Childhood body size and pubertal timing in relation to adult mammographic density phenotype

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Abstract

Background

An earlier age at onset of breast development and longer time between pubertal stages has been implicated in breast cancer risk. It is not clear whether risk associations with puberty, or with predictors of onset of puberty such as weight and height, are mediated via mammographic density, an important risk factor for breast cancer.

Methods

We investigated whether childhood body size and pubertal timing and tempo, collected by questionnaire, are associated with percentage and absolute area mammographic density at ages 47-73 years in 1,105 women recruited to a prospective study.

Results

After controlling for adult adiposity, weight at ages 7 and 11 was strongly significantly inversely associated with percentage and absolute dense area (p trend<0.001 for all), and positively associated with absolute nondense area. Greater height at age 7, but not age 11, was associated with lower percentage density (p trend=0.016). Later age at menarche and age at establishing regular periods was associated with increased density, but additional adjustment for childhood weight attenuated these associations. A longer interval between thelarche and menarche, and between thelarche and regular periods, was associated with increased dense area, even after adjusting for childhood weight (p trend=0.013 and 0.028, respectively), and was independent from age at pubertal onset.

Conclusions

Greater prepubertal weight and earlier pubertal onset are associated with lower adult breast density, but pubertal timing does not appear to have an independent effect on adult density after controlling for childhood adiposity. A possible effect of pubertal tempo on density needs further investigation.

Key words: body weight; body height; breast neoplasms; cross-sectional study; mammographic density; puberty; adolescent

Background

Breast cancer is the most common type of cancer in females, and incidence has been increasing [1]. The distribution of risk factors for breast cancer have changed over time, such as increasing obesity [2] and height [3] and declining age at onset of puberty [4]. Mammographic density is one of the strongest risk factors for breast cancer [5], with 4-5 fold increases in risk in those with at least 75 percent density. Density reflects variations in the tissue composition of the breast, with dense area representing collagen and epithelial cells and nondense area representing adipose tissue. The amount of dense tissue is thought to be the aetiologically relevant parameter related to breast cancer risk, although percentage density (amount of dense area over total breast area expressed as a percentage) has been found to be a stronger risk predictor than absolute dense area, and whether there is an independent protective role of non-dense tissue is still unclear [6].

While earlier menarche is an established risk factor for breast cancer, we recently reported that other pubertal stages also contribute to risk based on data from a large prospective cohort study. Earlier breast development (thelarche), and a longer interval between thelarche and menarche were independently associated with a 20-30 percent increase in breast cancer risk. Risk was also increased in women with an earlier age at which menses became regular and attained height was reached [7].

Whether pubertal associations with breast cancer risk are mediated via mammographic density is unclear. Breast tissue composition has been hypothesised to be determined by genetic factors and growth and development in early life [8]. During pubertal development breast tissue undergoes substantial cellular proliferation and is subject to hormonal surges and it is possible that the age and the speed at which such growth occurs affects breast density and cancer risk. Previous studies of the association between puberty and adult breast density have mostly investigated menarche [9-16], and one study previously reported on linear growth and Wolfe's grade density [14]. To our knowledge, no previous studies have addressed associations of pubertal stages other than menarche, and time intervals between pubertal stages, with quantitative measures of adult density.

Childhood height and adiposity are established predictors of pubertal onset (Collaborative Group on Hormonal Factors in Breast Cancer [17]), and childhood height has been associated with greater density in some studies [13, 18]. Childhood adiposity, on the contrary, has been reported to be inversely associated with mammographic density, although not in consistently so, with a recent review concluding that additional research is needed to clarify this complex association [19]. Besides investigating pubertal and adiposity associations in their own right, it is of interest to investigate these together so as to evaluate whether potential associations of density with pubertal stages are independent from the effect of adiposity.

We analysed the association of childhood weight and height, and pubertal stages and timing with adult mammographic density phenotype in a sample of women who participated in a large UK-based prospective cohort study focussed on breast cancer aetiology.

Methods

Participants

Study subjects were identified from the Generations Study, a United Kingdom-based cohort study with over 113,000 participants designed to investigate breast cancer aetiology [20]. Volunteers completed a postal questionnaire about established and putative breast cancer risk factors and, if willing, donated a blood sample. Participants are contacted approximately every three years to collect follow-up information on breast cancer diagnoses and updated risk factor information. The study was approved by the South Thames Multicentre Research Ethics Committee.

The study subjects in the current analysis are the control subjects included in a nested case-control study of breast cancer occurring within the cohort. One or more controls per case were randomly selected from subjects who had been breast cancer-free for at least as long as the matched case, within strata of categories of year and age at study entry, ethnicity and the number of days between blood draw and receipt of the blood sample in the laboratory. For women who reported in their questionnaire that they had had a mammogram on their questionnaire, mammograms were requested from breast cancer screening centres in the UK matching the self-reported location of screening. These centres invite, under the National Breast Cancer Screening Programme, women for routine 3-yearly screening from ages 50 to 70 years, recently extended to 47-73 years.

The film mammograms from the screening visits were digitised with a VIDAR Diagnostic Pro Plus scanner, which covers an optical density range of 0-3.85. With the roll-out of digital mammography in the UK, we increasingly also received digital images in electronic format, but these are excluded from this analyses due to small numbers. The mammograms from the screening visit closest (before or after) to the date of entry to the cohort study at screening ages 47-73 years were selected for this analysis. Percentage mammographic density (%) and absolute dense and non-dense area (in cm^2) was determined using Cumulus software [21]. Images were assessed by one observer, blinded to case-control status, who was trained by an experienced breast radiologist (S. Allen). The two mediolateral oblique (MLO) views per subject were selected for reading. The images were randomly allocated to batches that included repeats, based on which the intraclass correlation coefficient for percent density was

0.93. Analyses were based on the average of the density readings of the views for the left and right breast.

The baseline questionnaire included information on weight and height relative to peers at age 7 and 11 years, in five categories (e.g. for weight: much thinner, a little thinner, about the same, a little heavier, much heavier, don't remember). It also included information on age at first breast development, menarche, regular cycles and at reaching attained height, based on which the time interval between stages were computed, and on other breast cancer risk factors including adult height and weight which were used to compute a participant's body mass index (BMI). Information on follow-up questionnaires was used to update exposures, where applicable, for women whose mammography was conducted after them completing the baseline questionnaire.

Statistical analysis

We analysed mammographic density parameters in relation to pubertal factors and childhood body size with a linear regression model using density parameters which were square-root transformed to ensure normality of residuals. We derived absolute differences in density parameters between categories of explanatory factors so that effect estimates could be presented as percentage point differences for percent density and in cm^3 for dense and nondense area. This was done by backtransforming the coefficients relative to a predetermined reference level of 25 percent density, 30 cm^2 dense area and 110 cm^2 nondense area, respectively, so that the effect estimates could be directly compared between variables because the absolute difference would otherwise depend on the average of the density parameter in the reference group. The statistical package Stata 14.0 was used throughout [22]. All reported p-values are 2-sided.

Analyses were adjusted for age at mammogram and other mammographic density risk factors possibly associated with childhood body size or pubertal onset: age at first birth and parity, duration of oral contraceptive use, alcohol consumption and physical activity level, menopausal status and, for postmenopausal women, time since menopause and postmenopausal oestrogen and progestogen hormone therapy use. In the literature, analyses of percentage density with respect to breast cancer risk are conventionally adjusted for BMI, as the same percentage density for a woman with high BMI does not represent the same amount of dense tissue (thought to be the aetiological parameter with respect to breast cancer risk) than in a woman with low BMI. For our analyses, however, of determinants of density, given the correlation of BMI with childhood weight, adjustment for BMI potentially results in overadjustment of the association between childhood body size, puberty and density. We therefore conducted the analyses with and without adjusting for BMI, as recommended elsewhere [19]. We also repeated the puberty analyses with additional adjustment for childhood body size to investigate whether puberty-associations are independent from childhood body size. Alcohol consumption, BMI, and physical activity level were assessed at baseline questionnaire and all other factors were evaluated as closely as possible to the time of the mammogram, using data from calendar years and ages provided in the baseline and follow-up questionnaires.

Results

Mammograms were retrieved for 81.6 percent of subjects who were within screening ages 47-73 years at the time of baseline questionnaire, with the main reasons for non-retrieval being that films were no longer held at the screening centre or lack of detail on the questionnaire to locate the screening centre. A total of 1,105 subjects were included in the analysis: their mean age at mammography was 58.9 years, and 80.1% were postmenopausal at the time of the mammogram (Table 1). Median interval between baseline questionnaire and mammography was 1.0 year. Arithmetic mean values were 22.9 percent for mammographic density, 28.7 cm^2 for absolute dense area and 112.9 cm^2 for nondense area. Numbers of subjects per category of body size and pubertal factor are provided in table S1.

Women who had been heavier than their peers at age 11 reported an earlier onset of pubertal stages, consistent with an earlier report from the entire cohort of the Generations Study [23]. Heavier girls also reported longer intervals between thelarche or menarche and attained adult height, higher BMI at study entry, higher nondense mammographic area and lower percentage and absolute mammographic dense area than those who were lighter (Table S2). Taller girls had an earlier onset of pubertal stages but there was no difference in interval between stages compared with girls who were of similar or shorter height. Those who were tall at age 11 were taller in adulthood and had larger nondense and total mammographic breast area (Table S3). There was a modestly strong correlation between age at thelarche and menarche (r=0.74), but low correlation between other stages (Table S4).

Weight at age 7 and 11 was significantly inversely associated with percentage density and absolute dense area and significantly positively associated with nondense area (Table 2). These associations were attenuated but remained statistically significant after adjusting for adult BMI. A relative increase in weight compared with peers between age 7 and 11 was similarly associated with density parameters but estimates were no longer statistically significant after taking adult BMI into account.

There was a tendency for taller girls to have lower percentage density and increased nondense area compared to those who were shorter, even after adjusting for adult adiposity (Table 3), although the association with percentage density was only significant for height at age 7, not 11, years. There was no association with absolute dense area (Table 3) or with change in relative height between age 7 and 11 (Table S5).

In analyses of pubertal variables, age at thelarche was significantly positively associated with percentage density, but not with absolute dense area, in the basic model, but there was no association after taking into account adult adiposity (Table 4). However, there was an inverse association with nondense area which remained statistically significant in models accounting for adiposity in adulthood and childhood. A later age at menarche and age at which regular cycles were established was associated with increased percentage and absolute dense area in models with and without adult BMI, which were no longer significant after taking into account childhood adiposity. There was no association with the age at which participants reported to have reached their adult height (Table S5).

There was evidence for a longer time interval between thelarche and menarche and between thelarche to regular periods being associated with increased mammographic dense area, even after adjusting for childhood adiposity (Table 5). There was a similar tendency for percentage density but these differences were not statistically significant. The association with the thelarche to menarche interval remained statistically significant after controlling for age at thelarche (p trend=0.020), menarche (p trend=0.037), or total breast area (p trend=0.023) in a model accounting for adult and childhood adiposity. Likewise, the association with the thelarche to regular periods interval remained significant after controlling for age at thelarche (p trend=0.035) or became borderline significant after controlling for age at regular cycles (p trend=0.060), or total breast area (p trend=0.048) (not shown). Density was not associated with interval between age at menarche and regular cycles (Table S7) or thelarche and the age at which participant reached adult height, or menarche and adult height after accounting for BMI (Table S8).

Discussion

This is, to our knowledge, the first study to investigate pubertal stages other than age at menarche with respect to quantitatively assessed adult breast density. We found evidence for later onset of pubertal stages, in particular age at menarche and age at regular cycles, being associated with increased density. This study also showed that girls who were heavier than their peers in childhood had significantly lower mammographic density in adulthood, even after adjusting for adult adiposity, with which childhood adiposity is correlated. As expected, increased childhood weight predicted earlier pubertal onset, and we found that the positive association of delayed puberty with density appeared to be driven by childhood weight. We observed, however, a tendency for increased mammographic dense area in women with longer intervals between thelarche and menarche, and thelarche and regular cycles, which was independent of an effect of age at onset and it is of interest that a prolonged pubertal tempo has also been implicated in breast cancer risk in a previous publication of our study [7].

An inverse association of childhood weight with adult mammographic density is supported by most, but not all, previous studies [19]. A review suggested that evidence for such an association is stronger for postmenopausal than premenopausal women [19]; our study included too few premenopausal women to analyse by menopausal status. While these studies investigated adult density later in life, the inverse association of body size with density has also been demonstrated with a measure of density at young ages, using MRI [24, 25]. The biological mechanism through which increased adiposity is associated with mammographic density is possibly through lower IGF-I levels in heavier girls [26, 27], or a protective function of adipocytes [19]. There is increasing evidence that heavier body weight in childhood and adolescence is also inversely associated with subsequent breast cancer risk [28] and it seems likely that this may in part be through an effect of adiposity on breast density.

Our study suggested an inverse association of percentage density with height at age 7, and no association with height at age 11, contradicting the two previous studies of similar design, which noted a higher percentage density in those who reported to have been taller than their peers in childhood [13, 18]. Our findings are more compatible with those of a large study showing an inverse association between having mixed/dense breasts in adulthood and measured height at pre- and peripubertal ages [29]. Height at both ages was positively associated with nondense area in our study, even after adjusting for adult adiposity. This finding could reflect that taller girls had larger overall breast size (nondense area being the largest component), or possibly residual confounding by BMI as nondense area and BMI are strongly correlated. In contrast to our lack of association with age at reaching adult height or having had a relative growth spurt, a previous study reported an increase in Wolfe grade density with greater height velocity at ages 11-15 years and 15 to adulthood, based on measured height [14]. Studies investigating associations of adult height with density have not consistently shown associations, with some reporting positive [18, 30] or weak or no associations [31-33] with percentage density. Whether childhood or adult height is a determinant of breast density is therefore still not entirely clear.

Breast density has been hypothesised to represent the cumulative exposure of tissue to hormones and growth factors that stimulate cell division and it has been proposed that tissue composition reflects such exposures at young ages during the greatest susceptibility of the breast according to the Pike Model [8, 34]. The development of the human breast is a process that is initiated in utero, but the main growth spurt occurs with the formation of lobules during puberty (i.e. at thelarche). Increased estradiol production is thought to be largely responsible for breast development in pubescent girls, and increases in oestradiol levels have been demonstrated around onset of breast development [35]. The pubertal stage of peak growth, when linear height increase is accelerated, is accompanied by high levels of growth hormones, sex hormones and insulin-like growth factor-I [36, 37]. Around menarche the rate at which breast ducts grow and proliferate increases [38]. An earlier age at which regular menses are established is thought to be associated with higher cumulative exposure to ovarian hormones as women with irregular cycles spend relatively less time in the luteal phase of the menstrual cycle when hormone levels are highest [39].

Body adiposity is a strong predictor of pubertal onset, possibly mediated by leptin. Age at thelarche normally indicates gonadotropin-driven ovarian estrogen production, but it has been postulated that in obese girls breast development is a consequence of aromatisation from adrenal androgen precursors to estrogens in adipose tissue, which might explain that early onset of breast development appears to be compensated by slower progression to menarche [40]. Increased levels of total and free testosterone, lower levels of SHBG and higher levels of fasting insulin have been reported in peripubertally obese girls [41] and lower estradiol levels in heavier girls compared with lighter girls around time of thelarche [35]. Few studies have investigated the role of peripubertal hormone levels on determination of adult mammographic density. One study showed that higher premenarcheal SHBG or DHEAS levels were associated with increased mammographic dense area, with no association for other hormones including oestradiol [42], whereas in another study tall girls treated with high-dose estrogen to accelerate puberty were reported to have lower mammographic dense area in adulthood [43].

We found that women with later onset of pubertal stages had higher mammographic density than those with early onset after controlling for adult adiposity. Our finding is broadly in line with previous studies that have shown significant positive associations [10, 14-16] of density with menarche after controlling for adiposity, although some studies reported no association [9, 11-13]. Positive associations with pubertal onset appear to be largely a consequence of increased childhood body weight being a strong predictor of earlier pubertal onset, however, because we did not observe significant associations independent from relative childhood weight. We found that an early age at thelarche was associated with lower adult density and that this finding was in part explained by adult adiposity. This is supported by a study reporting, using the qualitative measure of Wolfe's grade, less dense breasts in girls who showed signs of breast development at age 11 [14] and another, of density in young girls measured by dual-energy absorptiometry, that showed that the major determinants of breast density during puberty were body fat, achieved menarche and Tanner breast stage [44].

Our analyses suggest that previously reported associations of breast cancer risk with earlier thelarche, menarche, regular periods and age reached adult height [7], are unlikely to be mediated by mammographic density. In fact, the associations we observed were in the opposite direction to that for breast cancer (i.e. a later pubertal onset was positively associated with density but is thought to be inversely associated with breast cancer risk). These findings imply that in analyses of age at menarche on breast cancer risk, controlling for density would strengthen associations. A prolonged interval between breast development and onset of menarche or regular periods appeared to increase dense breast area in our study, which could possibly be due to prolonged exposure of breast tissue to hormones and growth factors, but could also be due to chance or residual confounding, and would therefore need to be investigated in further studies.

Our study has the strength that subjects were selected from a prospective study with comprehensive information on breast cancer risk factors. A limitation is that the pubertal and weight variables that we collected were self-reported. Also, BMI was assessed at baseline and was not available at the exact time of mammography, and we were unable to collect exact weights in childhood and our proxy variables of weight in childhood relative to peers and the variable for growth spurt are therefore relatively crude measures. The reporting accuracy of age at menarche and body size in childhood is thought to be reasonably good [45], but recall of the onset of breast growth, regular menses and age at attained height is likely to be less accurate. It is unlikely that quality of recall is related to mammographic density measurement, however, and these variables previously showed significant associations with breast cancer risk in our prospective study, suggesting they are sufficiently discriminatory. We did not have information on peak growth but analysed age at attained adult height as a proxy, with which it is correlated [46, 47].

Conclusions

Adult mammographic density was inversely associated with weight compared to peers at ages 7 and 11 years, and was not independently associated with age at onset of pubertal stages. The role of a prolonged duration between breast development and onset of first or regular menses on breast density needs investigation in future studies.

Declarations

Abbreviations

BMI: body mass index; UK=United Kingdom

Ethical approval and consent to participate

The study was approved by the South Thames Multicentre Research Ethics Committee and participants provided informed consent.

Consent for publication

Not applicable

Availability of supporting data

No supporting data available. Access to data is subject to the Generations Study's data access policy.

Competing interests

The authors declare they have no conflict of interest.

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Authors' contributions

AJS and AA designed and obtained funding for the Generations Study and AJS and MD for the mammographic density study. AJS, MJS and MEJ set up and collected data in the Generations Study. MJS and JH collected and prepared data for the analysis. MJS conducted the analyses and drafted the manuscript. All authors contributed to data interpretation and preparation of the final manuscript.

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Authors' information

No further information

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Table 1: Characteristics of the study population, subjects with mammographic density in the Generations Study

	Participants		
Characteristic	Adjusted mean percentage density (%) (a)	Number	%
Age at mammogram, years			
47-54	25.5	303	27.4
55-59	21.3	344	31.1
60-64	18.0	279	25.2
65-73	16.6	179	16.2
Interval between mammogram and baseline questionnaire			
≥3 years prior	21.6	47	4.3
2-2.9 years prior	24.3	61	5.5
1-1.9 years prior	24.0	182	16.5
Within 1 year	21.1	554	50.1
1-1.9 years later	19.3	127	11.5
2-2.9 years later	22.0	59	5.3
≥ 3 years later	17.2	75	6.8
BMI at baseline questionnaire, kg/m^2			
<20	33.0	39	3.5
20-24	25.6	525	47.5
25-29	15.7	378	34.2
≥30	12.1	163	14.8
Menopausal status at mammogram			
Postmenopausal	20.5	885	80.1
Premenopausal	24.5	126	11.4
Status not known	23.2	94	8.5
Parity			
Nulliparous	24.5	113	10.2
Parous	20.9	992	89.8
Age at first birth, years			
<25	19.9	428	38.7
25-29	21.4	414	37.5
≥30	22.4	150	13.6
Number of births			
1	19.7	100	9.0
2	21.1	583	52.8
≥3	21.0	309	28.0
Postmenopausal hormone replacement at time of mammogram			
Never	21.0	839	75.9
Former	21.0	199	18.0
Current	25.7	67	6.1
Total	21.3	1,105	100.0

(a) Mean percentage density (back-transformed to ordinary scale) for average BMI 25 kg/m^2 and age 58 years at mammogram for all variables, except category of age at mammogram (at BMI 25 kg/m^2 only) and category of BMI (at age 58 years only).

Table 2: Difference in adult mammographic density parameters across categories of weight compared with peers at ages 7 and 11 years

Weight and age	Category	Mammographic density parameters: Percent density, Difference, percentage points (95% CI)(a)	Absolute area: Dense area, Difference, cm^2 (95% CI)(a)	Absolute area: Non-dense, Difference, cm^2 (95% CI)(a)
Weight relative to peers, age 7 years				
A:	Thinner	5.6 (3.0, 8.4)	6.1 (3.0, 9.3)	-10.8 (-17.7, -3.6)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Heavier	-4.1 (-7.0, -0.9)	-2.1 (-5.7, 1.8)	17.7 (6.9, 28.9)
	P trend (b)	**<0.001**	**<0.001**	**<0.001**
B: +BMI adjusted	Thinner	4.2 (1.8, 6.7)	5.7 (2.7, 8.9)	-4.6 (-10.3, 1.3)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Heavier	-1.6 (-4.5, 1.5)	-1.1 (-4.8, 2.8)	3.5 (-4.7, 12.0)
	P trend (b)	**<0.001**	**<0.001**	**0.050**
Weight relative to peers, age 11 years				
A:	Thinner	5.0 (2.4, 7.8)	4.3 (1.3, 7.5)	-12.8 (-19.7, -5.7)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Heavier	-7.0 (-9.3, -4.5)	-6.4 (-9.3, -3.4)	23.3 (14.0, 32.9)
	P trend (b)	**<0.001**	**<0.001**	**<0.001**
B: +BMI adjusted	Thinner	3.0 (0.7, 5.5)	3.8 (0.8, 7.0)	-4.1 (-9.9, 1.9)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Heavier	-4.1 (-6.5, -1.6)	-5.4 (-8.3, -2.2)	5.8 (-1.3, 13.1)
	P trend (b)	**<0.001**	**<0.001**	**0.017**
Change in relative weight age 7 to 11 years (c)				
A:	Decrease	0.2 (-4.6, 5.6)	-0.7 (-6.3, 5.5)	2.8 (-12.3, 19.0)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Increase	-6.3 (-9.0, -3.3)	-6.1 (-9.4, -2.6)	24.1 (13.3, 35.3)
	P trend (b)	**<0.001**	**0.007**	**<0.001**
B: +BMI adjusted	Decrease	0.2 (-4.3, 5.1)	-0.3 (-5.9, 5.8)	3.2 (-8.8, 15.9)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Increase	-2.8 (-5.6, 0.2)	-4.4 (-7.9, -0.7)	5.9 (-2.2, 14.2)
	P trend (b)	0.11	0.054	0.36

(a) Differences derived with respect to reference levels: 25% for percentage density, 30 cm^2 for dense area and 110 cm^2 for nondense area. Models defined as follows: Model A: Analyses adjusted for age at mammogram (47-50, 50-54, 55-59 (baseline), 60-64, 65-69, 70-73 years), duration of oral contraception use (never (baseline), <5, 10-14, ≥15 years, not known), postmenopausal hormone treatment (never (baseline), former, current/<5, current/5-9, current/≥10 years duration), menopausal status and time since menopause (<5 (baseline), 10-14, 15-19, ≥20, unknown years postmenopausal, not postmenopausal), age at first birth and parity (nulliparous, 10-24y/1-2, 10-24y/≥3, 25-29y/1-2 (baseline), 25-29y/≥3, 30y/≥1), alcohol units (none (baseline), 1-4 to ≥25, in 5-unit increments), physical activity (<31 (baseline), 32-55, 56-88, ≥88 MET-hr/wk) Model B: adjusted for covariates in model A plus BMI (<20.0 (baseline) to >35.0, in 2.5 kg/m^2 increments)

(b) P trend for linear regression fitted through categories of exposure

(c) Increase or decrease in category of weight compared with peers between ages 7 and 11 years

Table 3: Difference in adult mammographic density parameters across categories of height compared with peers at ages 7 and 11 years

		Mammographic density parameters		
			Absolute area	
		Percent density	Dense area	Non-dense area
Height and age	Category	Difference, percentage points (95% CI)(a)	Difference, cm^2 (95% CI)(a)	Difference, cm^2 (95% CI)(a)
Height relative to peers, age 7 years				
A:	Shorter	3.7 (0.9, 6.7)	3.7 (0.4, 7.2)	-10.7 (-18.5, -2.7)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Taller	0.0 (-2.5, 2.6)	1.2 (-1.9, 4.4)	2.5 (-5.4, 10.8)
	P trend (b)	**0.027**	0.227	**0.006**
B: +BMI adjusted	Shorter	2.8 (0.2, 5.5)	3.1 (-0.1, 6.5)	-7.7 (-13.9, -1.3)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Taller	-0.8 (-3.1, 1.6)	0.5 (-2.5, 3.6)	5.6 (-0.7, 12.1)
	P trend (b)	**0.016**	0.190	**<0.001**
C: +weight age 11 years	Shorter	1.9 (-0.7, 4.6)	1.8 (-1.4, 5.2)	-6.9 (-13.2, -0.3)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Taller	-0.3 (-2.6, 2.1)	1.2 (-1.8, 4.3)	4.9 (-1.5, 11.4)
	P trend (b)	0.158	0.788	**0.002**
Height relative to peers, age 11 years				
A:	Shorter	3.0 (0.2, 5.9)	3.3 (0.1, 6.7)	-7.8 (-15.5, 0.3)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Taller	0.6 (-1.9, 3.2)	1.6 (-1.4, 4.7)	1.7 (-6.0, 9.6)
	P trend (b)	0.141	0.405	**0.036**
B: +BMI adjusted	Shorter	2.3 (-0.2, 4.9)	2.9 (-0.3, 6.3)	-5.0 (-11.2, 1.3)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Taller	-0.3 (-2.5, 2.1)	1.0 (-2.0, 4.0)	5.6 (-0.5, 11.9)
	P trend (b)	0.065	0.298	**0.002**
C: +weight age 11 years	Shorter	1.5 (-1.0, 4.1)	1.9 (-1.3, 5.2)	-4.3 (-10.6, 2.2)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Taller	0.3 (-2.0, 2.7)	1.7 (-1.3, 4.8)	4.9 (-1.3, 11.2)
	P trend (b)	0.401	0.989	**0.010**

(a) Differences derived with respect to reference levels: 25% for percentage density, 30 cm^2 for dense area and 110 cm^2 for nondense area. Models defined as follows: Model A: Analyses adjusted for age at mammogram (47-50, 50-54, 55-59 (baseline), 60-64, 65-69, 70-73 years), duration of oral contraception use (never (baseline), <5, 10-14, ≥15 years, not known), postmenopausal hormone treatment (never (baseline), former, current/<5, current/5-9, current/≥10 years duration), menopausal status and time since menopause (<5 (baseline), 10-14, 15-19, ≥20, unknown years postmenopausal, not postmenopausal), age at first birth and parity (nulliparous, 10-24y/1-2, 10-24y/≥3, 25-29y/1-2 (baseline), 25-29y/≥3, 30y/≥1), alcohol units (none (baseline), 1-4 to ≥25, in 5-unit increments), physical activity (<31 (baseline), 32-55, 56-88, ≥88 MET-hr/wk)
Model B: adjusted for covariates in model A plus BMI (<20.0 (baseline) to >35.0, in 2.5 kg/m^2 increments)
Model C: adjusted for covariates in model B plus weight compared with peers at age 11 years (thinner (baseline), about the same, heavier, not known)

(b) P trend for linear regression fitted through categories of exposure
Increase or decrease in category of height compared with peers between ages 7 and 11 years

Table 4: Difference in adult mammographic density parameters across categories of age at onset of pubertal stages

		Mammographic density parameters		
			Absolute area	
		Percent density	Dense area	Non-dense area
Age at pubertal stage	Category	Difference, percentage points (95% CI)(a)	Difference, cm^2 (95% CI)(a)	Difference, cm^2 (95% CI)(a)
Age at thelarche, years				
A:	≤10	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	11-12	2.6 (-1.2-6.7)	0.8 (-3.6, 5.5)	-8.8 (-19.3, 2.4)
	≥13	5.7 (1.6-10.1)	1.7 (-2.8, 6.6)	-23.1 (-33.1, -12.5)
	P trend (b)	**0.002**	0.42	**<0.001**
B: +BMI adjusted	≤10	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	11-12	1.0 (-2.4, 4.6)	0.0 (-4.2, 4.6)	-3.7 (-12.2, 5.1)
	≥13	2.2 (-1.4, 6.0)	-0.1 (-4.5, 4.6)	-11.7 (-20.1, -3.0)
	P trend (b)	0.20	0.95	**0.002**
C: +weight age 11 years	≤10	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	11-12	0.2 (-3.1, 3.8)	-1.0 (-5.1, 3.5)	-3.0 (-11.5, 5.9)
	≥13	0.3 (-3.3, 4.1)	-2.5 (-6.8, 2.2)	-10.0 (-18.8, -0.7)
	P trend (b)	0.88	0.24	**0.012**
Age at menarche, years				
A:	≤12	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	13-14	4.7 (2.1, 7.3)	3.5 (0.6, 6.6)	-12.7 (-19.5, -5.7)
	≥15	6.9 (2.7, 11.3)	5.7 (1.0, 10.8)	-17.7 (-28.1, -6.8)
	P trend (b)	**<0.001**	**0.003**	**<0.001**
B: +BMI adjusted	≤12	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	13-14	2.9 (0.6, 5.2)	2.9 (0.0, 5.9)	-5.2 (-10.8, 0.6)
	≥15	3.2 (-0.4, 7.1)	4.2 (-0.4, 9.1)	-3.1 (-12.1, 6.2)
	P trend (b)	**0.014**	**0.023**	0.18
C: +weight age 11 years	≤12	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	13-14	2.0 (-0.3, 4.4)	1.7 (-1.1, 4.7)	-4.0 (-9.8, 1.9)
	≥15	1.8 (-1.8, 5.6)	2.3 (-2.2, 7.1)	-1.4 (-10.6, 8.2)
	P trend (b)	0.13	0.20	0.40
Age at regular cycles, years				
A:	≤12	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	13-14	5.2 (1.9, 8.7)	5.4 (1.3, 9.7)	-10.0 (-18.8, -0.8)
	≥15	6.4 (2.5, 10.5)	5.3 (0.7, 10.3)	-12.4 (-22.4, -2.0)
	P trend (b)	**<0.001**	**0.013**	**0.014**
B: +BMI adjusted	≤12	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	13-14	3.3 (0.3, 6.5)	4.6 (0.6, 8.8)	-2.2 (-9.8, 5.6)
	≥15	4.3 (0.8, 8.1)	4.4 (-0.1, 9.2)	-4.3 (-12.8, 4.5)
	P trend (b)	**0.010**	**0.036**	0.33
C: +weight age 11 years	≤12	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	13-14	2.5 (-0.6, 5.7)	3.6 (-0.4, 7.9)	-0.5 (-8.2, 7.5)
	≥15	3.4 (-0.1, 7.1)	3.4 (-1.1, 8.2)	-2.6 (-11.2, 6.5)
	P trend (b)	0.051	0.12	0.59

(a) Differences derived with respect to reference levels: 25% for percentage density, 30 cm^2 for dense area and 110 cm^2 for nondense area. Models defined as follows: Model A: Analyses adjusted for age at mammogram (47-50, 50-54, 55-59 (baseline), 60-64, 65-69, 70-73 years), duration of oral contraception use (never

(baseline), <5, 10-14, ≥15 years, not known), postmenopausal hormone treatment (never (baseline), former, current/<5, current/5-9, current/≥10 years duration), menopausal status and time since menopause (<5 (baseline), 10-14, 15-19, ≥20, unknown years postmenopausal, not postmenopausal), age at first birth and parity (nulliparous, 10-24y/1-2, 10-24y/≥3, 25-29y/1-2 (baseline), 25-29y/≥3, 30y/≥1), alcohol units (none (baseline), 1-4 to ≥25, in 5-unit increments), physical activity (<31 (baseline), 32-55, 56-88, ≥88 MET-hr/wk)
Model B: adjusted for covariates in model A plus BMI (<20.0 (baseline) to >35.0, in 2.5 kg/m^2 increments)
Model C: adjusted for covariates in model B plus weight compared with peers at age 11 years (thinner (baseline), about the same, heavier, not known)

(b) P trend for linear regression fitted through categories of exposure

Table 5: Difference in adult mammographic density parameters across categories of timing between pubertal stages

Interval between pubertal stages	Category	Mammographic density parameters: Percent density, Difference, percentage points (95% CI)(a)	Absolute area: Dense area, Difference, cm^2 (95% CI)(a)	Absolute area: Non-dense area, Difference, cm^2 (95% CI)(a)
Thelarche to menarche, years				
A:	<0	-0.4 (-4.8, 4.5)	-0.3 (-5.6, 5.5)	-3.9 (-17.6, 10.6)
	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	2.2 (-0.7, 5.2)	4.1 (0.5, 7.8)	-0.1 (-8.7, 8.8)
	≥2	2.0 (-1.9, 6.2)	4.0 (-0.7, 9.1)	-1.3 (-12.6, 10.8)
	P trend (b)	0.14	**0.022**	0.87
B: +BMI adjusted	<0	-0.5 (-4.5, 3.9)	-0.7 (-5.8, 5.0)	-4.7 (-15.3, 6.4)
	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	1.7 (-0.9,4.5)	4.1 (0.6, 7.8)	1.9 (-4.8, 8.8)
	≥2	2.1 (-1.5, 5.8)	3.8 (-0.8, 8.7)	-1.7 (-10.5, 7.5)
	P trend (b)	0.13	**0.019**	0.64
C: +weight age 11 years	<0	-1.3 (-5.3, 3.0)	-1.7 (-6.8, 3.8)	-3.5 (-14.2, 7.7)
	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	1.7 (-1.0, 4.4)	4.0 (0.6, 7.7)	2.0 (-4.8, 8.9)
	≥2	1.8 (-1.7, 5.5)	3.4 (-1.1, 8.3)	-1.3 (-10.2, 7.9)
	P trend (b)	0.10	**0.013**	0.69
Thelarche to regular cycles, years				
A:	<0	-5.6 (-11.4, 1.1)	-7.8 (-14.7, 0.3)	6.2 (-14.4, 28.9)
	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	1.7 (-2.2, 5.9)	1.8 (-2.9, 6.9)	-2.5 (-13.6, 9.3)
	≥2	1.6 (-2.3, 5.9)	2.6 (-2.3, 7.8)	1.6 (-10.0, 13.8)
	P trend (b)	0.083	**0.039**	0.97
B: +BMI adjusted	<0	-2.9 (-8.6, 3.7)	-6.2 (-13.2, 2.0)	-7.3 (-23.0, 9.7)
	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	1.8 (-1.8, 5.6)	1.8 (-2.9, 6.7)	-3.5 (-12.3, 5.8)
	≥2	2.5 (-1.2, 6.4)	3.3 (-1.5, 8.5)	-1.5 (-10.6, 8.1)
	P trend (b)	0.068	**0.029**	0.87
C: +weight age 11 years	<0	-3.6 (-9.2, 2.9)	-7.2 (-14.1, 0.8)	-6.6 (-22.5, 10.5)
	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	1.8 (-1.8, 5.6)	1.8 (-2.8, 6.7)	-3.4 (-12.3, 5.9)
	≥2	2.3 (-1.4, 6.2)	3.0 (-1.8, 8.1)	-1.4 (-10.5, 8.2)
	P trend (b)	0.064	**0.028**	0.89

(a) Differences derived with respect to reference levels: 25% for percentage density, 30 cm^2 for dense area and 110 cm^2 for nondense area. Models defined as follows: Model A: Analyses adjusted for age at mammogram (47-50, 50-54, 55-59 (baseline), 60-64, 65-69, 70-73 years), duration of oral contraception use (never (baseline), <5, 10-14, ≥15 years, not known), postmenopausal hormone treatment (never (baseline), former, current/<5, current/5-9, current/≥10 years duration), menopausal status and time since menopause (<5 (baseline), 10-14, 15-19, ≥20, unknown years postmenopausal, not postmenopausal), age at first birth and parity (nulliparous, 10-24y/1-2, 10-24y/≥3, 25-29y/1-2 (baseline), 25-29y/≥3, 30y/≥1), alcohol units (none (baseline), 1-4 to ≥25, in 5-unit increments), physical activity (<31 (baseline), 32-55, 56-88, ≥88 MET-hr/wk)

Model B: adjusted for covariates in model A plus BMI (<20.0 (baseline)to >35.0, in 2.5 kg/m^2 increments)
Model C: adjusted for covariates in model B plus weight compared with peers at age 11 years (thinner (baseline), about the same, heavier, not known)

(b) P trend for linear regression fitted through categories of exposure

Table S1: Number of subjects included in analyses of categories of body size and pubertal factors.

Factor	Categories, numbers (%)				Missing or not applicable
	Thinner	*About the same*	*Heavier*		
Weight at age 7 years	311 (28.8)	633 (58.7)	135 (12.5)		26
Weight at age 11 years	299 (27.4)	589 (53.9)	204 (18.7)		13
	Shorter	*About the same*	*Taller*		
Height at age 7 years	245 (23.0)	542 (50.8)	280 (26.2)		38
Height at age 11 years	281 (26.0)	458 (42.3)	343 (31.7)		23
	≤10 years	*11-12 years*	*≥13 years*		
Age at thelarche	111 (12.6)	415 (47.0)	357 (40.4)		222
	≤12 years	*13-14 years*	*≥15 years*		
Age at menarche	454 (45.6)	435 (43.7)	107 (10.7)		109
Age at regular cycles	243 (36.3)	265 (40.0)	162 (24.2)		435
	≤14 years	*15-16 years*	*≥17 years*		
Age reached adult height	192 (32.1)	255 (42.6)	152 (25.4)		506
	<0 years	*0 years*	*1 years*	*≥2 years*	
Thelarche to menarche	73 (9.0)	315 (38.7)	310 (38.1)	116 (14.3)	291
Thelarche to regular cycles	31 (5.3)	141 (24.1)	223 (38.1)	190 (32.5)	520
Menarche to regular cycles		395 (59.0)	196 (29.3)	79 (11.8)	435
	<2 years	*2-3 years*	*≥4 years*		
Thelarche to adult height	96 (17.6)	209 (38.4)	239 (43.9)		561
Menarche to adult height	169 (30.9)	195 (35.6)	184 (33.6)		557

Table S2: Adjusted means of pubertal variables, anthropometric and mammographic density characteristics by weight compared with peers at age 11 years

	Weight at age 11 years relative to peers			
	Thinner	About the same	Heavier	
	Mean	Mean	Mean	P trend (c)
Pubertal variables (a)				
Age at thelarche, years	12.9	12.0	11.4	<0.001
Age at menarche, years	13.3	12.6	12.1	<0.001
Age at regular cycles, years	14.3	13.7	13.4	0.004
Age reached attained height, years	15.9	15.3	15.1	0.001
Thelarche to menarche, years	0.51	0.62	0.68	0.12
Thelarche to regular cycles, years	1.22	1.28	1.58	0.15
Thelarche to attained height, years	3.07	3.40	3.97	0.001
Menarche to regular cycles, years	0.66	0.65	0.86	0.29
Menarche to attained height, years	2.58	2.72	3.15	0.037
Adult anthropometrics (a)				
Attained height, cms	163.6	162.6	163.8	0.97
Body mass index at mammogram, kg/m^2	24.4	25.8	27.9	<0.001
Mammographic density, mean (b)				
Percentage density, %	23.8	21.3	17.3	<0.001
Absolute dense area, cm^2	29.3	25.9	20.7	<0.001
Absolute nondense area, cm^2	94.5	97.5	103.5	0.017
Absolute total breast area, cm^2	129.4	129.1	130.3	0.83

(a) Adjusted mean for age at mammogram of 58 years

(b) Adjusted mean (back-transformed to ordinary scale) for age at mammogram of 58 years and BMI at study entry of 25 kg/m^2

(c) From linear regression model per category of weight compared with peers at age 11 years

Table S3: Adjusted means of pubertal variables, anthropometric and mammographic density characteristics by height compared with peers at age 11 years

	Height at age 11 years relative to peers			
	Shorter	About the same	Taller	
	Mean	Mean	Mean	P trend (c)
Pubertal variables (a)				
Age at thelarche, years	12.6	12.1	11.8	<0.001
Age at menarche, years	13.1	12.7	12.5	<0.001
Age at regular cycles, years	14.2	13.8	13.5	0.019
Age reached attained height, years	15.7	15.6	15.1	0.003
Thelarche to menarche, years	0.59	0.59	0.62	0.79
Thelarche to regular cycles, years	1.38	1.41	1.13	0.20
Thelarche to attained height, years	3.18	3.63	3.39	0.49
Menarche to regular cycles, years	0.72	0.75	0.60	0.37
Menarche to attained height, years	2.56	3.01	2.69	0.73
Adult anthropometrics (a)				
Attained height, cms	157.7	162.7	168.1	<0.001
Body mass index at mammogram, kg/m^2	25.7	26.1	25.5	0.46
Mammographic density, mean (b)				
Percentage density, %	22.5	21.0	20.7	0.16
Absolute dense area, cm^2	27.0	25.1	26.4	0.72
Absolute nondense area, cm^2	93.2	96.7	102.6	0.003
Absolute total breast area, cm^2	125.8	127.6	135.2	0.002

(a) Adjusted mean for age at mammogram of 58 years

(b) Adjusted mean (back-transformed to ordinary scale) for age at mammogram of 58 years and BMI at study entry of 25 kg/m^2

(c) From linear regression model per category of height compared with peers at age 11 years

Table S4: Correlations between pubertal factors and adult body mass index

	Age at thelarche	Age at menarche	Age at regular cycles	Age reached adult height	Attained height	Adult BMI
Age at thelarche	1.00					
Age at menarche	0.74	1.00				
Age at regular periods	0.34	0.51	1.00			
Age reached attained height	0.27	0.30	0.17	1.00		
Attained height	0.09	0.11	0.05	0.22	1.00	
Adult BMI	-0.16	-0.15	-0.08	0.003	-0.18	1.00

Table S5: Difference in adult mammographic density parameters in relation to change in height compared with peers between age 7 and 11 years.

		Mammographic density parameters		
			Absolute area	
		Percent density	Dense area	Non-dense area
Change in relative height age 7 to 11 years (c)	Category	Difference, percentage points (95% CI)(a)	Difference, cm^2 (95% CI)(a)	Difference, cm^2 (95% CI)(a)
A:	Decrease	-4.8 (-8.9, -0.4)	-3.4 (-8.4, 2.1)	18.8 (3.7, 34.9)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Increase	-1.3 (-5.0, 2.7)	-1.2 (-5.5, 3.6)	8.9 (-3.3, 21.7)
	P trend (b)	0.36	0.66	0.59
B: +BMI adjusted	Decrease	-3.6 (-7.4, 0.6)	-2.5 (-7.5, 3.0)	13.0 (1.3, 25.3)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Increase	-0.7 (-4.1, 3.0)	-0.9 (-5.2, 3.8)	6.3 (-3.1, 16.2)
	P trend (b)	0.41	0.75	0.65
C: +weight age 11 years	Decrease	-3.6 (-7.4, 0.5)	-2.5 (-7.5, 2.9)	13.2 (1.6, 25.4)
	About the same	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	Increase	-0.3 (-3.7, 3.4)	-0.3 (-4.6, 4.3)	6.2 (-3.3, 16.0)
	P trend (b)	0.30	0.61	0.62

(a) Differences derived with respect to reference levels: 25% for percentage density, 30 cm^2 for dense area and 110 cm^2 for nondense area. Models defined as follows: Model A: Analyses adjusted for age at mammogram (47-50, 50-54, 55-59 (baseline), 60-64, 65-69, 70-73 years), duration of oral contraception use (never (baseline), <5, 10-14, ≥15 years, not known), postmenopausal hormone treatment (never (baseline), former, current/<5, current/5-9, current/≥10 years duration), menopausal status and time since menopause (<5 (baseline), 10-14, 15-19, ≥20, unknown years postmenopausal, not postmenopausal), age at first birth and parity (nulliparous, 10-24y/1-2, 10-24y/≥3, 25-29y/1-2 (baseline), 25-29y/≥3, 30y/≥1), alcohol units (none (baseline), 1-4 to ≥25, in 5-unit increments), physical activity (<31 (baseline), 32-55, 56-88, ≥88 MET-hr/wk) Model B: adjusted for covariates in model A plus BMI (<20.0 (baseline) to >35.0, in 2.5 kg/m^2 increments) Model C: adjusted for covariates in model B plus weight compared with peers at age 11 years (thinner (baseline), about the same, heavier, not known)

(b) P trend for linear regression fitted through categories of exposure

(c) Increase or decrease in category of height compared with peers between ages 7 and 11 years

Table S6: Difference in adult mammographic density parameters across categories of age reaching adult height

		Mammographic density parameters		
			Absolute area	
		Percent density	Dense area	Non-dense area
Age at pubertal stage	Category	Difference, percentage points (95% CI)(a)	Difference, cm^2 (95% CI)(a)	Difference, cm^2 (95% CI)(a)
Age reached adult height, years				
A:	≤14	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	15-16	-0.5 (-3.9, 3.0)	-0.6 (-4.5, 3.5)	4.3 (-6.3, 15.4)
	≥17	0.9 (-2.9, 5.0)	1.3 (-3.2, 6.0)	-0.4 (-11.9, 11.8)
	P trend (b)	0.70	0.62	0.99
B: +BMI adjusted	≤14	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	15-16	-1.2 (-4.2, 1.9)	-1.1 (-4.8, 2.9)	7.4 (-1.0, 16.2)
	≥17	0.6 (-2.9, 4.3)	0.5 (-3.7, 5.2)	0.0 (-9.1, 9.5)
	P trend (b)	0.80	0.85	0.89
C: +weight age 11 years	≤14	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	15-16	-1.7 (-4.7, 1.5)	-1.5 (-5.2, 2.5)	8.6 (0.1, 17.5)
	≥17	0.0 (-3.4, 3.7)	0.0 (-4.2, 4.6)	1.3 (-7.9, 10.9)
	P trend (b)	0.94	0.97	0.69

(a) Differences derived with respect to reference levels: 25% for percentage density, 30 cm^2 for dense area and 110 cm^2 for nondense area. Models defined as follows: Model A: Analyses adjusted for age at mammogram (47-50, 50-54, 55-59 (baseline), 60-64, 65-69, 70-73 years), duration of oral contraception use (never (baseline), <5, 10-14, ≥15 years, not known), postmenopausal hormone treatment (never (baseline), former, current/<5, current/5-9, current/≥10 years duration), menopausal status and time since menopause (<5 (baseline), 10-14, 15-19, ≥20, unknown years postmenopausal, not postmenopausal), age at first birth and parity (nulliparous, 10-24y/1-2, 10-24y/≥3, 25-29y/1-2 (baseline), 25-29y/≥3, 30y/≥1), alcohol units (none (baseline), 1-4 to ≥25, in 5-unit increments), physical activity (<31 (baseline), 32-55, 56-88, ≥88 MET-hr/wk) Model B: adjusted for covariates in model A plus BMI (<20.0 (baseline) to >35.0, in 2.5 kg/m^2 increments) Model C: adjusted for covariates in model B plus weight compared with peers at age 11 years (thinner (baseline), about the same, heavier, not known)

(b) P trend for linear regression fitted through categories of exposure

Table S7: Difference in adult mammographic density parameters across categories of time interval between menarche and regular cycles

		Mammographic density parameters		
			Absolute area	
		Percent density	Dense area	Non-dense area
Time interval	Category	Difference, percentage points (95% CI)(a)	Difference, cm^2 (95% CI)(a)	Difference, cm^2 (95% CI)(a)
Menarche to regular cycles, years				
A:	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	-1.1 (-4.0, 2.1)	-2.5 (-6.0, 1.4)	0.27 (-9.0, 9.9)
	≥2	-0.5 (-4.8, 4.1)	-0.1 (-5.3, 5.6)	6.5 (-6.9, 20.8)
	P trend (b)	0.63	0.55	0.44
B: +BMI adjusted	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	-2.0 (-4.7, 0.9)	-2.8 (-6.3, 0.9)	5.1 (-2.6, 13.0)
	≥2	-0.4 (-4.3, 3.9)	0.2 (-5.0, 5.8)	5.9 (-5.1, 17.3)
	P trend (b)	0.46	0.55	0.17
C: +weight age 11 years	0	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	1	-1.9 (-4.7, 0.9)	-2.7 (-6.2, 1.0)	5.2 (-2.5, 13.1)
	≥2	-0.4 (-4.3, 3.8)	0.0 (-5.1, 5.6)	5.8 (-5.1, 17.1)
	P trend (b)	0.46	0.54	0.16

(a) Differences derived with respect to reference levels: 25% for percentage density, 30 cm^2 for dense area and 110 cm^2 for nondense area. Models defined as follows: Model A: Analyses adjusted for age at mammogram (47-50, 50-54, 55-59 (baseline), 60-64, 65-69, 70-73 years), duration of oral contraception use (never (baseline), <5, 10-14, ≥15 years, not known), postmenopausal hormone treatment (never (baseline), former, current/<5, current/5-9, current/≥10 years duration), menopausal status and time since menopause (<5 (baseline), 10-14, 15-19, ≥20, unknown years postmenopausal, not postmenopausal), age at first birth and parity (nulliparous, 10-24y/1-2, 10-24y/≥3, 25-29y/1-2 (baseline), 25-29y/≥3, 30y/≥1), alcohol units (none (baseline), 1-4 to ≥25, in 5-unit increments), physical activity (<31 (baseline), 32-55, 56-88, ≥88 MET-hr/wk) Model B: adjusted for covariates in model A plus BMI (<20.0 (baseline) to >35.0, in 2.5 kg/m^2 increments) Model C: adjusted for covariates in model B plus weight compared with peers at age 11 years (thinner (baseline), about the same, heavier, not known)

(b) P trend for linear regression fitted through categories of exposure

Table S8: Difference in adult mammographic density parameters in relation to time interval between thelarche or menarche and age reached adult height

		Mammographic density parameters		
			Absolute area	
		Percent density	Dense area	Non-dense area
Time interval	Category	Difference, percentage points (95% CI)(a)	Difference, cm^2 (95% CI)(a)	Difference, cm^2 (95% CI)(a)
Thelarche to reaching adult height, years				
A:	<2	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	2-3	2.0 (-2.5, 6.9)	-0.3 (-5.2, 5.2)	-11.8 (-24.2, 1.4)
	≥4	-0.4 (-4.6, 4.1)	0.0 (-4.8, 5.4)	3.6 (-9.5, 17.3)
	P trend (b)	0.57	0.95	0.18
B: +BMI adjusted	<2	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	2-3	-0.1 (-4.1, 4.2)	-1.3 (-6.1, 3.9)	-4.0 (-14.3, 6.9)
	≥4	-0.1 (-4.0, 4.0)	0.1 (-4.7, 5.2)	2.4 (-7.9, 13.2)
	P trend (b)	0.95	0.81	0.40
C: +weight age 11	<2	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	2-3	0.2 (-3.8, 4.5)	-0.9 (-5.8, 4.3)	-4.2 (-14.5, 6.7)
	≥4	0.5 (-3.4, 4.7)	0.8 (-4.1, 6.1)	1.4 (-8.9, 12.2)
	P trend (b)	0.80	0.60	0.54
Menarche to reaching adult height, years				
A:	<2	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	2-3	-4.0 (-7.4, -0.4)	-5.1 (-9.1, -0.9)	5.6 (-6.4, 18.2)
	≥4	-4.4 (-7.7, -0.8)	-3.8 (-7.8, 0.5)	13.9 (1.7, 26.7)
	P trend (b)	**0.020**	0.10	**0.025**
B: +BMI adjusted	<2	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	2-3	-4.5 (-7.6, -1.2)	-5.6 (-9.4, -1.4)	7.0 (-2.6, 16.9)
	≥4	-3.3 (-6.5, 0.0)	-3.4 (-7.3, 0.9)	8.0 (-1.4, 17.7)
	P trend (b)	0.061	0.14	0.10
C: +weight age 11	<2	0.0 (baseline)	0.0 (baseline)	0.0 (baseline)
	2-3	-4.5 (-7.6, -1.2)	-5.5 (-9.3, -1.3)	7.3 (-2.3, 17.3)
	≥4	-3.1 (-6.3, 0.3)	-3.0 (-7.0, 1.3)	7.8 (-1.6, 17.6)
	P trend (b)	0.082	0.19	0.11

(a) Differences derived with respect to reference levels: 25% for percentage density, 30 cm^2 for dense area and 110 cm^2 for nondense area. Models defined as follows: Model A: Analyses adjusted for age at mammogram (47-50, 50-54, 55-59 (baseline), 60-64, 65-69, 70-73 years), duration of oral contraception use (never (baseline), <5, 10-14, ≥15 years, not known), postmenopausal hormone treatment (never (baseline), former, current/<5, current/5-9, current/≥10 years duration), menopausal status and time since menopause (<5 (baseline), 10-14, 15-19, ≥20, unknown years postmenopausal, not postmenopausal), age at first birth and parity (nulliparous, 10-24y/1-2, 10-24y/≥3, 25-29y/1-2 (baseline), 25-29y/≥3, 30y/≥1), alcohol units (none (baseline), 1-4 to ≥25, in 5-unit increments), physical activity (<31 (baseline), 32-55, 56-88, ≥88 MET-hr/wk)
Model B: adjusted for covariates in model A plus BMI (<20.0 (baseline) to >35.0, in 2.5 kg/m^2 increments)
Model C: adjusted for covariates in model B plus weight compared with peers at age 11 years (thinner (baseline), about the same, heavier, not known)

(b) P trend for linear regression fitted through categories of exposure