

Dietary isoflavone intake, polymorphisms in estrogen receptor genes and the risk of breast cancer in case-control studies in Japanese, Japanese Brazilians, and non-Japanese Brazilians

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Isoflavone intake and breast cancer risk: meta-analysis

	No. of studies	Odds ratio	95% confidence interval
Studies conducted in Asia and in Asian Americans			
Highest (> 20 mg/day) vs. Lowest (< 5 mg/day)			
All studies	8	0.71	0.61-0.85
Case-control studies	7	0.75	0.62-0.89
Premenopausal women	6	0.65	0.50-0.85
Postmenopausal women	6	0.63	0.46-0.85
Moderate (median 10 mg/day) vs. Lowest (< 5 mg/day)			
All studies	8	0.88	0.78-0.98
Studies conducted in Western populations			
Highest (> 0.8 mg/day) vs. Lowest (< 0.15 mg/day)			
All studies	11	1.04	0.97-1.11
Cohort / nested case-control	4	1.08	0.95-1.24
Case-control studies	7	1.02	0.95-1.11

Possible mechanisms of action of isoflavones in breast cancer

- Estrogen-dependent mechanisms:
 - the mediation of **estrogen receptor α and β** , owing to the similar chemical structure of isoflavones to the human estrogen hormone and their binding affinity to estrogen receptors.
 - inhibition of the key enzyme involved in estrogen biosynthesis and metabolism
 - to inhibit **aromatase (CYP19)** and **17 β -hydroxysteroid dehydrogenase type I (17 β -HSD1)**
 - to increase the synthesis of **sex hormone-binding globulin (SHBG)** level
- Estrogen-independent mechanisms:
 - induction of apoptosis
 - inhibition of tyrosine kinase activity
 - inhibition of topoisomerase II activity
 - inhibition of angiogenesis
 - antioxidant activity

Purpose of this study

- To test the hypothesis that **polymorphisms in the estrogen receptor genes** may modify the association between isoflavone intake and breast cancer risk, we conducted hospital-based case-control studies in Nagano, Japan and São Paulo, Brazil.

Subjects

- Cases were a consecutive series of female patients **aged 20-74** years who were newly diagnosed with **histologically confirmed invasive breast cancer**.
- Control selection
 - **age- and area- matched** controls were selected from medical checkup examinees in Nagano, Japan
 - **age- and ethnic-matched** controls were selected from cancer-free patients in São Paulo, Brazil.
- A total of **877 matched pairs** (405 Japanese, 83 Japanese Brazilians and 389 non-Japanese Brazilians) participated.
 - Participation rate (case): 98% Japanese, 91% Japanese Brazilians and 99% non-Japanese Brazilians
 - Participation rate (control): 99% Japanese, 100% Japanese Brazilians and 95% non-Japanese Brazilians

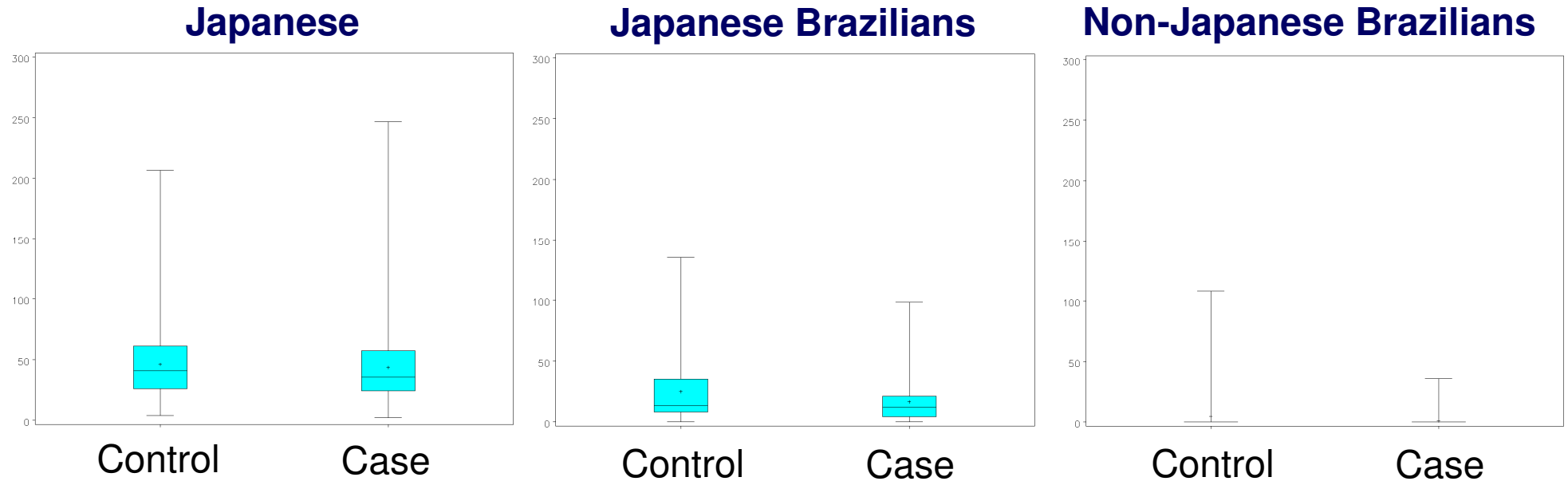
Exposure assessment

- Isoflavone intake was calculated by the FFQ
 - Correlation between energy-adjusted intake calculated by FFQ and dietary records
 - Japanese version: Genistein: $r = 0.59$, Daidzein: $r = 0.60$
 - Brazilian version: Genistein: $r = 0.76$, Daidzein: $r = 0.76$
- Genotyping of single nucleotide polymorphisms
 - estrogen receptor- alpha gene
 - rs9340799, rs1913474, and rs2234693
 - estrogen receptor- beta gene
 - rs4986938 and rs1256049

Statistical analysis

- A total of **846 matched pairs** (388 Japanese, 79 Japanese Brazilians and 379 non-Japanese Brazilians) were used for the present analyses.
- An unconditional logistic regression model was used to estimate odds ratio (OR) and 95% confidence interval (CI) of breast cancer according to isoflavone intake stratified by genotypes.
- The following variables were adjusted for as potential confounders.
 - Japanese: age, area, menopausal status and age at menopause, number of births, family history of breast cancer, and smoking status.
 - Japanese Brazilians: age, hospital, menopausal status and age at menopause, number of births, and smoking status.
 - non-Japanese Brazilians: age, ethnicity, menopausal status and age at menopause, number of births, and smoking status.

Dietary isoflavone intake among three populations

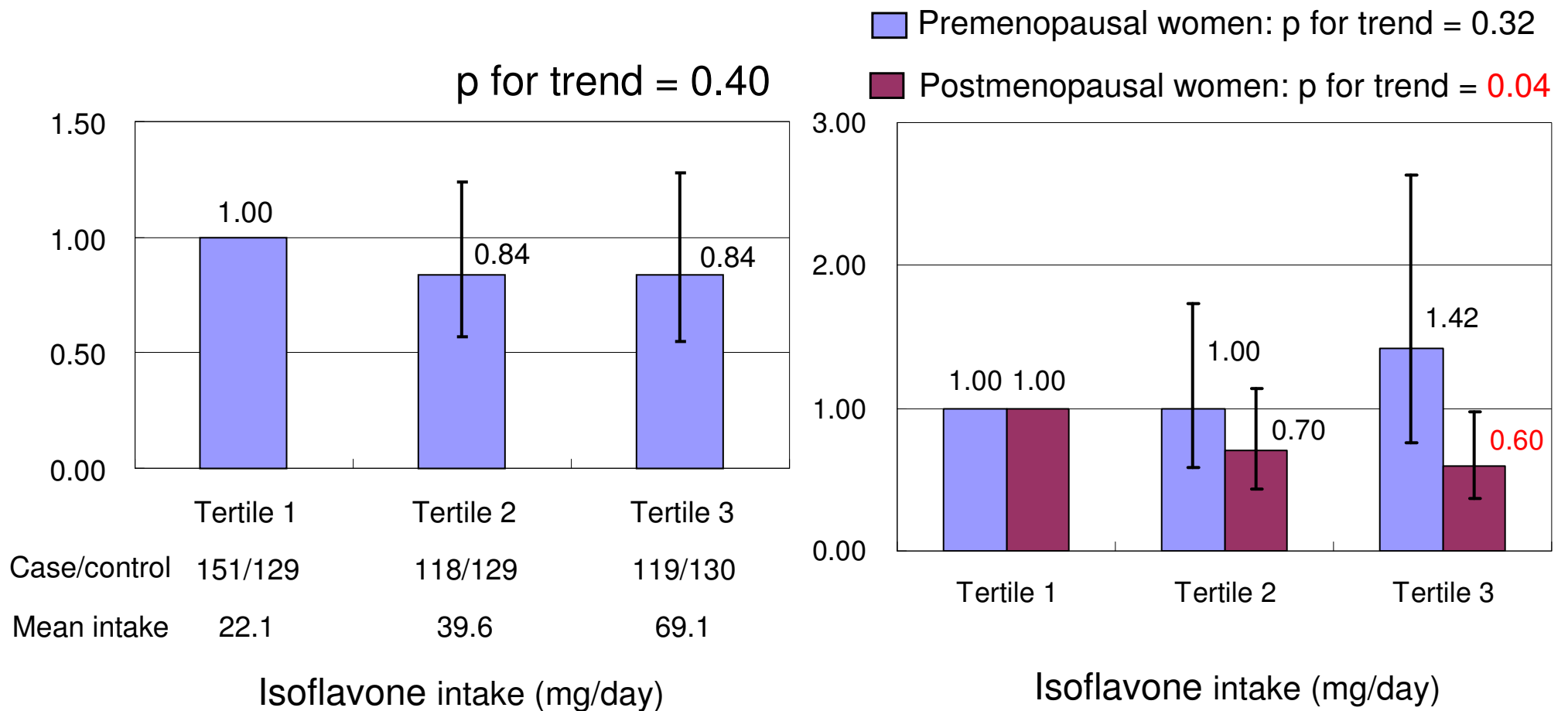


Isoflavone intake (mg/day)	Japanese		Japanese Brazilians		Non-Japanese Brazilians	
	Case	Control	Case	Control	Case	Control
Median	35.5	40.7	12.1	13.4	0	0
Q1	24.0	25.8	3.9	8.1	0	0
Q3	57.4	61.4	22.2	35.0	0	0
Mean	43.5	46.2	16.7	23.5	1.1	4.4

Isoflavone intake and breast cancer risk

Japanese

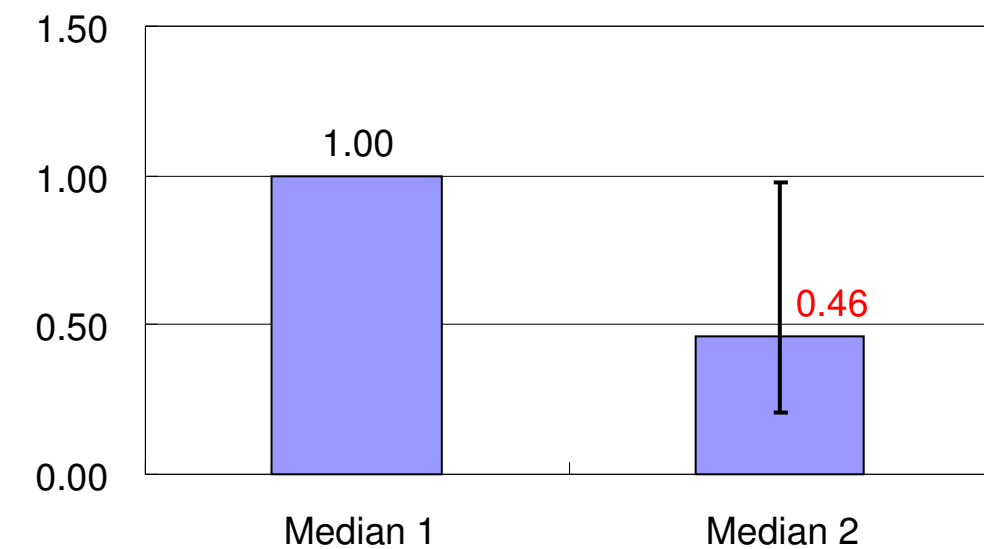
Stratified by menopausal status



Isoflavone intake and breast cancer risk

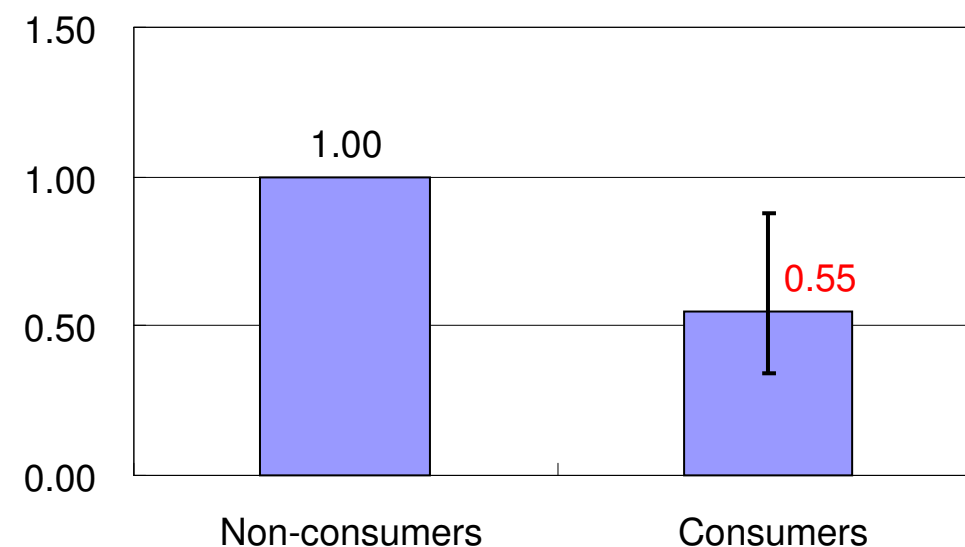
Japanese Brazilians

Non-Japanese Brazilians



Case/control	46/39	33/40
Mean intake	8.0	35.0

Isoflavone intake (mg/day)



Case/control	343/318	36/61
Mean intake	0.0	15.0

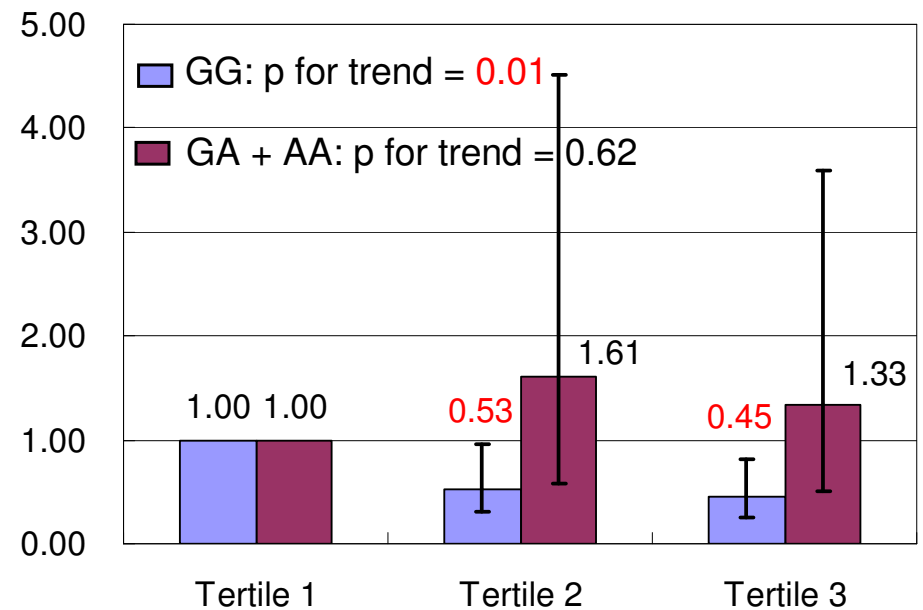
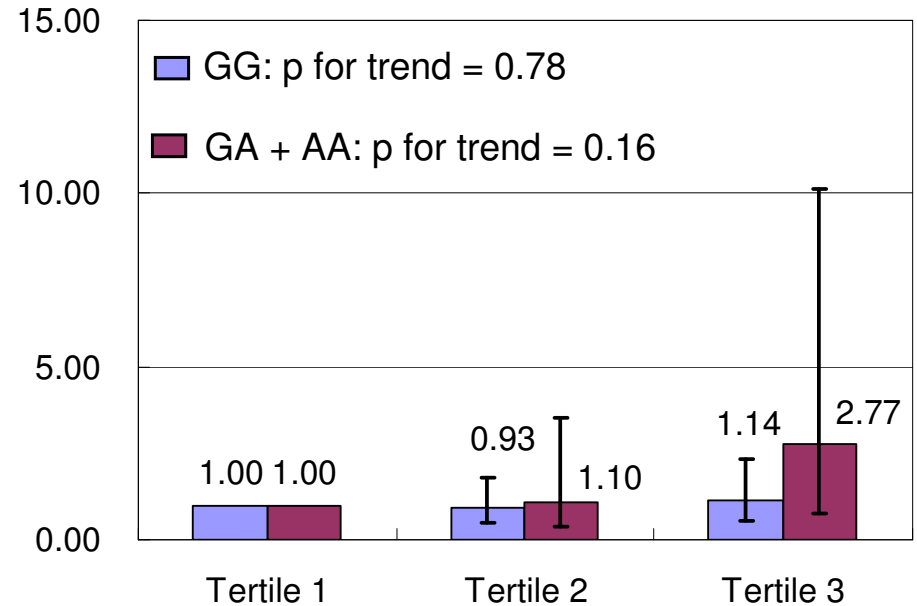
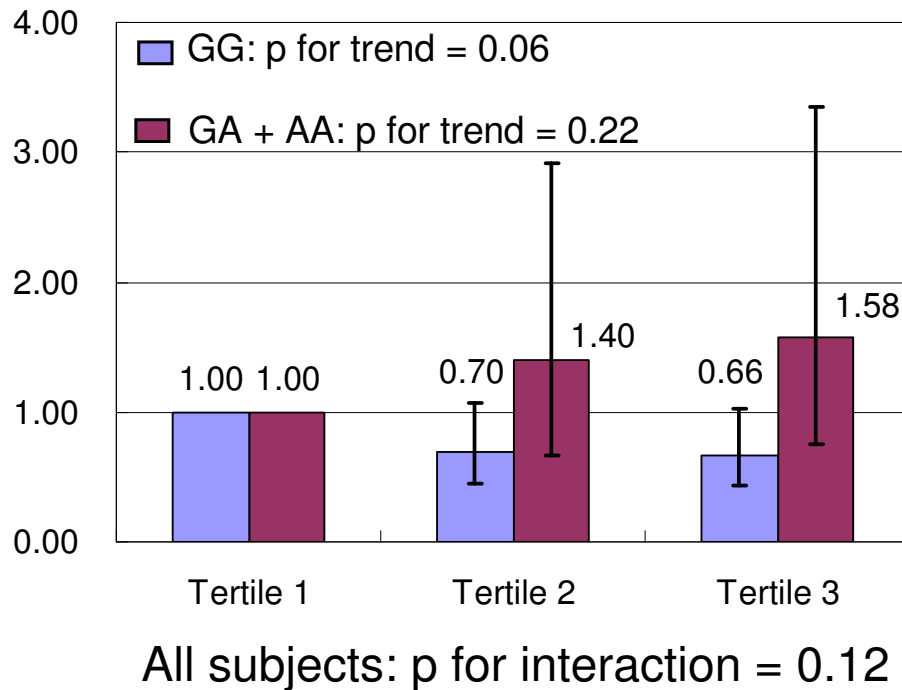
Isoflavone intake (mg/day)

SNPs in the estrogen receptor genes and breast cancer risk

	Japanese		Japanese Brazilians		Non-Japanese Brazilians	
	OR	95% CI	OR	95% CI	OR	95% CI
Estrogen receptor 1 gene (rs9340799)						
AA	1.00		1.00		1.00	
AG	0.69	(0.46- 1.02)	0.71	(0.28- 1.81)	1.18	(0.86- 1.61)
GG	0.64	(0.24- 1.75)	1.17	(0.17- 7.93)	1.31	(0.81- 2.12)
Estrogen receptor 1 gene (rs1913474)						
CC	1.00		1.00		1.00	
CT	1.23	(0.84- 1.81)	1.33	(0.58- 3.06)	1.03	(0.76- 1.41)
TT	1.07	(0.69- 1.64)	0.79	(0.28- 2.23)	0.87	(0.42- 1.81)
Estrogen receptor 1 gene (rs2234693)						
TT	1.00		1.00		1.00	
TC	0.70	(0.49- 0.99)	0.62	(0.27- 1.41)	0.98	(0.68- 1.40)
CC	0.63	(0.40- 1.00)	0.81	(0.27- 2.43)	1.50	(0.98- 2.28)
Estrogen receptor 2 gene (rs4986938)						
GG	1.00		1.00		1.00	
GA	0.87	(0.59- 1.29)	1.19	(0.47- 3.04)	1.12	(0.81- 1.55)
AA	1.23	(0.31- 4.79)	0.60	(0.08- 4.61)	0.95	(0.60- 1.50)
Estrogen receptor 2 gene (rs1256049)						
GG	1.00		1.00		1.00	
GA	0.73	(0.53- 1.02)	0.82	(0.39- 1.70)	1.25	(0.74- 2.13)
AA	0.83	(0.44- 1.58)	3.69	(0.39- 35.29)	0.55	(0.05- 6.49)

Stratified by **rs4986938** polymorphism in estrogen receptor beta gene

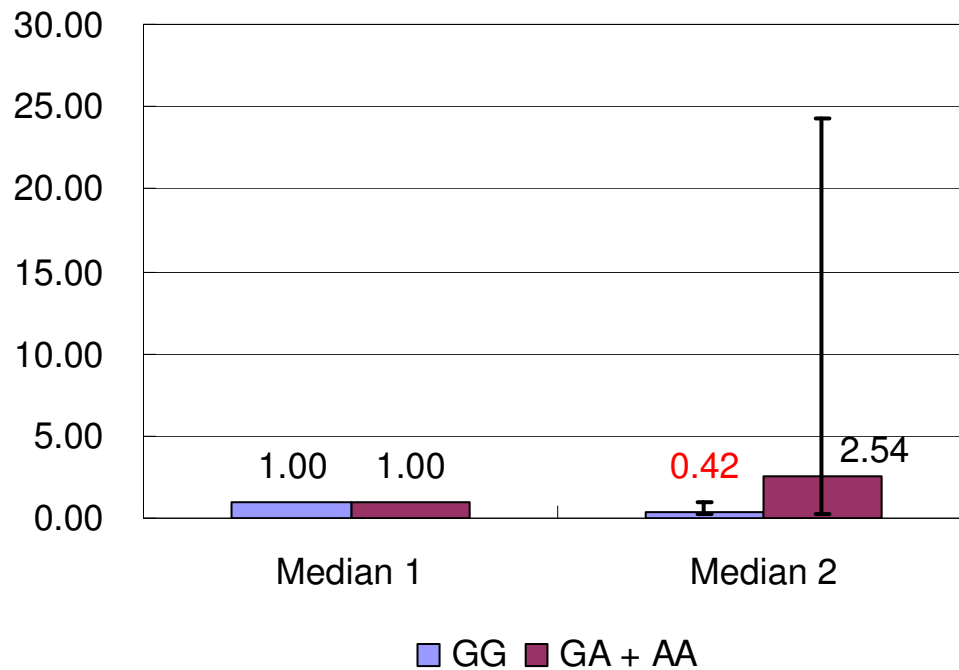
Japanese



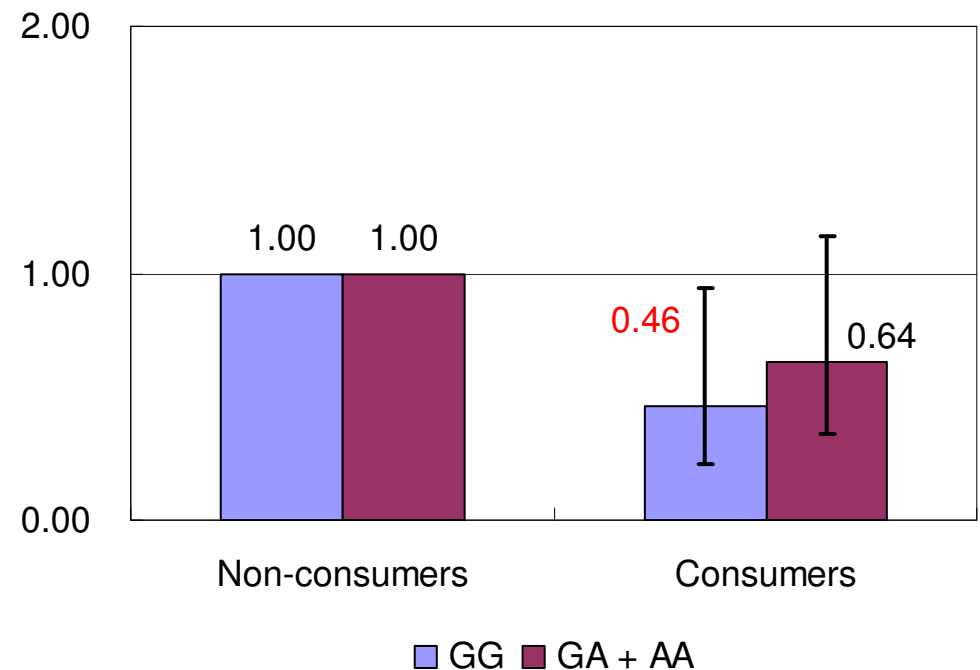
Stratified by **rs4986938** polymorphism in estrogen receptor beta gene

Japanese Brazilians

Non-Japanese Brazilians



p for interaction = **0.046**



p for interaction = 0.32

Comments 1

- We found an interaction between isoflavone intake and the rs4986938 polymorphism of estrogen receptor beta gene in the risk of breast cancer.
 - An interaction between phytoestrogen intake and the rs2987983 polymorphism in the risk of prostate cancer.
 - An interaction between urinary genistein level and the RsaI polymorphism in the risk of advanced endometriosis.
- Overall consistency of findings in the three populations suggest that potential mechanisms by which isoflavone may reduce the risk of hormone-related diseases might be involved in estrogen receptor beta.

Conclusion

- Our finding suggests that polymorphisms in estrogen receptor- beta gene may modify the association between isoflavone intake and breast cancer risk.

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Thank you for your attention.