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Appendix

TA1, FA1-FA3

Table A1. Interaction Between Participation and Treatment Regimen

Variable	HR*	95% CI	*P*
Participant *v* nonparticipant†	1.01	0.65 to 1.57	.96
CPT-11 + CDDP *v* FU	0.42	0.17 to 1.02	.06
S-1 *v* FU	0.54	0.34 to 0.86	.01
Participant and CPT-11 + CDDP	1.19	0.45 to 3.16	.72
Participant and *S*-1	1.37	0.77 to 2.44	.29

Abbreviations: HR, hazard ratio; FU, fluorouracil; CPT-11, irinotecan; CDDP, cisplatin; FU, fluorouracil.
* HRs and 95% CIs were obtained by using a Cox proportional hazards model adjusted for sex, age, histology, clinical stage, performance status, and peritoneal dissemination.
† Right-hand sides were used as the reference groups.

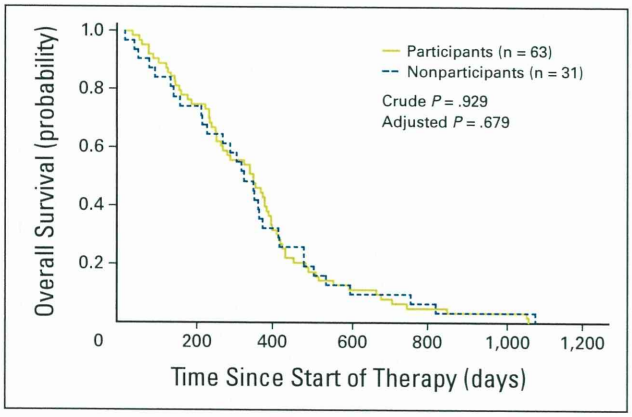

Figure A1. Overall survival of patients who were treated with fluorouracil.

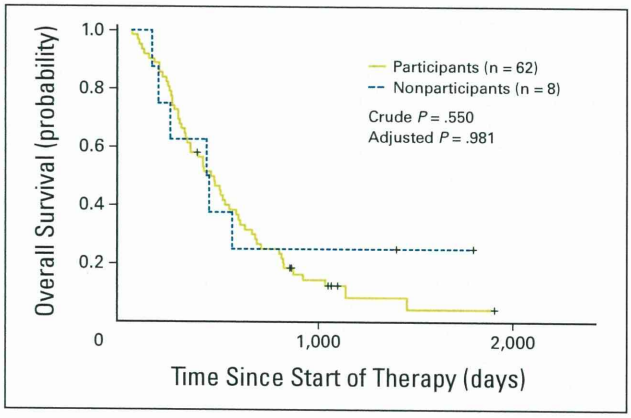

Figure A2. Overall survival of patients who were treated with irinotecan plus cisplatin.

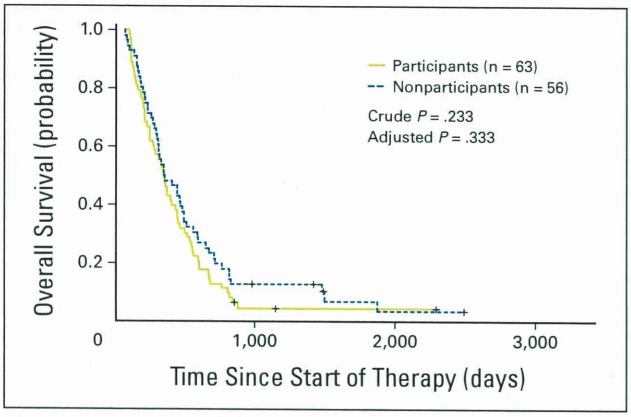

Figure A3. Overall survival of patients who were treated with *S*-1.

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Review Article

Risk factors for breast cancer: epidemiological evidence from Japanese studies

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Although our understanding of the etiology of breast cancer has improved, many well-known risk factors are not modifiable and present knowledge has proved insufficient to allow the disease to be overcome. Indeed, incidence and mortality among Japanese women have increased over the past three decades. Here, we review epidemiological evidence from our cohort and case–control studies among Japanese women in comparison with other published findings. Our studies confirm the important role of established factors derived primarily from Western populations, such as menstrual and reproductive factors, anthropometric factors, physical activity, and alcohol intake, in the development of breast cancer. In addition, we provide further evidence to better understand the role of traditional Japanese foods in the etiology of breast cancer. Our cohort study found that a higher intake of isoflavone and higher levels of plasma genistein, but not daidzein, were associated with a decreased risk of breast cancer. Our case–control studies reveal a dose–response pattern for these compounds; specifically, decreased risk as women move from "no" to "moderate" intake and leveling off thereafter. In addition, gene–environment interactions have been revealed in the effects of isoflavones. The evidence reviewed suggests that isoflavone has a protective effect against breast cancer in Asian populations. Conversely, our cohort study did not observe an inverse association between breast cancer risk and the intake of green tea and/or the plasma level of tea polyphenols, but we did find an association between increased risk and active and passive smoking. In conclusion, based on current knowledge, primary prevention according to individual lifestyle modification should focus on alcohol intake, weight control, physical activity, and tobacco smoking. (*Cancer Sci* 2011; 102: 1607–1614)

The incidence and mortality rates of breast cancer vary considerably across countries and regions, with a four to five-fold variation in incidence. Rates are highest in Europe and North America and lowest in Asia.[1] Despite Japan's status as a low-risk country, the incidence and mortality of breast cancer among Japanese women have increased over the past three decades (Fig. 1),[2–5] with age-standardized incidence rates (per 100 000 population) of 17.0 in 1975 compared with 44.4 in 2005 according to the Monitoring of Cancer Incidence in Japan (MCIJ) project.[6] Breast cancer is the most common cancer diagnosis and the fourth-leading cause of cancer death among Japanese women. For example, in 2005 the MCIJ estimated that more than 47 583 Japanese women were diagnosed with breast cancer[6] and that 10 721 died of it.[7] In contrast, mortality rates in the UK and US have been in decline since the early 1990s, possibly attributable to improvements in screening practices and treatment effectiveness.[3,8] Moreover, incidence rates in the US and several other developed countries have decreased since 2002, due, in part, to the results of the Women's Health Initiative's randomized trial in July 2002, which saw a rapid fall in the use of hormone-replacement therapy (HRT).[9]

In addition to differences in the incidence and mortality rates of breast cancer between Asian and Western countries, age-specific incidence curves also differ: in Japan, the incidence of breast cancer increases until 50 years of age and decreases or plateaus thereafter, whereas in Western countries the incidence of breast cancer continues to increase after 50 years of age (Fig. 2).[2] This pattern may be explained by differences in the distribution of risk factors for postmenopausal breast cancer, particularly the low prevalence of obesity and HRT use in Japan.[10,11] Of note, the rapid rise in rate with increasing age slows somewhat around 50 years of age, near the time of menopause, which strongly suggests a role for reproductive hormones in the etiology of this disease.

Geographical distribution and secular trends in cancer incidence and mortality, as well as studies of migrants, highlight the relative importance of environmental and lifestyle influences in cancer etiology. Studies in migrants have shown increases in breast cancer incidence and mortality following migration from a lower- to a higher-risk country.[12–14] For example, Japanese immigrants in Los Angeles County had a clearly higher rate of breast cancer than Japanese in Japan.[12] Furthermore, the incidence of breast cancer in first-generation Japanese immigrants in São Paulo from 1968 to 1978 was higher than that among Japanese living in Japan, whereas mortality increased from 1979 to 2001 to a rate intermediate between that of Japanese living in Japan and Brazilians living in the state of São Paulo.[13,14] These findings strongly suggest that breast cancer risk is influenced by factors associated with the lifestyle or environment of the destination country.

Current knowledge of preventive or risk factors

Accumulating evidence obtained mainly from Western countries has established a relatively large number of preventative or risk factors for breast cancer (Table 1).[15–17] Many established risk factors are linked to ovarian hormones, and estrogens in particular, and prospective studies in postmenopausal women have shown a direct association between higher levels of estrogens and their androgen precursors and an increased risk of breast cancer.[18] One possible biological mechanism of the effect of ovarian hormones on risk is that both endogenous and exogenous hormones increase cellular proliferation in the breast, thereby increasing the likelihood of random genetic errors during cell division.[19]

Although our understanding of the etiology of breast cancer has improved, many well-known risk factors, such as menstrual

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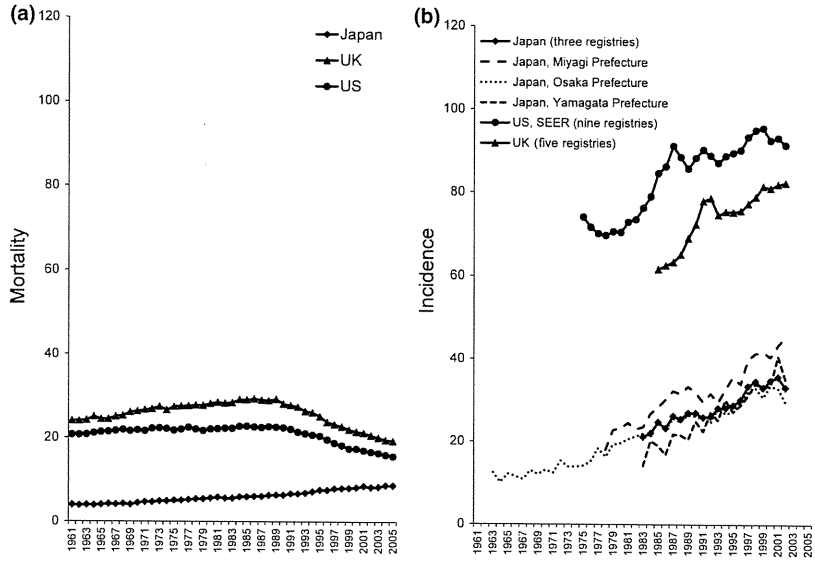

Fig. 1. Annual (a) mortality and (b) incidence rates of breast cancer in Japan, the US, and UK (standardized rate per 100 000 by age to world population). Data for the incidence rate are from Ferlay *et al.*:[2] Japan (three registries: Miyagi, Yamagata, and Osaka) from 1963 to 2002; US (Surveillance Epidemiology and End Results [SEER]; nine registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) from 1975 to 2002; and UK (five registries in England: Birmingham and West Midlands Region, Merseyside and Cheshire, North Western, Oxford, and Yorkshire) from 1985 to 2002. Mortality data are from Ferlay:[3] Japan, US, and UK from 1961 to 2005.

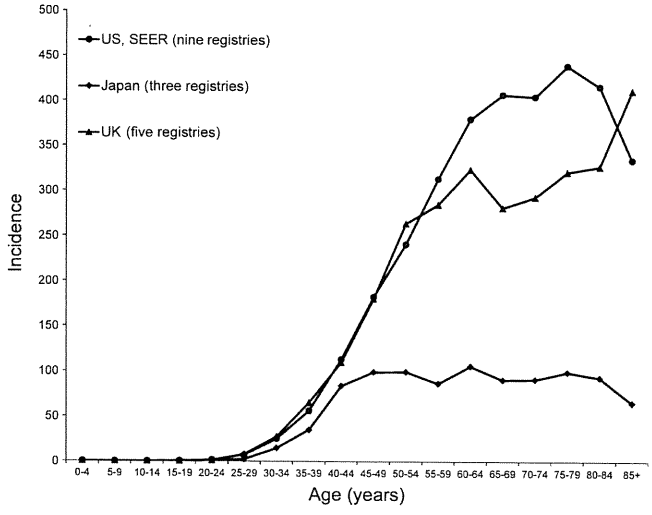

Fig. 2. Age-specific breast cancer incidence rate (per 100 000) in 2002 in Japan (three registries: Miyagi, Yamagata, and Osaka), the US (Surveillance Epidemiology and End Results [SEER]; nine registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah), and UK (five registries in England: Birmingham and West Midlands Region, Merseyside and Cheshire, North Western, Oxford, and Yorkshire). Data are from Ferlay *et al.*[2]

and reproductive factors, are not modifiable for the purpose of reducing risk. In addition, only a few dietary factors have been causally related to the etiology of breast cancer, even thought diet is an environmental factor that may contribute to the population distribution of breast cancer risk (Table 1). Not surprisingly, present knowledge has proved insufficient to allow the disease to be overcome and the identification of other important etiological factors is thus required.

Rational for epidemiological studies among Japanese

Given that the population distribution of breast cancer risk is determined by variations in exposure, the substantial difference in lifestyle and environment between Japan and Western countries leads to the following general hypothesis: if a factor is characterized by high exposure in Japan (a low-risk country), but low exposure in those Western countries that are considered high-risk countries, it may be associated with a decreased risk of breast cancer. Good examples are traditional foods in Japan, such as soy foods and green tea. Similarly, a factor with low exposure in Japan but high exposure in Western countries may be associated with increased risk. We have used this hypothesis to conduct population-based cohort and hospital-based case–control studies among Japanese women with the goal of identifying risk factors and to further our understanding of the etiology of breast cancer, as detailed below.[20,21]

Briefly, the Japan Public Health Center-based Prospective (JPHC) study, which began in 1990 for Cohort I and in 1993 for Cohort II, enrolled 140 420 subjects (68 722 men and 71 698 women) living in municipalities supervised by 11 public health centers.[20] The study population consisted of registered Japanese inhabitants aged 40–59 years in Cohort I and 40–69 years in Cohort II. Approximately 55 000 women returned a self-administered questionnaire (response rate ~83%) and approximately 25 000 women provided a blood sample (response rate ~45%) in the baseline survey from 1990 to 1995. We conducted 5- and 10-year follow-up surveys to collect information regarding dietary habits, changes in lifestyle, and disease occurrence, as well as information regarding residential status, mortality, and incidence of cancer and cardiovascular diseases.

Regarding the multicenter, hospital-based case–control studies, these were conducted from 2001 to 2005 at four hospitals in Nagano Prefecture, Japan, and from 2001 to 2006 at eight hospitals in São Paulo, Brazil.[21] Cases were recruited from a consecutive series of female patients aged 20–74 years who were newly diagnosed with histologically confirmed invasive breast cancer. In the Nagano study, healthy controls were selected from

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Table 1. Established risk factors for breast cancer and corresponding results from the Japan Public Health Center-based Prospective (JPHC) study

Factor	High-risk group	Results from the JPHC study	
		Category	HR (95% CI)
Endogenous and exogenous hormones			
Endogenous estrogen levels	Higher levels	NA	
Oral contraceptive use	Users	NA	
Hormone replacement therapy	Users	NA	
Menstrual and reproductive factors			
Age at menarche	Earlier age	≥16 years *vs* <14 years†	0.73 (0.53–1.00)
Age at menopause	Later age	≥54 years *vs* <48 years‡	1.98 (1.12–3.52)
Parity	Nulliparity	Nulliparous *vs* parous†	1.92 (1.38–2.65)
Age at first birth	Later age	≥30 years *vs* <22 years†	1.63 (1.05–2.52)
History of breast feeding	No history	Have history *vs* no history†	0.86 (0.65–1.15)
Anthropometric factors			
Height	Taller women	≥160 cm *vs* 148 cm‡	2.39 (1.43–3.98)
Body fatness (postmenopausal)	Heavier women	BMI ≥30 kg/m^2 *vs* BMI <19 kg/m^2‡	2.28 (0.94–5.53)
Body fatness (premenopausal)	Leaner women	NA	
Diet and physical activity			
Alcohol intake	Drinkers	Regular drinkers (>150 g ethanol/week) *vs* never drinkers†	1.75 (1.16–2.65)
Physical activity	Inactive women	≥3 days/week *vs* <3 days/month†§	0.73 (0.54–1.00)
Other factors			
History of benign breast disease	Have history	NA	
Mammographically dense breasts	More dense	NA	
Family history in first-degree relatives	Have history	NA	
Ionizing radiation	Exposure	NA	

†All women (both premenopausal and postmenopausal women). ‡Postmenopausal women. §Participation in sports and physical activity in leisure time. Data are from Iwasaki *et al.*[23,26] and Suzuki *et al.*[34,37] BMI, body mass index; CI, confidence interval; HR, hazard ratio; NA, not available.

medical checkup examinees who were confirmed to be cancer free, with one control matched for each case according to age and residential area. In the São Paulo study, controls were preferentially selected from cancer-free patients who visited the same hospital as the index cases with one control matched for age and ethnicity. Eventually, a total of 877 matched pairs participated (405 Japanese in Nagano, along with 83 Japanese Brazilians and 389 non-Japanese Brazilians in São Paulo).

Here, we review our findings in the JPHC study and case–control studies in Nagano and São Paulo in comparison with those from other Japanese and Western studies.

Epidemiological evidence from Japanese studies: established risk factors

Menstrual and reproductive factors. Menstrual and reproductive factors play an important role in the development of breast cancer. A meta-analysis of eight case–control studies in Japan showed that early age at menarche, nulliparity and low parity, and late age at first birth were associated with increased risk.[22] Similar to previous studies from both Western and Asian countries,[15–17] the JPHC study confirmed that early age at menarche, late age at menopause, nulliparity and low parity, and late age at first birth were associated with an increased risk of breast cancer (Table 1).[23] Although a 2007 report of the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) concluded that lactation protects against breast cancer,[24] the JPHC study failed to replicate this association.[23] Furthermore, although a recent pooled analysis of 35 568 invasive breast cancer cases showed that nulliparity and late age at first birth were more closely associated with hormone receptor-positive than -negative tumors,[25] the JPHC study observed no significant difference in association by hormone receptor-defined breast cancer.[23]

Anthropometric factors. The 2007 WCRF/AICR report identified adult height as a convincing risk factor for postmenopausal breast cancer and a probable factor for premenopausal breast cancer.[24] The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood, including energy intake and exposure levels to growth hormone and insulin-like growth factor.[24] Consistent with the WCRF/AICR report, the JPHC study observed an increased risk associated with greater height, primarily among postmenopausal women (Table 1).[26]

The 2007 WCRF/AICR report documented that the association between body fatness and breast cancer risk depends on menopausal status: although greater body fatness probably protects against premenopausal breast cancer, convincing evidence suggests that it is a cause of postmenopausal breast cancer.[24] In addition, adult weight gain is a probable cause of

postmenopausal breast cancer. The mechanism of this association likely relates to levels of circulating estrogen: specifically, a decrease in levels due to an increased frequency of anovulatory cycles in premenopausal women and an increase in levels due to both an increase in estrogen production by aromatase in adipose tissue and a decrease in circulating level of sex hormone-binding globulin (SHBG) in postmenopausal women.[27]

In the JPHC study, we found a positive association between body mass index (BMI) and breast cancer risk, with the association being stronger in post- than premenopausal women (Table 1).[26] We also found an association between an increase in BMI from age 20 years to recent age with increased risk among postmenopausal women.[28] These findings generally agree with those of studies in Japan and other Asian countries.[29,30] A recent meta-analysis of cohort studies showed that risk was increased by 16% and 31% per 5 kg/m^2 increment of BMI in pre- and postmenopausal Asian women, respectively, but decreased by 9% in premenopausal and increased by 15% in postmenopausal North American women.[30] The lack of an inverse association among premenopausal women may be due to the lower prevalence of overweight women in Asian countries, with few who are sufficiently overweight to likely develop anovulation. Conversely, risk reduction due to greater body fatness in early adulthood appears to continue into the postmenopausal years, which may explain the stronger association among postmenopausal Asian than North American women. In addition, a recent meta-analysis showed a 10% decrease in risk per 5 kg/m^2 increment of BMI among premenopausal women and a 33% increase among postmenopausal women for estrogen and progesterone receptor-positive (ER^+PR^+) tumors, although no association was seen for estrogen receptor-positive and progesterone receptor-negative (ER^+PR^-) or estrogen and progesterone receptor-negative (ER^-PR^-) tumors.[31] In the JPHC study, BMI was more strongly associated with estrogen receptor-positive (ER^+) than -negative (ER^-) tumors in postmenopausal women. These findings may support the involvement of an ER-mediated estrogen-dependent mechanism.

Physical activity. The 2007 WCRF/AICR report concluded that the evidence that any type of physical activity, including occupational, household, transport, and recreational activity, protects against breast cancer is limited-suggestive for premenopausal and probable for postmenopausal breast cancer.[24] A meta-analysis showed a 6% decrease in risk for each additional hour of physical activity per week.[32] The proposed mechanisms behind this association include the beneficial effect of physical activity on body fatness, effects on endogenous sex hormone levels, and possible improvement of immune function.[33]

In the JPHC study, we observed an inverse association between leisure time physical activity and breast cancer risk (Table 1).[34] Compared with women who participated in sports and physical activity on <3 days/month, adjusted hazard ratio (HR) and 95% confidence intervals (CI) for women who participated in sports on >3 days/week was 0.73 (0.54–1.00; P_{trend} = 0.037) for overall breast cancer and 0.43 (0.19–1.00; P_{trend} = 0.022) for ER^+PR^+ tumors. Conversely, we did not observe an inverse association between daily total physical activity and risk of overall breast cancer, but did see an inverse association for ER^+PR^+ tumors. In addition, we also investigated associations between age- and intensity-specific leisure time physical activity and the risk of hormone receptor-defined breast cancer in the case–control study in Nagano.[35] Strenuous, but not moderate, physical activity at age 12 years was inversely associated with breast cancer risk regardless of menopausal status and hormone receptor-defined breast cancer. Among postmenopausal women, moderate physical activity in the previous 5 years was somewhat more closely associated with ER^+PR^+ than ER^+PR^- and ER^-PR^- tumors. Our findings generally agree with those of the WCRF/AICR report and other Japanese studies.[24,36] Moreover, our findings regarding hormone receptor-defined breast cancer may support the involvement of an ER-mediated estrogen mechanism.

Alcohol intake. We found a significant positive association between alcohol intake and the risk of breast cancer in the JPHC study (Table 1).[37] An increase in consumption of 10 g ethanol/day (continuous) was associated with a 6% (95% CI 1–13; P_{trend} = 0.047) increase in the risk of breast cancer. Our findings generally agree with those from the WCRF/AICR report.[24] A meta-analysis of cohort studies reported a 10% increase in risk per 10 g increment of ethanol/day.[24] However, Nagata *et al.* concluded that epidemiological evidence from Japanese populations remains insufficient, given that a systematic review revealed that only three of three cohort and eight case–control studies observed a positive association.[38]

Several biological mechanisms for this association have been proposed, including an increase in circulating hormone levels, a direct carcinogenic effect of alcohol metabolites (e.g. acetaldehyde, a known mutagen), and an antagonistic effect on folate absorption and metabolism.[39] In the JPHC study, we found positive associations for both ER^+PR^+ and ER^+PR^- tumors, but not for ER^-PR^- tumors, although the associations failed to reach statistical significance. A recent meta-analysis showed that the relative risk (RR) and 95% CI per 10 g increment of ethanol/day was 1.12 (1.08–1.15) for all ER^+ tumors, 1.07 (1.00–1.14) for all ER^- tumors, and 1.11 (1.07–1.14) for ER^+PR^+, 1.15 (1.02–1.30) for ER^+PR^-, and 1.04 (0.98–1.09) for ER^-PR^- tumors.[40] These findings suggest that the biological mechanism involves both an ER-mediated estrogen-dependent and hormone-independent mechanism.

Notable epidemiological evidence from Japanese studies

Body weight at age 20 years. A number of epidemiological studies have shown that greater body fatness during childhood and adolescence is associated with a decreased risk of breast cancer.[41–43] The proposed biological mechanism behind this risk reduction is that obese women tend to have an increased frequency of menstrual irregularities and anovulatory cycles, which reduces their lifetime number of ovulations and alters their circulating hormone levels.[27] To date, most studies have been conducted in Western countries, where the prevalence of obesity is high, and little is known about whether greater body fatness during childhood and adolescence is associated with a decreased risk of breast cancer among the lean population.

In the JPHC study, we found a significant inverse association between BMI at age 20 years and the risk of breast cancer. This inverse association was not modified by menopausal status or recent BMI level. Adjusted HR for each 5 unit increment was 0.75 (95% CI 0.61–92).[28] Similarly, the Miyagi Cohort Study also observed a decreased risk associated with higher BMI at age 20 years.[44] These findings from a lean population generally agree with those from Western countries. Interestingly, few women are likely to be sufficiently overweight to cause anovulation in Japan. Moreover, the Nurses' Health Study II reported that the observed inverse association of BMI in early adulthood with risk was not eliminated after adjustment for ovulatory disorders.[41] Therefore, our findings from Japan imply the presence of other biological mechanisms apart from anovulation.

Soy foods and isoflavone. Soy foods, which are rich in isoflavones, are habitually consumed by Asian populations in large amounts. Isoflavones, of which genistein and daidzein are the major examples, are classified as phytoestrogens, which are plant-derived non-steroidal compounds with estrogen-like biological properties. A high intake of isoflavones has been hypothesized to contribute to the lower incidence of breast cancer in Asian compared with Western countries.[45]

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In the JPHC study, we observed an approximate 50% decrease in breast cancer risk associated with higher isoflavone intake, as assessed by a food frequency questionnaire.[46] Moreover, a nested case–control study within the JPHC study revealed a decrease in risk associated with a higher level of plasma genistein, but not plasma daidzein (Fig. 3).[47] Although accumulating evidence suggests that risk is reduced with higher isoflavone intake,[48,49] there is little available evidence for a dose–response relationship. In the case–control studies in Nagano and São Paulo, we evaluated the dose–response relationship using the three populations combined, because the respective amount of and variation in isoflavone intake is high and large for Japanese, intermediate and relatively large for Japanese Brazilians, and low and small for non-Japanese Brazilians.[21] We found that breast cancer risk decreased linearly from "no" to "moderate" isoflavone intake (20–30 mg/day) and thereafter leveled off (Fig. 4), suggesting that isoflavones have a risk-reducing rather than risk-enhancing effect on breast cancer within the range achievable from dietary intake alone.

Several biological mechanisms have been proposed to explain how isoflavones may reduce the risk of breast cancer. Isoflavones and human estrogen share similar chemical structures; given the consequent binding affinity of isoflavones to estrogen receptors, they may act as estrogen agonists and antagonists that compete for estradiol at the receptor complex.[50,51] Isoflavones may also influence risk by altering the biosynthesis, metabolism, and bioavailability of endogenous hormones.[52,53] In this regard, isoflavones have been shown to inhibit aromatase[52] and 17β-hydroxysteroid dehydrogenase Type I (17β-HSD1),[52] as well as to increase the synthesis of SHBG.[53] Considering these mechanisms, we tested the hypothesis that polymorphisms in estrogen receptor genes and genes related to the biosynthesis, metabolism, and bioavailability of endogenous hormones may modify the association between isoflavone intake and breast cancer risk in the case–control studies in Nagano and São Paulo.[54,55] The results showed several suggestive interactions between isoflavone intake and polymorphisms of *estrogen receptor beta* (*ESR2*), *17β-HSD1*, and *SHBG*: an inverse association between intake and risk in women with the GG genotype of the rs4986938 polymorphism in *ESR2* among postmenopausal Japanese, Japanese Brazilians, and non-Japanese Brazilians (Fig. 5);[54] an inverse association in women with at least one A allele of the rs605059 polymorphism in *17β-HSD1* among the three populations;[55] and an inverse association in women with the GG allele of the rs6259 polymorphism in *SHBG* among Japanese populations and women with at least one A allele among non-Japanese Brazilians.[55] Our findings support the idea that isoflavones may reduce the risk of breast cancer via mechanisms that involve estrogen receptors or the biosynthesis, metabolism, and bioavailability of endogenous hormones.

A recent meta-analysis observed risk reduction with higher isoflavone intake among Asian, but not Western, populations.[49] Overall, our studies suggest that isoflavone intake has a protective effect against breast cancer. Because we found a decreased risk not only in Japanese, but also Japanese Brazilians and non-Japanese Brazilians, our findings are somewhat inconsistent with those of the meta-analysis. This heterogeneity of findings across populations and studies warrants careful consideration. In this regard, Nagata noted that the association between soy isoflavone intake and the risk of breast cancer may be variously modified by the amount of soy isoflavones consumed, the form and food source of the isoflavones, the timing of isoflavone exposure, the estrogen receptor status of tumors, the equol-producer status, and the hormonal profile of individuals.[56]

Green tea. Although rarely consumed in Europe and North America, where black tea is the common tea beverage, green tea is one of the most popular beverages in Japan and China. Green tea has a higher catechin content than black tea, which may contribute to its protective effects against cancer via the strong antioxidant activity of catechin, its inhibition of cell proliferation and angiogenesis, induction of apoptosis, and antiestrogenic properties.[57,58]

In the JPHC study, we found no significant inverse association between green intake and the risk of breast cancer.[59] Compared with women who drank less than one cup of *Sencha* or *Bancha/Genmaicha* per week, the adjusted HR for those who

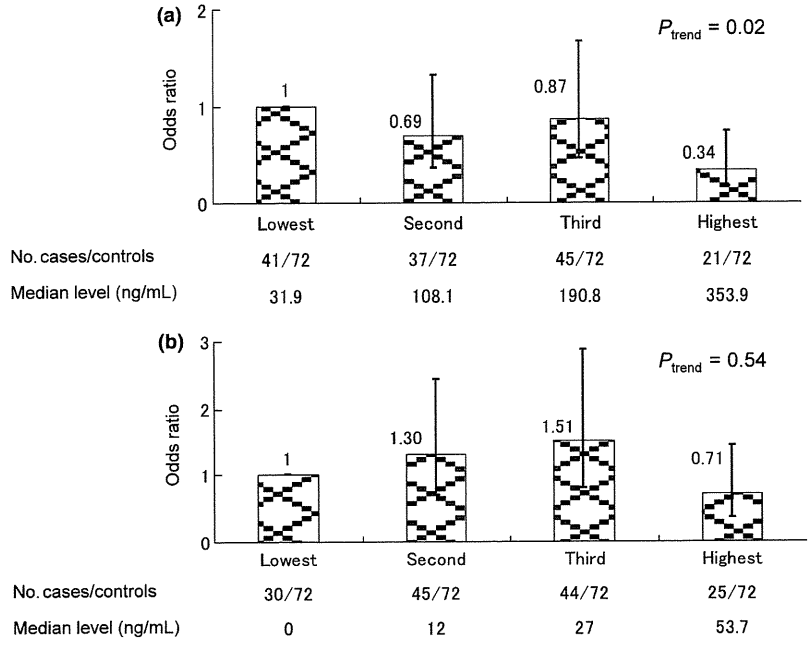

Fig. 3. Plasma isoflavones and the risk of breast cancer: the Japan Public Health Center-Based Prospective (JPHC) study. (a) Genistein; (b) daidzein. Odds ratios were adjusted for the numbers of births and the age at first birth. Data are from Iwasaki *et al.*[47]

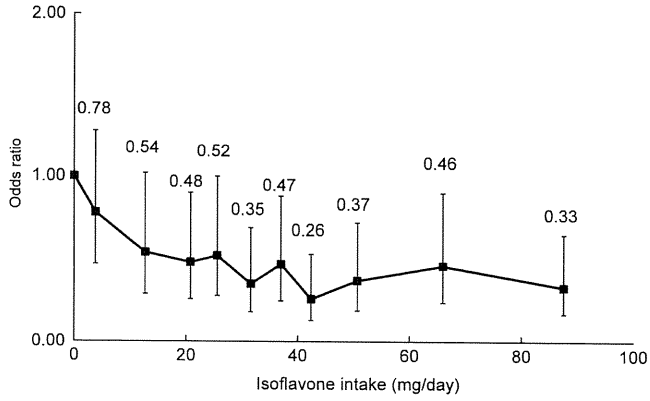

Fig. 4. Isoflavone intake and the risk of breast cancer in hospital-based case–control studies among Japanese, Japanese Brazilians, and non-Japanese Brazilians. Subjects were categorized into 11 groups: non-consumers and deciles of isoflavone consumers based on the control distribution. Odds ratios were estimated using matching pairs with adjustment for menopausal status, number of births, family history of breast cancer, smoking status, moderate physical activity in the past 5 years, and vitamin supplement use. Data are from Iwasaki *et al.*[21]

drank 10 or more cups per day was 1.02 (95% CI 0.55–1.89; P_{trend} = 0.48) for *Sencha* and 0.86 (0.34–2.17; P_{trend} = 0.66) for *Bancha/Genmaicha*. One noteworthy strength of this study over previous studies is its remarkably wide variation in green tea intake, from women who drank less than one cup per week to those who drank 10 or more cups per day.

Tea polyphenol content in green tea varies according to preparation, the type and amount of green tea leaves, the frequency of renewing the tea batch in the pot, water temperature, and brewing time, among others. To reduce misclassification due to these factors, we conducted a nested case–control study within the JPHC study and measured plasma levels of (−)-epigallocatechin (EGC), (−)-epicatechin (EC), (−)-epigallocatechin-3-gallate (EGCG), and (−)-epicatechin-3-gallate (ECG).[60] We found no significant association between plasma tea polyphenol levels and breast cancer risk. Adjusted odds ratios (OR) for the highest versus lowest group were 0.90 (95% CI 0.42–1.96; P_{trend} = 0.98) for EGC, 0.95 (95% CI 0.43–2.08; P_{trend} = 0.86) for EC, 1.21 (95% CI 0.52–2.80; P_{trend} = 0.53) for EGCG, and 1.75 (95% CI 0.81–3.78; P_{trend} = 0.15) for ECG.

To our knowledge, four cohort and three case–control studies have been published on the association between green tea intake and breast cancer, but findings have been inconsistent.[61–67] Our findings generally agree with those of three of the cohort studies, including two Japanese cohorts, which found no association between green tea intake and risk,[64–66] but contradict those of the three case–control studies, which showed an inverse association between green tea intake and risk.[61–63] Possible explanations for these apparent discrepancies in results include the influence of recall and selection bias stemming from the case–control design; differences in the type of tea and drinking methods; and possible effect modification by dietary and genetic factors.[59,63,66] Moreover, among studies investigating the association between circulating tea polyphenol levels and breast cancer risk using prediagnostic biological specimens, the Shanghai Women's Health Study found no dose–response relationship between urinary levels of tea polyphenols and their metabolites and the risk of breast cancer,[68] which is similar to the results of our JPHC study.

Smoking and passive smoking. The JPHC study found that both active and passive smoking were associated with an increased risk of breast cancer among premenopausal women.[69] When the reference group was defined as never-active smokers without passive smoking, adjusted HR (95% CI) for ever-smokers were 3.9 (1.5–9.9) and 1.1 (0.5–2.5) in pre- and postmenopausal women, respectively. In never-active smokers, the adjusted HR (95% CI) for passive smoking was 2.6 (1.3–5.2) in premenopausal women and 0.6 (0.4–1.0) in postmenopausal women. Subsequently, Nagata *et al.*[70] concluded that tobacco smoking possibly increases the risk of breast cancer in the Japanese population, considering that a systematic review of evidence showed a positive association in five of three cohort and eight case–control studies in Japan.

In 2004, the International Agency for Research on Cancer (IARC) endorsed the "lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast".[71] However, large cohort studies published since 2002 have observed an increased risk associated with a long duration and/or high number of pack-years of smoking.[72] Moreover, a meta-analysis found a significant interaction between smoking, *N*-acetyltransferase 2 (*NAT2*) genotype, and risk of breast cancer: higher pack-years were associated with an increased risk among women with the *NAT2* slow genotype, but not among rapid acetylators.[73] Recent reappraisals have therefore suggested an increased risk of breast cancer and the IARC concluded that there is limited evidence that tobacco smoking causes breast cancer.[74] With regard to passive smoking, a meta-analysis published in 2007 showed that this was associated with a 60–70% increase in breast cancer risk among younger, primarily premenopausal women who had never smoked.[75] However, a more recent meta-analysis found an increased risk associated with passive smoking based on case–control, but not cohort, studies.[76]

Conclusions

Evidence establishing menstrual and reproductive factors, anthropometric factors, physical activity, and alcohol intake

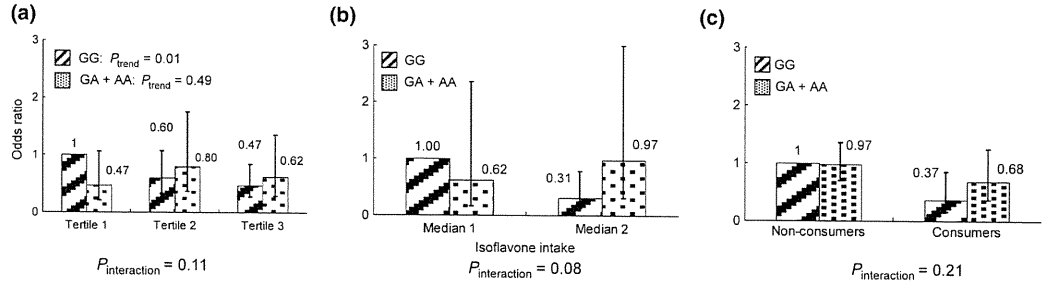

Fig. 5. Isoflavone, polymorphisms in the estrogen receptor beta gene (rs4986938) and breast cancer risk in hospital-based case–control studies among (a) Japanese (postmenopausal), (b) Japanese Brazilians (all), and (c) non-Japanese Brazilians (all). Odds ratios were estimated using matching pairs with adjustment for menopausal status, the number of births, family history of breast cancer, smoking status, moderate physical activity in the past 5 years, and vitamin supplement use. Data are from Iwasaki *et al.*[54]

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as risk factors for breast cancer was derived primarily from Western countries, but only a few dietary factors have been causally related to this disease.[15–17,24] Our studies among Japanese women have confirmed that these previously established factors play an important role in the development of breast cancer.[23,26,34,37] In addition, we have provided further evidence of the role of traditional Japanese foods in the etiology of breast cancer.[21,46,47,54,55,59,60] In particular, our studies of isoflavones and breast cancer have clarified a dose–response relationship and gene–environment interactions.[21,54,55] Given the evidence reviewed above, we suggest that isoflavones exert a protective effect against breast cancer in Asian populations. Finally, current knowledge of protective and risk factors for breast cancer suggest that primary prevention by lifestyle modification in individuals should focus on alcohol intake, weight control, physical activity, and tobacco smoking.

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Disclosure Statement

The authors have no conflicts of interest.

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Leisure-time physical activity and breast cancer risk defined by estrogen and progesterone receptor status—The Japan Public Health Center-based Prospective Study

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ABSTRACT

Objective. The study aims to investigate the association between leisure-time physical activity and breast cancer risk in consideration of tumor estrogen-receptor/progesterone-receptor status.

Methods. We conducted a population-based prospective cohort study among 53,578 women in the Japan Public Health Center-based Prospective Study. Leisure-time physical activity was assessed by self-reported questionnaires. A Cox proportional hazards regression model was used to derive relative risks and 95% confidence intervals.

Results. From 1990–1993 to the end of 2007, 652 cases were identified. The breast cancer rates (per 100,000 person-years) in the sedentary groups (≤3 days/month) was 84 in overall, 97 in premenopausal and 75 in postmenopausal women. We observed a statistically significant inverse association between leisure-time physical activity and breast cancer risk (relative risk$_{\geq 3 \text{ days/week vs. } \leq 3 \text{ days/month}}$ = 0.73; 95% confidence interval 0.54–1.00; p_{trend} 0.037), particularly in estrogen receptor+progesterone receptor+ (relative risk 0.43; 0.19–1.00; p_{trend} 0.022), and this inverse trend was apparent among postmenopausal women (relative risk 0.25; 0.06–1.06; p_{trend} 0.041). An inverse trend was also observed between daily total physical activity and postmenopausal estrogen receptor+progesterone receptor+ risk (p = 0.046). Among body mass index ≥25 kg/m^2 group, leisure-time physical activity was associated with decreased risk (relative risk$_{\geq 1 \text{ day/week vs. } \leq 3 \text{ days/month}}$ = 0.65; 0.43–0.97; p_{trend} 0.033).

Conclusion. Active participation in leisure-time physical activity may contribute to a decrease in breast cancer risk, particularly for postmenopausal estrogen receptor+progesterone receptor+ tumors.

Introduction

The latest report of the World Cancer Research Fund (World Cancer Resarch Fund/American Institute for Cancer Resarch, 2007) states that physical activity (PA) probably contributes to a decrease in the risk of breast cancer. The biological mechanisms underlying this inverse association have yet to be confirmed but may partly include the decreased production or bioavailability of endogenous female hormones (McTiernan et al., 2004), or of metabolic-related hormones and growth factors, such as estrogens, insulin (Regensteiner et al., 1991) and insulin-like growth factors (Raastad et al., 2000), which may stimulate cellular proliferation/differentiation in the breast (Bernstein and Ross, 1993; Hankinson et al., 1998). Other proposed mechanisms include an improvement in immune function (Shephard et al., 1995).

Owing to the possible involvement of hormone-related mechanisms, the association has been evaluated with consideration to the estrogen- and progesterone-receptor (ER/PR) status of tumors (Adams et al., 2006; Bardia et al., 2006; Bernstein et al., 2005; Britton et al., 2002; Chlebowski et al., 2007; Dallal et al., 2007; Enger et al., 2000; Lee et al., 2001; Leitzmann et al., 2008; Peters et al., 2009; Schmidt et al., 2008). The majority of studies were conducted among Western populations, however, and the results have been inconsistent.

In Japan, the incidence rate of breast cancer has increased steeply over the last three decades, and this cancer is currently the most

Abbreviations: CIs, confidence intervals; BMI, body mass index; DTPA, daily total physical activity; EFH, exogenous female hormone; ER, estrogen receptor; PA, physical activity; PHC, public health center; PR, progesterone receptor; FFQ, food frequency questionnaire; LPA, leisure-time physical activity; METs, metabolic equivalents; RR, relative risk; SD, standard deviation.

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common cancer (Matsuda et al., 2010). Among Asian populations, however, few epidemiological studies have prospectively evaluated the association in consideration of ER/PR (Suzuki et al., 2010).

We hypothesized that PA may be associated with a decreased risk of breast cancer partly through hormone-related mechanisms, on the basis that PA may lead to a decrease in body fat (Sternfeld et al., 2005), the main source of endogenous estrogen after menopause (Cleland et al., 1985). Here, we evaluated the association between PA and ER/PR-defined breast cancer risk in 53,578 Japanese women in the Japan Public Health Center-based Prospective Study (JPHC).

Methods

Study participants

The JPHC was launched in 1990 to evaluate the association between lifestyle factors, cancer, and cardiovascular disease among the Japanese population. Details have been provided elsewhere (Tsugane and Sobue, 2001). The target population was all Japanese residents aged 40–69 years enrolled in the residential registries of 11 public health centers (PHCs). Two cohorts were enrolled (cohort I, Iwate-Ninohe, Akita-Yokote, Nagano-Saku, Okinawa-Chubu, and Tokyo-Kastushika; and cohort II, Ibaraki-Mito, Niigata-Nagaoka, Kochi-Chuohigashi, Nagasaki-Kamigoto, Okinawa-Miyako, and Osaka-Suita). Initially, 71,698 women were invited. Kastushika (cohort I) could not be included due to a lack of information on cancer incidence ($n=4,178$). We excluded women who did not possess Japanese nationality, moved before the start of follow-up, were not aged 40–69 years, or who had duplicate data ($n=146$).

Of the remainder, 55,838 completed the baseline questionnaires (response rate 83%). All eligible subjects were sent 5-year (1995–1998; response rate 80%) and 10-year follow-up questionnaires (2000–2003; response rate 78%). We excluded women with a self-reported history of cancer before the start of follow-up ($n=1,509$). To investigate the impact of leisure-time physical activity (LPA) on breast cancer risk, we excluded women with missing information on LPA ($n=751$). Age–area-adjusted analysis was conducted in 53,578 women.

Further, we then excluded women who had missing or unreliable information on height, BMI, BMI at age 20 years (<14 or ≥ 40), alcohol intake, smoking, or use of exogenous female hormones (EFH) ($n=13,804$), as well as those with a family history of breast cancer ($n=210$) and women who reported unreasonable estimates of total energy intake (± 3SD) ($n=395$). Finally, 39,169 women were included in multivariable-adjusted analysis. We also performed sub-analyses to evaluate the impact of daily total physical activity (DTPA) in cohort II only because baseline information on DTPA was available.

Exposure measurement

The main exposure of interest was participation frequency in LPA. We inquired about the frequency of participation in non-occupational LPA, such as sports and exercise, at the baseline and 5-year follow-up surveys. In both questionnaires, we asked 'How many times did you participate in sports and PA other than during working hours,' with five predefined categories of almost never exercise: 1–3 days per month, 1–2 days per week, 3–4 days per week, and almost daily.

In cohort II, we evaluated the impact of DTPA on breast cancer risk. DTPA was measured as metabolic equivalents (METs-hours/day). Calculation in METs has been explained elsewhere (Inoue et al., 2008). The same methods were used in the baseline and 5-year follow-up surveys because they contained common questions on sleeping time, heavy physical work or strenuous exercise, standing or walking time, and sitting time.

Although LPA was not directly validated, the validity and reproducibility of the total METs/day score for the 5-year follow-up questionnaire was previously evaluated using 4-day, 24-hour PA records as an objective standard in 108 volunteer subjects in the cohort. In brief, correlations between the 5-year follow-up questionnaire and 4-day, 24-h record showed reasonable validity, with a Spearman rank correlation coefficient of 0.35 in women (Inoue et al., 2008). Reproducibility for the 5-year follow-up questionnaire was also supported, with a Spearman rank correlation coefficient of 0.68 (Imai et al., 2010).

Ascertainment of cases and follow-up

Breast cancer cases were identified by active patient notification from major local hospitals and data linkage with population-based cancer registries, with permission from the local governments responsible for the registries. Cases were defined as codes C500–509 (World Health Organization, 2000). Diagnosis was microscopically verified for 97% of all case patients. ER/PR status was evaluated by either immunohistochemical assay or enzyme-linked immunoassay. The cut-off point for positive receptor status was defined by clinical estimation at the treating hospital or by the assay method of the clinical laboratory. In most but not all cases, hormone receptor-positivity was defined as the presence of ≥ 10 fmol/mg protein in enzyme-linked immunoassay or by the finding of any positive cells in a specimen in immunohistochemical assay.

Follow-up was started on the date of administration of the baseline questionnaire and continued until the date of diagnosis of breast cancer, date of death, date of moving, or end of follow-up (December 31, 2007), whichever occurred first. Date of death or moving was verified through linkage with the death or residential registry at the respective PHC.

Statistical analysis

We used time-dependent multivariable Cox proportional hazards regression models to evaluate relative risks (RRs) and 95% confidence intervals (CIs) using age as the time scale (Korn et al., 1997). Women were subdivided into three categories by LPA [≤ 3 days/month, 1–2 days/week, ≥ 3 days/week]. The multivariable adjusted model included height, recent BMI, BMI at age 20 years, smoking status, age at menarche, age at first birth, parity, age at menopause, use of EFH, alcohol intake and isoflavone intake. These factors were based on the self-administered baseline questionnaires and were updated with the follow-up surveys, if available. If they could not be properly adjusted due to the small number of ER/PR-defined cases, these covariates were excluded, as mentioned in the footnotes in Table 2. For DTPA, women were subdivided according to tertile. Trend tests were conducted by creating a continuous variable in the rank order of each category. Additional analyses were conducted with stratification by menopausal and BMI status. All analyses were performed using the SAS statistical package version 9.1 (SAS Institute, Cary, NC). All statistical tests were two-sided, and statistical significance was defined as $p<.05$.

Results

After an average 14.5 years of follow-up, 652 breast cancer cases were diagnosed among 53,578 women. Information on ER/PR status was available for 299, showing 135 cases of ER+PR+, 64 of ER+PR−, and 83 of ER−PR−. Although height and BMI did not appear to differ by LPA level, women who tended to participate were more likely to be older and not to use EFH (Table 1).

Overall, we observed a statistically significant inverse association between LPA and breast cancer risk [multivariable-adjusted $RR_{\geq 3 \text{ days/week vs. } \leq 3 \text{ days/week}}=0.73$; 95% CI 0.54–1.00; p_{trend} 0.038]. In particular, the observed inverse association was apparent for ER+PR+ tumors (corresponding $RR_{ER+PR+}=0.43$ (0.19–1.00) p_{trend} 0.022), but not for others (Table 2). Without updating exposure information (i.e. by using the baseline information only), the corresponding result for ER+PR+ was no longer statistically significant [0.64 (0.29–1.38) $p_{trend}=0.13$ (text only)], although the point estimates of RRs were less than 1 at either baseline alone or with updated information. Further analyses without adjustment of recent BMI or BMI at 20 years old gave similar results.

In analyses stratified by menopausal status, LPA participation was marginally inversely associated with overall breast cancer risk among premenopausal women, although null association was observed after considering ER/PR tumor status. Among postmenopausal women, in contrast, LPA was associated with a decreased risk of ER+PR+ tumors using repeated exposure information (i.e. both baseline and 5-year follow-up surveys) [multivariable-adjusted $RR_{\geq 3 \text{ days/week vs. } \leq 3 \text{ days/month}}=0.25$ (0.06–1.06) p_{trend} 0.041; Table 2].

Table 1
Subject characteristics according to category of participation in leisure-time activity in the Japan Public Health Center-based Prospective Study (1990/1993–).

Characteristic	Frequency of participation in leisure-time physical activity		
	≤3 days/month	1–2 days/week	≥3 days/week
At baseline survey (%)	81.4	9.7	8.9
At 5-year follow-up survey (%)	78.1	10.8	11.2
Age at baseline survey, y, mean (SD)	51.1 (7.8)	50.5 (7.9)	54.2 (8.2)
Body mass index at age 20, kg/m^2, mean (SD)	21.5 (2.6)	21.2 (2.4)	21.6 (2.7)
Body mass index at baseline, kg/m^2, mean (SD)	23.3 (3.1)	23.2 (2.9)	23.5 (3.2)
Height, cm, mean (SD)	152.2 (5.4)	153.4 (5.3)	152.1 (5.7)
Age at menarche, y, mean (SD)	14.5 (1.8)	14.3 (1.8)	14.9 (1.9)
Age at first birth, y, mean (SD)[a]	24.9 (3.4)	25.1 (3.1)	25.0 (3.5)
Number of children, *n*, mean (SD)	2.6 (1.5)	2.6 (1.4)	2.7 (1.6)
Age at menopause, y, mean (SD)	48.3 (4.7)	48.4 (4.8)	48.7 (4.5)
Use of exogenous hormones at baseline (ever), %	12.6	12.5	11.7
Alcohol drinking status at baseline (ever), %	22.4	29.9	23.1
Smoking status at baseline (ever), %	8.0	7.6	7.2
Intake of isoflavones, mg, mean[b]	36.2	39.0	42.9

BMI = body mass index, SD = standard deviation.
[a] Based on information among parous women.
[b] Standardized according to food frequency questionnaires.

In cohort II, the impact of DTPA on breast cancer risk showed no overall association (multivariable-adjusted $RR_{\text{tertile3 vs. tertile1 METs/day score}} = 1.03$ (0.75–1.41) p_{trend} 0.86; Table 3). On consideration of menopausal and ER/PR status, however, we observed a substantial inverse trend between DTPA and ER+PR+ tumors among Postmenopausal women (age-area adjusted $RR_{\text{tertile3 vs. tertile1 METs/day score}} = 0.43$ (0.17–1.08) p_{trend} 0.046; Table 3).

On stratification by BMI (<25 or ≥25 kg/m^2), no association between LPA and breast cancer risk was seen among women with BMI <25 kg/m^2. Among overweight women (BMI ≥25 kg/m^2), however, participation in LPA was associated with a decreased risk of breast cancer risk overall ($RR_{\geq 1 \text{ day/week vs. } \leq 3 \text{ days/month}} = 0.65$ (0.43–0.97) p_{trend} 0.033; Table 4).

Discussion

This is the first large prospective cohort study to evaluate the association between LPA and breast cancer risk in consideration of ER/PR status in a Japanese population. Overall, LPA showed a substantial inverse association with breast cancer risk after adjustment for all covariates. Among premenopausal women, LPA was marginally associated with a decreased risk overall but not for specific ER/PR tumors. Among postmenopausal women, LPA was associated with a decreased risk for ER+PR+ tumors. Although there was no overall association between DTPA and breast cancer risk, we observed a considerable inverse trend between DTPA and postmenopausal ER+PR+ tumors in a JPHC sub-cohort. Further, on stratification by BMI, we observed a substantial inverse association between LPA and breast cancer risk among overweight women.

Our observed favorable impact of LPA against breast cancer risk was consistent with previous results for overall (Bardia et al., 2006) and ER+ tumors (Bernstein et al., 2005), although a cohort study suggested an inverse association for ER− but not ER+ tumors (Dallal et al., 2007).

Among premenopausal women, the marginal inverse trend of an association of LPA with breast cancer risk was found for overall tumors but not for any tumor subtypes. PA has been reported to exert a protective effect on risk for overall tumors (Maruti et al., 2008) and irrespective of hormone receptor positivity (Enger et al., 2000) (Adams et al., 2006) (Suzuki et al., 2010). The observed weak inverse trend might be due to the fact that our follow-up period did not cover the entire premenopausal period because follow-up started at around age 40.

Unlike previous results (McTiernan et al., 2003) (Lee et al., 2001), we found no inverse trend among postmenopausal women. For ER+PR+ tumors, however, a substantial inverse trend was found, in line with some (Chlebowski et al., 2007; Peters et al., 2009; Schmidt et al., 2008) but not all previous studies (Lee et al., 2001) (Leitzmann et al., 2008). A protective effect of PA on both ER+PR+ and ER+PR− tumors has also reported (Bardia et al., 2006).

Among overweight women, a substantial decreased in risk with LPA was observed overall. Similarly, a weak inverse trend was also observed for ER+PR+ tumors. In other studies, however, an inverse association was observed among a low-BMI group (Leitzmann et al., 2008), particularly for ER+PR+ tumors (Enger et al., 2000). These inconsistent results indicate the need for further careful evaluation.

Unlike LPA, our sub-analyses for DTPA (average 9.2 person-years of follow-up) did not show any overall favorable impact, which was consistent with our previous analysis with an average 7.5 person-years of follow-up (from 1995–1999 to 2004) (Inoue et al., 2008). In contrast, our corresponding present results for the postmenopausal ER+PR+ tumors showed a substantial inverse trend with DTPA. Although these results could not be clearly explained and might not exclude the possible involvement of non-hormone-related mechanisms, the observed results for postmenopausal ER+PR+ tumors might support the idea that PA is associated with a decreased risk of breast cancer partly through hormone-related mechanisms. After menopause, exercise may lead to a decrease in adipose tissue (Sternfeld et al., 2005), a major source of endogenous estrogen derived from the peripheral conversion of androgens to estrogens (Cleland et al., 1985) or to an increase in sex hormone-binding globulin (van Gils et al., 2009), the main protein carrier of estradiols, or both. A lack of association of DTPA with overall breast cancer risk in the present and a previous JPHC study (Inoue et al., 2008) might be explained without consideration of menopausal and ER/PR status. Further study with regard to menopausal status, ER/PR status or type of PA is required.

Strengths of our study include its prospective population-based cohort study design and large study size, adjustment for a broad range of potential confounders, and availability of repeated measurements for exposure as well as some covariates, which can change during long follow-up. Time-dependent analyses may reduce the misclassification of exposure and improve statistical efficiency. The study design, with a long follow-up period and repeated exposure measurements, might have aided detection of this inverse association.

Our main limitation was that ER/PR status was available for only about 46% of cases. The major reason for an unknown ER/PR status was likely that data collection began in 2002, while data during follow-up from 1990 to 2002 were obtained by retrospective review of medical records or pathology reports. Potential bias due to this relatively large number of cases with unknown ER/PR status should be

Table 2
Relative risks (RRs) and 95% confidence intervals (CIs) for the association between leisure-time activity and breast cancer risk among Japanese women in the Japan Public Health Center-based Prospective Study, 1990–2007.

Type of tumor	All					Premenopausal women[b]					Postmenopausal women[c]				
	Participation frequency in leisure-time physical activity					Participation frequency in leisure-time physical activity					Participation frequency in leisure-time physical activity				
		≤3 days/ month	1–2 days/ week	≥3 days/ week			≤3 days/ month	1–2 days/ week	≥3 days/ week			≤3 days/ month	1–2 days/ week	≥3 days/ week	
	Cases/*n*	Ref.	RR (95% CI)	RR (95% CI)	p_{trend}	Cases/*n*	Ref.	RR (95% CI)	RR (95% CI)	p_{trend}	Cases/*n*	Ref.	RR (95% CI)	RR (95% CI)	p_{trend}
Cases		529	59	64			254	25	21			275	34	43	
Total person-years		627669	73985	78439			260618	33986	24129			367051	39999	54310	
Model[a]	652/53,578	1.00 (ref.)	0.98 (0.75–1.29)	0.83 (0.64–1.08)	0.19	300/21,799	1.00 (ref.)	0.76 (0.50–1.15)	0.70 (0.45–1.10)	0.06	352/31,779	1.00 (ref.)	1.16 (0.81–1.66)	0.98 (0.71–1.36)	0.89
		389	45	45			200	23	17			189	22	28	
Model[d]	479/39,169	1.00 (ref.)	0.86 (0.63–1.18)	0.73 (0.54–1.00)	0.037	240/17,332	1.00 (ref.)	0.82 (0.53–1.27)	0.66 (0.40–1.09)	0.074	239/21837	1.00 (ref.)	0.88 (0.56–1.38)	0.78 (0.52–1.17)	0.21
ER+PR+		115	10	10			55	3	4			60	7	6	
Model[a]	135/53,578	1.00 (ref.)	0.83 (0.43–1.58)	0.61 (0.32–1.18)	0.12	62/21,799	1.00 (ref.)	0.48 (0.15–1.54)	0.61 (0.22–1.70)	0.19	73/31,779	1.00 (ref.)	1.13 (0.51–2.47)	0.67 (0.29–1.54)	0.44
		89	6	6			48	3	4			41	3	2	
Model[d]	101/39,169	1.00 (ref.)	0.55 (0.24–1.26)	0.43 (0.19–1.00)	0.022	55/17,332	1.00 (ref.)	0.54 (0.17–1.74)	0.64 (0.23–1.78)	0.25	46/21,837	1.00 (ref.)	0.62 (0.19–2.01)	0.25 (0.06–1.06)	0.041
ER+PR−		50	6	8			25	4	2			25	2	6	
Model[a]	64/53,578	1.00 (ref.)	1.21 (0.52–2.82)	1.18 (0.55–2.50)	0.60	31/21,799	1.00 (ref.)	1.45 (0.50–4.20)	0.73 (0.17–3.11)	0.91	33/31,779	1.00 (ref.)	0.83 (0.20–3.50)	1.60 (0.65–3.94)	0.37
		33	5	8			19	4	2			14	1	6	
Model[e]	46/39,169	1.00 (ref.)	1.28 (0.49–3.32)	1.93 (0.87–4.26)	0.11	25/17,332	1.00 (ref.)	2.04 (0.68–6.16)	0.90 (0.20–3.94)	0.74	21/21,837	1.00 (ref.)	0.56 (0.07–4.56)	3.12 (1.15–8.50)	0.049
ER−PR−		66	6	11			28	1	4			38	5	7	
Model[a]	83/53,578	1.00 (ref.)	0.91 (0.39–2.11)	1.30 (0.68–2.47)	0.51	33/21,799	1.00 (ref.)	0.34 (0.045–2.47)	1.35 (0.47–3.89)	0.92	50/31,779	1.00 (ref.)	1.35 (0.53–3.45)	1.34 (0.59–3.02)	0.41
		49	4	8			22	3				27	4	5	
Model[e]	61/39,169	1.00 (ref.)	0.67 (0.24–1.88)	1.06 (0.49–2.26)	0.92	25/17,332	1.00 (ref.)	0.55 (0.16–1.86)[f]		0.34	36/21,837	1.00 (ref.)	1.32 (0.46–3.82)	1.07 (0.41–2.82)	0.79
Unknown		285	35	33			137	15	9			148	20	24	
Model[a]	353/53,578	1.00 (ref.)	0.99 (0.70–1.42)	0.75 (0.52–1.07)	0.15	161/21,799	1.00 (ref.)	0.74 (0.43–1.28)	0.53 (0.27–1.04)	0.038	192/31,779	1.00 (ref.)	1.22 (0.76–1.95)	0.96 (0.62–1.48)	0.97
		210	28	22			104	14	7			106	14	15	
Model[d]	260/39,169	1.00 (ref.)	0.94 (0.63–1.40)	0.64 (0.41–1.00)	0.06	125/17,332	1.00 (ref.)	0.85 (0.48–1.51)	0.51 (0.23–1.10)	0.08	135/21,837	1.00 (ref.)	0.95 (0.54–1.67)	0.72 (0.41–1.24)	0.25

[a] Cox proportional hazards models was adjusted for age (time-scales) and area (10).
[b] For premenopausal women, multivariable Cox proportional hazards models were adjusted for all covariates (footnote d or e), except age at menopause.
[c] For postmenopausal women, multivariable Cox proportional hazards models were adjusted for all covariates (footnote d or e) and age at menopause (≤44, 45–54, ≥55 years).
[d] Multivariable Cox proportional hazards models were adjusted for age (time-scales), area (10), height (continuous), recent BMI (continuous), BMI at age 20 years (continuous), smoking status (never, ever), age at menarche (≤13, 14, 15, ≥16 years, or missing), age at first birth (nulliparous, <26 years, ≥26 years, or missing), parity (nulliparous, 1–2 times, 3 times, and ≥4 times, or missing), age at menopause (pre, ≤44, 45–54, ≥55 years), use of exogenous female hormones (ever, never), alcohol intake (non-/past-/occasional drinkers, regular drinkers ≤150 or >150 ethanol g/week), and energy-adjusted intake of isoflavones (continuous) and daily total physical activity (tertile of METs or missing).
[e] Multivariable Cox proportional hazards models were adjusted for age (time-scales), area (10), height (continuous), recent BMI (continuous), BMI at age 20 years (continuous), smoking status (never, ever), age at menarche (≤13, 14, 15, ≥16 years, or missing), age at menopause (pre, ≤44, 45–54, ≥55 years), use of exogenous female hormones (ever, never), alcohol intake (non-/past-/occasional drinkers, regular drinkers), and energy-adjusted intake of isoflavones (continuous) and daily total physical activity (tertile of MET or missing).
[f] Participation frequency in leisure-time physical activity was categorized (≤ 3 days/month vs. ≥1 day/week).

Table 3
Relative risks (RRs) and 95% confidence intervals (CIs) for the association between daily total physical activity (DTPA) level and breast cancer risk among Japanese women in the Japan Public Health Center-based Prospective Study (Cohort II), 1990–2007.

	All					Premenopausal women[b]					Postmenopausal women[c]				
	DTPA (METs/day score)					DTPA (METs/day score)					DTPA (METs/day score)				
	Cases/*n*	Tertile 1 Ref.	Tertile 2 RR (95% CI)	Tertile 3 RR (95% CI)	p_{trend}	Cases/*n*	Tertile 1 Ref.	Tertile 2 RR (95% CI)	Tertile 3 RR (95% CI)	p_{trend}	Cases/*n*	Tertile 1 Ref.	Tertile 2 RR (95% CI)	Tertile 3 RR (95% CI)	p_{trend}
Total person-years		128960	143178	152199			46084	57485	53928			82875	85694	98270	
All		106	92	96			41	44	43			65	48	53	
Model[a]	294/31917	1.00 (ref.)	1.08 (0.82–1.43)	0.90 (0.68–1.19)	0.48	128/11953	1.00 (ref.)	1.07 (0.70–1.65)	0.86 (0.56–1.32)	0.48	166/19964	1.00 (ref.)	1.07 (0.73–1.55)	0.93 (0.65–1.34)	0.72
		82	70	76			35	40	35			47	30	41	
Model[d]	228/23977	1.00 (ref.)	1.13 (0.82–1.56)	1.03 (0.75–1.41)	0.86	110/9979	1.00 (ref.)	1.24 (0.78–1.97)	0.89 (0.55–1.43)	0.61	118/13998	1.00 (ref.)	1.02 (0.64–1.63)	1.11 (0.72–1.70)	0.65
ER+PR+		22	32	43			4	5	5			18	5	6	
Model[a]	43/31917	1.00 (ref.)	0.61 (0.29–1.30)	0.57 (0.27–1.17)	0.11	14/11953	1.00 (ref.)	1.35 (0.36–5.04)	1.19 (0.31–4.56)	0.81	29/19964	1.00 (ref.)	0.42 (0.16–1.13)	0.43 (0.17–1.08)	0.046
ER+PR−		7	10	5			4	4	3			3	6	2	
Model[a]	22/31917	1.00 (ref.)	1.94 (0.73–5.18)	0.79 (0.25–2.50)	0.74	11/11953	1.00 (ref.)	1.03 (0.26–4.12)	0.59 (0.13–2.64)	0.49	11/19964	1.00 (ref.)	3.87 (0.89–16.91)	0.98 (0.16–5.91)	0.88
ER−PR−		4	8	9			2	3	2			2	5	7	
Model[a]	21/31917	1.00 (ref.)	2.38 (0.71–7.93)	2.36 (0.72–7.70)	0.17	7/11953	1.00 (ref.)	1.58 (0.26–9.46)	0.90 (0.13–6.37)	0.90	14/19964	1.00 (ref.)	3.20 (0.62–16.55)	4.17 (0.86–20.14)	0.07
Unknown		71	64	70			31	32	32			40	32	38	
Model[a]	205/31917	1.00 (ref.)	1.10 (0.79–1.55)	0.95 (0.68–1.32)	0.73	95/11953	1.00 (ref.)	1.01 (0.62–1.66)	0.83 (0.50–1.36)	0.44	110/19964	1.00 (ref.)	1.14 (0.72–1.82)	1.03 (0.66–1.61)	0.90

[a] Cox proportional hazards models was adjusted for age (time-scales) and area (10).
[b] For premenopausal women, multivariable Cox proportional hazards models were adjusted for all following covariates (d or e) except age at menopause.
[c] For postmenopausal women, multivariable Cox proportional hazards models were adjusted for all following covariates (d or e) and age at menopause (≤44, 45–54, ≥55 years).
[d] Multivariable Cox proportional hazards models were adjusted for age (time-scales), area (10), height (continuous), recent BMI (continuous), BMI at age 20 years (continuous), smoking status (never, ever), age at menarche (≤13, 14, 15, ≥16 years, or missing), age at first birth (nulliparous, <26 years, ≥26 years, or missing), parity (nulliparous, 1–2 times, 3 times, and ≥4 times, or missing), age at menopause (pre, ≤44, 45–54, ≥55 years), use of exogenous female hormones (ever, never), alcohol intake (non-/past-/occasional drinkers, regular drinkers ≤150 or >150 ethanol g/week), and energy-adjusted intake of isoflavones (continuous) and participation frequency in leisure-time physical activity (≤3 days/month, 1–2 days/week, ≥3 days/week).

Table 4
Relative risks (RRs) and 95% confidence intervals (CIs) for the association between leisure-time physical activity and hormone receptor status-defined breast cancer risk stratified by BMI in the Japan Public Health Center-based Prospective Study 1990–2007.

Type of tumor	BMI <25 ($n=38,959$)				BMI ≥25 ($n=14,619$)			
	Cases	Leisure-time physical activity			Cases	Leisure-time physical activity		
		≤3 days/month	≥1 day/week			≤3 days/month	≥1 day/week	
		Ref.	RR (95% CI)	p_{trend}		Ref.	RR (95% CI)	p_{trend}
Person-years		454047	110033			173623	42391	
		359	94			170	29	
All[a]	453/38959	1.00 (ref.)	1.02 (0.81–1.28)	0.90	199/14619	1.00 (ref.)	0.65 (0.43–0.97)	0.033
		75	15			40	5	
ER+PR+[a]	90/38959	1.00 (ref.)	0.84 (0.48–1.48)	0.55	45/14619	1.00 (ref.)	0.50 (0.20–1.27)	0.14
		32	12			18	2	
ER+PR−[a]	44/38959	1.00 (ref.)	1.61 (0.82–3.16)	0.17	20/14619	1.00 (ref.)	0.51 (0.12–2.23)	0.37
		51	14			15	3	
ER−PR−[a]	65/38959	1.00 (ref.)	1.11 (0.61–2.01)	0.74	18/14619	1.00 (ref.)	0.93 (0.27–3.27)	0.91
		192	49			93	19	
Unknown[a]	241/38959	1.00 (ref.)	0.92 (0.67–1.26)	0.6	112/14619	1.00 (ref.)	0.72 (0.43–1.18)	0.19

[a] Cox proportional hazards models were adjusted for age (time-scales), area (10).

considered. Nevertheless, RR for unknown tumors was similar to that for overall tumors, suggesting that there was little bias in our results. Further, our information on LPA included frequency only and not intensity or duration. Finally, we are unable to rule out the possibility of a chance finding, measurement error in exposure information due to self-reporting, and residual confounding due to unmeasured/unknown information.

Conclusion

LPA was associated with a decreased risk of breast cancer in overall and postmenopausal ER+PR+ tumors. Among overweight women, a substantially decreased risk with LPA was observed. We also observed a substantial inverse trend between DTPA and postmenopausal ER+PR+ tumors, although DTPA was not associated with overall breast cancer risk. Active participation in LPA might represent a useful public health message against breast cancer, particularly among elderly women, given that the majority of breast tumors occurring after menopause are ER+PR+ tumors.

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Conflict of interest statement
The authors declare that there are no conflicts of interest.

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Appendix

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Comparison of postmenopausal endogenous sex hormones among Japanese, Japanese Brazilians, and non-Japanese Brazilians

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Abstract

Background: Differences in sex hormone levels among populations might contribute to the variation in breast cancer incidence across countries. Previous studies have shown higher breast cancer incidence and mortality among Japanese Brazilians than among Japanese. To clarify the difference in hormone levels among populations, we compared postmenopausal endogenous sex hormone levels among Japanese living in Japan, Japanese Brazilians living in the state of São Paulo, and non-Japanese Brazilians living in the state of São Paulo.

Methods: A cross-sectional study was conducted using a control group of case-control studies in Nagano, Japan, and São Paulo, Brazil. Participants were postmenopausal women older than 55 years of age who provided blood samples. We measured estradiol, estrone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), testosterone and free testosterone by radioimmunoassay; bioavailable estradiol by the ammonium sulfate precipitation method; and sex hormone-binding globulin (SHBG) by immunoradiometric assay. A total of 363 women were included for the present analyses, comprising 185 Japanese, 44 Japanese Brazilians and 134 non-Japanese Brazilians.

Results: Japanese Brazilians had significantly higher levels of estradiol, bioavailable estradiol, estrone, testosterone and free testosterone levels, and lower SHBG levels, than Japanese. Japanese Brazilians also had significantly higher levels of bioavailable estradiol, estrone and DHEAS and lower levels of SHBG and androstenedione than non-Japanese Brazilians. Levels of estradiol, testosterone and free testosterone, however, did not differ between Japanese Brazilians and non-Japanese Brazilians. These differences were observed even after adjustment for known breast cancer risk factors. We also found an increase in estrogen and androgen levels with increasing body mass index, but no association for most of the other known risk factors.

Conclusions: We found higher levels of estrogens and androgens in Japanese Brazilians than in Japanese and levels similar to or higher than in non-Japanese Brazilians. Our findings may help explain the increase in the incidence and mortality rate of breast cancer among Japanese Brazilians.

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Background

The incidence and mortality rate of breast cancer vary considerably across countries and regions [1]. Although Japan has a lower risk for female breast cancer than Western countries, the incidence has gradually increased over the past 30 years [2,3]. The incidence and mortality rates in Japanese immigrants living in the United States and Brazil have approximated those in the host country [4-8]. For example, the mortality rate of first-generation Japanese immigrants to São Paulo, Brazil, increased from 1979 to 2001, with rates being intermediate between Japanese living in Japan and Brazilians living in the state of São Paulo [6].

Many epidemiologic studies have indicated that endogenous sex hormones, particularly estrogens, play an important role in the etiology of breast cancer [9]. A pooled analysis of nine prospective studies showed that higher estrogens and their androgen precursors were associated with a higher risk of breast cancer in postmenopausal women [9]. Differences in sex hormone levels among populations might therefore contribute to the variation in breast cancer incidence across countries and regions. Clarification of the difference in sex hormone levels among populations and their determinants might help our understanding of the etiology and prevention of breast cancer.

A relatively large number of epidemiological studies have examined sex hormone levels among ethnic groups and factors associated with sex hormone levels [10-16]. To our knowledge, however, no study has investigated sex hormone levels among Japanese Brazilians. In addition, although previous studies consistently showed that body weight and obesity were associated with higher estrogen levels in postmenopausal women [10-12,15], findings regarding other factors that influence circulating sex hormone levels have been inconsistent [10-14,16].

We have conducted a cross-sectional study using a control group of case-control studies in Nagano, Japan, and São Paulo, Brazil. The present study compared postmenopausal endogenous sex hormone levels among Japanese living in Japan, Japanese Brazilians living in São Paulo and non-Japanese Brazilians living in São Paulo, and examined factors associated with these levels.

Methods

Study participants

Participants were postmenopausal women who were enrolled as controls in multicenter, hospital-based, case-control studies of breast cancer. In addition to determining lifestyle factors and genetic susceptibility to the risk of breast cancer, the protocols of these studies were also designed to compare potential risk factors among Japanese living in Nagano, Japan, and Japanese Brazilians and non-Japanese Brazilians living in the state of São Paulo, Brazil. Details of this study have been described previously [17]. The study protocol was approved by Comissão Nacional de Ética em Pesquisa, Brasília, Brazil, and by the institutional review board of the National Cancer Center, Tokyo, Japan.

Briefly, eligible cases were a consecutive series of female patients ages 20 to 74 years with newly diagnosed and histologically confirmed invasive breast cancer. Inhabitants of the state of São Paulo were recruited and asked their ethnicity. Japanese and their descendants were defined as Japanese Brazilians, and Caucasian, black and mixed ethnicity populations were defined as non-Japanese Brazilians. A total of 405 individuals (98%) participated in Nagano, and 83 Japanese Brazilians (91%) and 389 non-Japanese Brazilians (99%) participated in São Paulo. In the study in Nagano, eligible controls were selected from among medical checkup examinees in two of the four hospitals and were confirmed not to have cancer. One control was matched for each case by age (within 3 years) and by residential area. Among potential controls, one examinee refused to participate and two refused to provide blood samples. In the study in São Paulo, eligible controls were preferentially selected from among cancer-free patients who visited the same hospital as the index cases. One control was matched for each case by age (within 5 years) and by ethnicity. Among potential controls, 22 patients refused to participate (participation rate, 96%). Consequently, we obtained written, informed consent from a total of 877 matched pairs (405 for Japanese, 83 for Japanese Brazilians and 389 for non-Japanese Brazilians).

Of 877 controls, we selected postmenopausal women over 55 years of age who provided blood samples and reported an energy intake between 500 and 4,000 kcal. Menopausal status was determined by self-report, and energy intake was assessed using a food frequency questionnaire (FFQ). The present study included a total of 382 women comprising 185 Japanese, 46 Japanese Brazilians and 151 non-Japanese Brazilians.

Data collection

Participants in Nagano were asked to complete a self-administered questionnaire, while in-person interviews were conducted in São Paulo 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, smoking habits and dietary factors assessed by FFQ.

Participants in Nagano provided blood samples at the time they returned their self-administered questionnaire, and those in São Paulo provided blood samples at the time of the interview. Blood samples were divided into

serum aliquots in Nagano and into plasma aliquots and buffy coat layers in São Paulo. All blood samples were shipped to the Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan, and stored at -80°C until analysis.

Laboratory analysis

We used a radioimmunoassay method to measure estradiol, estrone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), testosterone and free testosterone in serum for the Nagano participants and in plasma for the São Paulo participants. The following kits were used: estradiol (DSL-4800 Ultra-Sensitive Estradiol Radioimmunoassay Kit; Diagnostic System Laboratories, Inc., Webster, TX, USA), estrone (DSL-8700 Estrone Radioimmunoassay Kit; Diagnostic System Laboratories, Inc.), androstenedione (DPC · Androstenedione; Diagnostic Products Corporation, Llanberis, UK), DHEAS (DPC · DHEA-S Kit, Diagnostic Products Corporation), testosterone (DPC · Testosterone Kit; Diagnostic Products Corporation) and free testosterone (DPC · Free Testosterone Kit; Diagnostic Products Corporation). Bioavailable estradiol (free and albumin-bound estradiol) was measured using the ammonium sulfate precipitation method. Sex hormone-binding globulin (SHBG) was measured by immunoradiometric assay (IRMA) using Spectria SHBG IRMA (Orion Diagnostica, Espoo, Finland). The kit for estrone was applicable to serum samples only, although other kits or methods were applicable to both serum and plasma samples. We therefore measured estrone levels in both serum and plasma from the same women over 50 years of age (n = 38) and calibrated estrone levels in plasma on the basis of a regression function, although the two levels were highly correlated (correlation coefficient = 0.94) and the percentage difference was relatively small (mean = -4%; 95% confidence interval, -9% to 1%). Lower detection limits (LODs) were 5 pg/mL for estradiol, 15 pg/mL for estrone, 6.25 nM/L for SHBG, 0.1 ng/mL for androstenedione, 5 μg/dL for DHEAS, 0.05 ng/mL for testosterone and 0.4 pg/mL for free testosterone. Measurement values below the LOD were assigned half the value of the LOD if measurable values below the LOD were not available. The intra-assay coefficients of variation were 6.5% for estradiol at a mean concentration of 24.9 pg/mL (n = 12), 10.6% for bioavailable estradiol at a mean concentration of 48.1% (n = 10), 5.6% for estrone at a mean concentration of 101.7 pg/mL (n = 10), 4.7% for SHBG at a mean concentration of 104.6 nM/L (n = 10), 9.4% for androstenedione at a mean concentration of 1.33 ng/mL (n = 10), 5.2% for DHEAS at a mean concentration of 75 μg/dL (n = 10), 4.5% for testosterone at a mean concentration of 0.83 ng/mL (n = 10) and 11.6% for free testosterone at a mean concentration of 5.4 pg/mL (n = 10). Interassay coefficients of variation were 9.7% for estradiol at a mean concentration of 28.0 pg/mL (n = 8), 11.9% for bioavailable estradiol at a mean concentration of 52.3% (n = 9), 11.1% for estrone at a mean concentration of 90.1 pg/mL (n = 8), 5.5% for SHBG at a mean concentration of 124.0 nM/L (n = 10), 9.8% for androstenedione at a mean concentration of 1.10 ng/mL (n = 20), 5.3% for DHEAS at a mean concentration of 92.5 μg/dL (n = 20), 7.7% for testosterone at a mean concentration of 0.90 ng/mL (n = 20) and 9.0% for free testosterone at a mean concentration of 6.4 pg/mL (n = 10). All hormone assays were performed by a commercial laboratory (Mitsubishi Kagaku Bio-Clinical Laboratories, Tokyo, Japan).

Statistical analysis

We excluded a total of 19 participants with estrone values >125 pg/mL, estradiol values >75 pg/mL or testosterone values >125 ng/dL (indicating postmenopausal hormone use), leaving 185 Japanese, 44 Japanese Brazilians and 134 non-Japanese Brazilians for inclusion in the present analyses.

All hormone values were natural log-transformed to produce approximately normal distributions. Geometric mean hormone levels according to the three populations, known breast cancer risk factors and lifestyle factors were calculated using multivariate regression analysis. The following variables were used for adjustment: age, ethnic group, age at first menarche, age at menopause, number of births, age at first birth, height, body mass index (BMI), smoking status, alcohol drinking habits and physical activity during the past 5 years. Analysis of covariance was used to test for differences in mean hormone levels across the three populations, known breast cancer risk factors and lifestyle factors. For comparisons among the three populations, Japanese Brazilians living in São Paulo were used as the reference group. Linear trends for mean hormone levels were tested in the multivariate regression model using categories of each factor as ordinal or continuous variables. All P values reported are two-sided, and the statistical significance level was set at $P < 0.05$. All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

The characteristics of the study populations are presented in Table 1. Japanese participants had a later menarche, fewer births and lower BMI, and they smoked less, drank more and were physically more active than the other two populations. On the other hand, non-Japanese Brazilians had earlier ages at menopause and at first birth, more births and greater BMI,