Table 1 Characteristics of breast cancer case subjects and their matched controls

Characteristic	Cases ($n = 403$)[a]		Controls ($n = 403$)[a]		P for difference[b]
Age (years), mean (SD)	53.7	(0.52)	53.9	(0.51)	0.62
Age at menarche (years), mean (SE)	13.4	(0.09)	13.2	(0.08)	0.14
Age at first childbirth (years), mean (SE)	26.8	(0.19)	26.4	(0.17)	0.11
Age at menopause (years), mean (SE)[c]	49.0	(0.29)	49.4	(0.26)	0.10
Number of live births, mean (SE)	1.9	(0.05)	2.0	(0.05)	0.04
Height (cm), mean (SE)	155.4	(0.29)	155.6	(0.29)	0.88
Body-mass index (kg/m^2), mean (SE)	22.9	(0.21)	23.0	(0.16)	0.08
Total lipid concentration in serum (%; w/w), mean (SE)	0.617	(0.01)	0.632	(0.01)	0.005
Recent fish consumption (g/day), mean (SE)[d]	87.7	(2.75)	94.7	(2.97)	0.08
Recent vegetable consumption (g/day), mean (SE)[d]	256.6	(8.09)	310.8	(10.3)	0.0001
Recent meat consumption (g/day), mean (SE)[d]	58.2	(1.96)	57.6	(2.04)	0.56
Recent fruit consumption (g/day), mean (SE)[d]	287.9	(10.7)	287.7	(10.2)	0.86
Recent total energy intake (kcal/day), mean (SE)[d]	1882	(27.3)	1949	(27.7)	0.07
Recent alcohol intake (one day per week or more), n (%)	74	(26.6)	101	(30.6)	0.50
Premenopausal women, n (%)	183	(45.4)	141	(35.0)	<0.0001
Previous benign breast diseases, n (%)	46	(12.0)	30	(7.5)	0.04[e]
Previous breast feeding, n (%)	317	(80.9)	331	(82.1)	0.64[e]
Breast cancer in a first-degree relative, n (%)	31	(7.8)	23	(5.7)	0.48[e]
Previous breast cancer screening, n (%)					<0.0001[e]
1–2 times in the past five years	92	(23.9)	78	(19.5)	
3–4 times in the past five years	41	(10.7)	64	(16.0)	
One or more times per year in the past five years	62	(16.1)	215	(53.8)	
Education (college degree or higher), n (%)	21	(5.3)	85	(21.1)	<0.0001[e]
Smoking status, n (%)					<0.0001[e]
Former	50	(12.5)	8	(2.0)	
Current	34	(8.5)	23	(5.7)	
Physical activity (moderate, ≥1/week, past 5 years), n (%)	91	(22.9)	127	(31.5)	0.053[e]

[a] Sample size varied among variables because of missing information. Percentages were calculated among case or control subjects who provided answers

[b] Wilcoxon rank-sum test for continuous variables; Cochran-Mantel-Haenszel test based on rank scores for categorical variables

[c] Postmenopausal women only

[d] For 391 matched pairs

[e] Subjects with unknown or missing values were excluded from analysis

variables, positive or inverse associations with breast cancer were seen for a history of breast cancer screening, number of live births, menopausal status, educational level, smoking status, history of benign breast disease, vegetable consumption, and serum total lipid concentration.

Median serum organochlorine concentrations were not as high among cases as among controls (Table 2). All organochlorines, including *o,p'*-DDT and mirex, were detected in 100% of serum samples, except for 14 PCB peaks. Based on comparison of median values, average total PCBs among control participants consisted of the following PCB congeners: 153 (23.5%), 180 (13.4%), 138 (12.0%), 182/187 (6.7%), 118 (6.2%), 164/163 (5.0%), 170 (4.4%), 74 (3.7%), 99 (3.4%), 146 (3.0%), 156 (2.2%), 194 (1.9%), 198/199 (1.8%), 183 (1.6%), 177 (1.3%), 105 (1.2%), 203 (1.1%), and the remaining PCBs. PCB77 was not detected in any serum sample.

Table 3 shows that none of the serum organochlorines, including DDTs, *p,p'*-DDE, and total PCBs, was associated with an increased risk of breast cancer. In fact, risk was inversely associated with serum concentrations of *cis*-nonachlor, mirex and total PCBs, but not with those of the other compounds. For example, adjusted ORs (95%CIs; *P*-values for trend) of breast cancer risk for the highest vs. lowest quartile of exposure for total PCBs, mirex, and *cis*-nonachlor were 0.33 (0.14–0.78; P for trend = 0.008), 0.40 (0.19–0.84; P for trend = 0.02), and 0.41 (0.19–0.91; P for trend = 0.07), respectively. Adjustment for possible confounding variables attenuated the results for *o,p'*-DDT, *p,p'*-DDT, and *p,p'*-DDE and widened the 95% CI range for

Table 2 Lipid-adjusted serum organochlorine concentrations (ng/g lipid) in breast cancer case subjects and matched controls

Compound	Median (interquartile range)				*P* for
	Cases ($n = 403$)		Controls ($n = 403$)		difference[a]
o,p'-DDT	1.5	(1.0, 2.3)	1.6	(1.1, 2.7)	0.02
p,p'-DDT	9.3	(6.2, 15)	9.9	(7.2, 16)	0.03
p,p'-DDE	360	(190, 620)	370	(220, 660)	0.10
trans-Nonachlor	22	(15, 30)	23	(17, 32)	0.02
cis-Nonachlor	3.5	(2.3, 5.0)	3.9	(2.7, 5.4)	0.004
Oxychlordane	8.2	(5.9, 11)	8.6	(6.6, 11)	0.02
HCB	27	(22, 33)	27	(23, 34)	0.22
Mirex	1.9	(1.5, 2.5)	2.1	(1.6, 2.8)	<0.0001
β-HCH	65	(41, 110)	64	(41, 110)	0.75
Total PCBs[b]	170	(120, 220)	180	(140, 240)	0.004

[a] Wilcoxon rank-sum test

[b] Sum of the 41 PCB peaks (International Union of Pure and Applied Chemistry numbers 17, 28, 51, 52/69, 43/49, 48/47, 44, 74, 66, 77, 90/101, 99, 123, 118, 114, 105, 126, 146, 153, 164/163, 138, 128/162, 167, 156, 169, 182/187, 183, 183, 174, 177, 180, 170, 189, 202, 201, 198/199, 196, 203, 194, 208, 206, and 209)

every compound, whereas the results for mirex and the PCBs were substantially changed. The main contributors to these changes were adjustment for history of breast cancer screening and smoking status. Additional analyses in the 349 complete pairs showed no substantial changes in ORs, indicating that these attenuations of estimates were not caused by either (or both) the reduced sample size or nonuniform lack of data.

Additional conditional logistic analysis for 34 individual PCB congeners (7 congeners were not analyzed here because of their lower detection frequency) showed no association with risk for any congener. To the contrary, half were associated with a significant decrease in risk: adjusted ORs (95% CIs; *P*-values for trend) for the highest vs. lowest quartile of exposure for PCB 153, 138, and 180, for example, were 0.40 (0.18–0.91; *P* for trend = 0.04), 0.61 (0.28–1.35; *P* for trend = 0.29), and 0.29 (0.13–0.66; *P* for trend = 0.004), respectively. In addition, the adjusted OR (95% CI; *P*-value for trend) for the highest vs. lowest quartile of exposure for PCB 48/47 was 0.45 (0.17–1.19; *P* for trend = 0.06). With regard to Wolff et al.'s functional groupings of PCBs [21] also, adjusted ORs (95% CIs; *P*-values for trend) for the highest vs. lowest quartile of exposure for PCB Group 1A (sum of PCB 44, 43/49 and 52/69), Group 1B (sum of PCB 90/101 and 182/187), Group 2A (sum of PCB 74, 66, 105 and 118), Group 2B (sum of PCB 128/162, 138 and 170), and Group 3 (sum of PCB 99, 153, 180, 196 and 203) were 0.53 (0.25–1.09; *P* for trend = 0.06), 0.28 (0.12–0.65; *P* for trend = 0.005), 0.82 (0.35–1.95; *P* for trend = 0.94), 0.28 (0.12–0.65; *P* for trend = 0.07), and 0.40 (0.18–0.91; *P* for trend = 0.03), respectively.

Further, no significant association was seen between serum organochlorines and an increased risk of breast cancer by hormone-receptor subtype (Table 4). The decrease in risk with increased serum concentration of *trans*-nonachlor or *cis*-nonachlor was greater in ER−PR− than ER+PR+ cases (*P* for heterogeneity = 0.01 or 0.04, respectively). A significant association was seen between increased serum concentrations of mirex or total PCBs and decreased risk of ER+PR− breast cancer, and this subtype was more sensitive to mirex than the ER+PR+ or ER−PR− subtypes (*P* for heterogeneity = 0.007 or 0.004, respectively).

Stratified analysis showed different patterns of association by menopausal status (Table 5). Postmenopausal women had a statistically significant decrease in breast cancer risk with increased serum concentration of *trans*-nonachlor. In contrast, point estimates of ORs for *o,p'*-DDT or *p,p'*-DDT were higher than 1.0 among postmenopausal women, albeit the trends were not linear. A marginal decrease in risk with increased serum concentrations of *o,p'*-DDT or *p,p'*-DDT was observed in premenopausal women but did not reach statistical significance. These associations are not shown in Table 3. Serum mirex or total PCBs were inversely associated with breast cancer risk regardless of menopausal status. Similar patterns were observed on stratification by the median age of controls (data not shown).

Discussion

In this study, we found no increase in the risk of breast cancer among women with higher serum concentrations of any organochlorine, including DDTs and PCBs. To the contrary, we found statistically significant inverse associations between risk and total PCBs, *cis*-nonachlor, and mirex. This finding contrasts with that of the Seveso Italy study, which reported an association between breast cancer risk and an organochlorine, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [22]. Our findings suggest that, as in other countries, organochlorines are not related to an increased risk of breast cancer in Japan, a low-incidence country. Our lack of association with DDE is consistent with the null results of a nested case–control study of associations between serum DDE and PCBs and breast cancer risk in Asian women by Krieger et al. [15] (50 pairs), whereas our statistically significant inverse association for PCBs is not consistent with the null result for PCBs in most previous studies. Krieger et al. [15] also showed an insignificant positive association between serum DDE and breast cancer in white and black women, which is inconsistent with the majority of previous studies [6, 23]. The interethnic

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer according to quartiles of serum lipid-adjusted organochlorine concentration

Compound	Quartile median (ng/g lipid)	No. of cases	No. of controls	Simple OR[a] (403 matched pairs)		Adjusted OR[a,b] (349 matched pairs)	
				OR	95% CI	OR	95% CI
o,p'-DDT	0.90	103	81	1.00	(referent)	1.00	(referent)
	1.3	100	104	0.72	0.47–1.10	0.57	0.25–1.29
	2.0	122	109	0.81	0.54–1.22	1.13	0.53–2.38
	4.1	78	109	0.51	0.33–0.81	0.67	0.30–1.52
	P for trend				0.007		0.48
p,p'-DDT	5.6	136	100	1.00	(referent)	1.00	(referent)
	8.5	79	101	0.53	0.35–0.80	0.58	0.27–1.25
	12.0	97	95	0.68	0.45–1.03	0.99	0.47–2.07
	23.0	91	107	0.55	0.35–0.84	0.58	0.27–1.25
	P for trend				0.06		0.33
p,p'-DDE	160	116	97	1.00	(referent)	1.00	(referent)
	300	89	99	0.75	0.51–1.11	0.47	0.24–0.92
	490	107	103	0.84	0.57–1.26	0.99	0.48–2.02
	1100	91	104	0.68	0.44–1.06	1.02	0.46–2.26
	P for trend				0.17		0.46
trans-Nonachlor	13	126	89	1.00	(referent)	1.00	(referent)
	20	89	103	0.52	0.34–0.81	0.69	0.33–1.46
	27	96	104	0.54	0.34–0.84	0.72	0.33–1.57
	41	92	107	0.50	0.32–0.79	0.49	0.22–1.06
	P for trend				0.02		0.08
cis-Nonachlor	2.0	132	94	1.00	(referent)	1.00	(referent)
	3.3	98	107	0.58	0.38–0.87	0.51	0.25–1.06
	4.7	90	96	0.56	0.36–0.86	0.69	0.33–1.47
	7.0	83	106	0.45	0.28–0.71	0.41	0.19–0.91
	P for trend				0.002		0.07
Oxychlordane	5.4	128	100	1.00	(referent)	1.00	(referent)
	7.8	92	95	0.66	0.43–1.02	0.73	0.35–1.51
	9.7	77	93	0.57	0.37–0.89	0.60	0.28–1.31
	15	106	115	0.63	0.41–0.97	0.65	0.31–1.38
	P for trend				0.09		0.33
HCB	20	107	95	1.00	(referent)	1.00	(referent)
	25	92	86	0.90	0.59–1.38	0.67	0.32–1.37
	30	110	120	0.77	0.50–1.17	0.91	0.43–1.92
	38	94	102	0.75	0.47–1.20	0.95	0.43–2.11
	P for trend				0.18		0.90
Mirex	1.4	130	87	1.00	(referent)	1.00	(referent)
	1.9	109	98	0.73	0.50–1.08	0.56	0.28–1.13
	2.4	86	112	0.50	0.34–0.75	0.60	0.30–1.19
	3.5	78	106	0.48	0.32–0.73	0.40	0.19–0.84
	P for trend				0.0003		0.02
β-HCH	26	96	98	1.00	(referent)	1.00	(referent)
	52	100	102	1.01	0.66–1.53	0.81	0.39–1.72
	82	99	91	1.12	0.71–1.78	0.72	0.31–1.69
	160	108	112	1.00	0.61–1.62	1.04	0.43–2.52
	P for trend				0.91		0.63

Table 3 continued

Compound	Quartile median (ng/g lipid)	No. of cases	No. of controls	Simple OR[a] (403 matched pairs)		Adjusted OR[a,b] (349 matched pairs)	
				OR	95% CI	OR	95% CI
Total PCBs	110	126	99	1.00	(referent)	1.00	(referent)
	160	96	85	0.82	0.53–1.26	0.79	0.36–1.72
	200	102	116	0.61	0.40–0.92	0.57	0.28–1.15
	290	79	103	0.48	0.30–0.77	0.33	0.14–0.78
	P for trend				0.002		0.008

[a] Cases and controls were matched for age and area

[b] Adjusted for total lipid concentration in serum (<0.5409%, 0.5409–0.6144%, 0.6145–0.701%, or ≥0.702%); body-mass index (<20.93, 20.93–22.59, 22.6–24.88, or >24.88 kg/m^2); menopausal status and age at menopause (premenopause, <48, 48–50, 51–52, or ≥53 years); smoking status (never, former, or current); fish consumption (<54.9, 54.9–82.2, 82.4–115.4, or ≥115.9 g/day); vegetable consumption (<177.27, 177.27–260.2, 261.2–378.3, or ≥379.1 g/day); family history of breast cancer in a first-degree relative (yes or no); age at first childbirth (nulliparous, <25, 25–26, 27–28, ≥29 years)—Ordinal variable; parity (nulliparous, 1, 2, or ≥3); age at menarche (<12, 12, 13, 14, or ≥15 years); history of breast cancer screening (never, 1–2 times in the past five years, 3–4 times in the past five years, or one or more times per year in the past five years); and history of breast feeding (yes or no)

Subjects with missing values in any of the variables included in the models were not used, nor was the corresponding subject in the matched case–control pair

variation between Caucasian and Asian women suggested by Krieger et al. [15] has not been confirmed.

Our null finding for *p,p′*-DDE is consistent with the results of a previous meta-analysis [23] and inconsistent with our marginal decrease in risk of ER+PR+ breast cancer or breast cancer in premenopausal women for *o,p′*-DDT. This difference in effects between *p,p′*-DDE and *o,p′*-DDT might be partly explained as follows. First, *p,p′*-DDE is androgenic but only weakly estrogenic or negative, whereas *o,p′*-DDT is the most estrogenic of all DDT-related compounds [9]. Second, it is unclear whether serum *p,p′*-DDE represents *o,p′*-DDT intake because most serum *p,p′*-DDE results from *p,p′*-DDE intake, because of the slow conversion of ingested DDT to *p,p′*-DDE in humans [24]. The association of breast cancer risk with the specific serum levels of *o,p′*-DDT, *p,p′*-DDT, or *p,p′*-DDE was not always consistent, but in some analyses showed similar patterns owing to the correlation of their serum concentrations (Spearman correlation coefficient among controls = 0.57–0.86). Further, no previous study with a small sample size has found an increased risk of breast cancer in relation to *o,p′*-DDT exposure [17, 25]. In addition, the lack of association with *p,p′*-DDT is consistent with the majority of previous studies [17, 20, 25–40], including three nested case–control studies [26–28], whereas other studies found significant or marginal inverse [41, 42] or positive [43–47] associations.

Our inverse association between serum total PCBs and breast cancer is inconsistent with the majority of previous studies, which had null results [10]. This difference may be due in part to the lower blood levels of total PCBs in our subjects than in any previous population studied (mean, median, or geometric mean in controls 257.1–2885.8 ng/g lipid) [10, 16, 46] and to the lower sex hormone levels in Asian women [48]. Given that some PCB congeners did not show the same risk pattern as total PCBs, the effect of total PCBs might also depend on the congener pattern. The inverse associations were consistent across Wolff et al.'s functional PCB groups, except for Group 2A (moderately persistent; potentially antiestrogenic and immunotoxic, dioxin-like PCBs); but despite the lack of association for this group, the association of total PCBs with decreased risk remained because the major components of total PCBs were PCB 153 and 180 (Group 3). At least two prospective studies which found inverse associations for total PCBs also found inverse associations for the PCBs of Group 3 (enzyme inducers) [28, 42].

Among other agents, no increase in the risk of breast cancer was seen for serum levels of chlordane-related compounds. This finding is in general agreement with previous studies [28, 29, 32, 39, 42, 45, 47, 49, 50], as follows. Oxychlordane's lack of association or only insignificant inverse association with breast cancer is consistent with most previous studies [28, 29, 32, 45, 49, 50], with a significant inverse association seen in a recent nested case–control study in postmenopausal women only [42]. An inverse association for *cis*-nonachlor was also found in two case–control studies, but was insignificant in both [29, 49], whereas a third case–control and a prospective study reported no association [42, 45]; while *trans*-nonachlor's lack of association is consistent with previous studies [28, 32, 39, 42, 47, 50].

In contrast to the consistency of findings between the present and past studies for chlordane-related compounds,

Table 4 Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of hormone receptor-defined breast cancer according to lipid-adjusted organochlorine concentration in serum

Compound	Quartile median (ng/g lipid)	Adjusted ORs[a]						*P* for heterogeneity		
		ER−PR− (75 cases)		ER+PR− (64 cases)		ER+PR+ (203 cases)				
		OR	95% CI	OR	95% CI	OR	95% CI	P^b	P^c	P^d
o,p'-DDT	0.90	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	1.3	1.00	0.41–2.41	0.59	0.23–1.56	0.69	0.38–1.27			
	2.0	1.43	0.61–3.35	1.15	0.49–2.68	0.93	0.51–1.69			
	4.1	0.96	0.37–2.47	0.78	0.30–2.04	0.55	0.28–1.08			
	P for trend		0.79		0.82		0.12	0.98	0.40	0.38
p,p'-DDT	5.6	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	8.5	0.60	0.26–1.36	1.42	0.58–3.47	0.68	0.37–1.26			
	12	0.66	0.28–1.54	1.26	0.50–3.19	0.99	0.54–1.81			
	23	0.53	0.23–1.25	0.94	0.36–2.49	0.91	0.48–1.72			
	P for trend		0.25		0.60		0.96	0.64	0.59	0.24
p,p'-DDE	160	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	300	0.68	0.29–1.58	0.40	0.16–1.00	0.68	0.37–1.26			
	490	0.81	0.35–1.92	0.70	0.30–1.62	0.93	0.51–1.67			
	1100	1.06	0.42–2.64	0.49	0.19–1.27	0.95	0.49–1.85			
	P for trend		0.55		0.40		0.75	0.24	0.31	0.72
trans-Nonachlor	13	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	20	0.64	0.28–1.44	0.93	0.37–2.31	0.66	0.35–1.23			
	27	0.48	0.19–1.17	1.11	0.42–2.92	0.81	0.42–1.56			
	41	0.26	0.10–0.69	0.53	0.18–1.52	0.79	0.41–1.54			
	P for trend		0.006		0.17		0.73	0.29	0.27	0.01
cis-Nonachlor	2.0	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	3.3	1.10	0.49–2.45	0.90	0.37–2.18	0.55	0.30–1.02			
	4.7	0.63	0.25–1.56	0.72	0.28–1.89	0.85	0.45–1.60			
	7.0	0.35	0.13–0.95	0.57	0.21–1.52	0.70	0.36–1.36			
	P for trend		0.01		0.22		0.50	0.31	0.46	0.04
Oxychlordane	5.4	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	7.8	1.12	0.49–2.55	1.14	0.47–2.74	0.68	0.36–1.27			
	9.7	0.54	0.21–1.38	0.81	0.31–2.13	0.73	0.39–1.40			
	15	0.60	0.24–1.53	0.49	0.18–1.37	0.83	0.43–1.57			
	P for trend		0.17		0.08		0.77	0.68	0.13	0.25
HCB	20	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	25	0.81	0.35–1.89	0.75	0.30–1.87	0.62	0.33–1.15			
	30	0.80	0.34–1.88	1.05	0.43–2.53	1.01	0.55–1.83			
	38	0.80	0.31–2.04	0.58	0.21–1.56	1.03	0.53–2.00			
	P for trend		0.64		0.33		0.65	0.67	0.22	0.44
Mirex	1.4	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	1.9	0.86	0.36–2.04	0.43	0.19–1.00	0.89	0.50–1.60			
	2.4	0.97	0.41–2.29	0.30	0.13–0.71	0.46	0.25–0.86			
	3.5	0.69	0.27–1.75	0.10	0.03–0.32	0.57	0.29–1.10			
	P for trend		0.43		<0.0001		0.049	0.004	0.007	0.50
β-HCH	26	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	52	1.86	0.79–4.38	2.21	0.86–5.67	1.09	0.58–2.04			
	82	0.79	0.30–2.11	1.45	0.55–3.86	1.29	0.67–2.47			
	160	1.19	0.43–3.25	0.91	0.30–2.80	1.10	0.54–2.24			
	P for trend		0.77		0.29		0.90	0.52	0.27	0.71

Table 4 continued

Compound	Quartile median (ng/g lipid)	Adjusted ORs[a]						*P* for heterogeneity		
		ER−PR− (75 cases)		ER+PR− (64 cases)		ER+PR+ (203 cases)				
		OR	95% CI	OR	95% CI	OR	95% CI	P^b	P^c	P^d
Total PCBs	110	1.00	(referent)	1.00	(referent)	1.00	(referent)			
	160	1.09	0.47–2.58	0.62	0.25–1.56	1.20	0.64–2.25			
	200	0.68	0.29–1.58	0.35	0.14–0.88	0.80	0.44–1.45			
	290	0.38	0.13–1.05	0.20	0.07–0.59	0.54	0.26–1.11			
	P for trend		0.03		0.003		0.055	0.41	0.10	0.46

[a] Cases were stratified by combined estrogen and progesterone receptor status. Each analysis used 381 controls. ORs were adjusted for age (continuous); residential area (urban or rural); total lipid concentration in serum (<0.5409%, 0.5409–0.6144%, 0.6145–0.701%, or ≥0.702%); body-mass index (<20.93, 20.93–22.59, 22.6–24.88, or >24.88 kg/m^2); menopausal status and age at menopause (premenopause, <48, 48–50, 51–52, or ≥53 years); smoking status (never, former, or current); fish consumption (<54.9, 54.9–82.2, 82.4–115.4, or ≥115.9 g/day); vegetable consumption (<177.27, 177.27–260.2, 261.2–378.3, or ≥379.1 g/day); menopausal status and age at menopause (premenopause, <48, 48–50, 51–52, or ≥53 years); smoking status (never, former, or current); family history of breast cancer in a first-degree relative (yes or no); age at first childbirth (nulliparous, <25, 25–26, 27–28, ≥29 years)—Ordinal variable; parity (nulliparous, 1, 2, or ≥3); age at menarche (<12, 12, 13, 14, or ≥15 years); history of breast cancer screening (never, 1–2 times in the past five years, 3–4 times in the past five years, or one or more times per year in the past five years); and history of breast feeding (yes or no)

[b] *P* value for heterogeneity in odds ratios between ER−PR− and ER+PR−

[c] *P* value for heterogeneity in odds ratios between ER+PR− and ER+PR+

[d] *P* value for heterogeneity in odds ratios between ER−PR− and ER+PR+

however, our finding of an inverse association between mirex and breast cancer risk is inconsistent with past studies. Four previous hospital-based case–control studies in the US have assessed this association, with null results [29, 45, 51, 52], although one reported a borderline association in a group with no history of lactation ($OR = 2.42$, 95% CI 0.98–4.32) [52]. A second noted a higher range of mirex exposure (mean 0.037 ng/g serum among controls [52]) than that seen here, likely because of the history of use of this agent in the US versus no use in Japan [53]. Furthermore, Asian women have lower sex hormone levels [48] and higher dietary intake of phytoestrogens [54, 55] than Caucasian women in Western countries. These differences may partly explain why these previous results were not reproduced here.

The lack of association, in our study, of breast cancer risk with serum concentration of HCB or β-HCH is consistent with the majority of previous studies of HCB [29, 33, 35, 37, 45, 46, 49, 52, 56–58] and β-HCH [17, 28, 29, 31, 32, 35, 41, 43, 45, 47, 49, 59, 60], respectively. Moreover, a recent nested case–control study of HCB in postmenopausal women reported a significant inverse association [42]. In contrast, several case–control studies found positive associations between breast cancer risk and HCB [30, 61] or β-HCH [33, 37, 44], and also observed much higher blood concentrations of HCB (mean 0.79 ppb [61]; mean 0.11 μg/g lipid [30]) or β-HCH (mean 0.31 mg/l [44]) in breast cancer patients.

Many of our findings by hormone-receptor subtype are inconsistent with previous studies. Of interest, we found no significant increase in the risk of organochlorines on ER+PR+ breast cancer, which is suggested to be the most sensitive breast cancer to estrogen-related risk factors [62, 63]. Indeed, several organochlorines were inversely associated with ER+PR− or ER−PR− breast cancers, although these associations did not always agree with previous studies. In contrast to our results for total PCBs in breast cancer subtypes, most previous studies found no difference in risk by hormone receptor status [15, 28, 32, 39, 47, 49, 51, 56, 57, 64–68]. On the other hand, inverse associations between PCBs and ER−PR− breast cancer [34] or ER− breast cancer in postmenopausal women [42] have also been reported. Our findings of inverse associations between ER+PR− breast cancer and serum total PCBs or mirex are also inconsistent with previous studies [51, 67]. In addition, the inverse association between *trans*-nonachlor and ER−PR− breast cancer is consistent with a recent prospective study of ER− breast cancer in postmenopausal women [42], whereas the majority of other studies reported a null finding [28, 32, 39, 49–51]. Further, our inverse association between *cis*-nonachlor and ER−PR− breast cancer is inconsistent with the two previous studies of this risk, which observed no association [42, 49]. Finally, our finding of marginal inverse associations of ER+PR+ breast cancer with mirex or *o,p'*-DDT may be inconclusive, because no previous study has found them.

Stratification by menopausal status showed several different patterns of association between breast cancer and organochlorines. Similar patterns were seen on stratification by median age, suggesting that those by menopausal

Table 5 Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer according to quartiles of serum lipid-adjusted organochlorine concentration by menopausal status

Compound	Quartile median (ng/g lipid)	Adjusted OR[a]			
		Premenopause		Postmenopause[b]	
		(164 cases; 134 controls)		(193 cases; 247 controls)	
		OR	95% CI	OR	95% CI
o,p'-DDT	0.90	1.00	(referent)	1.00	(referent)
	1.3	0.46	0.22–0.98	1.07	0.44–2.65
	2.0	0.60	0.27–1.34	1.63	0.71–3.75
	4.1	0.46	0.17–1.26	1.03	0.44–2.42
	P for trend		0.26		0.71
p,p'-DDT	5.6	1.00	(referent)	1.00	(referent)
	8.5	0.54	0.25–1.16	1.53	0.64–3.68
	12	0.39	0.17–0.88	2.26	0.95–5.35
	23	0.45	0.17–1.17	1.55	0.68–3.52
	P for trend		0.08		0.67
p,p'-DDE	160	1.00	(referent)	1.00	(referent)
	300	0.64	0.30–1.36	0.58	0.24–1.40
	490	0.57	0.28–1.20	1.09	0.47–2.57
	1100	0.92	0.32–2.63	0.89	0.38–2.08
	P for trend		0.72		0.81
trans-Nonachlor	13	1.00	(referent)	1.00	(referent)
	20	0.54	0.26–1.16	0.54	0.20–1.40
	27	0.88	0.36–2.15	0.40	0.15–1.08
	41	0.78	0.31–1.97	0.35	0.13–0.93
	P for trend		0.67		0.06
cis-Nonachlor	2.0	1.00	(referent)	1.00	(referent)
	3.3	0.67	0.32–1.39	0.49	0.20–1.23
	4.7	0.78	0.32–1.93	0.52	0.20–1.32
	7.0	0.53	0.20–1.42	0.42	0.16–1.06
	P for trend		0.21		0.15
Oxychlordane	5.4	1.00	(referent)	1.00	(referent)
	7.8	0.57	0.26–1.27	0.90	0.36–2.27
	9.7	0.72	0.30–1.71	0.46	0.17–1.24
	15	1.01	0.41–2.47	0.50	0.19–1.32
	P for trend		0.94		0.11
HCB	20	1.00	(referent)	1.00	(referent)
	25	1.05	0.52–2.13	0.53	0.20–1.39
	30	0.95	0.44–2.06	0.91	0.38–2.17
	38	0.88	0.30–2.58	0.77	0.32–1.87
	P for trend		0.80		0.95
Mirex	1.4	1.00	(referent)	1.00	(referent)
	1.9	0.84	0.39–1.83	0.44	0.19–1.02
	2.4	0.43	0.19–0.98	0.29	0.13–0.66
	3.5	0.28	0.10–0.75	0.36	0.16–0.85
	P for trend		0.005		0.06

Table 5 continued

Compound	Quartile median (ng/g lipid)	Adjusted OR[a]			
		Premenopause		Postmenopause[b]	
		(164 cases; 134 controls)		(193 cases; 247 controls)	
		OR	95% CI	OR	95% CI
β-HCH	26	1.00	(referent)	1.00	(referent)
	52	2.06	0.98–4.32	1.21	0.44–3.31
	82	1.69	0.72–3.97	1.02	0.37–2.81
	160	0.63	0.21–1.90	0.93	0.33–2.60
	P for trend		0.71		0.58
Total PCBs	110	1.00	(referent)	1.00	(referent)
	160	1.62	0.73–3.60	0.53	0.21–1.35
	200	0.45	0.21–0.99	0.47	0.20–1.15
	290	0.31	0.08–1.16	0.30	0.12–0.75
	P for trend		0.04		0.01

[a] Adjusted for age (continuous); residential area (urban or rural); total lipid concentration in serum (<0.5409%, 0.5409–0.6144%, 0.6145–0.701%, or ≥0.702%); body-mass index (<20.93, 20.93–22.59, 22.6–24.88, or >24.88 kg/m^2); smoking status (never, former, or current); fish consumption (<54.9, 54.9–82.2, 82.4–115.4, or ≥115.9 g/day); vegetable consumption (<177.27, 177.27–260.2, 261.2–378.3, or ≥379.1 g/day); smoking status (never, former, or current); family history of breast cancer in a first-degree relative (yes or no); age at first childbirth (nulliparous, <25, 25–26, 27–28, ≥29 years)—Ordinal variable; parity (nulliparous, 1, 2, or ≥3); age at menarche (<12, 12, 13, 14, or ≥15 years); history of breast cancer screening (never, 1–2 times in the past five years, 3–4 times in the past five years, or one or more times per year in the past five years); and history of breast feeding (yes or no)

[b] Additionally adjusted for age at menopause (<48, 48–50, 51–52, or ≥53 years)

status might rather have resulted from the difference in age or period, at least in part, in addition to the difference in endogenous estrogen levels between menopausal statuses. Age may be a critical determinant of the association between serum organochlorines and breast cancer risk, as suggested by the most recent study [69], because the human body burden of persistent organochlorines is positively correlated with age, and has historically decreased in Japan [12] as well as in the US [53] and Norway [28], at the least. On this basis, age-stratified analysis may be essential to any risk evaluation of highly persistent substances.

Our study has four main strengths. First, owing to their biological persistence, serum concentrations of organochlorines reflect long-term cumulative exposure to the compounds and their individual differences, allowing a greater degree of certainty about the exposure at risk. Second, because surgery may change the blood levels of organochlorines, blood samples were collected from case patients before surgery [70]. Third, our use of measurement methods with low LODs allowed us to detect serum *o,p′*-DDT in serum with adequate frequency (100%) and directly assess its association with breast cancer. The inadequate LODs and subsequent low detection frequencies in most previous studies prevented them from explicitly assessing this association, notwithstanding the greater estrogenicity of *o,p′*-DDT than *p,p′*-DDT and *p,p′*-DDE [6]. Although some PCBs with a value between 0 and the LOD were assigned the LOD value, additional analysis showed that any subsequent misclassification was inconsequential. Even when we assigned no value (e.g. LOD/2 or LOD) for individuals with a PCB level below the LOD to ensure that values between 0 and the LOD were retained, the results for total PCBs were not substantially changed. The PCB congeners, including those with nondetectable values, made only a minor contribution to total PCBs. Fourth, almost all invited subjects participated in the study, likely eliminating the possibility of nonresponse bias. Moreover, our null result for DDE is consistent with the majority of previous nested case–control studies, although a certain discrepancy between the results of prospective and case–control studies has been noted [6, 23].

Several limitations of the study also warrant mention. First, although we considered a large number of covariates in all analyses, the observational design of the study means that unmeasured or residual confounding could not be completely excluded. Because serum concentrations of organochlorines are highly correlated with each other and can be correlated with unmeasured substances, the associations observed here might not always have represented the direct effect of organochlorines. As examples, the results for *trans*-nonachlor, *cis*-nonachlor, and oxychlordane, which are impurities or metabolites of chlordane, showed a similar but not always consistent pattern, whereas

their serum concentrations were highly correlated (Spearman correlation coefficient among controls = 0.83–0.97). Further, PCB48/47 and 51, which are usually not detected in biological samples, were frequently detected in serum. This may suggest the possibility of sample contamination during sampling or sample storage. In addition, although the substantially high participation rates among both eligible cases and controls minimized potential biases related to control selection, the use of controls from medical checkup examinees, whose distribution of risk factors for breast cancer may differ from the general population due to greater health consciousness, might have led to selection bias. This possibility is heightened by the lack of differences between patients and controls in the distribution of several established risk factors for breast cancer (family history, reproductive factors, etc.). Finally, samples collected from cases post-diagnosis may less likely reflect serum levels at the time relevant to carcinogenesis than those collected prospectively in cohort studies.

Conclusions

In conclusion, our results do not support the hypothesis that higher serum organochlorine concentrations increase the risk of breast cancer in Japanese women. Overall, the present study suggests that breast cancer risk in Japan, a low-incidence country, is similar to that in western countries in terms of organochlorine exposure.

Acknowledgements This study was supported by a Health and Labour Sciences Research Grant for Research on the Risk of Chemical Substances. Hiroaki Itoh is an awardee of a Research Resident Fellowship from the Japan Food Hygiene Association for Research on the Risk of Chemical Substances, which is supported by this grant.

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Isoflavone, polymorphisms in estrogen receptor genes and breast cancer risk in case-control studies in Japanese, Japanese Brazilians and non-Japanese Brazilians

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(Received December 7, 2008/Revised January 18, 2009/Accepted January 20, 2009)

Epidemiologic studies have shown an inverse association between isoflavones and breast cancer risk. Because isoflavones bind estrogen receptors, we hypothesized that polymorphisms in the estrogen receptor genes might modify the association between isoflavone intake and breast cancer risk. We conducted hospital-based case-control studies of patients aged 20–74 years with primary, incident, histologically confirmed invasive breast cancer, and matched controls from among medical checkup examinees in Nagano, Japan, and from cancer-free patients in São Paulo, Brazil. A total of 846 pairs (388 Japanese, 79 Japanese Brazilians and 379 non-Japanese Brazilians) completed validated food frequency questionnaires, and provided blood samples. Five single nucleotide polymorphisms in the estrogen receptor alpha (rs9340799, rs1913474, and rs2234693) and beta (rs4986938 and rs1256049) genes were genotyped. We found no consistent association between the five single nucleotide polymorphisms and breast cancer risk among the three populations. In analyses of combinations of isoflavone intake and single nucleotide polymorphisms, an inverse association between intake and risk was limited to women with the GG genotype of the rs4986938 polymorphism for postmenopausal Japanese (odds ratio for highest *versus* lowest tertile = 0.47; *P* for trend = 0.01), Japanese Brazilians (odds ratio for highest *versus* lowest median = 0.31) and non-Japanese Brazilians (odds ratio for consumers *versus* non-consumers = 0.37) (*P* for interaction = 0.11, 0.08, and 0.21, respectively). We found no remarkable difference for the other four polymorphisms. Our findings suggest that polymorphisms in the estrogen receptor beta gene may modify the association between isoflavone intake and breast cancer risk. (*Cancer Sci* 2009)

Soy foods are a traditional staple dish in Asian countries. They are a primary source of isoflavones such as genistein and daidzein, which are classified as phytoestrogens. Because breast cancer risk is substantially lower in Asian than Western countries,[1] the contribution of a high isoflavone intake to low breast cancer risk has been hypothesized.[2] A meta-analysis supported this hypothesis and found a small decrease in breast cancer risk with higher soy intake.[3] On the other hand, a more recent meta-analysis indicated that risk reduction was limited to Asian populations.[4] This discrepancy might reflect differences in exposure levels and genetic factors between Asian and Western populations.

Several mechanisms by which isoflavones may reduce the risk of breast cancer have been proposed.[5,6] The most prominent and thoroughly investigated are those mediated via estrogen receptors, which arise due to the similarity in chemical structures between isoflavones and human estrogen hormone, and the consequent binding affinity of isoflavones for estrogen receptors.[6,7] Isoflavones can therefore act as estrogen agonists and antagonists competing for estradiol at the receptor complex,[5] suggesting in turn that isoflavones might interact with estrogen receptor genes in the development of breast cancer. However, the possible joint effect of isoflavone intake and polymorphisms in the estrogen receptor genes on the risk of breast cancer has not been investigated.

Here, we conducted hospital-based case-control studies in Nagano, Japan and São Paulo, Brazil, targeting three populations with a substantially different intake of isoflavones and distribution of polymorphisms in the estrogen receptor genes: Japanese living in Japan, Japanese Brazilians living in São Paulo, and non-Japanese Brazilians living in São Paulo. In a previous report, we found a non-significant inverse association between isoflavone intake and the risk of breast cancer in postmenopausal Japanese women but a statistically significant inverse association in Japanese Brazilians and non-Japanese Brazilians.[8] Based on this finding, the present study tested the hypothesis that polymorphisms in estrogen receptor genes may modify the association between isoflavone intake and breast cancer risk.

Materials and Methods

Study subjects. These multicenter, hospital-based case-control studies of breast cancer were designed to determine lifestyle factors and genetic susceptibility to the risk of breast cancer, and to compare potential risk factors among Japanese living in Nagano, Japan, and Japanese Brazilians and non-Japanese Brazilians living in São Paulo, Brazil. Eligible cases were a consecutive series of female patients aged 20–74 years with newly diagnosed and histologically confirmed invasive breast cancer. Patients with cancer were recruited between 2001 and 2005 at four hospitals in Nagano, and between 2001 and 2006 at eight hospitals in São Paulo, totaling 405 patients (98%) in Nagano, and 83 Japanese Brazilians (91%) and 389 non-

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Abbreviations: CI, confidence interval; CYP17, cytochrome P450c17α; CYP19, aromatase; CYP2E1, cytochrome P450 2E1; ESR1, estrogen receptor alpha; ESR2, estrogen receptor beta; FFQ, food-frequency questionnaire; NAT2, N-acetyltransferase 2; OR, odds ratio; SNP, single-nucleotide polymorphism.

doi: 10.1111/j.1349-7006.2009.01118.x

Table 1. Single-nucleotide polymorphisms in estrogen receptor genes and their allele frequency

Gene	SNP rs number	Synonym	Region	Major/minor allele	Minor allele frequency among control groups		
					Japanese living in Nagano, Japan	Japanese Brazilians living in São Paulo, Brazil	Non-Japanese Brazilians living in São Paulo, Brazil
Estrogen receptor alpha gene	rs9340799	XbaI	intron 1	A/G	0.19	0.20	0.31
	rs1913474		intron 3	C/T	0.48	0.48	0.21
	rs2234693	PvuII	intron 1	T/C	0.45	0.45	0.42
Estrogen receptor beta gene	rs4986938	AuII	3'-UTR	G/A	0.14	0.13	0.33
	rs1256049	RsaI	exon 6	G/A	0.30	0.20	0.05

SNP, single-nucleotide polymorphism.

Japanese Brazilians (99%) in São Paulo. In the Nagano study, eligible controls were selected from medical checkup examinees in two of the four hospitals and confirmed not to have cancer. One control was matched for each case by age (within 3 years) and residential area. Among potential controls, one examinee refused to participate and two refused to provide blood samples. Eventually, we obtained written informed consent from 405 matched pairs. In the study in São Paulo, eligible controls were preferentially selected from cancer-free patients who visited the same hospital as the index cases. One control was matched for each patient with cancer by age (within 5 years) and ethnicity. Among potential controls, 22 patients refused to participate (participation rate = 96%). Eventually, we obtained written informed consent from 472 matched pairs (83 for Japanese Brazilians and 389 for non-Japanese Brazilians). The study protocol was approved by Comissão Nacional de Ética em Pesquisa (CONEP), Brasília, Brazil and by the institutional review board of the National Cancer Center, Tokyo, Japan.

Questionnaire. Participants in Nagano were asked to complete a self-administered questionnaire, while those in São Paulo were interviewed by trained interviewers using a structured questionnaire. The two questionnaires contained similar questions concerning demographic characteristics, medical history, family history of cancer, menstrual and reproductive history, anthropometric factors, physical activity and smoking habits. For dietary habits, we used a semiquantitative food frequency questionnaire (FFQ) (136 items for the Japanese version and 118 items for the Brazilian version), which was developed and validated in each population.[9–11] In the FFQ, participants were questioned on how often they consumed the individual food items (frequency of consumption), as well as relative sizes compared to standard portions. Daily food intake was calculated by multiplying frequency by standard portion and relative size for each food item in the FFQ. Daily intakes of genistein and daidzein were calculated using a food composition table of isoflavones developed previously.[12,13] Isoflavone intake was defined for this study as the sum of genistein and daidzein intake. Other nutrients were calculated using the Japanese Standard Tables of Food Composition for the Japanese version,[14] and the United States Department of Agriculture (USDA) food composition tables for the Brazilian version.[15] For some Japanese-specific foods in the Brazilian version, the Japanese Standard Tables of Food Composition[14] was used.

The validity of isoflavone intake estimated from the Japanese version of the FFQ was evaluated in a subsample of the Japan Public Health Center-based Prospective Study by comparing the estimated intake according to the FFQ to that in four consecutive seven-day dietary records, one conducted in each of the four seasons. Spearman's correlation coefficients between energy-adjusted genistein and daidzein intake estimated from the FFQ and from dietary records to be 0.59 for genistein and 0.60 for daidzein.[10] For the Brazilian version, the validity of isoflavone intake estimated from the FFQ was evaluated in a subsample of the control group of this case-control study by comparing the estimated intake according to the FFQ to that in two consecutive four-day dietary records, one each in two seasons. Spearman's correlation coefficients between energy-adjusted genistein and daidzein intake estimated from the FFQ and from dietary records were 0.76 for genistein and 0.76 for daidzein.[11]

Genotyping. Genomic DNA samples were extracted from the peripheral blood using FlexiGene® DNA kits (Qiagen K.K., Tokyo, Japan) according to the manufacturer's protocol. We selected five single nucleotide polymorphisms (SNPs) in the estrogen receptor alpha (*ESR1*) gene (rs9340799, rs1913474, and rs2234693) and estrogen receptor beta (*ESR2*) gene (rs4986938 and rs1256049), which were the most frequently studied SNP in relation to breast cancer risk.[16–20] Genotyping of the five SNPs was performed by a commercial laboratory (Genetic Laboratory, Inc., Sapporo, Japan) using TaqMan® SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA) (Table 1). Patients with cancer and matched controls were analyzed in the same well by laboratory personnel unaware of the case-control status. For quality control assessment, we genotyped six SNPs of four genes (N-acetyltransferase 2 [*NAT2*], cytochrome P450c17α [*CYP17*], aromatase [*CYP19*], and cytochrome P450 2E1 [*CYP2E1*]) in our laboratory using about 24% of the samples in the present study. However, SNPs used in the present study were not included. The concordance rates between Genetic Laboratory Inc. and our laboratory varied between 97.6 and 99.5% among the six SNPs.

Statistical analysis. Comparison of baseline characteristics between cases and controls was evaluated by the Mantel–Haenszel test using matched-pair strata in each population. Genotype frequencies were tested for deviation from the Hardy–Weinberg equilibrium with the χ^2-test. Dietary intake of isoflavones was adjusted for total energy intake by the residual method and divided into median or tertile categories based on control distribution for Japanese and Japanese Brazilians, respectively. Because of the small proportion of consumers, non-Japanese Brazilians were categorized into non-consumers and consumers of isoflavones. Using a conditional logistic regression model, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer for isoflavone intake, SNPs, and the joint effect between isoflavone intake and genotypes. An unconditional logistic regression model was used for stratified analyses according to menopausal status. Linear trends for ORs were tested in the logistic regression model using the exposure categories as ordinal variables. Tests for the interaction were performed based on the difference between two likelihood ratios of the models with and without the interaction terms between isoflavone intake and the SNP of interest. Adjustments were made for the following variables, selected mainly on the basis of comparison of baseline characteristics between patients with cancer and controls, as potential confounders: menopausal status, number of births, family history of breast cancer, smoking status, moderate physical activity in the past 5 years and vitamin

doi: 10.1111/j.1349-7006.2009.01118.x

Table 2. Odds ratios and 95% confidence intervals of breast cancer according to polymorphisms in estrogen receptor genes

	Japanese living in Nagano, Japan				Japanese Brazilians living in São Paulo, Brazil				Non-Japanese Brazilians living in São Paulo, Brazil			
	No.		OR†	95% CI	No.		OR†	95% CI	No.		OR†	95% CI
	Case	Control			Case	Control			Case	Control		
Estrogen receptor alpha gene (rs9340799)												
AA	273	256	1		54	50	1		161	182	1	
AG	103	119	0.68	(0.45–1.02)	22	26	0.75	(0.31–1.84)	175	161	1.16	(0.84–1.59)
GG	12	13	0.75	(0.28–1.98)	3	3	0.68	(0.10–4.57)	43	36	1.27	(0.78–2.07)
AG + GG	115	132	0.69	(0.47–1.02)	25	29	0.74	(0.31–1.79)	218	197	1.18	(0.88–1.59)
Estrogen receptor alpha gene (rs1913474)												
CC	100	113	1		25	24	1		237	239	1	
CT	192	176	1.19	(0.81–1.76)	39	34	1.24	(0.55–2.81)	127	122	1.09	(0.80–1.49)
TT	96	99	1.08	(0.70–1.66)	15	21	0.79	(0.28–2.20)	14	18	0.80	(0.38–1.67)
CT + TT	288	275	1.15	(0.80–1.64)	54	55	1.07	(0.51–2.27)	141	140	1.05	(0.78–1.42)
Estrogen receptor alpha gene (rs2234693)												
TT	144	115	1		25	22	1		107	122	1	
TC	180	196	**0.70**	**(0.49–0.995)**	39	43	0.66	(0.29–1.47)	187	194	0.99	(0.68–1.43)
CC	64	77	0.64	(0.40–1.02)	15	14	0.93	(0.31–2.86)	85	63	1.51	(0.98–2.31)
TC + CC	244	273	**0.68**	**(0.49–0.96)**	54	57	0.71	(0.32–1.54)	272	257	1.15	(0.83–1.61)
Estrogen receptor beta gene (rs4986938)												
GG	289	281	1		59	60	1		169	176	1	
GA	94	102	0.88	(0.59–1.31)	17	17	1.32	(0.53–3.31)	163	154	1.09	(0.78–1.51)
AA	5	5	1.53	(0.39–6.07)	3	2	0.71	(0.09–5.57)	47	49	0.93	(0.59–1.47)
GA + AA	99	107	0.91	(0.62–1.34)	20	19	1.22	(0.51–2.93)	210	203	1.05	(0.77–1.42)
Estrogen receptor beta gene (rs1256049)												
GG	203	182	1		47	48	1		342	345	1	
GA	161	178	0.79	(0.56–1.10)	26	30	0.95	(0.46–1.98)	36	32	1.21	(0.71–2.04)
AA	24	28	0.84	(0.44–1.60)	6	1	4.80	(0.50–46.19)	1	2	0.54	(0.04–6.53)
GA + AA	185	206	0.79	(0.57–1.09)	32	31	1.04	(0.50–2.13)	37	34	1.16	(0.70–1.94)

†Conditional model adjusting for menopausal status (premenopausal, postmenopausal), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no). ORs and 95% CIs with statistical significance are written in bold letter. CIs, confidence intervals; OR, odds ratio.

supplement use. We did not include a history of benign breast disease as a covariate since we regarded it as an intermediate variable in the causal pathway between isoflavone intake and breast cancer. All *P*-values reported are two-sided, and significance level was set at $P < 0.05$. All statistical analyses were performed with SAS version 9.1 software (SAS Institute, Inc., Cary, NC, USA).

Results

We excluded subjects who reported extremely low or high total energy intake (<500 or ≥4000 kCal) or had no DNA sample, leaving 388 pairs of Japanese, 79 pairs of Japanese Brazilians and 379 pairs of non-Japanese Brazilians for inclusion in the present analyses.

Characteristics of patients with cancer and controls are shown in a previous report (data not shown in table).[8] For Japanese women, the proportion of premenopausal women, current smokers, and vitamin supplement users was higher in cases than in controls, and patients with cancer tended to have a family history of breast cancer and history of benign breast disease. Patients with cancer were less likely than controls to breast-feed, be physically active and eat vegetables. For Japanese Brazilians, patients with cancer were less likely than controls to give birth and be physically active, and more likely to eat vegetables and fruits. For non-Japanese Brazilians, the proportion of premenopausal women and current smokers was higher in patients with cancer than controls, while the proportion of physically active women and vitamin supplement users was lower. Isoflavone intake substantially varied among populations, with mean intakes in control subjects of 46.2 mg/day for Japanese, 23.5 mg/day for Japanese Brazilians, and 4.4 mg/day for non-Japanese Brazilians.

The distributions of SNPs in the *ESR1* gene (rs9340799, rs1913474 and rs2234693) and *ESR2* gene (rs4986938 and rs1256049) are shown in Tables 1 and 2. No deviation from the Hardy–Weinberg equilibrium was observed among the controls in any population. The prevalence of the minor allele in the rs9340799 and rs4986938 polymorphisms was lower in the control group of Japanese and Japanese Brazilians than in that of non-Japanese Brazilians, while that of the minor allele in the rs1913474 and rs1256049 polymorphisms was higher in the control group of Japanese and Japanese Brazilians. We found a decreased risk of breast cancer among Japanese women with at least one minor allele of the rs9340799 or rs2234693 polymorphism in comparison with those with the major allele homozygote, but not among Japanese Brazilian and non-Japanese Brazilian women. This decrease was statistically significant for the rs2234693 polymorphism but not for the rs9340799 polymorphism. Stratified analyses by menopausal status showed that this decreased risk occurred primarily among postmenopausal Japanese for both SNPs (data not shown). In contrast, no association was observed for the rs1913474, rs4986938, or rs1256049 polymorphisms in the three populations, regardless of menopausal status.

Analyses of combinations of isoflavone intake and the rs4986938 polymorphism in the *ESR2* gene revealed that the risk of breast cancer significantly decreased with increasing isoflavone intake only among women with the GG genotype among postmenopausal Japanese (OR for highest *versus* lowest tertile = 0.47; 95%CI 0.27–0.84; *P* for trend = 0.01), Japanese Brazilians (OR for highest *versus* lowest median = 0.31; 95%CI 0.12–0.78), and non-Japanese Brazilians (OR for consumers *versus* non-consumers = 0.37; 95%CI

Table 3. Odds ratios and 95% confidence intervals of breast cancer for combinations of dietary intake of isoflavones and polymorphisms in estrogen receptor genes among Japanese

	All subjects				Premenopausal women				Postmenopausal women			
	Isoflavone intake (mg/day), tertile category			P for trend	Isoflavone intake (mg/day), tertile category			P for trend	Isoflavone intake (mg/day), tertile category			P for trend
	1	2	3		1	2	3		1	2	3	
Estrogen receptor alpha gene (rs9340799)												
AA												
No.†	109/83	76/90	88/83		54/41	30/31	33/19		55/42	46/59	55/64	
OR‡	1	0.73	0.78	0.32	1	0.68	1.13	0.96	1	0.75	0.64	0.15
(95% CI)		(0.45–1.18)	(0.47–1.29)			(0.34–1.35)	(0.53–2.39)			(0.41–1.34)	(0.36–1.15)	
AG + GG												
No.†	42/46	42/39	31/47		25/25	22/12	12/7		17/21	20/27	19/40	
OR‡	**0.52**	0.68	0.51	0.75	0.64	1.38	1.13	0.54	0.59	0.56	**0.38**	0.15
(95% CI)	**(0.27–0.99)**	(0.37–1.24)	(0.26–1.01)		(0.31–1.35)	(0.59–3.23)	(0.39–3.30)		(0.26–1.32)	(0.26–1.20)	**(0.18–0.79)**	
	P for interaction = 0.39				P for interaction = 0.15				P for interaction = 0.87			
Estrogen receptor alpha gene (rs1913474)												
CC												
No.†	41/38	32/42	27/33		20/16	16/12	13/4		21/22	16/30	14/29	
OR‡	1	0.68	0.76	0.62	1	1.15	2.39	0.08	1	0.60	0.47	0.09
(95% CI)		(0.34–1.36)	(0.37–1.59)			(0.40–3.26)	(0.61–9.30)			(0.24–1.47)	(0.18–1.21)	
CT + TT												
No.†	110/91	86/87	92/97		59/50	36/31	32/22		51/41	50/56	60/75	
OR‡	0.97	0.97	0.84	0.33	0.91	0.86	0.97	0.99	1.20	1.08	0.80	0.14
(95% CI)	(0.54–1.74)	(0.55–1.72)	(0.45–1.55)		(0.41–2.02)	(0.37–2.04)	(0.39–2.44)		(0.56–2.59)	(0.51–2.29)	(0.38–1.68)	
	P for interaction = 0.69				P for interaction = 0.58				P for interaction = 0.73			
Estrogen receptor alpha gene (rs2234693)												
TT												
No.†	58/36	38/41	48/38		33/21	12/16	21/11		25/15	26/25	27/27	
OR‡	1	0.55	0.68	0.54	1	0.41	1.15	0.77	1	0.79	0.58	0.28
(95% CI)		(0.26–1.16)	(0.32–1.43)			(0.15–1.12)	(0.43–3.10)			(0.32–1.92)	(0.24–1.40)	
TC + CC												
No.†	93/93	80/88	71/92		46/45	40/27	24/15		47/48	40/61	47/77	
OR‡	**0.51**	**0.52**	**0.42**	0.46	0.64	0.99	0.86	0.39	0.54	**0.42**	**0.35**	0.14
(95% CI)	**(0.28–0.96)**	**(0.28–0.98)**	**(0.21–0.82)**		(0.31–1.34)	(0.45–2.16)	(0.35–2.15)		(0.24–1.21)	**(0.19–0.92)**	**(0.16–0.76)**	
	P for interaction = 0.37				P for interaction = 0.08				P for interaction = 0.97			
Estrogen receptor beta gene (rs4986938)												
GG												
No.†	115/86	88/96	86/99		57/46	39/32	32/21		58/40	49/64	54/78	
OR‡	1	0.74	0.65	0.06	1	0.96	1.03	0.94	1	0.60	**0.47**	**0.01**
(95% CI)		(0.47–1.16)	(0.39–1.07)			(0.51–1.83)	(0.49–2.15)			(0.33–1.07)	**(0.27–0.84)**	
GA + AA												
No.†	36/43	30/33	33/31		22/20	13/11	13/5		14/23	17/22	20/26	
OR‡	0.57	0.78	0.90	0.23	0.80	0.91	1.99	0.20	0.47	0.80	0.62	0.49
(95% CI)	(0.31–1.08)	(0.40–1.50)	(0.45–1.82)		(0.37–1.72)	(0.35–2.34)	(0.62–6.46)		(0.21–1.06)	(0.36–1.75)	(0.28–1.35)	
	P for interaction = 0.17				P for interaction = 0.48				P for interaction = 0.11			
Estrogen receptor beta gene (rs1256049)												
GG												
No.†	85/62	59/62	59/58		43/32	28/20	23/12		42/30	31/42	36/46	
OR‡	1	0.74	0.82	0.16	1	1.05	0.98	0.80	1	0.56	0.51	0.08
(95% CI)		(0.43–1.27)	(0.46–1.48)			(0.49–2.27)	(0.39–2.47)			(0.28–1.13)	(0.26–1.01)	
GA + AA												
No.†	66/67	59/67	60/72		36/34	24/23	22/14		30/33	35/44	38/58	
OR‡	0.70	0.74	0.61	0.93	0.79	0.78	1.31	0.20	0.50	0.60	**0.41**	0.35
(95% CI)	(0.41–1.19)	(0.43–1.27)	(0.35–1.07)		(0.39–1.58)	(0.36–1.69)	(0.55–3.08)		(0.24–1.03)	(0.31–1.18)	**(0.21–0.80)**	
	P for interaction = 0.63				P for interaction = 0.65				P for interaction = 0.31			

†No. of patients with cancer/No. of controls.
‡Conditional model adjusting for menopausal status (premenopausal, postmenopausal), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smoker), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no). For stratified analyses according to menopausal status, an unconditional model adjusting for age, area, number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smoker), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no). ORs and 95% CIs with statistical significance are written in bold letter. CIs, confidence intervals; OR, odds ratio.

0.16–0.85) (*P* for interaction = 0.11, 0.08 and 0.21, respectively) (Tables 3 and 4). Moreover, we found no remarkable difference in the association between isoflavone intake and breast cancer risk by the four other polymorphisms.

Discussion

In these case-control studies of Japanese, Japanese Brazilians, and non-Japanese Brazilians, we found that a statistically significant

doi: 10.1111/j.1349-7006.2009.01118.x

Table 4. Odds ratios and 95% confidence intervals of breast cancer for combinations of dietary intake of isoflavones and polymorphisms in estrogen receptor genes among Japanese Brazilian and non-Japanese Brazilian subjects

	Japanese Brazilians living in São Paulo, Brazil		Non-Japanese Brazilians living in São Paulo, Brazil	
	Isoflavone intake (mg/day), median category		Isoflavone intake (mg/day)	
	1	2	Non-consumers	Consumers
Estrogen receptor alpha gene (rs9340799)				
AA				
No.†	31/21	23/29	145/157	16/25
OR‡	1	**0.36**	1	0.68
(95% CI)		**(0.14–0.95)**		(0.32–1.43)
AG + GG				
No.†	15/18	10/11	198/161	20/36
OR‡	0.44	0.34	1.23	0.61
(95% CI)	(0.14–1.45)	(0.09–1.32)	(0.89–1.68)	(0.33–1.13)
	P for interaction = 0.36		*P* for interaction = 0.52	
Estrogen receptor alpha gene (rs1913474)				
CC				
No.†	13/12	12/12	213/204	24/35
OR‡	1	0.76	1	0.65
(95% CI)		(0.18–3.18)		(0.36–1.19)
CT + TT				
No.†	33/27	21/28	129/114	12/26
OR‡	1.25	0.55	1.13	0.49
(95% CI)	(0.42–3.72)	(0.17–1.78)	(0.82–1.56)	(0.24–1.01)
	P for interaction = 0.52		*P* for interaction = 0.40	
Estrogen receptor alpha gene (rs2234693)				
TT				
No.†	17/12	8/10	97/106	10/16
OR‡	1	0.41	1	0.57
(95% CI)		(0.10–1.65)		(0.22–1.47)
TC + CC				
No.†	29/27	25/30	246/212	26/45
OR‡	0.65	0.36	1.20	0.65
(95% CI)	(0.23–1.84)	(0.12–1.08)	(0.84–1.71)	(0.37–1.15)
	P for interaction = 0.71		*P* for interaction = 0.94	
Estrogen receptor beta gene (rs4986938)				
GG				
No.†	38/30	21/30	156/148	13/28
OR‡	1	**0.31**	1	**0.37**
(95% CI)		**(0.12–0.78)**		**(0.16–0.85)**
GA + AA				
No.†	8/9	12/10	156/170	23/33
OR‡	0.62	0.97	0.97	0.68
(95% CI)	(0.16–2.35)	(0.31–3.01)	(0.70–1.35)	(0.37–1.24)
	P for interaction = 0.08		*P* for interaction = 0.21	
Estrogen receptor beta gene (rs1256049)				
GG				
No.†	27/23	20/25	308/286	34/59
OR‡	1	0.49	1	**0.55**
(95% CI)		(0.21–1.17)		**(0.35–0.90)**
GA + AA				
No.†	19/16	13/15	35/32	2/2
OR‡	0.97	0.53	1.10	0.84
(95% CI)	(0.36–2.58)	(0.18–1.58)	(0.64–1.87)	(0.10–6.97)
	P for interaction = 0.89		*P* for interaction = 0.78	

†No. of patients with cancer/No. of controls.
‡Conditional model adjusting for menopausal status (premenopausal, postmenopausal), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no). ORs and 95% CIs with statistical significance are written in bold letter. CIs, confidence intervals; OR, odds ratio.

inverse association between isoflavone intake and breast cancer risk appeared only among women with the GG genotype of the rs4986938 polymorphism in the *ESR2* gene, but the interaction was not statistically significant. Our findings support the hypothesis that polymorphisms in the *ESR2* gene may modify the association between isoflavone intake and breast cancer risk.

To date, many studies investigating the possible effect of SNPs in the *ESR2* gene on breast cancer risk have focused on the

rs4986938 and rs1256049 polymorphisms, although their functional importance has yet to be clarified. Here, we found no association between either SNP and the risk of breast cancer, which is in general agreement with most previous studies.[16,17] In contrast, we did see an inverse association between isoflavone intake and breast cancer risk with the rs4986938 polymorphism in three populations, but only among women with the GG genotype. We also saw a suggestive interaction in the case-control studies of Japanese and Japanese Brazilians but not in the case-control study of non-Japanese Brazilians. Although the reason for the inconsistency in interactions among populations remains unclear, it might reflect the amount of intake, on the basis that the findings were relatively consistent among the populations with a high intake (Japanese and Japanese Brazilians). Moreover, the prevalence of the GG genotype of the rs4986938 polymorphism among the control group was higher in Japanese (72.4%) and Japanese Brazilians (75.9%) than in non-Japanese Brazilians (46.4%). This might partly explain the previous inconsistencies in results for isoflavone exposure and breast cancer risk between Asian and Western populations.[4]

To our knowledge, only two studies have investigated interactions between phytoestrogen exposure and polymorphisms in the *ESR2* gene in the risk of hormone-related diseases.[21,22] Hedelin *et al.* reported a significant interaction between phytoestrogen intake and a promoter SNP in the *ESR2* gene (rs2987983) in the risk of prostate cancer in a population-based case-control study in Sweden.[22] Tsuchiya *et al.* reported a significant interaction between urinary genistein level and RsaI polymorphism in the *ESR2* gene in the risk of advanced endometriosis among infertile Japanese women.[21] These findings suggest that isoflavones may reduce the risk of hormone-related diseases via a mechanism that involves estrogen receptor beta. Considering that functional data are not presently available, our finding suggests that the rs4986938 polymorphism, or some other genetic variants in strong linkage disequilibrium with this SNP, modify the protective effect of isoflavones on breast cancer. In this regard, we provide further evidence for a role of isoflavones in the development of breast cancer.

We found a decreased risk of breast cancer among Japanese women with at least one minor allele of the rs9340799 or rs2234693 polymorphism in comparison with those with the major allele homozygote. Although these are the most frequently studied SNPs, results have been inconsistent.[18–20] Most studies have shown no association between the rs2234693 polymorphism and breast cancer risk.[18–20] On the other hand, several but not all studies have reported that the G allele of the rs9340799 polymorphism was associated with a decreased risk of breast cancer,[18,20] which is consistent with our findings in Japanese women. Since we failed to observe an overall consistency of findings in our three populations, however, our findings in Japanese women might be merely due to chance.

Although interactions between phytoestrogen exposure and polymorphisms in the *ESR1* gene in the risk of breast cancer have not been investigated, we are aware of two studies examining interactions on circulating sex hormone levels.[23,24] In their study of 125 postmenopausal women in the European Prospective Investigation of Cancer and Nutrition–Norfolk cohort, Low *et al.* reported that urinary and serum isoflavones were negatively correlated with plasma estradiol among women with the CC genotype for PvuII polymorphism in the *ESR1* gene, but not those with other genotypes.[23] Moreover, they reported a significant interaction between urinary lignans and rs9340835 polymorphism in the *ESR1* gene, affecting plasma estrone levels in a cross-sectional study of 1988 healthy postmenopausal women from the same cohort.[24] Although these studies imply the presence of gene–nutrient interaction, we found no remarkable difference in the association between isoflavone intake and breast cancer risk by polymorphisms in the *ESR1* gene. Further studies based on a comprehensive evaluation of this gene would clarify this gene–nutrient interaction.

Our study has methodological advantages over studies conducted previously. First, and unique to this study, we assessed gene–nutrient interactions using three populations with substantially different isoflavone intakes and allele frequencies of SNPs. For example, isoflavone intake differed considerably among the three populations, with median levels (interquartile range) in the control group of (mg/day) 40.7 (25.8–61.4) among Japanese, 13.4 (7.9–31.1) among Japanese Brazilians, and 0 (0–0) among non-Japanese Brazilians. In addition, allele frequency also differed among the populations, such as that of the G allele of the rs4986938 polymorphism in the *ESR2* gene, at 0.86 for Japanese, 0.87 for Japanese Brazilians, and 0.67 for non-Japanese Brazilians. Second, the overall consistency of findings in the three populations could allow the results to be more generalized than those from a single population.

Several limitations of the study also warrant mention. First, dietary intake of isoflavones was assessed after the diagnosis of breast cancer, and therefore, is sensitive to recall bias. Second, although the substantially high participation rates among both eligible patients with cancer and controls minimized potential biases related to control selection, the use of controls from medical checkup examinees and cancer-free patients, whose dietary habits may differ from those of the general population due to health consciousness or disease, might have led to selection bias. For example, isoflavone intake was higher among women aged 50–69 years in the control group of the Nagano study (median intake = 46.3 mg/day) than in participants aged 50–69 years living in Nagano in the 10-year follow-up survey of the Japan Public Health Center-based Prospective Study (median intake = 38.8 mg/day), which used a similar FFQ and had a high response rate. Third, the evaluation of gene–nutrient interactions was performed in a relatively small number of patients with cancer. The interpretability of our results might therefore be limited.

Allowing for these methodological issues, we found a suggestive interaction between isoflavone intake and the rs4986938 polymorphism of the *ESR2* gene in the risk of breast cancer in case-control studies of Japanese and Japanese Brazilians. Our findings support the hypothesis that polymorphisms in the *ESR2* gene may modify the association between isoflavone intake and breast cancer risk. Further, they provide additional evidence that the mechanisms by which isoflavones may reduce the risk of breast cancer might involve estrogen receptor beta.

Acknowledgments

This study was supported by a Grant-in-Aid for Research on Risk of Chemical Substances from the Ministry of Health, Labour and Welfare of Japan, and Grants-in-Aid for Scientific Research on Priority Areas (17015049) and for Young Scientists (B) (17790378 and 19790415) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Japan Society for the Promotion of Science.

We are grateful to the members of the São Paulo-Japan Breast Cancer Study Group: S. Ikeda and C. Nishimoto (Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo); C.I. Yamaguchi, C.M. Kunieda, and S.S. Sugama (Nikkei Disease Prevention Center, São Paulo); C.K. Taniguchi and J.A. Marques (Departamento de Ginecologia, Hospital Pérola Byington, São Paulo); M.R. Eichhorn (Departamento de Nutrição, Hospital Pérola Byington, São Paulo); H. Iyeyasu, M.S. Maciel, S.M.T. Carvalho, J.B.D. Collins, and C.E.M. Fontes (Departamento de Mastologia, Hospital A.C. Camargo, São Paulo); L.P. Kowalski and J.M.F. Toyota (Departamento de Cirurgia de Cabeça e Pescoço e Otorrinolaringologia, A.C. Camargo Hospital, São Paulo); E.M. Barbosa (Departamento de Mastologia, Instituto Brazileiro de Controle ao Câncer, São Paulo); O. Ferraro (Departamento de Mastologia, Hospital do Servidor Público Estadual Francisco Morato de Oliveira, São Paulo); R. Anzai (Departamento de Mastologia, Hospital Santa Cruz); E.H. Hotta and D.A. Petti (Instituto de Ginecologia e Mastologia, Hospital Beneficencia Portuguesa); and S. Mendes (Instituto Brazileiro de Mastologia e Ginecologia, Hospital Beneficencia Portuguesa).

doi: 10.1111/j.1349-7006.2009.01118.x

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Current Organ Topics:

Breast and Endocrine Tumor
乳腺・内分泌 腫瘍

Ⅲ. 乳がんのリスクファクター 世界のエビデンスと日本のエビデンス

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〔*Jpn J Cancer Chemother* 35(13): 2351-2356, *December*, 2008〕

1．乳がんの動向

乳がんは世界的にみても女性の最も多いがんであり，International Agency for Research on Cancer（IARC，国際がん研究機関）の推計によると，2002年に新たに115万人が罹患している。また，女性のがんによる死亡の第1位となっており，2002年における女性乳がん死亡者数は41万人であった[1]。

欧米諸国のなかには，罹患率の増加に歯止めがかかり，死亡率の減少がみられる国もあるが，日本ではいまだに罹患率（粗罹患率，年齢調整罹患率），死亡率（粗死亡率，年齢調整死亡率）ともに増加している。地域がん登録による推計では，2002年における全国の乳がん粗罹患率は人口10万対64.4人と大腸がんに次いで2番目に高く（大腸がんを結腸がんと直腸がんに分けると乳がんが最も高い），年齢調整罹患率では，人口10万対52.2人と，乳がんが女性のがんにおいて最も高くなっている[2]。乳がんは他のがんに比べ比較的予後のよいがんであるが，人口動態統計によると，2006年の女性の乳がん死亡者数は11,177人であり，粗死亡率は人口10万対17.3人と，大腸がん，胃がん，肺がん，肝臓がんに次いで高い。また，年齢調整死亡率では人口10万対11.7人と，大腸がん，胃がん，肺がんに次いで高くなっている[3]。

年齢調整罹患率でみると，日本人の乳がんは増加傾向にあるものの，日本を含む東アジアの人々の乳がんは国際的には依然として少なく，米国白人やヨーロッパ人などに比べ罹患率は低い。また，アメリカに移住した日系人の移民の罹患率は，移住国の罹患率に近くなり，日本に住む日本人よりも高くなっている[4]。このことからも，乳がん罹患率における国際的な違いは，生活習慣など環境要因が強く影響していることが示唆される。そのため，乳がん予防において，食事や栄養，身体活動などの生活習慣が注目されてきた。そこで本稿では，乳がんのリスクファクターとしてこれら生活習慣に焦点を当て，世界と日本のエビデンスレビューを紹介する。

2．世界におけるエビデンス

世界におけるエビデンスについては，World Cancer Research Fund（WCRF，世界がん研究基金）/American Institute for Cancer Research（AICR，米国がん研究財団）が食事，栄養，身体活動に関してレビューを行っている。本稿では，2007年11月に出版された報告書"Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective"[5]の内容を紹介したい。

この報告書の前に発行されたFirst reportである"Food, Nutrition and the Prevention of Cancer: a Global Perspective"はがんと食事に関する疫学研究を中心に論文のレビューを行い，がんを予防するための食事の勧告を全世界に向けて策定し，発信した。このなかで特に野菜や果物ががん予防にはきわめて重要であることが示されている。First reportは1997年に発行されて以来10年の間，がんと食事に関する最も権威と影響力のある報告とされてきた。また，政府関係者や医療従事者，研究者などの標準的なテキストとして，広く世界中で用いられてきた。

この分野における論文が劇的に増加したことや，エビデンスの分析や評価における新たな方法が開発されたことにともない，Second reportであるこの報告書が作成された。この報告書では，食事や栄養に加えて，前回には取り上げられなかった体格や身体活動についても検討が行われ，過体重や肥満，身体活動量の少なさががんのリスクファクターとなることが強調されている。

報告書の作成にあたっては，評価の客観性と透明性を最大限にするために，エビデンスの収集と，評価および判定とを分けて行った。具体的なプロセスは下記のとおりである。1）専門家委員会により，膨大な科学論文のシステマティックレビューを行う方法を作成，2）作成された方法論に基づき，リサーチチームが文献の収集とレビューを行う，3）専門家パネルがエビデンスと推奨の評価と判定を行う。

構成は，まず要約（Summary）に全体像が述べられており，Part 1の背景（Background）では，がんに関する統計や国際比較，エビデンスの判定などについて書かれている。Part 2のエビデンスと判定（Evidence and

表 1 WCRF/AICR による食事，栄養，身体活動と乳がんとの関連（閉経前）

	リスクを減少させるもの	リスクを上昇させるもの
Convincing（確実）	授乳	アルコール摂取
Probable（ほぼ確実）	体脂肪（肥満）	成人期の身長[a] 出生時体重の大きさ
Limited-suggestive（可能性あり）	身体活動[b]	
Limited-no conclusion（証拠不十分）	穀類と穀類製品，食物繊維，芋類，野菜，果物，マメ科の植物（マメ類），大豆と大豆製品，肉，鶏肉，魚，卵，牛乳と乳製品，脂質，総食物脂肪，植物性脂肪，脂肪酸組成，トランス脂肪酸，コレステロール，砂糖（スクロース），その他の糖類，糖類を含む食品と飲み物，コーヒー，紅茶，炭水化物，でんぷん，グリセミックインデックス（GI），プロテイン，ビタミン A，リボフラビン，ビタミン B6，葉酸，ビタミン B12，ビタミン C，ビタミン D，ビタミン E，カルシウム，鉄分，セレン，カロテノイド，イソフラボン，ジクロロジフェニルジクロロエチレン（DDE），ジヒドロジフェニルトリクロロエタン（DDT），ディルドリン，ヘキサクロロベンゼン，ヘキサクロロシクロヘキサン，トランス-ノナクロル，ポリ塩化ビフェニール類(PCB)，食事パターン，文化的に規定される食事，成人後の体重の増加，エネルギー摂取，母乳で育てられること	
Substantial effects on risk unlikely（大きな関連なし）	特定されるものはない	

a）成人期の身長はがんのリスクに直接影響するものではおそらくない。成人期の身長は，受胎前から成人までの成長期間における，成長に影響する遺伝的，環境的，ホルモン的，栄養的な要因のマーカーである。
b）すべての身体活動：仕事，家事，移動，余暇

出典：World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. http://www.dietandcancerreport.org/（Accessed October 12, 2008）

Judgments）では，食事，飲酒，運動，体型，肥満などのリスクやがんの部位別のリスク，がんサバイバーの予後などについて述べられている。Part 3 の推奨（Recommendations）では，公衆衛生上の目標や推奨について述べられている。

がんサバイバーについても，研究が行われ始めているが，エビデンスの判定に十分な結果は得られていない。しかし，定期的な身体活動などにより体重を維持することは，少なくとも乳がんにとっては再発を防ぐ可能性もあり，また一般的な健康にもよいと記載されている。

報告書では最後に，レビュー結果に基づき，がん予防に有用な 10 の推奨事項が示されている。

推奨 1 体脂肪：適正体重の範囲内で，体重をできるだけ少なめに維持する

推奨 2 身体活動：毎日の生活の中で身体活動を活発に行う

推奨 3 体重増加を促進する食品と飲料：エネルギー密度の高い食品の摂取を制限し，砂糖入り飲料を避ける

推奨 4 植物性食品：植物性食品を多く摂取する

推奨 5 動物性食品：赤身肉の摂取を制限し，加工肉製品は避ける

推奨 6 アルコール飲料：アルコール飲料を制限する

推奨 7 保存，加工，調理：食塩の摂取を減らす．カビの生えた穀類や豆類は避ける

推奨 8 サプリメント：必要な栄養素は食事のみから摂取する

推奨 9 授乳：母親が授乳を行うことも，子どもが母乳で育てられることも重要である

推奨 10 がんサバイバー：がんサバイバーはがん予防のための推奨に従う

以下では，報告書のなかで乳がんのリスクファクターについて具体的に取り上げている部分を紹介する。

乳がんはホルモン関連がんであり，閉経前に診断される場合と閉経後に診断される場合（閉経後に診断される方が多い）で，リスクファクターは同じではない。そのため，リスクファクターに関しては閉経前乳がん，閉経後乳がんに分けられている。

パネルの判定結果のまとめを，閉経前乳がんについては表 1，閉経後乳がんについては表 2 に示す。

1）ホルモン関連

授乳が乳がんリスクを低減することは，閉経前後を問