, the magnitude of the PHV effect was stronger (OR=1.47, p=.02; not shown).

DISCUSSION

To our knowledge, this is the first prospective study of factors measured during childhood and adolescence, rather than recalled later in life, and risk of BBD in young women. This work is significant because studies in the past decade have suggested that adult height,[5,24–26] height growth during ages 8–14yr,[6] during ages 4–7 and 11–15yr,[7] and peak height growth velocity[5,6] are associated with increased risk of breast cancer, and benign breast disease is itself a risk factor for breast cancer. Whether the rapid growth itself or related factors, such as dietary intakes or hormones that promote growth, are cancer initiators/promoters is unknown. Prior longitudinal studies showed that high milk intakes were associated with more rapid growth in the fetus and child,[27–30] and in older GUTS girls, milk and dairy protein were positively associated with height growth, peak height velocity, and adult height.[17] The age period studied here, 9yr to 15yrs at baseline and followed up to twelve years, encompasses a critical period for exposures that may lead to the development of breast cancer and other adult diseases.

These analyses provide evidence that thinner children and taller young women are at increased risk of biopsy-confirmed BBD. Higher adult BMI was not significantly protective, indicating that detection bias is not responsible for these findings, and larger increases in BMI during adolescence were also not protective. Our findings regarding age at menarche were unexpected, for we did not observe that girls with later menarche had lower BBD risk. Girls with more intense height growth spurts (PHV) were at higher risk for BBD, particularly those with a maternal history (BBD, breast cancer).

There are few prior studies relating early factors to BBD; one study, in which childhood body size was recalled in adulthood, found that being heavier in childhood is inversely associated with risk of proliferative BBD.[31] Though we do not yet have BBD histologic subtype data and have included both non-proliferative and proliferative cases in these analyses, there is likely heterogeneity in the effects that we were unable to assess.

Our estimated associations between these risk factors and BBD are on the whole consistent with our earlier findings regarding these same factors and breast cancer in a different longitudinal study (NHS).[5] That cohort of women, when aged 30yrs and older, recalled their age at menarche and body fatness at ages 10yr and 20yr, and provided their adult heights. Similar to our BBD findings, being slimmer at10yr and taller in adulthood was associated with elevated risk of breast cancer, as was more rapid peak height growth. That work similarly found that increasing body fatness from childhood up to adulthood was not protective against breast cancer. The one discrepancy between these BBD and our earlier breast cancer[5] conclusions regarded age at menarche; in the NHS cohort, later age at menarche was significantly associated with lower risk of pre-menopausal and post-menopausal breast cancer. But more recent analyses of the NHS data have revealed that women with BBD are not protected against breast cancer by later menarche, though women without BBD are.[32] Moreover, younger women with biopsy-confirmed BBD are more likely

to have non-proliferative BBD,[33] and women with non-proliferative BBD are at higher risk of breast cancer with later age at menarche.[33] When viewed in light of these findings, our BBD results appear more consistent with the breast cancer literature. Others have concluded that the relationship between age at menarche and breast cancer requires further research.[24]

Our results on childhood BMI and adult height may be explained by mammographic density, which in young women (aged 15–30yrs) was inversely related to age and weight, and positively related to a woman's own height and her mother's mammographic density.[34] Another study found that postmenopausal levels of prolactin, which may increase risk of breast cancer, were lower among women who were heavier in childhood (ages 5 and 10yr), but there was no association with height.[35] Greater childhood adiposity, but not adult height, was also associated with lower IGF-I levels in premenopausal women.[36]

The longitudinal design of this investigation is a strength, for height, weight, and menarche data were collected many years prior to the collection of BBD data in this large cohort of females from all over the US. Our study findings should be more valid than associations obtained from childhood exposures that are recalled decades later, often after disease diagnosis as in case-control studies. Though we controlled for age in all models and included other potential confounders in multivariate models (adolescent drinking, pregnancy, and maternal disease history), some residual and unmeasured confounding may remain. We cannot exclude the possibility of incomplete adjustment of some covariates, or confounding through variables not considered, but little is known about childhood/adolescent risk factors for BBD. Although our cohort is not representative of US females, the comparison of risks within our cohort should still be valid and generalizable.[37] Because participants are daughters of nurses, this reduces confounding by socioeconomic and other unmeasured factors, while enhancing the accuracy of the information provided. But the racial/ethnic makeup of our cohort (95% white/non-Hispanic) hinders generalization to other races.

A major limitation was the necessity to collect data by self-report on (paper and web-based) questionnaires, but with our large, geographically dispersed cohort, alternatives were not feasible. We cited a validation study demonstrating that young women who reported BBD confirmed by biopsy were very reliable,[13] so most of our conclusions were based upon those disease reports, but further including those not confirmed by biopsy generally provided similar findings. Reporting errors in childhood height, weight, and menarche are likely non-differential with respect to BBD status later on, resulting in underestimates of true associations. Though not shown here, conclusions regarding childhood body fatness were similar when measured in different ways (BMI near menses-onset, BMI at age 14, pictograms on 1996 survey, waist circumferences on 2000 survey). And conclusions regarding adult height were similar when we analyzed height at 14 yrs, when most girls have stopped growing (not shown).

In summary, these data suggest that girls who were slimmer as children and girls who became taller women are at greater risk of BBD as young women, consistent with many earlier studies that found similar associations with breast cancer in women. But contrary to our expectations, later age at menarche was not generally protective against BBD, consistent with another study[33] finding that women with BBD are not protected against breast cancer by later menarche. After taking childhood BMI into account, higher adult BMI was not protective against BBD, nor were greater increases in BMI during adolescence. More rapid height growth spurts may increase the risk of BBD, as has been shown for breast cancer.[5–6] Future work will investigate whether the rapid growth itself, or certain foods or beverages that promote more rapid growth,[17] are responsible for the elevated risk.

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References

1. 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. [PubMed: 7549816]
2. Buell P. Changing incidence of breast cancer in Japanese-American women. J Natl Cancer Inst. 1973; 51:1479–83. [PubMed: 4762931]
3. Land CE, Tokunaga M, Koyama K, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. Radiat Res. 2003; 160:707–17. [PubMed: 14640793]
4. Ziegler RG, Hoover RN, Pike MC, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst. 1993; 85:1819–27. [PubMed: 8230262]
5. Berkey CS, Frazier AL, Gardner JD, Colditz GA. Adolescence and breast carcinoma risk. Cancer. 1999; 85:2400–9. [PubMed: 10357411]
6. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. NEJM. 2004; 351:1619–26. [PubMed: 15483280]
7. De Stavola BL, dos Santos Silva I, McCormack V, Hardy RJ, Kuh DJ, Wadsworth ME. Childhood growth and breast cancer. Am J Epidemiol. 2004; 159:671–682. [PubMed: 15033645]
8. Schnitt, SJ.; Connolly, JL. Pathology of benign breast disorders. In: Harris, JR.; Lippman, ME.; Morrow, M.; Osborne, CK., editors. Diseases of the Breast. 3. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 77-99.
9. Berkey CS, Willett WC, Frazier L, Rosner B, Tamimi R, Rockett H, Colditz G. Prospective study of adolescent alcohol consumption and risk of benign breast disease in young women. Pediatrics. 2010 May.
10. Boyle P, Boffetta P. Alcohol consumption and breast cancer risk. Breast Cancer Research. 2009; 11(Supp3):S3. Epub 2009 Dec 18. [PubMed: 20030878]
11. Colditz GA, Hankinson SE. The Nurses' Health Study: Lifestyle and health among women. Nat Rev Cancer. 2005; 5:388–96. [PubMed: 15864280]
12. Berkey CS, Rockett HRH, Gillman MW, Colditz GA. One-year changes in activity and in inactivity among 10- to 15-year old boys and girls. Relationship to change in BMI. Pediatrics. 2003; 111:836–843. [PubMed: 12671121]
13. Su X, Colditz GA, Willett WC, et al. Genetic variation and circulating levels of IGF-I and IGFBP-3 in relation to risk of proliferative benign breast disease. International Journal of Cancer. 2010; 126:180–90.
14. Strauss RS. Comparison of measured and self-reported weight and height in a cross-sectional sample of young adolescents. Int J Obes Relat Metab Disord. 1999; 23:904–908. [PubMed: 10490794]
15. Goodman E, Hinden BR, Khandelwal S. Accuracy of teen and parental reports of obesity and body mass index. Pediatrics. 2000; 106:52–58. [PubMed: 10878149]
16. Kuczmarksi, RJ.; Ogden, CL.; Grummer-Strawn, LM., et al. 2000 CDC growth charts: United States. National Center for Health Statistics/CDC; 2000. Web site http://www.cdc.gov/growthcharts [Accessed April 30, 2004]
17. Berkey CS, Colditz GA, Rockett H, Frazier AL, Willett WC. Dairy consumption and female height growth: prospective cohort study. Cancer Epidemiology, Biomarkers & Prevention. 2009 Jun. 18:1881–7.
18. SAS Institute Inc. Proc Logist. Cary, NC: SAS Institute Inc; 1997. SAS/STAT Software: Changes and Enhancements Through Release 6.12.

19. Rosner B, Colditz G, Willett W. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. Am J Epi. 1994; 139:819–35.
20. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. The influence of family history on breast cancer risk in women with biopsy-confirmed BBD. Cancer. 2006; 107:1240–7. [PubMed: 16902983]
21. Berkey CS, Gardner J, Frazier AL, Colditz GA. Childhood diet and body size related to menarche and adolescent growth in girls. Am J Epidemio. 2000; 152:446–52.
22. Berkey CS, Wang X, Dockery W, Ferris BG Jr. Adolescent height growth in a US population. Ann Hum Biol. 1994; 21:435–42. [PubMed: 7985992]
23. Bock, RD.; Thissen, D. Statistical problems of fitting individual growth curves. In: Johnston, FE.; Roche, AF.; Susanne, C., editors. Human Physical Growth & Maturation: Methodologies and Factors. London, UK: Plenun Press; 1980. p. 265-290.
24. Ruder E, Dorgan J, Kranz S, Kris-Etherton P, Hartman T. Examining breast cancer growth and lifestyle risk factors; early life, childhood, and adolescence. Clin Breast Cancer. 2008; 8:334–42. [PubMed: 18757260]
25. Baer HJ, Rich-Edwards JW, Colditz G, Hunter D, Willett W, Michels KB. Adult height, age at attained height, and incidence of breast cancer in premenopausal women. Int J Cancer. 2006; 119:2231–5. [PubMed: 16823843]
26. Okasha M, McCarron P, Gunnell D, Smith GS. Exposures in childhood, adolescence and early adulthood and breast cancer risk: a systematic review of the literature. Breast Cancer Res Treat. 2003; 78:223–76. [PubMed: 12725422]
27. Du X, Zhu K, Trube A, et al. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10–12 years in Beijing. Br J Nutr. 2004; 92:159–68. [PubMed: 15230999]
28. Okada T. Effect of cow milk consumption on longitudinal height gain in children. Am J Clin Nutr. 2004; 80:1088–9. [PubMed: 15447933]
29. Olsen SF, Halldorsson TI, Willett WC, et al. NUTRIX Consortium. Milk consumption during pregnancy is associated with increased infant size at birth: prospective cohort study. Am J Clin Nutr. 2007; 86:1104–10. [PubMed: 17921389]
30. Wiley AS. Does milk make children grow? Relationships between milk consumption and height in NHANES 1999–2002. Am J Hum Biol. 2005; 17:425–41. [PubMed: 15981182]
31. Baer HJ, Schnitt SJ, Connolly JL, et al. Early life factors and incidence of proliferative benign breast disease. Cancer Epidemiol Biomarkers Prev. 2005; 14:2889–97. [PubMed: 16365006]
32. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol. 2000; 152:950–964. [PubMed: 11092437]
33. Tamimi RM, Rosner B, Colditz GA. Evaluation of a breast cancer risk prediction model expanded to include category of prior benign breast disease lesion. Cancer. [in press].
34. Boyd N, Martin L, Chavez S, Gunasekara A, Salieh A, Meinichouk O, Yaffe M, Friedenreich C, Minkin S, Bronskill M. Breast-tissue composition and other risk factors for breast cancer in young women: a cross-sectional study. Lancet Oncol. 2009; 10:569–80. [PubMed: 19409844]
35. Su X, Hankinson S, Clevenger C, Eliassen A, Tworoger S. Energy balance, early life body size, and plasma prolactin levels in postmenopausal women. Cancer Causes Control. 2009; 20:253–62. [PubMed: 18853263]
36. Schernhammer ES, Tworoger SS, Eliassen AH, Mismer SA, Holly JM. Body shape throughout life and correlations with IGFs and GH. Endocr Relat Cancer. 2007; 14:721–32. [PubMed: 17914102]
37. Willett WC, Blot WJ, Colditz GA, Folsom AR, Henderson BE, Stampfer MJ. Merging and emerging cohorts: Not worth the wait. Nature. 2007; 445:257–258. [PubMed: 17230171]

Table 1

Prospectively collected measures of growth, and adjustment factors, in older girls and adolescents, by benign breast disease (BBD) case status (reported from 2005 through 2008): means or percents with standard errors (no age-adjustment)

	Never Reported BBD	Biopsy-confirmed BBD Case
Total N=	6752	67
Baseline Age (yr)[a]	12.0 (.02)	12.6 (.19)
Baseline BMI (kg/m^2)[a]	19.2 (.04)	18.7 (.34)
PHV (cm/yr)[b]	8.58 (.05)	8.54 (.47)
Age at Menarche (yr)	12.8 (.01)	13.0 (.13)
Adult age (yr)[c]	22.0 (.02)	22.7 (.20)
Adult BMI (kg/m^2)[c]	23.7 (.06)	22.9 (.42)
Adult Height (inches)[c]	65.4 (.03)	66.0 (.33)
BMI change from baseline to adult	4.52 (.04)	4.22 (.25)
Multivariate Model Adjustment Factors:		
Alcohol consumption (drinks/day)[d]	0.21 (.005)	0.39 (.07)
Pregnancy ever (through 2005)	4.59% (0.3)	5.97% (2.9)
Mother BBD	18.5% (0.5)	26.9% (5.4)
Mother breast cancer	3.18 (0.2)	5.97% (2.9)

[a] Baseline survey was in 1996

[b] Peak Height Growth Velocity (PHV) computed from observed height increments in girls who were still growing at baseline (n=3926).

[c] Adult measurements were means of values provided on 2005 and 2007 surveys (returned through 2008).

[d] Cumulative average of alcohol intakes from year 2000 to 2003.

Table 2

Distributions of prospectively ascertained risk factors from 6899 females, born 1981 to 1987 and followed from 1996 through 2008 for reported diagnoses of BBD

	Mean (sd)	**Categories, and proportion of study population within each group**				
Age (yrs) at menarche	12.85 (1.2)	<=**11**	**12**	**13**	>=**14**	
		0.228	0.329	0.282	0.161	
Adult height (in)	65.4 (2.7)	**<=62in**	**63**	**64–65**	**66**	**>=67in**
		0.158	0.112	0.261	0.143	0.327
Childhood BMI (kg/m^2)	18.17 (3.35)	**<=15.50**	**to 16.83**	**to 18.23**	**to 20.38**	**>20.38**
		0.198	0.198	0.202	0.201	0.201
Adult BMI (kg/m^2)	23.65 (4.6)	<=**20.37**	**to 21.79**	**to 23.39**	**to 26.13**	**>26.13**
		0.20	0.193	0.206	0.20	0.201
PHV (cm/yr)	8.58 (3.1)	**<=7.6**	**to 8.1**	**to 8.5**	**to 8.9**	**>8.9**
		0.333	0.15	0.089	0.035	0.394

Table 3

Age-adjusted and multivariate odds ratios (95% CI) for Benign Breast Disease in GUTS women followed from 1996 through 2008, when the oldest were 27 years of age

		Risk-Factor Categories					Continuous Beta	
AGE AT MENARCHE		**<=11**	**12**	**13**	**>=14**		**β (95%CI)**	**(P-value)**
N cases (all reported BBD)		23	52	43	28			
Age-adj [a]	**OR**	1.0 (ref)	1.57+ (.96–2.58)	1.53 (.92–2.55)	1.73+ (.99–3.01)		1.08/yr (.94–1.24)	(.27)
Multiv-adj [b]	**OR**	1.0 (ref)	1.48 (.90–2.45)	1.36 (.80–2.31)	1.46 (.81–2.65)		1.00/yr (.86–1.16)	(.97)
N cases (Biopsy-confirmed)		7	27	19	14			
Age-adj [a]	**OR**	1.0 (ref)	2.68* (1.16–6.18)	2.22+ (.93–5.29)	2.83* (1.14–7.03)		1.11/yr (.91–1.35)	(0.32)
Multiv-adj [b]	**OR**	1.0 (ref)	2.42* (1.04–5.63)	1.87 (.77–4.56)	2.20 (.84–5.74		1.00/yr (.80–1.24)	(0.96)
ADULT HEIGHT (in)		**<=62in**	**63**	**64–65**	**66**	**>=67in**	**Continuous β**	**P-value**
N cases (all reported)		20	15	34	19	59		
Age-adj [a]	**OR**	1.0 (ref)	1.04 (.53–2.04)	1.01 (.58–1.77)	1.02 (.54–1.91)	1.39 (.83–2.32)	1.06/inch (1.0–1.12)	(.06)
Multiv-adj [b]	**OR**	1.0 (ref)	1.05 (.53–2.06)	0.97 (.56–1.71)	0.94 (.50–1.79)	1.29 (.77–2.17)	1.05/inch (.99–1.12)	(<.10)
N cases (Biopsy-confirmed)		9	8	12	7	31		
Age-adj [a]	**OR**	1.0 (ref)	1.22 (.47–3.19)	0.79 (.33–1.89)	0.82 (.31–2.23)	1.61 (.76–3.40)	1.08/inch (.99–1.18)	(.07)
Multiv-adj [b]	**OR**	1.0 (ref)	1.19 (.46–3.12)	0.74 (.31–1.77)	0.77 (.28–2.09)	1.48 (.69–3.16)	1.08/inch (.99–1.18)	(.09)
CHILDHOOD BMI (kg/m^2)		**<15.50**	**to 16.83**	**to 18.23**	**to 20.38**	**>20.38**	**Continuous β**	**P-value**
N cases (all reports)		33	32	35	23	24		
Age-adj [a]	**OR**	1.0 (ref)	0.97 (.60–1.59)	1.01 (.63–1.64)	0.67 (.39–1.15)	0.70 (.41–1.19	0.94/(kg/m^2) (.89–.99)	(.02)
Multiv-adj [b]	**OR**	1.0 (ref)	1.14 (.68–1.91)	1.24 (.72–2.15)	0.84 (.44–1.59)	0.92 (.45–1.85)	0.96/(kg/m^2) (.89–1.04)	(0.35)
N cases (biopsy-conf)		14	18	19	7	9		
Age-adj [a]	**OR**	1.0 (ref)	1.29 (.64–2.61)	1.29 (.64–2.58)	0.48 (.19–1.19)	0.62 (.27–1.43)	0.91/(kg/m^2) (.84–.99)	(.039)
Multiv-adj [b]	**OR**	1.0 (ref)	1.32 (.63–2.75)	1.30 (.60–2.85)	0.47 (.17–1.32)	0.58 (.20–1.69)	0.91/(kg/m^2) (.81–1.03)	(0.14)
ADULT BMI (kg/m^2)		**<20.37**	**to 21.79**	**to 23.39**	**to 26.13**	**>26.13**	**Continuous β**	**P-value**
N cases (all reports)		38	25	31	27	26		
Age-adj [a]	**OR**	1.0 (ref)	0.64+ (.39–1.07)	0.74 (.46–1.20)	0.67 (.41–1.11)	0.63+ (.38–1.04)	0.96/(kg/m^2) (.92–.99)	(.04)
Multiv-adj [b]	**OR**	1.0 (ref)	0.66 (.39–1.12)	0.79 (.46–1.34)	0.77 (.43–1.38)	0.79 (.41–1.52)	0.98/(kg/m^2) (.93–1.04)	(.49)

				Risk-Factor Categories			Continuous Beta	
N cases (biopsy-conf)		13	16	14	12	12		
Age-adj [a]	**OR**	1.0 (ref)	1.19 (.57–2.50)	0.96 (.45–2.06)	0.87 (.39–1.91)	0.84 (.38–1.85)	0.95/(kg/m^2) (.90–1.02)	(.14)
Multiv-adj [b]	**OR**	1.0 (ref)	1.22 (.57–2.63)	1.14 (.51–2.58)	1.23 (.51–2.96)	1.56 (.58–4.15)	1.00/(kg/m^2) (.92–1.09)	(.98)
PHV (cm/yr)		**<=7.6**	**to 8.1**	**to 8.5**	**to 8.9**	**>8.9**	**Continuous β**	**P-value**
N cases (all reports)		21	10	9	1	33		
Age-adj [a]	**OR**	1.0 (ref)	1.26 (.59–2.72)	2.04$^+$ (.91–4.55)	0.61 (.08–4.61)	1.88* (1.04–3.41)	1.054/(cm/yr) (.98–1.14)	(.17)
Multiv-adj[c]	**OR**	1.0 (ref)	1.26 (.59–2.73)	2.01$^+$ (.90–4.49)	0.58 (.08–4.40)	1.89* (1.04–3.42)	1.057/(cm/yr) (.98–1.14)	(.16)
N cases (biopsy-conf)		10	5	2	1	16		
Age-adj [a]	**OR**	1.0 (ref)	1.40 (.47–4.17)	1.02 (.22–4.73)	1.40 (.17–11.27)	2.12$^+$ (.90–5.00)	1.05/(cm/yr) (.94–1.18)	(.37)
Multiv-adj[c]	**OR**	1.0 (ref)	1.39 (.47–4.15)	1.00 (.22–4.68)	1.34 (.17–10.84)	2.10$^+$ (.89–4.96)	1.054/(cm/yr) (.94–1.18)	(.36)

$^+$P<0.10

*P<0.05

[a] Adjusted for baseline age (to the month).

[b] Multivariate model included baseline age, menarche age, adult height, childhood BMI, adult BMI, adolescent alcohol consumption, pregnancy (never, ever), and maternal history of BBD and breast cancer.

[c] Multivariate model included baseline age, peak height growth velocity (PHV), adolescent alcohol consumption, pregnancy (never, ever), and maternal history of BBD and breast cancer.

Table 4

Age-adjusted odds ratios stratified by maternal history of BBD or breast cancer. Results reported (above) from analyses including all reported BBD cases (n=147 cases), whether confirmed by biopsy or not, and from analyses (below) on Biopsy-Confirmed BBD cases (n=67 cases)

	No Maternal History			**Maternal History**		
N Cases (All reported BBD)		98			49	
RISK FACTOR	**OR**	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Age at menarche	1.17	(.99–1.38)	(.055)	0.88	(.69–1.12)	(.30)
Adult height	1.09	(1.01–1.17)	(.03)	1.01	(.91–1.12)	(.86)
Childhood BMI	0.93	(.87–.99)	(.04)	0.96	(.87–1.05)	(.36)
Adult BMI	0.95	(.90–.99)	(.04)	0.98	(.91–1.05)	(.53)
Peak Height Velocity	0.99	(.91–1.10)	(.99)	1.194	(1.05–1.36)	(.006)
N Cases (Biopsy-Confirmed BBD)		47			20	
RISK FACTOR	**OR**	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Age at menarche	1.16	(.92–1.47)	(.20)	0.95	(.66–1.38)	(.79)
Adult height	1.10	(.99–1.22)	(.07)	1.04	(.89–1.22)	(.61)
Childhood BMI	0.88	(.79–.98)	(.02)	0.99	(.86–1.14)	(.87)
Adult BMI	0.92	(.85–1.00)	(.053)	1.01	(.93–1.11)	(.77)
Peak Height Velocity	1.01	(.89–1.16)	(.85)	1.185	(.97–1.45)	(.096)