Short Communication

Relationship between Age Maximum Height Is Attained, Age at Menarche, and Age at First Full-Term Birth and Breast Cancer Risk

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Abstract

Several pubertal and reproductive events are well established risk factors for breast cancer. Age maximum height attained is an understudied potential breast cancer risk factor that may affect risk through mechanisms different from those of other pubertal and reproductive events. We assessed the relationships between different pubertal/reproductive events and risk of different types of breast cancer in a prospective cohort of 27,536 women. Women were recruited between 2000 and 2002 and completed a mailed questionnaire. As of 2005, 585 women were diagnosed with breast cancer. Using a Cox proportional hazards model, women who reached their maximum height at ≤12 years of age had a 1.4-fold [95% confidence interval (95% CI), 1.0-1.8] increased risk of breast cancer compared with women who reached their maximum height at ≥17 years of age (P_{trend} = 0.04). This association was primarily limited to more aggressive tumors, specifically those that were estrogen receptor–negative (hazard ratio, 1.9; 95% CI, 1.0-3.9) and diagnosed at a regional or distant stage (hazard ratio, 1.8; 95% CI, 1.0-3.1). There was no difference in the relation of age at menarche with breast cancer by tumor stage, whereas late age at first full-term pregnancy primarily increased risks of less-aggressive disease, including lobular, estrogen receptor–positive, and localized stage tumors. Age at maximum height seems to be an independent risk factor for breast cancer that is more strongly associated with relatively aggressive tumors that have a poorer prognosis compared with the types of tumors that are associated with ages at menarche and first full-term birth. (Cancer Epidemiol Biomarkers Prev 2007;16(10):2144–9)

Introduction

Early age at menarche and late age at first full-term pregnancy are two well-established breast cancer risk factors (1, 2). These two ages are associated with breast cancer risk because they mark both the beginning and end of a period over which the nulligravid breast is undifferentiated and, thus, particularly susceptible to the potentially carcinogenic effects of endogenous hormones that circulate with menstrual cycling (3-6). A less studied early-life event that may also be associated with breast cancer risk is the age maximum adult height is attained. We first reported an inverse association between the age maximum height is reached and premenopausal breast cancer risk in 1997 (7), and this finding has since been replicated in three (8-10) of four studies (11). The three studies with consistent results each focused on different populations of women including postmenopausal U.S. women (9), African American women (10), and Danish women (8). A later age at attained height is a marker of having a later pubertal growth spurt. So a potential hypothesis explaining this association is that an earlier exposure to the undifferentiated nulligravid breast to the high levels of growth hormones and insulin-like growth factor-I, which accompany pubertal growth spurts, may increase breast cancer risk (7, 12). There is also evidence that the earlier puberty begins, the greater the intensity and duration of the pubertal growth peak (13).

We evaluated the understudied association between age maximum adult height is attained and breast cancer risk over age 50 in the VITamins And Lifestyle study, a large prospective study. We also compared this association with the risks associated with two other early-life events that are well-established breast cancer risk factors, age at menarche and age at first full-term birth.

Materials and Methods

The VITamins And Lifestyle study is a prospective cohort of women and men between the ages of 50 and 76 years living in the 13 county areas of western Washington State covered by the Seattle-Puget Sound

Received 3/22/07; revised 7/2/07; accepted 7/11/07.

Grant support: NIH grants R25 CA94880 and R01 CA74846 and American Institute of Cancer Research grant 05A072.

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doi:10.1158/1055-9965.EPI-07-0242

Surveillance, Epidemiology and End Results (SEER) cancer registry. The primary objective of the VITamins And Lifestyle study is to investigate the associations between use of vitamin and mineral supplements and other lifestyle factors with cancer incidence, and this study's methods are described in detail elsewhere (14). Briefly, recruitment of women into the cohort involved mailing a cover letter and a baseline questionnaire to 168,953 women. From October 2000 to December 2002, 41,157 (24.4%) questionnaires were returned by women, of which 40,339 passed questionnaire quality control checks and were eligible for this study. The 3,164 women with a prior history of breast cancer or an unknown prior history of breast cancer were excluded. In addition, given that the purpose of this analysis was to assess the associations between ages maximum height was attained, age at menarche, and age at first full-term birth and breast cancer risk including adjustments for each other, the 5,919 women with missing or out-of-range data for any one of these variables were excluded. The majority of the women excluded were eliminated because they did not report the age they reached their maximum height (n = 4,952). In addition, for age at maximum height, ages <10 and >25 were considered implausible, resulting in the exclusion of 31 women who reported reaching their maximum height at age <10 years and 489 women who reported reaching their maximum height at age >25 years. Multivariate adjusted analyses were conducted, so women with missing data for the confounders included in the models were also excluded including 60 missing height data, 448 missing family history of breast cancer data, and 3,212 missing data on ever use of menopausal hormone therapy. The remaining 27,536 women contributed a total of 110,995 person-years at risk with a mean follow-up time of 4.0 years. The majority of these women reported being postmenopausal (92.4%). Of the remaining women, 3.7% were premenopausal, 2.9% were perimenopausal, and 1.0% had an unknown menopausal status.

The baseline 24-page, self-administered, optically scanned questionnaire included items on demographic factors, vitamin and other supplement use, medical history, various life-style characteristics, anthropometric characteristics, and several breast cancer–specific risk factors, including age at menarche and age at first full-term birth. For both of these questions, participants were asked to select from answer choices provided. There were seven choices for age (years) at menarche: 11 or younger, 12, 13, 14, 15, 16 or older, or never had a period. For women who reported having a full-term birth, the choices for age (years) at first full-term birth were: 19 or younger, 20 to 24, 25 to 29, 30 to 34, 35 to 39, and 40 or older. With respect to height, women were asked two questions: ''What was your height when you were the tallest?'', followed by ''How old were you when you first reached that height?'' Because both questions required participants to write in their answers, actual heights and ages were obtained.

Cases were identified through a linkage with the SEER cancer registry using a multistep linkage system described in detail elsewhere (15). A total of 589 incidents *in situ* or invasive breast cancers were identified among the eligible members of the cohort between baseline and December 31, 2005. Four cancers were excluded due to morphology of sarcoma, phyllodes, or lymphoma, leaving 585 cases.

We also ascertained breast cancer stage, histology, and estrogen receptor (ER) status from SEER. SEER routinely collects data on all of these tumor characteristics for all breast cancer cases through their abstraction of pathology reports and medical records relating to breast cancer diagnosis. For women who had two or more primary cancers diagnosed within the follow-up time, we took the earliest diagnosis, or if both tumors were diagnosed on the same date, the tumor characteristics are those associated with the larger tumor. For this analysis,

Table 1. Distributions of demographic, medical, anthropometric, and reproductive factors in the VITamins And Lifestyle cohort (n = 27,536)

Characteristic	n (%)
Age at baseline, y	
50-54	7,326 (26.6)
55-59	6,811 (24.7)
60-64	4,770 (17.3)
65-69	3,895 (14.2)
70-74	4,734 (17.2)
Race/ethnicity	
Non-Hispanic White	25,582 (93.3)
Asian/Pacific islander	721 (2.6)
American Indian/Alaska native	435 (1.6)
African American	302 (1.0)
Hispanic White	242 (0.9)
Missing/Other	254
Education	
<High school	932 (3.4)
High school graduate/GED	5,295 (19.3)
Some college/technical school	11,376 (41.5)
College graduate	6,109 (22.3)
Advanced degree	3,709 (13.5)
Missing	115
First degree family history of breast cancer	
No	23,263 (84.5)
Yes	4,273 (15.5)
Ever use of hormone therapy	
Never	9,951 (36.1)
Only ever used unopposed estrogen	8,745 (31.8)
Only ever used estrogen + progestin	7,086 (25.7)
Ever used both unopposed estrogen and estrogen + progestin	1,754 (6.4)
Body mass index at baseline, kg/m^2	
≤19.9	1,257 (4.7)
20.0-24.9	9,265 (34.8)
25.0-29.9	8,984 (33.8)
≥30.0	7,093 (26.7)
Adult height, in	
≤62	5,579 (20.3)
63-64	7,436 (27.0)
65-66	7,606 (27.6)
≥67	6,915 (25.1)
Age at maximum height, y	
≤12	2,901 (10.5)
13-14	6,357 (23.1)
15-16	7,712 (28.0)
≥17	10,566 (38.4)
Age at menarche, y	
≤11	5,205 (18.95)
12	8,224 (29.9)
13	7,991 (29.0)
≥14	6,116 (22.2)
Age at first full-term birth, y	
≤19	4,990 (18.1)
20-24	11,158 (40.5)
25-29	5,419 (19.7)
30-34	1,899 (6.9)
≥35	586 (2.1)
Nulliparous	3,484 (12.7)

Table 2. Relationship between ages at maximum height, menarche, and first full-term birth and breast cancer risk

Pubertal/ reproductive event	All cases			*In situ* cases			Invasive cases		
	No. cases	Multivariate adjusted	Adjusted for other variables in the table	No. cases	Multivariate adjusted	Adjusted for other variables in the table	No. cases	Multivariate adjusted	Adjusted for other variables in the table
		HR* (95% CI)	HR† (95% CI)		HR* (95% CI)	HR† (95% CI)		HR* (95% CI)	HR† (95% CI)
Age at maximum height, y									
≥17	201	1.0 (Reference)	1.0 (Reference)	46	1.0 (Reference)	1.0 (Reference)	155	1.0 (Reference)	1.0 (Reference)
15-16	163	1.1 (0.9-1.4)	1.1 (0.9-1.4)	37	1.1 (0.7-1.7)	1.1 (0.7-1.7)	126	1.1 (0.9-1.4)	1.1 (0.9-1.4)
13-14	141	1.2 (0.9-1.4)	1.1 (0.9-1.4)	34	1.2 (0.8-1.9)	1.2 (0.8-1.9)	107	1.1 (0.9-1.5)	1.1 (0.9-1.4)
≤12	80	1.5 (1.1-1.9)‡	1.4 (1.0-1.8)‡	20	1.5 (0.9-2.6)	1.5 (0.8-2.6)	60	1.5 (1.1-2.0)‡	1.3 (1.0-1.8)
P_{trend}		0.006	0.04		0.12	0.18		0.03	0.10
Age at menarche, y									
≥14	117	1.0 (Reference)	1.0 (Reference)	25	1.0 (Reference)	1.0 (Reference)	92	1.0 (Reference)	1.0 (Reference)
13	165	1.1 (0.9-1.4)	1.1 (0.8-1.4)	44	1.4 (0.9-2.1)	1.3 (0.8-2.1)	121	1.0 (0.8-1.3)	1.0 (0.8-1.3)
12	167	1.1 (0.9-1.4)	1.1 (0.8-1.3)	36	1.0 (0.6-1.6)	1.0 (0.6-1.7)	131	1.2 (0.9-1.5)	1.1 (0.8-1.4)
≤11	136	1.4 (1.1-1.7)‡	1.3 (1.0-1.7)‡	32	1.3 (0.8-2.2)	1.3 (0.7-2.2)	104	1.4 (1.1-1.8)‡	1.3 (1.0-1.8)
P_{trend}		0.01	0.06		0.57	0.67		0.01	0.053
Age at first full-term birth, y									
≤19	86	1.0 (Reference)	1.0 (Reference)	26	1.0 (Reference)	1.0 (Reference)	60	1.0 (Reference)	1.0 (Reference)
20-24	236	1.2 (1.0-1.5)	1.2 (0.9-1.5)	46	0.8 (0.5-1.2)	0.9 (0.5-1.3)	190	1.4 (1.1-1.8)‡	1.4 (1.0-1.8)‡
25-29	116	1.3 (1.0-1.7)	1.3 (1.0-1.7)	29	1.1 (0.6-1.8)	1.1 (0.7-1.9)	87	1.4 (0.9-2.2)	1.4 (1.0-1.9)
30-34	39	1.5 (1.0-2.1)‡	1.4 (0.9-2.0)	9	1.6 (0.8-3.0)	1.1 (0.5-2.4)	30	1.4 (0.9-2.2)	1.5 (0.9-2.3)
≥35	17	2.1 (1.3-3.3)‡	2.0 (1.2-3.3)‡	5	2.1 (0.9-5.1)	2.0 (0.8-5.3)	12	2.1 (1.2-3.7)‡	2.0 (1.1-3.7)‡
Nulliparous	91	1.7 (1.3-2.3)‡	1.7 (1.3-2.3)‡	22	1.5 (0.9-2.6)	1.4 (0.8-2.5)	69	1.8 (1.3-2.5)‡	1.8 (1.3-2.6)‡
P_{trend} (excluding nulliparous women)		0.002	0.01		0.049	0.24		0.02	0.02

Abbreviation: HR, hazard ratio.

*Hazard ratios are adjusted for age at cohort enrollment, height, first-degree family history of breast cancer, and ever use of hormone therapy.

†Hazard ratios are adjusted for age at cohort enrollment, height, first degree family history of breast cancer, ever use of hormone therapy, and the other two pubertal/reproductive events in the table.

‡$P < 0.05$.

SEER summary stage was categorized as *in situ*, local, or regional/distant. Two histologic types of invasive breast cancer were assessed: ductal carcinoma and lobular carcinoma. Histology was defined using International Classification of Diseases for Oncology codes, wherein invasive tumors with International Classification of Diseases for Oncology code 8500 were classified as ductal carcinomas and those with International Classification of Diseases for Oncology codes 8520 or 8522 were classified as lobular carcinomas. Other rarer histologic types of breast cancer were not assessed due to their small numbers. ER status was coded as either ER+ or ER−.

Subjects were censored at the time they withdrew from the study (0.05%), died (1.8%), moved out of the 13 county catchment areas of the SEER registry (3.7%), or December 31, 2005. Deaths were ascertained by linkage to Washington State death files, using similar procedures to the SEER linkage. Moves out of area were identified by linkage to the National Change of Address System and by follow-up of possible moves with letters and phone calls to participants or a contact person identified by participants at baseline.

Cox proportional hazard models were used to estimate the hazard ratios of breast cancer associated with each of the three pubertal/reproductive events of interest. Age was treated as the time variable, with participants entering at their age at baseline (in days, months, and years) and exiting at their age (in days, months, and years) at breast cancer diagnosis or their censored date, as described above. Standardized and unstandardized residuals for our models were examined on time, log time, and rank scales to identify potential departures from proportional hazards. No statistically significant deviations from proportional hazards were observed. In all analyses, each of the three pubertal/reproductive events of interest were adjusted for each other and for potential confounders hypothesized *a priori*, including age at cohort enrollment, maximum attained height (continuous), first degree family history of breast cancer (yes/no), duration of unopposed estrogen use (continuous), and duration of combined estrogen and progestin use (continuous). Further adjustment for body mass index at age of 18 years did not change the results and, thus, was not adjusted for in our final models. Tests for linear trends across the used in the analysis categories were computed by treating these categorical variables as continuous variables. In our analyses of breast cancer subtypes, participants diagnosed with breast cancer subtypes, other than the one of interest in an analysis of a particular breast cancer subtype, were excluded from that analysis. Differences in the risk estimates obtained for the three primary exposures of interest by case type (e.g., ductal versus lobular, ER+ versus ER−, and localized versus regional/distant stage) were evaluated using unconditional logistic regression modeling, comparing the two case groups of interest only, adjusted for all of the covariates included in the main analyses. All analyses were conducted using Stata for Windows, Version 9.2.

Results

Table 1 provides the distributions of various demographic, medical, anthropometric, and reproductive

Table 3. Relationship between ages at maximum height, menarche, and first full-term birth and risk of different types of breast cancer

Pubertal/reproductive event	Ductal carcinoma		Lobular carcinoma		*P* for difference between groups
	No. cases	HR* (95% CI)	No. cases	HR* (95% CI)	
Age at maximum height, y					
≥17	108	1.0 (Reference)	38	1.0 (Reference)	
15-16	89	1.1 (0.9-1.5)	20	0.7 (0.4-1.2)	
13-14	75	1.2 (0.9-1.6)	22	0.9 (0.5-1.5)	
≤12	45	1.5 (1.0-2.2)†	12	1.0 (0.5-1.9)	0.39
P_{trend}		0.045		0.72	
Age at menarche, y					
≥14	71	1.0 (Reference)	14	1.0 (Reference)	
13	85	0.9 (0.7-1.2)	26	1.5 (0.8-2.9)	
12	86	0.9 (0.6-1.2)	30	1.7 (0.9-3.3)	
≤11	75	1.2 (0.8-1.7)	22	2.2 (1.1-4.4)†	0.19
P_{trend}		0.41		0.02	
Age at first full-term birth, y					
≤19	46	1.0 (Reference)	7	1.0 (Reference)	
20-24	130	1.2 (0.9-1.7)	43	2.6 (1.2-5.8)†	
25-29	58	1.2 (0.8-1.8)	20	2.5 (1.1-6.1)†	
30-34	22	1.4 (0.8-2.4)	6	2.4 (0.8-7.2)	
≥35	9	1.9 (0.9-4.0)	3	4.0 (1.0-15.6)†	
Nulliparous	52	1.8 (1.2-2.7)	13	2.8 (1.1-7.0)†	0.60
P_{trend} (excluding nulliparous women)		0.09		0.06	

Pubertal/reproductive event	ER+		ER−		*P* for difference between groups
	No. cases	HR* (95% CI)	No. cases	HR* (95% CI)	
Age at maximum height, y					
≥17	145	1.0 (Reference)	23	1.0 (Reference)	
15-16	109	1.0 (0.8-1.3)	27	1.6 (0.9-2.7)	
13-14	104	1.2 (0.9-1.5)	12	0.8 (0.4-1.6)	
≤12	50	1.2 (0.9-1.7)	16	1.9 (1.0-3.9)†	0.89
P_{trend}		0.13		0.30	
Age at menarche, y					
≥14	85	1.0 (Reference)	14	1.0 (Reference)	
13	114	1.0 (0.8-1.3)	22	1.2 (0.6-2.4)	
12	121	1.1 (0.8-1.4)	15	0.8 (0.4-1.7)	
≤11	88	1.2 (0.9-1.7)	27	2.2 (1.1-4.5)†	0.51
P_{trend}		0.25		0.050	
Age at first full-term birth, y					
≤19	54	1.0 (Reference)	10	1.0 (Reference)	
20-24	165	1.3 (1.0-1.8)	37	1.7 (0.8-3.4)	
25-29	77	1.4 (1.0-1.9)	16	1.5 (0.7-3.2)	
30-34	28	1.6 (1.0-2.5)†	7	1.8 (0.7-4.9)	
≥35	13	2.5 (1.3-4.6)†	0	0.0 (n/a)	
Nulliparous	71	2.2 (1.5-3.1)†	8	1.1 (0.4-2.9)	0.01
P_{trend} (excluding nulliparous women)		0.005		0.80	

Pubertal/reproductive event	Localized stage		Regional/distant stage		*P* for difference between groups
	No. cases	HR* (95% CI)	No. cases	HR* (95% CI)	
Age at maximum height, y					
≥17	111	1.0 (Reference)	44	1.0 (Reference)	
15-16	89	1.1 (0.8-1.5)	37	1.2 (0.8-1.8)	
13-14	68	1.0 (0.7-1.3)	39	1.5 (0.9-2.3)	
≤12	36	1.1 (0.8-1.7)	24	1.8 (1.0-3.1)†	0.09
P_{trend}		0.72		0.02	
Age at menarche, y					
≥14	61	1.0 (Reference)	31	1.0 (Reference)	
13	88	1.1 (0.8-1.6)	33	0.8 (0.5-1.2)	
12	89	1.2 (0.8-1.6)	42	0.9 (0.5-1.4)	
≤11	66	1.4 (1.0-2.0)	38	1.2 (0.7-2.0)	0.84
P_{trend}		0.09		0.36	
Age at first full-term birth, y					
≤19	40	1.0 (Reference)	20	1.0 (Reference)	
20-24	135	1.4 (1.0-2.1)†	55	1.2 (0.7-2.0)	
25-29	57	1.4 (0.9-2.1)	30	1.3 (0.8-2.4)	
30-34	22	1.7 (1.0-2.9)†	8	1.0 (0.5-2.4)	
≥35	9	2.4 (1.2-5.0)†	3	1.3 (0.4-4.3)	
Nulliparous	41	1.7 (1.1-2.7)†	28	2.1 (1.2-3.7)†	0.63
P_{trend} (excluding nulliparous women)		0.02		0.53	

*HRs are adjusted for age at cohort enrollment, height, first degree family history of breast cancer, ever use of hormone therapy, and the other two pubertal/reproductive events in the table.
†$P < 0.05$.

characteristics of the cohort. Among the 27,536 women included in this analysis, 93.3% were non-Hispanic White and 35.8% had at least a college degree; 15.5% had a first-degree family history of breast cancer. With respect to body mass index at baseline, 33.8% were overweight (a body mass index between 25.0 and 29.9 kg/m^2) and 26.7% were obese (a body mass index of $\geq$30.0 kg/m^2). Five hundred eighty-five women in the cohort were diagnosed with breast cancer during follow-up. The majority were early-stage cancers; 137 (23%) had *in situ* disease and 304 (52%) had a localized stage.

Age at maximum height was inversely associated with risk of breast cancer overall and with risk of invasive breast cancer (P_{trend} = 0.006 and 0.03, respectively; Table 2). In particular, women who reached their maximum height at age 12 or younger had a 1.5-fold [95% confidence interval (95% CI), 1.1-2.0] increased risk of invasive breast cancer. When the risk estimates were also adjusted for age at menarche and age at first full-term birth, this relationship persisted for risk of breast cancer overall (hazard ratio, 1.4; 95% CI, 1.0-1.8), but was no longer statistically significant for risk of invasive cancer. A similar inverse association between age at menarche and breast cancer risk was observed. Age at first full-term pregnancy was also inversely associated with breast cancer risk, although the magnitude of the risk estimates were higher. For example, compared with women who had their first full-term pregnancy at age 19 or younger, those who had their first full-term pregnancy at age 35 or older had a 2.0-fold (95% CI, 1.1-3.7) increased risk of invasive breast cancer, even after adjusting for both ages at maximum height and menarche, with a strong linear trend (P_{trend} = 0.02).

There were some suggestions that there were differences in the associations described above when these results were stratified by various tumor characteristics, although almost all of these differences were within the limits of chance (Table 3). Comparing invasive ductal and invasive lobular carcinomas, age at maximum height was related to risk of ductal carcinoma (P_{trend} = 0.045), but not to risk of lobular carcinoma (P_{trend} = 0.72). In contrast, age at menarche was more strongly related to risk of lobular carcinoma than to risk of ductal carcinoma, whereas age at first full-term birth was related to risk of both histologies. With respect to ER status, ages at maximum height and menarche were more strongly related to risk of ER− disease, whereas age at first-full term birth was more strongly related to risk of ER+ disease. The latter difference between ER+ and ER− disease was the only statistically significant difference between breast cancer subgroups observed (P = 0.01). Age at maximum height was also more strongly related to risk of regional/distant stage disease (P_{trend} = 0.02) compared with localized disease, whereas age at first full-term pregnancy was more strongly related to risk of localized disease (P_{trend} = 0.02).

Discussion

Before interpreting the results of this study it is important to acknowledge its limitations. The primary exposures of interest are all early-life events, and given that this is a cohort of women 50 to 76 years of age at baseline, recall of exact ages when these events occurred may have been poor for some women resulting in exposure misclassification. The resultant bias would be nondifferential, given that a cohort design was used and, thus, would lead to underestimations of the true relative risks. Generalization of these results is somewhat limited, given that women self-selected into the cohort and the distribution of demographic characteristics indicate that the population enrolled has much less racial/ethnic diversity and is more educated compared with the U.S. population as a whole. Our analyses of certain breast cancer subtypes were also limited by small numbers of cases. Finally, we were only able to include 74% of the potentially eligible women in this study because 16% were missing data for one of our three primary exposures of interest and 10% were missing confounder data. Given the prospective nature of this study these exclusions are unlikely to bias our results.

Our results suggest that the age maximum height is attained is a modest risk factor for breast cancer with an association on the order of that between age at menarche and breast cancer risk. Whereas age at maximum height is correlated with age at menarche, the association between age at maximum height and breast cancer risk seemed to be independent of age at menarche and a variety of other established breast cancer risk factors given that this association held after adjusting for all of them. Our main finding is also supported by previous work as four (7-10) of the five (11) prior studies evaluating the relationship between age at maximum height at breast cancer risk have shown associations and risk estimates similar to what we have found here.

Adding to the evidence that age at maximum height is a distinct risk factor from other pubertal/reproductive events is our observation that age at maximum height was associated with very different types of breast cancer then, age at menarche or age at first full-term pregnancy. Specifically, age at maximum height was associated more strongly with risks of ductal carcinomas, ER− cancers, and regional/distant stage tumors, whereas age at first full-term birth was more strongly associated with completely different types of tumors, including lobular carcinomas, ER+ cancers, and localized stage tumors. Given the hormonal changes associated with pregnancy and their effect on breast cancer risk, it is not surprising that age at first full-term birth is associated with tumors that are more hormonally responsive, such as ER+ tumors and lobular carcinomas, and results similar to these have been reported previously (16-18). None of the prior studies evaluating age at maximum height have stratified their results by tumor type, and it is difficult to hypothesize why this age would be more strongly associated with tumors that are more aggressive and have a poorer prognosis, because it is unclear why earlier exposure to high levels of growth hormones and insulin-like growth factor-I that accompany pubertal growth spurts would have this effect. Further studies are needed to confirm these findings, given that this is the first study to report these associations by breast cancer subtype.

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