Growth trajectories, breast size, and breast-tissue composition in a British pre-birth cohort of young women

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FOOTNOTES PAGE

List of abbreviations:

ALSPAC: Avon Longitudinal Study of Parents and Children

BMI: body mass index

CI: confidence interval

DXA: dual energy x-ray absorptiometry

IQR: inter-quartile range

MAR: missing at random

MRI: magnetic resonance imaging

RC: relative change in MRI breast measure associated one standard deviation increase in the exposure of interest

SD: standard deviation

SE: standard error

VIF: variance inflation factor

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Growth, breast size and breast-tissue composition

ABSTRACT

Mammographic ~~percent~~% density, the proportion of fibroglandular tissue in the breast, is a strong risk factor for breast cancer, but its determinants in young women are unknown. We examined associations between MRI breast-tissue composition at age 21 years and prospectively-collected measures of body size and composition from birth to early adulthood, and markers of puberty (all standardized), in a sample of 500 nulliparous women from a pre-birth cohort of children born in England in 1991-2. Linear models were fitted to estimate relative change (RC) in MRI ~~percent~~% water, which is equivalent to mammographic ~~percent~~% density, associated with one SD increase in the exposure of interest. In mutually-adjusted analyses, ~~percent~~% water was positively associated with birth weight (RC=1.03~~;~~ (95% CI: -1.00, 1.06)) and pubertal height growth (1.07~~;~~ (1.02, 1.13)), but inversely associated with pubertal weight growth (0.86~~;~~ (0.84, 0.89)) and changes in DXA ~~percentage~~% body fat mass (e.g. 0.96~~;~~ (0.93, 0.99)), for change between ages 11-13.5 years). Ages at thelarche and menarche were positively associated with ~~percent~~% water, but these associations did not persist upon adjustment for height and weight growth. These findings support the hypothesis that growth trajectories influence breast-tissue composition in young women, whereas puberty plays no independent role.

KEY WORDS

Breast cancer, breast density, birth size, height, weight, childhood, puberty, ALSPAC

There is established evidence of a positive association of childhood height (1) with breast cancer risk later in life, whilst late age at menarche (2) and higher adolescent body mass index (BMI) have been found to be protective (3). Childhood and adolescent growth patterns are hypothesised to be associated with levels of sex and growth hormones, with these potentially affecting breast development and, hence, subsequent breast cancer risk (4). Age- and BMI-adjusted mammographic ~~percent~~% density, which represents the proportion of fibro-glandular tissue in the breast accounting for a woman's age and BMI, is one of the strongest predictors of breast cancer risk (5). Thus, a possible mechanism through which early-life body size and maturation may influence breast cancer risk is through breast-tissue composition.

Several studies have suggested possible associations between mammographic ~~percent~~% density in late adulthood and early-life growth, body fatness and pubertal development (6-8). However, few have investigated the influence of body growth trajectories from birth to young adulthood on breast-tissue composition based on prospectively-collected life-course data. Furthermore, existing studies have mostly recruited women of screening ages, who had already experienced reproductive-related events and who therefore have an altered breast-tissue composition. As yet, there has been no investigation of the influence of childhood and adolescence growth trajectories on breast-tissue composition in young nulliparous women.

In this study, we investigate the relationship between prospectively-collected growth measures from birth to early adulthood, including height and weight trajectories and markers of pubertal development and body composition, with absolute (i.e. breast size and its components) and relative measures of breast-tissue composition~~, as assessed by magnetic resonance imaging (MRI),~~ in young ~~(aged ~21 years)~~ nulliparous women within a British pre-birth cohort.

METHODS

Study population

The study is nested within the Avon Longitudinal Study of Parents and Children (ALSPAC) (9, 10), a prospective pre-birth cohort of 14,775 children born in Avon, England, between April 1st 1991 and December 31st 1992 (representing 72% of the eligible population (9)). Nulliparous women born from singleton pregnancies, who participated regularly in follow-up surveys were invited to attend a MRI examination of their breasts at the University of Bristol Clinical Research and Imaging Centre ~~(CRIC)~~ between June 2011-November 2014. Women who had ever been diagnosed with cancer or a hormone-related disease, or had contra-indications for MRI (e.g. pregnancy, metal implants), were excluded. Of the 2,530 potentially eligible women invited, 500 (19.8%) attended. The low response rate reflects the inconvenience of participating in the study (i.e. time and travel to the MRI examination centre) and relocation away from the study area (i.e. to attend university). However, socio-demographic and anthropometric measures were similar in eligible women who did and did not participate in the study~~. were similar with regard to socio-demographic variables and anthropometric measures.~~ For example, mean birthweight and height at ages 7 and 16 years were 3390.9g (standard deviation, SD=21.6g), 125.6cm (SD=0.32cm) and 165.5cm (SD=0.32cm), respectively, in participants, and 3397.4g (SD=11.4g), 125.5cm (SD=0.13cm) and 165.0cm (SD=0.20cm), respectively, amongst non-participating ~~non-participating~~ eligible women ~~who were not in the study~~.

The study received approval from the ALSPAC Law and Ethics Committee, the South-West NRES Committee Frenchay, and the ~~Xxxxxx Xxxxxxx xx Xxxxxxx xxx Xxxxxxxx Xxxxxxxx~~ London School of Hygiene and Tropical Medicine ethics committee. Participants provided written informed consent.

Growth and development measures

Participant's birth weight and length were collected from obstetric records. Height and weight measures from birth to 5 years were available from health visitor records, which form part of

standard childcare in Britain~~, for the majority of the cohort~~. On average, up to 4 measurements were taken at 2, 10, 21, and 48 months of age. Between ages 4 months and 5 years, direct height and weight measurements were taken for a random 10% of the cohort every ≈6 months. All cohort members were invited to annual clinics from age 7 to 13 years, and at ages 15 and 17 years, during which standing height (without shoes) and weight were measured using the Harpenden stadiometer (Holtain) and Tanita Body Fat Analyses (Model TBF 305), respectively. ~~Participants also attended dual-energy x-ray absorptiometry (DXA) examinations to assess body composition at ages 9, 11, 13.5 and 15.5 years; t~~Total body and trunk fat, bone and lean masses were measured using a Lunar Prodigy dual-energy x-ray absorptiometry (DXA) scanner (GE Medical Systems Lunar, Madison, WI, USA) at ages 9, 11, 13.5 and 15.5 years.

Age of menarche was asked during ~~the~~ clinic visits at ages 12-13 years. Annual puberty questionnaires were also sent to participants between ages 8 and 17 years, during which ~~the development of~~ breast and pubic hair development was recorded by either the mother or child prior to age 14 years, and participants only thereafter. ~~If the breast assessment at age 8 years was missing, w~~We assumed ~~the~~ participants were~~was~~ at Tanner stage 1 ~~at that age~~ if the breast assessment at age 8 years was missing.

During the MRI breast examination (at age ~21 years), participants completed a short questionnaire on menstrual-related variables, and anthropometric measurements were taken using a standard protocol.

The study website contains details of all available data through a fully searchable data dictionary (11).

Breast-tissue composition assessment

The breast-tissue composition assessment methodology is described in (12). Briefly, each participant underwent a non-contrast MRI examination using a 3T Siemens Skyra system and a set of T1-weighted VIBE 3-D images (≈176 images/woman), with a voxel size of 0.76x0.76x0.90mm^3, and T2-weighted trans-axial images (≈40 images/woman), with in-plane resolution 0.85x0.85 mm^2 and

slice thickness of 4mm, of both breasts were obtained. Fully-automated algorithms were developed to estimate breast volume using both T1-weighted and T2-weighted images, and perform fat/water segmentation on T2-weighted images. Left-right average estimates of volumes (in cm^3) of breast, water and fat (the latter two correspond to mammographic dense and non-dense tissues, respectively), as well as ~~percent~~% water, were generated. Percent water is highly positively correlated with mammographic ~~percent~~% density on the same women (13-15). Valid breast parameters were obtained for 491 of the 500 participants who underwent the MRI examination.

Statistical analysis

To examine associations between participants' MRI breast values and the available height and weight measurements, two sets of growth summaries were generated (~~all~~ standardised using ~~their~~ respective sample mean and SD). The first were observed pre-pubertal and pubertal/post-pubertal (hereafter referred ~~simply~~ as pubertal) height and weight growth increments, where age at onset of breast development, i.e. age at thelarche (described below), was used as a marker of each girl's onset of puberty. Thus, pre-pubertal ~~height/weight~~ growth was calculated by subtracting height~~/~~ or weight at age 7 years from height or weight at age of thelarche, whilst pubertal ~~height/weight~~ growth was calculated by subtracting height~~/~~ or weight at age of thelarche from height or ~~/~~weight at age 21 years (both standardised after subtraction).

The second set of growth summaries was derived using linear spline multilevel models. Standardised measures (z-scores) of rate of height and ~~/~~weight growth during five periods (birth to 3 months, 3 to 12 months, 1 to 3 years, and 3 to 7 years) had been derived previously and are fully described elsewhere (16). For this study, additional standardised measures ~~(z-scores)~~ of growth velocities from age 7 to ~~age~~ 21 years were calculated using the same approach ~~as previously~~ (16), i.e. piecewise linear mixed effect models (with three knots set at ages 10,12 and 15 years)~~,~~. ~~This led~~ to estimate~~d~~ height and weight velocities during four distinct ~~growth~~ periods: ages 7 to 10, 10 to 12, 12 to 15, and 15 to 21 years (Appendices 1-2).

DXA total body mass was estimated by summing fat, bone and lean masses, and ~~percentage~~% body bone and fat masses derived and standardised. Changes in DXA ~~percentage~~% body bone and fat

masses between ~~surveys (i.e. between~~ ages 9 and 11, 11 and 13.5, and 13.5 and 15.5 years~~)~~ were ~~also~~ calculated and standardised.

Age at thelarche was estimated using non-linear mixed models for the probability of transitioning from Tanner stage 1 to ~~Tanner stage~~ 2. Similarly, age of completion of breast development was estimated modelling the transition from Tanner stages 1/3 to ~~Tanner stages~~ 4/5. Interpolation between predicted probabilities gave the predicted age at transition ~~that was~~ used to calculate the first set of growth summaries described above.

Linear models were fitted to study the relationship of MRI breast measures (i.e. breast, fat and water volumes; ~~percent~~% water) with height/weight growth measures, puberty markers and changes in DXA body composition variables. Initial models consider the influence of each of these sets of dimensions~~growth, puberty and DXA variables~~, separately, while adjusting for age and menstrual phase at MRI examination~~, and for the other variables within the same category. When the influence of growth during a defined period was investigated, height/weight at the start of that period was also included~~. In the DXA models, age at DXA examination was also included. To achieve near-normal distributions of the residuals, breast tissue measures were log-transformed, but exponentiated estimated regression coefficients are presented; these represent the expected relative change (RC) in MRI breast measures associated with a unit increase in the exposure of interest. Growth measures, puberty markers and DXA variables were also modelled jointly as indicated in the tables and figures.

Sensitivity analyses were conducted using multiple imputation (MI) by chain equations (17) to deal with missing exposure and confounder data under the missing at random (MAR) assumption (18) to obtain results based on all participants with valid MRI breast measures (*n*=491). The MAR assumption was explored by comparing the distribution of observed variables among those with/without complete records. ~~A total of 20~~Twenty imputed datasets were generated and overall estimates obtained using Rubin's rules (19).

Data analysis was conducted in STATA, version 14. All tests of significance are two-sided.

RESULTS

Study subjects

Table 1 presents the distributions of puberty, DXA and MRI breast measures of participants. Figure 1 shows the median height and weight by ~~year of~~ age, alongside the median age of selected puberty markers. At age of thelarche (median=10.2 years; Table 1), median height and weight were 144cm (inter-quartile range (IQR)=7.5cm) and 37kg (IQR=10.3kg), respectively. By age 21 years, participants had on average, grown 19.6cm (IQR=10.4cm) and gained 24.6kg (IQR=13.7kg) in weight. Over time, there was a high level of correlation across growth and DXA measures~~, as shown in the high level of tracking across quintiles of growth measures~~ (Appendix 3)~~.~~; ~~F~~for example, 75.9%, 64.0% and 84.2% of participants remained in the same fifth for height between the ages of 7 and 8, 11 and 12, and 15 and 17 years. ~~, respectively, and 98.4%, 97.1%, and 100% were in the same±1 fifth~~. ~~Findings were similar across weight and DXA measures (Appendix 3).~~ Weight at any given age was positively correlated with all available age-specific DXA ~~percentage~~% body fat mass estimates (Pearson regression coefficient, r=0.60-0.80; P<0.001 for all). Correlations between height measurements and DXA ~~percentage~~% body bone mass estimates were much weaker (r<0.20 for all). Participants who had an earlier thelarche were, on average, more likely to be younger at menarche and at the end of breast development, but breast development took longer, compared to those whose thelarche was at an older age (Appendix 4).

Growth trajectories and MRI breast-tissue composition

In mutually-adjusted analyses of the first set of growth summaries (Figure 2), both pre-pubertal and pubertal height growth increments were positively associated with ~~percent~~% water but inversely associated with breast volume (Figure 2). One SD increase in pre-pubertal height growth (=8.3cm) was associated with an 18% (RC=1.18; 95% CI: 1.12, 1.24) ~~increase in~~ higher ~~percent~~% water and a 19% (0.81; 0.73, 0.91) ~~reduction in~~lower breast volume, with these changes being driven mainly by ~~a decline in~~lower fat volume (Appendix 5). Similar associations were seen with pubertal height growth. In contrast, one SD increase in pre-pubertal (=6.00kg) and ~~in~~ pubertal weight growths (=11.44kg) were associated, respectively, with a 14% (0.86; 0.83, 0.89) and a 16% (0.84; 0.82, 0.86)

~~decrease in~~lower ~~percent~~% water but a 23% (1.23; 1.14, 1.34) and 79% (1.79; 1.68, 1.89) ~~increase in~~ higher breast volume (Figure 2). Weight, but not length, at birth was found to be independently (and positively) associated with ~~percent~~% water (Figure 2). ~~Similar patterns emerged when the~~ Examination of height and weight growth velocity estimates from birth to age 21 years, as derived by the linear spline multilevel models (Figure 3), showed similar patterns while highlighting the lack of association of height and weight velocity measures prior to age 7 years with total breast volume and % water.

Markers of puberty were also associated with MRI breast measures. In mutually-adjusted analyses (Figure 2), age at thelarche and menarche were positively associated with ~~percent~~% water, and~~but~~ age of thelarche and breast completion were inversely associated with breast volume. ~~Age at menarche was also positively associated with percent water, but had no influence on breast volume, while age~~ Age at breast development completion ~~was inversely associated with breast volume, but~~ did not affect breast-tissue composition, whilst age at menarche had no influence on breast volume.

In mutually-adjusted analyses of the DXA variables, DXA ~~percent~~% body fat mass at age 9, and increments from age 9 to 15.5 years, were all associated with a markedly higher ~~increases in~~ breast volume, but ~~reductions in~~lower ~~percent~~% water, reflecting larger proportional increases in fat volume than water volume (Appendix 5). For example, one SD (=3.81%) increase in DXA ~~percent~~% body fat mass between ages 9 and 11 years was associated with an 8% (RC=0.92; 95% CI: 0.90, 0.95) lower~~decrease in~~ ~~percent~~% water but a 22% (1.22; 1.13, 1.32) ~~increase in~~higher breast volume. In contrast, there was some borderline evidence that DXA ~~percent~~% body bone mass at age 9, and increments from age 9 to 15.5 years, were associated with ~~increases in~~higher ~~percent~~% water but ~~decreases in~~lower breast volume. For example, one SD (=0.22%) increase in DXA ~~percent~~% body bone mass between ages 9 and 11 years was associated with a 2% (1.02; 0.99, 1.06) ~~increase in~~higher ~~percent~~% water, but an 8% (0.92; 0.86, 1.00) ~~reduction in~~lower breast volume (Figure 2).

When the growth measures were modelled jointly with the puberty variables (Table 2-model 1) the ~~percent~~% water associations with birthweight, and pre-pubertal and pubertal height and weight growths persisted, with their magnitude being little affected, while its associations with all puberty

markers were no longer present. In contrast, when the growth measures were modelled jointly with the DXA variables (Table 2-model 2), ~~percent~~% water was found to be independently associated with pubertal height and weight growths, but not with their pre-pubertal counterparts. Further inclusion of the puberty variables into the latter model (Table 2-model 3) affected little the magnitude of these associations. Thus, one SD increase in birth weight (=470g) and in pubertal height growth (=7.42cm) were associated, respectively, with a 3% (RC=1.03; 95% CI: 1.00, 1.06) and a 7% (1.07; 1.02, 1.13) ~~increase in~~higher ~~percent~~% water, with no changes in breast volume, while one SD (=11.44kg) increase in pubertal weight growth was associated with a 14% ~~reduction~~ lower (0.86; 0.84, 0.89) ~~in percent~~% water and a 70% ~~increase~~ higher (1.70; 1.58, 1.82) ~~in~~ breast volume. DXA ~~percent~~% body fat mass at age 9 years, and changes from age 9 to 11 and from 11 to 13.5 years, were also found to be independently associated with ~~decreases in~~lower ~~percent~~% water, but only DXA body fat mass at age 9 years was independently (and positively) associated with breast volume. DXA ~~percent~~% body bone mass at age 9 years was positively related to ~~percent~~% water, but did not influence breast volume, whilst increments between ages 13.5 and 15.5 years were inversely associated with breast volume, but did not affect ~~percent~~% water.

Both height-adjusted weight and DXA ~~percentage~~% body fat mass capture body adiposity but~~, interestingly,~~ the inverse association of ~~percent~~% water with pubertal weight growth was associated with ~~increases in the~~higher volumes of both fat and, to a lesser extent, water (fibro-glandular tissue) whereas the inverse associations of ~~percent~~% water with DXA ~~percentage~~% body fat mass resulted entirely from ~~an increase in~~higher fat volume, with no association with water volume (Appendix 6).

Sensitivity analyses

Some of the growth velocities included in our models were strongly correlated (particularly, height and weight pre-pubertal growth; Appendix 9) but examination of variance inflation factors (VIF) for all variables included in models 1-3 found no evidence of multicollinearity, i.e. VIF<10 for all except pre-pubertal height velocity in model 3 for breast volume and % water (VIF=11.2).

However, removal of pre-pubertal height velocity from these models changed minimally (at most ~15%) the standard errors (SEs) of the other variables.

Models that ~~F~~further adjusted~~ment~~ for height and BMI at the MRI examination suffered from multicollinearity (e.g. Model 3, % water, BMI at 21 years: VIF=34.5); hence, the results are not reported~~did not affect the results reported above (not shown)~~. ~~Similarly,~~

~~findings~~Results were comparable when using multiple imputation under MAR to deal with missing confounder and exposure data (Appendices 7-8).

DISCUSSION

Findings from this unique study indicate that height and weight trajectories from birth to age 21 years are associated with breast-tissue composition in young adulthood ~~independently of current body size~~. Puberty does not affect breast-tissue composition independently of height and weight growth.

Strengths and limitations

Strengths of this study include the pre-birth cohort design with multiple indicators of growth, collected prospectively from birth to age 21 years. Breast-tissue measures were obtained from ionising radiation-free MRI examinations, making this the first study to examine the influence of childhood and adolescent growth patterns on breast-tissue composition in young adulthood, prior to changes induced by pregnancies and breastfeeding. Fully-automated and, hence, observer-independent volumetric breast-tissue composition measurements were taken using a previously-developed and evaluated approach (12, 20).

The response rate was low (≈20%), although comparable to a similar MRI breast study (15), but there was no evidence that participants were a biased sample. Data were missing for some variables but analyses of complete records and imputed datasets produced similar findings (albeit under MAR). A weakness~~, however,~~ was the lack of information on age at peak height velocity or, its proxy, the age when adult height was attained.

Consistency with other studies

The finding of an independent association of birthweight with breast-tissue composition is in line with our previous investigation into the relationship between birth size and MRI breast measures in this cohort, as well as our recent systematic review (20). The observed strong independent inverse associations between ~~percent~~% water and adiposity, as ascertained by weight and DXA ~~percent~~% body fat mass, are also consistent with those from previous studies (6-8, 21-25). There is increasing evidence that childhood and adolescent weight is inversely associated with breast cancer risk in pre- (26) and post-menopausal women (7, 26), with one study indicating that the association may be partly mediated by breast density (7).

In our study, both pre-pubertal and pubertal height growth were positively associated with ~~percent~~% water in mutually-adjusted analyses; however, the association with pre-pubertal height growth did not persist upon further adjustment for the DXA body fat mass measurements. As no DXA measurements were taken after age 15.5 years it is conceivable that the pubertal height growth association might be due to residual confounding~~; however, the association persisted after further adjustment for height and weight, or BMI, at the time of the MRI examination~~. Two previous longitudinal cohorts ~~found no evidence~~ did not reveal positive associations ~~that increases in~~between adolescent height growth ~~were associated with increases in~~and breast density (6, 7). Evidence from cross-sectional studies is mixed (15, 23, 24, 27). Between-study heterogeneity may be due to variability in breast density assessment, with those using categorical or binary measures finding no associations with adolescent height growth (6, 7, 27) whilst those based on quantitative methods detecting positive associations (15, 23, 24).

Total body adiposity, as captured by height-adjusted weight and DXA ~~percentage~~% body fat mass, was inversely associated with ~~percent~~% water but positively associated with breast volume. Interestingly, height-adjusted weight was positively associated with both fat and water volumes whilst DXA ~~percentage~~% body fat mass was positively associated with fat volume only. Previous studies have reported positive associations between body adiposity and fibroglandular volume, as estimated by MRI (15) or mammography (28, 29), but null (30) or even inverse associations (31) have also been

observed. Bone mineral density, as a proxy for cumulative exposure to endogenous estrogens, has been found to be positively associated with mammographic density (32) but no relationship between DXA % body bone mass, a proxy for bone density, and breast-tissue composition was observed in our study.

Although ages at thelarche and menarche were found to be associated with ~~percent~~% water, after adjustment for height and weight growth, these markers of pubertal development no longer influenced breast-tissue composition. Previous research has provided evidence in favour of a positive association between age at menarche and breast density (6, 22), in opposition to the well-established inverse association between age at menarche and breast cancer risk (2). However, our findings are consistent with an Australian study that showed that age at menarche did not influence ~~percent~~% density, or breast cancer risk, after accounting for childhood and adolescent BMI (8). These results indicate that it is the changes to the growth velocity during pubertal development, not their timing, which affect breast-tissue composition.

Plausibility

Our ~~F~~findings ~~from this study~~ are consistent with increasing evidence that height and weight growth ~~trajectories~~ in early life, when the mammary glands differentiate and the terminal structure of mammary tissue is determined, are markers of susceptibility to breast cancer later in life (3, 4). However, the specific mechanisms through which growth trajectories may influence breast-tissue composition in young adulthood, and through the latter subsequent breast cancer risk, are not well understood. Findings from Boyd et al. (15) suggest that the positive height – MRI ~~percent~~% water association in premenopausal women may be mediated by growth hormone. Growth factors, e.g. insulin-like growth factor-1 (IGF-1), are known to be positively associated with breast cancer risk (33). Early-life body fatness may decrease the number of menstrual ovulatory cycles and hence reduce circulating levels of sex hormones (34); however, there is conflicting evidence on whether endogenous sex hormones affect breast density in pre-menopausal women (15, 35, 36). Childhood body fatness is also associated with lower levels of IGF-1 (37), and subsequently, slower adolescent growth, which may have a protective effect on breast cancer risk (3, 4).

Conclusions

These findings provide the strongest evidence so far that growth trajectories in early life influence breast-tissue composition in young adulthood and, together with recent evidence that density phenotypes track from young adulthood (38), they raise the prospect that high-risk women can be identified in young adulthood, at an age when they may benefit the most from early prevention strategies (e.g. chemoprevention, tailored screening). Longitudinal studies from puberty to young adulthood will help to further elucidate the early-life origins of breast-tissue composition.

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