IJC
International Journal of Cancer

Metabolic conditions and breast cancer risk among Los Angeles County Filipina Americans compared with Chinese and Japanese Americans

Anna H. Wu [1], Cheryl Vigen[1], Lesley M. Butler[2] and Chiu-Chen Tseng[1]

[1] Keck School of Medicine, University of Southern California, Los Angeles, CA
[2] University of Pittsburgh Cancer Institute, Pittsburgh, PA

Cancer Epidemiology

Accumulating evidence suggests that the aggregation of common metabolic conditions (high blood pressure, diabetes and dyslipidemia) is a risk factor for breast cancer. Breast cancer incidence has risen steadily in Asian American women, and whether these metabolic conditions contribute to breast cancer risk in certain Asian American subgroups is unknown. We investigated the role of physician-diagnosed hypertension, high cholesterol and diabetes separately, and in combination, in relation to the risk of breast cancer in a population-based case–control study of 2,167 Asian Americans diagnosed with breast cancer and 2,035 age and ethnicity matched control women in Los Angeles County. Compared to Asian American women who did not have any of the metabolic conditions, those with 1, 2 or 3 conditions showed a steady increase in risk (respective odds ratios were 1.12, 1.42 and 1.62; P trend = 0.001) with adjustment for covariates including body mass index. Similar significant trends were observed in Filipina Americans (P trend = 0.021), postmenopausal women (P trend =0.001), Asian women who were born in the United States (US) (P trend = 0.052) and migrants who have lived in the US for at least 20 years (P trend = 0.004), but not migrants who lived in the US for <20 years (P trend = 0.64). These results suggest that westernization in lifestyle (diet and physical inactivity) and corresponding increase in adiposity have contributed to the rising prevalence of these metabolic conditions, which in turn, are associated with an increase in breast cancer.

Introduction

There is accumulating epidemiologic evidence that metabolic syndrome, namely, the clustering of conditions including abdominal adiposity, high blood pressure (HBP), diabetes and dyslipidemia may have a significant influence on breast cancer risk. In a meta-analysis of nine studies (three US [largely whites and African Americans], four Europe, one Uruguay and one Japan), history of metabolic syndrome was associated with an elevated risk (odds ratio [OR] = 1.52, 95% confidence intervals [CI] 1.20–1.93) of breast cancer in postmenopausal women.[1] However, the evidence is less consistent in Asians. These metabolic factors, separately or in combination, were not associated with breast cancer in a prospective cohort study from Japan in which relevant covariates including parity, age at menarche and body mass index (BMI) were adjusted for in the analysis.[2] In a case–control study from Korea, postmenopausal women with a history of metabolic conditions had a significant twofold greater risk of breast cancer that was due largely to the increased risk associated with high BMI but risk was unrelated to the individual metabolic conditions (i.e., elevated levels of triglycerides or high-density lipoprotein cholesterol [HDL-C], HBP or fasting serum glucose) after adjustment for various cofactors.[3] These metabolic conditions individually and in combination were associated with higher breast cancer risk in a cohort analysis from Japan[4] and a case–control study from Taiwan,[5] but neither study had information on parity, BMI and other relevant cofactors. Lack of information on potential confounders in some studies and differences in distribution of menopausal status in the study population may have contributed to inconsistencies in study findings. As we have previously reported, Filipina women have one of the highest breast cancer incidence rates in Asia and among Asian Americans for poorly understood reasons. Breast cancer risk factors varied in their magnitude in Asian ethnic subgroups and body size risk factors were more prominently associated with risk in

Key words: Filipina, Japanese, Chinese, metabolic factors, diabetes, hypertension, high cholesterol, body size
Additional Supporting Information may be found in the online version of this article.
The authors declare that they have no potential conflicts of interest.
Grant sponsor: California Breast Cancer Research Program; **Grant number:** 1RB-0287, 3PB-0120, 5PB-0018, 10PB-0098; **Grant sponsor:** USC Norris Comprehensive Cancer Center Core Support; **Grant number:** P30 CA14089; **Grant sponsor:** NIEHS; **Grant number:** 2P30 ES007048021
DOI: 10.1002/ijc.31018
History: Received 6 June 2017; Accepted 17 Aug 2017; Online 26 Aug 2017
Correspondence to: Anna H. Wu, Department of Preventive Medicine, University of Southern California Keck School of Medicine, 1441 Eastlake Avenue, Rm 4443, Los Angeles, CA 90089, USA, Tel.: 323-865-0484, Fax: 323-865-0139, E-mail: anna.wu@med.usc.edu

What's new?

Breast cancer incidence in Asian Americans is rising, for reasons that remain unclear. Possible factors involved include metabolic conditions such as high blood pressure, diabetes and dyslipidemia. In this case–control study of Asian–American women, history of metabolic conditions was associated with a significant trend in increasing breast cancer risk. Subgroup analyses revealed significant associations among Filipina Americans, postmenopausal women and Asian women who were born in the United States or who were long-term US residents. The findings suggest that increase in metabolic disorders and breast cancer in these populations is linked to the adoption of a Western lifestyle.

postmenopausal Filipina and Japanese Americans than in Chinese Americans.[6]

We conducted a comprehensive analysis of breast cancer risk and physician-diagnosed metabolic conditions (HBP, diabetes and high cholesterol) separately and in combination, among Filipina, Japanese and Chinese Americans in a population-based case–control study in Los Angeles (LA) County. We investigated risk patterns by menopausal status, Asian ethnicity and migration status, with adjustment for BMI and other potential confounders. We also considered risk associations in relation to timing of diagnosis of the metabolic conditions as well as treatment for metabolic conditions.

Subjects and Methods

Study design and population

The study population and methods used in this population-based case–control study have been described previously.[7,8] In brief, breast cancer patients were identified by the LA County Cancer Surveillance Program, the population-based cancer 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. This analysis included 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 including *in situ* 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 and 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 and 272 Filipina), 77 had died (17 Chinese, 24 Japanese and 36 Filipina) and 548 could not be located (175 Chinese, 72 Japanese and 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.[9,10] 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 (not necessarily the first willing control subject). 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. 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 control (range was 64% for Filipina and 67% for Chinese), 18% were the second-identified eligible control and 18% were the third or later eligible control.

Data collection

Cases and controls were interviewed using a standardized, structured questionnaire. Almost all Filipina and Japanese American women were interviewed in English; only 5 Japanese (4 cases and 1 control) and 67 Filipina (52 cases and 15 controls) were interviewed with a mix of English and respective Asian language with the help of interpreters who were either family members of the study participants or study staff. A Chinese-translated questionnaire was used for subjects when appropriate. Interviews were in Mandarin or Cantonese for 62.5% (337 Mandarin and 234 Cantonese) of Chinese cases and 51.2% (301 Mandarin and 162 Cantonese) 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.[11,12] Subjects were asked about height and usual weight history at age 18 years, at age 30 years and each decade thereafter when they were not pregnant. Trained interviewers measured the circumferences of the waist and hips of study participants. Waist circumference was measured at the narrowest torso circumference and hip circumference was measured at the widest hip circumference. Relative body weight was evaluated by BMI, calculated as the weight in kilograms divided by the square of height in meters (kg/m^2). We examined BMI using the recommended five category cut points (<22.9, 23–24.9, 25–27.4, 27.5–29.9, and ≥ 30 kg/m^2) for studies in

Asian Americans,[13] which incorporated the standard World Health Organization (WHO) definition (<25, 25–29.9 and ≥30 kg/m^2) of normal, overweight and obese as well as the corresponding WHO Asian BMI definition (<22.9, 23–27.5, and ≥27.5 kg/m^2). Subjects were asked about history of specific conditions, including HBP, diabetes and high cholesterol that were diagnosed by a physician at least 1 year before diagnosis (for cases) and interview (for controls). Participants who responded positively were then asked a series of additional questions including the age they were first diagnosed of the condition, and if they were treated for the condition by medication, lifestyle intervention or other means.

Statistical analysis

The results presented below are based on 2,167 cases and 1,967 controls without any history of previous cancers and for whom we have information on these metabolic conditions, body size, menstrual and reproductive factors as well as the covariates included for adjustment. We calculated Asian ethnic-specific ORs and their corresponding 95% CIs and p values by conditional logistic regression methods, with matched sets defined jointly by Asian ethnicity (Filipina, Japanese and Chinese) and reference age (<39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69 and 70+ years).[11] All regression models included the following covariates: years of residence in the US (US born, >20 years, 11–20 years and ≤10 years), education (less than high school, high school, some college and college graduate), income, interviewer, family history of breast cancer (no, yes any first degree relative with breast cancer), history of benign breast disease (no and yes), age at menarche (≤11, 12, 13, 14 and 15+ years) and parity (0, 1, 2, 3 and 4+ births). In addition, current (*i.e.*, before diagnosis or interview) BMI (<22.9, 23–24.9, 25–27.4, 27.5–29.9 and ≥30 kg/m^2) was included in the analysis.[13] $p < 0.05$ were considered statistically significant and all p values quoted are two-sided. All analyses were performed using EPILOG Windows (version 1.01 sec) statistical software system (Pasadena, CA) and the SAS statistical software system (version 9.3; SAS Institute, Cary, NC).

Results

Breast cancer cases compared to control women had significantly fewer births and were more likely to have a family history of breast cancer and a personal history of benign breast diseases but they did not differ significantly in age at menarche, history of alcohol intake or energy intake (Supporting Information Table 1). Table 1 shows distribution of select lifestyle factors by history of three metabolic conditions (HBP, high cholesterol and diabetes) combined (none, 1, 2+ conditions or any conditions) for Asian American control women and breast cancer cases. History of these conditions was higher in Filipina (46.8%) and Japanese (46.3%) than Chinese (34.1%) control women, among Asia Americans who were US born or were long-term (>20 years) residents in the US and those who were older, postmenopausal, parous and had higher BMI or higher waist/hip ratios (WHR). Any history of metabolic conditions was weakly associated with age at menarche and family history of breast cancer but was unrelated to education level and physical activity. These patterns in control women were similarly observed among breast cancer cases (data not shown).

Table 2 shows risk associations between the individual metabolic conditions and breast cancer risk after adjustment for BMI and other established risk factors. In Filipina, Chinese and Japanese Americans combined, risk of breast cancer increased with having a history of any one (OR 1.19, 95% CI 1.03–1.37) or two or more (OR 1.45, 95% CI 1.16–1.80) metabolic conditions. Specifically, Asian American women with a history of high cholesterol (OR 1.26, 95% CI 1.08–1.47) and long-standing (>10 years) diabetes (OR 1.63, 95% CI 1.10–2.41) experienced significantly elevated risk. Results by Asian ethnicity showed that among Filipina–Americans, risk was higher among those with a history of HBP (OR 1.34, 95% CI = 1.03–1.76) and diabetes for 10 years or more (OR 1.95, 95% CI 0.97–3.93). There was a trend of increasing risk with increasing number of conditions so that compared to Filipina women who did not have any of the three conditions, the ORs were 1.20,1.42, 1.88, respectively (P trend = 0.021) for Filipina who had 1, 2 or 3 conditions. Risk of breast cancer among Japanese Americans was higher (OR = 1.39, 95% CI 1.02–1.90) for those with a history of high cholesterol. Japanese Americans who reported two metabolic conditions had a significantly increased risk (OR 1.60, 95% CI 1.01–2.54). Although there was no further increase in risk among those with all three conditions, this was based on small numbers. Breast cancer risk of Chinese Americans was not significantly related to history of these conditions, separately or in combination.

Breast cancer risk among premenopausal Asian American women was not significantly associated with history of HBP, high cholesterol or diabetes or the three conditions combined (Table 3). In contrast, history of high cholesterol and long-history (>10 years) of diabetes were significantly associated with risk in postmenopausal Asian American women; risks increased with increasing duration of these conditions. For example, risk of breast cancer doubled in postmenopausal women who had diabetes for >10 years (OR 2.03, 95% CI 1.24–3.34). Compared to postmenopausal women who had none of the conditions, the adjusted ORs were 1.27, 1.43 and 1.87, respectively, in association with 1, 2 or 3 conditions (P trend = 0.001) after adjustment for BMI and other risk factors. The increase in risk was less marked for postmenopausal women who reported they received treatment (OR 1.21, 95% 0.99–1.49) compared to those who were not treated (OR 1.80, 95% 1.33–2.42) for these metabolic conditions.

Prevalence of these conditions and the corresponding risk patterns differed by migration status (Table 4). History of HBP and high cholesterol were most prevalent in the US born Asian control women (28.4% and 26.9%, respectively), intermediate in long-term migrants who lived >20 years in

Table 1. History of three conditions (hypertension, high cholesterol, and diabetes) by demographic and select breast cancer risk factors among control women in Los Angeles County

	Combined metabolic condition								
Variable	**None, *N* = 1161**	**%**	**One, *n* = 595**	**%**	**Two+, *n* = 211**	**%**	***p* value[1]**	**% Any**	***p* value[2]**
Ethnic group									
Chinese	583	65.9	239	26.9	64	7.2	<0.001	34.1	<0.001
Japanese	270	53.8	168	33.5	64	12.8		46.3	
Filipino	308	53.2	188	32.5	83	14.3		46.8	
Age									
<40	202	81.8	39	15.8	6	2.4	<0.001	18.2	<0.001
40–49	525	71.6	180	24.6	28	3.8		28.4	
50–59	292	51.6	205	36.2	69	12.2		48.4	
≥60	142	33.7	171	40.6	108	25.7		66.3	
Migration									
US born (USB)	276	53.0	174	33.4	71	13.6	<0.001	47.0	<0.001
Non USB>20yrs	415	57.7	220	30.6	84	11.7		42.3	
Non USB≤20yrs	470	64.7	201	27.7	56	7.7		35.4	
Education									
≤High school	188	57.9	98	30.2	39	12.0	0.84	42.2	0.52
Some college	249	56.6	142	32.3	49	11.1		43.4	
College	509	59.7	255	29.9	88	10.3		40.2	
Graduate	215	61.4	100	28.6	35	10.0		38.6	
Menopause									
Premenopause	753	72.5	245	23.6	41	4.0	<0.001	27.6	<0.001
Postmenopause	408	44.0	350	37.7	170	18.3		56.0	
BMI									
≤22.9	773	67.5	294	25.7	79	6.9	<0.001	32.6	<0.001
>22.9 to ≤24.9	204	53.0	130	33.8	51	13.3		47.1	
>24.9 to ≤27.5	130	47.5	99	36.1	45	16.4		52.5	
>27.5 to ≤29.9	27	32.5	39	47.0	17	20.5		67.5	
>29.9	27	34.2	33	41.8	19	24.1		65.9	
WHR									
≤0.76	298	76.4	76	19.5	16	4.1	<0.001	23.6	<0.001
≤0.80	311	64.5	139	28.8	32	6.6		35.4	
≤0.845	295	57.0	168	32.4	55	10.6		43.0	
>0.845	239	44.2	198	36.6	104	19.2		55.8	
DK	18	50.0	14	38.9	4	11.1		50.0	
Age at menarche									
≤11	174	52.7	113	34.2	43	13.0	0.28	47.2	0.05
12	297	57.0	156	29.9	56	10.8		40.7	
13	298	58.0	151	30.1	52	10.4		40.5	
14	203	61.5	84	26.6	29	9.2		35.8	
≥15	189	60.8	91	29.3	31	10.0		39.3	
Parity									
0	210	63.4	95	28.7	26	7.9	<0.001	36.6	<0.001
1	223	67.4	81	24.5	26	7.9		32.4	
2	423	61.9	201	29.4	57	8.4		37.8	
≥3	305	48.8	218	34.9	102	16.3		51.2	

Table 1. History of three conditions (hypertension, high cholesterol, and diabetes) by demographic and select breast cancer risk factors among control women in Los Angeles County (Continued)

	Combined metabolic condition								
Variable	None, $N = 1161$	%	One, $n = 595$	%	Two+, $n = 211$	%	p value[1]	% Any	p value[2]
Physical activity									
0–4 years	148	55.0	93	34.6	28	10.4	0.19	45.0	0.13
5–9	259	62.0	112	26.8	47	11.2		38.0	
10–19	392	61.0	180	28.0	71	11.0		39.0	
≥20	361	56.8	210	33.0	65	10.2		43.2	
Family history of breast cancer (first degree relatives)									
No	1063	60.0	525	29.6	184	10.4	0.11	40.0	0.03
yes	81	49.7	60	36.8	22	13.5		50.3	
Dk	17	53.1	10	31.3	5	15.6		46.9	

[1] p values–χ^2 test (2 df) comparing between none, one, two or more conditions.
[2] p values–χ^2 test (1 df) comparing between none versus any conditions.

the US (25.6% and 23.6%, respectively) and less prevalent in recent migrants who lived <20 years in the US (20.1% and 17.1%, respectively). History of diabetes was comparable among long-term (7.8%) and recent (8.4%) migrants and was higher in the US born Asian American control women (10.0%). Breast cancer risks among long-term migrants increased in association with history of diabetes (OR 1.41, 95% CI 0.97–2.06, $p = 0.075$), high cholesterol (OR 1.29, 95% CI 1.02–1.65, $p = 0.037$) and HBP (OR 1.24, 95% CI 0.95–1.60, $p = 0.096$). Although elevated risks were also observed among the US born Asian Americans, results were statistically significant only for high cholesterol (OR 1.45, 95% CI 1.06–1.99), while no significant associations were observed among recent migrants. Risk of breast cancer increased with increasing number of these conditions among long-term migrants (P trend= 0.004) and the US born Asian American women (P trend = 0.052) but not among more recent migrants (P trend = 0.64).

We investigated the joint effects of history of the three conditions separately and combined by categories of normal BMI (≤24.9 kg/m^2) and high BMI (>24.9 kg/m^2) as well as by low (≤86 cm) and high (>86 cm) waist circumference (Table 5). No significant associations were observed in premenopausal women (data not shown). Among postmenopausal women, breast cancer risk increased among Asian American women with both high BMI and a history of HBP (OR 1.42, 95% CI 0.98–2.06, $p = 0.065$), whereas the increased risk was more modest among women with normal BMI (OR 1.08). Elevated risk with high cholesterol was observed among those with normal BMI and high BMI. Interestingly, the increased risk associated with diabetes was higher among women with normal BMI (OR 1.62, 95% 1.09–2.41), whereas those with high BMI showed no increased risk (OR 0.89, 95% CI 0.56–1.40). This difference was borderline statistically significant ($p = 0.097$). Results were essentially identical when we considered low (≤86 cm) versus high (>86 cm) waist circumference in relation to metabolic conditions (Table 5). We also investigated history of these three conditions stratified by a combined index of BMI and WHR. History of any three conditions was associated with a statistically significant increased risk of breast cancer among those with both low BMI and low waist circumference (OR 1.39, 95% 1.09–1.77) or low BMI and high waist circumference (OR 2.22, 95% CI 1.02–4.81), but there were no significant increased risks among those with high BMI and low waist circumference (OR 1.44, 95% 0.56–3.78) or high BMI and high waist circumference (OR 1.29, 95% 0.78–2.12) (data not shown).

Compared to women with no reported metabolic conditions, those with any metabolic conditions showed elevated risk of both *in situ* (adjusted OR = 1.26, 95% CI 0.98–1.61, $p = 0.067$) and invasive (adjusted OR = 1.17, 95% CI 1.01–1.36) breast cancer (data not shown). History of any metabolic conditions was associated with an increased risk of hormone receptor positive (estrogen receptor positive [ER+] and progesterone receptor positive [PR+]) tumors (OR 1.22, 95% CI 1.03–1.45, $p = 0.023$). This was observed separately for history of high cholesterol (OR 1.27, 95% CI 1.05–1.53, $p = 0.012$), diabetes (OR 1.28, 95% CI 0.98–1.67, $p = 0.065$) and HBP (OR 1.18, 95% CI 0.98–1.43, $p = 0.083$). There was also a borderline statistically significant increased risk of ER-PR+ tumors (OR 1.77, 95% CI 0.97–3.22, $p = 0.063$) with any metabolic condition which was due, primarily, to an increased risk among those with a history of high cholesterol (Supporting Information Table 2).

Discussion

Previous studies conducted in mostly western (non-Asian) populations support a significant positive association between metabolic conditions and breast cancer risk primarily in

Table 2. Risk of breast cancer and history of hypertension (HBP), high cholesterol and diabetes in Chinese, Japanese and Filipina Americans in Los Angeles County

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[1] (95%CI)	Ca	Co	OR[1] (95%CI)	Ca	Co	OR[1] (95%CI)	OR[2] (95%CI)
HBP										
No	689	724	1.00	349	362	1.00	468	402	1.00	1.00
Yes	191	161	0.87 (0.66, 1.14)	167	140	0.99 (0.71, 1.37)	303	177	1.34 (1.03, 1.76)	1.11 (0.94, 1.30)
Lag time[3]										
≤10 years	120	106	0.86 (0.63, 1.18)	98	83	0.96 (0.66, 1.41)	199	97	1.66 (1.21, 2.28)	1.18 (0.99, 1.42)
>10 years	71	55	0.89 (0.58, 1.35)	69	57	1.03 (0.66, 1.62)	104	80	0.94 (0.64, 1.36)	0.98 (0.78, 1.23)
P trend[4]			0.39			0.95			0.43	0.61
High cholesterol										
No	668	723	1.00	330	368	1.00	544	441	1.00	1.00
Yes	212	162	1.21 (0.94, 1.56)	185	134	1.39 (1.02, 1.90)	226	138	1.21 (0.91, 1.60)	1.26 (1.08, 1.47)
Lag time[3]										
≤10 years	178	143	1.15 (0.88, 1.50)	146	108	1.42 (1.02, 1.99)	203	117	1.28 (0.96, 1.72)	1.26 (1.07, 1.48)
>10 years	34	19	1.69 (0.91, 3.14)	39	26	1.28 (0.71, 2.28)	23	21	0.79 (0.41, 1.53)	1.26 (0.89, 1.78)
P trend[4]			0.076			0.075			0.43	0.006
Diabetes										
No	801	821	1.00	463	458	1.00	678	519	1.00	1.00
Yes	78	65	1.11 (0.77, 1.61)	53	44	1.10 (0.68, 1.77)	93	60	1.18 (0.81, 1.73)	1.20 (0.95, 1.50)
Lag time[3]										
≤10 years	53	50	0.98 (0.64, 1.50)	31	28	0.99 (0.55, 1.77)	64	45	0.97 (0.63, 1.51)	1.04 (0.80, 1.36)
>10 years	25	15	1.55 (0.78, 3.06)	22	16	1.32 (0.63, 2.78)	29	15	1.95 (0.97, 3.93)	1.63 (1.10, 2.41)
P trend[4]			0.36			0.55			0.16	0.033
3 Conditions[5]										
None	513	583	1.00	241	270	1.00	352	308	1.00	1.00[6]
1	282	239	1.13 (0.89, 1.42)	169	168	1.02 (0.73, 1.41)	258	188	1.20 (0.91, 1.58)	1.12 (0.96, 1.30)
2	69	57	0.99 (0.65, 1.49)	92	51	1.60 (1.01, 2.54)	130	70	1.42 (0.97, 2.07)	1.42 (1.13, 1.78)
3	16	7	1.64 (0.62, 4.33)	14	13	1.02 (0.42, 2.45)	31	13	1.88 (0.90, 3.93)	1.62 (1.02, 2.57)
P trend[4]			0.41			0.17			0.021	0.001
Any condition	367	303	1.11 (0.89, 1.39)	275	232	1.12 (0.83, 1.53)	419	271	1.28 (0.99, 1.64)	1.19 (1.03, 1.37)
2 or 3 conditions	85	64	1.06 (0.71, 1.56)	106	64	1.49 (0.96, 2.30)	161	83	1.48 (1.04, 2.13)	1.45 (1.16, 1.80)

Table 2. Risk of breast cancer and history of hypertension (HBP), high cholesterol and diabetes in Chinese, Japanese and Filipina Americans in Los Angeles County (Continued)

	Chinese			Japanese			Filipina			All
	Ca	Co	OR[1] (95%CI)	Ca	Co	OR[1] (95%CI)	Ca	Co	OR[1] (95%CI)	OR[2] (95%CI)
Yes treatment	239	191	1.04 (0.80, 1.37)	183	165	1.01 (0.71, 1.43)	330	203	1.32 (1.00, 1.74)	1.15 (0.98, 1.36)
No treatment	128	112	1.21 (0.90, 1.63)	92	67	1.32 (0.89, 1.97)	89	68	1.19 (0.81, 1.74)	1.24 (1.02, 1.51)

[1]Adjusted for age, education, income, years of residence in the US among non-US born, interviewer, family history of breast cancer, benign breast diseases, parity, age at menarche, age at and type of menopause, education and BMI.
[2]As above and also adjusted for Asian ethnicity.
[3]Lagtime is defined as years between first diagnosis of metabolic condition and breast cancer diagnosis.
[4]For the P trend analyses, the baseline group comprised those with no metabolic condition.
[5]Included HBP, high cholesterol, and diabetes. Yes treatment means for any 1 of the 3 conditions; no treatment means no for all 3 conditions.
[6]There were no changes in ORs with further adjustment for alcohol intake (never, former and current) for none, 1, 2, 3 conditions combined (ORs were 1.00, 1.12 (0.96, 1.30), 1.42 (1.13, 1.78) and 1.62 (1.02, 2.57), respectively).

postmenopausal women.[1] To our knowledge, this is one of the first population-based studies of breast cancer among Asian Americans to examine risk patterns in association with three common metabolic conditions (HBP, high cholesterol and diabetes) separately and in combination, with consideration of duration as well as any treatment for these conditions. We explored risk patterns separately in Filipina, Chinese and Japanese Americans, by migration history, menopausal status and body size and adjusted for relevant potential confounders. While there is consensus that high BMI[14] is a significant risk factor for postmenopausal breast cancer in western and Asian populations,[15] there is less consistency whether breast cancer risk is also increased in relation to diabetes and other metabolic conditions such as high cholesterol, HBP or a combination of these factors in Asians.[2,3,5,15] Recent national studies show that history of diabetes and dyslipidemia patterns are more prevalent in Asian Americans than in non-Hispanic whites[16,17] despite lower BMI in Asians, suggesting that Asians may be more susceptible to metabolic conditions at a given BMI.

Before discussing the significance of our findings, some limitations and strengths of our study should be mentioned. First, our results are limited to self-reported metabolic conditions that were diagnosed by a physician. Although we asked about age at diagnosis as well as treatment for these metabolic conditions, our questions on treatment were not detailed precluding analysis by type of treatment (*e.g.*, specific medications). Thus, our results may not be directly comparable to previous studies, which have included a range of definitions for single conditions including hypertension (HBP values or self-reported hypertension diagnosed by a physician), reported diabetes or fasting glucose values, reported history of high cholesterol or reported blood values of triglyceride, HDL-C and total cholesterol as well as combination of these factors.[1,18] In our question on high cholesterol, we did not ask specifically about cholesterol fraction. In addition, the overall participation rate of our study was modest (61% among cases and 64% among controls). While we cannot rule out the possibility of recall bias in case–control studies, there was internal consistency in our data such as higher prevalence of metabolic conditions in relation to increasing age and BMI among control women and case patients. The study strengths include its large sample size allowing comparison of risk association by hormone receptor status of breast cancer and separately by Asian ethnicity, migration and menopausal status and body size measures and the ability to adjust for potential confounders.

Among Filipina American women, breast cancer risk was significantly higher among those with a history of hypertension and nearly doubled for those with a long-standing (10 or more years) history of diabetes (Table 2). Compared to Filipina women, who did not have any metabolic conditions, risk increased in a stepwise manner for Filipina women with 1, 2 and 3 metabolic conditions. Although the prevalence of any metabolic condition was comparable between Filipina

Table 3. Risk of breast cancer and history of hypertension (HBP), high cholesterol and diabetes in pre- and postmenopausal Asian American women in Los Angeles County

	Premenopausal			Postmenopausal		
	Ca	Co	OR[1] (95%CI)	Ca	Co	OR[2] (95%CI)
HBP						
No	811	906	1	695	582	1
Yes	141	132	1.09 (0.81, 1.45)	520	346	1.11 (0.92, 1.35)
Lag time						
≤10 years	106	88	1.20 (0.86, 1.66)	311	198	1.19 (0.95, 1.49)
>10 years	35	44	0.85 (0.52, 1.40)	209	148	1.00 (0.77, 1.30)
P trend			0.94			0.65
High cholesterol						
No	804	905	1	738	627	1
Yes	147	134	1.15 (0.87, 1.51)	476	300	1.35 (1.11, 1.63)
Lag time						
≤10 years	128	115	1.15 (0.86, 1.53)	399	253	1.34 (1.09, 1.64)
>10 years	19	19	1.16 (0.59, 2.30)	77	47	1.40 (0.93, 2.09)
P trend			0.34			0.004
Diabetes						
No	889	966	1	1053	832	1
Yes	62	73	1.01 (0.69, 1.48)	162	96	1.30 (0.97, 1.73)
Lag time						
≤10 years	47	54	1.00 (0.65, 1.56)	101	69	1.05 (0.74, 1.47)
>10 years	15	19	1.05 (0.51, 2.14)	61	27	2.03 (1.24, 3.34)
P trend			0.92			0.014
3 conditions[3]						
None	669	753	1	437	408	1
1	227	245	0.96 (0.78, 1.23)	482	350	1.27 (1.03, 1.56)
2	50	34	1.69 (1.03, 2.77)	241	144	1.43 (1.09, 1.88)
3	6	7	0.87 (0.27, 2.84)	55	26	1.87 (1.11, 3.15)
P trend			0.31			0.001
Any condition	283	286	1.05 (0.85, 1.30)	778	520	1.34 (1.11, 1.62)[4]
2 or 3 conditions	56	41	1.56 (0.97, 2.46)	296	170	1.50 (1.16, 1.93)
Yes treatment	152	137	1.15 (0.87, 1.54)	600	422	1.21 (0.99, 1.49)[5]
No treatment	131	149	0.97 (0.73, 1.27)	178	98	1.80 (1.33, 2.42)

[1]Adjusted for Asian ethnicity, age, education, income, years of residence in the US among non-US born, interviewer, family history of breast cancer, benign breast diseases, parity, age at menarche, education and BMI.
[2]As above, also adjusted for age at menopause and type of menopause.
[3]Included HBP, high cholesterol and diabetes. Yes treatment means for any one of the three conditions; no treatment means no for all three conditions.
[4]P interaction—any of three metabolic condition for premenopausal versus postmenopausal women was 0.034.
[5]P interaction—yes treatment to any metabolic condition for premenopausal versus postmenopausal women was 0.01.

and Japanese–American control women, the risk associations were weaker in Japanese Americans than in Filipina women. For reasons that are not apparent, studies on metabolic conditions and breast cancer risk in Japan have generally found no or a weak association.[2,19] We are not aware of previous studies on metabolic conditions and breast cancer risk in Filipina women in the US or in the Philippines. However, Filipino Americans have been found to have higher prevalence of various metabolic conditions,[20,21] including dyslipidemia,[16] hypertension[22–24] and diabetes[16,22] than Japanese and Chinese Americans and to experience high risks of cardiovascular disease and mortality.[25] The high prevalence of these metabolic conditions and risk of cardiovascular diseases are observed in the Philippines as well.[26–28]

Table 4. Risk of breast cancer and history of hypertension (HBP), high cholesterol and diabetes for the US born and the Non-US born Asian American women combined in Los Angeles County

	US born			Non-US born—≥20 years in the US			Non-US born—<20 years in the US		
	Ca	Co	OR[1] (95%CI)	Ca	Co	OR[1] (95%CI)	Ca	Co	OR[1] (95%CI)
HBP									
No	291	373	1	572	534	1	643	581	1
Yes	163	148	1.03 (0.74, 1.43)	296	184	1.24 (0.96, 1.60)	202	146	0.93 (0.70, 1.24)
Lag time									
≤10 years	93	84	1.04 (0.71, 1.53)	185	102	1.42 (1.06, 1.91)	139	100	0.95 (0.69, 1.30)
>10 years	70	64	1.02 (0.66, 1.58)	111	82	0.99 (0.69, 1.41)	63	46	0.90 (0.57, 1.42)
P trend			0.89			0.44			0.60
High cholesterol									
No	281	381	1	586	549	1	675	602	1
Yes[2]	172	140	1.45 (1.06, 1.99)	282	170	1.29 (1.02, 1.65)	169	124	0.95 (0.72, 1.27)
Lag time									
≤10 years	136	117	1.43 (1.02, 2.00)	237	137	1.38 (1.06, 1.78)	154	114	0.93 (0.69, 1.24)
>10 years	36	23	1.54 (0.83, 2.83)	45	33	0.96 (0.58, 1.58)	15	10	1.29 (0.53, 3.16)
P trend			0.027			0.14			0.90
Diabetes									
No	398	469	1	776	663	1	768	666	1
Yes	56	52	1.22 (0.77, 1.94)	91	56	1.41 (0.97, 2.06)	77	61	0.88 (0.59, 1.30)
Lag time									
≤10 years	32	32	1.10 (0.62, 1.94)	54	42	1.05 (0.67, 1.66)	62	49	0.83 (0.54, 1.27)
>10 years	24	20	1.44 (0.71, 2.92)	37	14	2.54 (1.31, 4.92)	15	12	1.11 (0.49, 2.53)
P trend			0.31			0.016			0.69
3 Conditions[3]									
None	186	276	1	410	415	1	510	470	1
1	167	174	1.24 (0.89, 1.72)	299	220	1.25 (0.98, 1.59)	243	201	0.87 (0.68, 1.13)
2	87	57	1.67 (1.07, 2.63)	128	75	1.39 (0.97, 1.99)	76	46	1.01 (0.67, 1.53)
3	14	14	1.18 (0.48, 2.86)	31	9	2.83 (1.25, 6.39)	16	10	0.94 (0.40, 2.25)
P trend			0.052			0.004			0.64
Any condition	268	245	1.33 (0.98, 1.81)	458	304	1.32 (1.05, 1.65)	335	257	0.90 (0.71, 1.14)
2 or 3 conditions	101	74	1.59 (1.03, 2.46)	159	84	1.54 (1.09, 2.16)	92	56	1.01 (0.67, 1.53)
Yes treatment	180	177	1.13 (0.80, 1.61)	343	219	1.28 (0.99, 1.66)	229	163	0.96 (0.72, 1.29)
No treatment	88	68	1.71 (1.14, 2.57)	115	85	1.39 (1.00, 1.93)	106	94	0.82 (0.59, 1.14)

[1]Adjusted for Asian ethnicity, age, education, income, interviewer, family history of breast cancer, benign breast diseases, parity, age at menarche, education, BMI and age and type of menopause.
[2]P interaction: High cholesterol: the US born versus the non-US born <20 years was 0.04; the non-US born 20+ years versus the non-US born <20 years was 0.089.
[3]Included HBP, high cholesterol and diabetes; Yes treatment means for any one of the three conditions; no treatment means no for all three conditions.

Table 5. Risk of breast cancer and history of hypertension (HBP), high cholesterol and diabetes by BMI (kg/m^2) and waist circumference (cm) in postmenopausal Asian American women in Los Angeles County

	BMI $\leq$ 24.9[1]			BMI > 24.9[1]			Waist $\leq$ 86 cm			Waist > 86 cm		
	Ca	Co	OR[2] (95%CI)	Ca	Co	OR[2] (95%CI)	Ca	Co	OR[2] (95%CI)	Ca	Co	OR[2] (95%CI)
HPB												
No	525	457	1	149	120	1	510	450	1	164	127	1
Yes	287	214	1.08 (0.86, 1.37)	217	124	1.42 (0.98, 2.06)	277	205	1.12 (0.88, 1.42)	227	133	1.31 (0.92, 1.86
P interaction				0.28						0.38		
High Cholesterol												
No	487	450	1.00	228	170	1	486	446	1.00	229	174	1
Yes	325	220	1.38 (1.09, 1.73)	137	74	1.27 (0.86, 1.89)	300	208	1.35 (1.07, 1.71)	162	86	1.42 (0.98, 2.05)
P interaction				0.82						0.88		
Diabetes												
No	727	625	1.00	293	195	1	707	611	1.00	313	209	1
Yes	85	46	1.62 (1.09, 2.41)	73	49	0.89 (0.56,1.40)	73	44	1.61 (1.07, 2.42)	78	51	1.10 (0.71, 1.70)
P interaction				0.097						0.18		
Any 3 Conditions												
No	325	323	1.00	98	81	1	322	319	1.00	101	85	1.00
Yes	487	348	1.40 (1.12, 1.75)	268	163	1.30 (0.87, 1.95)	465	336	1.39 (1.10, 1.74)	290	175	1.43 (0.97, 2.10)
P interaction				0.72						0.87		

[1]We excluded 37 cases and 13 control women who had data on BMI but did not have information on waist circumferences in the above analyses. All the above stratified results by BMI remained largely the same when we included these 37 cases and 13 control women in the analyses.
[2]Adjusted for Asian ethnicity, age, education, income, years of residence in the US among non-US born, interviewer, family history of breast cancer, benign breast diseases, parity, age at menarche, education and age and type of menopause.

In all Asian American women combined, history of any one metabolic condition conferred a significant 19% increased risk and those with 2 or 3 metabolic conditions showed a significant 45% increased risk. Somewhat stronger associations were observed for postmenopausal Asian American women (Table 3). These results in postmenopausal Asian American women are compatible with findings from a meta-analysis of nine studies of primarily Caucasian postmenopausal women in which breast cancer risk was significantly increased 50% in relation to history of metabolic syndrome (obesity, hypertension, diabetes and dyslipidemia).[1]

Our results by single metabolic factors showed a significant effect of high cholesterol that was diagnosed by a physician; the increased risk was found in all three Asian groups, in pre- and postmenopausal women and among those who had the condition for <10 years or for a longer time. However, a significant increased risk (29% to 45%) was observed among the US born Asians and those who had lived in the US for at least 20 years but there was no increased risk among more recent migrants. Prevalence of high cholesterol was higher in the US born (27%) and long-term migrants (24%) than recent migrants (17%). Although foreign-born and US born Asians in the National Health and Nutrition Examination Survey (NHANES) 2011–2012 did not show significant differences in prevalence of high total and LDL-cholesterol, these results were presented for all Asian Americans and in men and women combined.[29] Self-reported history of high cholesterol[30] and hyperlipidemia[31] were not associated with breast cancer risk in case–control studies conducted in the US and Italy, but disorder of lipid metabolism was a significant risk factor in a population-based study in Taiwan.[5] The relationship between serum cholesterol and breast cancer risk also differed in previous studies. A meta-analysis of 14 prospective studies found that total blood cholesterol and more specifically HDL-C was significantly inversely associated with risk of breast cancer after excluding cancer cases diagnosed during the first years of follow-up.[18] In two separate prospective studies in Korea, total serum cholesterol was positively associated with breast cancer after adjustment for BMI.[32,33] In another Korean study that investigated risk associations separately by BMI, the positive association with high cholesterol was stronger among women with lower BMI (<25 kg/m^2) (1.13, 95% CI 1.02–1.25) than those with higher BMI (1.01, 95% CI 0.90–1.14).[32] Abnormal levels of lipids and lipoproteins may increase breast cancer risk by having adverse influence on endogenous sex steroid hormone profiles and promoting low-grade inflammation.[34]

Breast cancer risk was nonsignificantly higher by 20% among Asian American women with a history of diabetes; this risk was 63% higher and was statistically significant among women who were diabetic for at least 10 years of more (Table 2). Similar to our initial report based on a subset of study participants,[12] the diabetes–breast cancer association was stronger among postmenopausal women who were diabetic for 10 years or more (Table 3). Larger numbers in these analyses allowed investigation of risk patterns by migration status, showing an increased risk among long-term migrants (Table 4) and those with normal BMI or low waist circumference (Table 5). In a comprehensive meta-analysis of 40 independent risk estimates from largely western populations, the risk of breast cancer in women with type 2 diabetes was increased by 27%, which was lowered to 16% after adjustment for BMI.[15] Nevertheless, the role of diabetes and risk of breast cancer is less consistent in studies in Asian and in Asian Americans. Diabetes was unrelated to breast cancer risk in a pooled analysis of cohort studies from Japan[19] and among Japanese Americans in the Multiethnic Cohort study.[35] However, diabetes was significantly associated with breast cancer mortality in a prospective cohort study from Korea[36] and in a recent Asia Cohort Consortium pooled analysis in which BMI was considered.[37] Hyperinsulinemia, impaired secretion of adipokines and chronic inflammation have been implicated to link diabetes to breast cancer risk.[38]

Breast cancer risk in Asian Americans was significantly associated with history of hypertension among Filipina women, particularly among those who had HBP within the 10 years before diagnosis of breast cancer/interview. Prevalence of HBP was also highest among Filipina (30.6%), intermediate among Japanese (27.9%) and lowest (18.2%) among Chinese American control women. High prevalence of hypertension and other components of metabolic syndrome has been reported in other studies of Filipino in the US.[21,23,39] In a meta-analysis of 30 studies on hypertension and breast cancer, a significant positive association was found in postmenopausal women (RR 1.20, 95% CI 1.09–1.31) but not in premenopausal women (RR 0.97, 95% CI 0.84–1.12) and was more consistent in studies conducted in western than in Asian populations.[40] Hypertension may increase risk of breast cancer by mediating effects via adipose tissues, inflammation or other pathways. These results in Filipina American women emphasize the need to further understand the mechanism of breast cancer pathogenesis affected by hypertension and the need for better monitoring and treatment of these common metabolic conditions as breast cancer risk factors.

It is of interest that our findings on metabolic conditions and breast cancer risks were observed in the US born Asians and long-term migrants but not among recent migrants (Table 4). Long-term Asian control migrants in our study have lived an average of 30.1 years in the US compared to 12.2 years for short-term migrants. The prevalence of each of the metabolic conditions, separately and in combination increased steadily and was highest in the US born, intermediate in long-term migrant and lowest in short-term migrants. Thus, while it has been difficult to pinpoint the specific individual factors, westernization in lifestyle (diet, physical inactivity) have undoubtedly contributed to the rising prevalence of these metabolic conditions, independent of obesity, which in turn, increase the risk of breast cancer. It is concerning that these metabolic conditions have now emerged to be significant breast cancer risk factors for the three groups of Asian American women combined and particularly for Filipina Americans, which may have contributed, in part, to

the high breast cancer incidence rates among women in Asia and specifically among Filipinas residing in Asia or in the US. It is a priority to develop strategies to prevent these modifiable metabolic conditions and to treat these conditions by lifestyle intervention and/or medication whenever possible.

Acknowledgements

The Asian American Breast Cancer Study was supported by the California Breast Research Program (grants 1RB-0287, 3PB-0120, 5PB-0018, 10PB-0098) (to A.H.W. and C.-C.T.), USC Norris Comprehensive Cancer Center Core Support (grant P30-CA14089) (to A.H.W.), and a NIEHS (grant 2P30-ES007048021) (to A.H.W.).

References

1. Esposito K, Chiodini P, Capuano A, et al. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. *Menopause* 2013;20:1301–9.
2. Inoue M, Noda M, Kurahashi N, et al. Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. *Eur J Cancer Prev* 2009;18:240–7.
3. Noh HM, Song YM, Park JH, et al. Metabolic factors and breast cancer risk in Korean women. *Cancer Causes Control* 2013;24:1061–8.
4. Osaki Y, Taniguchi S, Tahara A, et al. Metabolic syndrome and incidence of liver and breast cancers in Japan. *Cancer Epidemiol* 2012;36:141–7.
5. Chuang SC, Wu GJ, Lu YS, et al. Associations between medical conditions and breast cancer risk in Asians: a nationwide population-based study in Taiwan. *PLoS One* 2015;10:e0143410
6. Wu AH, Vigen C, Lee E, Tseng CC, et al. Traditional breast cancer risk factors in Filipina Americans compared to Chinese and Japanese Americans in Los Angeles County. *Cancer Epidemiol Biomarkers Prev* 2016;25:1572–85.
7. Wu AH, McKean-Cowdin R, Tseng CC. Birth weight and other prenatal factors and risk of breast cancer in Asian-Americans. *Breast Cancer Res Treat* 2011;130:917–25.
8. Wu AH, Vigen C, Razavi P, et al. Alcohol and breast cancer risk among Asian-American women in Los Angeles County. *Breast Cancer Res* 2012; 14:R151
9. Pike MC, Peters RK, Cozen W, et al. Estrogen-progestin replacement therapy and endometrial cancer. *J Natl Cancer Inst* 1997;89:1110–6.
10. Ross RK, Paganini-Hill A, Wan PC, et al. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000;92:328–32.
11. Wu AH, Yu MC, Tseng CC, et al. Body size, hormone therapy and risk of breast cancer in Asian-American women. *Int J Cancer* 2007;120:844–52.
12. Wu AH, Yu MC, Tseng CC, et al. Diabetes and risk of breast cancer in Asian-American women. *Carcinogenesis* 2007;28:1561–6.
13. Jih J, Mukherjea A, Vittinghoff E, et al. Using appropriate body mass index cut points for overweight and obesity among Asian Americans. *Prev Med* 2014;65:1–6.
14. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569–78.
15. Boyle P, Boniol M, Koechlin A, et al. Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer* 2012;107:1608–17.
16. Frank AT, Zhao B, Jose PO, et al. Racial/ethnic differences in dyslipidemia patterns. *Circulation* 2014;129:570–9.
17. Menke A, Casagrande S, Geiss L, et al. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. *JAMA* 2015;314: 1021–9.
18. Touvier M, Fassier P, His M, et al. Cholesterol and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Br J Nutr* 2015;114:347–57.
19. Sasazuki S, Charvat H, Hara A, et al. Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan. *Cancer Sci* 2013;104: 1499–507.
20. Araneta MR, Barrett-Connor E. Subclinical coronary atherosclerosis in asymptomatic Filipino and white women. *Circulation* 2004;110:2817–23.
21. Zhao B, Jose PO, Pu J, et al. Racial/ethnic differences in hypertension prevalence, treatment, and control for outpatients in northern California 2010–2012. *Am J Hypertens* 2015;28:631–9.
22. Ye J, Rust G, Baltrus P, et al. Cardiovascular risk factors among Asian Americans: results from a National Health Survey. *Ann Epidemiol* 2009;19: 718–23.
23. Ma GX, Lee M, Bhimla A, et al. Risk assessment and prevention of hypertension in Filipino Americans. *J Community Health* 2017;42:747–805.
24. Angel A, Armstrong MA, Klatsky AL. Blood pressure among Asian-Americans living in northern California. *Am J Cardiol* 1989;64:237–40.
25. Jose PO, Frank AT, Kapphahn KI, et al. Cardiovascular disease mortality in Asian Americans. *J Am Coll Cardiol* 2014;64:2486–94.
26. Morales DD, Punzalan FE, Paz-Pacheco E, et al. Metabolic syndrome in the Philippine general population: prevalence and risk for atherosclerotic cardiovascular disease and diabetes mellitus. *Diab Vasc Dis Res* 2008;5:36–43.
27. Sy RG, Morales DD, Dans AL, et al. Prevalence of atherosclerosis-related risk factors and diseases in the Philippines. *J Epidemiol* 2012;22:440–7.
28. Tanchoco CC, Cruz AJ, Duante CA, et al. Prevalence of metabolic syndrome among Filipino adults aged 20 years and over. *Asia Pacific J Clin Nutr* 2003;12:271–6.
29. Aoki Y, Yoon SS, Chong Y, et al. Hypertension, abnormal cholesterol, and high body mass index among non-Hispanic Asian adults: United States, 2011–2012. *NCHS Data Brief* 2014; 1–8.
30. Weiss HA, Brinton LA, Potischman NA, et al. Breast cancer risk in young women and history of selected medical conditions. *Int J Epidemiol* 1999;28:816–23.
31. Talamini R, Franceschi S, Favero A, et al. Selected medical conditions and risk of breast cancer. *Br J Cancer* 1997;75:1699–703.
32. Ha M, Sung J, Song YM. Serum total cholesterol and the risk of breast cancer in postmenopausal Korean women. *Cancer Causes Control* 2009;20: 1055–60.
33. Kitahara CM, Berrington de Gonzalez A, Freedman ND, et al. Total cholesterol and cancer risk in a large prospective study in Korea. *J Clin Oncol* 2011;29:1592–8.
34. Zhao YWH, Pan Y, Li N, et al. Association of lipid profile levels in premenopausal and postmenopausal women with breast cancer: a meta-analysis. *Int J Clin Exp Med* 2016;9:552–63.
35. Maskarinec G, Jacobs S, Park SY, Haiman CA, Setiawan VW, Wilkens LR, Le Marchand L. Type 2 diabetes, obesity, and breast cancer risk: the multiethnic cohort. *Cancer Epidemiol Biomarkers Prev* 2017;26:854–61.
36. Jee SH, Ohrr H, Sull JW, et al. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005;293:194–202.
37. Chen Y, Wu F, Saito E, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. *Diabetologia* 2017;60: 1022–32.
38. Goodwin PJ, Ennis M, Bahl M, et al. High insulin levels in newly diagnosed breast cancer patients reflect underlying insulin resistance and are associated with components of the insulin resistance syndrome. *Breast Cancer Res Treat* 2009;114:517–25.
39. Dalusung-Angosta A, Gutierrez A. Prevalence of metabolic syndrome among Filipino-Americans: a cross-sectional study. *Appl Nurs Res* 2013;26: 192–7.
40. Han H, Guo W, Shi W, et al. Hypertension and breast cancer risk: a systematic review and meta-analysis. *Sci Rep* 2017;7:44877.