Table 3 Adjusted geometric mean hormone levels[a] of three populations with stratification by body mass index[b]

	Japanese living in Nagano, Japan	Japanese Brazilians living in São Paulo, Brazil	Non-Japanese Brazilians living in São Paulo, Brazil	*P* for difference
Estradiol, pg/mL				
Low (BMI < 25)	9.5	14.2	15.0	<0.01
P[c]	<0.01	Reference	0.60	
High (BMI ≥25)	8.2	12.2	14.5	<0.01
P[c]	<0.01	Reference	0.06	
Bioavailable estradiol, %				
Low (BMI <25)	22.4	28.7	17.9	<0.01
P[c]	<0.01	Reference	<0.01	
High (BMI ≥ 25)	25.6	32.5	23.4	<0.01
P[c]	<0.01	Reference	<0.01	
Estrone, pg/mL				
Low (BMI < 25)	22.5	40.4	32.1	<0.01
P[c]	<0.01	Reference	<0.01	
High (BMI ≥25)	23.2	38.4	34.2	<0.01
P[c]	<0.01	Reference	0.19	
Sex hormone-binding globulin, nM/L				
Low (BMI < 25)	76.6	62.8	85.8	0.03
P[c]	0.04	Reference	<0.01	
High (BMI ≥25)	59.6	43.8	59.5	0.03
P[c]	0.02	Reference	0.02	
Androstenedione, ng/mL				
Low (BMI < 25)	0.64	0.63	0.91	0.03
P[c]	0.90	Reference	0.02	
High (BMI ≥25)	0.76	0.51	1.05	<0.01
P[c]	0.03	Reference	<0.01	
DHEAS, μg/dL				
Low (BMI < 25)	51.9	64.7	48.7	0.21
P[c]	0.13	Reference	0.11	
High (BMI ≥25)	54.6	52.2	43.4	0.29
P[c]	0.81	Reference	0.32	
Testosterone, ng/mL				
Low (BMI < 25)	0.01	0.07	0.13	<0.01
P[c]	<0.01	Reference	0.27	
High (BMI ≥25)	0.04	0.15	0.18	<0.01
P[c]	<0.01	Reference	0.69	
Free testosterone, pg/mL				
Low (BMI < 25)	0.18	0.32	0.31	<0.01
P[c]	<0.01	Reference	0.90	
High (BMI ≥25)	0.26	0.46	0.48	<0.01
P[c]	<0.01	Reference	0.85	

BMI, body mass index; DHEAS, dehyroepianrosterone sulfate; [a]Adjusted for age (continuous), age at first menarche (continuous), age at menopause (continuous), number of births (0, 1, 2 or 3, 4+), age at first birth (≤22, 23 to 26, ≥27, nulliparous), height (continuous), BMI (continuous), smoking (never smokers, past smokers, current smokers), alcohol drinking (nondrinkers, occasional drinkers, regular drinkers) and physical activity in the past 5 years (no, ≤2 days/wk, ≥3 days/wk); [b]The total participants in the low and high BMI groups were 199 and 156, respectively; [c]*P* values for comparison with Japanese Brazilians living in São Paulo, Brazil.

proportion of participants with levels below the LOD was relatively high for testosterone (24%) and free testosterone (69%). Our findings for testosterone and free testosterone should therefore be interpreted cautiously. Third, since our study included only a small number of Japanese Brazilians (n = 44), the findings might be due to chance and should be interpreted with caution.

We found higher circulating levels of estrogen and androgen in Japanese Brazilians than in Japanese, which were not accounted for by differences in the prevalence

Table 4 Adjusted geometric mean hormone levels by breast cancer risk factors and lifestyle-factors[a]

Breast cancer risk and lifestyle factors	Participants, *n*	Estradiol, pg/mL	Bioavailable estradiol, %	Estrone, pg/mL	Sex hormone-binding globulin, nM/L	Androstenedione, ng/mL	DHEAS, μg/dL	Testosterone, ng/mL	Free testosterone, pg/mL
Family history of breast cancer									
No	327	13.9	22.7	32.6	66.2	0.84	52.7	0.09	0.34
Yes	36	13.8	21.2	31.6	74.6	0.80	51.4	0.05	0.36
P for difference		0.90	0.18	0.57	0.12	0.66	0.83	0.08	0.40
History of benign breast disease									
No	339	13.9	22.6	32.5	66.9	0.84	52.9	0.09	0.34
Yes	23	14.3	22.0	33.5	69.0	0.78	52.1	0.08	0.31
P for difference		0.69	0.68	0.67	0.75	0.61	0.92	0.72	0.38
Age at first menarche, yr									
<12	101	13.7	22.9	31.6	66.7	0.83	49.5	0.08	0.33
13 or 14	166	13.9	22.2	32.4	65.2	0.83	54.8	0.09	0.34
15+	96	13.9	22.6	33.6	69.7	0.85	53.3	0.08	0.35
P for trend		0.81	0.81	0.18	0.51	0.78	0.43	0.99	0.60
P for trend[b]		0.70	0.47	0.30	0.24	0.68	0.29	0.83	0.39
Age at menopause, yr									
<48	116	14.0	23.0	32.6	64.5	0.89	57.0	0.08	0.34
49 to 51	108	14.0	22.0	33.1	70.2	0.78	51.6	0.09	0.34
52+	139	13.6	22.5	32.1	67.0	0.80	48.5	0.09	0.33
P for trend		0.47	0.65	0.68	0.57	0.20	0.05	0.66	0.75
P for trend[b]		0.80	0.06	0.93	0.02	0.32	0.51	0.59	1.00
Parity									
Parous	326	13.8	22.0	32.3	67.5	0.80	48.4	0.08	0.33
Nulliparous	37	13.7	23.3	32.9	67.2	0.87	58.0	0.10	0.34
P for difference		0.89	0.28	0.73	0.95	0.42	0.11	0.51	0.86
Number of births[c]									
1	32	13.7	20.6	32.8	69.6	0.77	43.7	0.10	0.30
2 or 3	219	13.4	22.2	31.6	67.8	0.79	43.9	0.08	0.32
4+	75	14.7	22.3	33.2	65.8	0.86	56.0	0.08	0.35
P for trend		0.27	0.26	0.71	0.55	0.38	0.046	0.76	0.20
Age at first birth[c], yr									
<22	79	13.2	21.3	31.5	70.9	0.80	44.0	0.09	0.31
23 to 26.9	138	13.9	21.5	33.1	68.1	0.78	46.7	0.07	0.33
27+	109	14.7	22.3	33.1	64.3	0.84	52.2	0.10	0.32
P for trend		0.09	0.29	0.52	0.16	0.47	0.11	0.40	0.89
P for trend[b]		0.10	0.32	0.53	0.37	0.58	0.39	0.47	0.81
Breast-feeding[c]									
No	27	14.3	23.2	33.5	63.4	0.82	46.9	0.09	0.33
Yes	296	13.7	21.9	32.2	67.6	0.81	47.2	0.08	0.32

Table 4 Adjusted geometric mean hormone levels by breast cancer risk factors and lifestyle-factors[a] *(Continued)*

P for difference		0.59	0.33	0.53	0.47	0.87	0.96	0.85	0.87
Height, cm									
<150.9	107	13.8	22.3	32.2	69.4	0.84	54.7	0.09	0.34
151 to 156.9	126	14.3	22.1	33.4	67.2	0.81	51.9	0.08	0.34
157+	124	13.7	23.2	32.2	63.8	0.85	51.7	0.09	0.34
P for trend		0.83	0.31	0.99	0.16	0.91	0.54	0.71	0.86
P for trend[b]		0.62	0.07	0.65	0.01	0.33	0.96	0.47	0.72
BMI, kg/m^2									
<24.9	199	13.3	20.9	31.1	75.3	0.77	51.1	0.07	0.30
25 to 29.9	116	14.5	24.2	32.2	60.2	0.79	48.4	0.09	0.34
30+	40	15.5	26.4	38.4	51.2	1.15	65.3	0.16	0.50
P for trend		0.01	<0.01	<0.01	<0.01	0.01	0.21	0.01	<0.01
P for trend[b]		<0.01	<0.01	<0.01	<0.01	<0.01	0.13	0.01	<0.01
Smoking									
Never smoker	310	13.2	24.3	32.0	62.9	0.80	53.5	0.09	0.35
Past smoker	37	13.6	23.7	32.4	62.3	0.77	51.4	0.06	0.38
Current smoker	14	14.9	20.0	33.2	76.3	0.94	52.8	0.12	0.29
P for difference		0.48	0.06	0.91	0.28	0.55	0.95	0.43	0.28
Alcohol drinking									
Nondrinker	266	14.0	22.0	32.7	69.9	0.85	49.4	0.10	0.34
Occasional drinker	39	14.1	23.5	32.4	63.7	0.82	59.1	0.08	0.34
Regular drinker	58	13.5	22.2	32.4	67.1	0.83	49.8	0.08	0.34
P for difference		0.76	0.48	0.97	0.42	0.89	0.29	0.48	0.98
Physical activity in past 5 years									
No	231	14.0	22.5	32.8	66.7	0.84	52.2	0.11	0.34
≤2 days/wk	63	13.8	22.1	32.1	67.5	0.79	50.6	0.05	0.33
≥3 days/wk	68	13.5	23.3	32.1	66.8	0.85	55.8	0.07	0.35
P for trend		0.46	0.48	0.58	0.95	0.97	0.56	0.02	0.60

DHEAS, dehyroepianrosterone sulfate; BMI, body mass index; [a]Adjusted for age (continuous), ethnic group (Japanese, Japanese Brazilians, non-Japanese Brazilians (Caucasian, mixed, Black), age at first menarche (continuous), age at menopause (continuous), number of births (0, 1, 2 or 3, 4+), age at first birth (≤22, 23 to 26, ≥27 yr, nulliparous), height (continuous), BMI (continuous), smoking (never smokers, past smokers, current smokers), alcohol drinking (nondrinkers, occasional drinkers, regular drinkers) and physical activity in the past 5 years (no, ≤2 days/wk, ≥3 days/wk); [b]Continuous variables; [c]Among parous women only.

of known breast cancer risk factors. This hormonal profile in Japanese Brazilians is consistent with the higher incidence and mortality rate of breast cancer in this population [4-6]. For instance, the age-adjusted incidence per 100,000 population for breast cancer among first-generation Japanese Brazilians from 1969 to 1978 was 24, while the incidences among Japanese from 1973 to 1977 were 12.7 in Osaka and 17.5 in Miyagi [4]. The standard mortality ratio for breast cancer among first-generation Japanese Brazilians from 1999 to 2001 on the basis of age-specific rates for Japanese in 2000 was 139 [5].

We also found higher circulating levels of bioavailable estradiol and estrone in Japanese Brazilians than in non-Japanese Brazilians, although levels of estradiol, testosterone and free testosterone did not significantly differ between the two populations. In the Multiethnic Cohort Study, Japanese Americans had significantly higher

estradiol levels than Caucasians and a slightly higher risk factor-adjusted incidence of breast cancer [10,18]. Although previous studies have shown lower incidence and mortality rates of breast cancer among Japanese Brazilians than among non-Japanese Brazilians [4-6], our findings suggest that the recent incidence and mortality rates among Japanese Brazilians might be similar to or higher than those of non-Japanese Brazilians.

The significant difference in sex hormone levels between Japanese Brazilians and Japanese might be determined by long-term exposure to environmental and lifestyle factors in Brazil. These differences were observed even after adjustment for known breast cancer risk factors, including BMI, which is a major determinant of estrogen levels in postmenopausal women. Although diet is one environmental factor that substantially differs between Japan and Brazil, the present study did not take into account dietary factors because we used different FFQ in the case-control studies in Nagano and São Paulo. Given that the report from the World Cancer Research Fund and American Institute for Cancer Research in 2007 showed no convincing or probable dietary risk factors for breast cancer [19], however, the difference in sex hormone levels between the two populations might not be explained by dietary factors only.

We observed an increase in estrogen and androgen levels and a decrease in SHBG levels with increasing BMI. Our findings are in general agreement with those of previous studies, and these associations have been consistently observed among both Asian and Western populations [10-13,15]. On the other hand, the determinants of sex hormone levels in postmenopausal women have not been firmly established, notwithstanding a relatively large number of epidemiological studies [10-14,16]. In the present study, we found a higher level of SHBG among women who had a later age at menopause and among shorter women. We also observed a higher level of DHEAS among women who had more births and a lower level of testosterone among physically more active women. In addition to the lack of consistency in these findings between the two study sites (that is, the study in Nagano vs. the study in São Paulo), our findings are inconsistent with those of previous studies, which found no significant associations among age at menopause, height and SHBG level, for example, or number of births and DHEAS level [12-14]. Higher physical activity levels were associated with lower levels of both estrogen and androgen [11,16], while another study reported no such association [10]. Given this lack of consistency with previous studies, our findings might be explained by multiple comparisons.

Conclusions

We found that levels of estrogen and androgen in Japanese Brazilians were higher than those in Japanese and similar to or higher than levels in non-Japanese Brazilians. Our findings may explain the previously observed increase in the incidence and mortality rate of breast cancer among Japanese Brazilians.

Abbreviations

BMI: body mass index; DHEAS: dehydroepiandrosterone sulfate; FFQ: food frequency questionnaire; IRMA: immunoradiometric assay; LOD: lower detection limit; SHBG: sex hormone-binding globulin.

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Authors' contributions

MI made substantial contribution to the conception and design of the study, as well as the analysis and interpretation of data, and was involved in drafting the manuscript. YK, SY, HO, HN, RK, GSH, INN, MSM, JM, FML and RA made substantial contributions to the study conception and design and the acquisition of data and were involved in critically revising the manuscript for important intellectual content. ST made substantial contributions to the study conception and design, as well as the analysis and interpretation of data, and was involved in critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Evaluation of Trastuzumab Without Chemotherapy as a Post-operative Adjuvant Therapy in HER2-positive Elderly Breast Cancer Patients: Randomized Controlled Trial [RESPECT (N-SAS BC07)]†

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Objective: This trial is conducted to investigate the benefit of trastuzumab monotherapy compared with a combination therapy of trastuzumab and chemotherapy in women over 70 years with human epidermal growth factor receptor type-2-positive primary breast cancer.

Methods: Inclusion criteria are the following: histologically diagnosed as invasive breast cancer and received curative operation for primary breast cancer; Stage I, IIA, IIB or IIIA/M0; and baseline left ventricular ejection fraction is $\geq$55%. Patients are randomized to receive either trastuzumab (8 mg/kg loading dose, 6 mg/kg every 3 weeks for 1 year) plus chemotherapy selected from regimens specified on the protocol or trastuzumab monotherapy. The primary endpoint is disease-free survival. Secondary endpoints are overall survival, relapse-free survival, safety, health-related quality of life, comprehensive geriatric assessment and cost effectiveness.

Results: Patients recruitment has been commenced in October 2009. Enrollment of 300 patients is planned during the 4-year recruitment period.

Conclusions: We hereby report the study concept.

*Key words: breast cancer – Phase III – elderly – HER2/*neu *– trastuzumab – monotherapy*

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INTRODUCTION

Trastuzumab with chemotherapy is the standard treatment as an adjuvant systemic therapy for human epidermal growth factor receptor type-2 (HER2)-positive primary breast cancer (1–4). Overexpression of HER2 has also been associated with potentially more aggressive tumors; therefore, trastuzumab is a key drug in the treatment of HER2-positive primary cancer. However, monotherapy of trastuzumab as an adjuvant treatment without concurrent or preceding chemotherapy is not conducted in clinical practice since its benefit has not been investigated as well as elderly patients (5). It has clinical significance to demonstrate the benefit of trastuzumab monotherapy without toxicity induced by chemotherapy, especially in elderly patients. Chemotherapy is not always a standard therapy in elderly patients based on the analysis of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) because of limited data (6). Careful monitoring is necessary for elderly patients due to toxicity, cardiac toxicity associated with anthracycline-containing chemotherapy (7,8), increasing in acute myeloid leukemia (AML) after adjuvant chemotherapy (9).

This trial is conducted to investigate the clinical positioning between trastuzumab monotherapy (H group) and a combination therapy of trastuzumab and chemotherapy (H + CT group) based on a randomized controlled trial in women over 70 years with HER2-positive primary breast cancer.

DIGEST OF THE STUDY PROTOCOL

Purpose

This study is conducted to investigate the clinical positioning between trastuzumab (Herceptin) monotherapy (H group) and a combination therapy of trastuzumab and chemotherapy (H + CT group) based on a randomized controlled trial in women over 70 years with HER2-positive primary breast cancer (Fig. 1). Our hypothesis includes the following two points:

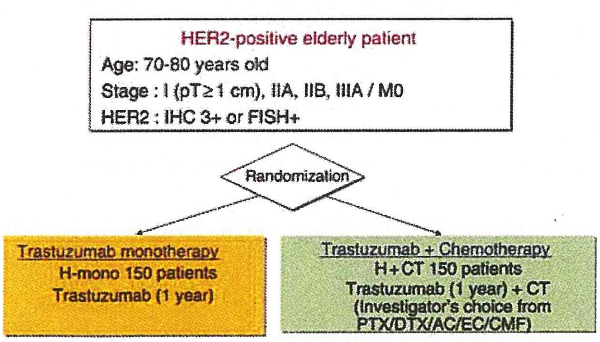

Figure 1. Study schema. Evaluation of trastuzumab without chemotherapy as a post-operative adjuvant therapy in HER2-positive elderly breast cancer patients: randomized controlled trial [RESPECT (N-SAS BC07)].
HER2, human epidermal growth factor receptor type-2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; PTX, paclitaxel; DTX, docetaxel; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-fluorouracil.

(i) H group is non-inferior to the H + CT group in disease-free survival (DFS).
(ii) H group is superior in safety and health-related quality of life (HRQOL).

Study Setting

This study is a multi-institutional prospective randomized controlled trial with 56 participating centers as of 31 August 2010.

Study Support

This study was funded by Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. All decisions concerning the planning, implementation and publication of this study were made by the executive committee of this study.

Endpoints

The primary endpoint is DFS. Secondary endpoints are overall survival, relapse-free survival, adverse events, HRQOL, comprehensive geriatric assessment and cost-effectiveness analysis.

Eligibility Criteria

Inclusion Criteria

(i) Histologically diagnosed as invasive breast cancer and received curative operation for primary breast cancer.
(ii) Stage I [tumor size (pT) ≥1 cm), IIA, IIB or IIIA/M0; female between 70 and 80 years old.
(iii) Primary cancer is HER2-positive (either 3+ overexpression or positive by fluorescence *in situ* hybridization).
(iv) Baseline left ventricular ejection fraction is ≥55% measured by echocardiography or multigated acquisition scan within 4 weeks before registration.
(v) Performance status (PS) 0–1.
(vi) Sufficient organ function meeting the following criteria within 4 weeks before registration:
  (a) Leukocyte ≥2500 mm^3
  (b) Neutrophil ≥1500 mm^3
  (c) Platelet ≥100 000 mm^3
  (d) Serum total bilirubin ≤2.0× the upper limit of normal (ULN)
  (e) Alanine aminotransferase (glutamic pyruvic transaminase) or aspartate aminotransferase (glutamic oxaloacetic transaminase) ≤2.5× ULN
  (f) Serum creatinine ≤2.0× ULN
  (g) Alkaline phosphatase ≤2.5× ULN
(vii) No previous endocrine therapy or chemotherapy for breast cancer.
(viii) Signed written informed consent.

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Exclusion Criteria

(i) Active multiple primary cancer (synchronous multiple primary cancer and invasive cancer of other organs).
(ii) Post-operative histological axillary lymph node metastasis ≥ 4.
(iii) Axillary lymph node is not histologically evaluated.
(iv) Histologically confirmed positive margin in breast conservation surgery (evaluation of margin status is based on the policy of site).
(v) History of drug-related allergy which could hinder planned treatment.
(vi) Any history or complication of the following cardiac disorders.
(vii) History of congestive heart failure, cardiac infarction.
(viii) Complication requires treatment such as ischemic cardiac disorder, arrhythmia and valvular heart disease.
(ix) Poorly controlled hypertension (e.g. systolic arterial pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg).
(x) Poorly controlled diabetes.
(xi) Continuous visit to a medial institution is considered difficult due to deterioration of activity of daily living.
(xii) Difficult to participate in the trial because of psychiatric disorder or psychiatric symptoms.
(xiii) Ineligible to the trial based on the decision of an investigator.

Patient Assignment

The CSPOR Data Center will confirm patient eligibility, and treatment will be automatically assigned according to the assignment adjustment factors for eligible patients. The following five variables will be used as assignment adjustment factors: age (70–75/76–80), PS (0/1), hormone sensitivity, lymph node metastasis and hospital.

Treatment

Combination Therapy of Trastuzumab and Chemotherapy Arm

The loading administration dose of trastuzumab is 8 mg/kg of body weight, and the maintenance dose is 6 mg/kg every 3 weeks for 1 year. Chemotherapy is selected from regimens specified on the protocol based on the decision of a physician or a patient.

(i) Paclitaxel (PTX) 80 mg/m^2 weekly administered every week for 11 cycles.
(ii) Docetaxel (DTX) 75 mg/m^2 every 3 weeks for four cycles.
(iii) Doxorubicin (A) 60 mg/m^2 and cyclophosphamide (C) 600 mg/m^2 every 3 weeks for four cycles.
(iv) Epirubicin (E) 90 mg/m^2 and cyclophosphamide (C) 600 mg/m^2 every 3 weeks for four cycles.
(v) Cyclophosphamide (C) 75–100 mg orally from days 1 to 14, methotrexate (M) 40 mg/m^2 on days 1 and 8 intravenously, and 5-fluorouracil (F) 500–600 mg/m^2 intravenously on days 1 and 8, every 4 weeks for six cycles.

Administration of trastuzumab initiates after completion of chemotherapy as a sequential combination. However, concomitant administration is allowed when combining trastuzumab with PTX, DTX and CMF.

If the hormone receptor is positive, hormone therapy is indicated. In the case of after breast conservative operation, irradiation for breast is indicated after chemotherapy.

Trastuzumab Monotherapy Arm

The loading dose of trastuzumab is 8 mg/kg of body weight, and the maintenance dose is 6 mg/kg every 3 weeks for 1 year.

If hormone receptor is positive, hormone therapy is indicated. In case of after breast conservative operation, irradiation for breast is indicated after surgery or concurrent with trastuzumab.

Stratification Factors

(i) Age at registration: 70–75/76–80
(ii) PS: 0/1
(iii) Hormone receptor status: positive/negative
(iv) Pathological nodal status: positive/negative
(v) Institution

Statistical Analysis

Main Analysis and Assessment Criteria

To evaluate the clinical position of each treatment, the estimated hazard ratio is compared with a threshold hazard ratio of 1.69. Concretely, the threshold will be used to determine whether the H + CT group is equivalent (not inferior) to the H group with regard to DFS. As an aid to interpret the trial result, we will estimate the three posterior probabilities between and outside the following two thresholds: 'the upper threshold of hazard ratio (1.69) to select the combination therapy of trastuzumab and chemotherapy' and 'the lower threshold (1.22) to select the monotherapy of trastuzumab', using the posterior distribution of log hazard ratio based on a non-informative prior.

Sample Size and Follow-up Period

The primary endpoint will require 120 events in total, given a power of 80% and a threshold hazard ratio of 1.69. Giving that the 3-year DFS probability in the study population is 68% and assuming that the survival time follows the exponential distribution, a total of 260 patients will be necessary for 3 years of follow-up after 4 years of registration to assess the 120 events. Therefore, the target number of registration was determined to be 300 since exponential distribution of survival might not be shown because of the elderly population and dropout patients were expected.

This study has been started from October 2009 and completion is scheduled in October 2016 with a registration period for 4 years and a follow-up period for 3 years.

Registration of the Protocol

The protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000002349), on 1 September 2009. Details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000002854&language=E.

And also registered at ClinicalTrials.gov (protocol ID NCT01104935), on 6 November 2009. Details are available at the following address: http://clinicaltrials.gov/show/NCT01104935.

Funding

This study is supported by the Public Health Research Foundation, Japan. The corporate and individual sponsors of this study are listed on the CSPOR website (http://www.csp.or.jp/cspor/kyousan_e.html).

Conflict of interest statement

Hiroji Iwata and Yasuo Ohashi receive honoraria for speaking events from Chugai Pharmaceutical Co., Ltd.

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ほら、あなたのまちでも…
そこに「がん予防」が…

連載

エビデンスの最前線&ナラティブな実践事例
【第3回】

ソーシャルマーケティングを活用したがん予防行動の「普及」の試み

独立行政法人国立がん研究センターがん対策情報センター
溝田友里　山本精一郎

がん予防に関しては、日本人を対象とした疫学研究により、発症に関わる原因の科学的根拠が蓄積され、「日本人のためのがん予防法」が示されています。多くのがんは喫煙や飲酒、食事、身体活動などの生活習慣の改善で予防できますが、「たばこを吸わない」「野菜不足にならない」「日常生活を活動的に過ごす」といったことは十分知られている情報にもかかわらず、実践には結びついていません。そこで私たちは、がん予防に関する科学的根拠（エビデンス）と実践（プラクティス）とのギャップ（エビデンス・プラクティスギャップ）を埋め、国民にがん予防行動を普及させることを目的として、厚生労働科学研究費補助金による研究班「エビデンスに基づいたがん予防知識・行動の普及および普及方法の評価」研究班（研究代表者＝山本精一郎）を立ち上げました。ここでは、その成果の一端を紹介します。

がん予防行動の普及と現場のサポート方法の開発

がん予防に関し、研究者の多くは、研究結果を学術誌や報告書等に掲載するだけで、それが実践に活かされるところまでは立ち入っていませんでした。一方、行政や自治体、学校などの現場でも、研究結果に関する情報が少なく、また普及についての専門家でもないため、十分ながん予防行動の普及が行えていないことが少なくありませんでした。

そこで、私たちの研究班では、研究者と普及のための専門家との協働により、がん予防行動を全国規模で戦略的効果的に普及するとともに、現場のサポートを行うための方法を開発し、実践することを目的として、研究を行いました（図1）。

この研究班の最大の特徴は、ソーシャルマーケティングの手法をがん予防行動を普及させるために取り入れるという点です。ソーシャルマーケティングとは、費用対効果を重視し、徹底した市場調査にもとづいて商品を売るためのプロモーション（広告、PRなど）を行うマーケティング手法を公衆衛生分野に取り入れて、一般市民への普及啓発を戦略的に行う取り組みです。すでに欧米では、国の施策として積極的に活用されはじめています。

二点目の特徴としては、がん予防に関する新しい規範を形成し、メディア等を戦略的に活用し、より広い普及と社会規範としての醸成を目指すという点が挙げられます。一例を挙げれば、「たばこはがんの原因」というメッセージだけでは禁煙や防煙（たばこを吸いはじめるのを防ぐこと）には結びつかないことが多いため、たばこの不利益に関する新しいメッセージを開発し、それをメディアなどを通じて広げていくことにより、たばこに関する新しい社会規範をつくり出し、結果としてたばこを吸う人を減らすことなどを目指しました。

その実現のために研究班では、研究者だけではなく、普及のための専門家として、実際に大手企業で商品の広告などを担当していたマーケティングの専門家や、PRの実務者にも加わってもらっています。

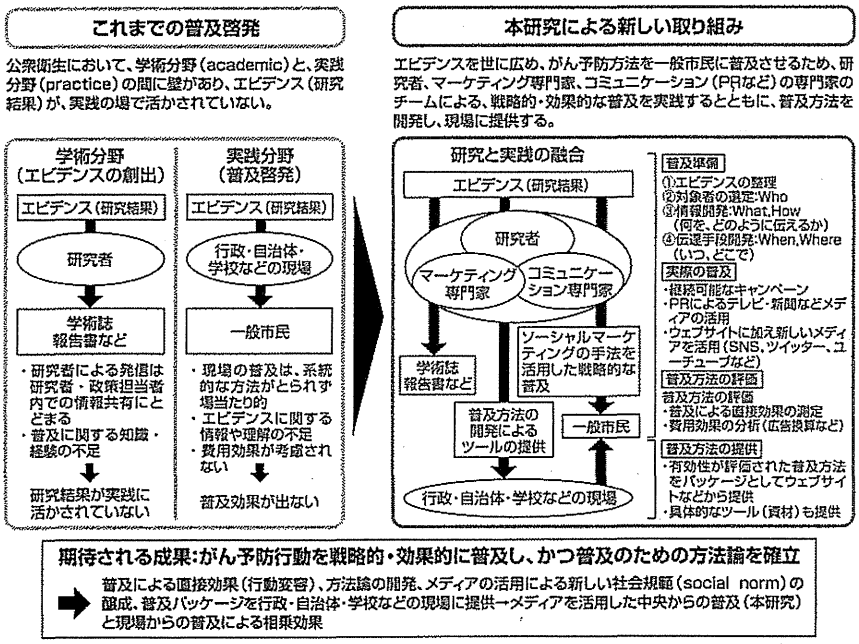
禁煙・防煙プロジェクトの戦略―開発

禁煙等を促すコンセプトづくり

研究班では、「禁煙・防煙」「野菜摂取量の増加」「身体活動の増加」の三つを柱にするとともに、がん予防の知識と行動を普及させるための教育的なゲーム（シリアスゲーム）の開発を行っています。今回は、そのなかで「禁煙・防煙」の普及のための取り組みをご紹介します。普及を行うにあたっては、何を、誰に、どのように、伝えるかを決めるために、各段階について綿密な調査と分析を繰り返しました（二二頁図2）。

そして、対象者の選定を行いました。既存データの利用や推計を行い、①男性喫煙者の三割が一八～二二歳の間に喫煙を開始してい

図1　ソーシャルマーケティングを活用したがん予防行動の普及



る、②そのうち四分の一がたばこを吸わなければ、年間約一万五、〇〇〇人のがん死亡が防げる、③喫煙開始を大学卒業時まで遅らせることができれば、年間約一、二〇〇人のがん死亡を防げると推定される、④中高生、職域での喫煙対策に比べ、大学生を対象とした喫煙対策が十分行われていない、⑤吸いはじめた年数が短いため、禁煙治療の保険適応ではない、⑥若いうちはニコチン依存の程度が高くない――などの理由から、大学生を対象とすることにしました。

次いで、マーケティングの手法に則り、大学生に対する個別インタビューやグループインタビュー、インターネット調査などを繰り返し、「どうしてたばこを吸っているのか?」「どのような生活を送っているのか?」「現在、何に関心があるのか?」「どのような価値観を持っているのか?」「大学生はどのようなタイプに分けられるのか?」などを調べました。

それらの結果から、大学生の禁煙・防煙を促すコンセプトの開発を行いました。すなわち、「たばこによってストレス解消できると思っているけど、実はニコチン中毒によるイライラをニコチンを補うことによって鎮めているだけ」「たばこを吸うと異性にモテない」「ニコチン依存のメカニズムは薬物依存と同じ」「たばこの臭いは嫌われる」などさまざまなコンセプトの候補を練り、実際の大学生の反応を調べる調査を行いました。

そしてその調査から、「たばこを吸うと就職に不利」というコンセプトが最も強い影響力を持つことが明らかになりました。

禁煙・防煙プロジェクトの戦略――実行「たばこと就職」に着目したプラン

①全体の計画

次のステップは、戦略的にPRを行うことです。すなわち、「たばこを吸うと就職に不利」というコンセプトを世の中に広げていくための具体的な準備です。

企業が商品をPRする際に考えられているのは、「広告投下量を多くすると認知度が上がる」×「認知度が上がると買おうとする気持ちが強くなる」という関係です。そこで、その考え方と同様に、「たばこを吸うと就職に不利というコンセプトをメディアに載せて認知度を上げる」×「このコンセプトを知ると、たばこを吸わない（禁煙・防煙）という気持ちが強くなる」という二つの柱を普及のための目標とし、その実現に向けた方策をとることにしました。

また、コンセプトを具体化していく際には、「たばこを吸うと就職できない」と脅すようなアピールをするのではなく、「就職活動を機に自分の人生や社会に出ることを考えることと同様に、たばこを吸うことについても考えてみよう」というメッセージが伝わるように注意を払いました。

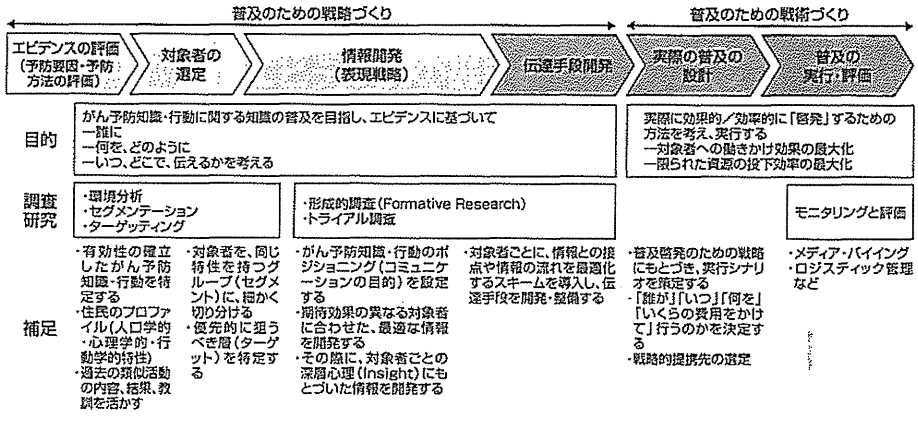
②「喫煙と就職」の科学的根拠づくり

「認知度を上げやすく（メディアなどでも話題になりやすく）」、かつ「たばこを吸わない（禁煙・防煙）という気持ちが強くなりやすい」というコンテンツの作成を目指し、まずは喫煙と就職に関する科学的根拠の構築を進めました。非喫煙者であることを採用条件とする企業がいくつか存在していることは、すでに新聞報道などにも紹介されていましたが、実際にどのくらいの企業が非喫煙者を採用条件にしているのか、企業の人事担当者は新卒者の喫煙をどのように考えているのか、については明らかになっていませんでした。

そこで、このコンセプトに説得力を持たせるために、喫煙と就職に関する定量的、定性的な科学的根拠を得ることを目的に、企業の人事担当者を対象として、喫煙と採用に関する三つの調査（インタビュー調査、郵送調査、インターネット調査）を実施しました。

インターネット調査の結果の一

図2　ソーシャルマーケティングの手法を活用した普及までの流れ



部をご紹介すると、企業の人事担当者八三八人のうち、「新卒採用の際に、応募者の喫煙が採用に影響した可能性」について、約三割が「これまでに何らかの影響があった」と回答しており、さらに、約半数が「今後、何らかの影響がある」と回答していました。また、自分の所属する会社に関して、「現在、喫煙の有無を採用基準としている」と回答したのは三・七%、「現在、検討中」としたのが一四・三%という結果でしたが、現在のところ、「設定も検討もしていない」または「わからない」と答えた六八七人も、七・六%が「今後採用基準としてもいいと思う」、四五・七%が「採用基準ではないが、考慮してもいいと思う」と回答しており、半数以上の人事担当者が何らかの考慮を行うつもりであることが明らかになりました。ちなみに詳しい調査結果は、後述の研究班ウェブサイトで公開中なので、参照して下さい。

③クリエイティブ（普及資材）の開発

続いて、人を惹きつけるコンテンツづくりのプロである広告代理店の担当者との協働によって、クリエイティブ（普及資材など）の開発を進めました。具体的には、さまざまな候補のなかから大学生を対象に調査を行ったり、研究班で討議を重ねた結果、最終的には「TRUE FALSE ―就活と喫煙にまつわる不都合な真実」を平成二十二年度の禁煙・防煙プロジェクトのテーマとしました。

すなわち、就活に関するTRUE FALSE（ウソホント）として、就活に関して学生の間でまことしやかに言われているような「都市伝説」をFALSEとし、喫煙と就職に関する研究班の調査結果などをTRUEとして、さまざまなTRUE FALSEを作成したのです。このTRUE FALSEをもとに、研究班のウェブサイト（http://prev.ncc.go.jp/truefalse/index.html）を立ち上げたほか、音楽と映像を組み合わせたムービーや、ロゴを使った文具なども作製しました。なお、研究班のウェブサイトでは、TRUE FALSEだけでなく、調査結果の詳細やたばこによる健康被害、禁煙方法などについても紹介しています（図3）。

また、平成二十三年一月十四日には、大手企業人事担当者に参加してもらい、大学生の就職活動と喫煙の関係を考えるシンポジウム「就活と喫煙にまつわる不都合な真実」と題して、大学生を対象にシンポジウムを開催しました。

④PR活動

コンテンツづくりと並行して、認知度を上げるためのPR活動を進めました。すなわち、禁煙・防煙プロジェクトの企画の段階からNHKとタイアップし、調査結果やシンポジウムを番組で取り上げてもらうこととしました。また、シンポジウムに関しては、インターネットを中心とするメディアや新聞記事、就職活動を行う大学生が数多く登録する大手メーリングリスト、SNS（ソーシャル・ネットワーキング・サービス）、twitter（ツイッター）などを使って告知を行いました。なお、TRUE FALSEのムービーは、研究班のウェブサイトのほか、youtube（ユーチューブ）でも公開しています。

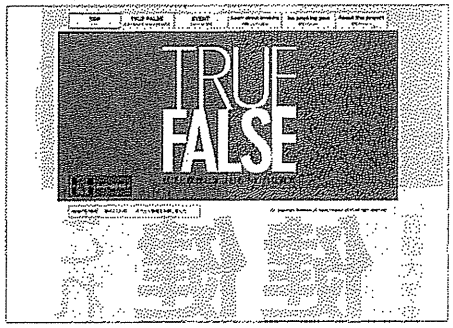
禁煙・防煙プロジェクトの戦略―評価
大きな反響を与え、目標を達成

禁煙・防煙プロジェクトの二つの柱である「たばこと就活のコンセプトをメディアに載せて認知度を上げる」×「コンセプトを知ると、たばこを吸わない（禁煙・防煙）という気持ちが強くなる」について、平成二十二年度の活動をもとに、目標が達成できたかの評価を行いました。

①「たばこを吸うと就職に不利のコンセプトをメディアに載せて認知度を上げる」の評価

研究班で実施したシンポジウムの様子は、当日のNHK「ニュースウォッチ9」で大きく取り上げられ、七分二十秒にわたって放送されました。このほかにも、企業の人事担当者を対象に実施した喫煙と採用に関する調査結果がNHK「お昼のニュース」、NHK

図3「エビデンスに基づいたがん予防知識・行動の普及および普及方法の評価」研究班のウェブサイト



(http://prev.ncc.go.jp/truefalse/index.html)

「ｂｉｚ・スポ」でそれぞれ一分三〇秒ほど放送されるとともに、日本経済新聞をはじめとする新聞五紙にも掲載されました。さらに、時事通信から発信されたほか、asahi.com、gooニュース、excite.ニュースといった数多くのポータルサイトからも発信されました。このうち、Yahoo!ニュースでは、記事に対するコメントが一週間で五、七〇〇件寄せられ、コメントに対する「私もそう思う」という投票は多いもので二万件以上も寄せられました。

そのほか、個人のブログや2ちゃんねる、mixi（ミクシィ）といった媒体でも非常に多くの話題に上っており、ネット上のさまざまなところで議論が沸き起こりました。

②「コンセプトを知ると、たばこを吸わない（禁煙・防煙）という気持ちが強くなる」の評価

「たばこを吸うと就職に不利」というコンセプトを知ると、どのように思うかを調べるため、シンポジウム参加者に対する会場アンケートによる評価を行いました。

参加者のうちアンケートに回答した三九人の回答によると、シンポジウムの前後による比較では、「喫煙で就職が不利になる可能性」があると思っていたのは、シンポジウム前では二五・六％でしたが、シンポジウム後では八二・一％に増加していました。また、「今後、喫煙と就職の関係は強くなっていくと思う」と回答したのは七六・九％、「喫煙で就職が不利になる可能性について周囲の人に教えてあげたい」と答えたのは八四・六％となり、このコンセプトが信頼され、また口コミ効果も期待できることが明らかになりました。

そもそもたばこをテーマとしたシンポジウムへの参加者であるため、喫煙者の割合が少なかったのですが、喫煙者からは「就職のために禁煙しよう」と思ったという感想が多く寄せられました。

③「たばこを吸うと就職に不利のコンセプトをメディアに載せて認知度を上げる」×「コンセプトを知ると、たばこを吸わない（禁煙・防煙）という気持ちが強くなる」の評価

テレビや新聞、ポータルサイトによる報道を広告換算してみると、テレビ三件で四、五五七万円、新聞五件で九五二万円、ポータルサイト（広告料金がわかったものだけ）で二、九〇〇万円相当となり、少なくとも七、六三〇万円以上の広告効果があったことがわかりました。また、テレビと新聞の報道に触れた人数の推計については、テレビでは視聴率換算で延べ一、九七〇万人、新聞では発行部数が四三九万部で、推計二、四〇〇万人以上の目に触れたことが期待されます（サイトの閲覧数は評価方法を検討中）。

さらに、シンポジウム参加者に関しては、シンポジウム参加後に喫煙と就職が関係あると思うようになったという割合が五六・四％増えていました。

実際には、報道を目にしただけでは、シンポジウムに参加するほどの効果は得られないと考えられますが、十分効果があったとした場合、単純計算で、コンセプトに触れた人二、四〇〇万人×五六・四％、すなわち一、三四四万人の人々の認識に変容を促したことになります。

一方、複数のポータルサイトや2ちゃんねる、mixiなどでも、「愛煙家vs.嫌煙家」の大議論が巻き起こっており、多くのネットユーザーに対して、喫煙と就活についての問題を考える機会を与える効果があったことが推測されます。

風潮づくりと現場からのアプローチが一体化することが今後の課題

ソーシャルマーケティングを活用して行った禁煙・防煙プロジェクトは、認知度を上げるという点、たばこを吸わないという気持ちを強めるという点で、効果があったと期待できます。そして、「新しい社会規範」の醸成を前進させることができたと考えています。禁煙・防煙プロジェクトは今回だけで終わらず、今後もイベントの開催やウェブサイトの充実など、より広い展開を行っていく予定です。また、「禁煙・防煙」だけでなく、「野菜摂取量増加」や「身体活動増加」についても、今後活動を行っていく予定です。

がん予防行動の普及には、今回ご紹介したような風潮づくりだけでなく、現場からのアプローチも当然必須です。現場で取り組みを行う際などには、私たちの研究班のウェブサイト(http://prev.ncc.go.jp/truefalse/index.html)をご活用いただけると幸いです。

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Dietary Isoflavone Intake, Polymorphisms in the CYP17, CYP19, 17β-HSD1, and SHBG Genes, and Risk of Breast Cancer in Case-Control Studies in Japanese, Japanese Brazilians, and Non-Japanese Brazilians

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We tested the hypothesis that polymorphisms in cytochrome P450c17α (CYP17), aromatase (CYP19), 17β-hydroxysteroid dehydrogenase type I (17β-HSD1) and sex hormone-binding globulin (SHBG) 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. A total of 846 pairs (388 Japanese, 79 Japanese Brazilians, and 379 non-Japanese Brazilians) completed validated food frequency questionnaires. Four single nucleotide polymorphisms (SNPs) in CYP17 (rs743572), CYP19 (rs10046), 17β-HSD1 (rs605059), and SHBG (rs6259) genes were genotyped. We found no association between the 4 SNPs and breast cancer risk. In combination analyses of isoflavone intake and SNPs, an inverse association between intake and risk was limited to women with at least one A allele of the rs605059 polymorphism for all 3 populations, albeit without statistical significance. For the rs6259 polymorphism, the inverse association was limited to postmenopausal Japanese with the GG genotype (odds ratio [OR] for highest vs. lowest tertile = 0.50, 95% confidence interval [CI] = 0.29–0.87; *P* for trend < 0.01), and to non-Japanese Brazilians with at least one A allele (OR for consumers vs. nonconsumer = 0.21, 95% CI = 0.06–0.77). We found no remarkable difference for the rs743572 and rs10046 polymorphisms. Our findings suggest that polymorphisms in the 17β-HSD1 and SHBG genes may modify the association between isoflavone intake and breast cancer risk.

INTRODUCTION

Soy foods, a traditional staple dish in Asian countries, 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 high isoflavone intake to low breast cancer risk has been hypothesized (2). A recent meta-analysis supported this hypothesis and found a small decrease in breast cancer risk with higher soy intake (3). In contrast, a more recent meta-analysis indicated that the 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 owe to the similarity in the chemical structures of isoflavones and the human estrogen hormone, and the former's consequent binding affinity to estrogen receptors (6,7). Isoflavones can therefore act as estrogen agonists and antagonists competing for estradiol at the receptor complex (5). It has also been suggested that isoflavones may influence breast cancer risk by altering the biosynthesis, metabolism, and bioavailability of endogenous hormones. In this regard, isoflavones have been shown to inhibit aromatase (CYP19) (8–10) and 17β-hydroxysteroid dehydrogenase type I (17β-HSD1) (10–12) and to increase the synthesis of sex hormone-binding globulin (SHBG) (13,14). These findings in turn suggest that isoflavone might interact with these genes in the development of breast cancer.

Few studies have investigated whether genetic variants of genes involved in the biosynthesis, metabolism, and bioavailability of endogenous hormones modify the association between phytoestrogen exposure and risk of breast cancer (15,16). McCann et al. (15) reported that the risk-reducing effect of lignan intake on breast cancer was observed among premenopausal Caucasian women with at least one A2 allele of polymorphism in the cytochrome P450c17α (CYP17) gene but not among those with the A1A1 genotype (15). A similar result was found in a population-based case-control study in Germany in which an inverse association of plasma enterolactone and lignan intake with breast cancer risk was found among premenopausal women with the A2A2 genotype in the rs743572 polymorphism of the CYP17 gene (16). To our knowledge, however, the possible joint effect of phytoestrogen exposure and polymorphisms in the CYP19, 17β-HSD1, and SHBG genes on breast cancer risk has not been investigated.

Here, to test the hypothesis that polymorphisms in the CYP17, CYP19, 17β-HSD1, and SHBG genes might modify the association between isoflavone intake and breast cancer risk, we conducted hospital-based case-control studies in Nagano, Japan and São Paulo, Brazil, targeting 3 populations with substantially different intake of isoflavone and distribution of polymorphisms in the CYP17, CYP19, 17β-HSD1, and SHBG genes, namely Japanese living in Japan, Japanese Brazilians living in São Paulo and non-Japanese Brazilians living in São Paulo.

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 to 74 yr with newly diagnosed and histologically confirmed invasive breast cancer. Cases were recruited between 2001 and 2005 at 4 hospitals in Nagano and between 2001 and 2006 at 8 hospitals in São Paulo. A total of 405 cases (98%) participated in Nagano and 83 Japanese Brazilians (91%) and 389 non-Japanese Brazilians (99%) in São Paulo. In the Nagano study, eligible controls were selected from medical checkup examinees in 2 of the 4 hospitals and confirmed not to have cancer. One control was matched for each case by age (within 3 yr) 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 case by age (within 5 yr) and ethnicity.

Among potential controls, 22 patients refused to participate (participation rate = 96%). Eventually, we obtained written informed consent from 472 matched pairs (83 Japanese Brazilians and 389 non-Japanese Brazilians). The study protocol was approved by CONEP (Comissão Nacional de Ética em Pesquisa), 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, whereas those in São Paulo were interviewed by trained interviewers using a structured questionnaire. The two questionnaires contained closely 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 (17–19). 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 (20,21). 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 (5th ed.) for the Japanese version (22) and the United States Department of Agriculture (USDA) food composition tables for the Brazilian version (23). For some Japanese-specific foods in the Brazilian version, the Japanese Standard Tables of Food Composition 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 4 consecutive 7-day dietary records, one conducted in each the 4 seasons. Spearman's correlation coefficients between energy-adjusted genistein and daidzein intake estimated from the FFQ and from dietary records were 0.59 for genistein and 0.60 for daidzein (18). 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 4-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 (19).

Genotyping

Genomic DNA samples were extracted from the peripheral blood using Qiagen FlexiGene DNA Kits (Qiagen K.K., Tokyo, Japan) according to the manufacturer's protocol. We selected 4 single-nucleotide polymorphisms (SNPs) in CYP17 (rs743572), CYP19 (rs10046), 17β-HSD1 (rs605059), and SHBG (rs6259); these genes were the most frequently studied SNPs in relation to breast cancer risk (24–31). Genotyping of the 4 SNPs was performed by a commercial laboratory (Genetic Lab, Inc., Sapporo, Japan) using the TaqMan SNP Genotyping Assays developed by Applied Biosystems (Foster City, CA; Table 1). Cases and matched controls were analyzed in the same well by laboratory personnel who did not know the case-control status. As quality control assessment, we genotyped 6 SNPs of 4 genes (N-acetyltransferase 2 [NAT2], CYP17, CYP19, and cytochrome P450 2E1 [CYP2E1]) in our laboratory using about 24% of the samples in this study. The concordance rates between Genetic Lab. and our laboratory were varied between 97.6% and 99.5% among the 6 SNPs. In particular, the concordance rates of rs743572 and rs10046 polymorphism were 98.3% and 97.6%, respectively.

Statistical Analysis

We excluded subjects who reported extremely low or high total energy intake ($<$500 or $\geq$4,000 Kcal) or had no DNA sample, leaving 388 pairs of Japanese, 79 pairs of Japanese Brazilians, and 379 pairs of non-Japanese Brazilians for use in these analyses. 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 chi-square 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 nonconsumers 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 intakes and the SNP of interest. The following variables, selected mainly based on the basis of 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 yr, 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 2-sided, and significance level was set at $P < 0.05$. All statistical analyses

TABLE 1
Single-nucleotide polymorphisms (SNPs) in CYP17, CYP19, 17β-HSD1, and SHBG genes and their allele frequency[a]

Gene	SNP rs Number	Amino Acid Change	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
CYP17A1	rs743572	5′-UTR	T/C	0.45	0.50	0.39
CYP19A1	rs10046	3′-UTR	C/T	0.43	0.44	0.42
HSD17B1	rs605059	Ser312Gly	G/A	0.47	0.49	0.48
SHBG	rs6259	Asp327Asn	G/A	0.12	0.17	0.10

[a]Abbreviations are as follows: CYP, cytochrome P450; 17β-HSD1, 17β-hydroxysteroid dehydrogenase type I; SHBG, sex hormone-binding globulin.

were performed with SAS software version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of cases and controls were described in a previous report (32) (data not shown in table). 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, whereas 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 46.2 for Japanese, 23.5 for Japanese Brazilians, and 4.4 for non-Japanese Brazilians.

The distribution of SNPs in the CYP17 (rs743572), CYP19 (rs10046), 17β-HSD1 (rs605059), and SHBG (rs6259) genes is presented in Tables 1 and 2. Among controls in each population, genotype frequencies of each SNP were consistent with the Hardy Weinberg equilibrium except for the rs743572 polymorphism in non-Japanese Brazilians ($P = 0.04$). The prevalence of the minor allele in the rs743572 and rs6259 polymorphisms was somewhat higher in the control group of Japanese and Japanese Brazilians than in that of non-Japanese Brazilians. None of the individual SNPs was associated with the risk of breast cancer for any of the 3 populations (Table 2). In stratified analyses by menopausal status, none of the adjusted ORs showed statistical significance for all 4 SNPs in any of the 3 populations except for ORs for premenopausal women with the CC vs. TT genotype of the rs743572 polymorphism (OR = 2.88, 95% CI = 1.30–6.37) and for postmenopausal women with the CT vs. CC genotype of the rs10046 polymorphism (OR = 0.61, 95% CI = 0.40–0.95) among non-Japanese Brazilians (data not shown).

In a previous report, we found a nonsignificant inverse association between isoflavone intake and the risk of breast cancer in postmenopausal Japanese but a statistically significant inverse association for Japanese Brazilians and non-Japanese Brazilians (32). Analyses of combinations of isoflavone intake and the rs605059 polymorphism in the 17β-HSD1 gene revealed that the risk of breast cancer only decreased with increasing isoflavone intake for women with at least one A allele for postmenopausal Japanese (OR for highest vs. lowest tertile = 0.62, 95% CI = 0.28–1.39; P for trend = 0.03), Japanese Brazilians (OR for highest vs. lowest median = 0.74, 95% CI = 0.28–2.00), and non-Japanese Brazilians (OR for consumers vs. nonconsumers = 0.51, 95% CI = 0.28–0.94), although no statistically significant interaction was found (P for interaction = 0.49, 0.15, and 0.33, respectively; Tables 3 and 4). For the rs6259 polymorphism in the SHBG gene, the significant inverse association was limited to women with the GG genotype for postmenopausal Japanese (OR for highest vs. lowest tertile = 0.50, 95% CI = 0.29–0.87; P for trend < 0.01) and Japanese Brazilians (OR for highest vs. lowest median = 0.38, 95% CI = 0.16–0.89; P for interaction = 0.06 and 0.32, respectively). In contrast, the association was limited to women with at least one A allele for non-Japanese Brazilians (OR for consumers vs. nonconsumer = 0.21, 95% CI = 0.06–0.77; P for interaction = 0.16). We found no remarkable difference in the association between isoflavone intake and breast cancer risk by polymorphisms in the CYP17 and CYP19 genes.

DISCUSSION

In these case-control studies of Japanese, Japanese Brazilians, and non-Japanese Brazilians, we found that an inverse association between isoflavone intake and breast cancer risk only appeared among women with at least one A allele of the rs605059 polymorphism in the 17β-HSD1 gene. Moreover, an inverse association was limited to women with the GG

TABLE 2
Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer according to polymorphisms in CYP17, CYP19, 17β-HSD1, and SHBG genes[a]

	Japanese Living in Nagano, Japan				Japanese Brazilians Living in São Paulo, Brazil				Non-Japanese Brazilians Living in São Paulo, Brazil			
	No.				No.				No.			
	Case	Control	OR[a]	95% CI	Case	Control	OR[a]	95% CI	Case	Control	OR[b]	95% CI
CYP17A1 gene (rs743572)												
TT	111	122	1.00		17	23	1.00		135	130	1.00	
TC	189	182	1.30	(0.91–1.86)	48	33	2.34	(0.93–5.88)	185	200	0.94	(0.69–1.29)
CC	88	84	1.42	(0.92–2.18)	13	23	0.53	(0.17–1.64)	59	49	1.08	(0.68–1.71)
TC + CC	277	266	1.33	(0.95–1.87)	61	56	1.53	(0.68–3.45)	244	249	0.97	(0.71–1.31)
CYP19A1 gene (rs10046)												
CC	118	125	1.00		24	22	1.00		133	121	1.00	
CT	188	194	1.05	(0.73–1.51)	41	44	0.97	(0.43–2.16)	179	200	0.82	(0.59–1.13)
TT	82	69	1.30	(0.82–2.05)	14	13	1.02	(0.39–2.72)	67	58	1.01	(0.65–1.57)
CT + TT	270	263	1.12	(0.80–1.57)	55	57	0.99	(0.47–2.09)	246	258	0.86	(0.63–1.17)
HSD17B1 gene (rs605059)												
GG	108	109	1.00		21	18	1.00		103	101	1.00	
GA	199	187	1.04	(0.71–1.53)	36	45	0.84	(0.37–1.95)	187	187	0.98	(0.70–1.39)
AA	78	88	0.87	(0.54–1.38)	13	16	1.19	(0.39–3.65)	84	88	0.94	(0.62–1.43)
GA + AA	277	275	0.99	(0.68–1.43)	49	61	0.93	(0.43–2.00)	271	275	0.97	(0.70–1.34)
SHBG gene (rs6259)												
GG	304	303	1.00		62	55	1.00		317	306	1.00	
GA	80	78	0.89	(0.60–1.33)	17	22	0.59	(0.25–1.39)	57	71	0.74	(0.50–1.09)
AA	4	7	0.28	(0.06–1.30)	0	2	—	—	5	1	5.77	(0.64–51.71)
GA + AA	84	85	0.83	(0.56–1.22)	17	24	0.53	(0.23–1.22)	62	72	0.80	(0.54–1.17)

[a]Abbreviations are as follows: CYP, cytochrome P450, 17β-HSD1, 17β-hydroxysteroid dehydrogenase type I; SHBG, sex hormone-binding globulin.

[b]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 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), and vitamin supplement use (yes, no).

TABLE 3

Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer for combinations of dietary intake of isoflavone and polymorphisms in CYP17, CYP19, 17β-HSD1, and SHBG genes among Japanese[a]

	All Subjects				Premenopausal Women				Postmenopausal Women			
	Isoflavone Intake (mg/Day), Tertile Category				Isoflavone Intake (mg/Day), Tertile Category				Isoflavone Intake (mg/Day), Tertile Category			
	1	2	3	*P* for Trend	1	2	3	*P* for Trend	1	2	3	*P* for Trend
CYP17A1 gene (rs743572)												
TT												
No.[b]	51/40	29/39	31/43		28/19	13/16	10/11		23/31	16/23	21/32	
OR[c]	1.00	0.76	0.67	0.22	1.00	0.57	0.59	0.62	1.00	0.79	0.54	0.20
(95% CI)		(0.37–1.57)	(0.32–1.43)			(0.21–1.53)	(0.19–1.84)			(0.32–1.98)	(0.23–1.30)	
TC + CC												
No.[b]	100/89	89/90	88/87		51/47	39/27	35/15		49/42	50/63	53/72	
OR[c]	1.14	1.06	1.03	0.76	0.85	1.12	1.55	0.21	0.98	0.78	0.65	0.19
(95% CI)	(0.64–2.03)	(0.61–1.86)	(0.56–1.91)		(0.40–1.81)	(0.50–2.51)	(0.63–3.79)		(0.45–2.10)	(0.37–1.64)	(0.31–1.36)	
	P for interaction = 0.78				*P* for interaction = 0.18				*P* for interaction = 0.91			
CYP19A1 gene (rs10046)												
CC												
No.[b]	46/36	36/46	36/43		28/19	15/15	18/11		18/17	21/31	18/32	
OR[c]	1.00	0.62	0.53	0.14	1.00	0.68	0.88	0.67	1.00	0.77	0.49	0.09
(95% CI)		(0.30–1.26)	(0.25–1.14)			(0.26–1.80)	(0.32–2.45)			(0.31–1.90)	(0.19–1.27)	
CT + TT												
No.[b]	105/93	82/83	83/87		51/47	37/28	27/15		54/46	45/55	56/72	
OR[c]	0.78	0.79	0.75	0.72	0.66	0.81	1.05	0.24	1.10	0.90	0.75	0.16
(95% CI)	(0.43–1.42)	(0.43–1.45)	(0.39–1.43)		(0.31–1.39)	(0.36–1.82)	(0.42–2.64)		(0.49–2.46)	(0.40–2.03)	(0.34–1.66)	
	P for interaction = 0.35				*P* for interaction = 0.52				*P* for interaction = 0.81			
HSD17B1 gene (rs605059)												
GG												
No.[b]	39/40	28/36	41/33		20/23	14/19	17/7		19/17	14/17	24/26	
OR[c]	1.00	0.96	1.51	0.31	1.00	0.80	2.76	0.13	1.00	1.02	1.02	0.82
(95% CI)		(0.44–2.11)	(0.69–3.30)			(0.31–2.11)	(0.89–8.58)			(0.36–2.91)	(0.40–2.57)	
GA + AA												
No.[b]	111/89	88/90	78/96		59/43	38/24	28/18		52/46	50/66	50/78	
OR[c]	1.31	1.13	0.80	0.08	1.50	1.76	1.44	0.92	1.19	0.89	0.62	**0.03**[d]
(95% CI)	(0.71–2.41)	(0.62–2.06)	(0.42–1.51)		(0.70–3.19)	(0.77–4.01)	(0.58–3.59)		(0.52–2.70)	(0.40–1.98)	(0.28–1.39)	
	P for interaction = 0.12				*P* for interaction = 0.14				*P* for interaction = 0.49			
SHBG gene (rs6259)												
GG												
No.[b]	123/104	90/103	91/96		57/55	38/32	36/17		66/49	52/71	55/79	
OR[c]	1.00	0.91	0.81	0.30	1.00	1.13	1.72	0.12	1.00	0.64	**0.50**	**<0.01**
(95% CI)		(0.59–1.39)	(0.51–1.30)			(0.61–2.12)	(0.82–3.61)			(0.37–1.11)	**(0.29–0.87)**	
GA + AA												
No.[b]	28/25	28/26	28/34		22/11	14/11	9/9		6/14	14/15	19/25	
OR[c]	0.81	0.71	0.77	0.94	1.75	1.17	0.92	0.15	**0.28**	0.79	0.59	0.24
(95% CI)	(0.41–1.62)	(0.38–1.35)	(0.40–1.48)		(0.74–4.15)	(0.46–2.95)	(0.32–2.68)		**(0.10–0.85)**	(0.33–1.87)	(0.28–1.25)	
	P for interaction = 0.92				*P* for interaction = 0.26				*P* for interaction = 0.06			

[a]Abbreviations are as follows: CYP, cytochrome P450, 17β-HSD1, 17β-hydroxysteroid dehydrogenase type I; SHBG, sex hormone-binding globulin.

[b]No. of cases/No. of controls.

[c]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 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), 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 smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), and vitamin supplement use (yes, no).

[d]ORs and 95% CIs with statistical significance are written in bold.

TABLE 4

Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer for combinations of dietary intake of isoflavone and polymorphisms in CYP17, CYP19, 17β-HSD1, and SHBG genes among Japanese Brazilians and non-Japanese Brazilians[a]

	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	Nonconsumers	Consumers
CYP17A1 gene (rs743572)				
TT				
No.[b]	11/12	6/11	121/110	14/20
OR[c]	1.00	0.47	1.00	0.73
(95% CI)		(0.10–2.09)		(0.33–1.60)
TC + CC				
No.[b]	34/27	27/29	222/208	22/41
OR[c]	1.93	0.86	1.00	**0.49**[d]
(95% CI)	(0.65–5.72)	(0.31–2.38)	(0.73–1.38)	**(0.27–0.91)**
	P for interaction = 0.96		P for interaction = 0.43	
CYP19A1 gene (rs10046)				
CC				
No.[b]	15/10	9/12	120/104	13/17
OR[c]	1.00	0.46	1.00	0.63
(95% CI)		(0.13–1.58)		(0.27–1.44)
CT + TT				
No.[b]	31/29	24/28	223/214	23/44
OR[c]	0.89	0.48	0.88	**0.46**
(95% CI)	(0.33–2.41)	(0.16–1.42)	(0.62–1.23)	**(0.25–0.84)**
	P for interaction = 0.83		P for interaction = 0.73	
HSD17B1 gene (rs605059)				
GG				
No.[b]	13/12	8/6	91/86	12/15
OR[c]	1.00	1.78	1.00	0.81
(95% CI)		(0.32–10.07)		(0.36–1.86)
GA + AA				
No.[b]	27/27	22/34	247/230	24/45
OR[c]	1.93	0.74	1.04	**0.51**
(95% CI)	(0.61–6.14)	(0.28–2.00)	(0.73–1.47)	**(0.28–0.94)**
	P for interaction = 0.15		P for interaction = 0.33	
SHBG gene (rs6259)				
GG				
No.[b]	38/27	24/28	285/258	32/48
OR[c]	1.00	**0.38**	1.00	0.64
(95% CI)		**(0.16–0.89)**		(0.38–1.06)
GA + AA				
No.[b]	8/12	9/12	58/59	4/13
OR[c]	0.29	0.29	0.88	0.21
(95% CI)	(0.08–1.04)	(0.07–1.21)	(0.58–1.34)	(0.06–0.77)
	P for interaction = 0.32		P for interaction = 0.16	

[a]Abbreviations are as follows: CYP, cytochrome P450, 17β-HSD1, 17β-hydroxysteroid dehydrogenase type I; SHBG, sex hormone-binding globulin.

[b]No. of cases/No. of controls.

[c]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 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), and vitamin supplement use (yes, no).

[d]ORs and 95% CIs with statistical significance are written in bold.