Research Article

Cancer Epidemiology, Biomarkers & Prevention

Traditional Breast Cancer Risk Factors in Filipina Americans Compared with Chinese and Japanese Americans in Los Angeles County

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Abstract

Background: Filipina Americans have one of the highest breast cancer incidence rates among Asian Americans for poorly understood reasons.

Methods: Breast cancer risk factors were investigated in a population-based study of Filipina (790 cases, 587 controls), Japanese (543 cases, 510 controls), and Chinese (913 cases, 904 controls) Americans. Cases were identified by the Los Angeles County Cancer Surveillance Program, and controls were matched to cases on age, ethnicity, and neighborhood. Multivariable conditional logistic regression was performed by Asian ethnicity.

Results: In Filipina, Chinese, and Japanese Americans, breast cancer risk decreased significantly with increasing parity (all $P_{trend} < 0.0001$). Breast cancer risk increased with increasing quartiles of cumulative menstrual months in premenopausal ($P_{trend} = 0.019$) and postmenopausal Filipina ($P_{trend} = 0.008$), in premenopausal ($P_{trend} = 0.0003$) but not postmenopausal Chinese ($P_{trend} = 0.79$), and in neither premenopausal ($P_{trend} = 0.092$) nor postmenopausal ($P_{trend} = 0.75$) Japanese Americans. For postmenopausal Filipina and Japanese, greater weight gain since age 18 ($P_{trend} = 0.019$ and 0.053, respectively), high current body mass index (both $P_{trend} < 0.01$), and greater waist circumferences (both $P_{trend} < 0.04$) were statistically significant; these associations were weaker for postmenopausal Chinese women.

Conclusions: Cumulative menstrual months and body size factors were statistically significant risk factors for Filipina. Total menstrual months were associated with breast cancer among Chinese but not for Japanese, while body size factors were significantly associated with risk among Japanese but not among Chinese.

Impact: Characterization of breast cancer risk factors in Filipina will help to generate hypotheses for their high breast cancer incidence. *Cancer Epidemiol Biomarkers Prev; 25(12); 1572–86. ©2016 AACR.*

Introduction

Historically, Asian women in Asia and in the United States have among the lowest incidence of breast cancer worldwide. Exceptions are the relatively high breast cancer incidence rates in the Philippines and among Filipina Americans. In 2013, age-adjusted breast cancer incidence rates (per 100,000) were higher in the Philippines (87.5) than in Japan (55.0) or China (45.4; ref. 1). Among Asians in the United States, the highest breast cancer incidence rates during the period 2004 to 2008 were for Japanese Americans (104.9) and Filipina Americans (103.7; ref. 2). However, compared with incidence during the period 1990 to 1994, there has been a 21% increase in Filipina women compared with a 6.2% increase in Japanese women. It is of note that most Filipina American women are recent immigrants, compared with the mostly U.S.-born, and second- or later-generation Japanese American women.

In one of the few analytic epidemiologic studies of breast cancer among Filipina women in Manila, Philippines, the "classical" risk factors (e.g., excess body weight) did not fully explain the high breast cancer incidence in Manila, especially when compared with other urban Asian populations. However, this previous study had few cases ($n = 123$) and limited information on lifestyle factors (3). To date, there are no epidemiologic studies of breast cancer focusing on Filipina-American women. We initiated a population-based case–control study among Filipina, Japanese, and Chinese American women in Los Angeles (LA) County between 1995 and 2001. Since then, to investigate Asian ethnicity–specific associations with breast cancer, we have expanded the database to include cases diagnosed between 2003 and 2006, and additional controls. To better understand the high breast cancer rates in Filipina Americans, we investigated traditional breast cancer risk factors in pre- and postmenopausal Filipina, Japanese, and Chinese Americans in LA County. We also calculated lifetime cumulative number of menstrual months (4, 5), as an index of total exposure to endogenous estrogens.

Materials and Methods

Study design and population

The study population and methods used in this population-based case–control study have been described previously (6, 7). In brief, breast cancer patients were identified by the LA County Cancer Surveillance Program, the population-based cancer

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registry covering LA 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 Filipina between the ages of 25 and 74 years inclusive at the time of diagnosis of an incident breast cancer. Case patients were diagnosed between 1995 and 2001 or between 2003 and 2006. In total, we identified 3,797 eligible case patients (1,496 Chinese, 865 Japanese, 1,436 Filipina) and interviewed 2,303 cases (929 Chinese, 547 Japanese, and 827 Filipina; response rate of 61%). Among those who did not participate, 869 declined to be interviewed (375 Chinese, 222 Japanese, 272 Filipina), 77 had died (17 Chinese, 24 Japanese, 36 Filipina), and 548 could not be located (175 Chinese, 72 Japanese, 301 Filipina). The 2,035 control subjects (923 Chinese, 518 Japanese, and 594 Filipina) were selected from the neighborhoods where the case patients resided at the time of diagnosis. A well-established algorithm was used to identify neighborhood controls for population-based case–control studies conducted in LA County as this provides a mechanism of matching on socioeconomic status which is likely to influence various lifestyle habits (8, 9). We initially defined a specified sequence of houses to be visited in the neighborhoods where index cases lived at the time of diagnosis. We then sought to interview 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 done by mail and telephone. 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 visiting a mean of 60 households (48.1 for Chinese, 58.0 for Japanese, and 74.6 for Filipina). Of the controls interviewed, 64% were the first identified eligible controls (range was 64% for Filipina and 67% for Chinese), 18% were the second-identified eligible controls, and 18% were the third or later eligible controls.

Data collection

Cases and controls were interviewed using a standardized, structured questionnaire. Filipina and Japanese American women were interviewed in English as almost all were English-speaking, whereas a Chinese-translated questionnaire was used for subjects who were not English-speaking. Interviews were conducted in Mandarin or Cantonese for 36.9% ($n = 337$) of Chinese cases and 33.3% ($n = 301$) of Chinese controls. To the extent possible, each case–control pair was interviewed by the same interviewer. The questionnaire covered demographic characteristics and migration history, menstrual and reproductive history, body size, physical activity, family history of breast cancer, and diet history (10). To assess menstrual history of subjects, we asked the age when they had their first menstrual period, age when their menstrual periods became established at regular intervals (i.e., there was a predictable amount of time between menstrual periods). Subjects were asked the total number of pregnancies they had. For each pregnancy, the outcome of the pregnancy (i.e., livebirth, stillbirth, induced abortion, spontaneous abortion, and tubal or ectopic pregnancy), the length of the pregnancy, the month/year when the pregnancy ended, whether the baby was breastfed, and the duration of breastfeeding of each birth were asked. Calendars were used to chart major life events, reproductive histories, and hormone use. Lifetime history of hormone use [oral contraceptives (OC) and menopausal hormones] was obtained with the aid of an album with color photographs of all preparations used in the United States. For each episode of exogenous hormone use, age at starting and age at stopping use were asked (10).

Subjects were asked about their height and usual weight history at age 18 years, at age 30 years, and each decade thereafter when they were not pregnant. Relative body weight was evaluated by body mass index (BMI), calculated as the weight in kilograms divided by the square of height in meters (kg/m^2). The change in weight from age 18 to current weight (i.e., before diagnosis or at interview) was calculated. We examined BMI using the recommended 5 category cut-off points (<22.9, 23–24.9, 25–27.4, 27.5–29.9, $\geq$30 kg/m^2) for studies in Asian Americans (11), which incorporated the standard WHO definition (<25, 25–29.9, and $\geq$30 kg/m^2) of normal, overweight, and obese as well as the corresponding WHO Asian BMI definition (<22.9, 23–27.5, and $\geq$27.5 kg/m^2). We calculated total months of menstruation as age at menarche subtracted from age at menopause for postmenopausal women and from age at interview or cancer diagnosis for premenopausal women, and then subtracted anovulatory periods due to months of complete and incomplete pregnancies, lactation, OC use, or missing periods (if 3 or more periods were missed in a row). We excluded women who started hormone therapy before menopause (112 cases, 56 controls) or had hysterectomy only (153 cases, 126 controls) because age at menopause was not known, women who did not have regular cycles (132 cases, 136 controls), and other reasons (5 cases, 7 controls).

Statistical analysis

The results presented below are based on 2,190 cases (393 *in situ*, 1,151 localized, 634 advanced stage, 12 stage unknown) and 1,983 controls for whom we have information on body size, menstrual, and reproductive factors as well as the covariates included for adjustment. We excluded 56 cases (22 Chinese, 24 Japanese, 10 Filipina) and 18 control women (8 Chinese, 5 Japanese, 5 Filipina) from the analysis because they were found to have had a previous cancer (mostly cervical, uterine, or colorectal cancer) diagnosis at the time of interview. We calculated Asian ethnic-specific 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 Asian ethnicity (Filipina, Japanese, Chinese), and reference age (<39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70+ years; ref. 10). All regression models included the following covariates: years of residence in the United States (U. S. born, >20 years, 11–20 years, $\leq$10 years), education (less than high school, high school, some college, college graduate), income, interviewer, family history of breast cancer (no, yes any first degree relative with breast cancer), and history of benign breast disease (no, yes). The menstrual and reproductive variables we considered included age at menarche, pregnancy [never, only incomplete pregnancy (i.e., did not result in live birth, or stillbirths at less than 28 weeks of pregnancy), complete pregnancy (i.e., live births and stillbirths at 28 weeks of pregnancy or more)], parity (no full-term pregnancy, full-term pregnancies), number of births (live births and stillbirths), age at birth (live births and stillbirths), breastfeeding, duration of breastfeeding, use of OCs, duration of OC use, type of menopause and age at menopause, and lifetime cumulative number of menstrual months. Menstrual and reproductive factors were mutually adjusted for. Age at menarche ($\leq$11, 12, 13, 14, 15+ years) and parity (0, 1, 2, 3, 4+ births) were also included in analyses to examine the effects of body size factors.

The body size variables we considered included height, current (i.e., before diagnosis or interview) BMI, BMI at ages 18, 30, and 40, weight change (current weight–weight at age 18 years), waist and hip circumferences and waist-to-hip ratio (WHR). For anthropometric exposures, test for trend (*P* values) were performed by coding each variable as a grouped (quartile) linear variable (i.e., as 1, 2, 3, and 4). In addition, we present risk associations with exposure variables of interest as a continuous variable. *P* values less than 5% were considered statistically significant and all *P* values quoted are two-sided. All analyses were performed by using EPILOG Windows (version 1.01s) statistical software system and the SAS statistical software system (version 9.3; SAS Institute).

Results

Filipina control women were more educated, were more likely to be foreign born, had spent fewer years in the United States, and had the oldest age at immigration, compared with Chinese and Japanese control women (Table 1). Filipina controls had more births and were younger at first birth compared with the other Asian women. Filipina and Japanese women displayed similar mean current BMI, which was higher than in Chinese women. Mean age at natural menopause and ovulatory months did not differ between the three Asian American groups. These patterns were similarly observed when Filipina breast cancer cases were compared with Chinese and Japanese cases. Table 1 also shows that breast cancer cases tended to display a higher risk profile compared with control women of the same Asian race/ethnicity for almost all the variables we studied.

Menstrual and reproductive factors and breast cancer risk associations did not differ by menopausal status among Asian ethnic subgroups, with the exception for age at menarche (see below), and thus ORs are presented in all women (Table 2). Women who were ever pregnant, including those who only had an incomplete pregnancy had lower risk than women who were never pregnant. Breast cancer risk decreased per increasing number of pregnancies (*P* values < 0.001 for all three Asian groups). Having a greater number of births was inversely associated with breast cancer (OR per birth) similarly among Filipina (0.78; 95% CI, 0.73–0.84), Chinese (0.82; 95% CI, 0.76–0.89), and Japanese women (0.78; 95% CI, 0.70–0.88). Age at first birth, age at last birth, and breastfeeding were not associated with risk in Filipina women or in the other Asian women. Use of OC was inversely associated with risk in all three Asian groups combined ($P_{trend} = 0.040$), but the trend was borderline statistically significant only in Chinese American women ($P_{trend} = 0.056$) and not in Japanese and Filipina women. Overall, age at menarche was not associated with risk in Filipina, Chinese, or Japanese women. However, the effect of age at menarche differed between premenopausal and postmenopausal women. In premenopausal women, risk was lower with each year that menarche was delayed in Filipina (OR 0.92; 95% CI, 0.83–1.03), Chinese (0.89; 95% CI, 0.81–0.98), and Japanese (0.88; 95% CI, 0.75–1.03) but risk increased with later age at menarche in postmenopausal women (respective $P_{interaction}$ was 0.02, 0.04, and 0.08). Breast cancer risk was nonsignificantly higher with later age at natural menopause (OR for >54 vs. ≤49) in Filipina (OR = 1.71) and Japanese (OR = 1.33) American women, but not in Chinese women (OR = 0.87; Table 2).

Table 1. Demographic and menstrual and reproductive factors of Filipina, Chinese, and Japanese women in Los Angeles County

	Controls			*P*[a]			Cases			*P*[a]			Cases vs. controls		
	Chinese	Japanese	Filipina	Fi vs. Ch	Fi vs. Jp	Ch vs. Jp	Chinese	Japanese	Filipina	Fi vs. Ch	Fi vs. Jp	Ch vs. Jp	Ch	Jp	Fi
N	896	505	582				891	519	780						
Mean age (SD)	49.3 (9.6)	52.8 (11.3)	52.0 (10.4)	<0.01	0.19	<0.01	52.2 (9.9)	55.8 (11.1)	53.0 (10.0)	0.12	<0.01	<0.01	<0.01	<0.01	0.07
Education level, %															
Less than high school	23.2	13.9	9.3				28.7	17.3	8.6						
High school/some college	19.4	34.1	17.0				18.2	34.9	14.2						
College graduate	37.1	35.0	59.3	<0.01	<0.01	<0.01	35.0	32.4	62.8	<0.01	<0.01	<0.01	0.06	0.39	0.47
Graduate	20.3	17.0	14.4				18.1	15.4	14.4						
Immigration history															
U.S. born, %	14.1	73.9	4.6	<0.01	<0.01	<0.01	9.8	67.2	2.8	<0.01	<0.01	<0.01	<0.01	0.02	0.10
Mean age at migration (SD)	30.9 (12.6)	24.1 (8.4)	33.6 (13.1)	<0.01	<0.01	<0.01	32.0 (13.0)	24.1 (9.2)	33.5 (12.1)	0.02	<0.01	<0.01	0.08	0.95	0.89
Mean years in U.S.	18.4 (11.4)	25.2 (12.8)	18.5 (10.6)	0.90	<0.01	<0.01	20.0 (11.1)	28.4 (12.3)	19.5 (10.4)	0.34	<0.01	<0.01	<0.01	0.03	0.09
Mean current BMI (SD)	22.1 (3.1)	23.3 (4.0)	23.4 (3.4)	<0.01	0.51	<0.01	22.4 (3.3)	23.4 (4.0)	23.9 (3.7)	<0.01	0.01	<0.01	0.04	0.83	0.02
Mean age at menarche (SD)	13.2 (1.6)	12.5 (1.6)	12.9 (1.7)	<0.01	<0.01	<0.01	13.2 (1.6)	12.6 (1.7)	13.0 (1.8)	0.03	<0.01	<0.01	0.81	0.09	0.34
Nulliparous, %	13.6	24.4	15.1	0.46	<0.01	<0.01	19.4	31.0	23.2	0.07	<0.01	<0.01	<0.01	0.02	<0.01
Mean # of births[b] (SD)	2.2 (1.1)	2.3 (1.1)	3.1 (1.9)	<0.01	<0.01	0.20	2.2 (1.1)	2.2 (0.9)	2.6 (1.6)	<0.01	<0.01	0.35	0.87	0.05	<0.01
Mean age at first birth[b] (SD)	27.1 (4.8)	27.4 (5.1)	26.4 (5.5)	<0.01	<0.01	0.41	27.0 (4.8)	27.3 (4.9)	27.3 (5.0)	0.36	0.96	0.44	0.69	0.77	<0.01
Mean months of breastfeed (SD)	5.9 (10.6)	7.7 (13.1)	8.9 (19.8)	<0.01	0.31	<0.01	6.1 (11.9)	5.3 (9.9)	6.7 (14.0)	0.39	0.10	0.29	0.69	<0.01	0.03
Postmenopausal, %	40.3	53.1	52.9	<0.01	0.99	<0.01	51.2	62.6	57.6	0.01	0.08	<0.01	<0.01	<0.01	0.10
Mean age at natural menopause (SD)	49.6 (4.2)	49.9 (4.2)	49.2 (4.0)	0.24	0.06	0.42	50.0 (3.7)	50.7 (4.1)	49.6 (4.0)	0.19	<0.01	0.04	0.24	0.08	0.22
Mean menstrual months[c] (SD)	339.6 (82.7)	331.3 (105.0)	342.4 (83.2)	0.56	0.08	0.14	362.9 (76.3)	361.0 (98.0)	365.4 (79.5)	0.55	0.42	0.71	<0.01	<0.01	<0.01
Family history breast cancer, %	7.1	8.9	9.3	0.17	0.92	0.28	13.7	15.6	12.8	0.65	0.18	0.36	<0.01	<0.01	0.05
Had breast cyst, %	12.8	15.8	15.5	0.18	0.93	0.14	20.3	16.0	23.5	0.13	<0.01	0.05	<0.01	0.98	<0.01

[a]*P* values in controls: Filipina vs. Chinese (Fi vs. Ch); Filipina vs. Japanese (Fi vs. Jp); and Chinese vs. Japanese (Ch vs. Jp).
[b]Births included live births and stillbirths.
[c]Based on 757 Chinese, 410 Japanese, and 489 Filipina controls and 746 Chinese, 403 Japanese, and 641 Filipina cases.

Table 2. Menstrual and reproductive factors and risk of breast cancer in Filipina, Chinese, and Japanese Americans in Los Angeles County

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	OR[b] (95% CI)
Pregnancy										
Never	143	87	1.0	113	82	1.0	159	66	1.00	1.00
Incomplete only	30	35	0.60 (0.33–1.08)	48	41	0.89 (0.52–1.53)	22	22	0.45 (0.22–0.90)	0.69 (0.49–0.96)
1+ livebirth	718	774	0.49 (0.36–0.66)	358	382	0.57 (0.40–0.82)	599	494	0.49 (0.35–0.69)	0.54 (0.45–0.64)
Pregnancy										
0	143	87	1.00	113	82	1.00	159	66	1.00	1.00
1	86	98	0.55 (0.37–0.83)	78	64	0.76 (0.48–1.21)	92	64	0.62 (0.39–0.99)	0.67 (0.52–0.86)
2	207	220	0.54 (0.38–0.76)	128	141	0.58 (0.39–0.87)	167	106	0.69 (0.46–1.04)	0.60 (0.48–0.74)
3	195	204	0.50 (0.35–0.71)	106	115	0.55 (0.36–0.84)	145	118	0.48 (0.32–0.72)	0.53 (0.43–0.66)
≥4	260	287	0.43 (0.30–0.60)	94	103	0.59 (0.38–0.92)	217	228	0.37 (0.25–0.53)	0.45 (0.37–0.56)
P_{trend}			<0.0001			0.008			<0.0001	<0.0001
Per pregnancy			0.84 (0.78–0.91)			0.89 (0.82–0.97)			0.84 (0.79–0.89)	0.87 (0.84–0.9)
P			<0.0001			0.008			<0.0001	<0.0001
Births[c]										
0	173	122	1.00	161	123	1.00	181	88	1.00	1.00
1	171	185	0.62 (0.44–0.86)	87	71	0.79 (0.52–1.20)	133	76	0.89 (0.59–1.34)	0.74 (0.60–0.91)
2	336	365	0.57 (0.42–0.76)	154	181	0.57 (0.40–0.81)	222	139	0.80 (0.56–1.16)	0.64 (0.53–0.77)
3	137	141	0.48 (0.33–0.69)	92	90	0.56 (0.37–0.86)	116	133	0.40 (0.27–0.59)	0.49 (0.39–0.61)
≥4	74	83	0.35 (0.22–0.55)	25	40	0.29 (0.15–0.53)	128	146	0.32 (0.22–0.48)	0.34 (0.26–0.44)
P_{trend}			<0.0001			<0.0001			<0.0001	<0.0001
Per birth			0.82 (0.76–0.89)			0.78 (0.70–0.88)			0.78 (0.73–0.84)	0.81 (0.77–0.84)
P			<0.0001			<0.0001			<0.0001	<0.0001
Age at first birth among parous women										
≤24	197	227	1.00	103	106	1.00	194	193	1.00	1.00
25–29	329	333	1.29 (0.98–1.71)	152	156	1.04 (0.69–1.56)	225	171	1.09 (0.78–1.52)	1.17 (0.98–1.41)
30–35	155	166	1.42 (1.00–2.00)	76	92	1.01 (0.61–1.68)	123	101	0.88 (0.59–1.32)	1.13 (0.91–1.42)
>35	37	48	0.94 (0.55–1.61)	27	28	0.93 (0.45–1.96)	57	29	1.08 (0.60–1.96)	1.11 (0.79–1.55)
P_{trend}			0.31			0.96			0.80	0.36
Per 5 years			1.06 (0.92–1.21)			1.01 (0.83–1.22)			1.00 (0.86–1.15)	1.04 (0.95–1.13)
P			0.43			0.96			0.96	0.42
Age at last birth among parous women										
≤25	84	76	1.00	42	39	1.00	58	42	1.00	1.00
26–30	262	271	0.87 (0.59–1.26)	122	106	1.15 (0.66–2.20)	150	124	0.98 (0.59–1.63)	0.97 (0.75–1.26)
30–35	249	275	0.94 (0.64–1.39)	122	156	0.87 (0.49–1.54)	208	172	1.10 (0.66–1.82)	0.98 (0.75–1.27)
>35	123	152	0.81 (0.53–1.24)	71	81	1.09 (0.58–2.05)	183	155	1.05 (0.62–1.76)	0.97 (0.73–1.29)
P_{trend}			0.52			0.82			0.70	0.89
Per 5 years			0.97 (0.86–1.10)			0.95 (0.79–1.14)			0.97 (0.85–1.12)	0.98 (0.90–1.06)
P			0.43			0.59			0.71	0.56
Breastfeeding among parous women										
0 months	382	370	1.00	185	181	1.00	284	236	1.00	1.00
>0–<0.5 y	136	178	0.74 (0.55–0.99)	78	63	1.28 (0.81–2.01)	157	110	1.18 (0.83–1.67)	0.96 (0.79–1.16)
0.5–≤1 y	77	103	0.82 (0.57–1.16)	47	55	1.17 (0.70–1.94)	61	40	1.55 (0.95–2.53)	1.01 (0.79–1.28)
>1–<2 y	64	78	0.78 (0.53–1.16)	28	54	0.82 (0.45–1.49)	40	55	0.68 (0.41–1.11)	0.76 (0.58–0.99)
≥2 y	57	44	1.49 (0.93–2.39)	19	29	1.04 (0.51–2.10)	56	53	1.10 (0.67–1.82)	1.18 (0.88–1.59)
P_{trend}			0.99			0.86			0.84	0.78
Per 6 months			1.03 (0.97–1.10)			0.97 (0.89–1.07)			0.96 (0.91–1.01)	0.99 (0.95–1.02)
P			0.36			0.57			0.14	0.39

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Table 2. Menstrual and reproductive factors and risk of breast cancer in Filipina, Chinese, and Japanese Americans in Los Angeles County (Cont'd)

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	OR[b] (95% CI)
Oral contraceptives										
Never used	484	444	1.00	242	191	1.00	475	309	1.00	1.00
>0–<1 y	186	187	1.03 (0.79–1.33)	76	67	1.24 (0.80–1.90)	136	119	0.95 (0.69–1.30)	1.03 (0.87–1.23)
1–5	142	147	0.96 (0.71–1.28)	98	117	0.87 (0.59–1.27)	111	88	1.07 (0.75–1.53)	0.97 (0.80–1.16)
>5–≤10	46	67	0.75 (0.49–1.15)	46	62	0.80 (0.49–1.31)	38	44	0.70 (0.42–1.16)	0.75 (0.57–0.97)
>10 y	32	51	0.61 (0.37–1.00)	57	68	0.84 (0.52–1.37)	20	22	0.84 (0.40–1.65)	0.80 (0.60–1.07)
P_{trend}			0.056			0.24			0.40	0.040
Per 5 years of use			0.84 (0.72–0.97)			0.94 (0.82–1.07)			0.89 (0.73–1.09)	0.91 (0.84–0.99)
P			0.0154			0.326			0.37	0.024
Age at menarche										
≤11	102	110	1.00	117	126	1.00	146	97	1.00	1.00
12	213	206	1.00 (0.71–1.43)	149	157	0.98 (0.68–1.41)	182	150	0.82 (0.57–1.19)	0.95 (0.77–1.16)
13	220	229	0.89 (0.63–1.27)	134	125	0.99 (0.68–1.44)	171	152	0.72 (0.50–1.03)	0.87 (0.71–1.07)
14	184	177	0.96 (0.67–1.39)	56	55	0.83 (0.51–1.36)	122	86	1.04 (0.69–1.57)	0.98 (0.79–1.23)
≥15	172	174	0.80 (0.55–1.19)	63	42	1.13 (0.67–1.91)	159	97	0.99 (0.67–1.48)	0.96 (0.76–1.21)
P_{trend}			0.23			1.00			0.64	0.85
Per 1-year delay			0.96 (0.90–1.03)			0.99 (0.91–1.08)			1.01 (0.95–1.08)	0.99 (0.95–1.03)
P			0.23			0.79			0.69	0.72
Age at menarche—premenopausal										
≤11	62	69	1.00	55	56	1.00	84	52	1.00	1.00
12	126	133	0.94 (0.60–1.48)	58	77	0.84 (0.48–1.48)	89	75	0.78 (0.47–1.30)	0.85 (0.64–1.12)
13	112	138	0.80 (0.51–1.27)	50	67	0.61 (0.34–1.10)	69	80	0.54 (0.32–0.90)	0.66 (0.50–0.88)
14	81	107	0.73 (0.45–1.18)	19	22	0.63 (0.28–1.43)	41	33	0.84 (0.45–1.58)	0.73 (0.53–1.01)
≥15	54	88	0.57 (0.34–0.97)	12	15	0.70 (0.27–1.83)	48	34	0.73 (0.39–1.36)	0.62 (0.44–0.88)
P			0.014			0.13			0.26	0.003
Per 1-year delay			0.89 (0.81–0.98)			0.88 (0.75–1.03)			0.92 (0.83–1.03)	0.91 (0.85–0.96)
P			0.016			0.11			0.14	0.0016
Age at menarche—postmenopausal										
≤11	40	41	1.00	62	70	1.00	62	45	1.00	1.00
12	87	73	1.19 (0.67–2.14)	91	80	1.26 (0.77–2.06)	93	75	0.94 (0.55–1.61)	1.12 (0.83–1.51)
13	108	91	1.09 (0.62–1.92)	84	58	1.57 (0.93–2.63)	102	72	0.97 (0.57–1.66)	1.18 (0.88–1.59)
14	103	70	1.41 (0.80–2.52)	37	33	1.11 (0.59–2.11)	81	53	1.30 (0.73–2.30)	1.34 (0.97–1.85)
≥15	118	86	1.25 (0.70–2.26)	51	27	1.67 (0.85–3.30)	111	63	1.30 (0.75–2.24)	1.43 (1.04–1.96)
P			0.37			0.17			0.14	0.015
Per 1-year delay			1.04 (0.94–1.14)			1.06 (0.95–1.18)			1.08 (0.99–1.18)	1.06 (1.01–1.12)
P			0.46			0.34			0.10	0.026
Age at natural menopause										
≤49	117	109	1.00	69	60	1.00	133	105	1.00	1.00
50–54	161	112	1.37 (0.91–2.05)	103	88	0.95 (0.56–1.60)	127	91	1.09 (0.71–1.67)	1.17 (0.91–1.49)
>54	29	26	0.87 (0.44–1.71)	35	21	1.33 (0.62–2.85)	36	18	1.71 (0.83–3.51)	1.23 (0.83–1.83)
P_{trend}			0.65			0.59			0.21	0.19
Per 5-year delay			1.02 (0.99–1.06)			1.01 (0.96–1.05)			1.02 (0.98–1.06)	1.02 (0.99–1.04)
P			0.25			0.84			0.42	0.17

(Continued on the following page)

Table 2. Menstrual and reproductive factors and risk of breast cancer in Filipina, Chinese, and Japanese Americans in Los Angeles County (Cont'd)

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	OR[b] (95% CI)
Age at menopause (natural + complete hysterectomy)										
≤49	161	144	1.00	96	93	1.00	181	141	1.00	1.00
50–54	172	117	1.36 (0.94–1.98)	114	95	1.09 (0.69–1.72)	137	96	1.07 (0.73–1.58)	1.22 (0.97–1.52)
>54	30	26	0.85 (0.45–1.61)	36	22	1.35 (0.67–2.00)	38	18	1.60 (0.80–3.20)	1.23 (0.85–1.79)
P_{trend}			0.61			0.42			0.26	0.098
Per 5-year delay			1.02 (0.99–1.06)			1.02 (0.97–1.06)			1.01 (0.97–1.04)	1.02 (1.00–1.04)
P			0.22			0.47			0.65	0.064

Abbreviations: Ca, cases; Co, controls.
[a]Adjusted for age, education, income, years of residence in the United States among non-U.S. born, interviewer, family history of breast cancer, benign breast diseases. All the other variables (except the ovulatory months) were mutually adjusted for each other.
[b]As above and also adjusted for Asian ethnicity.
[c]Included stillbirths reported in 28 cases and 25 controls.

To investigate whether the timing of births in relation to migration to the United States might explain the unexpected null associations with age at first birth and breastfeeding in this study, we examined risk associations separately for women who had all their births prior to migration, women who had all their births after migration, and women who had one or more birth before migration as well as after migration to the United States (Supplementary Table S1). The risk associations with births, age at first birth, and breastfeeding, were generally the same irrespective whether participants completed births before or after migration to the United States. We also compared the results in migrants to those of U.S.-born Asian Americans [314 cases (238 Japanese, 59 Chinese, and 17 Filipina) and 413 controls (290 Japanese, 102 Chinese, and 21 Filipina)]. Although the results in U.S.-born Asian Americans were not statistically significant, compared with migrants, the risk association per birth was similar (0.87; 95% CI, 0.74–1.03), while the increased risk per 5-year delay in age at first birth was higher (1.05; 95% CI, 0.86–1.29), and the risk reduction per 6 months of breastfeeding was stronger (0.95; 95% CI, 0.87–1.05).

Breast cancer risk increased with increasing number of menstrual months in Filipina women ($P_{trend} = 0.0008$); women in the highest quartile (>399 months) had more than a 2-fold increased risk (OR = 2.55; 95% CI, 1.50–4.33) than those in the lowest quartile (≤283 months); this was observed in both premenopausal ($P_{trend} = 0.019$), postmenopausal ($P_{trend} = 0.008$), and parous ($P_{trend} = 0.014$) but not nonparous ($P_{trend} = 0.24$) Filipina women (Table 3). Risk patterns were similar in Chinese ($P_{trend} = 0.003$), statistically significant in premenopausal ($P_{trend} = 0.0003$), and parous women ($P_{trend} = 0.017$) but not in postmenopausal ($P_{trend} = 0.79$) or nonparous Chinese women ($P_{trend} = 0.92$). Results were weaker in Japanese ($P_{trend} = 0.16$) but there was a borderline statistically significant association in premenopausal women ($P_{trend} = 0.092$). In the three Asian groups combined, there was a significant trend of increasing risk with increasing number of menstrual months in premenopausal ($P_{trend} < 0.0001$) but not in postmenopausal women ($P_{trend} = 0.12$). Risk associations were statistically significant in ever parous women ($P_{trend} = 0.002$) and borderline statistically significant in never parous women ($P_{trend} = 0.08$). The risk associations were similar when we fully adjusted for diabetes, physical activity, and dietary patterns (Table 3, footnote 4). The patterns of associations were also similar by tumor stage at diagnosis (Supplementary Table S2) and by hormone receptor status of breast cancer (Supplementary Table S3).

High BMI at age 18 was inversely associated with risk of breast cancer in premenopausal Filipina women ($P_{trend} = 0.03$) but risk was not significantly influenced by BMI at ages 30 and 40 years, current BMI, weight gain since age 18 years, waist and hip circumferences or WHR. There were no significant associations between these body size factors and risk in premenopausal Chinese and Japanese women (Table 4). Breast cancer risk of postmenopausal Asian women was unrelated to BMI at the age of 18 years ($P_{trend} = 0.93$) but was positively associated with BMI at ages 30 ($P_{trend} = 0.026$) and 40 years ($P_{trend} = 0.002$); results for BMI at ages 30 and 40 years were statistically significant in Filipina and Japanese women, respectively. Current BMI and weight gain since 18 were positively associated with breast cancer risk, regardless of Asian ethnicity (Table 5). High current BMI was positively associated with risk; the OR per 5-unit increase was 1.40 (95% CI, 1.11–1.78) in Filipina, 1.29 (95% CI, 1.02–1.62) in Japanese, and

Table 3. Cumulative menstrual months and risk of breast cancer in Filipina, Chinese, and Japanese Americans in Los Angeles County

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95%CI)	OR[b] (95% CI)
Menstrual months[c,d]										
≤283	102	168	1.00	79	118	1.00	90	106	1.00	1.00
284–≤345	173	214	1.16 (0.80–1.69)	70	81	1.06 (0.65–1.73)	124	123	1.11 (0.72–1.71)	1.07 (0.84–1.35)
346–≤399	220	192	1.57 (1.04–2.36)	84	87	1.05 (0.63–1.75)	192	139	1.61 (1.01–2.56)	1.36 (1.06–1.76)
>399	251	183	1.91 (1.20–3.03)	170	124	1.53 (0.88–2.68)	235	121	2.55 (1.50–4.33)	1.83 (1.38–2.44)
P_{trend}			0.003			0.16			0.0002	<0.0001
Per 50 months			1.16 (1.05–1.28)			1.07 (0.96–1.19)			1.22 (1.09–1.36)	1.13 (1.06–1.19)
P			0.0037			0.23			0.008	0.0001
						By menopausal status				
Premenopausal women										
≤283	70	145	1.00	57	88	1.00	62	69	1.00	1.00
284–≤345	112	165	1.26 (0.81–1.98)	42	59	0.99 (0.54–1.83)	66	72	0.96 (0.53–1.74)	1.07 (0.80–1.44)
346–≤399	126	117	2.30 (1.34–3.93)	39	41	1.18 (0.58–2.39)	97	70	1.44 (0.75–2.78)	1.65 (1.17–2.33)
>399	95	70	2.99 (1.55–5.78)	42	28	2.32 (0.99–547)	82	41	2.59 (1.15–5.84)	2.67 (1.75–4.08)
P_{trend}			0.0003			0.092			0.019	<0.0001
Per 50 months			1.23 (1.07–1.42)			1.11 (0.96–1.28)			1.26 (1.06–1.49)	1.18 (1.09–1.29)
P			0.0038			0.17			0.008	0.0001
Postmenopausal women										
≤283	32	23	1.00	22	30	1.0	28	37	1.00	1.00
284–≤345	61	49	1.00 (0.48–2.06)	28	22	1.36 (0.56–3.30)	58	51	1.32 (0.68–2.58)	1.08 (0.72–1.63)
346–≤399	94	75	0.93 (0.45–1.91)	45	46	0.88 (0.38–1.99)	95	69	1.69 (0.86–3.33)	1.08 (0.72–1.62)
>399	156	113	1.09 (0.51–2.31)	128	96	1.23 (0.54–2.80)	153	80	2.61 (1.24–5.52)	1.36 (0.89–2.08)
P_{trend}			0.79			0.75			0.008	0.12
Per 50 months			1.08 (0.93–1.26)			1.02 (0.87–1.20)			1.18 (1.01–1.39)	1.07 (0.98–1.17)
P			0.32			0.79			0.042	0.13
						By pregnancy history				
No										
≤283	15	16	1.0	19	27	1.00	10	9	1.00	1.00
284–≤345	20	11	2.39 (0.53–0.79)	18	10	1.87 (0.53–6.67)	16	12	0.83 (0.15–4.47)	1.64 (0.82–3.27)
346–≤399	33	19	2.80 (0.47–6.67)	20	13	1.02 (0.30–3.51)	34	16	0.97 (0.13–7.40)	1.64 (0.77–3.49)
>399	50	29	1.35 (0.22–8.23)	36	15	2.66 (0.75–9.46)	71	19	3.02 (0.29–1.32)	2.25 (0.96–5.30)
P_{trend}			0.92			0.21			0.24	0.08
Per 50 months			1.11 (0.79–1.56)			1.19 (0.98–1.46)			1.21 (0.83–1.76)	1.18 (1.01–1.37)
P			0.55			0.087			0.32	0.03
Yes										
≤283	87	152	1.00	60	91	1.0	80	97	1.00	1.00
284–≤345	153	203	1.07 (0.72–1.59)	52	71	0.85 (0.49–1.47)	108	111	1.11 (0.70–1.75)	1.00 (0.77–1.29)
346–≤399	187	173	1.41 (0.91–2.18)	64	74	0.92 (0.51–1.67)	158	123	1.47 (0.90–2.39)	1.25 (0.95–1.65)
>399	201	154	1.73 (1.05–2.84)	134	109	1.22 (0.65–2.29)	164	102	1.97 (1.11–3.49)	1.56 (1.14–2.13)
P_{trend}			0.017			0.50			0.014	0.0022
Per 50 months			1.13 (1.01–1.26)			1.01 (0.89–1.14)			1.14 (1.01–1.30)	1.08 (1.01–1.15)
P			0.028			0.93			0.037	0.0023

Abbreviations: Ca, cases; Co, controls.

[a]Adjusted for age, education, income, years of residence in the United States among non-U.S. born, interviewer, family history of breast cancer, benign breast diseases.

[b]As above and also adjusted for Asian ethnicity.

[c]Total menstrual months were calculated as age at menarche subtracted from age at menopause for postmenopausal women and from age at interview or cancer diagnosis for premenopausal women, and then subtracting anovulatory periods due to complete and incomplete pregnancies, lactation, OC use, or missing periods (if 3 or more periods were missing in a row). We excluded women who started hormone therapy before menopause (112 cases, 63 controls) or had hysterectomy only (153 cases, 126 controls) because age at menopause was not known, women who did not have regular cycles (122 cases, 136 controls), and other reasons (3 cases, 7 controls).

[d]The ORs per 50 menstrual months when additionally adjusted for history of diabetes, years of physical activity, and dietary pattern (vegetable/soy pattern, and ethnic meats and carbohydrates); the fully adjusted RR per 50 menstrual months were: Chinese: 1.18 (95% CI, 1.07–1.31), $P = 0.001$; Japanese: 1.07 (95% CI, 0.96–1.20), $P = 0.20$; and Filipina: 1.23 (95% CI 1.10–1.39), $P = 0.0005$.

1.20 (95% CI, 0.96–1.50) in Chinese women. Weight gain since the age of 18 years was also positively associated with risk; the OR per 5-kg increase was 1.18 (95% CI, 1.07–1.30) in Filipina, 1.10 (95% CI, 1.00–1.21) in Japanese, and 1.09 (95% CI, 0.99–1.21) in Chinese women. Breast cancer risk in postmenopausal Filipina women increased with increasing waist circumference ($P_{trend} = 0.04$) but risk was unrelated to hip circumference or WHR. Both waist ($P_{trend} = 0.013$) and hip ($P_{trend} = 0.01$) circumferences, but not WHR were positively associated with risk in postmenopausal Japanese women. Risk in postmenopausal Chinese women was not associated with waist and hip circumferences or WHR (Table 5). The patterns of associations with current BMI and weight gain and risk in postmenopausal women were also similar by tumor stage at diagnosis (Supplementary Table S2).

Table 4. Body size and risk of breast cancer in premenopausal Filipina, Chinese, and Japanese women in Los Angeles County

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	OR[b] (95% CI)
Height (cm)										
≤155	116	129	1.00	74	76	1.00	126	116	1.00	1.00
156–160	122	159	0.93 (0.65–1.34)	62	83	0.76 (0.46–1.28)	113	78	1.58 (1.02–2.45)	1.02 (0.81–1.29)
161–165	112	129	1.00 (0.68–1.46)	35	52	0.73 (0.40–1.33)	54	50	1.20 (0.71–2.02)	0.99 (0.76–1.29)
>165	85	118	0.82 (0.55–1.24)	23	26	1.12 (0.54–2.31)	38	30	1.28 (0.70–2.34)	1.01 (0.75–1.34)
P_{trend}			0.45			0.80			0.35	0.99
Per 10 cm			1.02 (0.80–1.30)			0.91 (0.61–1.37)			1.12 (0.81–1.55)	1.04 (0.88–1.23)
P			0.89			0.65			0.49	0.65
BMI at age 18 (kg/m^2)										
<20	306	378	1.00	98	107	1.00	261	193	1.00	1.00
20–≤22.9	87	114	1.01 (0.71–1.42)	74	101	0.86 (0.55–1.37)	53	62	0.58 (0.36–0.92)	0.83 (0.66–1.04)
>22.9	21	29	0.84 (0.46–1.55)	22	27	1.03 (0.51–2.06)	15	14	0.64 (0.28–1.49)	0.89 (0.60–1.32)
P_{trend}			0.71			0.80			0.03	0.18
Per 5 kg/m^2			0.99 (0.74–1.33)			1.04 (0.68–1.59)			0.70 (0.48–1.01)	0.94 (0.78–1.14)
P			0.96			0.85			0.059	0.54
BMI at age 30 (kg/m^2)										
<20	212	234	1.00	71	70	1.00	118	100	1.00	1.00
20–≤22.9	161	222	0.81 (0.60–1.09)	80	99	0.86 (0.52–1.41)	137	118	1.20 (0.79–1.82)	0.91 (0.74–1.12)
>22.9–≤24.9	34	41	0.98 (0.57–1.67)	23	36	0.79 (0.39–1.57)	40	30	1.15 (0.63–2.13)	0.91 (0.65–1.27)
>24.9	17	27	0.61(0.30–1.23)	19	27	0.72 (0.34–1.53)	29	20	2.02 (0.96–4.24)	1.00 (0.67–1.49)
P_{trend}			0.17			0.34			0.10	0.69
Per 5 kg/m^2			0.88 (0.66–1.71)			0.83 (0.58–1.17)			1.31 (0.93–1.84)	1.00 (0.83–1.19)
P			0.39			0.29			0.12	0.95
BMI at age 40 (kg/m^2)										
<20	99	99	1.00	41	29	1.00	47	33	1.00	1.00
20–≤22.9	156	183	0.93 (0.64–1.35)	62	72	0.80 (0.41–1.58)	102	80	1.01 (0.55–1.86)	0.91 (0.69–1.19)
>22.9–≤24.9	67	70	1.08 (0.68–1.72)	33	39	0.61 (0.28–1.34)	60	53	0.86 (0.44–1.65)	0.86 (0.62–1.20)
>24.9	47	62	0.74 (0.44–1.24)	25	30	0.78 (0.34–1.78)	61	47	0.97 (0.49–1.92)	0.84 (0.60–1.20)
P_{trend}			0.45			0.40			0.93	0.31
Per 5 kg/m^2			0.98 (0.75–1.28)			0.80 (0.55–1.17)			1.10 (0.79–1.53)	0.97 (0.82–1.16)
P			0.87			0.25			0.58	0.76
Current BMI (kg/m^2)										
≤22.9	304	381	1.00	127	144	1.00	182	150	1.00	1.00
>22.9–≤24.9	73	78	1.19 (0.81–1.74)	32	45	0.73 (0.41–1.32)	67	60	0.92 (0.57–1.46)	0.95 (0.74–1.22)
>24.9–≤27.5	41	59	0.76 (0.48–1.20)	23	23	1.02 (0.49–2.13)	46	43	0.85 (0.49–1.47)	0.85 (0.62–1.15)
>27.5–≤29.9	6	10	0.73 (0.24–2.23)	5	9	0.78 (0.23–2.69)	20	8	2.02 (0.79–5.17)	1.16 (0.66–2.05)
≥30	13	7	1.83 (0.67–4.97)	7	16	0.46 (0.16–1.30)	16	13	0.92 (0.38–2.24)	1.06 (0.63–1.77)
P_{trend}			0.96			0.19			0.81	0.82
Per 5 kg/m^2			1.02 (0.80–1.29)			0.77 (0.71–1.07)			1.14 (0.85–1.51)	0.99 (0.85–1.15)
P			0.91			0.099			0.38	0.82
Weight gain since age 18 (kg)										
≤3.6	127	171	0.88 (0.63–1.24)	85	89	1.37 (0.83–2.26)	49	56	0.65 (0.38–1.12)	0.93 (0.73–1.18)
>3.6–9.1	144	184	1.00	69	88	1.00	98	88	1.00	1.00
>9.1–≤14.1	85	83	1.10 (0.73–1.64)	20	28	0.83 (0.40–1.73)	85	47	1.61 (0.97–2.70)	1.22 (0.92–1.61)
>14.1–≤22.7	44	66	0.75 (0.47–1.20)	18	23	0.98 (0.44–2.18)	71	59	1.03 (0.61–1.73)	0.87 (0.64–1.17)
>22.7	14	17	0.88 (0.39–1.96)	2	7	0.37 (0.07–1.99)	26	19	1.24 (0.58–2.65)	0.94 (0.58–1.53)
P_{trend}			0.49			0.49			0.37	0.80
Per 5 kg			1.02 (0.92–1.12)			0.82 (0.69–0.97)[c]			1.15 (1.03–1.30)[c]	1.02 (0.95–1.08)
P			0.71			0.017			0.015	0.63

(Continued on the following page)

Table 4. Body size and risk of breast cancer in premenopausal Filipina, Chinese, and Japanese women in Los Angeles County (Cont'd)

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	OR[b] (95% CI)
Waist (cm)										
≤71.1	104	128	1.00	69	71	1.00	38	46	1.00	1.00
>71.1–≤75.5	161	198	1.01 (0.70–1.44)	48	57	0.74 (0.41–1.33)	100	76	1.84 (1.02–3.34)	1.07 (0.82–1.38)
>75.5–≤85.1	100	127	0.94 (0.63–1.42)	39	58	0.64 (0.35–1.19)	99	72	1.83 (0.99–3.38)	1.03 (0.78–1.36)
>85.1	57	66	1.01 (0.62–1.65)	34	46	0.76 (0.40–1.47)	87	77	1.67 (0.90–3.10)	1.03 (0.76–1.40)
P_{trend}			0.89			0.29			0.27	0.94
Per 5 cm			1.00 (0.92–1.09)			0.95 (0.86–1.05)			1.06 (0.96–1.17)	1.01 (0.96–1.06)
P			0.89			0.32			0.23	0.69
Hip (cm)										
≤92.7	136	170	1.00	70	69	1.00	87	66	1.00	1.00
>92.7–≤96.5	88	117	0.91 (0.62–1.33)	39	50	0.84 (0.46–1.51)	62	53	0.87 (0.50–1.52)	0.88 (0.68–1.15)
>96.5–≤102.9	138	155	1.08 (0.76–1.52)	51	67	0.84 (0.48–1.47)	105	87	0.96 (0.59–1.56)	1.03 (0.80–1.31)
>102.9	60	77	0.91 (0.58–1.43)	29	46	0.77 (0.40–1.50)	70	65	0.82 (0.48–1.40)	0.87 (0.65–1.16)
P_{trend}			0.99			0.44			0.57	0.62
Per 5 cm			1.00 (0.76–1.29)			0.92 (0.75–1.13)			1.04 (0.93–1.16)	1.01 (0.95–1.07)
P			0.96			0.42			0.51	0.80
WHR										
≤0.76	122	150	1.00	58	63	1.00	33	38	1.00	1.00
>0.76–≤0.80	132	150	1.15 (0.80–1.65)	45	59	0.77 (0.42–1.39)	70	56	1.79 (0.92–3.48)	1.08 (0.82–1.41)
>80.0–≤0.845	93	131	0.95 (0.64–1.41)	49	58	0.78 (0.42–1.42)	102	89	1.41 (0.73–2.65)	0.92 (0.70–1.21)
>0.845	75	88	1.07 (0.69–1.67)	37	52	0.62 (0.33–1.20)	119	88	1.84 (0.97–3.49)	1.08 (0.80–1.45)
P_{trend}			0.98			0.18			0.18	0.62
Per 0.01			0.99 (0.76–1.29)			0.94 (0.66–1.34)			1.28 (0.90–1.81)	1.01 (0.92–1.10)
P			0.94			0.73			0.17	0.92

Abbreviations: Ca, cases; Co, controls.

[a]Adjusted for age, education, income, years of residence in the United States among non-U.S. born, interviewer, age at menarche, parity, family history of breast cancer, and benign breast diseases.

[b]As above but also adjusted for Asian ethnicity.

[c]RR per 5-kg weight gain differed significantly between Japanese and Filipina American women ($P_{interaction} = 0.003$).

Discussion

Numerous observational studies have investigated reproductive factors (e.g., age at menarche, parity, breastfeeding) and breast cancer risk although few of these studies were conducted in Asian American women (10, 12), and even fewer had adequate sample size to examine risk patterns separately in Filipina, Chinese, and Japanese women. To explore reasons for the higher breast cancer rates among Filipina Americans (2), we examined the role of body size and menstrual and reproductive factors in Filipina Americans, comparing their risk profiles to those of Chinese and Japanese Americans. In addition, we investigated the influence of lifetime menstrual months as a marker of cumulative exposure to endogenous hormones. It is of interest that both total menstrual months, and body size factors (age 30 BMI, current BMI, weight gain since age 18, and waist circumferences) were statistically significant breast cancer risk factors for postmenopausal Filipina women. In contrast, cumulative number of menstrual months was a significant risk factor for Chinese, particularly premenopausal Chinese women, but not for Japanese women, while body size factors were significantly associated with risk among postmenopausal Japanese but not among postmenopausal Chinese women.

Breast cancer risk was lower with later age at menarche among premenopausal Filipina, Chinese, and Japanese Americans; the ORs ranged from 0.88 to 0.92 per year delay. However this inverse relationship was not observed in postmenopausal Asian Americans. Our findings in premenopausal women are consistent with results from a large international pooled analysis (13), but the positive association in postmenopausal women was unexpected. There was internal consistency in our data as average age at menarche was slightly older in postmenopausal then premenopausal Filipina (13.1 vs. 12.7), Chinese (13.4 vs. 13.1), and Japanese (13.1 vs. 12.4) women. Early menarche (i.e., $\leq$12 years) was also more common for Filipina (42%), Japanese (56%), and Chinese (35%) in LA County than their Asia counterparts in the Philippines (26%; ref. 3), Japan (7%–22%; refs. 14, 15), and China (9%; ref. 16). Although studies in China (16, 17) and a meta-analysis of case–control studies from Japan conducted prior to 1995 have found a significant risk reduction with later age at menarche (18), recent cohort studies from Japan have reported mixed results. No significant associations were found in either the Japan Collaborative Cohort Study (14) or the Miyagi (19) cohorts, whereas in the Japan Public Health Center cohort, a significant protective association of late menarche was found in premenopausal women but not in postmenopausal women (20). Secular changes in age at menarche in the United States, and in Asia, and the influence of increasing body size in U.S. adolescent girls, as well as small sample sizes, and recall biases may have contributed to some of the inconsistencies in the different studies.

Risk reduction with increasing parity was comparable for Filipina, Chinese, and Japanese women in LA County (OR per birth ranged from 0.78 to 0.82). Nulliparity was most prevalent in Japanese (24.5%), intermediate in Filipina (15.2%), and lowest for Chinese (13.5%) in LA County. Interestingly, the prevalence of nulliparity among U.S. Filipina control women is similar to that in the Philippines (13.5%; ref. 3), whereas the prevalence of nulliparity was higher for Chinese and Japanese in LA County than their respective counterparts in China (3%–5%; refs. 16, 21), or Japan (2%–10%; refs. 15, 19, 20). Compared with age at first birth $\leq$24 years, older age was associated with an increased risk in Filipina, Chinese, and Japanese women combined (ORs were 1.17, 1.13, and 1.11; $P_{trend} = 0.36$ with age at first birth 25–29, 30–35, and >35, respectively). These findings on age at first birth in Asian Americans are weaker than results from Asia (3, 14, 16, 20) and western populations (22). This discrepancy may be due to the few (9.7% Filipina, 3.9% Japanese, 3.2% Chinese) Asian American control women with young age at first birth (i.e., <20 years; data not shown) that typically comprise the reference group, compared to data in the Philippines (22%; ref. 3), Japan (8%; ref. 23), and China (5%; ref. 16).

Breastfeeding was not associated with breast cancer risk in the three Asian American groups. This is in contrast to an international pooled analysis which found a statistically significant 4.3% reduction in breast cancer risk for every 12 months of breastfeeding (24). Less than half of parous Filipina (48%), Chinese (48%), and Japanese (48%) in LA County reported breastfeeding and the average duration of breastfeeding was less than one year. Breastfeeding was not included in the previous case–control study from the Philippines (3) but was reported by approximately 80% of parous women in Japan and China (16, 19–21). In studies conducted in the 1970s and 1980s, long duration of breastfeeding (i.e., >3 years) had a significant protective effect of breast cancer risk in urban Shanghai and Tianjin, China (17, 25, 26). There was no significant association between risk and duration of breastfeeding in more recent studies conducted in Shanghai, China (16, 21). The highest category of breastfeeding ($\geq$24 months) was reported by 17% of control women in Shanghai in the 1990s (16) compared with 41% who reported breastfeeding 3 or more years in Shanghai in the mid-1980s (17). Results on breastfeeding and breast cancer risk in studies from Japan are mixed (27); no significant association was found in recent cohort studies but information on duration of breastfeeding was not provided (19, 20).

Our results showed that the risk associations with births, age at first birth, and breastfeeding, were generally the same irrespective whether participants completed births before or after migration to the United States (Supplementary Table S1). Much larger studies will be needed to better understand the complex interplay between age at migration and its corresponding influences on number and timing of pregnancy as well as breastfeeding practices in different Asian groups.

We explored whether risk of breast cancer in Asian Americans was associated with cumulative menstrual months, a surrogate of total endogenous exposure to estrogen (4, 5). Our data provided clear evidence that greater duration of menstrual months was positively associated with risk of breast cancer; this was particularly strong in all three groups of premenopausal Asian women (OR per 50 months was 1.18; 95% CI, 1.09–1.29). In pre- and postmenopausal women combined, the association was strongest in Filipina (OR per 50 months, 1.22; 95% CI, 1.09–1.36), intermediate in Chinese (OR per 50 months, 1.16; 95% CI, 1.05–1.28), and weakest in Japanese (OR, 1.07; 95% CI, 0.96–1.19) women. These novel findings in premenopausal women and in Filipina are supportive of the findings on lifetime cumulative number of menstrual cycles and risk in western populations (4, 5). Duration of menstruation was associated with breast cancer in Shanghai, China (21), and among postmenopausal women in Japan (19), although it is not clear whether duration of breastfeeding, pregnancy, and months of OC use were excluded from these analyses. To estimate the number of menstrual months, we used self-reported information on duration of each pregnancy,

Table 5. Body size and risk of breast cancer in postmenopausal Filipina, Japanese, and Chinese women in Los Angeles County

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	OR[b] (95% CI)
Height (cm)										
≤155	163	128	1.00	136	140	1.00	229	166	1.00	1.00
156–160	136	115	0.94 (0.66–1.36)	117	70	1.75 (1.14–2.67)	125	85	1.07 (0.73–1.56)	1.18 (0.95–1.46)
161–165	104	75	1.10 (0.73–1.65)	50	37	1.56 (0.9–2.69)	63	40	1.20 (0.74–1.94)	1.23 (0.95–1.59)
165	53	43	1.09 (0.66–1.81)	22	21	1.27 (0.63–2.56)	32	17	1.43 (0.72–2.84)	1.15 (0.83–1.61)
P_{trend}			0.61			0.10			0.30	0.13
Per 10 cm			1.08 (0.81–1.45)			1.28 (0.91–1.82)			1.12 (0.83–1.53)	1.12 (0.94–1.33)
P			0.60			0.16			0.46	0.21
BMI 18 (kg/m^2)										
<20	295	231	1.00	166	134	1.00	319	224	1.00	1.00
20–≤22.9	64	71	0.76 (0.50–1.14)	117	107	1.07 (0.72–1.60)	97	49	1.43 (0.94–2.19)	1.03 (0.82–1.29)
>22.9	25	16	1.20 (0.60–2.39)	35	26	1.41 (0.76–2.61)	15	19	0.42 (0.19–0.93)	0.94 (0.64–1.38)
P_{trend}			0.71			0.32			0.67	0.93
Per 5 kg/m^2			1.01 (0.72–1.41)			1.10 (0.76–1.61)			0.89 (0.63–1.27)	0.99 (0.85–1.16)
P			0.97			0.61			0.53	0.93
BMI at age 30 (kg/m^2)										
<20	208	165	1.00	112	83	1.00	150	117	1.00	1.00
20–≤22.9	150	124	1.03 (0.73–1.45)	137	118	0.92 (0.61–1.39)	192	122	1.36 (0.96–1.96)	1.11 (0.90–1.36)
>22.9–≤24.9	38	33	1.03 (0.58–1.80)	45	45	0.99 (0.56–1.74)	63	40	1.31 (0.78–2.19)	1.12 (0.83–1.51)
>24.9	18	12	1.41 (0.64–3.12)	30	22	1.39 (0.70–2.75)	31	14	2.48 (1.16–5.32)	1.71 (1.14–2.58)
P_{trend}			0.53			0.50			0.021	0.026
Per 5 kg/m^2			1.11 (0.81–1.53)			1.15 (0.82–1.62)			1.36 (0.99–1.86)	1.21 (1.01–1.45)
P			0.52			0.43			0.06	0.041
BMI at age 40 (kg/m^2)										
<20	126	119	1.00	76	59	1.00	78	60	1.00	1.00
20–≤22.9	180	143	1.34 (0.93–1.93)	126	114	0.81 (0.51–1.29)	166	119	1.28 (0.81–2.02)	1.21 (1.01–1.45)
>22.9–≤24.9	72	44	1.72 (1.05–2.82)	60	55	0.99 (0.57–1.73)	107	53	1.61 (0.96–2.71)	1.45 (1.09–1.92)
>24.9	42	38	1.33 (0.77–2.30)	63	39	1.77 (0.98–3.21)	91	63	1.40 (0.82–2.37)	1.50 (1.11–2.03)
P_{trend}			0.086			0.049			0.16	0.002
Per 5 kg/m^2			1.21 (0.98–1.37)			1.36 (1.03–1.81)			1.31 (0.99–1.74)	1.29 (1.11–1.51)
P			0.17			0.032			0.06	0.001
Current BMI (kg/m^2)										
≤22.9	244	217	1.00	146	137	1.00	163	127	1.00	1.00
>22.9–≤24.9	106	69	1.44 (0.98–2.12)	72	61	1.19 (0.74–1.88)	116	75	1.43 (0.94–2.16)	1.30 (1.03–1.64)
>24.9–≤27.5	65	47	1.30 (0.83–2.03)	58	31	2.56 (1.46–4.47)	94	71	1.14 (0.74–1.74)	1.39 (1.07–1.80)
>27.5–≤29.9	24	14	1.60 (0.77–3.35)	25	21	1.66 (0.82–3.34)	39	21	1.65 (0.87–3.13)	1.60 (1.09–2.33)
≥30	17	14	1.26 (0.58–2.74)	24	18	1.69 (0.80–3.57)	37	14	2.79 (1.35 -5.77)	1.83 (1.21–2.76)
P_{trend}			0.11			0.008			0.012	0.0001
Per 5 kg/m^2			1.20 (0.96–1.50)[c]			1.29 (1.02–1.62)[c]			1.40 (1.11–1.78)[c]	1.29 (1.13–1.46)[c]
P			0.12			0.032			0.005	0.0001
Weight gain										
≤3.64	81	70	1.01 (0.65–1.58)	91	91	1.07 (0.68–1.73)	40	39	0.83 (0.45–1.52)	0.95 (0.73–1.26)
>3.64–9.09	117	109	1.00	80	74	1.00	84	65	1.00	1.00
>9.09–≤14.1	77	63	1.14 (0.72–1.81)	60	49	1.23 (0.72–2.10)	103	72	1.34 (0.82–2.17)	1.22 (0.93–1.60)
>14.1–≤22.7	76	64	1.10 (0.69–1.75)	67	40	1.95 (1.11–3.42)	152	85	1.54 (0.97–2.44)	1.45 (1.11–1.90)
>22.7	33	12	2.76 (1.30–5.85)	20	18	1.25 (0.57–2.76)	52	31	1.61 (0.88–2.96)	1.74 (1.19–2.56)
P_{trend}			0.064			0.053			0.019	0.0002
Per 5 kg			1.09 (0.99–1.21)[d]			1.10 (1.00–1.21)			1.18 (1.07–1.30)	1.13 (1.07–1.19)[d]
P			0.082			0.058			0.001	<0.0001

(Continued on the following page)

Table 5. Body size and risk of breast cancer in postmenopausal Filipina, Japanese, and Chinese women in Los Angeles County (Cont'd)

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	Ca	Co	OR[a] (95% CI)	OR[b] (95% CI)
Waist (cm)										
≤71.1	80	55	1.00	50	46	1.00	26	22	1.00	1.00
>71.1–≤75.5	134	119	0.74 (0.47–1.16)	81	90	0.85 (0.48–1.48)	74	63	0.98 (0.47–2.05)	0.86 (0.63–1.16)
>75.5–≤85.1	122	101	0.87 (0.55–1.42)	77	64	1.08 (0.60–1.92)	139	98	1.16 (0.57–2.33)	1.04 (0.76–1.42)
>85.1	106	80	0.95 (0.58–1.56)	105	64	1.74 (0.97–3.12)	194	122	1.52 (0.77–3.02)	1.34 (0.98–1.83)
P_{trend}			0.79			0.0125			0.04	0.004
Per 5 cm			1.00 (0.92–1.09)			1.12 (1.03–1.22)			1.05 (0.97–1.14)	1.06 (1.01–1.11)
P			0.99			0.012			0.23	0.02
Hip (cm)										
≤92.7	119	91	1.00	80	76	1.00	94	59	1.00	1.00
>92.7–≤96.5	82	71	0.97 (0.65–1.57)	69	57	1.31 (0.78–2.22)	53	55	0.58 (0.33–1.00)	0.92 (0.69–1.21)
>96.5–≤102.9	158	119	1.12 (0.79–1.72)	84	64	1.17 (0.76–1.90)	151	92	1.15 (0.73–1.81)	1.17 (0.92–1.50)
>102.9	83	74	0.94 (0.60–1.48)	80	64	2.08 (1.21–3.56)	135	99	1.06 (0.67–1.68)	1.22 (0.94–1.60)
P_{trend}			0.95			0.01			0.44	0.05
Per 5 cm			1.02 (0.92–1.13)			1.12 (1.01–1.24)			1.03 (0.80–1.32)	1.06 (1.01–1.12)
P			0.70			0.038			0.81	0.03
WHR										
≤0.76	92	66	1.00	43	57	1.00	31	21	1.00	1.00
>0.76–≤0.80	117	93	0.92 (0.58–1.44)	75	66	1.17 (0.66–2.07)	55	64	0.54 (0.26–1.13)	0.88 (0.65–1.20)
>80.0–≤0.845	115	96	0.85 (0.54–1.34)	80	66	1.27 (0.72–2.25)	118	79	0.96 (0.48–1.94)	1.05 (0.78–1.43)
>0.845	118	100	0.86 (0.54–1.37)	115	75	1.53 (0.87–2.68)	229	141	0.98 (0.67–1.91)	1.13 (0.84–1.52)
P_{trend}			0.50			0.12			0.16	0.14
Per 0.1			0.93 (0.72–1.20)			1.31 (0.98–1.76)			1.03 (0.80–1.43)	1.08 (0.93–1.25)
P			0.56			0.021			0.81	0.30

Abbreviations: Ca, cases; Co, controls.

[a]Adjusted for age, education, income, years of residence in the United States among non-U.S. born, interviewer, age at menarche, parity, family history of breast cancer, benign breast disease, and type of menopause status and age at menopause.

[b]As above but also adjusted for Asian ethnicity.

[c]Full adjustment included history of diabetes, years of physical activity, and dietary pattern (vegetable/soy pattern, and ethnic meats and carbohydrates); the fully adjusted RR per 5 kg/m^2 current BMI were: Chinese 1.14 (95% CI, 0.90–1.44), $P = 0.27$; Japanese 1.23 (95% CI, 0.97–1.55), $P = 0.092$; Filipina 1.31 (95% CI, 1.02–1.67), $P = 0.036$; and all subjects combined 1.22 (95% CI, 1.07–1.39), $P = 0.003$.

[d]Full adjustment included history of diabetes, years of physical activity, and dietary pattern (vegetable/soy pattern, and ethnic meats and carbohydrates); the fully adjusted RR per 5 kg weight gain were: Chinese 1.07 (95% CI, 0.96–1.18), $P = 0.22$; Japanese 1.08 (95% CI, 0.98–1.20), $P = 0.13$; Filipina 1.16 (95% CI, 1.05–1.28), $P = 0.005$; and all subjects combined 1.11 (95% CI 1.05–1.17), $P = 0.0005$.

months of breastfeeding, months of OC use, and age at menopause (for postmenopausal women only). However, we did not calculate number of ovulatory cycles because this would require information on duration of menstrual cycles and assumptions about absence of cycles during lactation, other outcomes of pregnancy, and OC use. Although OC use is typically associated with a small increased risk of breast cancer in studies conducted in western populations (28), in this and a previous case–control study of Asian Americans we conducted in the 1980s (29), use of OCs was inversely associated with risk in combined analyses of Asian American women, but did not achieve statistical significance in Asian ethnic–specific analysis. No significant association between OC use and breast cancer risk was reported in recent studies in China, Japan, and the Philippines (3, 19, 30). The null findings in Asian populations may be due in part to the low prevalence of OC use and the relatively short duration of use in these study populations, compared with Asian Americans and western populations.

We reported few significant associations between body size factors and risk in premenopausal Filipina, Chinese, and Japanese women. This is in contrast to the positive association between current BMI and risk in premenopausal women in Shanghai, China (31, 32), Japan (23), and the Philippines (3) and the significant inverse association between recent BMI and risk in premenopausal Caucasian U.S. women (33, 34). The inconsistent direction in the association between current BMI and risk in premenopausal Asian versus Caucasian women is not well understood (34). Anovulation as a result of obesity (i.e., BMI $\geq$30 kg/m^2) has been hypothesized to explain the inverse association in Caucasian women (35). The extent to which this applies to Asian populations is not known but the prevalence of obesity (i.e., BMI $\geq$ 30 kg/m^2) is still low in Asian Americans; reported by 1.3% of Chinese, 4.7% of Filipina, and 6.8% of Japanese control women in LA County, compared with about 15% of premenopausal Caucasian women in studies that reported inverse associations (36, 37). In addition, BMI may not be the most appropriate measure of obesity in Asian Americans (38, 39). Previous studies on weight at age 20 and weight changes in relation to risk in premenopausal Asians are sparse and conflicting (32, 40).

The body size effects on risk among postmenopausal Filipina Americans in LA County (Table 4) were as strong as the risk associations observed among postmenopausal Japanese Americans in the Multiethnic Cohort (MEC) which showed HRs of 1.07 (95% CI, 1.03–1.12) per 5-kg increase of weight gain, and 1.15 (95% CI, 1.04–1.27) per 5 kg/m^2 increase in current BMI (41). Although BMI was not a risk factor for postmenopausal women in the Philippines, these results were based on 36 postmenopausal cases and 274 control women and the analysis was limited to dichotomizing BMI as above or below 25 kg/m^2 (3). Current BMI and weight gain since the age of 20 years were significant risk factors for postmenopausal women in China (32) and Japan (23, 42). While high BMI (>30 kg/m^2) was more prevalent in LA County Asian Americans (7.0% of Japanese, 4.5% of Filipina, and 4.0% of Chinese women) than in Japan (2.8%; ref. 23), it is still much lower than in Whites (16%; ref. 37). Weight gain of 9 kg or more since age 18 was reported by 65% of Filipina, 49% of Japanese, and 44% of Chinese women in LA County, comparable with results in China (51%; ref. 32) but higher than in Japan (33%; ref. 43). Our findings of high weight gain/obesity in Filipina are consistent with previous studies (44), showing that Filipina tend to be at higher risk of obesity than other Asian American groups. The high prevalence of obesity in Japanese American women is also consistent with the trends of increasing obesity with succeeding generations of Asians in the United States (45).

Some strengths and limitations of our study should be noted. The overall participation rate was modest (61% among cases and 64% among controls). Although our participation rate is not unlike that reported in other population-based studies conducted during this time period, 14% of the identified cases had moved outside of LA County (21% for Filipina, 12% for Chinese, and 8% for Japanese). The non-interviewed breast cancer patients tended to be older than those who were interviewed, but the interviewed and noninterviewed group did not differ in terms of neighborhood socioeconomic status or tumor stage at diagnosis (Supplementary Table S4). While we cannot rule out the possibility of recall bias in this case–control study, there was internal consistency in our data such as younger average age at menarche among U.S.-born than non-U.S.–born Asian Americans. In addition, we had the advantage of using a lifetime calendar approach which allowed us to collect detailed information on relevant menstrual and reproductive events that were used to calculate the cumulative index of menstrual months (see Materials and Methods). However, we did not have information on cycle length and assumed absence of ovulation during the duration of breastfeeding. Because a common questionnaire and study protocol was used in the three Asian American ethnic groups, we were able to compare risk estimates in Filipina, Chinese, and Japanese Americans as well as prevalence of risk factors. We recognize the challenges of comparing risk factor patterns between different studies conducted in Asia to those of Filipina, Japanese, and Chinese Americans because of cohort effects as well as economic and westernization effects on body size, and menstrual and reproductive factors. To the extent possible, we selected as comparison larger population-based studies in Asia that were conducted during comparable time frames as our study in LA County.

In summary, the current analysis represents a first attempt to examine reasons for the high breast cancer incidence in Filipina women compared to other Asian groups. Both cumulative menstrual months and body size factors were important risk factors for LA County Filipina women, while only menstrual months was a risk factor for Chinese and only body size factors were related to risk for Japanese women. The prevalence of weight gain since age 18 (i.e., at least 9 kg) was also higher in postmenopausal Filipina than postmenopausal Chinese and Japanese women. Thus, these factors may explain, in part, the higher incidence of breast cancer among Filipina women. However, this analysis only covered the well-established breast cancer risk factors related to menstrual and reproductive events and body size characteristics. Future analysis will need to examine the role of diet, comorbidities, physical activity, and other lifestyle factors to obtain a more complete understanding of the reasons for the high breast cancer incidence among Filipina women compared with other women in Asia as well as other Asian Americans in the United States.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, the California Department of Health Services, or the National Cancer Institute is not intended nor should be inferred.

Authors' Contributions

Conception and design: A.H. Wu
Development of methodology: A.H. Wu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.H. Wu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.H. Wu, C. Vigen, E. Lee, C.-C. Tseng
Writing, review, and/or revision of the manuscript: A.H. Wu, C. Vigen, E. Lee, L.M. Butler
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.H. Wu
Study supervision: A.H. Wu

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