CrossMark

ORIGINAL PAPER

Dietary fiber intake and risk of breast cancer defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study

Saki Narita[1] · Manami Inoue[2,3] · Eiko Saito[2,3] · Sarah K. Abe[1] · Norie Sawada[3] ·
Junko Ishihara[4] · Motoki Iwasaki[3] · Taiki Yamaji[3] · Taichi Shimazu[3] ·
Shizuka Sasazuki[3] · Kenji Shibuya[1] · Shoichiro Tsugane[3] · for the JPHC Study Group

Abstract

Purpose Epidemiological studies have suggested a protective effect of dietary fiber intake on breast cancer risk while the results have been inconsistent. Our study aimed to investigate the association between dietary fiber intake and breast cancer risk and to explore whether this association is modified by reproductive factors and hormone receptor status of the tumor.

Methods A total of 44,444 women aged 45 to 74 years from the Japan Public Health Center-based Prospective Study were included in analyses. Dietary intake assessment was performed using a validated 138-item food frequency questionnaire (FFQ). Hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer incidence were calculated by multivariate Cox proportional hazards regression models.

Results During 624,423 person-years of follow-up period, 681 breast cancer cases were identified. After adjusting for major confounders for breast cancer risk, inverse trends were observed but statistically non-significant. Extremely high intake of fiber was associated with decreased risk of breast cancer but this should be interpreted with caution due to limited statistical power. In stratified analyses by menopausal and hormone receptor status, null associations were observed except for ER-PR- status.

Conclusions Our findings suggest that extreme high fiber intake may be associated with decreased risk of breast cancer but the level of dietary fiber intake among Japanese population might not be sufficient to examine the association between dietary fiber intake and breast cancer risk.

Keywords Breast cancer · Dietary fiber intake · Estrogen receptor (ER) · Progesterone receptor (PR)

JPHC Study Group members are listed at the following site:
http://epi.ncc.go.jp/en/jphc/781/3838.html.

✉ Manami Inoue
   mnminoue@m.u-tokyo.ac.jp

✉ Shoichiro Tsugane
   stsugane@ncc.go.jp

[1] Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033, Japan

[2] AXA Department of Health and Human Security, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033, Japan

[3] Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

[4] Department of Nutrition Management, Sagami Women's University, 2-1-1 Bunkyo Minami Ward, Sagamihara, Kanagawa 252-0307, Japan

Introduction

Breast cancer is the most frequently diagnosed cancer among females in both developing and developed countries with an estimated 1.67 million new cases diagnosed in 2012 [1]. It is also the most common cancer among Japanese women with a predicted 72,500 newly diagnosed cases in 2011 [2]. Dissemination of breast cancer screening and changes in dietary, hormonal, and reproductive factors [3, 4] have rapidly increased the incidence in most regions of the world [5]. Wide international disparity in breast cancer incidence [6] and its different patterns among immigrants [7] indicate the importance of not only the genetic factors but also modifiable risk factors including dietary factors in the etiology of breast cancer.

Dietary fiber has been hypothesized to reduce the risk of breast cancer over three decades ago [8]. Soluble fiber is contained in oats, legumes and seaweeds, and could modulate insulin resistance and insulin-like growth factors, the increased concentrations of which have been associated with an increased breast cancer risk [9]. Insoluble fiber is, on the other hand, found in seeds and whole grains, and may help to inhibit intestinal reabsorption of estrogens and thus increase fecal excretion of estrogen. While prolonged exposure to estrogen can increase the risk of breast cancer, insoluble fiber may lower the level of circulating estrogen concentrations [10]. A meta-analysis of 16 prospective studies reported an inverse association between soluble fiber and breast cancer risk but not insoluble fiber, fruit fiber, vegetable fiber, or cereal fiber [11]. The findings from more recent studies found that vegetable fiber was associated with a decreased risk of breast cancer but not with other types of fiber [12, 13].

The previous JPHC Study has investigated the association between fiber-containing food items such as vegetables, fruits, and soyfoods including miso soup and breast cancer risk. While miso soup and isoflavone intake was significantly and inversely associated [14], and fruits and citrus fruits consumption with borderline significance [15], there has not been a study with total dietary fiber intake. Furthermore, fiber consumption in Japan is lower than that of Western populations [16], which highlights the importance of the study in Japan. Therefore, we explored the potential association between dietary fiber intake and risk of breast cancer in the Japanese population, and investigated whether the association is influenced by reproductive factors and hormone receptor status.

Materials and methods

Study population

The Japan Public Health Center-based Prospective Study (JPHC Study) is an ongoing cohort study designed to assess the association between lifestyle factors and cancer and cardiovascular disease in the Japanese population. The study was commenced in 1990 for Cohort I ($n = 61,595$) and 1993 for Cohort II ($n = 78,825$) with 140,420 participants (68,772 men and 71,698 women) residing in municipalities supervised by 11 public health centers across Japan. Details of the JPHC Study methodology have been described in a previous study [17]. The study protocol was approved by an institutional review board of the National Cancer Center, Tokyo, Japan (approval number: 13–021) and The University of Tokyo (approval number: 10508).

The study population consisted of women aged 40 to 59 years in Cohort I and 40 to 69 years in Cohort

II. Participants from two public health center areas ($n = 12,515$) were not included in the study due to unavailability of complete data on cancer incidence. The self-administered 5-year follow-up questionnaire was sent to subjects aged 45 to 74 years in 1995 and 1998 for Cohort I and Cohort II, respectively, and used as the starting point of this study. After excluding 208 ineligible participants and a total of 3,525 participants who had died, moved, or were lost to follow-up, the remaining 55,450 persons were eligible for participation. Of those, 48,279 returned the 5-year questionnaire (response rate 87.1%), and 3,835 women were further excluded due to past history of cancer, extreme caloric intake (lower and upper 2.0% of the distribution), or missing data on dietary fiber. The final analytical cohort of 44,444 women was included in the multivariable analyses.

Exposure measurement

Dietary information used in the present study was obtained through the common 5-year follow-up survey, in which the dietary assessment was carried out using a validated self-administered food frequency questionnaire (FFQ) [18]. Participants were asked to report average consumption frequency and portion size of 138 food and beverage items consumed in the past year. The consumption of seasonal fruits and vegetables (grams/day) were also calculated by asking the frequency of intake and considering length of each season [19].

The consumption of daily nutritional intake was calculated in reference to the Standard Tables of Food Composition in Japan (5th revised and enlarged ed.) and the amount of dietary fiber contained in each food item (grams/day) was estimated by the modified Prosky method, which separately quantifies soluble and insoluble fiber in food by imitating the bodily digestive system [20]. All of the nutritional covariates, except for alcohol, were adjusted for total energy intake using the residual method [21]. The validity and reproducibility of the FFQ for dietary assessment were evaluated and marked Spearman's correlation coefficients of 0.48 for total fiber, 0.53 for soluble fiber, and 0.46 for insoluble fiber [22], which are comparable to previous studies [23, 24]. In addition to analyses by fiber category, two commonly consumed food items were added as exposure variables, namely natto/fermented soybean and rice. Natto and rice were the highest contributors to the daily intake of soluble and insoluble fiber, accounting for 4% and 11%, respectively, in this study population [22]. Natto and rice each comprised 3% and 8% of total fiber intake, and other major sources also included miso/fermented soybean baste (5%), carrots (3%), apples (3%), and cabbage (3%). Information on other covariates, such as anthropometric measurements, reproductive, and lifestyle-related factors was

acquired using the self-reported questionnaire in the 5-year follow-up survey.

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

Incidence of breast cancer was identified via active patient notification from major local hospitals in each study area and record linkage with a population-based cancer registry. Breast cancer cases were classified using codes C500-509 of the International Classification of Diseases for Oncology (3rd ed.) [25]. Death certificates were used to ascertain 11 cases (Death Certificate Notification; DCN: 2.0% of total cases), of which information on diagnosis was unavailable for 9 cases (Death Certificate Only; DCO: 1.6%). Ninety-seven per cent of all the cases diagnosed during the follow-up period were verified microscopically. Estrogen receptor (ER) and progesterone receptor (PR) status were defined by either immunohistochemistry or enzyme-linked immuno-sorbent assay.

Participants were censored on the date of breast cancer diagnosis, migration from study area, death, or end of follow-up period (31 December, 2011) whichever came first. Person-years of follow-up were calculated for each participant from the 5-year follow-up survey until the date of censoring.

Statistical analysis

Participants were divided by quartiles according to their energy-adjusted intakes of each exposure variable, namely total fiber, soluble fiber, insoluble fiber, natto, and rice. The group with the highest consumption was indicated as Q4 and the lowest as Q1. Their baseline characteristics were compared between groups, using ANOVA or Pearson's chi–squared test where appropriate. A Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with Q1 as the reference group. The proportional hazards assumptions were verified and satisfied with Schoenfeld residuals. All the statistical analyses in the present study were performed using Stata version 13.0 (StataCorp, College Station, Texas USA).

In the primary analyses, the multivariable models were adjusted for age, areas of public health centers, BMI at 5-year follow-up (< 18.5, $18.5–23.9$, >23.9), age at menarche (≤ 13, 14, 15, ≥ 16 years), age at first birth (<26, ≥ 26 years), parity (nulliparous, 1–2, 3, ≥ 4), age at menopause (pre-menopause, ≤ 44, 45–54, ≥ 55 years), use of exogenous female hormones (never, ever), smoking status (never: non-smokers, ever: past or current smokers), leisure-time physical activity (≤ 3 days/month, 1–2 days/week, ≥ 3 days/week), alcohol intake (regular drinker:

>150 g of ethanol/week, non-regular drinker: ≤ 150 g of ethanol/week), total energy intake, and total energy-adjusted intakes of fat, isoflavones, carbohydrates, and vitamin C. Vitamin C was included in the model since high intake of vitamin C was associated with increased risk of breast cancer in our previous report [15]. Missing data were created for each covariate as an indicator variable. Further analysis explored whether extremely high intake of dietary fiber could modify the risk of breast cancer and was performed by dividing the highest consumption group (Q4) into tertiles.

In the secondary analyses, stratification by menopausal status (pre or post) and sub-group analysis by ER/PR status were further performed. All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

During 624,423 person-years of follow-up (an average of 14.0 years), 681 cases of breast cancer were newly diagnosed. The median age of diagnosis was 65 years. Of which, 333 cases (48.9%) had information on ER status and 326 cases (47.9%) on PR status. Mean age at 5-year follow-up was 58.4 years and people with higher fiber consumption were slightly older. The amount of total fiber intake ranged from the median of 7.9 g/day in the lowest category to 18.1 g/day in the highest.

Table 1 shows the characteristics of the study participants by categories of dietary fiber intake. Participants who consumed more fiber were less likely to be current smokers, regular drinkers, and more likely to be physically active on a regular basis. They also had higher level of isoflavone, fat, vitamin C, and carbohydrate intakes.

Table 2 shows the results of multivariate analyses. Overall, no significant association was detected between the consumption of fiber and breast cancer risk in this cohort after adjusting for all potential confounding factors (HR 0.78, 95% CI 0.55–1.09, comparing Q4 with Q1). Adjusting for total energy-adjusted intake of vitamin C and carbohydrates made an inverse trend with total fiber intake becoming evident but non-significant. These results did not substantially change in the analysis by dose or with non-smokers (results not shown). In the subtertile analysis, extremely high intake of dietary fiber was significantly associated with decreased risk of breast cancer. HRs for the highest tertile of total fiber were 0.63 (95% CI 0.40–0.98) for the highest category (Sub3); 0.68 (95% CI 0.45–1.04 for the middle category (Sub2); and 0.93 (95% CI 0.64–1.34) for the lowest category (Sub1), with p_{trend} of 0.04 and the lowest quartile (Q1) as the referent group (Fig. 1).

Table 3 reports the association of dietary fiber intake and risk of breast cancer by menopausal status. Among 41,501

Table 1 Baseline characteristics of the study subjects by dietary fiber intake

Characteristic	Total fiber (g/day)				p value[a]	Soluble fiber (g/day)				p value[a]
	Q1 (low)	Q2	Q3	Q4 (high)		Q1 (low)	Q2	Q3	Q4 (high)	
Mean, g/day (SD)	8.6 (3.9)	12.1 (4.5)	15.0 (5.3)	19.6 (7.9)		1.9 (1.0)	2.9 (1.2)	3.6 (1.4)	4.8 (2.1)	
Number of subjects	n=11,111	n=11,111	n=11,111	n=11,111		n=11,111	n=11,111	n=11,111	n=11,111	
Age at 5-year follow-up, year, mean (SD)	57.2 (8.0)	57.9 (7.9)	58.6 (7.7)	59.6 (7.7)	<0.01	57.4 (8.1)	57.9 (7.9)	58.6 (7.8)	59.5 (7.7)	<0.01
BMI at 5-year follow-up, kg/m², mean (SD)	23.6 (3.3)	23.5 (3.1)	23.6 (3.2)	23.6 (3.1)	<0.01	23.6 (3.3)	23.5 (3.1)	23.6 (3.1)	23.6 (3.1)	<0.01
Age at menarche, year, mean (SD)	14.8 (2.0)	14.8 (1.9)	14.7 (1.8)	14.8 (1.8)	<0.01	14.8 (2.0)	14.7 (1.9)	14.8 (1.9)	14.9 (1.9)	<0.01
Age at first birth, year, mean (SD)	24.7 (3.6)	24.9 (3.5)	24.8 (3.3)	24.8 (3.2)	<0.01	24.7 (3.6)	24.8 (3.4)	24.8 (3.3)	24.9 (3.3)	<0.01
Number of deliveries, n, mean (SD)	2.9 (1.6)	2.8 (1.5)	2.8 (1.4)	2.7 (1.5)	<0.01	2.9 (1.6)	2.8 (1.5)	2.8 (1.5)	2.8 (1.5)	<0.01
Age at menopause, year, mean (SD)	48.1 (4.9)	48.4 (4.4)	48.4 (4.6)	48.4 (4.8)	<0.01	48.1 (4.8)	48.4 (4.5)	48.3 (4.7)	48.4 (4.7)	<0.01
Use of exogenous hormones (ever), %	3.1	2.8	2.5	2.7	0.06	2.9	2.9	2.5	2.8	0.27
Current smoker (yes), %	8.9	4.9	4.2	3.7	<0.01	8.5	5.1	4.2	3.9	<0.01
Regular drinker (>150 g/week), %	10.7	6.5	5.7	5.2	<0.01	10.4	6.7	5.6	5.4	<0.01
Physical activity (>3 days/week), %	7.3	9.2	10.5	13.4	<0.01	6.8	9.2	10.8	13.5	<0.01
Dietary intake										
Total energy intake, kcal/day (SD)	1,857 (640)	1871 (583)	1,883 (563)	1,839 (562)	<0.01	1,859 (639)	1,895 (590)	1,885 (561)	1,811 (554)	<0.01
Fat, g/day (SD)	11.2 (8.0)	12.2 (7.1)	12.8 (6.8)	14.5 (8.4)	<0.01	11.1 (8.1)	12.5 (7.1)	13.0 (6.7)	14.2 (8.4)	<0.01
Isoflavones, mg/day (SD)	30.8 (32.1)	38.6 (28.7)	45.9 (32.7)	56.0 (44.5)	<0.01	28.9 (24.2)	39.1 (29.1)	46.4 (33.8)	56.3 (47.8)	<0.01
Vitamin C, mg/day (SD)	95.5 (56.1)	134.9 (65.6)	170.4 (79.2)	228.3 (117.6)	<0.01	95.7 (55.1)	137.6 (66.4)	172.2 (80.8)	223.4 (119.7)	<0.01
Carbohydrate, g/day (SD)	240.1 (72.3)	255.6 (72.0)	263.3 (74.5)	264.8 (81.6)	<0.01	243.8 (73.9)	257.2 (72.9)	262.9 (74.3)	260.0 (80.5)	<0.01

Characteristics	Insoluble fiber (g/day)				p value[a]	Natto/fermented soybean (g/day)				p value[a]
	Q1 (low)	Q2	Q3	Q4 (high)		Q1 (low)	Q2	Q3	Q4 (high)	
Mean, g/day (SD)	6.3 (2.7)	8.7 (3.2)	10.7 (3.8)	14.2 (5.7)		0.0 (0.0)	7.7 (8.1)	19.2 (14.7)	35.0 (32.2)	
Number of subjects	n=11,111	n=11,111	n=11,111	n=11,111		n=11,111	n=11,111	n=11,111	n=11,111	
Age at 5-year follow-up, year, mean (SD)	57.2 (8.1)	58.0 (7.9)	58.7 (7.8)	59.5 (7.7)	<0.01	60.5 (8.4)	56.8 (7.5)	57.4 (7.5)	58.8 (7.7)	<0.01
BMI at 5-year follow-up, kg/m², mean (SD)	23.7 (3.3)	23.5 (3.1)	23.6 (3.2)	23.6 (3.1)	<0.01	23.8 (3.4)	23.5 (3.1)	23.5 (3.1)	23.6 (3.1)	<0.01
Age at menarche, year, mean (SD)	14.8 (2.0)	14.8 (1.9)	14.7 (1.9)	14.8 (1.8)	<0.01	15.4 (2.1)	14.6 (1.8)	14.6 (1.7)	14.7 (1.7)	<0.01
Age at first birth, year, mean (SD)	24.7 (3.6)	24.9 (3.5)	24.8 (3.3)	24.8 (3.2)	<0.01	24.5 (3.7)	24.9 (3.4)	24.8 (3.3)	24.9 (3.2)	<0.01
Number of deliveries, n, mean (SD)	2.9 (1.6)	2.8 (1.5)	2.8 (1.4)	2.7 (1.5)	<0.01	3.3 (1.9)	2.7 (1.4)	2.6 (1.3)	2.6 (1.3)	<0.01
Age at menopause, year, mean (SD)	48.1 (4.9)	48.4 (4.5)	48.4 (4.5)	48.4 (4.8)	<0.01	48.4 (4.7)	48.3 (4.7)	48.3 (4.7)	48.4 (4.6)	<0.01
Use of exogenous hormones (ever), %	3.1	2.8	2.5	2.7	0.08	2.8	3.1	2.4	2.7	0.06
Current smoker (yes), %	9.0	4.9	4.3	3.4	<0.01	5.6	5.3	5.3	5.5	0.03
Regular drinker (>150 g/week), %	10.8	6.6	5.7	4.9	<0.01	8.3	7.0	6.3	6.5	0.75
Physical activity (>3 days/week), %	7.7	9.3	10.5	12.9	<0.01	9.6	9.3	10.1	11.3	<0.01
Dietary intake										
Total energy intake, kcal/day (SD)	1,864 (640)	1,861 (579)	1,872 (561)	1,852 (567)	<0.01	1,684 (565)	2,171 (634)	1,960 (547)	1,635 (414)	<0.01

Table 1 (continued)

Characteristics	Insoluble fiber (g/day)				p value[a]	Natto/fermented soybean (g/day)				p value[a]
	Q1 (low)	Q2	Q3	Q4 (high)		Q1 (low)	Q2	Q3	Q4 (high)	
Fat, g/day (SD)	11.3 (8.0)	12.1 (7.0)	12.7 (6.7)	14.6 (8.5)	<0.01	12.1 (8.3)	15.3 (8.8)	13.2 (6.9)	10.2 (5.4)	<0.01
Isoflavones, mg/day (SD)	31.1 (33.6)	39.0 (30.2)	45.5 (31.4)	55.1 (43.8)	<0.01	24.6 (28.8)	37.9 (32.9)	47.5 (30.3)	60.7 (41.6)	<0.01
Vitamin C, mg/day (SD)	97.4 (57.9)	134.7 (66.7)	168.7 (79.9)	228.2 (116.7)	<0.01	131.5 (88.7)	181.7 (108.2)	171.7 (98.7)	144.0 (78.2)	<0.01
Carbohydrate, g/day (SD)	239.2 (71.8)	254.7 (71.6)	262.4 (74.0)	267.4 (82.4)	<0.01	233.2 (72.8)	291.5 (81.7)	270.0 (71.6)	229.6 (57.0)	<0.01

[a] p values were determined by ANOVA or Chi-squared tests where appropriate

women whose menopausal status was available, 31,931 of them were postmenopausal with 465 cases of breast cancer. There was an overall reduction in the risk of postmenopausal breast cancer but it was statistically non-significant.

In sub-group analysis by ER/PR status of breast tumors, information on both receptors was available in 323 (47.4% of all) cases, as presented in Table 4. Consumption of soluble fiber showed a significant positive association with ER−PR−breast cancer risk (HR 5.45, 95% CI 1.02–29.20, p_{trend}: 0.03) but this should be interpreted with caution, as the number of cases was limited. Null associations were observed with the other types of hormone receptor-defined breast cancer.

Discussion

In the present population-based prospective study, extreme high intake of total fiber was associated with decreased risk of breast cancer. However, the findings with other types of dietary fiber showed inverse yet statistically non-significant trends. Given these results, the association between dietary fiber and breast cancer risk appears non-linear since only high level of consumption was significantly associated, but it should be interpreted with caution since the number of cases in the subtertile analysis was small. The overall null associations in the present study might be explained by small ranges of fiber consumption between quartiles. In a meta-analysis of 16 prospective cohort studies [11], the mean fiber intake of the highest category in an Asian cohort was the lowest in comparison to the rest of the cohorts in European and American countries (16.3, 29.9, and 25.7 g/day, respectively). Indeed, the inverse association was only evident among studies with high levels (≥25 g/day) or large ranges (≥13 g/day) of fiber consumption. Moreover, regional difference in sources of dietary fiber may be also noted as cereal, vegetables, and fruits were the main contributors in European countries [12, 13].

The overall risk of postmenopausal breast cancer was non-significantly lower than that of pre-menopausal breast cancer and the observation was consistent with some of the previous studies, which found an inverse association with postmenopausal cancer [26, 27]. Dietary fiber consumption may indirectly reduce the risk of postmenopausal breast cancer by preventing obesity and Type 2 diabetes through insulin resistance control [28, 29]. In the subanalysis by ER/PR status, the risk of ER-PR- breast cancer was significantly elevated with consumption of soluble fiber. However, previous studies found a strong inverse association with ER-PR- breast tumor [13, 30]. The interpretation of this result should be made with caution due to limited statistical power. Epidemiological studies have also suggested that factors related to estrogen metabolism are more

Table 2 Associations between dietary fiber intake and breast cancer risk in the JPHC Study

Food group	All ($n = 44,444$ 681 cases)				
	Q1. (low)	Q2	Q3	Q4. (high)	p_{trend}
Total fiber					
Median (g/day)	7.9 g/day	11.3 g/day	14.1 g/day	18.1 g/day	
Number of cases	180	164	170	167	
Multivariable adjusted[a]	1.00 (ref)	0.89 (0.70–1.13)	0.83 (0.63–1.10)	0.78 (0.55–1.09)	0.15
Soluble fiber					
Median (g/day)	1.7 g/day	2.7 g/day	3.4 g/day	4.4 g/day	
Number of cases	182	154	177	168	
Multivariable adjusted[a]	1.00 (ref)	0.79 (0.62–1.01)	0.84 (0.64–1.11)	0.77 (0.55–1.06)	0.20
Insoluble fiber					
Median (g/day)	5.9 g/day	8.2 g/day	10.1 g/day	13.1 g/day	
Number of cases	177	166	165	173	
Multivariable adjusted[a]	1.00 (ref)	0.97 (0.76–1.23)	0.88 (0.67–1.17)	0.89 (0.64–1.24)	0.47
Natto/fermented soybean					
Median (g/day)	0 g/day	3.3 g/day	10.7 g/day	25.0 g/day	
Number of cases	158	180	187	156	
Multivariable adjusted[a]	1.00 (ref)	0.87 (0.69–1.09)	0.98 (0.79–1.23)	0.87 (0.69–1.10)	0.68
Rice					
Median (g/day)	91.4 g/day	137.0 g/day	182.7 g/day	243.6 g/day	
Number of cases	181	182	155	163	
Multivariable adjusted[a]	1.00 (ref)	1.06 (0.85–1.32)	0.92 (0.73–1.17)	1.01 (0.78–1.31)	0.75

[a]Multivariable Cox proportional hazards models were adjusted for age, area (10), BMI at 5-year follow-up (<18.5, 18.5–23.9, >23.9), age at menarche (≤13, 14, 15, ≥16 years), age at first birth (<26, ≥26 years), parity (nulliparous, 1–2, 3, ≥4), age at menopause (pre-menopause, ≤44, 45–54, ≥55 years), use of exogenous female hormones (never, ever), smoking status (never, ever), leisure-time physical activity (≤3 days/month, 1–2 days/week, ≥3 days/week), alcohol intake (regular drinker: >150 g of ethanol/week, non-regular drinker: ≤150 g of ethanol/week), and total energy-adjusted intakes of fat, isoflavones, vitamin C, and carbohydrate
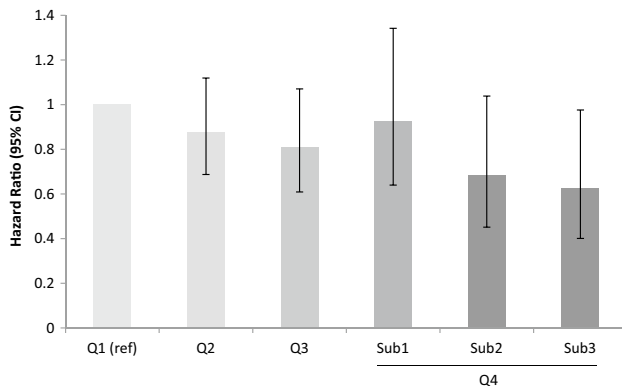

Fig. 1 Hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer risk within the highest quartile of total fiber intake. [a]The reference group is the lowest quartile (Q1) of total fiber intake and a subtertile (Sub 1–3) is tertiles of the highest quartile (Q4). Numbers of breast cancer cases were 180 for Q1, 164 for Q2, 170 for Q3, 63 for Sub 1, 52 for Sub 2, and 52 for Sub 3

strongly associated with ER+ tumors, while ER- tumors may be more susceptible to non-hormonal exposures such as diet [13, 30]. Further research may be needed to explore the association in the Japanese population to investigate how dietary fiber could play a role in carcinogenesis of both ER+ and ER− tumors.

Moreover, high intakes of citrus fruit [15] and carbohydrate [31] are observed to have an increased risk of breast cancer in previous studies. Although a null association was observed, participants with higher level of dietary fiber intake had higher vitamin C and carbohydrate intake in this study and thus the possibility of diluted effect of fiber in our data may not be eliminated. The latest report from the World Cancer Research Fund suggested a reduction in the breast cancer mortality with consumption of high-fiber foods [31], whilst the association with its incidence has yet been inconclusive [32]. Further research is required to examine the association between a wider range of dietary fiber intake and breast cancer mortality and recurrence.

There are a few limitations in the present study. First, the self-reported questionnaire would have introduced to a measurement bias. The FFQ may be a less accurate estimation of dietary intake when compared to a 24-hour recall method, and therefore has the potential to attenuate the estimated hazard ratios [33]. The correlation coefficients

Table 3 Associations between dietary fiber intake and breast cancer risk stratified by menopausal status in the JPHC Study

Food group	Pre-menopausal (n = 9,570 182 cases)					Postmenopausal (n = 31,931 465 cases)				
	Q1. (low)	Q2	Q3	Q4. (high)	p_{trend}	Q1. (low)	Q2	Q3	Q4. (high)	p_{trend}
Total fiber										
Median (g/day)	8.3 g/day	11.6 g/day	14.3 g/day	18.3 g/day		8.0 g/day	11.4 g/day	14.2 g/day	18.1 g/day	
Number of cases	52	54	48	28		116	104	114	131	
Multivariable adjusted[a]	1.00 (ref.)	1.09 (0.71–1.67)	0.91 (0.54–1.53)	0.62 (0.32–1.20)	0.11	1.00 (ref.)	0.80 (0.59–1.07)	0.78 (0.56–1.08)	0.82 (0.56–1.22)	0.48
Soluble fiber										
Median (g/day)	1.8 g/day	2.7 g/day	3.4 g/day	4.4 g/day		1.8 g/day	2.7 g/day	3.4 g/day	4.5 g/day	
Number of cases	50	51	48	33		121	98	119	127	
Multivariable adjusted[a]	1.00 (ref.)	1.05 (0.68–1.61)	0.96 (0.57–1.62)	0.82 (0.43–1.55)	0.47	1.00 (ref.)	0.69 (0.51–0.93)	0.78 (0.56–1.08)	0.74 (0.50–1.08)	0.29
Insoluble fiber										
Median (g/day)	6.1 g/day	8.5 g/day	10.3 g/day	13.2 g/day		5.9 g/day	8.2 g/day	10.2 g/day	13.2 g/day	
Number of cases	51	56	35	40		114	103	124	124	
Multivariable adjusted[a]	1.00 (ref.)	1.24 (0.81–1.90)	0.77 (0.45–1.32)	1.02 (0.55–1.89)	0.75	1.00 (ref.)	0.84 (0.62–1.13)	0.89 (0.64–1.24)	0.84 (0.57–1.24)	0.51
Natto/fermented soybean										
Median (g/day)	0 g/day	3.3 g/day	10.7 g/day	25.0 g/day		0 g/day	3.3 g/day	10.7 g/day	25.0 g/day	
Number of cases	36	51	58	37		110	122	125	108	
Multivariable adjusted[a]	1.00 (ref.)	0.86 (0.56–1.32)	1.06 (0.69–1.63)	0.84 (0.55–1.29)	0.54	1.00 (ref.)	0.87 (0.67–1.13)	0.95 (0.73–1.24)	0.88 (0.66–1.16)	0.92
Rice										
Median (g/day)	91.4 g/day	121.8 g/day	182.7 g/day	243.6 g/day		91.4 g/day	137.0 g/day	182.7 g/day	243.6 g/day	
Number of cases	51	37	37	57		120	135	115	95	
Multivariable adjusted[a]	1.00 (ref.)	0.77 (0.50–1.20)	0.79 (0.50–1.24)	1.44 (0.92–2.26)	0.32	1.00 (ref.)	1.20 (0.93–1.55)	1.01 (0.76–1.33)	0.86 (0.63–1.17)	0.34

[a] Multivariable Cox proportional hazards models were adjusted for age, area (10), BMI at 5-year follow-up (<18.5, 18.5–23.9, >23.9), age at first birth (<26, ≥26 years), parity (nulliparous, 1–2, 3, ≥4), use of exogenous female hormones (never, ever), smoking status (never, ever), age at menarche (≤13, 14, 15, ≥16 years), leisure-time physical activity (≤3 days/month, 1–2 days/week, ≥3 days/week), alcohol intake (regular drinker: >150 g of ethanol/week, non-regular drinker: ≤150 g of ethanol/week), and total energy-adjusted intakes of fat, isoflavones, vitamin C, and carbohydrate

Table 4 Associations between dietary fiber intake and breast cancer risk stratified by ER/PR status in the JPHC Study

All ($n = 44{,}444$ 681 cases)

ER/PR subtype	ER+ PR+ ($n = 157$)				
	Q1. (low)	Q2	Q3	Q4. (high)	p_{trend}
Total fiber	1.00 (ref)	1.20 (0.62–2.32)	0.94 (0.47–1.88)	1.03 (0.41–2.57)	0.80
Soluble fiber	1.00 (ref)	1.58 (0.84–2.96)	0.97 (0.50–1.89)	1.53 (0.70–3.37)	0.57
Insoluble fiber	1.00 (ref)	0.96 (0.50–1.85)	0.86 (0.42–1.78)	0.84 (0.36–1.95)	0.63
Natto/fermented soybean	1.00 (ref)	0.83 (0.44–1.57)	1.00 (0.55–1.81)	0.82 (0.42–1.61)	0.84
Rice	1.00 (ref)	0.53 (0.28–1.02)	1.38 (0.73–2.63)	1.11 (0.55–2.22)	0.21
ER/PR subtype	**ER− PR− ($n = 91$)**				
	Q1. (low)	Q2	Q3	Q4. (high)	
Total fiber	1.00 (ref)	1.21 (0.36–4.13)	1.05 (0.30–3.74)	1.50 (0.28–7.94)	0.73
Soluble fiber	1.00 (ref)	1.53 (0.43–5.36)	2.72 (0.65–11.31)	5.45 (1.02–29.20)	0.03*
Insoluble fiber	1.00 (ref)	1.97 (0.53–7.38)	0.89 (0.24–3.32)	1.19 (0.23–6.25)	0.83
Natto/fermented soybean	1.00 (ref)	0.27 (0.09–0.75)	0.70 (0.29–1.69)	0.47 (0.13–1.76)	0.52
Rice	1.00 (ref)	0.50 (0.20–1.24)	0.36 (0.10–1.26)	0.34 (0.08–1.54)	0.09
ER/PR subtype	**ER PR Known ($n = 323$)**				
	Q1. (low)	Q2	Q3	Q4. (high)	
Total fiber	1.00 (ref)	1.20 (0.84–1.73)	1.19 (0.79–1.81)	1.08 (0.66–1.78)	0.93
Soluble fiber	1.00 (ref)	1.05 (0.73–1.49)	1.01 (0.67–1.52)	0.88 (0.54–1.42)	0.48
Insoluble fiber	1.00 (ref)	1.23 (0.86–1.76)	1.15 (0.76–1.73)	1.02 (0.63–1.66)	0.82
Natto/fermented soybean	1.00 (ref)	0.96 (0.69–1.35)	1.33 (0.97–1.84)	0.96 (0.67–1.35)	0.23
Rice	1.00 (ref)	1.13 (0.82–1.56)	0.92 (0.65–1.30)	1.14 (0.79–1.64)	0.88
ER/PR subtype	**ER PR Unknown ($n = 358$)**				
	Q1. (low)	Q2	Q3	Q4. (high)	
Total fiber	1.00 (ref)	1.16 (0.78–1.71)	1.13 (0.72–1.79)	1.16 (0.68–1.99)	0.65
Soluble fiber	1.00 (ref)	0.76 (0.52–1.12)	0.96 (0.63–1.47)	0.95 (0.59–1.55)	0.90
Insoluble fiber	1.00 (ref)	0.99 (0.66–1.48)	1.09 (0.69–1.72)	1.01 (0.57–1.80)	0.94
Natto/fermented soybean	1.00 (ref)	1.12 (0.79–1.59)	0.73 (0.50–1.06)	0.74 (0.50–1.08)	0.37
Rice	1.00 (ref)	1.11 (0.78–1.58)	1.04 (0.72–1.52)	0.91 (0.62–1.34)	0.68

[a] Asterisk denotes statistically significant values ($p<0.05$)

[b] Cox propotional hazards models were adjusted for age, area (10), BMI at 5-year follow-up (<18.5, 18.5-23.9, >23.9), age at menarche (≤13, 14, 15, ≥16 years), age at first birth (<26, ≥26 years), parity (nulliparous, 1-2, 3, ≥4), age at menopause (premenopause, ≤44, 45-54, ≥55 years), use of exogenous female hormones (never, ever), smoking status (never, ever), leisure-time physical activity (≤3 days/month, 1-2 days/week, ≥3 days/week), alcohol intake (regular drinker: >150 g of ethanol/week, non-regular drinker: ≤150 g of ethanol/week), and total energy-adjusted intakes of fat, isoflavones, vitamin C and carbohydrate

between the FFQ and 28-day (or 14-day) dietary records were rather low (0.48 for total fiber, 0.53 for soluble fiber, and 0.46 for insoluble fiber). However, the results are similar to previous reports from Japan [23, 24].

Second, there is a possibility of further confounding due to the effect of health-conscious behavior of people who had breast cancer screening. In Japan, biennial mammography screening in combination with a clinical breast examination is recommended for women aged 40 years or older since 2004 [34]. The health-conscious behavior could affect the dietary pattern and thus be a confounding factor.

Nevertheless, the questionnaire asked whether a participant had mammography in the past year only and therefore was unable to capture the effect of biennial mammography screening.

Finally, information on ER/PR subtypes is available for 50% of the breast cancer cases in the present study. This was unavoidable since ER/PR status was not used to be regarded as substantial information for clinical treatment, and data prior to 2002 were attained by retrospective review of medical records or pathology reports [35]. In addition, some categories in the subanalyses by menopausal status

and ER/PR status had small number of cases. Interpretation should be made with caution due to limited statistical power and possibility of chance finding.

Despite these limitations, to our knowledge, this is the first large prospective study to investigate the potential link between dietary fiber and risk of ER/PR-defined breast cancer in the Japanese population although overall associations were not significant. The incidence of breast cancer in Japan has been steeply increasing over the past few decades, but it is still lower than that of European or North American countries [36]. The incidence of breast cancer observed in this study is in accordance with that in Japan [37]. Major strengths of this study also include high response rate (87.1%) and long follow-up period with negligible number of subjects lost to follow-up (0.1%). Possibility of recall and selection bias has been kept minimal as information on exposure was collected before diagnosis of breast cancer. Moreover, incidence of breast cancer was confirmed by cancer registry, rather than self-reporting, to reduce the potential for misclassification of the outcome.

In conclusion, while previous studies have found protective effects of high dietary fiber consumption against breast cancer, our findings were unable to draw clear comparison due to lower intake of fiber among Japanese population. Future research is needed to further investigate the association in the Japanese or Asian population between high levels of dietary fiber intake and the potential effect on breast cancer survival and recurrence.

Compliance with Ethical Standards

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al (2014) Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386. doi:10.1002/ijc.29210

2. National Cancer Center (2016) Cancer Registry and Statistics. http://ganjoho.jp/reg_stat/statistics/stat/summary.html.

3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61(2):69–90. doi:10.3322/caac.20107

4. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA (2005) Global trends in breast cancer incidence and mortality 1973–1997. Int J Epidemiol 34(2):405–412. doi:10.1093/ije/dyh414

5. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al (2013) Cancer incidence and mortality worldwide: IARC cancerbase no. 11. International Agency for Research on Cancer, Lyon

6. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127(12):2893–2917. doi:10.1002/ijc.25516

7. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM (1991) Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br J Cancer 63(6):963–966

8. Goldin BR, Adlercreutz H, Gorbach SL, Warram JH, Dwyer JT, Swenson L et al (1982) Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. N Engl J Med 307(25):1542–1547. doi:10.1056/NEJM198212163072502

9. Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ (2000) Beneficial effects of high dietary fiber intake in patients with Type 2 diabetes mellitus. N Engl J Med 342(19):1392–1398. doi:10.1056/NEJM200005113421903

10. Kaaks R, Berrino F, Key T, Rinaldi S, Dossus L, Biessy C et al (2005) Serum sex steroids in premenopausal women and breast cancer risk within the European prospective investigation into cancer and nutrition (EPIC). J Natl Cancer Inst 97(10):755–765. doi:10.1093/jnci/dji132

11. Aune D, Chan DS, Greenwood DC, Vieira AR, Rosenblatt DA, Vieira R et al (2012) Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. Ann Oncol 23(6):1394–1402. doi:10.1093/annonc/mdr589

12. Deschasaux M, Zelek L, Pouchieu C, His M, Hercberg S, Galan P et al (2013) Prospective association between dietary fiber intake and breast cancer risk. PLoS ONE 8(11):e79718. doi:10.1371/journal.pone.0079718

13. Ferrari P, Rinaldi S, Jenab M, Lukanova A, Olsen A, Tjonneland A et al (2013) Dietary fiber intake and risk of hormonal receptor-defined breast cancer in the European Prospective Investigation into Cancer and Nutrition study. Am J Clin Nutr 97(2):344–353. doi:10.3945/ajcn.112.034025

14. Yamamoto S, Sobue T, Kobayashi M, Sasaki S, Tsugane S, for the Japan Public Health Center-Based Prospective Study on Cancer Cardiovascular Diseases Group (2003) Soy, isoflavones, and breast cancer risk in Japan. J Natl Cancer Inst 95(12):906–913. doi:10.1093/jnci/95.12.906

15. Suzuki R, Iwasaki M, Hara A, Inoue M, Sasazuki S, Sawada N et al (2013) Fruit and vegetable intake and breast cancer risk defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective study. Cancer Causes Control 24(12):2117–2128. doi:10.1007/s10552-013-0289-7

16. Fukuda S, Saito H, Nakaji S, Yamada M, Ebine N, Tsushima E et al (2007) Pattern of dietary fiber intake among the Japanese general population. Eur J Clin Nutr 61(1):99–103

17. Tsugane S, Sawada N (2014) The JPHC study: design and some findings on the typical Japanese diet. Jpn J Clin Oncol 44(9):777–782. doi:10.1093/jjco/hyu096

18. Sasaki S, Kobayashi M, Ishihara J, Tsugane S, JHPC (2003) Self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study: questionnaire structure, computation algorithms, and area-based mean intake. J Epidemiol 13:S13–S22

19. Tsugane S, Kobayashi M, Sasaki S (2003) Validity of the self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I: comparison with dietary records for main nutrients. J Epidemiol 13:S51–S56

20. The Council for Science and Technology, Ministry of Education, Culture, Sports, Science and Technology (2005) Standard tables of food composition in Japan. 5th revised and enlarged edn. National Printing Bureau, Tokyo

21. Willett W (1998) Nutritional epidemiology. 2nd edn. Oxford University Press, New York

22. Sasaki S, Matsumura Y, Ishihara J, Tsugane S (2003) Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC study Cohort I to assess dietary fiber intake: comparison with dietary records. J Epidemiol 13 (1 Sup):S106–S114. doi:10.2188/jea.13.1sup_106

23. Sawada N, Iwasaki M, Yamaji T, Shimazu T, Sasazuki S, Inoue M et al (2015) Fiber intake and risk of subsequent prostate cancer in Japanese men. Am J Clin Nutr 101(1):118–125. doi:10.3945/ajcn.114.089581

24. Kokubo Y, Iso H, Saito I, Yamagishi K, Ishihara J, Inoue M et al (2011) Dietary fiber intake and risk of cardiovascular disease in the Japanese population: the Japan Public Health Center-based study cohort. Eur J Clin Nutr 65(11):1233–1241. doi:10.1038/ejcn.2011.100

25. Ministry of Education, Culture, Sports, Science and Technology (2000) International classification of diseases for oncology. 3rd edn. WHO, Geneva

26. Holmes MD, Liu S, Hankison SE, Colditz GA, Hunter DJ, Willett WC (2004) Dietary carbohydrates, fiber, and breast cancer risk. Am J Epidemiol 159(8):732–739. doi:10.1093/aje/kwh112

27. Liu Y, Colditz GA, Cotterchio M, Boucher BA, Kreiger N (2014) Adolescent dietary fiber, vegetable fat, vegetable protein, and nut intakes and breast cancer risk. Breast Cancer Res Treat 145(2):461–470. doi:10.1007/s10549-014-2953-3

28. Gunter MJ, Xie X, Xue X, Kabat GC, Rohan TE, Wassertheil-Smoller S et al (2015) Breast cancer risk in metabolically healthy but overweight postmenopausal women. Cancer Res 75(2):270–274. doi:10.1158/0008-5472.can-14-2317

29. Suzuki R, Rylander-Rudqvist T, Ye W, Saji S, Adlercreutz H, Wolk A (2008) Dietary fiber intake and risk of postmenopausal breast cancer defined by estrogen and progesterone receptor status–a prospective cohort study among Swedish women. Int J Cancer 122(2):403–412. doi:10.1002/ijc.23060

30. Park Y, Brinton LA, Subar AF, Hollenbeck A, Schatzkin A (2009) Dietary fiber intake and risk of breast cancer in postmenopausal women: the National Institutes of Health-AARP Diet and Health Study. Am J Clin Nutr 90:664–671. doi:10.3945/ajcn.2009.27758

31. World Health Organization (2014) Systematic review on diet, nutrition, physical activity and survival and second cancers in breast cancer survivors. Imperial College London, London

32. World Cancer Research Fund International Continuous Update Project Report (2010) Breast cancer 2010 report: Food, nutrition, physical activity, and the prevention of breast cancer. Imperial College London, London

33. Dahm CC, Keogh RH, Spencer EA, Greenwood DC, Key TJ, Fentiman IS et al (2010) Dietary fiber and colorectal cancer risk: a nested case-control study using food diaries. J Natl Cancer Inst 102(9):614–626. doi:10.1093/jnci/djq092

34. World Cancer Research Fund/American Institute for Cancer Research (2014) Guideline for breast cancer screening based on effectiveness evaluation 2013. National Cancer Center, Tokyo

35. Iwasaki M, Inoue M, Sasazuki S, Sawada N, Yamaji T, Shimazu T et al (2010) Green tea drinking and subsequent risk of breast cancer in a population-based cohort of Japanese women. Breast Cancer Res 12(5):R88. doi:10.1186/bcr2756

36. National Cancer Center (2012) Cancer fact sheets: breast cancer. https://gco.iarc.fr/today/fact-sheets-cancers?cancer=15&type=0&sex=2

37. International Agency for Research on Cancer (2015) Cancer incidence 3 prefectures (1985–2010). http://ganjoho.jp/reg_stat/statistics/dl/index.html