

Onset of Breast Development in a Longitudinal Cohort

AUTHORS: Frank M. Biro, MD,^a Louise C. Greenspan, MD,^b Maida P. Galvez, MD, MPH,^c Susan M. Pinney, PhD,^d Susan Teitelbaum, PhD,^c Gayle C. Windham, PhD,^e Julianna Deardorff, PhD,^f Robert L. Herrick, MS,^d Paul A. Succop, PhD,^d Robert A. Hiatt, MD, PhD,^g Lawrence H. Kushi, ScD,^h and Mary S. Wolff, PhDⁱ

^aDivision of Adolescent Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ^bDepartment of Pediatrics, Kaiser Permanente, San Francisco, California; ^cDepartment of Preventive Medicine, and ^dDivision of Environmental Health Sciences, Mount Sinai School of Medicine, New York, New York; ^eDepartment of Environmental Health, University of Cincinnati, Cincinnati, Ohio; ^fDivision of Environmental and Occupational Disease Control, California Department of Public Health, Richmond, California; ^gSchool of Public Health, University of California at Berkeley, Berkeley, California; ^hDepartment of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, California; and ⁱDivision of Research, Kaiser Permanente, Oakland, California

KEY WORDS

puberty, girls, breast development, obesity

ABBREVIATIONS

BCERP—Breast Cancer and the Environment Research Program
NHANES—National Health and Nutrition Examination Survey
PROS—Pediatric Research in Office Settings

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Address correspondence to Frank M. Biro, MD, Division of Adolescent Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave (ML-4000), Cincinnati OH 45229-3029.
E-mail: frank.biro@cchmc.org

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WHAT'S KNOWN ON THIS SUBJECT: Several studies have documented earlier onset of pubertal maturation in girls, with several potential factors attributed to the earlier onset.



WHAT THIS STUDY ADDS: This study demonstrates earlier maturation in white non-Hispanic girls, with greater BMI linked as a major factor. The entire distribution of pubertal timing has shifted to a younger age, suggesting redefinition of ages for both early and late maturation.

abstract



BACKGROUND AND OBJECTIVES: There is growing evidence of pubertal maturation occurring at earlier ages, with many studies based on cross-sectional observations. This study examined age at onset of breast development (thelarche), and the impact of BMI and race/ethnicity, in the 3 puberty study sites of the Breast Cancer and the Environment Research Program, a prospective cohort of >1200 girls.

METHODS: Girls, 6 to 8 years at enrollment, were followed longitudinally at regular intervals from 2004 to 2011 in 3 geographic areas: the San Francisco Bay Area, Greater Cincinnati, and New York City. Sexual maturity assessment using Tanner staging was conducted by using standardized observation and palpation methods by trained and certified staff. Kaplan-Meier analyses were used to describe age at onset of breast maturation by covariates.

RESULTS: The age at onset of breast stage 2 varied by race/ethnicity, BMI at baseline, and site. Median age at onset of breast stage 2 was 8.8, 9.3, 9.7, and 9.7 years for African American, Hispanic, white non-Hispanic, and Asian participants, respectively. Girls with greater BMI reached breast stage 2 at younger ages. Age-specific and standardized prevalence of breast maturation was contrasted to observations in 2 large cross-sectional studies conducted 10 to 20 years earlier (Pediatric Research in Office Settings and National Health and Nutrition Examination Survey III) and found to have occurred earlier among white, non-Hispanic, but not African American girls.

CONCLUSIONS: We observed the onset of thelarche at younger ages than previously documented, with important differences associated with race/ethnicity and BMI, confirming and extending patterns seen previously. These findings are consistent with temporal changes in BMI. *Pediatrics* 2013;132:1–9

Over the past several years, multiple studies have reported an earlier age at onset of breast development. In 2007, a consensus panel reported there were sufficient data to suggest a trend toward earlier breast development in the United States over the second half of the 20th century.¹ This trend has been noted internationally as well; for example, girls in the Copenhagen Puberty Study experienced breast development nearly a year earlier than those born 15 to 16 years previously.² These findings have been linked temporally to the increase in BMI and prevalence of obesity. The relationship between higher BMI and earlier onset of puberty in girls has been noted previously; in 2 large cross-sectional studies, Pediatric Research in Office Settings (PROS) and the National Health and Nutrition Examination Survey (NHANES) III, earlier maturation occurred in those girls with greater BMI³ and in those with BMI \geq 85th percentile.⁴ Here we report on timing of breast development from a longitudinal cohort of girls recruited at ages 6 to 8 years, to examine pubertal timing in association with higher BMI and by race/ethnicity.

METHODS

This project was carried out as part of the National Institute of Environmental Health Sciences/National Cancer Institute Breast Cancer and the Environment Research Program (BCERP). The Puberty Study of the BCERP is investigating environmental exposures and onset of puberty in girls, and has been described in detail elsewhere.⁵ Girls were enrolled between 2004 and 2008 at 6 through 8 years of age. They were recruited through the 3 puberty study sites of the Breast Cancer and the Environment Research Program: the San Francisco Bay Area in California (through members of Kaiser-Permanente of Northern California), the greater Cincinnati metropolitan area in Ohio and Kentucky

(through local schools, and Breast Cancer Registry of Greater Cincinnati), and east and central Harlem in New York City, New York (through community centers, clinics, and local schools).⁶ Recruitment was through a combined convenience sample at each site, with the sampling frame defined as those age-eligible girls in Kaiser Permanente membership at defined sites, selected schools in greater Cincinnati, or with a clinic appointment in Harlem. Each site had a time frame for recruitment, and used printed material for recruitment, describing the study as “a project of girls growing up today.” The current report includes longitudinal data in scheduled semiannual (Cincinnati) or annual visits (Mount Sinai and Kaiser Permanente of Northern California) through March 2012, with mean follow-up of 4.3 years. The local institutional review board approved the study at each center; consent was obtained from the parent/legal guardian, and assent was obtained from participants once they reached 10 years of age.

Sexual maturity was established through a standardized method based on Tanner staging.⁷ Breast development was assessed through both observation and palpation.⁵ Professional staff were trained and certified, and periodic cross-site validation was performed by a master trainer visiting all 3 sites. Onset of breast development was defined as attaining breast stage 2 or greater. We had noted previously that examiners had 87% agreement (ie, same breast stage) with a master trainer in blinded field assessments; the remaining assessments were within 1 stage.⁵

During the examination visits, trained and certified staff members obtained standardized anthropometric measurements, including height and weight, and made 2 measurements of each parameter. If the difference exceeded a preset amount, or the amount was

outside the 5th to 95th percentile values, a third measurement was taken and an average of the values was used for analysis. BMI was calculated from the mean values of height and weight measurements, as weight divided by the square of height. BMI percentile and z score were determined by using the 2000 growth charts from the Centers for Disease Control and Prevention (www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm).

We tested for the difference in median values for BMI percentile across sites by using the 2-sample median test, and for the difference proportions in race/ethnicity and BMI percentile groups across sites using the χ^2 and Fisher's exact tests. Survival analyses were performed by using SAS PROC LIFEREG (SAS Institute, Inc, Cary, NC) first to estimate age of breast development and then SAS PROC LIFETEST to determine the effect of race, education of head of household (as a proxy for socioeconomic status), site, and BMI on age of breast development.

The first step in these analyses was to determine an estimated date of breast development (thelarche). For these analyses, a “breast development interval” was defined for each participant. For girls who reached Tanner breast stage 2 or greater during follow-up (interval censored), the interval was defined as the period from the last research study visit at breast stage 1 to the first visit where the girls was noted to be at breast stage 2 or greater. For some girls, progression through breast stages was not consistent, such as apparent regression of breast stage 2 to breast stage 1 at a subsequent visit. For these girls, the breast development interval encompassed the period of inconsistency, until a consistent B2 was observed. For girls who were left-censored (breast stage 2 or greater at the first study visit), the beginning of the interval was defined as

the race-specific 1.0 percentile value of age from the PROS study data (data supplied by M. Herman-Giddens, PhD (personal communication, 2012), and the end of the interval was the date of the initial research study visit when breast stage 2 was observed. For both interval-censored and left-censored girls, an estimated date of breast development was calculated within the interval using age at the beginning and end of the interval as covariates. The estimated date of thelarche was calculated as the date associated with the median probability over the breast development interval. These probabilities were calculated for each girl by using an SAS macro developed by us, which incorporated σ (σ , the scale parameter of the Weibull distribution from LIFEREG)⁸ and the $x^T B$ matrix for the girl, and the dates at the beginning and end of her thelarche interval.

Kaplan-Meier analyses were used to determine mean and median age at breast development, incorporating interval censored data, with the SAS application LIFETEST. The Wilcoxon test was used to test trend across strata. For hazard function estimations, the validity of the proportionality assumption was assessed by plotting the log-log of the estimated survival function against survival time; these plots were parallel, so the proportionality assumption was valid. Time ratios and hazard ratios, with 95% confidence intervals, were calculated from the accelerated failure time model using a Weibull distribution derived by Carroll.⁹ This model accounts for varying amounts of time and varying ages of the girls while under observation. For these analyses, girls who were right-censored (never at breast stage 2 or greater while under observation) contributed to observational time, but no breast development event, to the analyses. We used PROC GLM to determine the proportion of the variance attributable to each of the covariates.

We compared results of age at breast development with cross-sectional data sets from PROS published by Kaplowitz et al³ and by Herman-Giddens et al.⁹ Differences between our data and the mean age of attaining breast stage 2 in the PROS data set were tested with a 2-sample *t* test, assuming unequal variance. Differences in age-specific prevalence of breast stage 2 or greater were examined by using χ^2 and Fisher's exact test.

RESULTS

The baseline cohort included 1239 girls (Table 1). The percentage of BCERP girls with BMI \geq 85th percentile included 39% of black, 44% of Hispanic, 26% of white non-Hispanic, and 12% of Asian girls. Differences in the distribution of BMI percentile groups by race and site were examined; the only significant difference noted was that at the end of follow-up, the distribution of BMI percentile groups for blacks differed significantly between Greater Cincinnati and the San Francisco Bay Area ($P = .028$), but not New York City and the San Francisco Bay Area ($P = .174$) or New York City and Greater Cincinnati ($P = .150$). The proportion of girls who had attained breast stage 2 during the study varied by age, race/ethnicity, BMI percentile, and site (Table 1 and 2). Mean and median ages of breast stage 2 varied by race/ethnicity, and were 8.8 and 8.8 years for black, 9.2 and 9.3 for Hispanic, 9.6 and 9.7 for non-Hispanic white, and 9.9 and 9.7 for Asian participants (Table 2). Hispanic BCERP participants had maturation at significantly older ages than black participants, and younger than non-Hispanic white BCERP participants. Girls in all BMI categories $>$ 50th percentile were progressively more likely to have reached breast stage 2 than those $<$ 50th percentile (P value for trend = .001), adjusting for race/ethnicity and site (Table 2); differences by race/ethnicity remained significant in adjusted models.

We examined the cumulative prevalence of breast stage 2 or greater by age, race/ethnicity, and BMI status ($<$ 85th percentile vs \geq 85th percentile). As noted in Figs 1 and 2, regardless of race (as well as ethnicity, not shown), participants with BMI \geq 85th percentile matured earlier than those $<$ 85th percentile.

Non-Hispanic white BCERP participants matured earlier than white participants in the PROS study (mean age 9.62 vs 9.96 years, $P = .0005$) (Fig 1). However, non-Hispanic white participants with BMI $<$ 85th percentile did not mature earlier than PROS white participants (mean age 9.84 vs 9.96, $P = .34$). Black BCERP participants matured at similar ages in both studies ($P = .36$), although those of higher BMI were younger (Fig 2).

Non-Hispanic white BCERP participants matured earlier than white PROS participants at every age between 7 and 12 years (Table 3). Of note, BMI accounted for the greatest amount of variance (14.2%) of all covariates included in the model, contrasted to race, which accounted for 4.4% of the variance. The proxy for socioeconomic status, education level of head of household, did not remain in the model.

DISCUSSION

This study examined timing of onset of breast development in an ongoing longitudinal study of girls. We observed the onset of breast development in white girls at younger ages than reported in previous publications, suggesting a continued trend to earlier ages of breast development; black girls continue to experience breast development earlier than white girls.

Higher BMI was the strongest predictor of earlier age at breast stage 2 in our study. Similar findings have been reported that noted the association between BMI and body fat with earlier timing of puberty in girls,^{2-4,10-13} although these data support, but do not establish, causality.

TABLE 1 BCERP Puberty Study Population Characteristics

Characteristic	New York City		Cincinnati		San Francisco Bay Area		Total Study Population	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Total no. of participants	416	34	379	31	444	36	1239	100
Age group at enrollment								
6.0–6.9 y	154	37	154	41	88	20	396	32
7.0–7.9 y	136	33	187	49	334	75	657	53
≥8.0 y	126	30	38	10	22	5	186	15
Mean age at enrollment, (y)	7.4 (0.9)		7.1 (0.6)		7.4 (0.4)		7.3 (0.7)	
Mean age at end of follow-up, (y)	11.2 (2.2)		11.5 (1.9)		12.0 (1.4)		11.6 (1.9)	
Mean length of follow-up, (y)	3.8 (2.1)		4.4 (1.8)		4.6 (1.3)		4.3 (1.8)	
Race/Ethnicity ^a								
Black	168	40	127	34	96	22	391	32
Asian	0	0	5	1	52	12	57	5
Hispanic	248	60	15	4	108	24	371	30
White	0	0	232	61	188	42	420	34
Education of family provider								
Grade School (1-8), Some High School (9-11) or High School Diploma/GED	232	58	35	10	83	20	350	31
Some College/technical/trade/vocational school or associate's degree	114	29	119	35	136	34	369	32
Bachelor's degree	39	10	106	31	128	32	273	24
Master's degree or greater	13	3	84	24	55	14	152	13
BMI% group at enrollment ^b								
>95th	97	23	52	14	67	15	216	17
85th–94.9th	66	16	62	16	65	15	193	16
50th–84.9th	135	32	122	32	163	37	420	34
<50th	116	28	143	38	149	34	408	33
No BMI data	2	0	0	0	0	0	2	0
Median BMI percentile at enrollment ^c	74.4		64.0		69.1		70.1	
BMI% group during follow-up ^{d,e}								
>95th	102	25	58	15	67	15	227	18.3
85th–94.9th	64	15	69	18	72	16	205	16.5
50th–84.9th	128	31	112	30	154	35	394	31.8
<50th	120	29	140	37	151	34	411	33.2
No BMI data	2	0	0	0	0	0	2	0.2
Median BMI% during follow-up ^d								
All girls ^f	76.3		65.8		66.4		70.9	
Girls at/above the 85th percentile only ^g	96.5		94.2		94.8		95.3	
Girls below the 85th percentile only ^h	52.7		44.9		50.1		48.7	
Thelarche								
Breast stage 2+ at enrollment	90	22	55	15	33	7%	178	14
Breast stage 2+ observed during study	244	59	278	73	359	81%	881	71
Not attained breast stage 2+ by end of follow-up	82	20	46	12	52	12%	180	15

^a Racial distributions were significantly different across sites ($P < .0001$).

^b BMI percentile groups were significantly different across sites ($P = .0021$); Greater Cincinnati ($P = .0013$) and the San Francisco Bay Area ($P = .0107$) were significantly different from New York City, but not each other ($P = .4125$).

^c Median BMI at enrollment in Cincinnati was significantly lower than New York City ($P = .0095$), but not the San Francisco Bay Area ($P = .3095$); New York City and the San Francisco Bay Area were not significantly different ($P = .1013$).

^d For girls who were breast stage 2+ at enrollment, BMI% during follow-up is BMI% at enrollment. For girls in whom breast stage 2+ was first observed during the study, BMI% during follow-up is the BMI% at the last exam with data before thelarche. For girls who had not attained breast stage 2+ by the end of follow-up, BMI% during follow-up is the BMI% at their last exam.

^e Distribution of BMI percentile groups for all girls at end of follow-up were significantly different across sites ($P = .0021$); Greater Cincinnati ($P = .0039$) and the San Francisco Bay Area ($P = .0055$) were significantly different from New York City, but not each other ($P = .4502$).

^f Median BMI percentile for all girls at end of follow-up in New York City was significantly higher than Cincinnati ($P = .0062$), and the San Francisco Bay Area ($P = .0041$); Cincinnati and the San Francisco Bay Area were not significantly different ($P = .9699$).

^g Median BMI percentile for girls at/above the 85th percentile at end of follow-up in New York City was significantly higher than Cincinnati ($P = .0018$), but not the San Francisco Bay Area ($P = .0576$); Cincinnati and the San Francisco Bay Area were not significantly different ($P = .7132$).

^h Median BMI percentile for girls below the 85th percentile at end of follow-up were not significantly different across sites ($.0669 \leq P \leq .5817$).

Longitudinal studies have demonstrated this relationship, where BMI, BMI z scores, and adiposity as early as 3 years of age were related to pubertal

outcomes, including onset of breast development, onset of the pubertal growth spurt, and age of menarche.^{2,14–19} The obesity epidemic appears to be a

prime driver in the decrease in age at onset of breast development in contemporary girls. In our study, white non-Hispanic BCERP participants with BMI

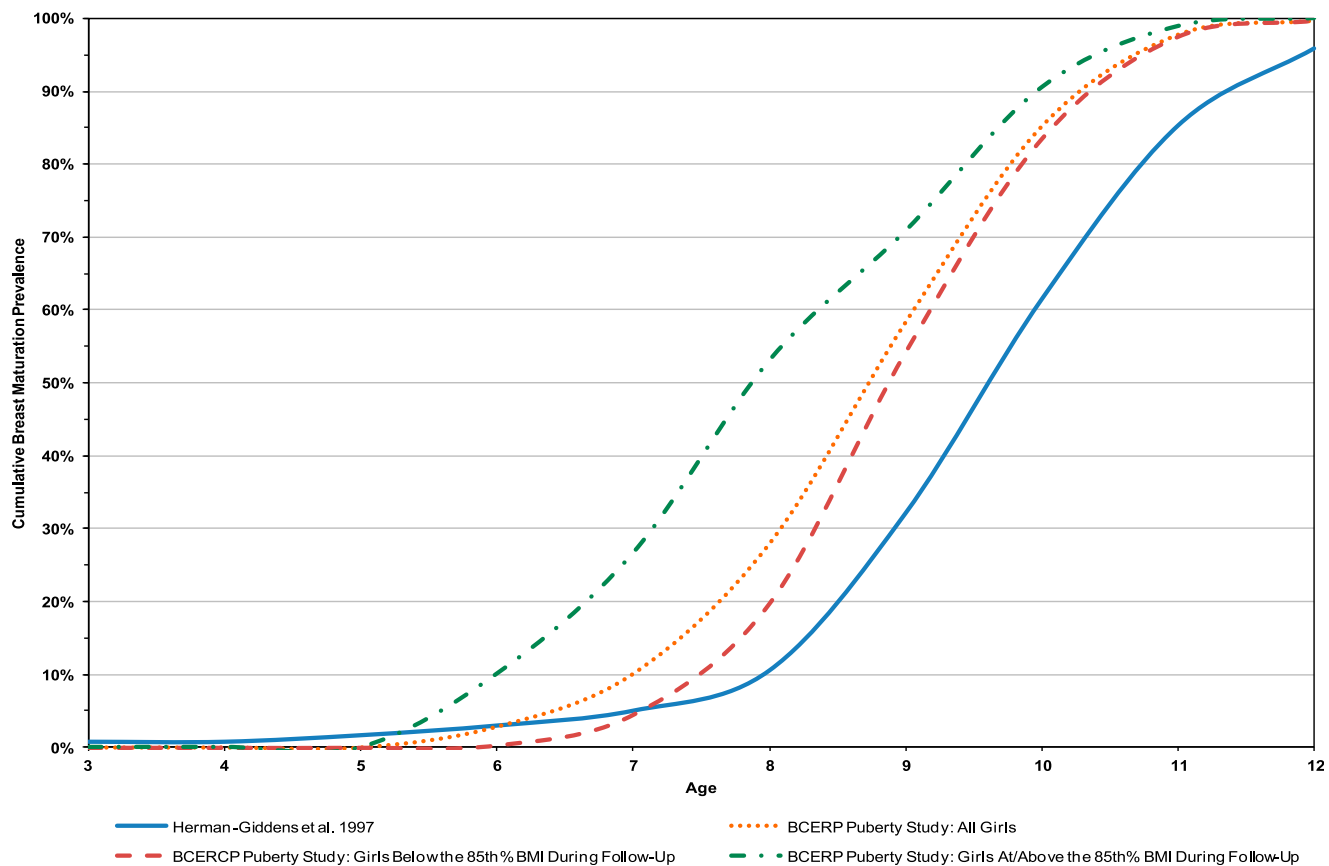
TABLE 2 Age at Thelarche and Hazard Ratios by BMI Percentile During Follow-Up, Race/Ethnicity and Site

Strata	Unadjusted Age (in Years) at Thelarche From Kaplan-Meier Survival Analysis ^a						Adjusted Likelihood of Thelarche By End of Follow-up From AFT Model ^b						
	<i>n</i>	Observed	Censored	Median	Mean	SE	Time Ratio	95% CI		Hazard Ratio	95% CI		<i>P</i> value
All girls	1239	1039	200	9.40	9.26	0.04	—	—	—	—	—	—	—
BMI percentile group during follow-up ^c													
>95th	227	195	32	8.50	8.44	0.10	0.86	0.84	0.88	3.20	2.67	3.84	<.0001
85th–94.9th	205	181	24	8.70	8.69	0.11	0.89	0.87	0.91	2.60	2.18	3.09	<.0001
50th–84.9th	394	330	64	9.20	9.23	0.07	0.93	0.91	0.95	1.82	1.59	2.07	<.0001
<50th	411	333	78	10.10	9.99	0.07	1.00			1.00			
Race/Ethnicity													
Non-Hispanic white	420	355	65	9.70	9.62	0.06	1.06	1.04	1.08	0.62	0.54	0.72	<.0001
Asian	57	50	7	9.70	9.92	0.15	1.04	1.00	1.08	0.72	0.56	0.94	.0428
Hispanic	371	310	61	9.30	9.23	0.08	1.05	1.03	1.07	0.69	0.60	0.81	<.0001
Black	391	324	67	8.80	8.76	0.08	1.00			1.00			
Site													
New York City	416	330	86	9.10	9.03	0.08	1.00			1.00			
Cincinnati	379	321	58	8.90	8.88	0.08	0.94	0.92	0.97	1.58	1.37	1.81	<.0001
San Francisco Bay Area	444	388	56	9.80	9.76	0.06	1.03	1.01	1.05	0.77	0.66	0.90	.0028

^a Girls who did not reach thelarche before end of follow-up are censored.

^b Hazard ratios and 95% confidence intervals calculated as described by Carroll.⁸

^c For girls who were breast stage 2+ at enrollment, BMI% during follow-up is BMI% at enrollment. For girls in whom breast stage 2+ was first observed during the study, BMI% during follow-up is the BMI% at the last examination with data before thelarche. For girls who had not attained breast stage 2+ by the end of follow-up, BMI% during follow-up is the BMI% at their last examination.

**FIGURE 1**

Comparing the cumulative prevalence of Breast Stage 2+ for non-Hispanic white participants between the BCERP Puberty Study and PROS.⁹

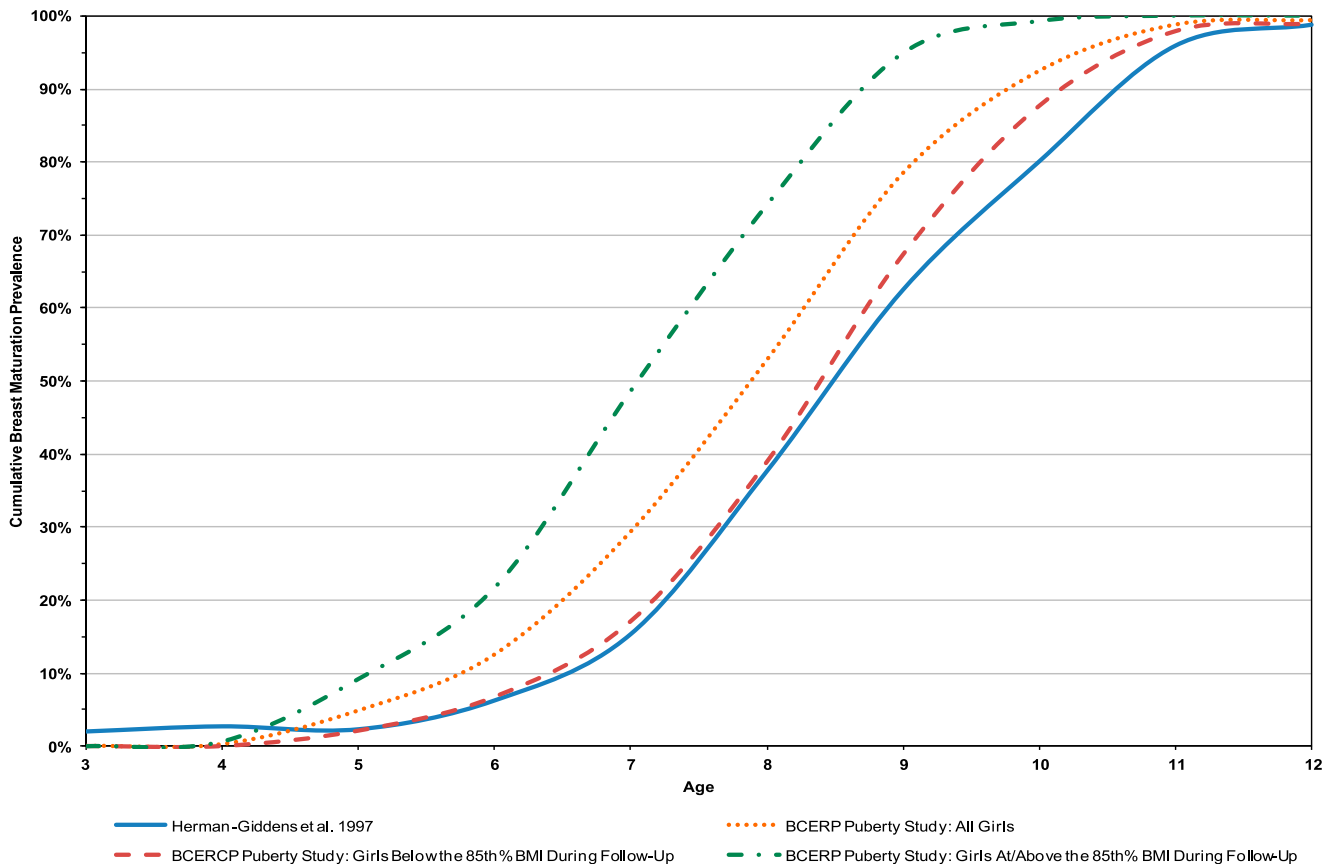


FIGURE 2 Comparing cumulative prevalence of Breast Stage 2+ for non-Hispanic black participants between the BCERP Puberty Study and PROS.⁹

<85th percentile had similar age at breast development as white girls in PROS (9.96 years).^{3,9} The percentage of girls 6 to 11 years of age who were obese in NHANES III (1988–1994), approximately the same time as PROS, was 9.8% for non-Hispanic white and 17.0% for non-Hispanic black girls. By the time of NHANES 2009–2010 (encompassing the age of girls in our study) it was 14.4% for non-Hispanic white and 24.0% for non-Hispanic black girls.²⁰

Several studies have suggested that earlier onset of breast development may occur independent of activation of the hypothalamic-pituitary-ovarian axis,² perhaps through endocrine-disrupting chemicals,^{1,21,22} which we will examine in future manuscripts. In a previous report, Parent et al²³ questioned whether the earliest onset had shifted downward, or if the entire distribution

shifted downward. Our data suggest that white, non-Hispanic girls throughout the entire distribution of relative timing of puberty (early, on-time, and late-maturing girls) are maturing at younger ages than previously reported. The impact of earlier maturation in girls has important clinical implications. Clinicians may need to examine additional contemporary studies to decide whether to lower the age for late maturation in girls, and possibly age of precocious puberty. Both the PROS study and our study excluded girls with pathologic conditions known to modify age of pubertal maturation. However, both studies likely included girls with undiagnosed conditions, such as ovarian cysts, which may explain some of the very early ages at breast development and some of the apparent breast development regression that we

observed. Previous authors have commented on the impact of timing of pubertal maturation, with several psychosocial and biologic outcomes, perhaps due to a discrepancy between biological and psychological transitions.²⁴ Girls with earlier maturation are at risk for lower self-esteem²⁵ and higher rates of depression.²⁶ They are more likely to be influenced by older peers and more deviant peers,²⁷ and initiate intercourse, substance use, and other norm-breaking behaviors at younger ages.^{28–30} Although the greatest impact on these psychosocial outcomes appears during the adolescent years, the impact on adult women who matured early includes greater rates of depression,^{26,29} lower levels of academic achievement,³⁰ and greater number of sexual partners.²⁶ The longer-term impact of early maturation on

TABLE 3 Comparing the Proportion with Breast Stage 2+ by Age Between BCERP Puberty Study Cross-Sectional Equivalent Data and PROS^a

Age Group	Black						White						
	PROS			BCERP Puberty Study ^a			PROS ^c			BCERP Puberty Study ^a			
	Total No. of Girls	Percent at Breast Stage 2+	P Value ^b	Total No. of Girls	Percent at Breast Stage 2+	χ Square ^b	Total No. of Girls	Percent at Breast Stage 2+	P Value ^b	Total No. of Girls	Percent at Breast Stage 2+	χ Square ^b	P Value ^b
6.0–6.9	126	6	.006	100	18	7.43	1506	3	.006	77	4	0.24	.496
7.0–7.9	136	15	.131	257	22	2.28	1128	5	.131	320	10	11.07	.001
8.0–8.9	143	38	.892	294	38	0.02	1334	11	.892	363	21	29.39	<.0001
9.0–9.9	115	63	.971	282	62	0.00	1067	32	.971	379	42	12.50	.000
10.0–10.9	112	80	.098	269	87	2.73	1153	62	.098	340	71	10.01	.002
11.0–11.9	126	96	.999	190	96	0.02	1104	85	.999	244	92	8.15	.004
12.0–12.9	91	99	.999	133	99	0.07	923	96	.999	156	98	1.63	.256

^a Every B visit in the BCERP Puberty Study was treated as if it were a separate girl; missing visits or visits with refused Tanner staging not included.

^b Fisher's Exact Test used where cell frequency is ≤ 5 .

^c PROS did not separate Hispanic and Non-Hispanic white subjects; the BCERP Puberty Study did.

psychosocial functioning may represent a complex interaction between factors associated with earlier maturation, such as family stress, with developmental outcomes during adolescence, such as depression. Several authors have described that girls maturing earlier are perceived to be aging more rapidly or have an accelerated life course, described as “weathering.”^{31,32} It is unclear if these adverse psychosocial outcomes associated with early maturation will be sustained when many girls mature at a younger age. The biologic impact of earlier maturation includes greater risk of several cancers, including breast,³³ ovarian,³⁴ and endometrial cancer,³⁵ as well as obesity, hyperinsulinemia, and hypertension.³⁶ The increased risk of cancer with earlier maturation might be mediated by the increased risk of obesity (reviewed by Renehan et al),³⁷ or through the association of early maturation with greater peak height velocity,^{38,39} or longer exposure to endogenous estrogen production.^{33,40,41}

The study does have several potential limitations. The participants in this study are not nationally representative, so this may limit generalizability, but they do include broad racial/ethnic as well as socioeconomic diversity. Additionally, the BMI distribution of our cohort is similar to those published recently regarding the NHANES data.⁴² There is a potential confounding of early maturation and greater BMI, as several girls were noted to have breast development at time of intake and we did not observe exact age of transition; however, girls in this study with later breast development have lower BMI values, consistent with the impact of BMI on timing of puberty. Additionally, the determination of age of breast development used a somewhat novel application of a well-established approach, an accelerated failure time model (specifically the Weibull model), which both allows determination of event rates as well as extension in survival time.⁸ The

direct comparison of our participants, from a longitudinal study, with participants from 2 cross-sectional studies that used different BMI standards from this study, might appear to be of limited relevance; when we excluded our participants with elevated BMI, the BMI distribution is similar to the results reported by Kaplowitz et al³ and by Rosenfield et al,⁴ and the remaining participants had similar age of breast maturation. Unlike the NHANES III and most (61%) of PROS participants, we used breast palpation for all of our participants, but this should have increased the age of breast development, rather than decreased it. Although BCERP participants appear to have a younger median age at breast stage 2 than NHANES III participants, because of the differences in study design methods we were unable to conduct statistical analyses to determine the difference in age between the 2 groups. Multiple studies have cautioned against overclassification of breast tissue in girls with greater BMI, particularly after onset of the obesity epidemic. Our study procedure used palpation as well as inspection, which limits misclassification of fat tissue deposited in the chest area. Additionally, as

previously reported, we validated our maturation assessment procedures with dual breast-development assessment, which demonstrated substantial agreement between examiners.⁵ Study site has a significant effect on the age of breast development, with effects for the Cincinnati (hazard ratio 1.58) and the San Francisco Bay Area (hazard ratio 0.77) sites being statistically different than the New York City site, which enrolled only black and Hispanic girls. The earlier age at maturation in Cincinnati may be attributed, in part, to performing maturation assessments every 6 months rather than once each year, which could account for an earlier age by 3 to 4 months (data not shown). The later age at maturation in the San Francisco Bay Area could represent other factors not included, such as country of origin differences not captured in our categorization of race and ethnicity, exposures, or lifestyle factors. In addition, our models may not have adequately accounted for differences in race/ethnicity and BMI at the 3 sites. Last, younger age of breast development may not lead to earlier age of menarche; this relationship will be examined when the sample achieves later pubertal milestones.

CONCLUSIONS

We noted earlier onset of breast stage 2 in non-Hispanic white girls, contrasted with 2 previous studies (PROS and NHANES III); this is likely due to greater obesity in the white non-Hispanic girls in our study compared with earlier reports. Girls with BMI >85th percentile matured earlier than those with lower BMI, and BMI explained much of the difference between studies. Black girls experienced breast development at a similar age to blacks from the 2 previous studies, and continued to mature at ages younger than whites.

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REFERENCES

1. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics*. 2008;121(suppl 3):S172–S191
2. Aksglaede L, Sørensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. *Pediatrics*. 2009;123(5). Available at: www.pediatrics.org/cgi/content/full/123/5/e932
3. Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. *Pediatrics*. 2001;108(2):347–353
4. Rosenfield RL, Lipton RB, Drum ML. The larche, pubarche, and menarche attainment in children with normal and elevated body mass index. *Pediatrics*. 2009;123(1):84–88
5. Biro FM, Galvez MP, Greenspan LC, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. *Pediatrics*. 2010;126(3). Available at: www.pediatrics.org/cgi/content/full/126/3/e583
6. Hiatt RA, Haslam SZ, Osuch J; Breast Cancer and the Environment Research Centers. The breast cancer and the environment research centers: transdisciplinary research on the role of the environment in breast cancer etiology. *Environ Health Perspect*. 2009;117(12):1814–1822
7. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child*. 1969;44(235):291–303
8. Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. *Control Clin Trials*. 2003;24(6):682–701
9. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics*. 1997;99(4):505–512
10. Ahmed ML, Ong KK, Dunger DB. Childhood obesity and the timing of puberty. *Trends Endocrinol Metab*. 2009;20(5):237–242
11. Jasik CB, Lustig RH. Adolescent obesity and puberty: the “perfect storm”. *Ann N Y Acad Sci*. 2008;1135:265–279
12. Kaplowitz PB. Link between body fat and the timing of puberty. *Pediatrics*. 2008;121(suppl 3):S208–S217

13. Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. *Reproduction*. 2010;140(3):399–410
14. Buyken AE, Karaolis-Danckert N, Remer T. Association of prepubertal body composition in healthy girls and boys with the timing of early and late pubertal markers. *Am J Clin Nutr*. 2009;89(1):221–230
15. Davison KK, Susman EJ, Birch LL. Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. *Pediatrics*. 2003;111(4 pt 1):815–821
16. Heger S, Körner A, Meigen C, et al. Impact of weight status on the onset and parameters of puberty: analysis of three representative cohorts from central Europe. *J Pediatr Endocrinol Metab*. 2008;21(9):865–877
17. Lee JM, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH, Lumeng JC. Weight status in young girls and the onset of puberty. *Pediatrics*. 2007;119(3). Available at: www.pediatrics.org/cgi/content/full/119/3/e624
18. Rubin C, Maisonet M, Kieszak S, et al. Timing of maturation and predictors of menarche in girls enrolled in a contemporary British cohort. *Paediatr Perinat Epidemiol*. 2009;23(5):492–504
19. Windham GC, Zhang L, Longnecker MP, Klebanoff M. Maternal smoking, demographic and lifestyle factors in relation to daughter's age at menarche. *Paediatr Perinat Epidemiol*. 2008;22(6):551–561
20. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA*. 2012;307(5):483–490
21. Biro FM, Wolfe MS. Puberty as a window of susceptibility. In: Russo J, ed. *Environment and Breast Cancer*. New York, NY: Springer; 2011:29–41
22. Buck Louis GM, Gray LE Jr, Marcus M, et al. Environmental factors and puberty timing: expert panel research needs. *Pediatrics*. 2008;121(suppl 3):S192–S207
23. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev*. 2003;24(5):668–693
24. Gluckman PD, Hanson MA. Evolution, development and timing of puberty. *Trends Endocrinol Metab*. 2006;17(1):7–12
25. Striegel-Moore RH, McMahon RP, Biro FM, Schreiber G, Crawford PB, Voorhees C. Exploring the relationship between timing of menarche and eating disorder symptoms in black and white adolescent girls. *Int J Eat Disord*. 2001;30(4):421–433
26. Copeland W, Shanahan L, Miller S, Costello EJ, Angold A, Maughan B. Outcomes of early pubertal timing in young women: a prospective population-based study. *Am J Psychiatry*. 2010;167(10):1218–1225
27. Ge X, Conger RD, Elder GH Jr. Coming of age too early: pubertal influences on girls' vulnerability to psychological distress. *Child Dev*. 1996;67(6):3386–3400
28. Deardorff J, Gonzales NA, Christopher FS, Roosa MW, Millsap RE. Early puberty and adolescent pregnancy: the influence of alcohol use. *Pediatrics*. 2005;116(6):1451–1456
29. Graber JA, Seeley JR, Brooks-Gunn J, Lewinsohn PM. Is pubertal timing associated with psychopathology in young adulthood. *J Am Acad Child Adolesc Psychiatry*. 2004;43(6):718–726
30. Johansson T, Ritzén EM. Very long-term follow-up of girls with early and late menarche. *Endocr Dev*. 2005;8(8):126–136
31. Foster H, Hagan J, Brooks-Gunn J. Growing up fast: stress exposure and subjective "weathering" in emerging adulthood. *J Health Soc Behav*. 2008;49(2):162–177
32. Graber JA, Nichols TR, Brooks-Gunn J. Putting pubertal timing in developmental context: implications for prevention. *Dev Psychobiol*. 2010;52(3):254–262
33. Clavel-Chapelon F; E3N Group. Cumulative number of menstrual cycles and breast cancer risk: results from the E3N cohort study of French women. *Cancer Causes Control*. 2002;13(9):831–838
34. Moorman PG, Palmieri RT, Akushevich L, Berchuck A, Schildkraut JM. Ovarian cancer risk factors in African-American and white women. *Am J Epidemiol*. 2009;170(5):598–606
35. McPherson CP, Sellers TA, Potter JD, Bostick RM, Folsom AR. Reproductive factors and risk of endometrial cancer: The Iowa Women's Health Study. *Am J Epidemiol*. 1996;143(12):1195–1202
36. Frontini MG, Srinivasan SR, Berenson GS. Longitudinal changes in risk variables underlying metabolic Syndrome X from childhood to young adulthood in female subjects with a history of early menarche: the Bogalusa Heart Study. *Int J Obes Relat Metab Disord*. 2003;27(11):1398–1404
37. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569–578
38. Ahlgren M, Melbye M, Wohlfahrt J, Sørensen TI. Growth patterns and the risk of breast cancer in women. *Int J Gynecol Cancer*. 2006;16(suppl 2):569–575
39. Li CI, Littman AJ, White E. Relationship between age maximum height is attained, age at menarche, and age at first full-term birth and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2007;16(10):2144–2149
40. MacMahon B, Trichopoulos D, Brown J, et al. Age at menarche, urine estrogens and breast cancer risk. *Int J Cancer*. 1982;30(4):427–431
41. Henderson BE, Ross RK, Judd HL, Krailo MD, Pike MC. Do regular ovulatory cycles increase breast cancer risk? *Cancer*. 1985;56(5):1206–1208
42. Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003–2006. *JAMA*. 2008;299(20):2401–2405

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