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Diabetes and risk of breast cancer in Asian-American women

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The role of diabetes in the etiology of breast cancer in Asian-Americans is not known. We investigated the relation between diabetes and breast cancer risk in a population-based case–control study in Los Angeles County that included 1248 Asian-American women with incident, histologically confirmed breast cancer and 1148 control women, who were frequency matched to cases on age, Asian ethnicity and neighborhood of residence. The relation between history of diabetes and serum concentrations of estrogens, androgens and sex hormone-binding globulin (SHBG) was investigated in 212 post-menopausal control women. A history of diabetes was statistically significantly associated with breast cancer risk [odds ratio (OR) = 1.68, 95% confidence interval = 1.15–2.47] after adjusting for reproductive and other factors. This increased risk was unchanged after further adjustment for body mass index (BMI) and waist to hip ratio (WHR). We found a stronger diabetes–breast cancer association in women with lower BMI (≤22.7) (adjusted OR = 3.50, $P = 0.011$) than those with higher BMI (>22.7) (adjusted OR = 1.39, $P = 0.23$) but this difference in ORs was not statistically significant. Our results also show that the diabetes–breast cancer association was observed only in low/intermediate soy consumers (OR = 2.48, $P = 0.0008$) but not among high soy consumers (OR = 0.75, $P = 0.41$) (P interaction = 0.014). Controls who were diabetic showed significantly lower SHBG (20%) ($P = 0.02$) but higher free testosterone levels (26%) ($P = 0.08$) than women without such a history after adjusting for BMI and WHR. Our results support the hypothesis that diabetes may have a role in the development of breast cancer, influencing risk via both sex hormone and insulin pathways.

Introduction

Diabetes mellitus has been implicated as a risk factor for a number of cancers—most consistently with pancreatic and liver cancer. In a recent review, Wolf *et al.* (1) reported that type 2 diabetes was associated with a 10–20% excess relative risk of breast cancer based on studies conducted in western populations in the USA (2–6), UK (7) and Europe (8–12). However, body weight was not adjusted for adequately in some of the studies included in the review and the potential confounding effect of weight cannot be ruled out completely (1). The role of diabetes in the etiology of breast cancer in Asians, whose body size and dietary factors differ from western populations, has been examined in few previous studies and may be particularly informative since Asians are especially prone to developing hyperinsulinemia and diabetes even at relatively low body mass index (BMI) (13).

We have examined the role of diabetes in our case–control study of breast cancer in Asian-American women in Los Angeles County. We previously reported that breast cancer risk was significantly reduced in association with intake of soy during childhood and adulthood (14), intake of green tea (15) and regular physical activity after 10 years of age (16) using data from the first 501 cases and 594 controls; these subjects are included in the present analysis that included 1248 cases and 1148 controls. Additionally, we investigated the effects of diabetes on circulating blood hormone levels in a subgroup of post-menopausal control women.

Abbreviations: A, androstenedione; BMI, body mass index; CI, confidence interval; E1, estrone; E2, estradiol; OR, odds ratio; PPAR, peroxisome proliferator-activated receptor; SHBG, sex hormone-binding globulin; T, testosterone; WHR, waist to hip ratio.

Materials and methods

The methods of this case–control study have been described previously (17). Briefly, this population-based case–control study included women who were identified as Chinese, Japanese or Filipino, between the ages of 25 and 74 years at the time of diagnosis of an incident breast cancer in the period January 1995 through December 2001. Cases were identified through the Los Angeles County Cancer Surveillance Program, the population-based cancer registry that is a member of the National Cancer Institute's Surveillance, Epidemiology and End Results Program and the statewide California Cancer Registry. Of the 2221 women (784 Chinese, 585 Japanese and 852 Filipino women), 1384 (492 Chinese, 384 Japanese and 508 Filipinos) were interviewed; 507 (193 Chinese, 143 Japanese and 171 Filipinos) declined to be interviewed; 42 (8 Chinese, 15 Japanese and 19 Filipinos) had died and 288 (91 Chinese, 43 Japanese and 154 Filipinos) could not be contacted.

One thousand two hundred and twenty-five controls (514 Chinese, 331 Japanese and 380 Filipinos) were selected from the neighborhoods where cancer cases resided at the time of diagnosis using a well-established, standard algorithm to identify neighborhood controls that the University of Southern California Epidemiology Program has used in numerous case–control studies (18). This algorithm defines a specified sequence of houses to be visited in the neighborhoods where index cases lived at the time of diagnosis. We sought to interview as the control the first eligible resident in the sequence. If the first eligible control refused to participate, the second eligible one in the sequence was asked, and so on. Letters were left when no one was home and follow-up was by mail and telephone (if a telephone number could be determined). Controls were sought to frequency match to the cases on specific Asian ethnicities and 5-year age groups. On average, a suitable control was identified after walking 65 houses. Of the controls interviewed, 62% were the first identified eligible controls, 21% were the second identified eligible controls and 17% were the third or later eligible controls.

Data collection

In-person interviews were conducted using a standardized, structured questionnaire that covered demographic characteristics and migration history, menstrual and reproductive history, body size, physical activity and diet history. The diet questionnaire was developed by Dr Jean Hankin at the University of Hawaii and was modeled after the validated diet instrument used in the Multiethnic Cohort Study being conducted in Hawaii and Los Angeles (19). As we have described previously, the assessment of soy intake during adolescence was crude, based on the usual frequency of intake of tofu between ages 12 and 18. Intake of soy isoflavones (mg/1000 Kcal) during adult life was estimated based on total combined levels of daidzein, genistein and glycitein measured in the 14 soy foods included in our diet questionnaire (14). Subjects were asked about their height and weight at age 18 years, at age 30 years and each decade thereafter. Trained interviewers measured the circumferences of the waist and hip of study participants. In addition, subjects were asked about their history of diabetes that was 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, type of diabetes (i.e. during pregnancy only or at other times) and if they were treated for diabetes.

Study participants were asked to donate a blood specimen at the completion of the interview. Blood specimens were provided by 72% of cases and 64% of controls. For blood hormone analysis in control women, we selected only those subjects who were naturally post-menopausal and were not using any menopausal hormone at the time of blood collection ($n = 221$).

Blood hormone analysis

Serum levels of estradiol (E2), estrone (E1), testosterone (T) and androstenedione (A) were measured by previously described radioimmunoassay methods (20,21). The interassay coefficients of variation were between 9 and 12%. Free [i.e. non-sex hormone-binding globulin (SHBG) bound] T and free E2 were calculated on the basis of measured total T and total E2 concentrations,

respectively, SHBG concentration and an assumed constant for albumin (22). This method has been found to have high validity compared with direct measurements (23). SHBG was measured by a chemiluminescent immunometric assay on the Immulite analyzer (Diagnostic Products Corporation, Inglewood, CA). The SHBG interassay coefficient of variation was 8%.

Statistical analysis

Results presented are based on 1248 cases and 1148 controls who have complete information on diabetes as well as the covariates included for adjustment. Of the 1384 cases and 1225 controls interviewed, we excluded 136 cases and 77 controls from the final analyses because of incomplete interview (22 cases and 13 controls), previous cancer (44 cases and 35 controls) or missing information on body size, menstrual or pregnancy history or one of the other adjustment covariates (71 cases and 29 controls). We calculated odds ratios (ORs; relative risk estimates), their corresponding 95% confidence intervals (CIs) (24) and statistical significance (*P*) values by conditional logistic regression methods, with matched sets defined jointly by reference age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69 and 70+), and specific Asian ethnicity (Chinese, Japanese and Filipino). All basic regression models in this study included as covariates years of residence in the USA (USA born, >20, 11–20 and ≤10 years), education (less than high school, high school, some college and college graduate), age at menarche (<12, 12–13 and 14+), parity (0, 1, 2, 3 and 4 + births), marital status (ever versus never married), menopausal status (pre-menopausal, natural menopause, bilateral oophorectomy, simple hysterectomy and 'hormone therapy menopause', i.e. naturally menopausal but age unknown due to starting hormone therapy before periods had stopped) and age at menopause (<45, 45–49, 50–54 and 55+). A more elaborate regression model included recent BMI (kg/m^2) (in quartiles), waist to hip ratio (WHR, in quartiles), height (in quartiles), total caloric intake (continuous) and years of regular (i.e. at least 1 h/week) recreational physical activity (<5, 5–9, 10–19 and 20+) (model 2, Table II). A final model further adjusted for intake of soy during childhood and adulthood and intake of tea (none, black tea only, green tea only, and black and green tea) (model 3, Table II). Tests for trend were performed by coding each variable as a grouped (quartile) linear variable (i.e. as 1, 2, 3 and 4). To examine the potential effect modification of the diabetes–breast cancer association by body size, soy intake and other variables, interaction terms were tested. *P* values <5% are considered statistically significant and all *P* values quoted are two sided.

Hormone measurements were transformed logarithmically to achieve approximate normal distributions for statistical analysis. Of the 221 post-menopausal control women, nine had E1 values >125 pg/ml, E2 values >75 pg/ml or T values >125 ng/dl (indicating post-menopausal hormone use) and they were excluded from the analysis. Geometric mean values were computed for concentrations of serum estrogens (total and free E2 and E1), androgens (total and free T and A) and SHBG. To determine whether geometric mean hormone levels differed between control women with and without diabetes, we used analysis of covariance models including specific Asian ethnicity, years of residence in the USA (USA born, 20+, 11–20 and ≤10 years) and age at natural menopause.

Results

This analysis included 1248 breast cancer patients (444 Chinese, 466 Filipino and 338 Japanese) and 1148 control women (479 Chinese, 360 Filipino and 309 Japanese). As reported previously, cases and controls were similar in terms of birthplace, education and age at menarche, but cases were significantly more likely to be nulliparous, had fewer live births, had lower consumption of soy and green tea, were less physically active, had a higher WHR and were more likely to have a family history of breast cancer. In addition, risk of post-menopausal breast cancer was increased in relation to high recent weight and use of menopausal hormones, particularly use of estrogen–progestin therapy (17).

Twenty-four breast cancer cases and 26 control subjects reported that they had a history of gestational diabetes but did not otherwise have a diagnosis of diabetes. These 50 women were excluded from all subsequent analyses. History of diabetes among cases and controls by select lifestyle determinants are shown in Table I. History of type 2 diabetes (referred to hereafter as diabetes) was reported by 4.3% of control women (48 of 1122) and 7.4% (90 of 1224) of case patients. In both cases and controls, history of diabetes was significantly and positively associated with age, physical inactivity, recent BMI and WHR after adjusting for Asian ethnicity, years of residence in the USA, menopausal status and education (Table I).

Table I. Characteristics of breast cancer patients and control women by history of diabetes

	All cases[a]		All controls[a]	
	Diabetes		Diabetes	
	No	Yes	No	Yes
Age				
≤44	274	2 (0.7%)	339	4 (1.2%)
45–54	420	24 (5.4%)	380	10 (2.6%)
55–64	265	30 (10.2%	221	17 (7.2%)
>64	175	34 (16.3%)	134	17 (11.3%)
P trend[b]		<0.001		0.04
Menopausal status				
Pre-menopausal	531	16 (2.9%)	570	10 (1.7%)
Post-menopausal	603	74 (10.9%)	504	38 (7.0%)
P[b]		0.61		0.66
Race				
Chinese	412	25 (5.7%)	454	17 (3.6%)
Japanese	307	25 (7.5%)	285	18 (5.9%)
Filipino	415	40 (8.8%)	335	13 (3.8%)
P (2 df)[b]		0.22		0.44
Birthplace				
USA born	254	26 (9.2%)	281	18 (6.0%)
Migrant, in USA 21+ years	401	38 (8.7%)	399	17 (4.1%)
Migrant, in USA ≤20 years	479	26 (5.1%)	394	13 (3.2%)
P trend[b]		0.04		0.16
Education				
≤High school	204	20 (8.9%)	186	15 (7.5%)
Some college	241	28 (10.4%)	258	16 (5.8%)
College graduate	500	30 (5.7%)	441	13 (2.9%)
>College	189	12 (6.0%)	189	4 (2.1%)
P trend[b]		0.46		0.19
Physical activity (years)				
0–4	188	21 (10.0%)	133	9 (6.3%)
5–9	275	25 (8.3%)	227	14 (5.9%)
10–19	377	28 (6.9%)	364	15 (4.0%)
20+	294	16 (5.2%)	350	10 (2.8%)
P trend[b]		0.04		0.04
Recent BMI (kg/m^2)				
≤20.4	294	9 (2.9%)	277	2 (0.7%)
>20.4–22.7	303	18 (5.2%)	336	10 (3.2%)
>22.7–24.6	235	22 (8.4%)	204	13 (5.0%)
>24.6	296	41 (12.2%)	255	22 (7.9%)
P trend[b]		0.09		0.01
WHR				
≤0.76	244	4 (1.6%)	278	4 (1.4%)
>0.76–0.80	278	14 (4.8%)	283	4 (1.4%)
>0.80–0.84	307	19 (5.8%)	261	14 (5.1%)
>0.84	305	53 (14.8%)	252	26 (9.4%)
P trend[b]		<0.001		0.008

[a]Cases (n = 24) and controls (n = 26) with a history of gestational diabetes were excluded.
[b]*P* values are mutually adjusted for all other variables included in the table.

Risk of breast cancer was significantly increased in women with a history of type 2 diabetes (adjusted OR = 1.68, 95% CI = 1.15–2.47). Risk increased with increasing years since first diagnosed with diabetes. History of diabetes that preceded breast cancer by >14 years was associated with a nearly 2-fold elevated risk (adjusted OR = 1.98, 95% CI = 0.92–4.25). Breast cancer risk was increased irrespective of whether treatment for diabetes was reported. The positive association between diabetes and breast cancer remained statistically significant after adjustment for recent BMI and WHR (model 2, Table II) and for intake of soy (model 3, Table II). The increased risk associated with diabetes was observed in both pre- and post-menopausal women although the OR was statistically significantly different from 1.0 only in post-menopausal women. The adjusted OR was 1.55 (95% CI = 0.64–3.73) in pre-menopausal and 1.74 (95% CI = 1.11–2.74) in post-menopausal women after adjusting for covariates including

Table II. Adjusted ORs and corresponding 95% CIs for breast cancer in relation to history of diabetes in Asian-American women

	Cases/ controls	OR[a]	95% CI	OR[b]	95% CI	OR[c]	95% CI
Diabetes[d]							
No	1134/1074	1.00		1.00		1.00	
Yes	90/48	1.68	1.15–2.47	1.66	1.12–2.45	1.71	1.15–2.54
P value			0.008		0.011		0.008
Years since first diagnosis of diabetes							
≤7 years	44/25	1.51	0.90–2.54	1.46	0.86–2.46	1.45	0.85–2.48
8–14 years	22/12	1.80	0.87–3.75	1.90	0.89–4.06	2.03	0.94–4.39
>14 years	24/11	1.98	0.92–4.25	1.91	0.88–4.14	2.04	0.93–4.49
P trend			0.009		0.011		0.007
Treated for diabetes							
No	19/9	1.98	0.87–4.48	1.95	0.86–4.44	2.06	0.90–4.73
Yes	71/39	1.61	1.05–2.47	1.59	1.02–2.45	1.55	1.00–2.42

[a]Covariates included are age, Asian ethnicity, education, birthplace and years of residence in the USA, years of physical activity, marital status, parity, age at menarche, type of menopause and age at menopause.
[b]All the covariates included in footnote 'a' and recent BMI (≤20.4, >20.4–22.7, >22.7 to ≤24.6 and >24.6) and WHR (≤0.76, >0.76-≤0.80. >0.80 to ≤0.84 and >0.84).
[c]All the covariates included in footnote 'b' and soy intake during adolescence (<monthly, 1–3 times/month, 1–3 times/week and 4+ times/week), soy intake during adult life (≤1.79, >1.79–6.24, >6.24–12.68 and >12.68 mg of isoflavones/1000 Kcal) and tea intake (no tea, black tea only, green tea only and black tea and green tea).
[d]We excluded 24 cases and 26 controls with gestational diabetes only.

physical activity, recent BMI, WHR and soy intake (model 3) (data not shown).

We reported previously a statistically significant positive association between recent weight or recent BMI (usual weight or usual BMI in the most recent decade prior to cancer diagnosis in cases and interviewed date in controls) and WHR and post-menopausal breast cancer (17). The relationship between recent weight or recent BMI and risk was more pronounced in women with higher (above median) than lower WHR. Thus, we examined the combined effects of diabetes and body size measures in post-menopausal women. The deleterious effect of diabetes was consistently observed in women with lower recent BMI or lower WHR although the differences in risk estimate were not statistically significant (Table III). We also considered recent BMI and WHR in a combined index and classified women with above median WHR (>0.80) and above median recent BMI (>22.7) as high body size whereas those with below median WHR (<0.80) or below median BMI (≤22.7) and above median WHR (>0.80) as low body size. The diabetes–breast cancer association was statistically significant in women with lower body size (adjusted OR = 3.33, $P = 0.004$) but not in women with higher body size (adjusted OR = 1.29, $P = 0.39$) (P for interaction = 0.038).

Breast cancer risk was significantly influenced by soy intake in this population (14). We examined the combined effects of diabetes and soy intake in pre- and post-menopausal women combined (Table IV). Diabetes was unrelated to risk in women who were high soy consumers during adult life (>6.24 mg isoflavones/1000 Kcal) (OR = 1.03, 95% CI = 0.60–1.77) but it was a significant risk factor for women who were low consumers during adult life (≤6.24 mg isoflavones/1000 Kcal) (OR = 3.06, 95% CI = 1.65–5.69) (P for interaction = 0.021) (data not shown). The modifying effect of soy was similarly observed when we considered soy intake during both adolescence and adult life. Diabetes was not a risk factor in women who were high soy consumers during both adolescence and adult life (OR = 0.75, $P = 0.41$). However, in women who were low/intermediate soy consumers, breast cancer risk was significantly increased (OR = 2.48, $P = 0.0008$) in association with diabetes (P for interaction = 0.014) even after adjustment for recent weight, WHR and other covariates (Table IV).

Table III. Adjusted ORs[a] and corresponding 95% CI for breast cancer in relation to history of diabetes and body size in post-menopausal Asian-American women

	Case	Control	OR	95% CI	Case	Control	OR	95% CI
Diabetes	Below median recent BMI (≤22.7)				Above median recent BMI (>22.7)			
No	280	263	1.00		317	240	1.00	
Yes	22	8	3.50	1.32–9.24	52	29	1.39	0.81–2.36
P interaction			0.105					
Diabetes	Below median WHR (≤0.80)				Above median WHR (>0.80)			
No	241	232	1.00		362	272	1.00	
Yes	15	6	4.32	1.25–14.8	59	32	1.48	0.89–2.46
P interaction			0.13					
Diabetes	WHR ≤ 0.80 or WHR > 0.80 and recent BMI ≤ 22.7				WHR > 0.80 and recent BMI > 22.7			
No	352	339	1.00		245	164	1.00	
Yes	29	11	3.33	1.47–7.57	45	26	1.29	0.72–2.32
P interaction			0.038					

[a]Age, Asian ethnicity, education, years of residence in the USA, years of physical activity, marital status, parity, age at menarche, type of menopause and age at menopause, soy intake during adolescence (<monthly, 1–3 times/month, 1–3 times/week and 4+ times/week), soy intake during adult life (≤1.79, >1.79–6.24, >6.24–12.68 and >12.68 mg of isoflavones/1000 Kcal) and tea intake (no tea, black tea only, green tea only and black tea and green tea) are adjusted for in the analysis.

We measured circulating levels of SHBG, E1, E2, free E2, T, free T and A in the subset of post-menopausal control women who were naturally menopausal and were non-users of menopausal hormones. Compared with women without a history of diabetes ($n = 178$), women with diabetes ($n = 34$) showed significantly lower (43%) SHBG levels ($P < 0.001$) and higher (53%) free T levels ($P = 0.001$) (Table V). Geometric mean levels of E1, E2, free E2, T and A were non-significantly higher (11–32%) in women with diabetes. These differences in SHBG and free T levels diminished after further adjusting for recent BMI and WHR; SHBG levels were 20% lower ($P = 0.02$) and free T were 26% higher ($P = 0.08$) in diabetic women. Differences in estrogen levels between women with diabetes and those without diabetes became negligible after further adjustment for recent BMI and WHR.

We investigated the interrelationships between circulating hormone levels and the combined effects of diabetes, WHR and recent BMI. Levels of SHBG were significantly influenced by history of diabetes and body size; they were highest (51.2 nmol/l) in leaner women without a history of diabetes and lowest in heavy women with diabetes (23.5 nmol/l) ($P < 0.001$). In contrast, free T levels were highest for women with diabetes and high body size (6.2 pg/ml) and lowest for women without diabetes and were lean (3.2 pg/ml) ($P < 0.001$). There were no significant relationships between hormone and SHBG levels and history of diabetes and soy intake combined (Table V).

Discussion

In this population-based case–control study, a history of type 2 diabetes significantly increased the risk of breast cancer in Asian-American women. Women with a history of diabetes experienced a 68% higher risk of breast cancer that remained statistically significant after additional adjustment for recent BMI, WHR, soy intake and other covariates. Risk increased further with longer duration of diabetes. The effect of diabetes was substantially stronger in women with lower BMI/WHR than those with higher BMI/WHR (Table III); the two sets of diabetes–breast cancer associations were statistically significantly different from each other. Intake of soy significantly influenced the diabetes–breast cancer association. History of diabetes was a significant risk factor in women who were low/intermediate soy consumers but it was not associated with risk in high soy consumers.

Before discussing the significance of these findings, several study limitations should be mentioned. A limitation is that we interviewed 63% of the cases we contacted. We compared cases we interviewed and those we did not interview in terms of age, social class (based on census tract of residence), birthplace and tumor stage at diagnosis and there were few differences (17). For example, cases interviewed and those not interviewed did not differ in terms of stage of disease at diagnosis; both groups had the same percentage (31%) of patients with regional/metastatic cancer at the time of diagnosis. On the other hand, cases we did not interview were somewhat older (mean age was 54.3) than cases we interviewed (mean age was 52.9) (17). Given that prevalence of diabetes increased with age at comparable rates in the case and control groups (Table I), it is unlikely that this age differential can contribute toward a spurious association between diabetes and breast cancer risk. Another limitation is that the information on diabetes was based on self-report of conditions that were diagnosed by a physician. Although selective recall bias may be a concern, there is a little public awareness of a link between diabetes and breast cancer so that there is no reason to suspect that breast cancer patients will selectively recall a history of diabetes. Additionally, we asked about diabetes that was diagnosed by a physician, the age at which they were first diagnosed and treatment they may have received. The prevalence of diabetes reported by Asian-American control women was 4.3%; this prevalence of diabetes is comparable with recent estimates for women in Japan (25) and Chinese in Singapore (26). Serum SHBG level was significantly lower (43%) in control women with a history of diabetes, supportive of published studies when diabetes was clinically diagnosed or was verified by medical records (27–29). Low SHBG concentration reflects hyperinsulinemic insulin resistance and has been proposed as a surrogate marker of type 2 diabetes (30).

The increased risk associated with diabetes was observed in both pre- and post-menopausal women although the finding was statistically significant only in post-menopausal women. The positive association with diabetes was not explained by adiposity; the risk estimate was only slightly reduced after adjustment for recent BMI and WHR (OR changed from 1.68 to 1.66) (Table II). In fact, our results suggest a stronger association between diabetes and breast cancer risk in Asian women with lower body size. The diabetes–breast cancer association was not significantly modified by body size in the Nurses' Health Study but the comparison was between women with BMI (kg/m^2) <30 versus those ≥30 (6). The majority of Asian-American women in this study are classified as thin or normal weight according to the standards used in Western countries; this may explain, in part, the stronger diabetes–breast cancer association we observed. In studies conducted in Western countries, the diabetes and breast cancer association is generally weaker; the combined risk estimate was 1.25 (95% CI = 1.19–1.31) in six cohort studies and 1.13 (95% CI = 0.99, 1.28) in four case–control studies (1).

Our interpretation of the stronger diabetes–breast cancer association in women with lower body size is that diabetes and body size share common pathways that have a threshold impact on breast cancer risk. In fact, the present study provides data in support of sex hormones, at least in part, as those common pathways. Specifically, our

Table IV. Adjusted ORs[a] and corresponding 95% CI for breast cancer in relation to history of diabetes and lifetime soy intake in Asian-American women

	Case	Control	OR	95% CI	Case	Control	OR	95% CI
Diabetes	High soy intake[b]				Low/intermediate soy intake[c]			
No	398	457	1.00		736	617	1.00	
Yes	22	24	0.75	0.38–1.45	68	24	2.48	1.46–4.20
P interaction			0.014					

[a]Covariates included age, ethnicity, education, years of residence in the USA, years of physical activity, marital status, parity, age at menarche, type of menopause and age at menopause, recent BMI and WHR.
[b]High means ≥weekly soy intake during adolescence and >6.24 mg isoflavones per day in adult life.
[c]Intermediate means ≥weekly soy intake during adolescence or >6.24 mg isoflavones/1000 Kcal in adult life. Low means <weekly soy intake during adolescence and ≤6.24 mg isoflavones/1000 Kcal in adult life.

Table V. Diabetes, body size and soy intake and circulating blood hormone levels in naturally post-menopausal control women

(*N*)	SHBG (nmol/l)	E1 (pg/ml)	E2 (pg/ml)	Free E2 (pg/ml)	T (ng/dl)	Free T (pg/ml)	A (pg/ml)
Diabetes[a]							
No (178)	43.6	31.9	9.5	0.28	18.1	3.8	474.2
Yes (34)	27.8	35.6	10.5	0.37	20.3	5.8	544.5
P	<0.001	0.15	0.28	0.08	0.26	0.001	0.10
Diabetes[b]							
No (178)	49.1	30.7	8.9	0.25	18.1	3.5	474.6
Yes (34)	34.5	31.3	8.4	0.26	19.4	4.4	518.3
P	0.02	0.78	0.48	0.89	0.50	0.08	0.31
Diabetes/WHR and weight[a]							
No diabetes/other[c] (111)	51.2	29.2	8.3	0.23	16.9	3.2	441.2
Diabetes/other (8)	42.7	35.4	10.9	0.26	26.0	4.5	645.1
No diabetes/WHR >0.80 and BMI >22.7 (67)	32.0	36.6	11.6	0.39	19.3	5.1	514.8
Diabetes/WHR >0.80 and recent BMI >22.7 (26)	23.5	35.7	10.3	0.42	18.5	6.2	512.5
P (3 df)	<0.001	0.002	<0.001	<0.001	0.10	<0.001	0.03
P trend	<0.001	0.03	0.03	<0.001	<0.001	<0.001	0.50
Diabetes/soy intake in adolescence and adult life[d]							
No diabetes/high soy (81)	46.8	31.1	9.1	0.25	17.9	3.5	493.1
Diabetes/high soy (14)	39.7	32.0	8.6	0.29	22.2	5.3	561.5
No diabetes/intermediate or low soy (97)	51.2	30.3	8.7	0.26	18.3	3.6	458.1
Diabetes/intermediate or low soy (20)	39.5	30.9	8.3	0.23	17.6	3.8	489.2
P (3 df)	0.10	0.96	0.84	0.82	0.56	0.13	0.47

[a]Adjusted for age, Asian ethnicity, education, birthplace and years of residence in the USA and age at menopause.
[b]Additionally adjusted for recent BMI and WHR.
[c]Other included women with WHR ≤ 0.80 or WHR > 0.80 and recent BMI ≤ 22.7.
[d]High soy means ≥weekly soy intake during adolescence and >6.24 mg isoflavones/1000 Kcal in adult life; intermediate soy means ≥weekly soy intake during adolescence or >6.24 mg isoflavones/day in adult life and low means <weekly soy intake during adolescence and ≤6.24 mg isoflavones/1000 Kcal in adult life. Adjusted for age, ethnicity, education, birthplace and years of residence in the USA, age at menopause, recent BMI and WHR.

data show that diabetes and body size independently contribute to changes in SHBG and free T (see Table V), which are related to breast cancer risk via their influence on endogenous estrogen, a recognized risk factor for breast cancer (31). We noted a monotonic decrease in SHBG by diabetes and body size status in combination. The highest levels were observed among thin women without a history of diabetes whereas the lowest levels were present among heavy women with diabetes. Similarly, free T shows a monotonic positive relationship with a combined diabetes–body size status; lowest levels were found among thin women without diabetes whereas the highest levels were observed among heavy women with diabetes. For serum estrogens (E1 and E2) and their precursor, A, the lowest levels were noted among thin women without diabetes, whose levels were roughly 20% less than the other women (i.e. women with diabetes or who were heavier).

The inverse association between SHBG levels and body size (weight and WHR) is well established (32–34). In addition, most studies have found a positive association between adiposity and T levels (32,35). SHBG has been found to predict the development of type 2 diabetes in women, over and above the effects of glucose and insulin concentrations (27–29,36). Likewise, free androgen has been shown to predict type 2 diabetes after controlling for insulin resistance (27). We hypothesize that the already low SHBG levels and high free T and estrogen/A levels in women with high body size means the additional changes in SHBG and free T and estrogen/A levels associated with the presence versus the absence of diabetes in this subgroup of heavy women are likely to be modest, thus yielding undetectable changes in relative risk between history of diabetes and breast cancer risk. In contrast, larger differences in sex hormone levels by diabetes status are likely among women with low/normal body size, which explain the larger difference in relative risk by diabetes status in this latter subgroup of thin women.

An intriguing observation is our finding of the interrelationship between diabetes, soy and breast cancer risk. A significant association between diabetes and breast cancer risk was found only among women who were non-high soy consumers whereas no increased risk was observed among women who were high soy consumers during both adolescence and adult life. There is accumulating evidence that soy intake may beneficially influence blood glucose and insulin levels and risk of diabetes (37). In a randomized controlled 2-month soy intervention study we conducted among healthy post-menopausal women, blood insulin levels decreased 33% among women randomized to the soy intervention arm compared with 21% in the control arm (38). Significant reductions in insulin concentration in association with soy supplementation were reported in women with type 2 diabetes (30,39,40) but not among non-diabetic women (39,40). In a cross-sectional study conducted among Chinese women in Shanghai, high intake of soy food was associated with a lower risk of glycosuria, a strong predictor of diabetes mellitus in post-menopausal women (41). Interestingly, soy genistein has been demonstrated to bind to peroxisome proliferator-activated receptors (PPARs)-γ, and both soy genistein and daidzein are potent activators of the PPARs (42). PPARγ is highly expressed in adipose tissues and plays a critical role in adipogenesis and in the metabolism of glucose and cholesterol. Common anti-diabetic drugs, including fibrates and glitazones, act on PPAR and it has been suggested that soy isoflavones may exhibit properties of this classes of anti-diabetic drugs (42). Our results support the accumulating evidence that soy isoflavones may influence insulin sensitivity. Further evaluation of the potential interaction effect of soy on the diabetes–breast cancer in larger samples sizes and in different populations will be worthwhile. It should be noted the suggested effects of soy and diabetes via the insulin pathway also support our previous observation of a stronger effect of recent weight on risk in women with high WHR than in women with lower WHR (17). The suggested interaction of recent weight and WHR on risk may be explained by the deleterious effects of high recent weight and WHR on circulating levels of sex hormones and additionally by the influence of high WHR on the insulin pathway.

It is well recognized that incidence of breast cancer is increasing rapidly among Asian women, both in Asia and elsewhere, including the USA. In this population-based case–control study of breast cancer in Asian-American women, we found that breast cancer risk is significantly increased in association with a history of diabetes, even after adjustment for BMI and WHR. We have found a biologically plausible modifying effect of soy in the diabetes–breast cancer association that warrants further investigation. Given the well-recognized secular increase in diabetes worldwide, even a small increase in breast cancer risk among diabetics will have substantial public health importance.

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