status in this study, we found no remarkable difference for either of the two SNPs examined regardless of population.

Given that the presence of antibodies against tumor-associated antigens is essential for the induction of ADCC, the association between polymorphisms in the FcgR gene and breast cancer risk might be more prominent among women with antibodies against tumor-associated antigens than in those without these antibodies. Although antibodies against most tumor-associated antigens are found in only 0–3% of healthy individuals, anti-MUC1 antibodies are found in 23.3% for IgG (weighted average of five studies) and 53% for IgM (weighted average of two studies) [7]. It is known that women develop MUC1 and anti-MUC1 antibodies during pregnancy and breast-feeding, presumably due to changes within the breast or uterus that alter MUC1 expression, glycosylation, or shedding [8]. Moreover, serum from multiparous women contained antibodies which selectively mediated ADCC against established mammary carcinoma cell lines [10]. In this regard, however, our stratified analyses showed no association between the two SNPs in the FcgR gene and risk of breast cancer regardless of parity. Further studies using information on the presence of antibodies against tumor-associated antigens will clarify the association between polymorphisms in the FcgR gene and breast cancer risk.

Previous studies have shown that risk factors such as parity and BMI differ among breast cancer subtypes defined by ER or PR status [23, 26]. We, therefore, examined whether the association of the two SNPs in the FcgR gene differed across subtypes, but found no significant difference in risk. On the other hand, given that ADCC is a potential anti-tumor mechanism behind targeted therapy with the humanized monoclonal antibody trastuzumab for HER2-positive breast cancer [15], the two SNPs in the FcgR gene might be more closely associated with the risk of HER2-positive breast cancer. Moreover, gene expression profiling in tumor tissues suggests that breast cancers may be divided into molecular subtypes consisting of two ER+ types (luminal A and B) and three ER− types [HER2-expressing, basal-like, and unclassified (normal-like)], with distinctive clinical outcomes [27, 28]. It is, therefore, of particular interest to test the hypothesis that the association of the two SNPs in the FcgR gene might differ by HER2 status or molecular subtype. However, the present study was not designed to collect tumor tissues or information on HER2 status at the start of recruitment. Further large studies are required to test this hypothesis.

In conclusion, we found no statistically significant association between two SNPs in the FcgR gene and breast cancer risk. Our findings suggest that ADCC might not play a major role in the etiology of breast cancer. Further studies are needed to clarify the role of the immune system in the etiology of breast cancer.

Acknowledgments This study was supported by a Grant-in-Aid for Research on Risk of Chemical Substances from the Ministry of Health, Labour and Welfare of Japan, and Grants-in-Aid for Scientific Research on Priority Areas (17015049) and for Young Scientists (B) (22700934) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Japan Society for the Promotion of Science, and Foundation for Promotion of Cancer Research in Japan. We are grateful to the participants of the "São Paulo-Japan Breast Cancer Study Group": T. Hanaoka, M. Kobayashi, J. Ishihara, S. Ikeda, and C. Nishimoto (Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo); C. I. Yamaguchi, C. M. Kunieda, and S. S. Sugama (Nikkei Disease Prevention Center, São Paulo); C. K. Taniguchi and J. A. Marques (Departamento de Ginecologia, Hospital Pérola Byington, São Paulo); M. R. Eichhorn (Departamento de Nutrição, Hospital Pérola Byington, São Paulo); M. M. Netto, M. S. Maciel, S. M. T. Carvalho, J. B. D. Collins, and C. E. M. Fontes (Departamento de Mastologia, Hospital A.C. Camargo, São Paulo); L. P. Kowalski and J. M. F. Toyota (Departamento de Cirurgia de Cabeça e Pescoço e Otorrinolaringologia, A. C. Camargo Hospital, São Paulo); E. M. Barbosa (Departamento de Mastologia, Instituto Brasileiro de Controle ao Câncer, São Paulo); O. Ferraro (Departamento de Mastologia, Hospital do Servidor Público Estadual Francisco Morato de Oliveira, São Paulo); E. H. Hotta and D. A. Petti (Instituto de Ginecologia e Mastologia, Hospital Beneficencia Portuguesa); and S. Mendes (Instituto Brasileiro de Mastologia e Ginecologia, Hospital Beneficencia Portuguesa).

Conflict of interest All authors declare that we have no conflict of interest in connection with this paper.

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Cancer Science
The official journal of the Japanese Cancer Association JCA

Review Article

Risk factors for breast cancer: epidemiological evidence from Japanese studies

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(Received May 1, 2011/Accepted May 26, 2011/Accepted manuscript online May 31, 2011/Article first published online July 1, 2011)

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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doi: 10.1111/j.1349-7006.2011.01996.x

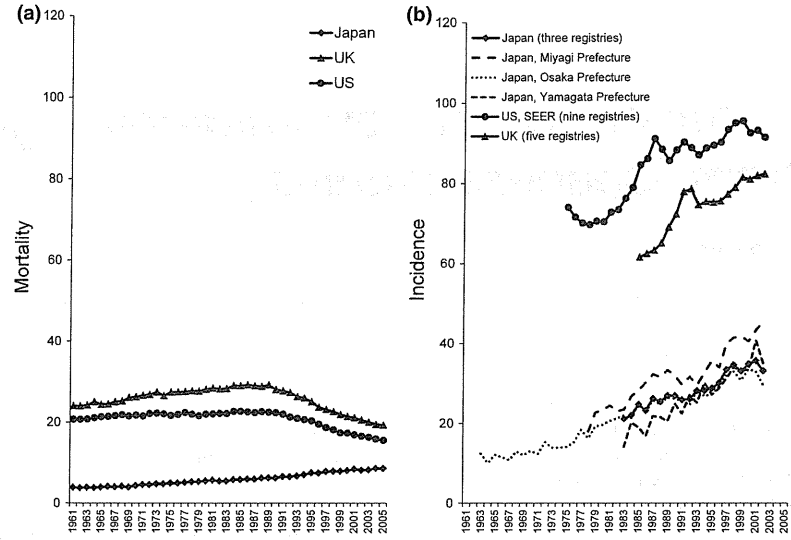

Fig. 1. Annual (a) mortality and (b) incidence rates of breast cancer in Japan, the US, and UK (standardized rate per 100 000 by age to world population). Data for the incidence rate are from Ferlay *et al.*:[2] Japan (three registries: Miyagi, Yamagata, and Osaka) from 1963 to 2002; US (Surveillance 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.

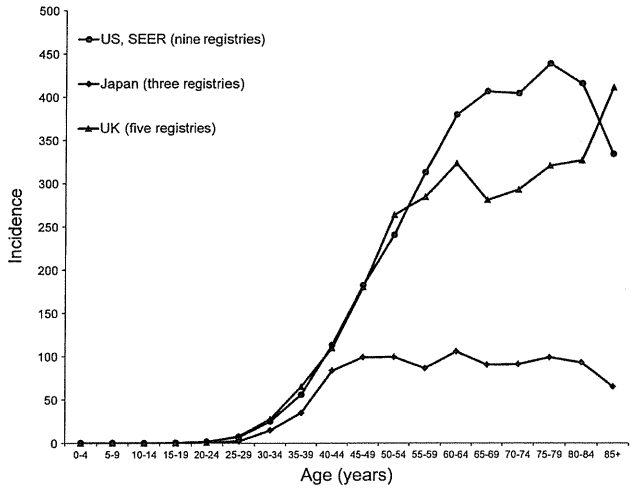

Fig. 2. Age-specific breast cancer incidence rate (per 100 000) in 2002 in Japan (three registries: Miyagi, Yamagata, and Osaka), the US (Surveillance Epidemiology and End Results [SEER]; nine registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, 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

doi: 10.1111/j.1349-7006.2011.01996.x

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]

doi: 10.1111/j.1349-7006.2011.01996.x

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

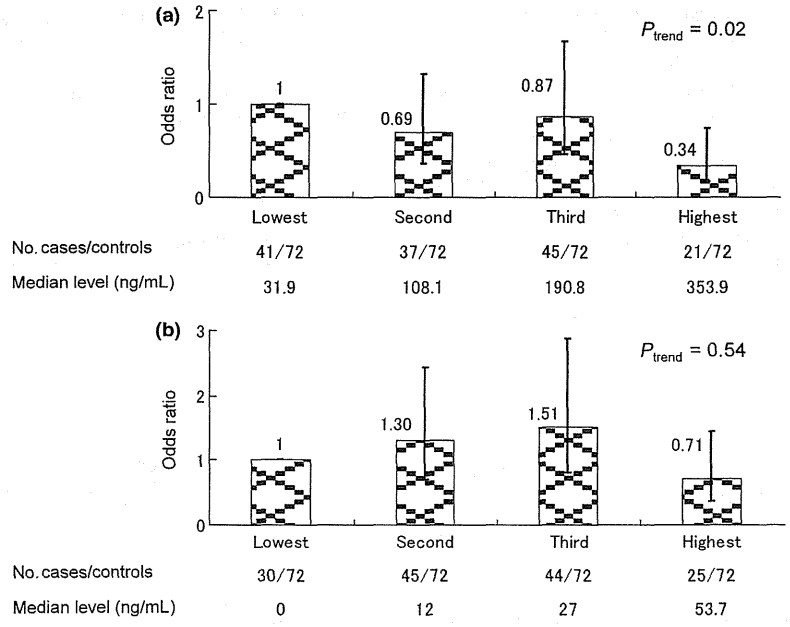

Fig. 3. Plasma isoflavones and the risk of breast cancer: the Japan Public Health Center-Based Prospective (JPHC) study. (a) Genistein; (b) daidzein. Odds ratios were adjusted for the numbers of births and the age at first birth. Data are from Iwasaki *et al.*[47]

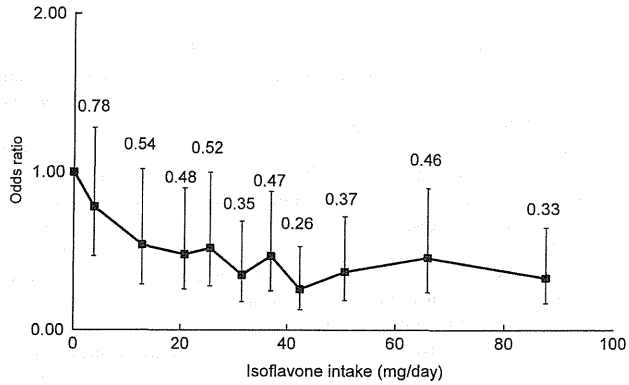

Fig. 4. Isoflavone intake and the risk of breast cancer in hospital-based case–control studies among Japanese, Japanese Brazilians, and non-Japanese Brazilians. Subjects were categorized into 11 groups: non-consumers and deciles of isoflavone consumers based on the control distribution. Odds ratios were 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

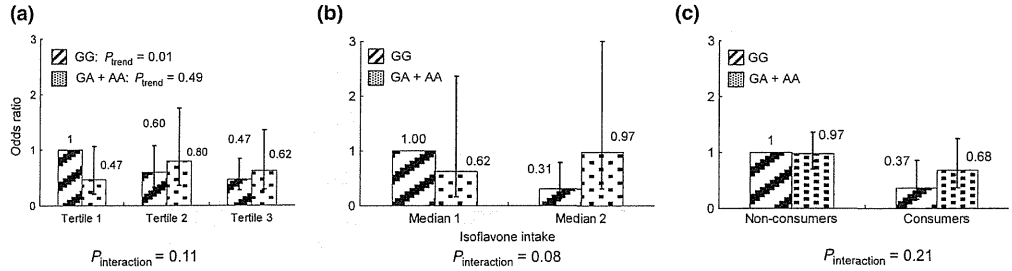

Fig. 5. Isoflavone, polymorphisms in the estrogen receptor beta gene (rs4986938) and breast cancer risk in hospital-based case–control studies among (a) Japanese (postmenopausal), (b) Japanese Brazilians (all), and (c) non-Japanese Brazilians (all). Odds ratios were estimated using matching pairs with 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]

doi: 10.1111/j.1349-7006.2011.01996.x

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.

Acknowledgments

The authors sincerely thank the members and coworkers of the Japan Public Health Center-based Prospective Study Group, Nagano Breast Cancer Study Group, and São Paulo-Japan Breast Cancer Study Group. The authors' work reported herein was supported by Management Expenses Grants from the Government to the National Cancer Center, Grant-in-Aid for the Third-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan, and Grants-in-Aid for Scientific Research on Innovative Areas (221S0001) and for Young Scientists (B) (22700934) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, the Japan Society for the Promotion of Science, and the Foundation for Promotion of Cancer Research in Japan.

Disclosure Statement

The authors have no conflicts of interest.

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doi: 10.1111/j.1349-7006.2011.01996.x

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Body weight at age 20 years, subsequent weight change and breast cancer risk defined by estrogen and progesterone receptor status—the Japan public health center-based prospective study

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Few prospective studies have investigated the association between BMI at age 20 years (BMI20y) and breast cancer risk with consideration to estrogen/progesterone receptor status (ER/PR). We evaluated the association between BMI20y and ER/PR-defined breast cancer risk among 41,594 women in the population-based Japan Public Health Center-based Prospective Study.

Key words: breast cancer, body weight at age 20, weight change, risk, estrogen receptor, progesterone receptor

Abbreviations: BMI20y: relative body weight at age 20 years; BMI: body mass index/relative body weight; CIs: confidence intervals; EFH: exogenous female hormones; ER: estrogen receptor; FFQ: food frequency questionnaire; HR: hazard ratio; PHC: public health center; PR: progesterone receptor; RR: risk ratio; SD: standard deviation; the JPHC Study: the Japan Public Health Center-based Prospective Study; the NHS: the Nurses' Health Study

Grant sponsor: Ministry of Health, Labour and Welfare of Japan (Grants-in-aid for Cancer Research); **Grant number:** No. 19 shi-2; **Grant sponsor:** Ministry of Health, Labour and Welfare of Japan (Grants-in-aid for the 3rd term Comprehensive 10-Year Strategy for Cancer Control); **Grant number:** H21-Sanjigan-Ippan-003; **Grant sponsor:** Ministry of Education, Culture, Sports, Science, and Technology of Japan (Grants-in-aid for Scientific Research on Priority Area); **Grant number:** 17015049; **Grant sponsor:** the Foundation for Promotion of Cancer Research, Japan (Research Resident Fellowship for the 3rd term Comprehensive 10-Year Strategy for Cancer Control) Grant awardee: (Dr. RS)

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DOI: 10.1002/ijc.25744

History: Received 17 Mar 2010; Accepted 30 Sep 2010; Online 25 Oct 2010

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Anthropometric factors were assessed using self-reported questionnaires. Relative risks (RRs) were estimated by Cox proportional hazards regression models. Through to the end of 2006, 452 breast cancer cases were identified. We observed a statistically significant inverse association between BMI20y and breast cancer incidence [multivariable-adjusted RR for each 5-unit increment 0.75 (95%CI = 0.61–0.92)], which was not modified by menopausal or recent BMI status. In contrast, recent BMI and subsequent BMI gain were not associated with increased risk among premenopausal women, but were substantially associated with increased risk among postmenopausal women [corresponding $RR_{recent\ BMI}$ = 1.31 (95%CI = 1.07–1.59); $RR_{subsequent\ BMI\ gain}$ = 1.32 (95%CI = 1.09–1.60)]. In subanalyses by receptor status (~50% of cases), the observed inverse association of BMI20y with risk was consistent with the result for ER–PR– [0.49 (95%CI = 0.27–0.88)], while the observed positive associations of BMI gain with postmenopausal breast cancer risk appeared to be confined to ER+PR+ tumors [corresponding $RR_{for\ subsequent\ BMI\ gain}$ =2.24 (95%CI = 1.50–3.34)]. Low BMI at age 20 years was substantially associated with an increased risk of breast cancer. In contrast, high recent BMI and subsequent BMI gain from age 20 were associated with increased risk of postmenopausal ER+PR+ tumors.

Introduction

Despite the lower prevalence of obesity in Japan than Western countries,[1] the incidence rate of breast cancer in this country has increased rapidly for a quarter of a century, and this cancer is now the most prevalent malignancy among women.[2] A national survey has identified a high overall prevalence of leanness rather than obesity, particularly among younger generations, and more than 20% of young Japanese female adults in their 20s and 30s are underweight.[3,4] Further, a recent nationwide cross-sectional survey showed that young female adults became thinner at an early life-stage.[5] In contrast, the prevalence of overweight among women tends to increase as age exceeds 50 years.[3]

A number of epidemiological studies have reported that both early adult body weight[6–16] and a subsequent change in body weight[6,7,9,10,12,15–19] are associated with breast cancer risk. Several of these have reported an inverse association between body weight in early adulthood and the incidence of breast cancer.[6,10,12,18,19] Almost all these previous studies were conducted in Western populations, however, in which the prevalence of obesity is high. This largely explains why the proposed biological mechanism for this inverse association involves a decrease in levels of estradiol[20] due to premenopausal obesity, including anovulatory disorder. However, the Nurses' Health Study (NHS) II reported that the observed inverse association of BMI in early adulthood with risk was not eliminated after adjustment for ovulatory disorders,[14] suggesting the presence of other biological mechanisms apart from anovulation.

As an alternative, we hypothesized that a certain level of body fat in the mammary gland (*i.e.*, mammary gland fat pad) might be essential to healthy differentiation in breast tissue,[21] particularly in early adulthood. Lean BMI might be an epidemiological indicator of a low level of fat tissue in the mammary gland, associated with an increased risk of breast cancer in later life resulting from the interruption of healthy differentiation in maturation in the breast in young adult women.

In this study, we prospectively investigated the impact of relative body weight at age 20 years (BMI20y) on the development of breast cancer among 41,594 Japanese women, with a relatively low prevalence of obesity, in the Japan Public Health Center-based Prospective Study (JPHC Study). We also evaluated the association of recent BMI and a subsequent change in BMI from age 20 years with breast cancer risk.

Material and Methods

Study population

The JPHC Study has been described in detail elsewhere.[22] The cohort was started in 1990 to evaluate the association between lifestyle factors and cancer and cardiovascular disease in the Japanese population. The study population consisted of all Japanese aged 40–59 years in Cohort I (the Iwate-Ninohe, Akita-Yokote, Nagano-Saku, Okinawa-Chubu, Tokyo-Katsushika public health center (PHC) areas) and 40–69 years in Cohort II (the Ibaraki-Mito, Niigata-Nagaoka, Kochi-Chuohigashi, Nagasaki-Kamigoto, Okinawa-Miyako and Osaka-Suita PHC areas) who were enrolled in the residential registries. Initially, 140,420 subjects were invited to the JPHC cohort, of whom 71,698 were female. For this study, subjects from one PHC area (Tokyo-Katsushika; n = 4,178) were excluded due to a lack of complete information on cancer incidence. A total of 55,907 women completed the baseline questionnaire (response rate 82.8%). All eligible cohort members received two further follow-up questionnaires for the 5-year (1995–1998; response rate 79.4%) and 10-year follow-up surveys (2000–2003; response rate 77.4%).

We excluded ineligible subjects (n = 21), women who moved before the start of follow-up or who could not be followed (n = 48), and those with a self-reported history of cancer before the start of follow-up (n = 1,509). In this study, we excluded women with missing or unreliable information on current BMI or BMI at age 20 (<14 or ≥ 40) (n = 10,146), alcohol drinking status, smoking and leisure-time physical activity (n = 1,954); women with a family history of breast cancer at baseline (n = 215); and those who reported unreasonable estimates of total energy intake (± 3SD) (n = 420). In this study, we defined menopausal status based on information from self-reported questionnaires, which asked subjects to describe menstrual bleeding in the three classifications of (*i*) yes, natural; (*ii*) no, natural

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menopause; and (*iii*) no, surgical menopause. Postmenopausal women were asked about age at menopause; if this information was not available (0.053% of the cohort), we considered those aged over 56 years at administration of the questionnaire as postmenopausal, since ~99% of subjects had stopped menstruating before this age. The final study cohort consisted of 41,594 women.

Exposure measurement

Information on weight and height was assessed through self-reported questionnaires in the baseline and 5- and 10-year follow-up surveys, while that on weight at age 20 years was collected in the baseline and 10-year follow-up surveys. In the baseline questionnaire, however, the question on weight at age 20 years was not included for Cohort I, so that we were unable to obtain any information on BMI20y among 22,273 women, or 53.5% of the study cohort. In the 10-year follow-up survey, in contrast, all questionnaires included an inquiry about weight at age 20, with responses received from 36,880 women (88.7%). Accordingly, we mainly used information from the 10-year follow-up survey, supplemented by that obtained at baseline.

Relative body weight was evaluated by body mass index (BMI), calculated as the weight in kilograms divided by the square of height in meters (kg/m^2). We previously reported a high correlation between self-reported and measured BMI in a subgroup of the JPHC study (Spearman rank correlation coefficient $r = 0.9$).[23] BMI20y was also calculated as weight at age 20 years in kilograms divided by the square of height in meters (kg/m^2). Reproducibility of self-reported BMI20y was assessed by comparison of baseline and 10-year follow-up survey information for those who answered both questionnaires in the JPHC cohort, giving a Spearman correlation coefficient of 0.81.

The change in BMI from age 20 to recent age was calculated as the difference between BMI at recent age and that at age 20, updated with the respective questionnaire cycle. Relative risks (RRs) according to ER/PR-defined tumor status were estimated by including exposure information in the model as a continuous variable, and presented per 5 kg/m^2 increment.

Information on other lifestyle-related factors, such as reproductive information (*i.e.*, parity, age at first birth, age at menarche, age at menopause), alcohol drinking status, and smoking status, was also collected using a self-reported questionnaire at the baseline survey and updated by the respective follow-up surveys, if available.

In the JPHC study, dietary information was accessed using a validated FFQ at baseline,[24] and in the 5- and 10-year follow-up surveys. In the present analyses, however, we used dietary information from the baseline survey only, because the number of food items in the 5-year and 10-year follow-up FFQs differed from that in the FFQ in the baseline survey.

Ascertainment of breast cancer cases and follow-up of the cohort

Breast cancer incident cases were identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries, with permission from the local governments responsible for the registries. Breast cancer cases were defined as codes C500–509 in accordance with the Third Edition of the International Classification of Diseases for Oncology.[25] Eight cases (1.8% of cases) were identified through information on death certificates (*i.e.*, Death Certificate Notification), of which 5 (1.1% of cases) had no information on diagnosis (*i.e.*, Death Certificate Only). Diagnosis was microscopically verified for 97% of all cases. ER and PR status were evaluated by either immunohistochemical assay or enzyme-linked immunoassay. The cut-off point for positivity for ER and PR in breast tumors was decided by clinical estimation at the hospital treating the case or as specified by the assay method at the clinical laboratory performing the assay.

We started follow-up on the date of administration of the baseline questionnaire. Participants contributed person-time from baseline to the date of diagnosis of breast cancer, date of death, date of moving away from the study area, or end of follow-up (Dec 31st, 2006), whichever occurred first. Date of death was verified through linkage with death registries at the PHCs, which are required by the Ministry of Health, Labour and Welfare. Date of moving was verified through linkage with the residential registries at the regional PHCs.

Statistical analysis

To estimate relative risks (RRs) and 95% confidence intervals (CIs), we used a time-dependent multivariate Cox proportional hazards regression model with age as the time scale.[26] The proportional hazards assumptions were verified using Kaplan-Meier curves.[27] In primary analyses, women were subdivided into five categories (BMI20y and recent BMI: <18.5, 18.5–19.9, 20–23.9, 24–28.9, ≥29 kg/m^2; with the cut-off point of 18.5 based on the WHO classification; 20 as a recommended cut-off point for international comparison;[28] and 24 as overweight and 29 as obesity for Japanese populations, in accordance with the WHO expert consultation[28]). For BMI20y, however, because the prevalence of obesity was too low to analyze (1% at age 20 years), we divided women into four categories (<18.5, 18.5–19.9, 20–23.9, ≥24) in the final analyses. According to the change in BMI from age 20 years to recent age, women were also subdivided into four groups, as follows: loss (<−2.5 BMI units), maintain (≥−2.5 to <2.5 BMI units), gain (≥2.5 to <5 BMI units) and major gain (≥5 BMI units). In the main analysis, we adjusted for age (time-scale), area, age at menarche (≤13, 14, 15, ≥16 years, missing), age at first birth (nulliparous, <26, ≥26 years, missing), parity (nulliparous, 1–2, 3, ≥4 children, missing), menopausal status (premenopausal, age at menopause ≤48, 48–53, ≥54 years), use of exogenous female hormones

(EFH) (never, ever, missing), smoking status (never, ever), leisure-time physical activity (no or 1–3 days/month, >1 days/week, 3–4 days/week, every day), alcohol intake (past-drinker, never-drinker, occasional drinker and regular drinker ≤150 or regular drinker >150 g of ethanol/week), total energy-adjusted intake of green-yellow vegetables (quintiles), total energy-adjusted intake of meat and meat products (quintiles) and total energy-adjusted intake of isoflavones (quintiles) as potential confounders on the basis that these covariates were likely associated with risk,[29–31] and correlated with the exposures of interest. Trend tests were performed using a continuous value of exposure in the model.

We assessed the association of BMI20y, recent BMI, and change in BMI from age 20 years to recent age with breast cancer incidence with stratification by menopausal status at baseline survey, by BMI at age 20 (<20 or ≥20) or recent BMI (<25 or ≥25), and by use of EFH (never- or ever-use).

Cross-product terms of these factors and BMI at 20 years, recent BMI or change in BMI were introduced into the Cox proportional hazards regression model. The P-value for interaction was calculated by a likelihood ratio test which compared models with and without the interaction terms. All analyses were performed using the PROC PHREG procedure of 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 approximate average of 14 years' follow-up, corresponding to 581,934 person-years, 452 invasive breast cancer cases were identified among 41,594 women.

Baseline characteristics of the study population are shown in Table 1. Compared to those with a high BMI20y, women with a low BMI20y were more likely to be younger, have a lower BMI, have fewer children, have a high intake of meat products, a low intake of isoflavones, and a higher prevalence of smoking and alcohol drinking. Women who gained BMI (≥5 units) tended to have a lower BMI20y, higher BMI, be younger at first birth, have more children, have a high intake of meat products and green-yellow vegetables, a low intake of isoflavones, and a higher EFH than women who lost BMI (<−2.5 units BMI).

Evaluation of the association between BMI20y and incidence of breast cancer revealed an inverse association [multivariable-adjusted RR for each 5-unit increment for BMI20y = 0.75 (95%CI = 0.61–0.92); Table 2].

In analyses stratified by menopausal status, the observed inverse association was similar across menopausal status ($P_{interaction}$ = 0.48; Table 2).

In stratification by level of recent BMI, RRs for the association between BMI20y and breast cancer incidence between the nonoverweight (recent BMI <24) and overweight groups (recent BMI ≥24) were not statistically heterogeneous ($P_{interaction}$ = 0.64; Table 2).

In this study, women with major weight gain (over 5 units BMI) were more likely to have a low body weight at age 20 years. To evaluate whether the observed inverse association of low BMI20y with risk was attributable to the impact of subsequent BMI gain, we performed subgroup analysis among 31,705 women who did not gain more than 5 units BMI. The results also support our observed substantial inverse association [multivariable-adjusted RR for each 5-unit increment for BMI20y= 0.73 (95%CI =0.57–0.93); text only].

Recent BMI was not associated with breast cancer risk among premenopausal women [multivariable-adjusted RR for each 5-unit increment = 1.02 (95%CI =0.81–1.27); Table 3], but was positively associated with increased risk among postmenopausal women [1.31 (95%CI =1.07–1.59); Table 3]. We also observed a statistically significant positive trend among women with BMI20y ≥20 (P_{trend} 0.016). However, there was no evidence for effect modification by these factors ($P_{interaction\ for\ menopausal\ status}$= 0.61; $P_{for\ BMI20y}$=0.82).

Similarly, change in BMI from age 20 to recent age was not associated with breast cancer risk among premenopausal women [multivariable-adjusted RR for increase in each 5-unit increment = 1.04 (95%CI =0.84–1.30)], but was statistically significantly associated with increased risk among postmenopausal women [corresponding multivariable-adjusted RR= 1.32 (95%CI =1.09–1.60); $P_{interaction}$ = 0.042; Table 3]. This observed positive association among postmenopausal women was not modified by BMI20y level (<20 *vs.* ≥20) ($P_{interaction}$ = 0.31; Table 3).

In analyses stratified by EFH use among postmenopausal women, the observed inverse association between BMI20y and breast cancer risk was not modified by EFH use ($P_{interaction}$ = 0.69; Table 4). Substantial positive associations of recent BMI and subsequent BMI gain from age 20 years with the development of postmenopausal breast cancer were confined to never-users of EFH. However, there was no statistical evidence for effect modification by EFH use ($P_{interactions\ for\ recent\ BMI}$ = 0.28; $P_{for\ change\ in\ BMI}$ = 0.77; Table 4).

With regard to ER/PR status, information about joint ER/PR status was available for 211 cases. Among these, 94 (45% of known cases) were ER+PR+, 45 (21%) were ER+PR−, and 60 (28%) were ER−PR−. The number of ER−PR+ tumor cases (n = 12) was too small to allow separate analyses.

We performed subanalyses by receptor status in ~50% of cases. Our finding of an overall inverse association of BMI20y with the incidence of breast cancer was not consistent for ER+PR+ tumors [RR for each 5-unit increment = 1.10 (95%CI = 0.71–1.70)], but was consistent for ER—PR— tumors [RR for ER—PR— = 0.49 (95%CI = 0.27–0.88); Table 5].

In contrast, the positive association of BMI gain from age 20 years to recent age with the development of postmenopausal breast cancer was consistent with the results for ER+PR+ [RR for each 5-unit increment =2.24(95%CI = 1.50–3.34)], but not for other tumor subtypes. These results for the association of recent BMI with the risk of ER/PR-

Table 1. Baseline characteristics according to category of BMI at age 20 years and change in BMI from age 20 to recent age among 41,594 women in the Japan Public Health Center-based Prospective Study, Cohort I (1990-) and Cohort II (1993-)

	Category of BMI at age 20 years(BMI, kg/m^2)					Change in BMI from age 20 to recent age, BMI unit			
Characteristic mean(SD)	Lean <18.5 *n*=4,413 10.6%	Slender 18.5–<20 *n*=7,422 17.8%	Reference 20–<24 *n*=23,294 56.0%	Overweight 24–28.9 *n*=6,047 14.5%	Obese ≥29 *n*=418 1.0%	Loss (<−2.5) *n*=3,524 8.5%	Reference (−2.5 to 2.49) *n*=21,344 51.3%	Gain (2.5–4.9) *n*=10,105 24.3%	Major gain (≥5.0 BMI) *n*=6,621 15.9%
Age at baseline (year)	49.6 (7.5)	49.6 (7.5)	51.5 (7.8)	54.7 (7.9)	57.0 (7.4)	55.3 (8.4)	51.1 (7.9)	50.8 (7.5)	52.0 (7.6)
BMI at age 20 (kg/m^2)	17.1 (0.8)	19.3 (0.4)	21.7 (1.1)	25.6 (1.2)	31.3 (2.3)	25.1 (2.9)	21.7 (2.3)	20.7 (2.1)	20.2 (2.2)
BMI at baseline (kg/m^2)	21.7 (3.0)	22.3 (2.8)	23.6 (2.9)	24.8 (3.3)	26.2 (3.7)	20.9 (2.4)	22.1 (2.3)	24.3 (2.2)	27.3 (2.9)
Age at menarche[1] (year)	14.5 (1.8)	14.4 (1.8)	14.6 (1.9)	15.0 (2.0)	15.3 (2.0)	15.1 (2.0)	14.5 (1.8)	14.5 (1.8)	14.8 (1.9)
Age at first birth[1] (year)	25.1 (3.6)	25.2 (3.5)	24.9 (3.4)	24.7 (3.4)	25.0 (3.9)	25.1 (3.5)	25.0 (3.4)	24.9 (3.4)	24.7 (3.5)
Number of children (*n*)	2.4 (1.5)	2.4 (1.4)	2.5 (1.5)	2.8 (1.7)	3.0 (2.0)	2.6 (1.7)	2.5 (1.4)	2.6 (1.5)	2.8 (1.7)
Age at menopause (year)	47.9 (5.2)	48.1 (4.8)	48.4 (4.6)	48.5 (4.7)	48.5 (5.0)	48.3 (4.8)	48.4 (4.5)	48.4 (4.8)	48.3 (5.0)
Use of exogenous female hormones (ever), %	11.6	12.4	11.9	10.5	10.3	10.4	11.7	12.2	12.2
Smoking status (ever), %	10.1	8.6	7.4	6.9	9.3	9.1	7.8	7.0	8.4
Alcohol drinking status (ever), %	26.3	26.3	22.5	17.4	17.0	18.6	24.1	23.3	19.7
Intake of meat and meat products (g/day)	29.8 (16.8)	29.6 (16.1)	28.8 (16.2)	27.7(16.6)	26.4 (16.9)	27.5 (16.4)	28.7 (16.0)	29.3(16.2)	29.4 (17.6)
Intake of green-yellow vegetables (g/day)	33.0 (22.2)	33.4 (21.6)	34.4 (21.7)	34.1(22.8)	33.1 (22.7)	33.5 (22.2)	33.9 (21.3)	33.9(21.7)	34.7 (23.8)
Intake of isoflavone (mg/day)	23.1 (13.2)	23.7 (12.9)	24.7 (12.8)	25.3(13.2)	24.8 (13.1)	24.9 (13.0)	24.4 (12.7)	24.4 (13.0)	24.2 (13.2)

SD, standard deviation, BMI= body mass index.
[1]Among women with information.

Table 2. Multivariable relative risks (RRs)[1] and 95% confidence intervals (CIs) for the association between relative body weight at age 20 years and breast cancer risk with stratification by menopausal status and BMI at the time of questionnaires (recent BMI) over 581,934 person-years in 41,594 women in the Japan Public Health Center-based Prospective Study, 1990–2006

	All			Menopausal status (Model[1])				Recent BMI (Model[1])			
		Model[1]	Model[2]		Premenopausal[3]		Postmenopausal[4]		BMI (<24)		BMI (≥24)
BMI at age 20 years	No.	(*n*=41,594) 452 cases RR (95%CI)	(*n*=41,594) 452 cases RR (95%CI)	No.	(*n*=17,886) 220 cases RR (95%CI)	No.	(*n*=23,708) 232 cases RR (95%CI)	No.	(*n*=22,280) 216 cases RR (95%CI)	No.	(*n*=19,314) 236 cases RR (95%CI)
<18.5	48	1.16 (0.84–1.59)	1.26 (0.91–1.74)	26	1.15 (0.74–1.78)	22	1.11 (0.70–1.77)	29	1.11 (0.73–1.67)	19	1.54 (0.95–2.50)
18.5–<20	100	1.38 (1.08–1.75)	1.45 (1.14–1.83)	58	1.57 (1.14–2.18)	42	1.20 (0.84–1.71)	57	1.34 (0.97–1.86)	43	1.66 (1.17–2.35)
20–<24 (Ref)	244	1.00 (ref.)	1.00 (ref.)	111	1.00 (ref.)	133	1.00 (ref.)	111	1.00 (ref.)	133	1.00 (ref.)
≥24	60	0.82 (0.61–1.11)	0.75 (0.56–1.00)	25	1.01 (0.63–1.61)	35	0.77 (0.52–1.14)	19	0.83 (0.51–1.36)	41	0.74 (0.52–1.06)
P_{trend}[5]		0.005	<.0001		0.11		0.07		0.048		0.0004
Per 5 kg/m^2 increase	452	0.75 (0.61–0.92)	0.68 (0.56–0.82)	220	0.78 (0.57–1.06)	232	0.77 (0.59–1.02)	216	0.74 (0.55–1.00)	236	0.63 (0.49–0.82)
$P_{interaction}$[6]					$P_{interaction\ pre\ vs.\ post} = 0.48$				$P_{interaction\ BMI\ <24\ vs.\ =>24} = 0.64$		

[1]Multivariable Cox proportional hazards models were adjusted for age time-scales, area (10), change in BMI from age 20 years (<−2.5; from −2.5 to +2.49 ; from +2.5 to +4.9; ≥+5 increment in BMI), age at menarche (≤13, 14, 15, ≥16 years or missing), age at first birth (nulliparous, <26, >26 years, or missing), parity (nulliparous, 1–2, 3, ≥4 or missing), menopausal status (premenopausal, age at menopause <48, 48–53, ≥54 years), use of exogenous female hormones (never, ever, or missing), smoking status (never, ever), leisure-time physical activity (no or 1–3 days/month, >1 days/week, 3–4 days/week, every day), alcohol intake (past drinker, never-drinker, occasional drinker, regular drinker ≤150, or >150 g of ethanol per week), total energy-adjusted intake of green-yellow vegetables (quintiles), total energy-adjusted intake of meat and meat products (quintiles), and total energy-adjusted isoflavones intake (quintiles). [2]Adjusted for all the above factors but with (change in BMI from age 20 years) exchanged for (recent BMI; <18.5; 18.5–19.9; 20–23.9; ≥24). [3]Adjusted for all the above factors but not adjusted for menopausal status. [4]Adjusted for all the above factors but menopausal status was adjusted according to (age at menopause <48, 48–53, ≥54 years). [5]Trend test was performed using continuous variables. [6]Test of interaction was conducted using (BMI at age 20 years; four categories <18.5; 18.5–19; 20–23.9; ≥24) and (recent BMI; 2 categories <24; ≥24).

Table 3. Multivariable relative risks (RRs) and 95% confidence intervals (CI) for the association of BMI at the time of the questionnaires (recent BMI) and change in BMI from age 20 years to recent age in relation to breast cancer risk with stratification by menopausal status as well as level of BMI at age 20 years over 581,934 person-years in the Japan Public Health Center-based Prospective Study, 1990–2006

	Menopausal status (n=41,594)				Postmenopausal women[2] (n=23,708)			
		Premenopausal[1]		Postmenopausal[2]		BMI age 20y (<20)		BMI age 20y (≥20)
Recent BMI	No.	(n=17,886) RR (95%CI)	No.	(n=23,708) RR (95%CI)	No.	(n=5,566) RR (95%CI)	No.	(n=18,142) RR (95%CI)
<18.5	8	0.98 (0.46–2.10)	10	0.76 (0.39–1.47)	5	0.75 (0.29–1.97)	5	0.75 (0.30–1.88)
18.5– <20	18	0.98 (0.59–1.62)	15	0.77 (0.44–1.34)	8	1.01 (0.45–2.26)	7	0.59 (0.26–1.31)
20– <24 (Ref.)	102	1.00 (ref.)	95	1.00 (ref.)	29	1.00 (ref.)	66	1.00 (ref.)
≥24	92	0.97 (0.73–1.31)	112	1.23 (0.93–1.63)	22	1.19 (0.67–2.13)	90	1.22 (0.89–1.69)
P_{trend}[3]		0.89		0.008		0.59		0.016
Per 5 kg/m^2 increase	220	1.02 (0.81–1.27)	232	1.31 (1.07–1.59)	64	1.12 (0.75–1.68)	168	1.32 (1.05–1.65)
$P_{interaction}$	$P_{interaction\ pre\ vs.post}$ = 0.61				$P_{interaction\ bmi20y\ <20\ vs\ \geq20}$ = 0.82[5]			

	Menopausal status				Postmenopausal women[2]			
		Premenopausal[1]		Postmenopausal[2]		BMI age 20y (<20)		BMI age 20y (≥20)
Change in BMI from age 20 to recent age	No.	(n=17,886) RR (95%CI)	No.	(n=23,708) RR (95%CI)	No.	(n=5,566) RR (95%CI)	No.	(n=18,142) RR (95%CI)
Loss (<−2.5 increment in BMI)	14	0.68(0.37–1.24)	20	1.41(0.86–2.33)				
Stable (−2.5 to 2.49)	91	1.00 (ref.)	108	1.00 (ref.)	24	1.00 (ref.)	104	1.00 (ref.)
Gain (2.5 to 4.9)	73	0.93 (0.49–1.74)	52	1.38 (0.79–2.39)	19	1.10 (0.59–2.03)	33	1.05 (0.71–1.57)
Major Gain (≥+5 increment in BMI)	42	0.71 (0.36–1.38)	52	1.79 (1.02–3.16)	21	0.98 (0.53–1.82)	31	1.67 (1.10–2.51)
P_{trend}[3]		0.70		0.0048		0.53		0.0006
Per 5 kg/m^2 increase	220	1.04 (0.84–1.30)	232	1.32 (1.09–1.60)	64	1.13 (0.77–1.67)	168	1.43 (1.16–1.76)
$P_{interaction}$	$P_{interaction\ pre\ vs.post}$ = 0.042				$P_{interaction\ 20y<20\ vs.\geq20}$ = 0.31[4]			

[1]Multivariable Cox proportional hazards models were adjusted for age time-scales, area (10), BMI at age 20-years old (<18.5; 18.5–19.9; 20–23.9; ≥24), age at menarche (≤13, 14, 15, ≥16 years or missing), age at first birth (nulliparous, <26, ≥26 years, or missing), parity (nulliparous, 1–2, 3, ≥4 or missing), use of exogenous female hormones (never, ever, or missing), smoking status (never, ever), leisure-time physical activity (no or 1–3 days/month, >1 days/week, 3–4 days/week, every day), alcohol intake (past-drinker, never-drinker, occasional drinker, regular drinker ≤150, or >150 g of ethanol per week), total energy-adjusted intake of green-yellow vegetables (quintiles), total energy-adjusted intake of meat and meat products (quintiles), and total energy-adjusted intake of isoflavones (quintiles). [2]Adjusted for all the above factors[1] and age at menopauose (<48, 48–53, ≥54) among postmenopausal women. [3]Trend tests were performed using continuous variables. [4]Test of interaction was conducted using (BMI at age 20 years; 2 categories <20; ≥20) and (change in BMI from age 20; 3 categories <+2.5; +2.5 to +4.9; ≥+5 increment in BMI).

defined breast cancer were consistent with those for the change in BMI from age 20 years (text only).

Compared to the stable BMI group (*i.e.*, range of BMI change from −2.5 to <2.5), an ~2.4 times' higher increase in risk for ER+PR+ tumors was observed among postmenopausal women who gained BMI ≥5 (RR = 2.44: 95%CI = 1.10–5.40; P_{trend} = 0.0002; text only).

Because this study used information on BMI20y mainly from the 10-year follow-up survey, we performed sensitivity analyses using information mainly from the baseline survey, supplemented by that from the 10-year follow-up survey. These analyses gave similar results. Further, risk estimates for further sensitivity analyses based on a statistical model with height were also similar to those in Table 2 [multivariable-adjusted RR for increase in each 5-unit increment = 0.75 (95%CI =0.61–0.93) text only].

Discussion

To our knowledge, this is the first large population-based prospective cohort study in Japan to evaluate the association between BMI20y and the incidence of ER/PR-defined breast cancer. Our observed inverse association was consistent with three prospective cohort[14,16,32] and four case-control studies,[7,8,11,15] but not with others.[33] Several studies[6,12,15] have suggested that this inverse association is more pronounced among younger/premenopausal than older/postmenopausal women, but this was not fully consistent with the present and previous results.[7,11] In our cohort, age at baseline was ≥40 years, and thus follow-up did not completely cover the premenopausal period.

With regard to ER/PR status, NHS II[14] reported that the association with BMI at age 18 years was strongest for ER+ [hazard ratio$_{\geq25\ vs.\ 20\text{–}22.4}$ 0.76] but their corresponding result

Table 4. Multivariable relative risks (RRs) and 95% confidence intervals (CIs) for the association of BMI at age 20 years, recent BMI, and change in BMI from age 20 to recent age with the incidence of breast cancer stratified by use of exogenous female hormones among 23,708 postmenopausal women with information on the use of exogenous female hormones in the Japan Public Health Center-based Prospective Study, 1990–2006

	Use of exogenous female hormones				
	Never-users (n=20,344) 167 cases		Ever-users (n=3,364) 65 cases		
	No.	RR (95%CI)	No.	RR (95 %CI)	$P_{interaction}$
BMI at age 20 years old[1]					
<18.5	14	0.92 (0.51–1.64)	8	1.59 (0.70–3.63)	0.69
18.5–<20	30	1.18 (0.78–1.80)	12	1.24 (0.63–2.45)	
20– <24 (Ref.)	98	1.00 (ref.)	35	1.00 (ref.)	
≥24	25	0.77 (0.48–1.23)	10	0.76 (0.35–1.62)	
Per 5 kg/m^2 increase		0.82 (0.59–1.13)		0.67 (0.40–1.13)	
P_{trend}[2]		*0.22*		*0.14*	
Recent BMI[3]					
<18.5	5	0.52 (0.21–1.30)	5	1.97 (0.71–5.42)	0.28
18.5–<20	10	0.73 (0.38–1.43)	5	1.08 (0.40–2.93)	
20– <24 (Ref.)	70	1.00 (ref.)	25	1.00 (ref.)	
≥24	82	1.31 (0.95–1.82)	30	1.19 (0.68–2.07)	
Per 5 kg/m^2 increase		1.38 (1.10–1.72)		1.04 (0.69–1.56)	
P_{trend}[2]		*0.006*		*0.85*	
Change in BMI from age 20 to recent age					
Loss (<−2.5 unit BMI)	14	0.64 (0.35–1.17)	6	0.95 (0.37–2.44)	0.77
Stable (−2.5 to −2.49)	78	0.99 (0.66–1.48)	30	1.00 (ref.)	
Gain (2.5 to 4.9)	37	1.00 (ref.)	15	0.96 (0.51–1.83)	
Major gain (≥+5 unit BMI)	38	1.40 (0.92–2.11)	14	1.07 (0.54–2.13)	
Per 5 kg/m^2 increase		1.42 (1.14–1.77)		1.08 (0.73–1.61)	
P_{trend}[2]		*0.002*		*0.70*	

[1]Multivariable Cox proportional hazards models were adjusted for age (time-scales), area (10), age at menarche (≤13, 14, 15, ≥16 years or missing), age at first birth (nulliparous, <26, ≥26 years, or missing), parity (nulliparous, 1–2, 3, ≥4 or missing), age at menopause (<48, 48–53, ≥54 years), smoking status (never, ever), leisure-time physical activity (no or 1–3 days/month, >1 days/week, 3–4 days/week, every day), alcohol intake (past-drinker, never-drinker, occasional drinker, regular drinker ≤150, or >150 g of ethanol per week), total energy-adjusted intake of green-yellow vegetables (quintiles), total energy-adjusted intake of meat and meat products (quintiles), and total energy-adjusted intake of isoflavones (quintiles). BMI at age 20 years (<18.5; 18.5–19.9; 20–23.9; ≥24) and change in BMI (<− 2.5; from -2.5 to +2.49 ; from +2.5 to +4.9; ≥+5 increment in BMI) were mutually adjusted in the model. [2]Trend tests were performed using continuous variables. [3]Adjusted for all the above factors[1] except change in BMI (<−2.5; from −2.5 to +2.49 ; from +2.5 to +4.9; ≥+5 increment in BMI).

for ER– was similar. Further, the most recent study (including NHS I and II) suggested that the inverse association between adolescent body fatness and breast cancer risk was stronger for ER– than ER+ tumors.[34] The main contribution to our inverse association appeared to derive from ER–PR– tumors, but ER/PR status was verified in fewer than half of the cases, and this result should therefore be interpreted with caution.

Regarding change in BMI from age 20, our null association among premenopausal women was consistent with several studies.[6,18] It has been reported that weight gain from age 18 years was inversely associated with premenopausal breast cancer risk, but that this association was attenuated by adjustment for BMI at enrollment.[16] Among postmenopausal women, our finding of a substantial positive association agrees well with most[6,7,12,17,19] but not all previous studies.[9,10]

Since women who gained BMI (≥5 units) from age 20 tended to have a lower BMI20y, our inverse association between BMI20y and risk might have been partly enhanced by the longitudinal amplitude of weight gain among lean women in early adulthood. When the analysis was restricted to women who maintained BMI (amplitude −2.5 to +2.5 units), the inverse association appeared attenuated, although this could be explained by lower power due to stratification. The lack of effect modification by BMI20y is consistent with a previous report.[19] Further, we observed two contrasting results, the inverse association of BMI20y with ER–PR– tumor incidence and positive association of BMI gain from age 20 years with postmenopausal ER+PR+ tumors. These associations therefore appear independent, albeit that receptor information was limited.

Table 5. Multivariable relative risks (RRs) and 95% confidence intervals (CIs) for the association of BMI at age 20 years and change in BMI (per increment of 5 kg/m^2) with the risk of breast cancer defined by estrogen and progesterone receptor status in the Japan Public Health Center-based Prospective Study, 1990–2006

	BMI at age 20 years[2]	Change in BMI from age 20 years to recent age[3]	
	Overall (n=41,594)	Premenopausal (n=17,886)	Postmenopausal (n=23,708)
Receptor status[1]	Per increment of 5 kg/m^2 RR (95%CI)	Per increment of 5 kg/m^2 RR (95%CI)	Per increment of 5 kg/m^2 RR (95%CI)
ER+PR+	94	49	45
	1.10(0.71–1.70)	1.31(0.82–2.09)	2.24(1.50–3.34)
ER+PR−	45	22	23
	0.64(0.32–1.24)	1.25(0.61–2.58)	0.63(0.31–1.27)
ER−PR−	60	24	36
	0.49(0.27–0.88)	0.72(0.36–1.47)	0.67(0.38–1.17)
Unknown	241	115	126
	0.79(0.59–1.05)	1.00(0.74–1.36)	1.41(1.09–1.84)

[1]The number of ER−PR+ cases was too small to analyse (12 cases). [2]Multivariable Cox proportional hazards models were adjusted for age time-scales, area (10), age at menarche (≤13, 14, 15, ≥16 years or missing), age at first birth (nulliparous, <26, ≥26 years or missing), parity (nulliparous, 1–2, 3, ≥4 or missing), menopausal status (premenopausal, age at menopause <48, 48–53, ≥54 years), use of exogenous female hormones (never, ever or missing), smoking status (never, ever), leisure-time physical activity (no or 1–3 days/month, >1 days/week, 3–4 days/week, every day), alcohol intake (past-drinker, never-drinker, occasional drinker, regular drinker ≤150, or >150 g of ethanol per week), total energy-adjusted intake of green-yellow vegetables (quintiles), total energy-adjusted intake of meat/meat products (quintiles), and total energy-adjusted intake of isoflavones (quintiles). BMI at age 20 years and change in BMI from age 20 years were mutually adjusted in the model. [3]Adjusted for all the above factors,[2] but menopausal status was not adjusted among premenopauosal women. Age at menopause was adjusted among postmenopausal women.

A meta-analysis with ER/PR status[35] agreed with our finding of a substantial positive association between recent BMI and ER+PR+ postmenopausal breast cancer risk. Further, our finding of a substantial positive association among EFH never-users is consistent with previous studies.[13,36] These results might indirectly support the validity of our information on BMI, EFH use and ER/PR status. Meanwhile, the observed inverse association between BMI20y and breast cancer risk was not modified by EFH use and was not consistent with one previous report.[34]

Plausible explanations for the biological mechanism underlying the inverse association between BMI20y and breast cancer risk include irregular menstruation and anovulation due to premenopausal obesity. These conditions might decrease exposure to ovarian hormones.[37] The inverse trend in our results for BMI20y ≥20, and in previous epidemiological studies among Western populations might be explained by this premenopausal overweight/obesity-related (decreased risk) mechanism.[14]

However, our finding among Japanese women, who have a low prevalence of overweight (overweight (9%) or obesity (0.65%) in our cohort), may suggest a nonobesity-related mechanism, because the inverse association was found not only for those over 20 (*i.e.*, BMI20y ≥20) but also those below 20 (*i.e.*, BMI20y <20). The inverse trend might thus be explained in two dimensions, namely obesity-related (*i.e.*, decreased risk) and lean-related (*i.e.*, increased risk) biological mechanisms.

Plausible lean-related mechanisms include various vital roles of the mammary fat pad in normal mammary gland morphogenesis,[21,38] possibly in close conjunction with other hormones, such as estrogens and progesterone.[39] Low BMI in early adulthood might indirectly indicate an insufficient mammary fat pad or progesterone deficiency, since progesterone may stimulate body fat deposition.[40] Incomplete differentiation in early adulthood due to either or both factors might predispose to breast cancer in later life.[21,41] Progression stage of mammary epithelial cells from undifferentiated ER-negative mammary stem cells to differentiated cells may be linked to tumor subtypes.[42]

In contrast, our finding for a positive association between recent BMI, BMI gain from age 20 years and postmenopausal ER+PR+ breast cancer risk could be explained by classic estrogen-dependent mechanism.[43] After menopause, the major source of endogenous estrogens shifts from the ovary to body fat[44] due to increased endogenous estrogen production by aromatization of androgens in peripheral fat tissue.[45] The obscure impact of BMI on postmenopausal breast cancer risk among EFH ever-users in our results might be explained by a stronger impact of EFH use on the risk than postmenopausal endogenous estrogen of body fat-origin.[46,47]

Several limitations warrant consideration. Some measurement error was inevitable, because exposure information was evaluated by self-reported weight values, which tend to be underreported.[23,48] In particular, information of body weight at age 20 years was obtained retrospectively. Nevertheless, BMI20y at baseline and at 10-year follow-up survey was highly correlated, supporting tolerable reproducibility.[49] Receptor status misclassification due to different assay methods or interlaboratory variation is also possible, although

good agreement between immunohistochemical assay and enzyme-linked immunoassay[50] has been reported. Possible selection bias due to the high percentage of unknown cases should be also considered. However, results for unknown ER/PR tumors were similar to overall results, suggesting the unlikelihood of any marked selection bias.

Major strengths of our study are its prospective population-based cohort design and large sample size. Three repeated exposure assessments of change in BMI from age 20 may have reduced misclassification due to the long follow-up. The prospective cohort study design meant that recall bias was rarely encountered, because exposure information was collected before diagnosis. If present, any misclassification of exposure was likely nondifferential, and would likely have moved the results toward the null (*i.e.*, move RR closer to 1). Further, the biological plausibility of a positive association between BMI gain and postmenopausal ER+PR+ tumors indirectly supports the validity of the data.

In summary, BMI in early adult life was inversely associated with breast cancer incidence in a Japanese population. This inverse association was partly attributable to increased risk due to leanness at age 20 years. In contrast, a subsequent BMI gain from age 20 was substantially positively associated with postmenopausal ER+PR+ tumors. Optimum weight for breast cancer prevention might change with women's life-stage. Further epidemiological study of the generalizability of our results to other populations is required.

Acknowledgements

The authors thank all the staff members in each study area and in the central offices for their cooperation and technical assistance. They also thank the Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki and Okinawa Cancer Registries for their provision of incidence data.

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