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Pubertal growth and adult height in relation to breast cancer risk in African American women

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Abstract

Adult height has been positively associated with breast cancer risk. The timing of pubertal growth – as measured by age at menarche and age at attained height – may also influence risk. We evaluated associations of adult height, age at attained height, and age at menarche with incidence of invasive breast cancer in 55,687 African American women in the prospective Black Women's Health Study. Over 20 years, 1,826 invasive breast cancers [1,015 estrogen receptor (ER) positive; 542 ER negative] accrued. We used multivariable Cox proportional hazards regression to estimate hazards ratios (HRs) and 95% confidence intervals (CIs) for associations with breast cancer overall and by ER status, mutually adjusted for the three factors of interest. Adult height was associated with increased risk of ER+ breast cancer (HR for ≥70 inches vs. ≤63 inches: 1.44; 95% CI: 1.09, 1.89) but not ER- (corresponding HR: 1.16; 95% CI: 0.78, 1.71) (*P*-heterogeneity=0.34). HRs for attained height before age 13 vs. age >17 were 1.30 (95% CI: 0.96, 1.76) for ER+ and 1.25 (95% CI: 0.80, 1.96) for ER- breast cancer. Results for age at menarche (≤11 years vs. ≥14 years) were similar for ER+ and ER- breast cancer (HR for breast cancer overall: 1.30; 95%CI: 1.12, 1.50). We confirmed height as a strong risk factor for ER+ breast cancer in African American women and identified early age at attained height as a risk factor for both ER+ and ER- breast cancer, albeit without statistical significance of the latter associations. While adult height and timing of pubertal growth are inter-related, our findings suggest that they may be independent risk factors for breast cancer.

Keywords

breast cancer; African American; height; pubertal growth; risk; epidemiology

Introduction

It has been hypothesized that adolescence and young adulthood represent critical periods of breast cancer risk accumulation [1], wherein the rapid proliferation of undifferentiated mammary cells confers increased vulnerability to hormonal and other carcinogenic influences [2]. Consistent evidence from epidemiologic studies shows that earlier age at menarche [3–6] and taller adult stature are associated with increased risk of breast cancer

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[7–11]. These associations have been observed in both white [11] and black women [6, 7, 12].

Maximum adult height is determined by several factors, including genetics [13], childhood and adolescent nutrition [14], and cumulative exposure to insulin-like growth factor 1 (IGF-1) and other growth hormones [15, 16]. IGF-1 levels are positively correlated with height in childhood [17–19] while taller height at any age during childhood has been associated with future risk of breast cancer [20–22]. In a large pooled study including >4700 breast cancer cases, a positive association between circulating IGF-1 and breast cancer risk was observed [23]. This association could be explained, at least in part, by IGF-1 stimulation of mitosis and inhibition of apoptosis during pubertal breast development [24, 25].

Less well studied in relation to breast cancer risk are the timing and rate of pubertal growth. Rapid physical growth during puberty may have an important role in breast carcinogenesis [26]. Earlier onset of puberty is thought to reflect earlier exposure to IGF-1 and other growth hormones [15, 27] and a more intense period and/or longer duration of pubertal growth and higher peak height velocity [28]. Thus, pubertal growth patterns could explain the somewhat paradoxical findings that both earlier age at menarche and taller adult height – which are inversely associated with each other [22, 29–31] – are associated with increased risk of breast cancer. Age at attained height is directly correlated with age at peak growth, also known as the pubertal growth spurt [32]. Of six studies published to date that evaluated associations of age at attained height and breast cancer risk [12, 27, 33–36], all but one [34] reported inverse associations. Only one of these studies [12] evaluated associations separately by estrogen receptor (ER) status, but it was limited by small numbers of ER- cases (n=78). Further, except for a preliminary report from the Black Women's Health Study (BWHS), published only in abstract form [37], none of prior studies included sufficient numbers to evaluate African American (AA) women separately. Given known differences in risk factor associations by hormone receptor subtype [38], stronger associations of age at attained height with ER- vs. ER+ breast cancer observed in one previous study [12], and the disproportionately high incidence of ER- breast cancer in AA women, we sought to investigate the joint effects of maximum adult height, age at attained height, and age at menarche on ER- and ER+ breast cancer risk among AA women in the prospective BWHS cohort.

Methods

Study population

The BWHS was established in 1995 with enrollment of 59,000 AA women ages 21 to 69 years (median age, 38 years) [39]. At baseline, women provided information on their medical history as well as demographic, reproductive, lifestyle, and early life factors via mailed self-administered questionnaires. Follow-up is ongoing and participants update information every two years. Notices of deaths are obtained from next-of-kin, the U.S. Postal Service, and yearly searches of the National Death Index. To date, follow-up of the baseline cohort has been successful for 87% of potential person-years.

For this analysis, women were excluded if they had been diagnosed with breast cancer (n=767) or any other type of cancer (except non-melanoma skin cancer) (n=531) before baseline in 1995 as well as if they were missing information on height, age at menarche, or body mass index at age 18 (n=1,303) or reported age at attained height as earlier than age at menarche (n=704); the final analytic cohort included 55,687 AA women ages 21–69 at baseline. The study protocol was approved by the Boston University Institutional Review Board.

Case ascertainment

Incident cases of invasive breast cancer in the BWHS were ascertained through self-report on biennial follow-up questionnaires (95% of cases) or identified through death records and linkage to 24 cancer registries in states covering 95% of participants (5% of cases). Diagnoses were confirmed by review of medical records, pathology reports, and cancer registry records. Data on tumor characteristics were also abstracted from these records. Of cases for which pathology records have been received to date (>80%), more than 99% were confirmed.

Through 2015, we identified 1,826 incident cases of invasive breast cancer, including 542 ER- tumors and 1,015 ER+ tumors; information on ER status was not available for the remaining 269 cases. The distribution of ER status was similar to that reported elsewhere for AA women [40]. In addition, the distribution of breast cancer risk factors was similar in cases with known and unknown receptor status [41, 42].

Exposure and covariate assessment

The baseline questionnaire collected information on established and putative risk factors for breast cancer including adult height, current weight, waist and hip circumferences, age at menarche, weight at age 18, oral contraceptive use, number and timing of births, breast cancer in first-degree relatives, menopausal status, age at menopause, and use of menopausal female hormone supplements. Except for adult height, age at menarche, and weight at age 18, all information was updated on follow-up questionnaires. Self-reports of weight and adult height were significantly correlated with technician measurements in a validation study [43]. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Our main exposures of interest were adult height, age at menarche, and age at attained height. On the 1999 questionnaire, women were asked the age at which they reached their full height, with response categories of “before age 13,” “13 to 17 years of age,” “after age 17,” or “don’t know.” Age at attained height was unknown for approximately 24% of women in the analytic cohort, many of whom had not completed the 1999 questionnaire.

Statistical analyses

For analyses of height and age at menarche, women contributed person-years from the beginning of follow-up in March 1995 until diagnosis of breast or other cancer, death, loss to follow-up, or end of follow-up in March 2015, whichever occurred first (1,046,258 total person-years). For analyses of age at attained height, we began follow-up in 1999 when this information was ascertained. We used Cox proportional hazards regression models, stratified by age in one-year intervals and questionnaire cycle such that age was the underlying time scale, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for adult height, age at attained height, and age at menarche in relation to risk of overall, ER-, and ER+ breast cancer, separately. We considered each factor as a categorical variable and tested for linearity in associations of height and age at menarche by entering the continuous term of the variable in the models. We also evaluated associations of height and age at attained height within strata defined by age at menarche (≤11 years, 12–13 years, and ≥14 years) as well as height within strata of age at attained height (<13 years, 13–17 years, and >17 years).

Multivariable models included mutual adjustment for the three factors of interest and for established breast cancer risk factors and potential confounders: first-degree family history of breast cancer, current BMI (continuous, kg/m^2), parity and age at first birth, oral contraceptive use, menopausal status and age at menopause, estrogen plus progestin use, and education. Exposures and covariates were categorized as shown in Table 1. Time-varying risk factors were updated at each questionnaire cycle. Missing indicator categories were used to account for missing information in covariates (generally 2–4%). *A priori*, we decided not to adjust for BMI at age 18, an established risk factor for breast cancer [44], because it could be a mediator on the pathway between early growth and risk of breast cancer later in life. However, results were virtually unchanged in models that included BMI at age 18 (data not shown). There was no evidence of significant statistical interaction between BMI and menopausal status for risk of ER+ breast cancer in our multivariable models (*P*-values ≥0.13); therefore, we did not retain interaction terms in our final multivariable models. Finally, to test whether associations differed by ER status, we used the contrast test method for heterogeneity by subtype [45]. All analyses were performed using SAS 9.3 (Cary, North Carolina).

Results

Five percent of BWHS participants were ≥70 inches tall at maximum adult height; 17% were at least 68 inches tall. Among those with known age at attained height, the majority (74.5%) reported reaching their maximum height at ages 13 to 17; 7.7% percent reported reaching their adult height prior to age 13 and 17.8% reported reaching their adult height after age 17. Approximately half of all women (52.2%) were 12–13 years old at the time of menarche; 28.8% were ≤11 years and 19.0% were ≥14 years. The distribution of other breast cancer risk factors at baseline is shown in Table 1.

In mutually adjusted models, height was positively associated with breast cancer risk and both age at attained height and age at menarche were inversely associated with risk (Table 2). Overall, the HR for women who were at least 70 inches tall relative to those who were ≤63 inches tall was 1.33 (95% CI: 1.08, 1.63; *P*-value for linearity: 0.04). The observed positive association was restricted to ER+ breast cancer (HR: 1.44; 95% CI: 1.09, 1.89; *P*-value for linearity: 0.04) with no statistically significant association observed for ER- breast cancer (HR: 1.16; 95% CI: 0.78, 1.71; *P*- value for linearity: 0.77); however, there was no evidence of statistical heterogeneity by subtype (*P*-heterogeneity=0.34). Early age at attained height was associated with a 24% increase in risk of breast cancer overall, although not statistically significantly (95% CI: 0.97, 1.57). Associations were similar for ER+ and ER- breast cancer (*P*-heterogeneity=0.90): HRs for attained height at ages <13 years relative to >17 years were 1.30 (95% CI: 0.96, 1.76) for ER+ breast cancer and 1.25 (95% CI: 0.80, 1.96) for ER- breast cancer. As expected, age at menarche was inversely associated with breast cancer risk, with inverse associations for both ER- breast cancer (HR: 1.37 for age at menarche ≤11 vs. ≥14; 95% CI: 1.06, 1.78; *P*- value for linearity: 0.07) and ER+ breast cancer (corresponding HR: 1.27; 95% CI: 1.04, 1.56; *P*-value for linearity: 0.04) (Table 2) (*P*-heterogeneity=0.78).

Adult height was associated with increased risk of ER+ breast cancer within each stratum of age at menarche, with the strongest association observed among women with menarche at ages ≤11 years (HR: 1.84; 95% CI: 1.14, 2.98). There was little evidence of a positive association of height with risk of ER- breast cancer, except among women with menarche at ages 12–13 years (Table 3). Similar patterns of associations were observed when analyses were stratified by age at attained height instead of age at menarche (Table 4).

Age at menarche and age at attained height are moderately positively correlated (r=0.23), but it was still possible to examine the association of age at attained height with breast cancer risk within strata of age at menarche. The weak association of early age at attained height with increased risk of breast cancer was observed at each level of age at menarche, and for both ER+ and ER- breast cancer, with non-statistically significant HRs ranging from 1.15 to 1.35 (Table 5).

Discussion

In this large prospective study of AA women, we found that being taller was associated with increased risk of ER+ breast cancer, but not ER- breast cancer, regardless of age at attained height. There was a suggestion of an increased risk of both ER+ and ER- breast cancer with younger age at attained height, independent of final attained height; however, the elevated HRs did not reach statistical significance. Our finding of a significant positive association between height and breast cancer risk is consistent with most of the current epidemiologic literature on this topic [10], including our earlier report in the BWHS [7], which was based on 674 prevalent and incident cases within the first two years of follow-up. Like others [11, 46], we noted stronger associations of height with risk of ER+ than ER- breast cancer.

The consistently observed association between height and breast cancer risk may reflect hormonal influences during the pubertal growth spurt. In support of this hypothesis, earlier age at menarche is well-established risk factor for breast cancer, with risk increasing by about 5% for every year earlier at menarche, regardless of ER status [5]. In the current analysis, we also found that earlier age at attained adult height was associated with an increased risk of breast cancer, regardless of final height or age at menarche, albeit without statistical significance of the associations. Again, this finding is consistent with results from other studies [12, 27, 33, 35, 36]. In contrast to our observations for adult height, the magnitude of association for age at attained height and breast cancer risk was similar for both ER- and ER+ breast cancer, corresponding to a 25–30% increased risk for women who reached their final adult height by age 13 compared to those who were >17 years old. Only one prior study considered the possibly differential association by ER status, noting a stronger association for ER- breast cancer (HR: 1.9 for age at maximum height ≤12 years vs. ≥17 years; 95% CI: 1.0, 3.9) than with ER+ breast cancer (HR: 1.2; 95% CI: 0.9, 1.7); however, that study included only 78 ER- cases and there was not statistical heterogeneity [12].

It is difficult to disentangle the effects of early age at menarche from those of early age at attained height. Age at menarche is strongly correlated with breast development and also with age at attained height: on average, women reach their final adult height within 2 years of menarche [32]. While girls who go through menarche earlier tend to be taller than their peers during the pubertal years [22, 28], the rapid skeletal growth that accompanies the pubertal growth spurt ends earlier, such that women with early menarche have shorter final adult heights [5, 22, 29–31]. We used age at attained height as a proxy for growth during childhood, as age at attained height is directly correlated with age at peak growth or the pubertal growth spurt [32], and we controlled for age at menarche in multivariable models. The pubertal growth spurt is characterized by high concentrations of estrogens as well as IGF-1 and other growth hormones [17–19, 25, 47]. Li et al. hypothesized that earlier activation of the IGF-1/growth hormone pathway might increase breast cancer risk [27]; later age at attained height could be protective because it reduces the duration of the susceptible period from menarche to terminal differentiation of breast tissue during first pregnancy [33].

Few previous studies have directly assessed growth velocity or timing of the pubertal growth spurt in relation to breast cancer risk. In a British cohort with available data on childhood anthropometric measures, DeStavola et al. [22] found that faster height velocities from ages 4 to 7 years and from ages 11 to 15 years were associated with 54% and 29% increased odds of breast cancer, respectively, and that these associations were especially strong among women with earlier ages at menarche. However, this study was limited by a small number of breast cancer cases (n=59). A derived measure of peak height velocity – estimated based on age at menarche, recalled body fatness at age 10, and final adult height – was also positively associated with breast cancer risk in the prospective Nurses' Health Study (n=806 premenopausal cases, 1485 postmenopausal cases) [26]. In contrast, in a Finnish record-linkage study, there was no apparent association between growth velocity as measured by change in Z score for height from ages 7 to 15 years and breast cancer risk; however, data on age at menarche was not available [20]. Finally, Bodicoat et al. [36] classified women as having had a growth spurt between ages 7 and 11 if their relative height compared to same-aged peers increased by at least one category, but found no association with breast cancer risk. Leg length has also been used as a proxy for exposures during the growth spurt [48], because most of the growth during this period occurs in the long bones [49]. Studies have shown associations of both leg length and sitting height with breast cancer risk [9, 11, 50], suggesting that both pubertal and pre-pubertal growth processes may influence future breast cancer risk.

Two previous studies considered a combination of age at menarche and height and showed a stronger association for breast cancer risk among women with both early menarche and tall stature [11, 22]. In the BWHS, we also found that the positive association between height and ER+ breast cancer was strongest among women who were ≤11 years old at menarche; however, taller height was an important risk factor for ER+ breast cancer regardless of age at menarche.

Some limitations of our analysis are worth noting. First, while current height was accurately reported [43], there may have been inaccurate reporting of age at menarche and age at attained height, which were recalled many years after these events. However, any misclassification would be expected to be non-differential with respect to breast cancer incidence. Second, we designed our question on age at attainment of height to have only three responses (<13, 13–17, later than 17) because our interest was in those with either early or late attainment; we did not expect participants to be able to characterize their age at adult height by exact year. In addition, we lacked information on age at attained height for nearly a quarter of our study population, those who did not complete the 1999 questionnaire or left that question blank, so statistical power was somewhat lower for these analyses. Finally, because all women in this study were AA, results may not be generalizable to other racial or ethnic groups.

The strengths of our study are considerable. With >1100 breast cancer cases, the current analysis is the largest to date to investigate associations of age at attained height with breast cancer risk and the first among AA women, who have a high incidence of the most aggressive subtypes of breast cancer, including ER- disease. Additionally, we were able evaluate the association for both ER+ and ER- breast cancer. Other strengths of this study include the prospective design and adjustment for established breast cancer risk factors that could act as confounders of the association.

In summary, results from this study add to the accumulating evidence that exposures during early life play an important role in breast cancer development later in life. While adult height, age at attained height, and age at menarche are inter-related, our findings suggest that they may be independent risk factors for breast cancer. Moreover, observations that earlier age at menarche and earlier age at attained height are associated with risk of both ER- and ER+ breast cancer – with similar magnitudes of association by ER status – while taller adult height is more strongly associated with ER+ than ER- breast cancer, suggest that these factors may reflect distinct etiological pathways for breast carcinogenesis. Further research, especially in the context of large prospective studies, is warranted to elucidate these complex associations.

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Abbreviations

AA African American

ER	estrogen receptor
BMI	body mass index
HR	hazard ratio
CI	confidence interval

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Novelty and impact

While taller adult stature and earlier age at menarche have been consistently associated with increased risk of breast cancer, fewer studies have evaluated age at attained height as a risk factor. Results from the prospective Black Women's Health Study suggest earlier age at attained height – a marker of earlier pubertal growth spurt – is a risk factor for ER+ and ER- breast cancer in African American women, regardless of final adult height and age at menarche.

Table 1

Age-adjusted baseline (1995) characteristics (n=55,687).

Age, mean (SD)	38.7 (10.7)
Body mass index (kg/m^2), mean (SD)	28.0 (6.7)
First-degree family history of breast cancer, %	8.9
Adult height (inches), %	
≤63	30.3
64–65	27.6
66–67	25.3
68–69	11.3
≥70	5.4
Age at attained height (years)[a], %	
>17	13.5
13–17	56.3
<13	5.8
Unknown	24.4
Age at menarche (years), %	
≥14	19.0
12–13	52.2
≤11	28.8
Parity and age at first birth	
Nulliparous, %	35.1
Age at first birth (years), %	
<20	22.1
20–24	23.1
≥25	18.4
Number of births, %	
1	22.1
2	22.7
≥3	19.6
Recent use of oral contraceptives (<5 years), %	27.5
Menopausal status, %	
Premenopausal	76.9
Postmenopausal	16.8
Unknown/missing	6.3
Estrogen plus progestin use, %	
Never	96.2
<5 years duration	2.8
≥5 years duration	1.0
Education (years), %	
≤12	19.0
13–15	36.1

16	23.8
≥17	21.0

Values are means or percentages standardized to the age distribution of the study population. Percentages may not sum to 100% due to missing data.

[a]Queried in 1999.

Table 2

Adult height, age at attained height, and age at menarche in relation to breast cancer incidence, 1995–2015.

		All invasive breast cancer (n=1,826)			ER+ breast cancer (n=1,015)			ER- breast cancer (n=542)		
	Person-years	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*
Adult height (inches)[a]										
≤63	316,811	541	1.0	Ref	294	1.0	Ref	170	1.0	Ref
64–65	288,848	516	1.08	(0.96, 1.22)	294	1.14	(0.97, 1.34)	144	0.96	(0.77, 1.20)
66–67	264,673	464	1.09	(0.96, 1.23)	261	1.12	(0.95, 1.33)	135	1.00	(0.80, 1.26)
68–69	119,411	196	1.09	(0.92, 1.28)	102	1.04	(0.83, 1.30)	63	1.11	(0.83, 1.48)
≥70	56,515	109	1.33	(1.08, 1.63)	64	1.44	(1.09, 1.89)	30	1.16	(0.78, 1.71)
per 1-inch increase	1,046,258	1,826	1.02	(1.00, 1.04)	1,015	1.02	(1.00, 1.05)	542	1.01	(0.97, 1.04)
P-value[b]				0.04			0.04			0.77
Age at attained height (years)[a,c]										
>17	142,431	201	1.0	Ref	122	1.0	Ref	55	1.0	Ref
13–17	594,043	843	0.98	(0.84, 1.15)	499	0.96	(0.78, 1.17)	264	1.11	(0.83, 1.48)
<13	61,203	117	1.24	(0.97, 1.57)	75	1.30	(0.96, 1.76)	34	1.25	(0.80, 1.96)
Age at menarche (years)[a]										
≥14	198,945	308	1.0	Ref	164	1.0	Ref	96	1.0	Ref
12–13	546,800	965	1.22	(1.07, 1.39)	552	1.30	(1.09, 1.55)	266	1.07	(0.85, 1.36)
≤11	300,514	553	1.30	(1.12, 1.50)	299	1.27	(1.04, 1.56)	180	1.37	(1.06, 1.78)
per 1-year increase	1,046,258	1,826	0.96	(0.93, 0.99)	1,015	0.96	(0.92, 1.00)	542	0.95	(0.90, 1.00)
P-value[b]				<0.01			0.04			0.77

ER, estrogen receptor; HR, hazard ratio; CI, confidence interval Multivariable HRs are adjusted for age, questionnaire cycle, family history of breast cancer, current BMI (continuous, kg/m^2), parity/age at first birth, oral contraceptive use, menopausal status, estrogen plus progestin use, and education.

[a]Models additionally include mutual adjustment for variables noted.

[b]Based on continuous term in multivariable model.

[c]Follow-up for this analysis begins in 1999.

Table 3

Adult height in relation to breast cancer incidence, stratified by age at menarche, 1995–2015.

	Age at menarche ≥14 years									
		All invasive breast cancer (n=308)			***ER+ breast cancer (n=164)***			***ER- breast cancer (n=96)***		
	Person-years	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***
Adult height (inches)										
≤63	51,178	94	1.0	Ref	45	1.0	Ref	36	1.0	Ref
64–65	51,632	79	0.84	(0.62, 1.13)	42	0.93	(0.61, 1.43)	21	0.59	(0.34, 1.02)
66–67	55,237	71	0.71	(0.52, 0.96)	40	0.83	(0.54, 1.27)	19	0.50	(0.29, 0.88)
68–69	25,974	37	0.78	(0.53, 1.15)	21	0.89	(0.52, 1.51)	13	0.74	(0.39, 1.42)
≥70	14,925	27	1.14	(0.74, 1.75)	16	1.43	(0.80, 2.55)	7	0.81	(0.35, 1.83)
per 1-inch increase	198,946	308	0.98	(0.94, 1.02)	164	1.01	(0.95, 1.06)	96	0.95	(0.89, 1.02)
P-value[a]				0.35			0.85			0.19
	Age at menarche 12–13 years									
		All invasive breast cancer (n=965)			*ER+ breast cancer (n=552)*			*ER- breast cancer (n=266)*		
	Person-years	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*
Adult height (inches)										
≤63	159,398	245	1.0	Ref	141	1.0	Ref	67	1.0	Ref
64–65	153,590	304	1.33	(1.12, 1.57)	183	1.41	(1.13, 1.76)	77	1.20	(0.87, 1.67)
66–67	139,513	260	1.27	(1.06, 1.51)	153	1.31	(1.04, 1.65)	73	1.27	(0.91, 1.77)
68–69	64,708	100	1.15	(0.91, 1.45)	47	0.94	(0.67, 1.31)	31	1.27	(0.82, 1.94)
≥70	29,591	56	1.44	(1.08, 1.93)	28	1.27	(0.84, 1.91)	18	1.66	(0.98, 2.81)
per 1-inch increase	546,800	965	1.03	(1.01, 1.06)	552	1.02	(0.99, 1.05)	266	1.04	(1.00, 1.09)
P-value[a]				<0.01			0.23			0.06
	Age at menarche ≤11 years									
		All invasive breast cancer (n=553)			*ER+ breast cancer (n=299)*			*ER- breast cancer (n=180)*		
	Person-years	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*
Adult height (inches)										
≤63	106,236	202	1.0	Ref	108	1.0	Ref	67	1.0	Ref
64–65	83,626	133	0.87	(0.70, 1.08)	69	0.84	(0.62, 1.14)	46	0.90	(0.62, 1.31)
66–67	69,923	133	1.07	(0.86, 1.33)	68	1.02	(0.75, 1.39)	43	1.03	(0.70, 1.52)

		Age at menarche ≥14 years								
		All invasive breast cancer (n=308)			***ER+ breast cancer (n=164)***			***ER- breast cancer (n=96)***		
	Person-years	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***
68–69	28,729	59	1.22	(0.91, 1.64)	34	1.34	(0.91, 1.98)	19	1.13	(0.68, 1.90)
≥70	12,000	26	1.27	(0.84, 1.91)	20	1.84	(1.14, 2.98)	5	0.70	(0.28, 1.74)
per 1-inch increase	300,514	553	1.02	(0.99, 1.05)	299	1.04	(1.00, 1.09)	180	0.98	(0.93, 1.04)
P-value[a]				0.33			0.04			0.47

ER, estrogen receptor; HR, hazard ratio; CI, confidence interval Multivariable HRs are adjusted for age, questionnaire cycle, family history of breast cancer, current BMI (continuous, kg/m^2), parity/age at first birth, oral contraceptive use, menopausal status, estrogen plus progestin use, education, and age at attained height.

[a]Based on continuous term in multivariable model.

Table 4

Adult height in relation to breast cancer incidence, stratified by age at attained height, 1999–2015.

		Age at attained height >17 years								
		All invasive breast cancer (n=201)			***ER+ breast cancer (n=122)***			***ER- breast cancer (n=55)***		
	Person-years	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***
Adult height (inches)										
≤63	26,477	51	1.0	Ref	28	1.0	Ref	18	1.0	Ref
64–65	28,870	48	0.91	(0.61, 1.36)	28	0.94	(0.55, 1.59)	12	0.69	(0.33, 1.44)
66–67	31,181	55	1.02	(0.69, 1.51)	35	1.18	(0.71, 1.95)	12	0.69	(0.33, 1.45)
68–69	16,692	26	1.01	(0.62, 1.63)	16	1.10	(0.59, 2.05)	8	0.96	(0.41, 2.27)
≥70	9297	21	1.55	(0.92, 2.62)	15	2.01	(1.05, 3.84)	5	1.13	(0.41, 3.13)
per 1-inch increase	112,517	201	1.04	(0.99, 1.09)	122	1.07	(1.00, 1.14)	55	1.00	(0.91, 1.10)
P-value[a]				0.12			0.04			0.99
		Age at attained height 13–17 years								
		All invasive breast cancer (n=843)			*ER+ breast cancer (n=499)*			*ER- breast cancer (n=264)*		
	Person-years	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*
Adult height (inches)										
≤63	142,785	254	1.0	Ref	148	1.0	Ref	86	1.0	Ref
64–65	131,155	245	1.07	(0.90, 1.27)	149	1.11	(0.89, 1.40)	74	0.96	(0.70, 1.30)
66–67	119,344	195	0.95	(0.79, 1.14)	120	1.00	(0.78, 1.27)	56	0.81	(0.58, 1.13)
68–69	52,167	98	1.16	(0.92, 1.47)	56	1.14	(0.84, 1.55)	31	1.08	(0.71, 1.63)
≥70	23,853	51	1.38	(1.02, 1.87)	26	1.24	(0.81, 1.89)	17	1.34	(0.80, 2.27)
per 1-inch increase	469,304	843	1.01	(0.99, 1.04)	499	1.01	(0.98, 1.05)	264	1.00	(0.96, 1.05)
P-value[a]				0.30			0.49			0.98
		Age at attained height <13 years								
		All invasive breast cancer (n=117)			*ER+ breast cancer (n=75)*			*ER- breast cancer (n=34)*		
	Person-years	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*
Adult height (inches)										
≤63	19,319	44	1.0	Ref	27	1.0	Ref	14	1.0	Ref
64–65	11,596	25	0.96	(0.58, 1.57)	18	1.20	(0.65, 2.21)	6	0.74	(0.28, 1.96)
66–67	10,436	33	1.27	(0.80, 2.00)	18	1.14	(0.62, 2.09)	11	1.36	(0.60, 3.07)

		Age at attained height >17 years								
		All invasive breast cancer (n=201)			***ER+ breast cancer (n=122)***			***ER- breast cancer (n=55)***		
	Person-years	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***
68–69	5146	11	0.99	(0.51, 1.94)	9	1.32	(0.61, 2.88)	2	0.59	(0.13, 2.65)
≥70	1801	4	1.01	(0.36, 2.87)	3	1.23	(0.36, 4.18)	1	0.74	(0.09, 5.83)
per 1-inch increase	48,298	117	1.00	(0.94, 1.07)	75	1.03	(0.95, 1.11)	34	0.98	(0.87, 1.11)
P-value[a]				0.96			0.52			0.76

ER, estrogen receptor; HR, hazard ratio; CI, confidence interval Multivariable HRs are adjusted for age, questionnaire cycle, family history of breast cancer, current BMI (continuous, kg/m^2), parity/age at first birth, oral contraceptive use, menopausal status, estrogen plus progestin use, education, and age at menarche.

[a]Based on continuous term in multivariable model.

Table 5

Age at attained height in relation to breast cancer incidence, stratified by age at menarche, 1999–2015.

Age at menarche ≥14 years										
		All invasive breast cancer (n=205)			***ER+ breast cancer (n=118)***			***ER- breast cancer (n=60)***		
	Person-years	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***	***Cases***	***HR***	***95% CI***
Age at attained height (years)										
>17	30,697	49	1.0	Ref	26	1.0	Ref	13	1.0	Ref
13–17	84,657	156	1.15	(0.83, 1.59)	92	1.26	(0.81, 1.97)	47	1.29	(0.69, 2.41)
Age at menarche 12–13 years										
		All invasive breast cancer (n=609)			*ER+ breast cancer (n=371)*			*ER- breast cancer (n=181)*		
	Person-years	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*
Age at attained height (years)										
>17	58,808	111	1.0	Ref	69	1.0	Ref	31	1.0	Ref
13–17	256,149	462	0.94	(0.76, 1.15)	277	0.89	(0.68, 1.16)	140	1.03	(0.70, 1.52)
<13	14,737	36	1.21	(0.83, 1.76)	25	1.32	(0.83, 2.09)	10	1.25	(0.61, 2.56)
Age at menarche ≤11 years										
		All invasive breast cancer (n=347)			*ER+ breast cancer (n=207)*			*ER- breast cancer (n=112)*		
	Person-years	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*	*Cases*	*HR*	*95% CI*
Age at attained height (years)										
>17	23,012	41	1.0	Ref	27	1.0	Ref	11	1.0	Ref
13–17	128,498	225	0.95	(0.68, 1.33)	130	0.85	(0.56, 1.29)	77	1.18	(0.63, 2.23)
<13	33,561	81	1.23	(0.84, 1.79)	50	1.15	(0.72, 1.85)	24	1.35	(0.66, 2.78)

ER, estrogen receptor; HR, hazard ratio; CI, confidence interval Multivariable HRs are adjusted for age, questionnaire cycle, family history of breast cancer, current BMI (continuous, kg/m^2), parity/age at first birth, oral contraceptive use, menopausal status, estrogen plus progestin use, education, and adult height.