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Birth weight and other prenatal factors and risk of breast cancer in Asian Americans

Anna H Wu[1], **Roberta McKean-Cowdin**, and **Chiu-Chen Tseng**
Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California 90089

Abstract

Little is known about the role of birth weight and other prenatal factors in the etiology of breast cancer in Asian-Americans. We investigated the relation between birth weight and other prenatal factors and breast cancer risk in a population-based case-control study in Los Angeles County that included 2,259 Asian American women with incident, histologically confirmed breast cancer and 2,019 control women, who were frequency matched to cases on age, Asian ethnicity and neighborhood of residence. Breast cancer risk nearly doubled (odds ratio (OR)=1.92, 95% confidence interval (CI)=1.12-3.29) among those with high (≥4000 g) birth weight compared to those with low (<2500 g) birth weight after adjusting for age at menarche, parity, adult weight and other covariates. Risk increased 8% per 500 g increase in birth weight (p trend=0.10). We observed a significant relationship between birth weight and age at menarche in both cases and controls. Mean birth weight was higher (2948 g) for control women who had early menarche (age ≤11 years) compared to those who had menarche late (age ≥15 years) (2807 g) (P trend =0.016); results were similar among case patients (P trend=0.022). Older maternal age was also a risk factor; risk increased by 6% (95% CI=1.01-1.12) per 5 years increase in maternal age with adjustment for parity and other risk factors. Our results support the hypothesis that high birth weight and older maternal age at pregnancy may have contributed to the rising breast cancer incidence in Asian Americans.

Introduction

Trichopoulos hypothesized that breast cancer risk may be influenced by in utero exposure to elevated concentrations of estrogens [1]. In the past two decades, studies have been conducted to evaluate breast cancer risk in relation to birth weight and other characteristics of pregnancy (e.g., twinning, birth order, maternal age, pre-eclampsia) as surrogates of low or high exposure to estrogen and other gestational hormones [2, 3, 4, 5, 6, 7]. The overall findings show a significant positive association between breast cancer risk and body size, measured by birth weight, birth length or head circumferences [5, 6]. Risk also tended to be higher in relation to older maternal or paternal age at delivery [5, 7] but reduced in association mother's preeclampsia during pregnancy [2, 5]. However, most of these studies

[1]To whom correspondence should be addressed: Anna H. Wu, Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California 90089 (annawu@usc.edu) phone: 323-865-0484; fax 323-865-0139.

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were conducted in western Caucasian populations. In the only two studies that included Asians, one conducted in Hawaii [8] and the other in Shanghai, China [9], breast cancer risk was non-significantly reduced among those with higher birth weight. There is some suggestion that maternal age or paternal age is positively associated with breast cancer risk in Asians [8, 10].

There is a trend of rising birth weight worldwide [11]; these changes are particularly relevant among Asians. Maternal height, pre-pregnancy body mass index and pregnancy weight gain are important determinants of birth weight [12, 13]. With increasing body weight and height in successive generations of Asians who move to the west [14] and with increasing westernization and economic growth in Asia, there are now reports of high (≥ 4000 g) birth weight in Asian migrants [15] and in urban areas in China [16] . There is also a substantial increase in delaying childbearing over the last quarter century in Asian and western populations. In 2006, Asian American women had the oldest average age at first birth compared to other racial/ethnic group in the US. Women in Japan were also among the oldest in their average age at first birth [17].

This study investigated whether birth weight, maternal age at pregnancy, and other prenatal factors influence the risk of breast cancer in a large population-based case-control study of Asian American women in Los Angeles County.

Subjects and Methods

Study design and population

The study population and methods used in this population-based case-control study have been described previously [18, 19]. Briefly, breast cancer patients were identified by the Los Angeles County Cancer Surveillance Program, the population-based cancer registry covering Los Angeles County, a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, and the statewide California Cancer Registry. Patients included in this analysis were women who were identified as Chinese, Japanese or Filipino between the ages of 25 and 74 inclusive at the time of diagnosis of an incident breast cancer. Cases were ascertained in two diagnostic periods. The first group of case patients was diagnosed between 1995 and 2001 and the second group of case patients was diagnosed between 2003 and 2006. In total, we identified 3,797 eligible patients (1496 Chinese, 865 Japanese, 1436 Filipino) and interviewed 2,303 (929 Chinese, 547 Japanese, 827 Filipino) women. Among those who did not participate, 869 declined to be interviewed (375 Chinese, 222 Japanese, 272 Filipino), 77 had died (17 Chinese, 24 Japanese, 36 Filipino), and 548 could not be located (175 Chinese, 72 Japanese, 301 Filipinos).

The 2,029 controls (923 Chinese, 518 Japanese, 594 Filipino) were selected from the neighborhoods where the cancer cases resided at the time of diagnosis. A well-established, standard algorithm was used to identify neighborhood controls that the University of Southern California Epidemiology Program has used in numerous case-control studies [20, 19] This algorithm defines a specified sequence of houses to be visited in the neighborhoods where index cases lived at the time of diagnosis. We sought to interview as the control the first eligible resident in the sequence. If the first eligible control subject refused to participate, the second eligible one in the sequence was asked, and so on. Letters were left when no one was home, and follow-up was by mail and telephone (if a number could be determined). Controls were sought to frequency-match to the cases on specific Asian-ethnicities and 5-year age groups. On average, a suitable control was identified after walking a median of 60 households. Of the controls interviewed, 64% were the first identified eligible control, 18% were the second identified eligible control, 18% were the third or later eligible control.

Data Collection

Cases and controls were interviewed in-person by trained interviewers using a standardized, structured questionnaire, typically about one year after diagnosis. Each interview was conducted in the language (English, Cantonese or Mandarin) chosen by study participant. Briefly, the questionnaire elicited information on race/ethnicity, education, residential and migration history, birthplace of parents and grandparents, family history, menstrual and reproductive histories, use of exogenous hormones (oral contraceptives and menopausal hormones), lifetime physical activity patterns, height and weight at age 18 years, at age 30 years, and each decade thereafter. Trained interviewers measured the circumferences of the waist and hip of study participants. The diet questionnaire was modeled after the validated diet instrument used in the Multiethnic Cohort Study being conducted in Hawaii and Los Angeles [21]. Our questionnaire also asked about early life factors including the subject's birth weight, the mother's age at the time of the subject's birth, the subject's birth order, whether the subject has a twin, and mother's smoking during her pregnancy with the index subject. For women who did not know their specific birth weight, we asked whether they weigh less than <2500 g or greater than 4000g. Results on adult body size, use of menopausal hormones, select dietary factors have been reported on the first group of cases (1,384 cases) and corresponding controls (1,225 controls) [18, 22, 19].

The study was approved by the Institutional Review Board of the Keck School of Medicine at the University of Southern California. Informed consent was obtained from each case and control before her interview.

Statistical Analysis

The results presented below are based on 2,259 cases and 2,019 controls for whom we have information on prenatal factors as well as the covariates included for adjustment. We calculated odds ratios (ORs; relative risk estimates) and their corresponding 95% confidence intervals (CIs) and P values by conditional logistic regression methods, with matched sets defined jointly by reference age (<39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70+ years), and specific Asian ethnicity (Chinese, Japanese, Filipino). All regression models included the following covariates: years of residence in the US (US born, >20 years, 11-20 years, ≤10 years), education (less than high school, high school, some college, college graduate), interviewer, age at menarche (<12, 12-13, 14+ years), parity (0, 1, 2, 3, 4+ births), current body mass index (BMI; quartiles of controls), years of regular (*i.e.*, at least 1 hour per week) recreational physical activity (<5, 5-9, 10-19, ≥20 hours), total calories (continuous), menopausal status (premenopausal, natural menopause, bilateral oophorectomy, simple hysterectomy, 'hormone therapy menopause', i.e., naturally menopausal but age unknown due to starting hormone therapy before periods had stopped), age at menopause (≤44, 45-49, 50-54, 55+ years), and family history of breast cancer. We conducted case-control comparisons for all subjects combined, and separately by various subgroups including menopausal status, Asian ethnicity, and nativity. To examine the potential effect modification of the birth weight (maternal age)-breast cancer association by menopausal status, Asian ethnicity, and migration history interaction terms were tested. We also used analysis of variance (ANOVA) and analysis of covariance (ANCOVA) to assess the relationships between birth weight and mother's age at delivery, birth weight and mother's smoking during pregnancy, as well as the relationship between birth weight and age at menarche after adjusting for age, Asian ethnicity, migration history, and education in cases and controls separately. P values less than 5% are considered statistically significant and all P values quoted are 2-sided. All analyses were performed by using EPILOG Windows (version 1.01s) statistical software system (Pasadena, CA) and the SAS statistical software system (version 8.0; SAS Institute, Cary, NC).

Results

Table 1 shows select demographic and lifestyle characteristics of 2259 cases and 2019 controls. The mean age of cases and controls was 53.5 (SD=10.4) years, and 51.0 (SD= 10.5) years, respectively. The percent of cases and controls women who were US born was highest among Japanese, intermediate among Chinese and lowest among Filipina women. Mean age at menarche did not differ between cases and controls (P=0.09) whereas a significantly higher percent of cases were nulliparous relative to control women (P<0.0001).

Table 2 shows risk associations with birth weight and other prenatal characteristics including birth order and twinning. Risk was highest (OR=1.92, 95% CI=1.12-3.29) among those with high (≥ 4000 g) birth weight compared to those with low (<2500 g) birth weight. The risk per 500 g increase in birth weight was 1.08 (95% CI=0.99-1.19). A nonsignificant positive association between birth weight and risk was found in both premenopausal and postmenopausal women, in Chinese and Japanese, and in US born and in non-US born women (Table 2). Breast cancer cases and controls did not differ by birth order (P trend= 0.24). Risk was non-significantly reduced in association with being a twin but this was based on very low prevalence of twinning. The results on birth weight remained statistically significant after further adjustment for birth order, twinning, mother's age and smoking history during pregnancy of index subject (see Table 3). The OR was 1.86 (95% CI=1.09-3.20) among those with high (≥4000 g) birth weight compared to those with low (<2500 g) birth weight.

Table 3 shows risk pattern in association with maternal age at delivery of the index subject. A statistically significant increased risk was observed in relation to older maternal age; risk increased by 6% (95%=1.01-1.12, p=0.03) per 5 years increase in maternal age with adjustment for parity and other risk factors. The association remained after further adjustment for age at first birth of the index subject (data not shown). Risk associated with older maternal age was found in both premenopausal and postmenopausal women although the result was statistically significant only in premenopausal women (P trend=0.023). Nonsignificant increasing trends were found in all three Asian ethnicities and by birthplace and years of residence in the US. Breast cancer risk tended to be lower among those who reported that their mothers smoked during the index pregnancy (OR=0.74, P=0.037). Results associated with maternal age at pregnancy and smoking during pregnancy were essentially unchanged after further adjustment for birth weight (OR=1.06, 95% CI=1.00-1.12, p=0.04 per 5 years increase in maternal age).

Table 4 shows that mean birth weight did not differ by birth order or maternal age at pregnancy. Birth weight was lower among controls who reported their mothers were smokers during pregnancy (2741 g) compared to those who were not smokers (2889 g) but this finding was not observed in relation to smoking among cases' mothers (P=0.81). There was a significant trend of decreasing birth weight by age at menarche. Among breast cancer cases, mean birth weight was 3029 g among those with an early age at menarche (ages 11 years or younger) compared to 2911 g among those who started menstruating at age 15 years or older (P trend=0.02). Similarly, among control women, mean birth weight was 2948 g for those who had menarche early (age 11 years or younger) versus 2807 g for those who had menarche late (age 15 years or older) (P trend=0.016).

Discussion

In this large population-based case-control study of breast cancer in Asian American women, there was a statistically significant doubling of risk among women in the highest weight category (>4000g) compared to those in the lowest weight category (<2500g) after adjustment for age at menarche, adult weight, and other potential confounding factors. Risk increased 8% per 500 g increase in birth weight; these results were generally consistent in subgroup analyses. These results in Asian American women are comparable to the meta-analysis results obtained in western populations. Based on a meta-analysis of 18 studies, Xu et al [23] estimated a summary effect of 1.07 (95% CI=1.02, 1.12) per 1 kg increase in birth weight. However, our results differed from those reported in two studies that included considerably smaller numbers of premenopausal Asian women [8, 9]. Among Chinese in Shanghai (288 cases, 350 controls), relative to women whose birth weight was 2500-2999 g, those who weighed <2500, 3000-3499, 3500-3999, ≥4000 g showed ORs of 0.9, 1.1, 0.8, and 0.8, respectively (P=0.34) [9] . In a study of Asians (89 cases, 240 controls) and non-Asians (69 cases, 181 controls) in Hawaii, relative to those in the lowest tertile of birth weight (<2948 g), women in the upper two tertiles (2949-3340, and >3341 gm) of birth weight showed ORs less than one [8].

Assuming that the finding on birth weight and breast cancer risk can be accepted at face value, a question of interest is the mechanism by which birth weight might influence risk. Maternal estrogen (particularly estriol) concentrations measured at different gestational times have been positively associated with birth weight in offspring [24, 25, 26, 27]. Birth size has been found to predict circulating estradiol levels in a cross-sectional study of premenopausal Polish women [28] but these results were not confirmed in the Nurses' Health Study [29].

Birth weight also has been suggested to influence age at menarche although the direction of association is not consistent. Asian American cases and control women who were heaviest at birth (≥4000 g) started menstruating significantly earlier than those who were lightest at birth (<2500 g) (Table 4). Our finding was remarkably consistent despite that information on birth weight and age at menarche was based on self-report and random misclassification may exist. There are supportive data from a follow-up study in the Philippines which found that girls who were heavier (>3.01 kg) at birth had earlier age at menarche (≤12 years) whereas girls who were lighter (<2.95 kg) had later age at menarche (>14 years) [30]. In contrast, most of the other studies conducted in primarily in Caucasian populations showed that girls with lower birth weight were more likely to experience menarche earlier than those who were heavier at birth [31, 32, 33, 34, 35]. However, the association between low birth weight and earlier age at menarche may be modified by childhood weight and girls with the highest weight gain or catch-up growth during childhood had earlier age at menarche [31, 33, 36]. Questions on postnatal growth pattern were not asked in our study; this information would be helpful to better understand differences in findings on birth weight and age at menarche in our study and previous studies.

Birth weight may influence mammographic density, considered as one of the strongest breast cancer risk factors [37]. Self-reported birth weight was significantly positively associated with mammographic percent density in Iowa; women with a birth weight of <2.95 kg had a mean density of 20.1% compared with 23.0% for women with a birth weight of ≥3.75 kg [38]. Birth weight abstracted from birth records was also significantly positively associated with mammographic density in Swedish women [39]. The positive association between birth weight and breast density provide support that women with higher birth weight might have a larger mammary gland mass [13] and potentially a larger breast stem cell burden [40].

There are supportive animal model data that mammary gland tumorigenesis is associated with prenatal estrogen concentrations and high birth weight [41, 42]. High-birth weight rats developed DMBA-induced mammary tumors significantly earlier, and the tumors grew larger than in the control counterparts [42].

Our results suggest a significant trend of increasing risk with increasing maternal age after adjustment for birth order, birth weight, and other potential confounders; this association was statistically significant in premenopausal Asian American women. Breast cancer risk was elevated among women born to older mothers in a study of Asians and non-Asians in Hawaii; a borderline statistically significant result was found in younger breast cancer cases [8]. Our observation is compatible with meta-analyses results which have found a positive association between higher maternal age and increased risk of breast cancer in both their premenopausal and postmenopausal daughters [5]. Although higher intrauterine exposure to endogenous estrogens in older mothers has been hypothesized to explain the elevated risk associated with maternal age and breast cancer risk in daughters, the association between maternal age at pregnancy and estrogen levels is not consistent. Estradiol concentrations were lower in older mothers in some studies [43, 44] but not in other studies [45, 46]. These studies included women with different pregnancy history (first vs multiple previous pregnancies) and the hormone levels were measured during different trimesters of the pregnancy.

Maternal smoking was inversely associated with risk after adjustment for birth weight, maternal age at pregnancy and other potential confounders. However, risk was slightly increased (OR=1.09, 95% 0.85-1.39) among those (173 cases, 134 controls) who did not know about their mother's smoking during pregnancy and the possibility of misclassification of mother's smoking during pregnancy exists. Our questions about maternal smoking during pregnancy were crude; we did not ask whether mothers smoked during the entire pregnancy or the amount they smoked. Most of the previous studies have found no relation between maternal smoking during pregnancy and risk [7] but nonsignificantly reduced risk was reported in two cohort studies [47, 48]. The inverse association between maternal smoking during pregnancy and risk is plausible since cigarette smoking during pregnancy has been associated with decreased maternal levels of estradiol and estriol [49, 50, 24].

Notwithstanding, there are several limitations of this study. About half the study subjects did not know the exact birth weight but only that they weighed more than >2500g but less than 4000g; their risk of breast cancer was slightly increased (see Table 2, footnote 2). The percent of Asian American cases and controls who did not know their specific birth weight is comparable to results in other US studies [51, 38]. Other breast cancer risk factors (e.g., parity, family history of breast cancer, soy, green tea) were very comparable in Asian American women who knew their specific birth weight and those who did not know their birth weight. The overall participation rate was 61% among cases and 64% among controls. Our refusal rate (23%) is comparable to rates reported in other US studies [51]. However, 14% of the reported cases had moved outside of Los Angeles County; this was highest for Filipino (21%), intermediate for Chinese (12%), and lowest for Japanese (8%). It is conceivable that some of the cases who are migrants, may return to the host country after cancer diagnosis for treatment or for other reasons [52]. A methodological concern is the comparability of cases we interviewed and those we did not interview in terms of birth weight and other prenatal factors. We have some confidence in our finding because the prevalence of high birth weight (>3500 g) was very similar for cases who were US born (16%) and those who were non-US born (15% among those who have lived in the US for 21 or more years, 16% among those who have lived in the US for <21 years). The birth weight-breast cancer association was also similar by migration status (Table 2). The prevalence of older maternal age (age 36 or older) at pregnancy of the index case was slightly lower (13%) among US born compared to non-US born cases (18% for who have lived in the US for 21 or more years, 17% for those who have lived in the US for <21 years). On the basis that cases that had moved were more likely to be migrants and assuming that the distribution of mother's age at pregnancy is similar between those we interviewed and failed to interview, our risk estimate associated with mother's age at pregnancy may be slightly diluted. Another study limitation is that our assessment of prenatal factors is not complete and was based solely on self-report and thus recall bias is a possibility. We asked very limited questions about mother's characteristics during the index pregnancy and did not have information on mothers' pre-pregnancy body size, or history of hypertension or diabetes during pregnancy.

In summary, this study represents one of the largest population-based case-control studies to examine breast cancer risk in relation to birth weight and other prenatal factors in Asian women. Our study suggests that breast cancer risk increases with birth weight and that high birth weight is also associated with earlier age at menarche, an established breast cancer risk factor. With the current trends of increasing birth weight [11, 15, 16] and delayed childbearing [17], further investigation of the influence of birth weight and other prenatal factors, and the combined effects of age at pregnancy of mothers and daughters on breast cancer risk is Asian populations is warranted. Very little is currently known about prenatal risk factors and breast cancer risk in Asians; our results help fill a knowledge gap.

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Table 1

Demographic characteristics of breast cancer patients and controls

	All		Chinese		Japanese		Filipino	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
N	2259	2019	917	916	547	514	795	589
Average age	53.5	51.0	52.4	49.3	56.1	52.9	53.1	52.0
Education (by %)								
≤ high school	19.1	16.6	29.0	23.0	17.6	13.8	8.7	9.2
Some college	20.8	22.8	18.2	19.8	34.9	34.6	14.2	17.1
College graduate	44.0	42.9	34.8	36.9	32.5	34.8	62.6	59.4
>graduate	16.0	17.6	18.0	20.3	15.0	16.7	14.5	14.3
Birth place, years in US among migrants								
%US born	21.3	26.8	10.0	14.4	67.3	74.1	2.8	4.8
Non US born (Yrs lived in US)								
%>20 yrs in US	39.9	36.1	43.3	39.3	24.7	17.3	46.4	47.4
%11-20 yrs in US	24.1	23.9	28.4	28.9	5.7	6.2	31.8	31.4
%<11 yrs in US	14.7	13.3	18.3	17.4	2.4	2.3	19.0	16.5
Age at menarche								
% ≤ 11 yrs old	16.6	16.7	11.3	12.3	22.7	24.5	18.5	16.8
% 12-13 yrs old	48.7	51.5	48.2	48.7	54.4	56.4	45.3	51.5
% >14 yrs old	34.7	31.8	40.5	39.0	22.9	19.1	36.2	31.7
Mean age	13.0	12.9	13.2	13.2	12.6	12.5	13.0	12.9
Parity								
% no birth	23.5	16.8	19.3	13.4	30.9	24.7	23.3	15.3
% 1-3 births	65.9	69.8	72.0	77.4	63.8	67.5	60.3	59.7
% 4+ births	10.6	13.4	8.7	9.2	5.3	7.8	16.4	25.0
Mean number	1.8	2.0	1.8	1.9	1.5	1.7	2.0	2.6

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Table 2

Birth weight and other prenatal factors and risk of breast cancer in Asian Americans

	Cases	Controls	Adj OR[1]	95% CI
Birth weight[2]				
<2500g	154	166	1.00	
2500-2999	395	404	1.09	0.82-1.43
3000-3499	294	308	1.06	0.79-1.42
3500-3999	102	101	1.12	0.77-1.64
≥ 4000	52	27	1.97	1.15-3.39
P trend			0.10	
			RR per 500 g birth weight	
All subjects			1.08	0.99-1.19
Menopausal status				
Premenopausal	518	604	1.08	0.95-1.23
Postmenopausal	479	402	1.11	0.96-1.28
Asian ethnicity				
Chinese	292	373	1.10	0.93-1.29
Japanese	321	402	1.17	0.98-1.48
Filipino	384	299	0.94	0.79-1.13
Birth place & yrs lived in US among non-US born				
US born	311	387	1.14	0.96-1.35
20+ years in US	358	308	1.06	0.89-1.25
<20 years in US	328	311	1.06	0.88-1.26
Birth order				
1	550	556	1.00	
2	475	434	1.14	0.95-1.37
3	380	341	1.06	0.87-1.29
4	282	235	1.13	0.90-1.40
5	186	163	1.03	0.80-1.32
6+	364	276	1.18	0.96-1.46
P trend				0.24
Twins[2]				
No	2235	1996	1.00	
Yes	3	9	0.37	0.10-1.39

3 21 cases and 14 controls were unknown. The OR for this don't know group was 1.23 (95% CI=0.59-2.54) compared to those who responded 'no'.

[1] Adjusted for age, Asian ethnicity, education, interviewer, years in US, age at menarche, menopausal status, age at menopause, current BMI, parity, total calorie, family history of breast cancer and physical activity

[2] 1262 cases and 1013 controls did not know the exact birth weight but reported birth weight >2500 and <3999 g; OR for this don't know birth weight group was 1.12 (95% CI=0.77-1.63) compared to those <2500 g.

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Table 3

Maternal age and smoking of index pregnancy and breast cancer risk

	Cases	Controls	Adj OR[1]	95% CI
Mother's age at delivery[2]				
<=20	159	156	1.0	
21-25	553	575	0.97	0.75-1.26
26-30	644	573	1.16	0.89-1.50
31-35	458	369	1.21	0.92-1.60
36+	350	283	1.15	0.87-1.53
P trend			0.03	
		RR per 5 years of mother's age at delivery		
All subjects	2164	1956	1.06	1.01-1.12
Menopausal status				
premenopausal	952	1054	1.10	1.01-1.19
postmenopausal	1212	902	1.03	0.96-1.11
Asian ethnicity				
Chinese	859	879	1.08	0.99-1.18
Japanese	537	509	1.02	0.90-1.15
Filipino	768	568	1.07	0.97-1.18
Birthplace & yrs lived in the US				
among non-US born				
US born	474	536	1.05	0.93-1.19
21+ yrs in US	871	705	1.07	0.98-1.17
<20 yrs in US	819	715	1.07	0.98-1.17
Mothers' smoking during pregnancy				
No	1966	1762	1.00	
Yes	117	123	0.74	0.56-0.98
DK	176	134	1.09	0.85-1.39

[1] Adjusted for age, Asian ethnicity, education, interviewer, years in US, age at menarche, menopausal status, age at menopause, current BMI, parity, total calorie, family history of breast cancer and physical activity

[2] Mother's age at delivery was missing on 95 cases and 74 controls

Table 4

Mean birth weight (95% CI) according to reported age at menarche in Asian American breast cancer cases and control women

	Cases		Controls	
	N	**Mean birth weight (g) (95% CI)** [1]	**N**	**Mean birth weight (g) (95% CI)** [1]
Age at menarche				
11	215	3029 (2947-3114)	219	2948 (2867-3031)
12	261	3021 (2947-3097)	265	2902 (2828-2978)
13	253	2956 (2884-3030)	275	2866 (2795-2940)
14	144	2941 (2852-3033)	139	2858 (2769-2950)
15+	124	2911 (2817-3009)	108	2807 (2707-2910)
P trend		0.020		0.016
Birth order				
1	276	2939 (2869-3011)	325	2852 (2783-2923)
2	240	3006 (2930-3084)	238	2913 (2836-2992)
3	165	3025 (2936-3116)	150	2859 (2771-2951)
4	117	2967 (2866-3071)	112	2947 (2844-3054)
5+	199	2961 (2882-3041)	181	2868 (2787-2951)
P trend		0.97		0.57
Mother's age at delivery				
<=20	68	2942 (2806-3084)	77	2922 (2786-3063)
21-25	262	3005 (2914-3099)	294	2845 (2754-2938)
26-30	318	2941 (2855-3031)	323	2871 (2777-2969)
31-35	209	2985 (2889-3083)	204	2915 (2810-3023)
36+	134	2984 (2879-3093)	101	2912 (2791-3038)
P trend		0.69		0.75
Mother's smoking during pregnancy				
No	883	2977 (2928-3027)	907	2889 (2838-2941)
Yes	53	2932 (2792-3079)	63	2741 (2618-2869)
Don't know	61	2993 (2857-3135)	36	2996 (2822-3181)
P (2 df)		0.81		0.033

[1] Adjusted for age, Asian ethnicity, migration history, education.