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

Motoki Iwasaki[1], Gerson Shigeaki Hamada[2], Ines Nobuko Nishimoto[3], Mario Mourão Netto[4], Juvenal Motola Jr.[5], Fábio Martins Laginha[5], Yoshio Kasuga[6], Shiro Yokoyama[7], Hiroshi Onuma[7], Hideki Nishimura[8], Ritsu Kusama[9], Minatsu Kobayashi[1], Junko Ishihara[1], Seiichiro Yamamoto[10], Tomoyuki Hanaoka[1], and Shoichiro Tsugane[1]

[1] Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan
[2] Nikkei Disease Prevention Center, São Paulo, Brazil
[3] Statistical Section/Head and Neck Surgery and Otorhinolaryngology Department, Hospital A.C. Camargo, São Paulo, Brazil
[4] Breast Surgery Department, Hospital A.C. Camargo, São Paulo, Brazil.
[5] Department of Breast Surgery, Hospital Pérola Byington, São Paulo, Brazil
[6] Department of Surgery, Nagano Matsushiro General Hospital, Nagano, Japan
[7] Department of Breast and Thyroid Surgery, Nagano Red Cross Hospital, Nagano, Japan
[8] Department of Surgery, Nagano Municipal Hospital, Nagano, Japan
[9] Department of Surgery, Nagano Hokushin General Hospital, Nagano, Japan
[10] Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

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

Wu AH, et al. Br J Cancer 2008;98:9-14.

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 17β-hydroxysteroid dehydrogenase type I (17β-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

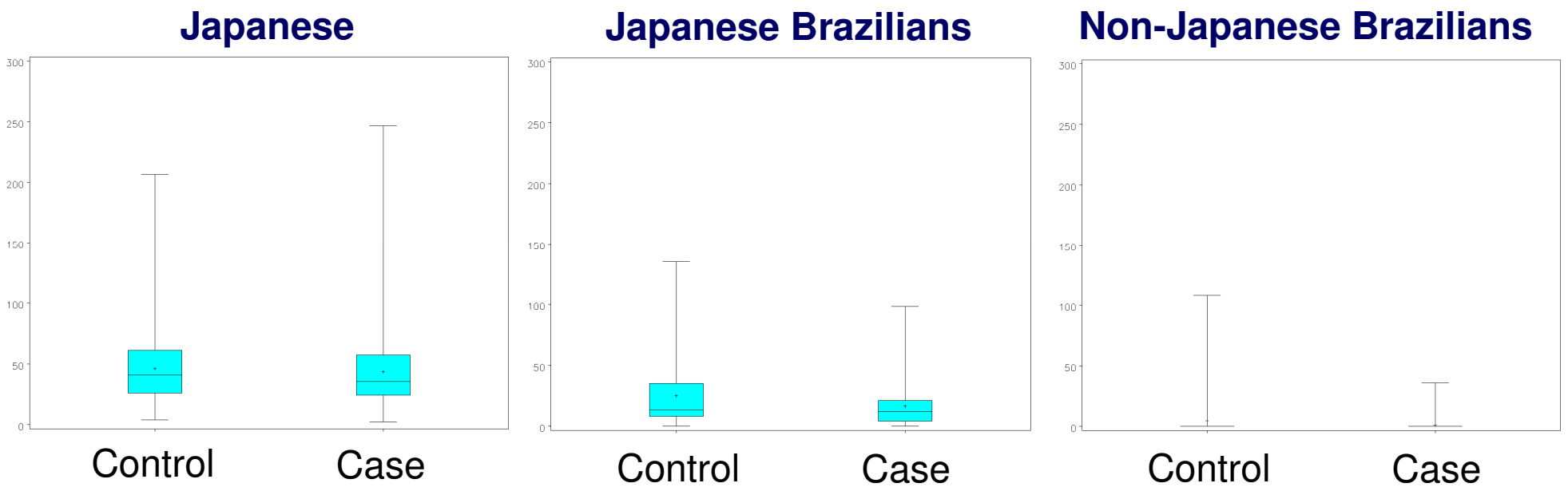
Exposure assessment

- 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

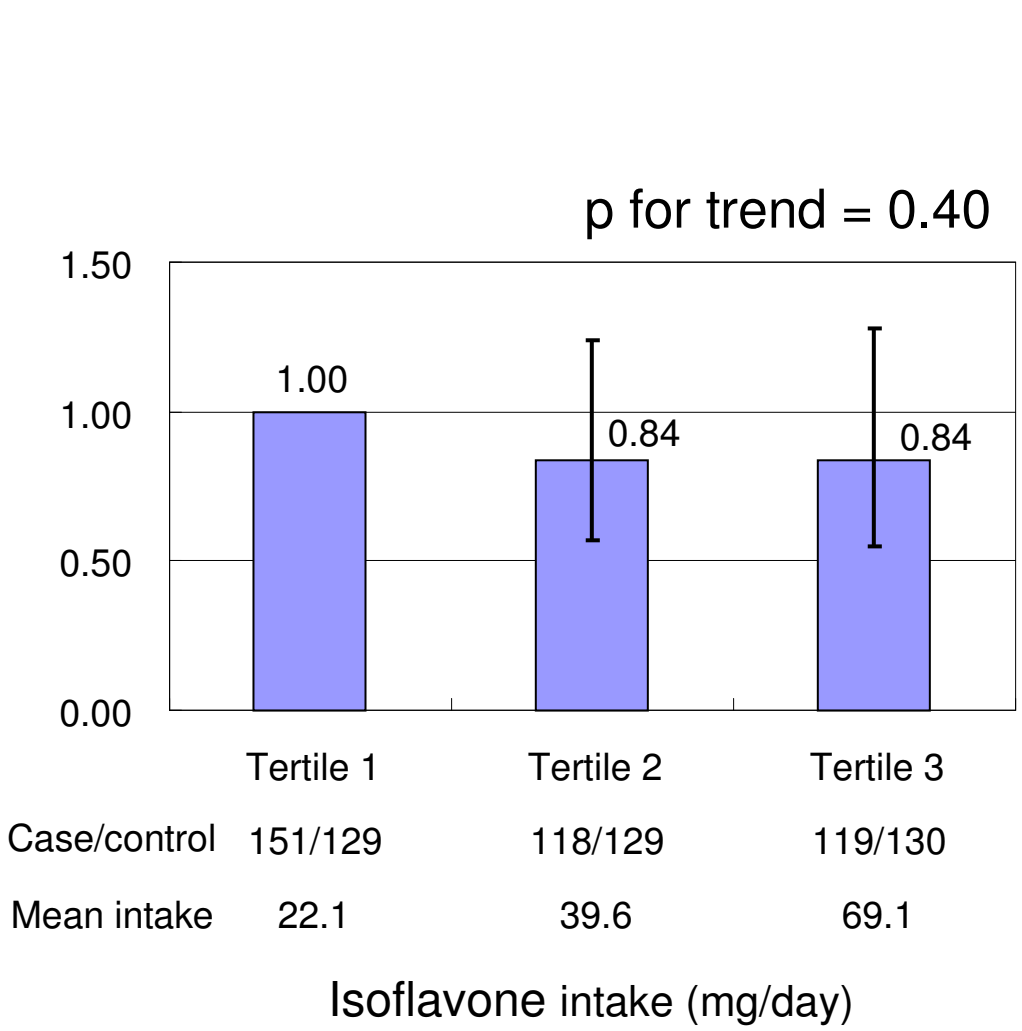
- A total of 846 matched pairs (388 Japanese, 79 Japanese Brazilians and 379 non-Japanese Brazilians) were used for the present analyses.
- An unconditional logistic regression model was used to estimate odds ratio (OR) and 95% confidence interval (CI) of breast cancer according to isoflavone intake 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.

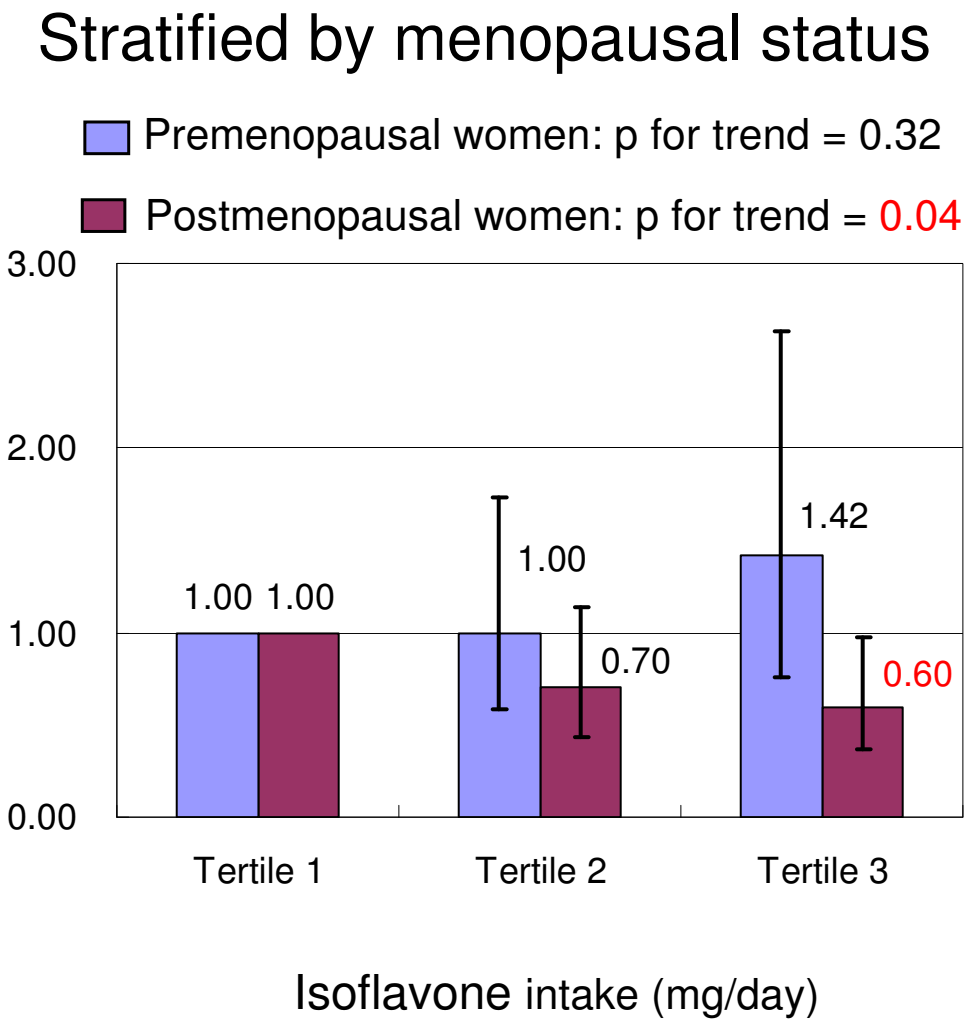
Dietary isoflavone intake among three populations



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

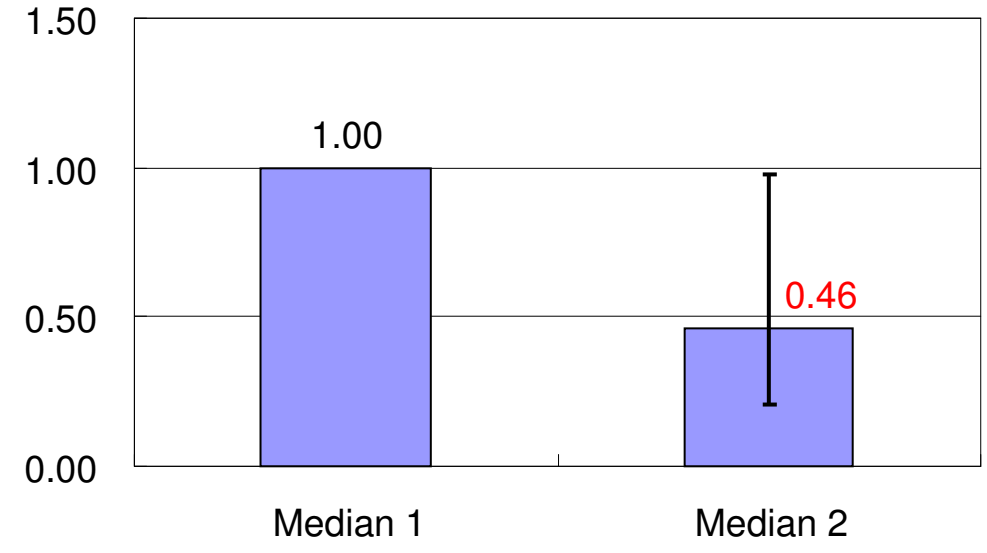
Isoflavone intake and breast cancer risk Japanese





Isoflavone intake and breast cancer risk

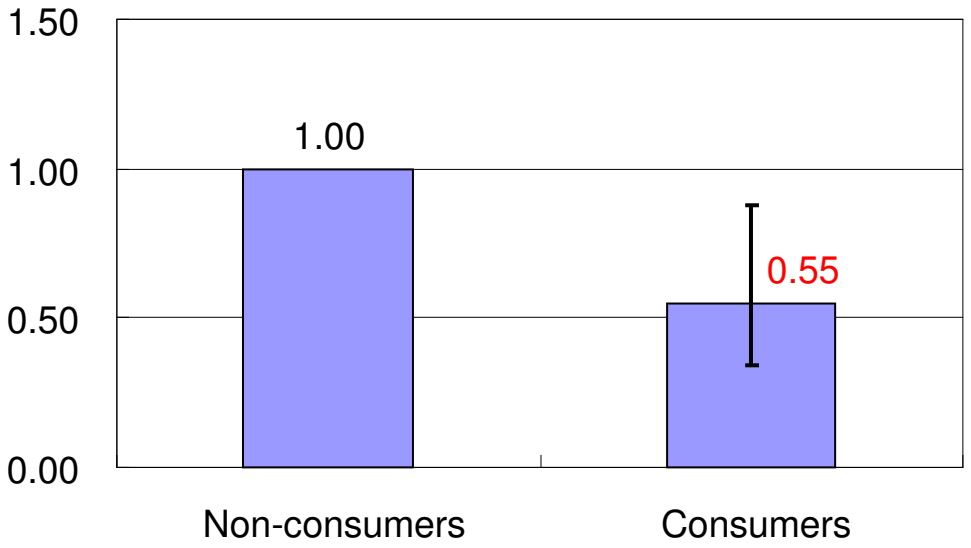
Japanese Brazilians



	Median 1	Median 2
Case/control	46/39	33/40
Mean intake	8.0	35.0

Isoflavone intake (mg/day)

Non-Japanese Brazilians



	Non-consumers	Consumers
Case/control	343/318	36/61
Mean intake	0.0	15.0

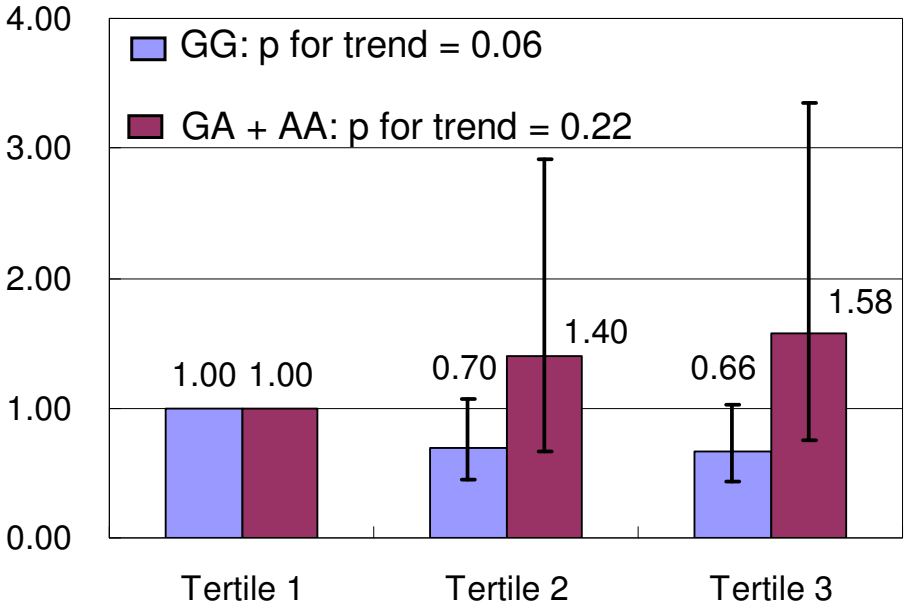
Isoflavone intake (mg/day)

SNPs in the estrogen receptor genes and breast cancer risk

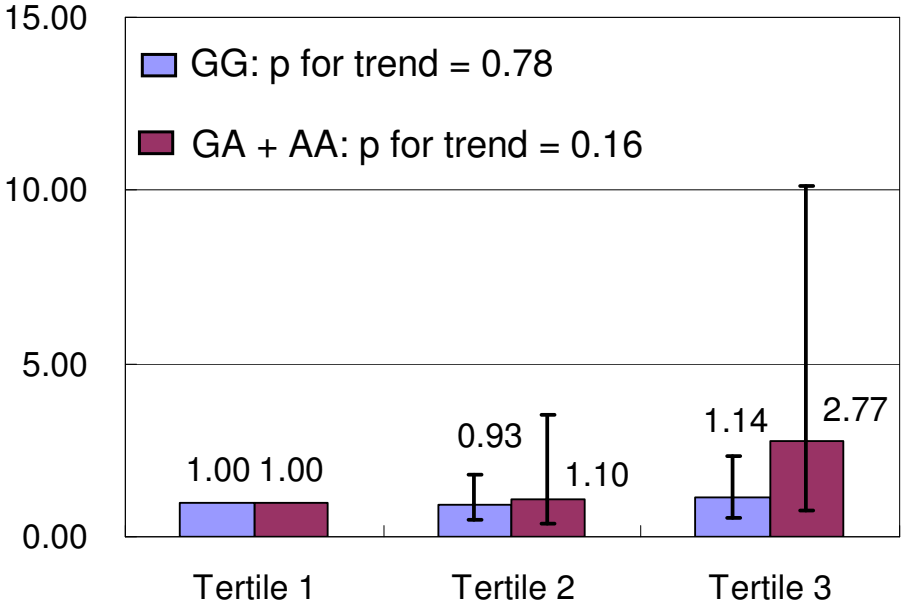
	Japanese		Japanese Brazilians		Non-Japanese Brazilians	
	OR	95% CI	OR	95% CI	OR	95% CI
Estrogen receptor 1 gene (rs9340799)						
AA	1.00		1.00		1.00	
AG	0.69	(0.46- 1.02)	0.71	(0.28- 1.81)	1.18	(0.86- 1.61)
GG	0.64	(0.24- 1.75)	1.17	(0.17- 7.93)	1.31	(0.81- 2.12)
Estrogen receptor 1 gene (rs1913474)						
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

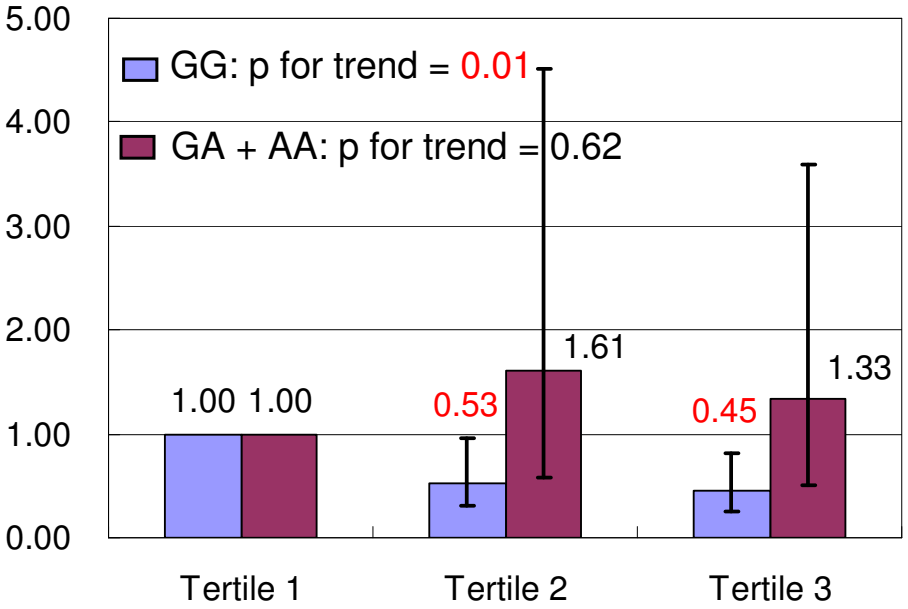
Japanese



All subjects: p for interaction = 0.12



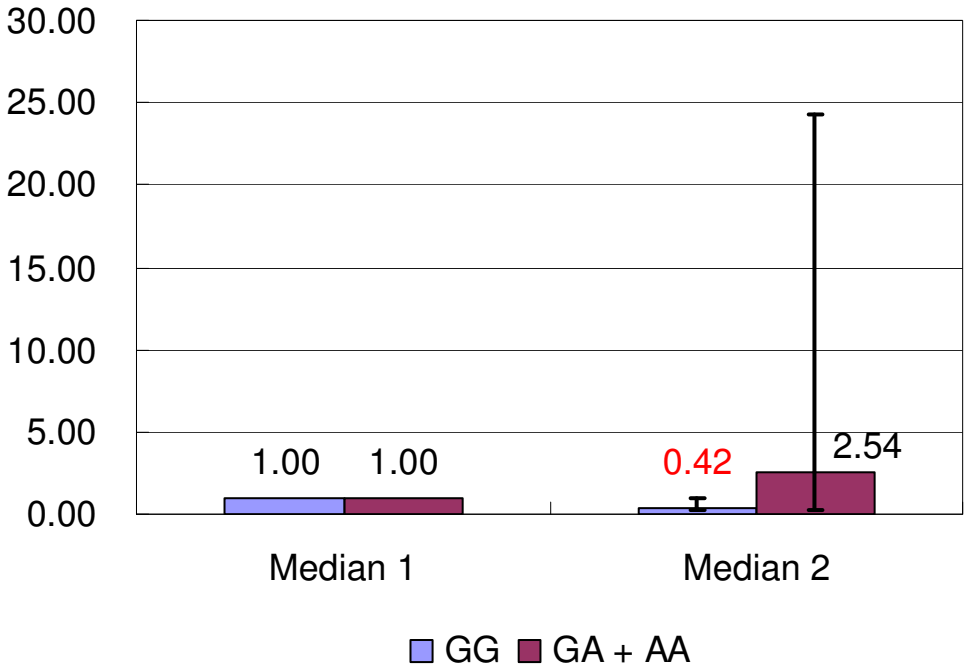
Premenopausal: p for interaction = 0.51



Postmenopausal: p for interaction = 0.13

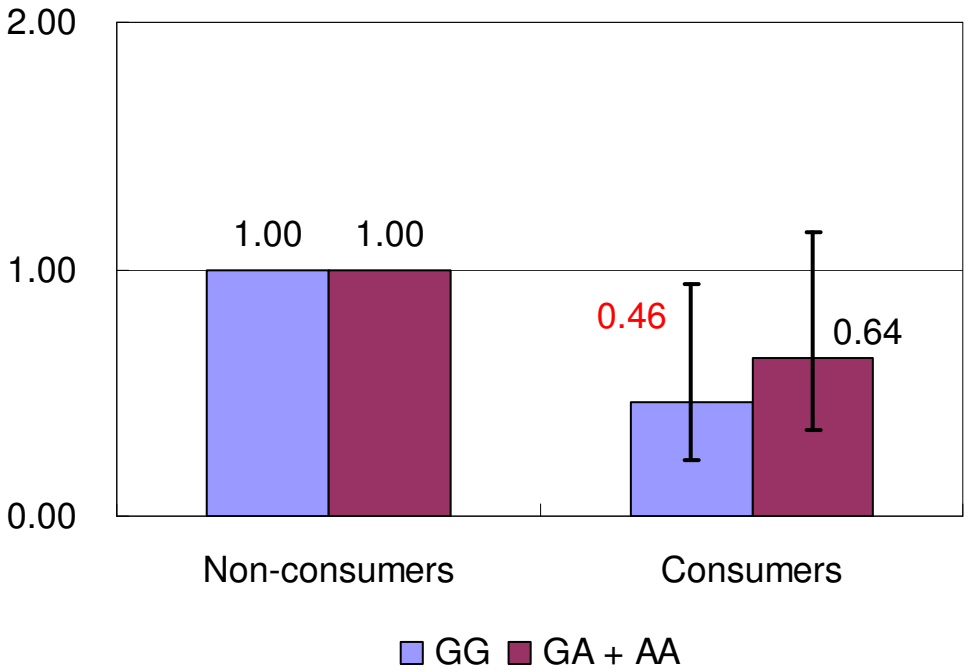
Stratified by rs4986938 polymorphism in estrogen receptor beta gene

Japanese Brazilians



p for interaction = 0.046

Non-Japanese Brazilians



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.

Acknowledgments

“São Paulo-Japan Breast Cancer Study Group”

- Nikkei Disease Prevention Center, São Paulo
  - C. I. Yamaguchi, C. M. Kunieda, and S. S. Sugama
- Departamento de Ginecologia, Hospital Pérola Byington, São Paulo
  - C. K. Taniguchi and J. A. Marques
- Departamento de Nutrição, Hospital Pérola Byington, São Paulo
  - M. R. Eichhorn
- Departamento de Mastologia, Hospital A.C. Camargo, São Paulo
  - H. Iyeyasu, M. S. Maciel, S. M. T. Carvalho, J. B. D. Collins, and C. E. M. Fontes
- Departamento de Cirurgia de Cabeça e Pescoço e Otorrinolaringologia, A. C. Camargo Hospital, São Paulo
  - L. P. Kowalski and J. M. F. Toyota
- Departamento de Mastologia, Instituto Brasileiro de Controle ao Câncer, São Paulo
  - E. M. Barbosa
- Departamento de Mastologia, Hospital do Servidor Público Estadual Francisco Morato de Oliveira, São Paulo
  - O. Ferraro
- Departamento de Mastologia, Hospital Santa Cruz
  - R. Anzai
- Instituto de Ginecologia e Mastologia, Hospital Beneficencia Portuguesa
  - E. H. Hotta and D. A. Petti
- Instituto Brasileiro de Mastologia e Ginecologia, Hospital Beneficencia Portuguesa
  - S. Mendes

Thank you for your attention.