(CIs) of breast cancer for isoflavone intake. An unconditional logistic regression model was used for stratified analyses according to menopausal status. Associations between isoflavone intake and hormone receptor-defined breast cancer were assessed by an unconditional polytomous logistic regression model. Linear trends for ORs were tested in the logistic regression model using the exposure categories as ordinal variables. The following variables, which were mainly selected based on comparison of baseline characteristics between cases and controls, were adjusted for 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 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 software version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of cases and controls and isoflavone intake (Table 1)

For Japanese, the proportion of premenopausal women, current smokers, and vitamin supplement users was higher in cases than in controls, and cases tended to have a family history of breast cancer and history of benign breast disease. Cases were less likely than controls to breast-feed, be physically active, and eat vegetables. For Japanese Brazilians, cases 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 cases than controls while the proportion of physically active women and vitamin supplement users was lower. Isoflavone intake substantially varied among populations, with mean intakes (mg/day) in control subjects of 46.1 for Japanese, 24.9 for Japanese Brazilians, and 4.4 for non-Japanese Brazilians. Because genistein and daidzein intakes were highly correlated, with a Spearman's correlation coefficient for the three populations of 0.99, only isoflavone intake was used for the following analyses.

ORs in the three populations (Table 2)

We found a statistically significant inverse association between isoflavone intake and the risk of breast cancer for Japanese Brazilians and non-Japanese Brazilians but not for Japanese. Adjusted OR for the highest versus lowest tertile of isoflavone intake was 0.25 (95% CI 0.09–0.68; P for trend <0.01) for Japanese Brazilians. For non-Japanese Brazilians, adjusted OR for consumers versus non-consumers of isoflavones was 0.56 (95% CI 0.35–0.90). No substantial change was seen after further adjustment for other potential confounders, such as age at menarche, age at menopause, age at first birth, history of breast feeding, body mass index, alcohol drinking, or vegetable and fruit intake.

A stratified analysis according to menopausal status revealed that an inverse association was limited to postmenopausal women in Japan although it was not statistically significant. Adjusted OR for the highest versus lowest tertile of isoflavone intake was 0.62 (95% CI 0.38–1.01; P for trend = 0.06) for postmenopausal women, but 1.35 (95% CI 0.72–2.54; P for trend = 0.41) for premenopausal women. The inverse association was stronger in premenopausal than postmenopausal women for Japanese Brazilians but no remarkable difference between the two strata was seen for non-Japanese Brazilians.

ORs of hormone receptor-defined breast cancer (Table 3)

Information on the combined ER and PR status of the breast tumor was available for 387 (99%) Japanese, 61 (75%) Japanese Brazilians, and 264 (70%) non-Japanese Brazilians cases. The following subtypes were used for modeling in an unconditional polytomous logistic regression model: positive for both receptors (ER+/PR+), ER-positive and PR-negative (ER+/PR−), and negative for both receptors (ER−/PR−) for Japanese, and ER+/PR+, ER+/PR−, ER−/PR−, and unknown for Japanese Brazilians and non-Japanese Brazilians. Overall, we found no remarkable difference in risk by hormone receptor-defined subtype.

Dose–response pattern (Table 4; Fig. 1)

To evaluate dose–response relations using a wide range of isoflavone intake, we combined individual study data from three populations and categorized the subjects into six groups, namely non-consumers and quintiles among isoflavone consumers based on the combined control distribution. Compared to non-consumers, adjusted ORs (95% CI) for consumers in increasing quintile categories (median intake in each category: 8.7, 23.1, 33.8, 45.7, and 71.3 mg/day) based on a conditional logistic regression model were 0.69 (0.44–1.09), 0.54 (0.31–0.94), 0.45 (0.26–0.77), 0.34 (0.19–0.62), and 0.43 (0.24–0.76), respectively. A stratified analysis according to menopausal status based on an unconditional logistic regression model revealed that this inverse association was more prominent in postmenopausal

Table 1 Characteristics of case and matched control subjects

	Japanese living in Nagano, Japan			Japanese Brazilians living in São Paulo, Brazil			Non-Japanese Brazilians living in São Paulo, Brazil		
	Case ($n = 390$)	Control ($n = 390$)	P^a	Case ($n = 81$)	Control ($n = 81$)	P^a	Case ($n = 379$)	Control ($n = 379$)	P^a
Age (years), mean	53.8	54.0	–	56.6	56.5	–	52.4	52.5	–
Premenopausal women, %	46	35	<0.01	31	30	0.80	42	38	0.04
Age at menopause (years), mean[b]	49.0	49.4	0.15	49.9	50.6	0.73	49.1	48.4	0.13
Age at menarche (years), mean[b]	13.4	13.2	0.42	12.9	12.9	0.20	13.2	13.1	0.96
Nulliparous women, %	13	14	0.66	23	16	0.24	11	10	0.91
Number of births (≥4 births), %	2	3	0.16	7	20	0.02	29	35	0.10
Age at first birth (years), mean[b, c]	26.9	26.4	0.42	28.6	27.5	0.25	23.2	22.5	0.24
Breast feeding (yes), %[c]	91	96	0.03	92	91	0.56	88	91	0.67
Oral contraceptives user, %	3	3	1.00	29	36	0.30	63	65	0.62
Family history of breast cancer, %	11	6	0.02	15	12	0.65	6	6	0.88
History of benign breast disease, %	12	7	0.03	12	6	0.17	7	7	1.00
Height (cm), mean[b]	155.3	155.5	0.50	154.0	153.9	0.91	158.2	158.4	0.96
Body mass index (kg/m^2), mean[b]	22.7	23.0	0.07	24.3	24.5	0.43	26.6	26.1	0.11
Smoking (current smoker), %	8	5	<0.01	11	2	0.07	17	11	0.04
Alcohol drinking (regular drinker), %	26	29	0.25	2	6	0.26	6	6	0.65
Moderate physical activity past 5 years (yes), %	32	40	0.02	19	32	0.03	9	14	0.03
Vitamin supplement user, %	18	12	0.03	19	26	0.27	3	9	<0.01
Total energy intake (kcal/day), mean[b]	1881.6	1949.3	0.27	1662.0	1587.7	0.44	1847.0	1752.8	0.09
Fish and shellfish intake (g/day), mean[b]	87.6	94.4	0.11	27.4	30.5	0.56	13.7	16.6	0.24
Meat or red meat intake (g/day), mean[b, d]	58.1	57.6	0.36	54.3	53.3	0.44	72.1	64.2	0.14
Vegetable intake (g/day), mean[b]	257.6	310.5	<0.01	146.7	93.0	<0.01	77.7	86.4	0.96
Fruit intake (g/day), mean[b]	288.6	287.7	0.69	364.0	311.0	0.02	260.2	250.9	0.35
Isoflavone intake (mg/day), mean[b]	43.5	46.1	<0.01	16.5	24.9	0.15	1.1	4.4	0.01
Genistein intake (mg/day), mean[b]	27.0	28.6	<0.01	10.2	15.8	0.15	0.73	3.1	0.01
Daidzein intake (mg/day), mean[b]	16.5	17.5	<0.01	6.3	9.1	0.15	0.33	1.4	0.01

[a] P for Mantel-Haenszel test with matched-pair strata

[b] Adjusted for age

[c] Among parous women

[d] Meat intake for Japanease and red meat intake for Japanese Brazilians and non-Japanese Brazilians

than premenopausal women. To clarify the effect of high isoflavone intake in detail, subjects were further categorized into 11 groups, namely non-consumers and deciles of isoflavone consumers. We found a linear decrease in breast cancer risk from zero to moderate intake (20–30 mg/day) and a leveling-off thereafter based on a conditional logistic regression model (Fig. 1). No increasing trend was found for relatively high intake.

Discussion

In these case–control studies of Japanese, Japanese Brazilians, and non-Japanese Brazilians, overall, we found an inverse association between dietary isoflavone intake and the risk of breast cancer. Our finding is in general agreement with those of a recent meta-analysis [11] and in five of the ten previous studies examining the association between isoflavone intake as estimated by FFQ and breast cancer risk [4–8]. It is noteworthy that, although several experimental studies have suggested adverse effects from soy constituents [2, 3, 13, 14], no epidemiological study estimating isoflavone intake by FFQ has reported an increased risk of breast cancer. Our study also suggests a risk-reducing rather than risk-enhancing effect of isoflavones on breast cancer within the range achievable from dietary intake alone. It remains unclear, however, whether isoflavone exposure other than dietary intake is associated with the risk of breast cancer.

We found a linear decrease in breast cancer risk from zero to moderate intake (20–30 mg/day) and thereafter a leveling-off. This dose–responses pattern might imply the

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer according to dietary isoflavone intakes

	Median isoflavone intake[a]	All subjects						Premenopausal women				Postmenopausal women			
		No.		OR[b]	95% CI	OR[c]	95% CI	No.		OR[d]	95% CI	No.		OR[d]	95% CI
		Case	Control					Case	Control			Case	Control		
Japanese living in Nagano, Japan															
Tertile 1	22.1	152	129	1.00		1.00		80	67	1.00		72	62	1.00	
Tertile 2	39.6	118	131	0.75	(0.53–1.07)	0.86	(0.59–1.27)	52	44	0.99	(0.58–1.71)	66	87	0.79	(0.48–1.29)
Tertile 3	69.1	120	130	0.75	(0.52–1.10)	0.83	(0.54–1.28)	46	26	1.35	(0.72–2.54)	74	104	0.62	(0.38–1.01)
P for trend				0.12		0.39				0.41				0.06	
Japanese Brazilians living in São Paulo, Brazil															
Tertile 1	4.7	41	26	1.00		1.00									
Tertile 2	13.4	25	28	0.51	(0.23–1.15)	0.48	(0.20–1.16)								
Tertile 3	42.8	15	27	**0.35**	**(0.15–0.80)**	**0.25**	**(0.09–0.68)**								
P for trend				**0.01**		**<0.01**									
Median 1	8.0	48	40	1.00		1.00		16	10	1.00		32	30	1.00	
Median 2	35.0	33	41	0.68	(0.37–1.26)	0.52	(0.26–1.06)	9	14	**0.17**	**(0.03–0.84)**	24	27	0.84	(0.37–1.92)
Non-Japanese Brazilians living in São Paulo, Brazil															
Non-consumers	0	343	318	1.00		1.00		147	124	1.00		196	194	1.00	
Consumers	15.0	36	61	**0.54**	**(0.34–0.84)**	**0.56**	**(0.35–0.90)**	14	21	0.54	(0.26–1.13)	22	40	0.58	(0.33–1.03)

[a] Crude intake (mg/day)

[b] Crude OR

[c] Conditional model adjusting for menopausal status (premenopausal women, postmenopausal women), 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)

[d] Unconditional model adjusting for matching factors (age and area for Japanese; age and hospital for Japanese Brazilians; age and ethnicity for non-Japanese Brazilians), 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)

Bold characters indicates statistically significant values

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) of hormone receptor-defined breast cancer according to dietary isoflavone intakes

	No. of controls	ER+/PR+			ER+/PR−			ER−/PR−			Unknown		
		No. of cases	OR[a]	95% CI	No. of cases	OR[a]	95% CI	No. of cases	OR[a]	95% CI	No. of cases	OR[a]	95% CI
Japanese living in Nagano, Japan, all subjects													
Tertile 1	129	82	1.00		23	1.00		38	1.00				
Tertile 2	131	70	0.98	(0.64–1.51)	24	1.10	(0.58–2.08)	21	0.58	(0.32–1.07)			
Tertile 3	130	67	0.97	(0.62–1.51)	22	0.71	(0.36–1.43)	28	0.71	(0.40–1.28)			
P for trend			0.89			0.35			0.23				
Japanese living in Nagano, Japan, premenopausal women													
Tertile 1	67	46	1.00		8	1.00		18	1.00				
Tertile 2	44	40	1.35	(0.74–2.46)	4	0.80	(0.22–2.89)	6	0.47	(0.17–1.32)			
Tertile 3	26	27	1.51	(0.74–3.07)	7	1.64	(0.48–5.58)	10	0.94	(0.34–2.56)			
P for trend			0.22			0.52			0.65				
Japanese living in Nagano, Japan, postmenopausal women													
Tertile 1	62	36	1.00		15	1.00		20	1.00				
Tertile 2	87	30	0.68	(0.37–1.25)	20	1.25	(0.57–2.73)	15	0.65	(0.30–1.44)			
Tertile 3	104	40	0.68	(0.38–1.22)	15	0.53	(0.22–1.26)	18	0.57	(0.27–1.22)			
P for trend			0.21			0.14			0.15				
Japanese Brazilians living in São Paulo, Brazil, all subjects													
Median 1	40	24	1.00		7	1.00		7	1.00		9	1.00	
Median 2	41	16	0.63	(0.27–1.45)	2	0.22	(0.04–1.36)	4	0.34	(0.08–1.49)	11	1.24	(0.38–4.03)
Non-Japanese Brazilians living in São Paulo, Brazil, all subjects													
Non-consumers	318	97	1.00		41	1.00		76	1.00		108	1.00	
Consumers	61	8	0.46	(0.21–1.004)	9	1.10	(0.50–2.41)	10	0.67	(0.33–1.40)	7	**0.35**	**(0.16–0.80)**

[a] Unconditional model adjusting for matching factors (age and area for Japanese; age and hospital for Japanese Brazilians; age and ethnicity for non-Japanese Brazilians), menopausal status (premenopausal women, postmenopausal women), 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 past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no)

Bold characters indicates statistically significant values

Table 4 Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer according to dietary isoflavone intake based on combined individual study data from three populations

	Non-consumers and quintile category among consumers						*P* for trend
	0	1	2	3	4	5	
Median isoflavone intake (mg/day)[a]	0	8.7	23.1	33.8	45.7	71.3	
Japanese living in Nagano, Japan							
No. of cases/No. of controls	0/0	49/31	93/90	89/85	72/96	87/88	
Japanese Brazilians living in São Paulo, Brazil							
No. of cases/No. of controls	9/5	46/41	16/12	3/8	1/6	6/9	
Non-Japanese Brazilians living in São Paulo, Brazil							
No. of cases/No. of controls	343/318	27/33	5/3	2/13	2/3	0/9	
All subjects in three populations							
No. of cases/No. of controls	352/323	122/105	114/105	94/106	75/105	93/106	
OR	1.00	0.69	**0.54**	**0.45**	**0.34**	**0.43**	**<0.01**
(95% CI)[b]		(0.44–1.09)	**(0.31–0.94)**	**(0.26–0.77)**	**(0.19–0.62)**	**(0.24–0.76)**	
Premenopausal women in three populations							
No. of cases/No. of controls	150/127	48/37	58/52	49/37	23/30	36/23	
OR	1.00	0.68	0.44	0.54	**0.27**	0.62	0.27
(95% CI)[c]		(0.33–1.39)	(0.19–1.01)	(0.24–1.24)	**(0.10–0.69)**	(0.25–1.54)	
Postmenopausal women in three populations							
No. of cases/No. of controls	202/196	74/68	56/53	45/69	52/75	57/83	
OR	1.00	0.70	0.52	**0.31**	**0.34**	**0.33**	**<0.01**
(95% CI)[c]		(0.40–1.24)	(0.26–1.04)	**(0.15–0.64)**	**(0.17–0.71)**	**(0.16–0.66)**	

[a] Energy adjusted by residual method

[b] Conditional model adjusting for menopausal status (premenopausal women, postmenopausal women), 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)

[c] Unconditional model adjusting for age (continuous), study population (Japanese living in Nagano, Japan; Japanese Brazilians living in São Paulo, Brazil; non-Japanese Brazilians living in São Paulo, Brazil), 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)

Bold characters indicates statistically significant values

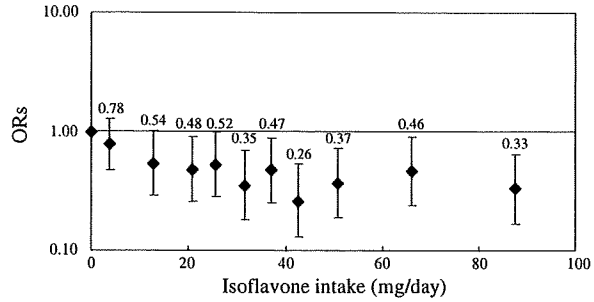

Fig. 1 Odds ratios (ORs) and 95% confidence intervals of breast cancer according to dietary isoflavone intake based on combined individual data from three populations. Subjects were categorized into 11 groups: non-consumers and deciles of isoflavone consumers based on the control distribution. ORs were estimated using matching pairs with adjustment for menopausal status (premenopausal women, postmenopausal women), 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)

presence of a ceiling effect and suggests that women may benefit from risk reduction if they consume at least a moderate amount of isoflavones. Alternatively, it might merely reflect differences in measurement errors due to the use of different FFQs, selection bias, and residual confounding among the three populations, notwithstanding that it clearly reflected the results of separate analyses. Specifically, consumers had lower risk than non-consumers in non-Japanese Brazilians, whose average intake of isoflavone was 4.4 mg/day among the control group; the risk of breast cancer decreased with increasing intake of isoflavone in Japanese Brazilians, whose average intake of isoflavone was 24.9 mg/day among the control group; while higher intake of isoflavone was not associated with further risk reduction in Japanese, whose average intake of isoflavone was 46.1 mg/day among the control group. Confirmation of this pattern would require further prospective cohort studies using blood or urine samples as an exposure assessment, because these could minimize the measurement errors and selection bias mentioned above.

Our stratified analysis by menopausal status using data from the three populations combined showed that an inverse association was more prominent among postmenopausal than premenopausal women. In addition, our separate analyses showed somewhat different patterns in the three populations: the inverse association was limited to postmenopausal women in Japanese; it was stronger in premenopausal than postmenopausal women in Japanese Brazilians; and no remarkable difference was found in non-Japanese Brazilians. These findings are inconsistent with a recent meta-analysis showing an inverse association regardless of menopausal status [11]. Moreover, findings to date on the association of isoflavone intake and the risk of breast cancer stratified by menopausal status have been inconsistent, with one prospective cohort study in Japan [4] and one case–control study in the United States [8] reporting that an inverse association was limited to postmenopausal women; one case–control study in Japan [5] showing it was limited to premenopausal women; and one prospective cohort study in the United States [16] and three case–control studies [6, 17, 18] finding no difference between the two strata.

Several mechanisms by which isoflavones may reduce the risk of breast cancer have been proposed [2, 3]. The most prominent and thoroughly investigated mechanisms are mediated via estrogen receptors, arising due to the similar chemical structure of isoflavones to the human estrogen hormone and their binding affinity to estrogen receptors [3, 29]. Given that the action of estrogen on breast cell proliferation appears to be mediated by estrogen receptors, therefore, any association between isoflavone intake and breast cancer risk might differ by hormone receptor-defined subtype. The present study did not support this hypothesis, however, showing no apparent difference in risk by subtype. Moreover, results for the few studies to date have been inconsistent [7, 16, 18, 19]. Although our findings might merely be explained by a lack of statistical power, they suggest that the anti-cancer effects of isoflavones might be evoked not only by mechanisms mediated by estrogen receptors but also by other mechanisms, such as the modulation of endogenous hormones via inhibition of the key enzyme involved in estrogen biosynthesis and metabolism; the arrest of cell cycle progression; induction of apoptosis; inhibition of tyrosine kinase activity, topoisomerase II activity, and angiogenesis; and antioxidant activity [2, 3].

Our study has several methodological advantages over previous studies of isoflavones and the risk of breast cancer. First, isoflavone intake differed considerably among the three populations, with median levels (interquartile rage) in the control group (mg/day) of 40.6 (25.9–61.2) among Japanese, 13.4 (8.1–35.0) among Japanese Brazilians, and 0 (0–0) among non-Japanese Brazilians. This range allowed the detailed evaluation of dose–response relations, ranging from zero to a relatively high level achievable from dietary intake only, and is unique to the present study. Second, the overall consistency of findings in the three populations allowed for the greater generalizability of results as compared to those from a single population.

Several limitations of this study warrant mention. First, dietary intake of isoflavone was assessed after the diagnosis of breast cancer and is therefore sensitive to recall bias. Second, 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 and cancer-free patients, whose dietary habits may differ from the general population due to health consciousness or disease, might have lead to selection bias. Third, stratified analyses were performed based on a relatively small number of cases. The interpretability of our results might therefore be limited.

Allowing for these methodological issues, we found an inverse association between dietary isoflavone intake and the risk of breast cancer in case–control studies of Japanese, Japanese Brazilians, and non-Japanese Brazilians. Our findings suggest a risk-reducing rather than risk-enhancing effect of isoflavones on breast cancer within the range achievable from dietary intake alone. In addition, women may benefit from risk reduction if they consume at least moderate amounts of isoflavones.

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