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limitation of the study was that, due to the relatively small number of lung cancer cases among ever smokers ($n = 9$), it was not possible to conduct stratified analyses by smoking status. Third, the current nested case–control study was conducted among health check-up participants, a subsample of the entire cohort that had different background characteristics from nonparticipants in health check-ups (45). Female participants in health check-ups had a favorable lifestyle profile. As compared with nonparticipants, they smoked and drank less, but tended to eat fruit and green vegetables more often and to participate more in sports and physical exercise in their leisure time. Thus, the associations between plasma isoflavone concentrations and lung cancer risk could differ from those of the entire cohort. However, because there was a similar inverse association between lung cancer and isoflavone in both the current participants and the entire cohort (20), the findings of the current study are not likely to be substantially biased as compared with those of the entire cohort.

Our study has several strengths. First, we directly measured plasma isoflavone concentrations, which reflect absorption and metabolism. Second, collecting blood samples before a diagnosis of lung cancer enabled us to infer a protective effect of genistein on lung cancer risk. Third, the quality of information measured at baseline was comparable in cases and controls, because both were selected from the same cohort.

In conclusion, plasma genistein concentration was associated with a decreased risk of lung cancer in Japanese women.

Appendix

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Disclosure of Potential Conflicts of Interests

No potential conflicts of interest were disclosed.

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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

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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

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).

Epidemiology

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$_{\geq25\ vs.\ 20-22.4}$ 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 lifestage. Further epidemiological study of the generalizability of our results to other populations is required.

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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 Research Fund/American Institute for Cancer Research, 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 $RR_{\geq 3\ days/week\ vs.\ \leq 3\ days/week}=0.73$; 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 $RR_{\geq 3\ days/week\ vs.\ \leq 3\ days/month}=0.25$ (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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