TABLE 1
Characteristics of case and matched control subjects

Characteristics	Case ($n = 369$)		Control ($n = 369$)		P^a
Age (yr), *M* (SE)	53.4	(0.53)	53.7	(0.53)	
Premenopausal women, *n* (%)	171	(46.3)	132	(35.8)	<0.01
Age at menopause (yr), *M* (SE)[b]	48.9	(0.30)	49.5	(0.27)	0.37
Age at menarche (yr), *M* (SE)[b]	13.4	(0.07)	13.2	(0.07)	0.24
Nulliparous women, n (%)	48	(13.0)	56	(15.2)	0.37
Number of births (≥ 4 births), *n* (%)	8	(2.2)	9	(2.4)	0.15
Age at first birth (yr), *M* (SE)[b, c]	27.0	(0.19)	26.4	(0.19)	0.41
Breast feeding (yes), *n* (%)[c]	283	(90.7)	297	(95.5)	0.03
Oral contraceptive use, *n* (%)	13	(3.5)	12	(3.3)	0.84
Family history of breast cancer, *n* (%)	43	(11.7)	24	(6.5)	0.02
History of benign breast disease, *n* (%)	45	(12.4)	27	(7.3)	0.03
Height (cm), *M* (SE)[b]	155.3	(0.27)	155.6	(0.27)	0.69
Body mass index (kg/m^2), *M* (SE)[b]	22.7	(0.17)	23.0	(0.17)	0.07
Smoking (current smoker), *n* (%)	29	(8.0)	19	(5.2)	<0.01
Alcohol drinking (regular drinker), *n* (%)	94	(25.5)	111	(30.1)	0.39
Moderate physical activity past 5 yr (yes), *n* (%)	116	(31.8)	146	(39.6)	0.03
Vitamin supplement use, *n* (%)	68	(18.4)	45	(12.2)	0.02
Sencha/Bancha, (≥4 cups per day), *n* (%)	114	(30.9)	120	(32.5)	0.41
Houjicha/Genmaicha, ≥4 cups per day), *n* (%)	27	(7.3)	24	(6.5)	0.33
Oolong tea, (≥1 cups per day), *n* (%)	51	(14.0)	46	(12.5)	0.59
Black tea, (≥1 cups per day), *n* (%)	18	(4.9)	19	(5.2)	0.97
Coffee, (≥1 cups per day), *n* (%)	185	(50.4)	204	(55.3)	0.39
Canned coffee, (≥1 cups per day), *n* (%)	9	(2.5)	5	(1.4)	0.07
Total energy intake (kcal/day), *M* (SE)[b]	1873.2	(28.1)	1960.2	(28.1)	0.19
Fish and shellfish intake (g/day), *M* (SE)[b]	87.1	(2.9)	95.5	(2.9)	0.09
Meat or red meat intake (g/day), *M* (SE)[b]	57.5	(2.0)	58.1	(2.0)	0.38
Vegetable intake (g/day), *M* (SE)[b]	254.2	(9.4)	311.6	(9.4)	<0.01
Fruit intake (g/day), *M* (SE)[b]	286.9	(10.4)	288.2	(10.4)	0.79
Isoflavone intake (mg/day), *M* (SE)[b]	43.1	(1.5)	46.1	(1.5)	<0.01

[a] *P* for Mantel-Haenszel test with matched-pair strata. [b] Adjusted for age. [c] Among parous women.

Moreover, no statistical difference in risk was observed across subtypes (*P* for heterogeneity = 0.08).

We examined whether the association between green tea consumption and breast cancer risk was modified by menopausal status, 4 SNPs of *CYP19A1*, *COMT*, and *MTHFR*, or dietary intake of folate and isoflavone (Table 3). None of the interactions was statistically significant. Furthermore, we investigated associations between green tea consumption, potential effect modifiers, and breast cancer risk by menopausal status (Table 4). No statistically significant interaction was seen for the 3 SNPs of *COMT* and *MTHFR* and dietary folate intake. Analyses by rs10046 polymorphisms in *CYP19A1* showed a decreased risk of breast cancer with increasing consumption among premenopausal women with the CC genotype only (OR for women who drank more than 600 ml vs. less than 120 ml per day = 0.22; 95% CI = 0.05–1.01; *P* for trend = 0.054) and a statistically significant interaction was seen for premenopausal women (*P* for interaction = 0.01). On the other hand, an increased risk with increasing consumption was seen among postmenopausal women with the CC genotype only (OR for women who drank more than 600 ml vs. less than 120 ml per day = 8.78; 95% CI = 1.01–76.44; *P* for trend = 0.04), but the test for interaction was not statistically significant (*P* for interaction = 0.70). Analyses by isoflavone intake showed that the risk of breast cancer tended to decrease with increasing consumption only among premenopausal women with lower isoflavone intake (OR for women who drank more than 600 ml vs. less than 120 ml per day = 0.41; 95% CI = 0.13–1.30; *P* for trend = 0.14), and *P* for interaction was marginally significant (*P* = 0.06). In contrast, risk increased with increasing consumption only among postmenopausal women with lower isoflavone intake (OR for women who drank more than 600 ml vs. less than 120 ml per

TABLE 2
Odds ratio (OR) and 95% confidence interval (CI) of breast cancer according to green tea consumption

	Green tea consumption[a]					
	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend
All breast cancer						
No. of cases/No. of controls	83/68	136/160		150/141		
OR (95% CI)	1.00	0.69	(0.46–1.04)	0.85	(0.56–1.31)	0.75
Adjusted OR (95% CI)[b]	1.00	0.86	(0.53–1.41)	1.27	(0.75–2.14)	0.20
ER+PR+ breast cancer						
No. of cases	54	77	74			
OR (95% CI)	1.00	0.62	(0.39–0.98)	0.70	(0.43–1.14)	0.23
Adjusted OR (95% CI)[c]	1.00	0.72	(0.43–1.18)	0.84	(0.50–1.43)	0.68
ER+PR- breast cancer						
No. of cases	12	20	31			
OR (95% CI)	1.00	0.68	(0.31–1.47)	1.12	(0.52–2.41)	0.50
Adjusted OR (95% CI)[c]	1.00	0.77	(0.32–1.82)	1.46	(0.62–3.45)	0.19
ER-PR- breast cancer						
No. of cases	13	33	40			
OR (95% CI)	1.00	1.06	(0.52–2.15)	1.42	(0.69–2.92)	0.27
Adjusted OR (95% CI)[c]	1.00	1.18	(0.54–2.54)	1.88	(0.86–4.14)	0.07

[a] Total green tea consumption was defined as the sum of Sencha/Bancha and Houjicha/Genmaicha consumption (ml per day). [b] Conditional model adjusting for menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day). [c] Unconditional model adjusting for matching factors (age and area), menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day).

day = 1.60; 95% CI 0.63–4.06; *P* for trend = 0.03), but *P* for interaction was not statistically significant (*P* = 0.38).

DISCUSSION

In this case-control study in Japanese women, we found no inverse association between green tea consumption and the risk of breast cancer. This lack of association is in general agreement with 5 prospective studies, including 3 Japanese cohort studies (6–10), but in disagreement with 3 case-control studies conducted outside Japan, which all showed an inverse association (3–5). We also found no inverse associations among tumor subtypes. Overall, no substantial effect modification was observed for menopausal status, 4 SNPs of *CYP19A1*, *COMT*, and *MTHFR*, or dietary intake of folate and isoflavone, which suggests that these factors might not be major explanation for the inconsistent findings among previous studies. Although many previous studies including our study have assessed green tea intake during adulthood, the timing of green tea exposure might be important and may account for the lack of association in previous studies. Therefore, further studies are needed to investigate the association between green tea intake during puberty and breast cancer risk, for example, given suggestions that some exposures during breast development are crucial to the development of breast cancer (22).

The present study does not support our hypothesis that green tea consumption is more closely associated with hormone receptor-positive than -negative breast cancer. Contrary to our expectation, consumption was associated with an increased risk of ER-PR- tumors, albeit without statistical significance. Among previous studies, an inverse association was found for both ER+PR+ and ER-PR- tumors in a case-control study of Asian Americans (2), whereas no inverse association for either subtype was seen in our cohort study in Japanese women (10). Overall, the findings of the few studies reported to date are inconsistent. A better understanding of the

TABLE 3
Odds ratio (OR) and 95% confidence interval (CI) of breast cancer according to green tea consumption by potential effect modifiers

	Green tea consumption[a]				
	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend
Menopausal status						
Premenopausal						
No. of cases/No. of controls	56/38	70/60		45/34		
Adjusted OR (95% CI)[b]	1.00	0.72	(0.38–1.35)	1.10	(0.54–2.23)	0.83
Postmenopausal						
No. of cases/No. of controls	27/30	66/100		105/107		
Adjusted OR (95% CI)[b]	1.00	0.83	(0.42–1.67)	1.42	(0.71–2.85)	0.08
	P for interaction = 0.56					
CYP19A1 gene (rs10046)						
CC						
No. of cases/No. of controls	31/19	46/56		39/42		
Adjusted OR (95% CI)[b]	1.00	0.57	(0.25–1.30)	0.82	(0.34–1.99)	0.82
CT + TT						
No. of cases/No. of controls	52/49	90/104		111/99		
Adjusted OR (95% CI)[b]	1.00	0.88	(0.51–1.51)	1.22	(0.70–2.14)	0.32
	P for interaction = 0.24					
COMT gene (rs4680)						
GG						
No. of cases/No. of controls	47/38	60/68		72/67		
Adjusted OR (95% CI)[b]	1.00	0.88	(0.46–1.68)	1.37	(0.71–2.65)	0.26
GA + AA						
No. of cases/No. of controls	36/30	76/92		78/74		
Adjusted OR (95% CI)[b]	1.00	0.68	(0.35–1.30)	0.88	(0.44–1.77)	0.98
	P for interaction = 0.77					
MTHFR gene (rs1801133)						
CC						
No. of cases/No. of controls	27/18	47/48		47/44		
Adjusted OR (95% CI)[b]	1.00	0.89	(0.37–2.12)	1.10	(0.45–2.66)	0.73
CT + TT						
No. of cases/No. of controls	56/50	89/112		103/97		
Adjusted OR (95% CI)[b]	1.00	0.89	(0.52–1.53)	1.21	(0.69–2.13)	0.37
	P for interaction = 0.46					
MTHFR gene (rs1801131)						
AA						
No. of cases/No. of controls	56/46	84/106		99/92		
Adjusted OR (95% CI)[b]	1.00	0.78	(0.45–1.36)	1.24	(0.70–2.18)	0.26
AC + CC						
No. of cases/No. of controls	27/22	52/54		51/49		
Adjusted OR (95% CI)[b]	1.00	0.80	(0.35–1.84)	0.79	(0.32–1.91)	0.64
	P for interaction = 0.54					
Folate intake						
Lower						
No. of cases/No. of controls	68/50	87/92		40/32		
Adjusted OR (95% CI)[b]	1.00	0.81	(0.47–1.39)	1.08	(0.54–2.13)	0.94
Higher						
No. of cases/No. of controls	15/18	49/68		110/109		
Adjusted OR (95% CI)[b]	1.00	0.82	(0.33–2.03)	1.22	(0.52–2.86)	0.26

(Continued on next page)

TABLE 3
Odds ratio (OR) and 95% confidence interval (CI) of breast cancer according to green tea consumption by potential effect modifiers *(continued)*

	Green tea consumption[a]					
	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend
	P for interaction = 0.28					
Isoflavone intake						
Lower						
No. of cases/No. of controls	46/29	71/88		84/67		
Adjusted OR (95% CI)[b]	1.00	0.60	(0.32–1.15)	1.05	(0.54–2.05)	0.45
Higher						
No. of cases/No. of controls	37/39	65/72		66/74		
Adjusted OR (95% CI)[b]	1.00	0.99	(0.51–1.93)	1.16	(0.58–2.35)	0.61
	P for interaction = 0.71					

COMT = catechol-O-methyltrasferease; CT + TT = ; AC + CC = .

[a] Total green tea consumption was defined as the sum of Sencha/Bancha and Houjicha/Genmaicha consumption (ml per day).[b] Unconditional model adjusting for matching factors (age and area), menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day).

protective role of green tea in the development of breast cancer will require further study aimed at clarifying the association between consumption and hormone receptor-defined subtype.

Given that the putative effect of green tea consumption on the development of breast cancer might be mediated by estrogen exposure, as mentioned in the **Introduction**, the association between consumption and risk may vary according to menopausal status or genetic polymorphisms in *CYP19A1*. A cohort study among Chinese women in Shanghai showed an association between green tea drinking and a decreased risk of breast cancer for premenopausal women but an increased risk for postmenopausal women (9). In the present study, no significant interaction between two strata was found, which is consistent with the results of 2 previous studies in our cohort study among Japanese women (10) and in a case-control study among Chinese women in Shanghai (5). To our knowledge, this is the first study to investigate effect modification of genetic polymorphisms in *CYP19A1* in the association between green tea consumption and breast cancer risk. We found a statistically significant interaction for the rs10046 polymorphisms in *CYP19A1* among premenopausal women. An inverse association between consumption and breast cancer risk was seen among premenopausal women with the CC genotype only. Give that the stratified analysis included only a relatively small number of cases and multiple comparisons were made, these findings might have been merely due to chance. Given that we genotyped only one SNP of *CYP19A1*, a full understanding of this gene–nutrient interaction awaits a more comprehensive evaluation of this gene. Replication of our findings would suggest that green tea might reduce the risk of breast cancer via a mechanism involving *CYP19A1*.

Isoflavones are classified as phytoestrogens, which are plant-derived nonsteroidal compounds with estrogen-like biological properties. Similarly to green tea, isoflavones have also been shown to inhibit aromatase (23). A meta-analysis reported an inverse association between isoflavone intake and breast cancer risk among Asian but not Western populations (24). A case-control study of Asian Americans found an inverse association between green tea consumption and breast cancer risk only among women whose soy intake was low (3), although this effect modification was not replicated by subsequent studies (5,7,10). In the present stratified analysis also, an inverse association between green tea consumption and breast cancer risk tended to be limited to premenopausal women with lower isoflavone intake, albeit it that this effect was not statistically significant and that the overall findings suggested that soy intake was unlikely to be an effect modifier. The different findings between the case-control study in Asian Americans and other previous studies might be explained by differences in the definition of soy intake and its level of consumption among studies; the former evaluated soy intake during both adolescence and adulthood (3), for

TABLE 4
Odds ratio (OR) and 95% confidence interval (CI) for associations between green tea consumption, potential effect modifiers and breast cancer risk by menopausal status

	Premenopausal women						Postmenopausal women					
	Green tea consumption[a]						Green tea consumption[a]					
	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend	1–119 ml per day	120–599 ml per day		600 ml + per day		*P* for trend
CYP19A1 gene (rs10046)												
CC												
No. of cases/No. of controls	23/10		26/22		12/12		8/9		20/34		27/30	
Adjusted OR (95% CI)[b]	1.00	0.20	(0.05–0.88)	0.22	(0.05–1.01)	0.054	1.00	4.21	(0.52–33.78)	8.78	(1.01–76.44)	0.04
CT + TT												
No. of cases/No. of controls	33/28		44/38		33/22		19/21		46/66		78/77	
Adjusted OR (95% CI)[b]	1.00	1.08	(0.49–2.37)	2.04	(0.83–5.04)	0.13	1.00	0.71	(0.31–1.67)	1.16	(0.51–2.65)	0.31
	P for interaction = 0.01						P for interaction = 0.70					
COMT gene (rs4680)												
GG												
No. of cases/No. of controls	35/22		30/25		20/21		12/16		30/43		52/46	
Adjusted OR (95% CI)[b]	1.00	0.67	(0.24–1.88)	0.81	(0.28–2.34)	0.68	1.00	0.98	(0.33–2.89)	2.12	(0.70–6.39)	0.06
GA + AA												
No. of cases/No. of controls	21/16		40/35		25/13		15/14		36/57		53/61	
Adjusted OR (95% CI)[b]	1.00	0.49	(0.18–1.31)	0.90	(0.26–3.09)	0.83	1.00	0.49	(0.17–1.43)	0.67	(0.23–1.93)	0.94
	P for interaction = 0.50						P for interaction = 0.24					
MTHFR gene (rs1801133)												
CC												
No. of cases/No. of controls	18/11		23/18		16/7		9/7		24/30		31/37	
Adjusted OR (95% CI)[b]	1.00	0.17	(0.03—0.92)	2.15	(0.40—11.60)	0.47	1.00	0.84	(0.19—3.71)	0.89	(0.21—3.71)	0.96
CT + TT												
No. of cases/No. of controls	38/27		47/42		29/27		18/23		42/70		74/70	
Adjusted OR (95% CI)[b]	1.00	0.81	(0.37—1.78)	0.85	(0.35—2.08)	0.72	1.00	0.80	(0.34—1.89)	1.71	(0.72—4.04)	0.048

			P for interaction = 0.72						P for interaction = 0.15			
MTHFR gene (rs1801131)												
AA												
No. of cases/No. of controls	40/24		47/40		35/26		16/22		37/66		64/66	
Adjusted OR (95% CI)[b]	1.00	0.65	(0.30—1.41)	1.05	(0.45—2.44)	0.92	1.00	0.82	(0.32—2.06)	2.13	(0.85—5.36)	0.02
AC + CC												
No. of cases/No. of controls	16/14		23/20		10/8		11/8		29/34		41/41	
Adjusted OR (95% CI)[b]	1.00	0.71	(0.19—2.61)	0.96	(0.19—4.83)	0.88	1.00	0.61	(0.15—2.46)	0.75	(0.19—2.95)	0.95
			P for interaction = 0.88						P for interaction = 0.11			
Folate intake												
Lower												
No. of cases/No. of controls	46/31		52/42		13/15		22/19		35/50		27/17	
Adjusted OR (95% CI)[b]	1.00	0.76	(0.36—1.62)	0.76	(0.25—2.28)	0.52	1.00	0.74	(0.29—1.85)	1.27	(0.44—3.65)	0.59
Higher												
No. of cases/No. of controls	10/7		18/18		32/19		5/11		31/50		78/90	
Adjusted OR (95% CI)[b]	1.00	0.43	(0.08—2.18)	1.23	(0.29—5.21)	0.37	1.00	1.26	(0.32—4.98)	2.02	(0.53–7.70)	0.11
			P for interaction = 0.18						P for interaction = 0.43			
Isoflavone intake												
Lower												
No. of cases/No. of controls	30/13		46/31		24/20		16/16		25/57		60/47	
Adjusted OR (95% CI)[b]	1.00	0.53	(0.18–1.53)	0.41	(0.13–1.30)	0.14	1.00	0.43	(0.16–1.13)	1.60	(0.63–4.06)	0.03
Higher												
No. of cases/No. of controls	26/25		24/29		21/14		11/14		41/43		45/60	
Adjusted OR (95% CI)[b]	1.00	0.47	(0.17–1.27)	1.90	(0.62–5.82)	0.44	1.00	2.18	(0.65–7.30)	1.59	(0.46–5.46)	0.93
			P for interaction = 0.06						P for interaction = 0.38			

CC = ; GA + AA; GG = ; COMT = catechol-O-methyltrasferease; CT + TT = ; AC + CC = .

Q3 [a]Total green tea consumption was defined as the sum of Sencha/Bancha and Houjicha/Genmaicha consumption (ml per day).

[b]Unconditional model adjusting for matching factors (age and area), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 yr (no, less than 3 days/mo, 1–4 days/wk, more than 5 days/wk), vitamin supplement use (yes, no), oolong tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), black tea consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day), and canned coffee consumption (less than 1 cup per wk, 1–6 cups per wk, 1 or more cups per day).

example, whereas the latter assessed intake during adulthood only (5,7,10).

Factors related to the bioavailability of tea catechins may modify the association between green tea and breast cancer risk. One important conjugation reaction of these compounds is *O*-methylation by COMT (25). The AA genotype of rs4680 has been associated with a decrease in *COMT* enzyme activity (26) and may modify the association. Indeed, green tea drinking was associated with a decreased risk of breast cancer among carriers of low-activity *COMT* alleles in the case-control study in Asian Americans but not among those who possessed high-activity *COMT* alleles (16), whereas subsequent studies, including a large case-control (number of case = 1116) and the present study, did not detect such interaction (5). The folate pathway has been suggested as one mechanism through which green tea might protect against breast cancer, on the basis that EGCG inhibits dihydrofolate reductase (27). As mentioned in the Introduction, a nested case-control study in Singapore suggested that folate intake and genetic polymorphism of *MTHFR* and *TYMS* modified the association between green tea intake and breast cancer risk (8). The present and a previous study, however, found no effect modification of folate intake and genetic polymorphisms of *MTHFR* (5,10).

Several limitations of the present study warrant mention. First, green tea consumption was assessed after the diagnosis of breast cancer and is therefore sensitive to recall bias. If patients considered green tea as a healthy drink, even though a preventive effect on breast cancer has not been established, their consumption of green tea might be under- or overestimated. We cannot deny the possibility that such bias might have affected our findings. Second, although the substantially high participation rates among both eligible cases and controls minimized potential biases related to control selection, the use of controls from medical checkup examinees, whose dietary habits may differ from those of the general population due to health consciousness or disease, might have led to selection bias. Third, because the evaluation of interactions was performed in a relatively small number of cases, power to evaluate interactions was limited. This might have also limited the interpretability of the results.

Allowing for these methodological issues, we found that green tea consumption was not associated with a decreased risk of breast cancer. Overall, our stratified analyses suggested that there were no subgroups in which the risk of breast cancer decreased with increasing consumption of green tea. However, further larger studies are required to identify such subgroups.

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ORIGINAL PAPER

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

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Abstract
Background Epidemiological evidence for the impact of fruit and vegetable intake on breast cancer risk among the Japanese populations is scarce.
Objective The purpose of this study was to evaluate the association between fruit and vegetable intake and breast cancer risk among 47,289 Japanese women.
Design The study was conducted under a population-based prospective cohort design. Dietary assessment was performed using a validated food frequency questionnaire. A Cox proportional hazards regression model was used to calculate relative risks (RRs) and their corresponding 95 % confidence intervals (CIs).
Results During an average of 10.2 years of follow-up, 452 cases of breast cancer were newly diagnosed. No association with breast cancer risk was seen for intake of total fruits and vegetables, cruciferous vegetables, green-leaf vegetables, yellow vegetables, or tomato products in overall or postmenopausal women. Cruciferous vegetable intake was associated with a statistically significant decrease in risk of premenopausal breast cancer [multivariable-$RR_{Q4\ vs.\ Q1}$ = 0.64 (95 % CI = 0.38–1.10; p_{trend} = .046)] and showed a marginally inverse association with ER+ PR+ tumors [$RR_{per\ 100\ g\ increment}$ = 0.64 (95 % CI = 0.41–1.00)]. In contrast, positive associations were seen between intake of total fruits and citrus fruits and breast cancer risk in overall and premenopausal women. However, these associations for fruit were all attenuated with additional adjustment for vitamin C intake.
Conclusions Our results suggest an overall null association between total fruit and vegetable intake and breast cancer risk. Intake of cruciferous vegetable showed a statistically significant association with a decreased risk of breast cancer among premenopausal women.

Keywords Breast cancer · Fruits · Vegetables · Risk · Receptor

Abbreviations

BMI	Body mass index
CIs	Confidence intervals
ER	Estrogen receptor
EFH	Exogenous female hormones
FFQ	Food frequency questionnaire
The JPHC Study	The Japan Public Health Center-based Prospective Study
OC	Oral contraceptive
PR	Progesterone receptor
RR	Relative risk
SD	Standard deviation
DCN	Death certificate notification
DCO	Death certificate only

Introduction

In Japan, the incidence of breast cancer has continuously and steeply increased over the last three decades, and this

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cancer is currently the most common female cancer, as in Western countries [1]. During this period, an approximately 20% reduction in the consumption of total fruits and vegetables has been reported [2].

Fruit and vegetables are rich sources of various bioactive compounds and micronutrients, such as vitamins, phytoestrogens and carotenoids [3]. These are potentially anticarcinogenic substances for which preventive effects against cancer have been proposed [4]. A majority of epidemiological evidence does not support an overall preventive association [5, 6], however, and the latest report from the World Cancer Research Fund made no conclusion due to insufficient evidence [7].

One explanation for the lack of any firm conclusion on the association of total fruits and vegetables on overall breast cancer risk might be the possible heterogeneity of impact on risk by sub-type of fruit or vegetable, or subtype of breast tumor, such as estrogens—and/or progesterone receptor (ER/PR) status. For instance, mechanisms hypothesized to explain a putative decrease in risk by cruciferous vegetables include a hormone-related mechanism [8, 9], inhibition of cell growth, and induction of apoptosis [10]. To date, the impact of consumption of total fruit and vegetables in consideration of estrogen and/or progesterone receptor (ER/PR) status has been reported by several studies [11, 12, 13, 14], as well as most recently in a large pooled analysis [15] of 20 cohort studies with the baseline data of the Japan Public Health Center-based Prospective Study (JPHC) [15]. Although this pooled overall result showed a statistically significant inverse association between total vegetable consumption and ER-negative (−) breast cancer risk, the study-specific risk estimates in JPHC at the baseline survey suggested the opposite direction to that in the overall pooled result for 20 studies [15]. However, the baseline survey of JPHC asked about information for four fruits and three vegetables and did not involve several commonly consumed vegetables in Japan, such as Japanese radish, Chinese cabbage, or Komatsuna. Further, in general, commonly consumed vegetables in Japan are not the same as those in Western countries [16]. For example, the food supply in 2009 (capita/day) was 5 kcal for tomatoes, 11 for onions, and 57 for other vegetables in Japan, versus respective values of 21, 9, and 46 kcal. Here, we prospectively evaluated the impact of total and subgroup fruit and/or vegetable intake on the risk of breast cancer in consideration of ER/PR status among 47,289 Japanese women using data from the 5-year follow-up survey of the JPHC with detailed dietary information. We also conducted secondary analyses to assess which specific vegetables contribute to the prevention of breast cancer.

Materials and methods

Study population

The study population of the JPHC study was defined as Japanese inhabitants of 11 public health center (PHC) areas and consisted of two cohorts, with Cohort I launched in 1990 and Cohort II in 1993. Details of the study design have been described previously [17]. The present study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

A total of 140,420 subjects were invited to participate in the baseline survey (1990–1994), of whom 71,698 were women. Subjects in the Tokyo-Katsushika PHC area ($n = 4,178$) were excluded because complete information on cancer incidence were not available. Three self-reported questionnaires were sent, one each at baseline (response rate 83 %), 5-year follow-up (1995–1998; response rate 79 %) and 10-year follow-up (2000–2003; response rate 77 %).

The present analysis was conducted in 53,600 women who completed the 5-year follow-up survey questionnaire, which covered information on diet in greater detail than that at baseline. We excluded those who moved before the start of follow-up or who could not complete follow-up, as well as those with a self-reported history of cancer before the start of the follow-up ($n = 3,347$). We also excluded women with missing data on total fruit or total vegetable intake, or with extreme total energy intake (±2SD) at the 5-year follow-up survey ($n = 971$). Consequently, 47,289 women were eligible for inclusion in the present analysis.

Exposure measurement

Dietary assessment was done using a validated self-administered food frequency questionnaire (FFQ). The 5-year follow-up survey inquired about 138 food and beverage items [18, 19], including 16 fruits and 30 vegetables. We asked about the average frequency and portion size in the past year, with nine frequency categories ranging from *almost never* to *7 or more times per day*. Standard portions/units were specified for each food item, with the three amount choices of small (50 % smaller than standard), medium (same as standard), and large (50 % larger). For seasonal fruit and vegetable products, we asked about the frequency of intake when in season and calculated the consumption (g/day) by taking account of seasonal length and portion size.

The consumption of fruits and vegetables [grams per day (g/day)] as well as other estimated dietary/nutritional information was calculated with reference to the Standard Tables of Food Composition in Japan, Fifth Revised Edition [20]. Items were classified into several sub-groups,

including eight cruciferous vegetables (cabbage, Japanese radish, Chinese cabbage, Komatsuna, broccoli, leaf mustard, qing-geng-cai, and chard), five green vegetables (spinach, Chinese chives, mugwort, green pepper, and garland chrysanthemums), four carotenoid-rich yellow vegetables (carrots, pumpkins, tomatoes, and tomato juice), three tomato products (tomato, tomato juice, and ketchup) and two citrus fruits (mandarin oranges, other oranges).

Nutritional covariates, except alcohol intake, were adjusted for total caloric intake using the residual method [21].

Validity and reproducibility of the FFQ for dietary assessment has been evaluated [22, 23]. Spearman correlation coefficients between the FFQ and 14- and 28-day dietary records as the objective standard were 0.25 for fruits and 0.34 for vegetables among 113 women [22]. Reproducibility was evaluated by administering two FFQs one year apart to 108 women, and showed Spearman correlation coefficients of 0.50 for fruits and of 0.53 for vegetables (energy-adjusted) [23].

Information on other covariates, such as anthropometric and reproductive characteristics, smoking status and menopausal status, was also collected using the self-administered questionnaire at 5 years and updated in the analysis whenever reasonable information was available from the 10-year follow-up survey.

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

Breast cancer cases were identified through active patient notification from major local hospitals in the study area and data linkage with population–based registries, with permission from the local governments responsible for the registries. Breast cancer cases were defined with reference to the Third Edition of the International Classification of Diseases for Oncology [24] as codes C500–509. Eight cases were identified by information on death certificates (i.e. Death Certificate Notification), of which five had no information on diagnosis (i.e. Death Certificate Only). Diagnosis was microscopically confirmed for 97 % of all cases. ER and PR status were evaluated by either immunohistochemical assay or enzyme-linked immunoassay. The cut-off point for a positive status for ER and PR was defined by clinical estimation for medical treatment or was specified by the assay method.

Subjects were entered into the study on the administration date of the 5-year follow-up survey and contributed person-time from the 5-year follow-up survey to the date of diagnosis of cancer, date of death, date of migration out of the study area, or end of follow-up (31 December 2007), whichever occurred first.

Dates of death were verified through linkage with the registration of deaths at the regional public health centers (PHCs) under the control of the Ministry of Health, Labour and Welfare. Dates of migration were verified through linkage with residential registries at the regional PHCs.

Statistical analysis

We used multivariable Cox proportional hazards regression models to estimate relative risks (RRs) and 95 % confidence intervals (CIs) with age as a time scale [25]. The proportional hazards assumptions were explored by Kaplan–Meier curves [26]. Participants were subdivided into quartiles according to consumption of fruits and vegetables. The multivariable adjusted model included age, height (<148, 148–151.9, 152–154.9, ≥155 cm), recent BMI (<18.5, 18.5–23.9, ≥24, missing), BMI at age 20 years (<20, 20–23.9, ≥24), smoking status (never, ever), leisure-time physical activity (≤3 days/month, 1–2 days/week, ≥3 days/week), 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), age at menopause (premenopausal, ≤44, 45–54, ≥54 years), use of exogenous female hormones (EFH) (ever, never), alcohol consumption (past drinkers, never-drinkers, occasional drinkers, drinkers ≤150 g ethanol/week, drinkers >150 g ethanol/week), energy-adjusted intake of isoflavones (continuous), and use of vitamin C supplementation (user, non-user). We partly performed additional analyses with adjustment for energy-adjusted intake of vitamin C.

We performed an overall analysis as well as stratified analyses by menopausal status (pre or post).

p values for trend were tested by creating a continuous variable from the median value for each intake of exposure category, which was then included in the regression model. For the sub-analyses of ER/PR tumors, RRs were presented per 100-g increment in daily intake of each fruit or vegetable. All analyses were performed using the SAS Statistical Package Release 9.1 (SAS Institute, Cary, NC). All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$.

Results

After an average of 10.2 years of follow-up, corresponding to 482,944 person-years, 452 breast cancer cases were newly diagnosed among 47,289 women. Information on ER and PR status was available for 224 cases (50 % of total), of which 105 were ER+ PR+ (47 % of all ER/PR known cases), 51 were ER+ PR−, and 61 were ER− PR−.

Table 1 Subject's characteristics at the study enrolment according to consumption of fruits and vegetables in the Japan Public Health Center-based Prospective Study (1995–2007)

Characteristic	Total fruits and vegetables (g/day)				Fruits (g/day)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Mean, g/day (SD)	229(69)	389(39)	532 (48)	829 (211)	76(36)	174(25)	270(33)	500 (185)
Number of subjects	$n = 11,435$	$n = 12,012$	$n = 12,078$	$n = 11,764$	$n = 11,352$	$n = 11,986$	$n = 12,097$	$n = 11,854$
Age at baseline, year, mean (SD)	56.0 (8.0)	56.9 (8.0)	57.5(7.8)	58.4 (7.8)	56.6 (8.1)	56.8 (7.9)	57.5 (7.9)	58.0 (7.9)
Body mass index at age 20 years, kg/m^2, mean (SD)	21.5(2.7)	21.5(2.6)	21.6 (2.6)	21.6 (2.7)	21.5 (2.7)	21.6 (2.6)	21.6 (2.6)	21.6 (2.7)
Body mass index at recent age, kg/m^2, mean (SD)	23.5(3.3)	23.5(3.2)	23.5 (3.2)	23.5 (3.1)	23.7 (3.4)	23.5 (3.2)	23.4 (3.1)	23.4 (3.1)
Height, cm, mean (SD)	151 (16)	151(15)	151 (14)	151 (15)	151 (19)	151 (12)	151 (15)	151 (14)
Age at menarche, year, mean (SD)	14.7 (2.0)	14.7 (1.9)	14.7 (1.9)	14.8 (1.9)	14.9 (2.1)	14.7 (1.9)	14.6 (1.8)	14.6 (1.8)
Age at first birth, year, mean (SD)[a]	25.0 (3.6)	24.9 (3.4)	24.9 (3.4)	24.8 (3.3)	24.9 (3.6)	24.9 (3.4)	24.9 (3.4)	24.8 (3.3)
Number of children, n, mean (SD)	2.2(1.7)	2.3 (1.7)	2.3 (1.6)	2.3(1.6)	2.3 (1.9)	2.3(1.7)	2.3(1.6)	2.2 (1.6)
Age at menopause, year, mean (SD)	48.2 (4.8)	48.4 (4.5)	48.5 (4.5)	48.3 (4.8)	48.3 (4.7)	48.5 (4.5)	48.5 (4.5)	48.2 (4.8)
Use of exgenous female hormones (ever),%	13.1	12.2	12	12.6	12.7	12.5	12.4	12.3
Smoking status (ever),%	12.8	8.1	6.8	5.6	12.8	8.4	6.5	5.7
Alcohol drinking status (ever drinkers),%	42.9	38.5	35.5	32.3	41.5	38.4	36.4	32.9
Supplement of vitamin C, (ever),%	3.5	4	4.3	4	3.9	3.9	4	4
Total energy intake, mean(SD), kcal/day	1,873 (613)	1,879 (561)	1,867 (537)	1,824 (540)	1,853 (619)	1,918 (557)	1,871(541)	1,799 (528)
Intake of isoflavone, mean(SD), mg/day	38.6 (35.8)	41.9 (29.5)	44.3 (28.7)	45.7 (29.4)	40.3 (35.9)	42.5 (30.4)	44.0 (28.9)	43.6 (28.6)
Characteristic	Vegetables (g/day)				Cruciferous (g/day)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Mean, g/day (SD)	104 (32)	180 (19)	254 (25)	427 (140)	23 (9.6)	48 (6.5)	73(8.7)	141 (67.3)
Number of subjects	$n = 11,462$	$n = 11,991$	$n = 12,054$	$n = 11,781$	$n = 11,361$	$n = 12,000$	$n = 12,099$	$n = 11,828$
Age at baseline, year, mean (SD)	56.3 (8.1)	56.7 (7.9)	57.5 (7.8)	58.4 (7.8)	56.7 (8.1)	56.5 (7.9)	57.1 (7.8)	58.4 (7.9)
Body mass index at age 20 years, kg/m^2, mean (SD)	21.5 (2.7)	21.5 (2.6)	21.6 (2.6)	21.7 (2.7)	21.6 (2.7)	21.5 (2.6)	21.5 (2.6)	21.7 (2.7)
Body mass index at recent age, kg/m^2, mean (SD)	23.4 (3.3)	23.4 (3.1)	23.5 (3.1)	23.7 (3.2)	23.5 (3.2)	23.4 (3.1)	23.5 (3.2)	23.6 (3.2)
Height, cm, mean (SD)	151 (17)	151(14)	151 (13)	151 (17)	151 (16)	151 (15)	152 (13)	151 (16)
Age at menarche, year, mean (SD)	14.6 (1.9)	14.6 (1.8)	14.7 (1.9)	14.9 (2.0)	14.7 (1.9)	14.6 (1.8)	14.6 (1.8)	14.9(2.0)
Age at first birth, year, mean (SD)[a]	24.9 (3.5)	24.9 (3.4)	24.9 (3.4)	24.8 (3.3)	24.9 (3.6)	24.9 (3.4)	24.9 (3.3)	24.8 (3.4)
Number of children, n, mean (SD)	2.1(1.6)	2.2 (1.6)	2.3 (1.6)	2.4(1.8)	2.2 (1.7)	2.2 (1.6)	2.3(1.6)	2.4 (1.8)
Age at menopause, year, mean (SD)	48.2 (4.8)	48.3 (4.6)	48.4 (4.6)	48.4 (4.6)	48.3 (4.6)	48.2 (4.7)	48.4 (4.6)	48.5 (4.6)
Use of exgenous female hormones (ever),%	13	12.2	12.6	11.9	12.7	12.8	12.4	11.9
Smoking status (ever),%	10.8	8.6	7.4	6.5	10.5	8.4	7.7	6.6
Alcohol drinking status (ever drinkers),%	41.0	39.3	36.4	32.4	40.5	39.5	37.2	32
Supplement of vitamin C, (ever),%	3.3	3.9	4.2	4.3	3.8	3.9	4.1	3.9

Table 1 continued

Characteristic	Vegetables (g/day)				Cruciferous (g/day)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Mean, g/day (SD)	104 (32)	180 (19)	254 (25)	427 (140)	23 (9.6)	48 (6.5)	73(8.7)	141 (67.3)
Number of subjects	$n = 11{,}462$	$n = 11{,}991$	$n = 12{,}054$	$n = 11{,}781$	$n = 11{,}361$	$n = 12{,}000$	$n = 12{,}099$	$n = 11{,}828$
Total energy intake, mean(SD), kcal/day	1,876 (613)	1,899 (559)	1,859 (534)	1,808(542)	1,856(609)	1,919(577)	1,880(517)	1,786(541)
Intake of isoflavone, mean(SD), mg/day	37.9 (36.0)	41.2 (28.6)	44.0 (27.8)	47.3 (30.7)	40.0 (37.0)	40.4 (28.7)	43.3 (27.6)	46.8 (29.9)

BMI body mass index, *SD* standard deviation

[a] Based on information among women with available data

The amount of total fruit consumed ranged from a mean value of 83 g/day in the lowest quartile to 444 g/day in the highest, while the amount of total vegetable intake ranged from a mean of 111 g/day in the lowest quartile to 384 g/day in the highest. The following food items made a major contribution: mandarin oranges (15.5 %), apples (6.2 %), Japanese radish (6.0 %), 100 percent apple juice (5.4 %), onions (5.2 %), 100 percent orange juice (5.0 %), carrots (4.7 %), cabbage (3.5 %), and 100 percent tomato juice (3.2 %).

Women with high consumption of total fruits were more likely to be older, and have a low recent BMI, early menarche, low prevalence of EFH use, no tobacco use, low alcohol consumption, low total energy intake, and high isoflavone intake (Table 1). Women with high consumption of total vegetables were more likely to be older, and have a high BMI, late menarche, more children, low tobacco use, low alcohol consumption, vitamin C supplementation, low total energy intake and high isoflavone intake compared to women with low consumption. We observed a modest positive correlation between fruit intake and vegetable intake (Spearman's $r = 0.2$).

For total fruit and vegetable consumption, our results did not provide any substantial association with a decreased risk of breast cancer in this cohort [multivariable-adjusted RR $_{\text{Q4 vs. Q1}}$ was 1.17 (95 % CI 0.89–1.53; $p_{\text{trend}} = 0.14$; Table 2)]. The corresponding result for total fruit intake was 1.35 (95 % CI 0.99–1.82; $p_{\text{trend}} = 0.051$) and that for total vegetable intake was 1.02 (95 % CI 0.77–1.34; $p_{\text{trend}} = 0.77$). By sub-types of fruits and vegetables, we observed no associations for cruciferous vegetables, green-leaf vegetables, yellow vegetables, or tomato products in overall analysis. In contrast, we observed a positive association between citrus fruits intake and breast cancer risk [multivariable-adjusted RR $_{\text{Q4 vs. Q1}}$ was 1.27 (95 % CI 0.95–1.70; $p_{\text{trend}} = 0.044$; Table 2)]. However, the observed association was attenuated by adjustment for vitamin C [1.23(95 % CI 0.87–1.75; $p_{\text{trend}} = 0.093$; Table 2)].

In analyses stratified by menopausal status, an appreciable reduction in the risk of breast cancer associated with increased consumption among premenopausal women was seen for cruciferous vegetables only [multivariable adjusted RR $_{\text{Q4 vs. Q1}} = 0.64$ (95 % CI 0.38 to 1.10; $p_{\text{trend}} = 0.046$; Table 3].

Consumption of total fruits and vegetables, total fruits, and citrus fruits was positively associated with breast cancer risk [corresponding RRs$_{\text{for total fruits and vegetables}} =$ 1.61 (95 % CI 0.90–2.85; $p_{\text{trend}} = 0.034$); $_{\text{for total fruits}} =$ 2.32 (95 % CI 1.23–4.38; $p_{\text{trend}} = 0.009$; $_{\text{for citrus fruits}} =$ 2.29 (95 % CI 1.28–4.10; $p_{\text{trend}} = 0.0036$; Table 3)]. However, the observed positive association between citrus fruit intake and breast cancer risk was attenuated by

Table 2 Relative risks (RRs) and 95 % confidence intervals (CIs) for the association between fruits, vegetables and breast cancer risk in the Japan Public Health Center-based Prospective Study, 1995–2007

Food group	All (N = 47,289 452 cases)				p_{trend}	100 g continuous
	Ref	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)		RR (95 % CI)
Total fruit and vegetables						
Median (g/day)	Q1. 246 g/day	Q2. 393/day	Q3. 530 g/day	Q4. 764 g/day		
Number of cases	103	105	128	116		
Age-area adjusted	1.00 (ref.)	1.02 (0.78–1.34)	1.24 (0.95–1.61)	1.12 (0.85–1.46)	0.23	
Multivariable adjusted[a]	1.00 (ref.)	1.07 (0.81–1.40)	1.29 (0.99–1.68)	1.17 (0.89–1.53)	0.14	1.01 (0.97–1.05)
Multivariable adjusted[b]	1.00 (ref.)	1.07 (0.81–1.40)	1.29 (0.99–1.68)	1.17 (0.89–1.54)	0.14	1.01 (0.97–1.05)
Fruits						
Median (g/day)	Q1. 83 g/day	Q2. 176 g/day	Q3. 269 g/day	Q4. 444 g/day		
Number of cases	90	122	131	109		
Age-area adjusted	1.00 (ref.)	1.37 (1.04–1.81)	1.50 (1.14–1.98)	1.28 (0.96–1.71)	0.086	
Multivariable adjusted[a,c]	1.00 (ref.)	1.43 (1.09–1.89)	1.57 (1.19–2.08)	1.35 (0.99–1.82)	0.051	1.03 (0.98–1.08)
Multivariable adjusted[b,c]	1.00 (ref.)	1.42 (1.07–1.88)	1.54 (1.15–2.07)	1.28 (0.89–1.85)	0.11	1.02 (0.94–1.10)
Vegetables						
Median (g/day)	Q1. 111 g/day	Q2. 182 g/day	Q3. 252 g/day	Q4. 384 g/day		
Number of cases	108	123	105	116		
Age-area adjusted	1.00 (ref.)	1.12 (0.86–1.44)	0.93 (0.71–1.21)	0.99 (0.76–1.30)	0.63	
Multivariable adjusted[a,d]	1.00 (ref.)	1.13 (0.87–1.47)	0.95 (0.72–1.25)	1.02 (0.77–1.34)	0.77	0.98 (0.91–1.05)
Multivariable adjusted[b,d]	1.00 (ref.)	1.13 (0.87–1.46)	0.95 (0.72–1.25)	1.02 (0.77–1.34)	0.78	0.98 (0.91–1.05)
Cruciferous vegetables						
Median (g/day)	Q1. 25 g/day	Q2. 48 g/day	Q3. 73 g/day	Q4. 120 g/day		
Number of cases	116	130	98	108		
Age-area adjusted	1.00 (ref.)	1.10 (0.85–1.41)	0.81 (0.62–1.06)	0.88 (0.68–1.15)	0.10	
Multivariable adjusted[a,e]	1.00 (ref.)	1.11 (0.87–1.43)	0.83 (0.63–1.09)	0.91 (0.69–1.19)	0.18	0.90 (0.75–1.08)
Multivariable adjusted[b,e]	1.00 (ref.)	1.11 (0.87–1.43)	0.83 (0.63–1.09)	0.91 (0.70–1.19)	0.18	0.90 (0.75–1.08)
Green leaf vegetables						
Median (g/day)	Q1. 8.4 g/day	Q2. 17.8 g/day	Q3. 28.7 g/day	Q4.51.1 g/day		
Number of cases	99	125	106	122		
Age-area adjusted	1.00 (ref.)	1.20 (0.92–1.57)	0.98 (0.75–1.30)	1.09 (0.83–1.42)	0.94	
Multivariable adjusted[a,e]	1.00 (ref.)	1.23 (0.94–1.60)	0.99 (0.75–1.31)	1.12 (0.85–1.47)	0.82	0.92 (0.63–1.35)
Multivariable adjusted[b,e]	1.00 (ref.)	1.23 (0.94–1.60)	0.99 (0.75–1.31)	1.12 (0.85–1.47)	0.82	0.92 (0.63–1.35)
Yellow vegetables 4						
Median (g/day)	Q1. 15.1 g/day	Q2. 34.4 g/day	Q3. 59.1 g/day	Q4. 108.4 g/day		
Number of cases	100	109	121	122		
Age-area adjusted	1.00 (ref.)	1.08 (0.82–1.41)	1. 19 (0.91–1.55)	1.20 (0.92–1.56)	0.14	
Multivariable adjusted[a,d]	1.00 (ref.)	1.08 (0.83–1.43)	1.21 (0.93–1.58)	1.21 (0.92–1.58)	0.13	1.10 (0.96–1.26)
Multivariable adjusted[b,d]	1.00 (ref.)	1.09 (0.83–1.43)	1.21 (0.93–1.58)	1.21 (0.92–1.59)	0.13	1.10 (0.96–1.26)
Tomatoes products						
Median (g/day)	Q1. 1.7 g/day	Q2. 7.4 g/day	Q3. 22.7 g/day	Q4. 66.7 g/day		
Number of cases	118	101	108	125		
Age-area adjusted	1.00 (ref.)	0.86 (0.65–1.12)	0.89 (0.68–1.16)	1.03 (0.80–1.32)	0.76	
Multivariable adjusted[a,d]	1.00 (ref.)	0.84 (0.64–1.10)	0.86 (0.66–1.13)	0.99 (0.76–1.29)	0.97	1.03 (0.85–1.24)
Multivariable adjusted[b,d]	1.00 (ref.)	0.84 (0.64–1.10)	0.86 (0.66–1.13)	0.99 (0.76–1.29)	0.96	1.03 (0.85–1.24)
Citrus fruits (without orange juice)						
Median (g/day)	Q1. 11.8 g/day	Q2. 43.2 g/day	Q3. 85.0 g/day	Q4. 188.5 g/day		
Number of cases	105	108	129	110		
Age-area adjusted	1.00 (ref.)	1.06 (0.81–1.39)	1.34 (1.03–1.76)	1.23 (0.92–1.63)	0.061	

Table 2 continued

Food group	All (N = 47,289 452 cases)				p_{trend}	100 g continuous
	Ref	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)		RR (95 % CI)
Multivariable adjusted[a,c]	1.00 (ref.)	1.09 (0.83–1.44)	1.38 (1.05–1.82)	1.27 (0.95–1.70)	0.044	1.03 (0.95–1.13)
Multivariable adjusted[b,c]	1.00 (ref.)	1.09 (0.83–1.44)	1.38 (1.05–1.82)	1.27 (0.95–1.70)	0.045	1.03 (0.95–1.13)
Multivariable adjusted[a,c,e]	1.00 (ref.)	1.09 (0.82–1.82)	1.37 (1.03–1.82)	1.23 (0.87–1.75)	0.093	1.00 (0.88–1.13)
Multivariable adjusted[b,c,e]	1.00 (ref.)	1.09 (0.82–1.44)	1.37 (1.03–1.82)	1.23 (0.87–1.74)	0.094	1.00 (0.88–1.13)

[a] Multivariable Cox proportional hazards models were adjusted for age time-scales, area (10), height (<148, 148–151.9,152–154.9, ≥155 cm), recent BMI (<18.5, 18.5–23.9, ≥24, missing), BMI at age 20 years (<20, 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), menopausal status (premenopause, age at 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 (past drinker, never-drinker, occasional drinker, regular drinker ≤150, or >150 g of ethanol per week), total energy-adjusted intake of isoflavones, and vitamin C supplement (use or non-use)

[b] The same as model[a] with adjustment for combination variables recent BMI and menopausal status (pre or postmenopause)

[c] Additionally included total energy-adjusted intake of total vegetables (continuous)

[d] Additionally included total energy-adjusted intake of total fruits (continuous)

[e] Additionally included total energy-adjusted intake of vitamin C (continuous)

adjustment for vitamin C intake. Among postmenopausal women, we did not observe any association between any fruit or vegetable intake and breast cancer risk.

In sub-analyses which considered the joint ER and PR status of breast tumors, intake of cruciferous vegetables showed a marginal inverse association with the development of ER+ PR+ tumors [age-area-adjusted $RR_{per\ 100\ g\ increment} = 0.64$ (95 % CI 0.41–1.00; $p = 0.051$ (Table 4)], while intake of citrus fruits was positively associated with ER+ PR− tumors [$RR_{per\ 100\ g\ increment} = 1.20$ (95 % CI 1.01–1.42); Table 4). Total fruits, total vegetables, and all other subgroups of fruits and/or vegetables showed no association with a decreased risk of any ER/PR tumor subtype.

Additional analyses for specific cruciferous vegetables showed that Japanese radish contributed to the inverse association among premenopausal women [age-area adjusted $RR_{Q4\ vs.\ Q1}$ was 0.50 (95 % CI 0.29–0.84; $p_{trend} = 0.003$; text only)]. The corresponding results by ER/PR tumor subtype were 0.28 (95 % CI 0.09–0.89; $p_{trend} = 0.02$ for ER+ PR+ (28 cases) and 0.48 (95 % CI 0.09–2.71; $p_{trend} = 0.15$ for ER− PR− (14 cases); text only).

Discussion

In this large prospective cohort study among Japanese women, our overall results suggested no substantial decrease in the risk of breast cancer with increased consumption of total fruits and vegetables. Our results did suggest a positive association of total fruit intake and citrus fruit intake with increased risk of breast cancer, particularly among premenopausal women, but these results were attenuated by adjustment for vitamin C intake. Further, we also observed a substantial preventive impact of cruciferous vegetables against breast cancer among premenopausal women, but no association between either total or any subgroup of fruit and vegetable intake and breast cancer risk among postmenopausal women. With regard to ER/PR breast tumors, intake of cruciferous vegetables, in particular Japanese radish, was substantially associated with a decreased risk of ER+ PR+ tumors. Our results also suggested a significant positive association between citrus fruit intake and the risk of ER+ PR− tumors. In contrast, no association with a decreased risk of any ER/PR tumor subtype was seen for total fruits, total vegetables, or any other subgroup of fruits and/or vegetables.

Similar to our present results, previous pooled analyses have reported an overall null association for total fruit and vegetable consumption [5, 6]. Median total fruit consumption (220 g/day) in the present study was within the range of median intake in one pooled analysis (164–355 g/day) [5], while median total vegetable intake (213 g/day) was within the range of median total vegetable intake (from 77 to 262 g/day) [5].

To our knowledge, this study is the first large prospective study to investigate the association between the intake of fruits and/or vegetables and breast cancer risk with consideration of ER/PR subtype in a Japanese population alone.

Unlike our present results, total vegetable intake was inversely associated with the risk of ER-negative (−) breast cancer risk in the pooled study [15]. The pooled study did evaluate the intake of total or cruciferous vegetables and involved baseline data in the JPHC. However, this baseline data took into account only three vegetables

Table 3 Relative risks (RRs) and 95 % confidence intervals (CIs) for the association between fruits, vegetables and breast cancer risk with stratified by menopausal statu in the Japan Public Health Center-based Prospective Study, 1995–2007

Consumption	Premenopausal (n = 10,527 115 cases)					Postmenopausal (n = 36,762 337 cases)				
Food group	Ref	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)	p_{trend}	Ref	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)	p_{trend}
Total fruit and vegetables										
Median (g/day)	Q1. 223 g/day	Q2. 354 g/day	Q3. 482 g/day	Q4. 703 g/day		Q1. 255 g/day	Q2. 406 g/day	Q3. 544 g/day	Q4. 780 g/day	
Number of cases	21	23	39	32		80	74	93	90	
Age-area adjusted	1.00 (ref.)	1.11 (0.61–2.01)	1.82 (1.07–3.11)	1.43 (0.82–2.51)	0.0798	1.00 (ref.)	0.92 (0.67–1.27)	1.15 (0.85–1.56)	1.11 (0.82–1.51)	0.29
Multivariable adjusted[a]	1.00 (ref.)	1.19 (0.65–2.17)	2.05 (1.19–3.53)	1.61 (0.90–2.85)	0.034	1.00 (ref.)	0.96 (0.70–1.32)	1.19 (0.87–1.61)	1.14 (0.84–1.56)	0.23
Fruits										
Median (g/day)	Q1. 72 g/day	Q2. 160 g/day	Q3. 244 g/day	Q4. 412 g/day		Q1. 87 g/day	Q2. 182 g/day	Q3. 275 g/day	Q3. 275 g/day	
Number of cases	17	31	36	31		72	92	93	80	
Age-area adjusted	1.00 (ref.)	1.83 (1.01–3.33)	2.25 (1.25–4.04)	2.03 (1.11–3.72)	0.02	1.00 (ref.)	1.29 (0.94–1.76)	1.31 (0.95–1.80)	1.31 (0.95–1.80)	0.47
Multivariable adjusted[a,b]	1.00 (ref.)	2.02 (1.10–3.71)	2.57 (1.40–4.69)	2.32 (1.23–4.38)	0.009	1.00 (ref.)	1.34 (0.98–1.83)	1.35 (0.98–1.87)	1.19 (0.84–1.67)	0.38
Multivariable adjusted[a,b,d]	1.00 (ref.)	1.88 (1.02–3.47)	2.21 (1.18–4.13)	1.65 (0.78–3.51)	0.16	1.00 (ref.)	1.35 (0.98–1.85)	1.38 (0.98–1.93)	1.23 (0.81–1.86)	0.29
Vegetables										
Median (g/day)	Q1. 104 g	Q2. 166 g	Q3. 228 g	Q4. 348 g		Q1. 114 g	Q2. 187 g	Q3. 259 g	Q4. 393 g	
Cases	25	31	30	29		82	88	80	87	
Age-area adjusted	1.00 (ref.)	1.25(0.74–2.12)	1.15 (0.67–1.96)	0.95 (0.55–1.65)	0.75	1.00 (ref.)	1.04 (0.77–1.41)	0.93 (0.68–1.27)	0.99 (0.73–1.35)	0.79
Multivariable adjusted[a,c]	1.00 (ref.)	1.24 (0.73–2.13)	1.16 (0.67–2.01)	0.95 (0.54–1.69)	0.77	1.00 (ref.)	1.06 (0.78–1.43)	0.95 (0.70–1.30)	1.03 (0.75–1.41)	0.95
Cruciferous vegetables										
Median (g/day)	Q1. 25 g	Q2. 45 g	Q3. 66 g	Q4. 108 g		Q1. 25 g	Q2. 50 g	Q3. 75 g	Q4. 124 g	
Number of cases	34	33	23	25		80	95	77	85	
Age-area adjusted	1.00 (ref)	0.98 (0.61–1.59)	0.64 (0.38–1.09)	0.64 (0.38–1.08)	0.038	1.00 (ref.)	1.16 (0.86–1.57)	0.92 (0.67–1.26)	1.02 (0.75–1.38)	0.69
Multivariable adjusted[a,c]	1.00 (ref.)	0.99 (0.61–1.61)	0.65 (0.38–1.11)	0.64 (0.38–1.10)	0.046	1.00 (ref.)	1.19 (0.89–1.61)	0.95 (0.69–1.30)	1.06 (0.78–1.45)	0.91
Green leaf vegetables										
Median (g/day)	Q1. 8.4 g	Q2. 16.8 g	Q3. 26.8 g	Q4.46.9 g		Q1. 8.4 g	Q2. 18.0 g	Q3. 29.4 g	Q4.52.2 g	
Number of cases	29	30	30	26		70	93	80	94	
Age-area adjusted	1.00 (ref.)	0.96 (0.57–1.61)	0.94 (0.56–1.58)	0.76 (0.45–1.31)	0.33	1.00 (ref.)	1.27 (0.93–1.73)	1.05 (0.76–1.45)	1.19 (0.87–1.63)	0.56
Multivariable adjusted[a,c]	1.00 (ref.)	0.97 (0.95–1.63)	0.95 (0.57–1.60)	0.78 (0.45–1.34)	0.38	1.00 (ref.)	1.28 (0.94–1.75)	1.06 (0.77–1.47)	1.22 (0.89–1.68)	0.47
Yellow vegetables										
Median (g/day)	Q1. 14.3 g	Q2. 30.7 g	Q3. 51.8 g	Q4. 95.7 g		Q1. 15.3 g	Q2. 35.6 g	Q3. 61.2 g	Q4. 111.8 g	
Number of cases	23	28	30	34		76	82	90	89	
Age-area adjusted	1.00 (ref.)	1.22 (0.70–2.12)	1.26 (0.73–2.17)	1.35 (0.79–2.31)	0.29	1.00 (ref.)	1.07 (0.78–1.46)	1.18 (0.87–1.60)	1.15 (0.85–1.57)	0.29
Multivariable adjusted[a,c]	1.00 (ref.)	1.21 (0.69–2.22)	1.27 (0.73–2.22)	1.38 (0.79–2.40)	0.27	1.00 (ref.)	1.07(0.78–1.46)	1.18 (0.87–1.61)	1.15 (0.83–1.57)	0.32
Tomatoes products										
Median (g/day)	Q1. 2.0 g	Q2. 6.9 g	Q3. 19.0 g	Q4. 58.2 g		Q1. 1.6 g	Q2. 7.5 g	Q3. 24.0 g	Q4. 69.2 g	
Number of cases	31	23	28	33		87	73	91	86	
Age-area adjusted	1.00 (ref.)	0.78 (0.45–1.35)	0.90 (0.53–1.52)	0.98 (0.59–1.61)	0.94	1.00 (ref.)	0.83 (0.61–1.13)	1.02 (0.76–1.38)	0.96 (0.71–1.29)	0.9
Multivariable adjusted[a,c]	1.00 (ref.)	0.78(0.45–1.35)	0.87(0.51–1.49)	0.97 (0.58–1.64)	0.97	1.00 (ref.)	0.81 (0.59–1.11)	0.99 (0.73–1.34)	0.91 (0.67–1.24)	0.87
Citrus fruits (without orange juice)										

Table 3 continued

Consumption	Premenopausal (n = 10,527 115 cases)					Postmenopausal (n = 36,762 337 cases)				
Food group	Ref	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)	p_{trend}	Ref	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)	p_{trend}
Median (g/day)	Q1. 9.8 g	Q2. 37.2 g	Q3. 74.8 g	Q4. 164.9 g		Q1. 12.5 g	Q2. 45.2 g	Q3. 88.1 g	Q4. 194.4 g	
Number of cases	23	25	29	38		81	80	101	75	
Age-area adjusted	1.00 (ref.)	1.19 (0.67–2.11)	1.37 (0.78–2.41)	2.01 (1.16–3.47)	0.010	1.00 (ref.)	1.00 (0.73–1.37)	1.35 (0.99–1.84)	1.06 (0.76–1.48)	0.35
Multivariable adjusted[a,b]	1.00 (ref.)	1.29 (0.72–2.32)	1.58 (0.88–2.84)	2.29 (1.28–4.10)	0.0036	1.00 (ref.)	1.02 (0.74–1.40)	1.38 (1.01–1.88)	1.08 (0.77–1.52)	0.30
Multivariable adjusted[a,b,d]	1.00 (ref.)	1.23 (0.68–2.23)	1.45 (0.79–2.65)	1.87 (0.95–3.69)	0.0645	1.00 (ref.)	1.02 (0.74–1.41)	1.40 (1.01–1.93)	1.12 (0.74–1.67)	0.23

[a] Multivariable Cox proportional hazards models were adjusted for age time-scales, area (10), height (<148, 148–151.9,152–154.9, ≥155 cm), recent BMI (<18.5, 18.5–23.9, ≥24, missing), BMI at age 20 years (<20, 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), menopausal status (premenopause, age at 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 (past drinker, never-drinker, occasional drinker, regular drinker ≤150, or >150 g of ethanol per week), total energy-adjusted intake of isoflavones (continuous), and vitamin C supplement (use or non-use)

[b] Additionally included total energy-adjusted intake of vegetables (continuous)

[c] Additionally included total energy-adjusted intake of fruits (continuous)

[d] Additionally included total energy-adjusted intake of vitamin C (continuous)

and the study-specific risk estimates suggested the opposite direction against the pooled result for the 20 studies [15]. Further, the observed favorable impact we saw against ER+ PR+ tumors was attributable to the intake of cruciferous vegetables, in particular Japanese radish, which was not taken into account in the pooled study. Further, consistent with previous results [27], our results for a substantial preventive impact of cruciferous vegetables against overall and ER+ PR+ breast cancer was confined to premenopausal women, who had a higher level of endogenous female hormones than postmenopausal women. Cruciferous vegetables contain glucosinolates, which are hydrolysed to isothiocyanates and indoles. Experimental and epidemiological studies suggest their potential to decrease breast cancer risk by inhibiting cell growth, inducing apoptosis [10] and affecting hormonal level through the hormone- and/or ER-related mechanism [28–30]. Our present results for ER+ PR+ tumors might support this hormone-related mechanism. Further epidemiological and experimental studies should be conducted in consideration of ER/PR status.

With regard to citrus fruits intake, we unexpectedly observed a positive association between citrus fruit intake and risk of overall and ER+ PR− tumors. Previous studies had reported inverse associations for ER− [11], for ER+ [13], and for both ER+ PR+ and ER+ PR− [12]. The results of sub-analyses for ER/PR tumors might be due to chance, because of the relatively small number of cases. For the overall results, however, a recent systematic review of five case–control studies [31] and a case–control study, the Shanghai Breast Cancer Study [32], also reported an inverse association between citrus fruits intake and breast cancer risk. Unlike these studies, our results showed a positive association overall. The quantity of citrus fruits intake in the highest quartile (Q4) was 188.5 g/day (median) in our study, while that in the highest quintile (Q5) of the Shanghai study was 30.4 g/day. Our data suggest that citrus fruits intake is correlated with vitamin C intake and that women taking supplemental vitamin C had a substantially higher risk than women who did not. Given these results, the association between citrus fruits intake and breast cancer risk might be explained by a U- or J- shaped relationship. That is, the appropriate amount of citrus fruits intake leads to risk reduction, while an extremely high intake might lead to an increased risk of breast cancer due to the extremely high dose of vitamin C. The dose-response impact of vitamin C on the development of breast cancer requires further research.

The strength of our study is its large sample size and prospective population-based cohort design. Exposure information was collected before diagnosis, ruling out the possibility of differential recall bias. Misclassification of disease was also unlikely due to the low percentages of

Table 4 Age-area adjusted relative risks (RRs) and 95 % confidence intervals (CIs) for the association between fruits, vegetables and ER/PR defined breast cancer risk in the Japan Public Health Center-based Prospective Study, 1995–2007

Variable	All ($n = 47,289$)				
ER/PR subtypes	All	ER+ PR+	ER+ PR−	ER− PR−	ERPR unknown
Number of cases	452	105	51	61	228
Food group	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)	RR (95 % CI)
Total fruit and vegetables	1.01 (0.97–1.04)	0.99 (0.91–1.07)	1.07 (0.97–1.19)	0.99 (0.89–1.10)	0.99 (0.94–1.05)
Fruits	1.03 (0.98–1.08)	1.04 (0.94–1.15)	1.12 (0.99–1.26)	1.02 (0.88–1.18)	0.99 (0.91–1.06)
Vegetables	0.97 (0.91–1.04)	0.89 (0.77–1.04)	1.04 (0.87–1.25)	0.93 (0.76–1.13)	1.00 (0.91–1.10)
Cruciferous vegetables	0.88 (0.73–1.06)	0.64 (0.41–1.00)	0.86 (0.49–1.50)	0.88 (0.53–1.47)	0.97 (0.77–1.24)
Green leaf vegetables	0.90 (0.61–1.31)	0.70 (0.30–1.61)	1.56 (0.67–3.65)	0.79 (0.27–2.31)	0.89 (0.52–1.54)
Yellow vegetables	1.11 (0.97–1.27)	1.11 (0.85–1.44)	1.22 (0.95–1.58)	1.12 (0.78–1.59)	1.08 (0.87–1.33)
Tomatoes products	1.05 (0.88–1.26)	0.62 (0.34–1.12)	1.15 (0.84–1.58)	1.07 (0.69–1.68)	1.15 (0.95–1.39)
Citrus fruits (without orange juice)	1.04 (0.95–1.13)	0.98 (0.79–1.20)	1.20 (1.01–1.42)	1.01 (0.76–1.33)	0.99 (0.87–1.12)

Unit (100 g/day)

[a] Cox proportional hazards models were adjusted for age time-scales and area (10). Multivariable adjusted model was not applied due to the small number of cases by ER/PR tumors subtype

DCN and DCO. Given the reasonable validity of fruit and vegetable intake, as measured by Spearman correlation coefficients between the FFQ and DR [33], as well as the consistency of the null results in the present and previous studies, the overall null association for total fruits and vegetables might be factual.

Several limitations should also be noted. One limitation is the small number of cases after stratification by tumor subtype and/or menopausal status. The lack of statistical power should be considered when interpreting the results. Dietary and other epidemiological information were assessed based on self-reported questionnaires, and measurement error was accordingly unavoidable. Although the FFQ-based fruits/vegetables intake was calculated using a purpose-developed database [34], some degree of seasonal, geographical and cultivational variation in micronutrient contents in food products might not be completely ruled out [35]. Our observed null association might be attributable to non-differential misclassification of exposure in prospective study design. The possibility of uncontrolled confounding and statistical chance finding due to multiple testing should also be considered.

In summary, our results do not support that the risk of breast cancer is decreased with increased consumption of total or any other subgroup of fruits and vegetables. For premenopausal women, however, our results suggest a substantial preventive association between cruciferous vegetable intake and breast cancer risk.

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Conflict of interest The authors declare no conflict of interest related to this manuscript.

Appendix

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