Physical exercise reduces risk of breast cancer in Japanese women

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To evaluate the effects of physical exercise on breast cancer risk, a large-scale case-referent study of 2376 incident breast cancer cases and 18 977 non-cancer referents was conducted using data from the hospital-based epidemiologic research program at Aichi Cancer Center (HERPACC). To adjust appropriately for possible confounders, we examined the effects within subgroups of the study population. The multivariable-adjusted odds ratio (OR) was 0.81 (95% confidence interval (CI): 0.69–0.94) for twice a week or more regular exercise. We observed a decreased risk of breast cancer for women who regularly exercised for health twice a week or more, irrespective of menopausal status, and were able to detect greater risk reductions within particular subgroups, including women who were parous, without a family history or non-drinkers. Among premenopausal women, a particularly strong protective effect of physical exercise was observed (OR=0.57, 95%CI: 0.28–1.15) for those women whose body mass index (BMI) was high (BMI≥25). In contrast, risk reduction was found (OR=0.71, 95%CI: 0.50–1.01) among postmenopausal women whose BMI was medium (BMI: 22–25). Stratification of history of stomach cancer screening to adjust modifying effects of healthy consciousness allows a more precise assessment of the protective effect of exercise twice a week or more, independent of stomach cancer screening history. This study provides evidence that physical exercise, especially exercise twice a week or more, reduces the risk of breast cancer among Japanese women. (Cancer Sci 2003; 94: 193–199)

Increasing physical exercise might be a realistic approach toward primary prevention of breast cancer because it is one of the few known modifiable, protective factors. Among the potential underlying mechanisms which have been discussed are reduction in endogenous steroid exposure, alteration in menstrual cycle patterns, delay of age at menarche, increased energy expenditure and reduction in body weight, changes in insulin-like and other growth factors, and enhancement of natural immune mechanisms.[1]

Although evidence for an inverse association between physical exercise and breast cancer has accumulated rapidly, the epidemiologic data are not unequivocal. While some have shown clear protection,[2–10] others have revealed only weak and often non-significant associations[11, 12] or no link at all.[13–16] It is not easy to assess exposure to all types of physical activity over the long-term because of the division into occupational, household, and recreational. Inconsistencies across studies may be attributable to error in the measurement of frequency, intensity and duration of physical activity. In addition, several other factors may modify any effects on breast cancer risk.

Since influence may be more evident in studies which control appropriately for possible confounders, we examined effects within subgroups of a study population, focusing in particular on differences in impact for breast cancer between high- and low-risk groups in Japan.

Materials and Methods

Data collection. Since 1988, we have conducted the hospital-based epidemiologic research program at Aichi Cancer Center (HERPACC) study, in which a self-administered questionnaire survey is completed by first-visit outpatients to the Aichi Cancer Center Hospital. All questionnaires are then collected after checking for incomplete responses by a trained interviewer and the data are loaded into the computer system of the Aichi Cancer Center Research Institute. Details of the questionnaire and data collection procedures have been described elsewhere.[17–22)]

Of all the first-visit outpatients, totaling 91 870 between January 1988 and December 2000, 8228 were excluded due to interviewer absence, age exclusion (younger than 18 years old), or a visit only for consultation. The questionnaire was ultimately administered to 83 642 patients. Among these, 82 553 (98.7%) completed the questionnaire adequately.

The questionnaire featured items on occupation, medical history, height, weight and weight at around 20 years of age (added since 1989), marital status, family history (parents and siblings), smoking and drinking habits, dietary habits, sleeping habits, physical activity, bowel habit and reproductive history. Questions on socioeconomic status and education level were not included, because Japanese are, in general, rather reluctant to answer such questions. The details were taken, prior to assessment of symptoms, and all information was collected before diagnoses were made.

Cases and referents. The data collected were linked with the hospital-based cancer registry files. The present analysis was restricted to women aged 30 and older who visited the Aichi Cancer Center Hospital between January 1989 and December 2000. Patients without information on menopausal status and those with no menstruation due to surgery or other causes were excluded. Among 8910 female cancer patients, 2376 women who were first diagnosed within 6 months of the first visit as having breast cancer confirmed by histological examination were recruited as the case group. In this analysis, non-cancer patients recommended after cancer screening and/or referred to our hospital by a physician were excluded because they were investigated for suspicion of cancer and might be substantially different from the general population. Finally, 18 977 female first-visit outpatients who had never been diagnosed as having cancer were recruited as the referents. Table 1 shows the age distribution of the study subjects according to the exercise level.

Statistical analysis. Logistic regression analysis was used to obtain odds ratios (ORs) and 95% confidence intervals (95%CI) as estimates of relative risk. Four categories of physical exercise level (none, occasional, three or four times per month and two or more times per week) were used for analysis. To determine the impact of exercise for health on established risk factors for breast cancer, ORs and 95%CIs were calculated separately for subgroups of women for which different breast cancer risks may exist.

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Family history may involve different types and numbers of relatives, i.e., distant relatives share less genetic information and fewer confounding environmental and/or behavioral factors than do close ones. Furthermore, information on breast cancer history of distant relatives is limited and less precise than that of close or first-degree relatives. In this study, the presence of either a mother or sister with breast cancer was therefore considered as a positive family history.

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2), according to Quetelet's formula. Data on current BMI were stratified into three categories. Since a BMI≥25 is defined as obese by the Japanese Society for the Study of Obesity, we set the top category for current BMI at ≥25.

Possible effect modification by menopausal status, age at menarche, parity, family history, drinking and greater BMI was examined, since these factors have been identified previously as established risk factors or have been suggested as possible effect modifiers.[23)]

Results

Table 1 shows the distribution of age and exercise status for the cancer cases and the non-cancer referent group. Compared with the referent group, cases were relatively old and were less likely to have undertaken regular exercise for health.

From the cross analysis between frequency of exercise and other selected factors among non-cancer referents, more frequent exercise was associated with consuming more fruit, raw vegetables and milk (Table 2). The proportion of physically active women is much higher among daily current smokers (≥10 cigarette per day) than non-smokers. Among referents with dietary restriction, the proportion of twice a week or more regular exercise was 19.7% and the figure of referents without dietary restriction was much lower (11.5%). Compared with women without experience of stomach cancer screening, women with history of stomach cancer screening were more likely to report regular exercise. To control potential confounding for exercise-related factors a multivariate analysis was used that included drinking, intake of fruit, dietary restriction and experience of stomach cancer screening.

Evidence for a trend in decreasing risk with increasing frequency of exercise for health was found. The multivariable-adjusted OR was 0.81 (95%CI: 0.69–0.94) for twice a week or more (Table 3). Risk reduction was similarly observed in each age group. The multivariable-adjusted risk associated with twice a week or more regular exercise among premenopausal women was 0.80 (95%CI: 0.64–1.00); for postmenopausal women, it was 0.85 (95%CI: 0.69–1.04) (Table 3).

Regarding influence among low- and high-risk groups of breast cancer, controlling for exercise-related factors, women with a later age at menarche (≥14) in the highest activity group had a risk of 0.82 (95%CI: 0.67–0.99), while it was 0.81 (0.64–1.01) for those with an early age at menarche (<14) (Table 4). There was a risk decrease among parous women (Table 4), the multivariable-adjusted OR being 0.79 (95%CI: 0.67–0.93). There was no such statistical trend among nulliparous women. When the risk was examined specifically by family history of breast cancer, there was a greater risk decrease among women

Table 1. Distribution and characteristics of breast cancer cases and referents according to age, exercise for health and other related factors (HERPACC DATA: 1989–2000)

	Cases		Referents	
	No.	(%)	No.	(%)
Age				
30–39	297	12.5	4380	23.1
40–49	905	38.1	6740	35.5
50–59	626	26.4	4494	23.7
60–69	402	16.9	2486	13.1
70–79	138	5.8	845	4.5
80+	8	0.3	32	0.2
Total	2376	(100%)	18977	(100%)
Age (years) (mean (SD[1)]))	51.2 (10.6)		48.4 (11.1)	
Frequency of exercise for health				
None	1358	57.2	10731	56.6
Occasional	540	22.7	4107	21.6
3–4 times/month	173	7.3	1462	7.7
≥2 times/week	305	12.8	2677	14.1
Total	2376	(100%)	18977	(100%)
Other related factors				
Age at menarche (years) (mean (SD))	13.7 (1.7)		13.8 (1.7)	
Age at menopause (years) (mean (SD))	50.5 (3.3)		50.0 (3.5)	
No. of live births (mean (SD))	2.2 (0.8)		2.2 (0.8)	
Age at first full-term pregnancy (years) (mean (SD))	25.8 (3.6)		25.4 (3.3)	
Height (cm) (mean (SD))	154.6 (5.2)		154.6 (5.5)	
Weight (kg) (mean (SD))	53.8 (7.8)		52.5 (7.4)	
BMI[1)] (kg/m^2) (mean (SD))	22.5 (3.1)		22.0 (2.9)	
Marriage (never/ever)	147/2147		1023/17319	
Parity (nulliparous/parous)	256/2118		1820/17157	
Menopausal status (premenopause/postmenopause)	1334/1024		11988/6989	
Housewife (%)	44.2		42.6	
Family history (mother or sister) of breast cancer (%)	6.6		4.3	

1) SD, standard deviation; BMI, body mass index.

without a family history (Table 4). There was little difference in the risk of breast cancer for level of exercise among subgroups of the women stratified by drinking status. Non-drinkers taking twice a week or more regular exercise had an adjusted risk of 0.81 (95%CI: 0.68–0.95) and the corresponding OR was 0.73 (95%CI: 0.49–1.08) for current drinkers.

Regarding BMI level, since menopausal status was identified as a modifier of body size, data were stratified by menopausal status to evaluate the impact of physical exercise. Among premenopausal women, strong effects of physical exercise were observed for those women whose BMI was high (OR=0.57, 95%CI: 0.28–1.15). In contrast, risk reduction was found among postmenopausal women whose BMI was medium (OR=0.71, 95%CI: 0.50–1.01) (Table 5).

We were concerned about the inverse association between history of stomach cancer screening and breast cancer risk as shown in Table 2. People with a healthy lifestyle (like healthy exercise) may focus on obtaining good medical care including cancer screening, and therefore, we examined the protective effect of exercise within subgroups of stomach cancer screening history. The multivariate OR for the category of twice a week or more regular exercise was 0.72 (95%CI: 0.57–0.92) for without screening history, or 0.89 (95%CI: 0.73–1.07) for with screening history (Table 6). Although the inverse association was weaker among those with a stomach cancer screening history, we observed a decreased risk of breast cancer for women who regularly exercised for health twice a week or more, independent of stomach cancer screening history.

Table 2. Comparison of frequency for general lifestyle factors related to health consciousness among referents (non-cancer patients) according to exercise status and ORs and 95%CI for breast cancer (HERPACC DATA: 1989–2000)

Life style factor	Exercise for health (%) among referents				OR (95%CI) for breast cancer
	None	Occasional	3–4/month	≥2/week	
Smoking					
None	14.7	7.9	21.9	55.6	1 (ref.)
Quit	13.0	7.6	20.2	59.2	0.94 (0.73–1.22)
Daily (<10 cigarettes/day)	12.8	8.5	25.4	53.3	1.09 (0.88–1.35)
Daily (≥10 cigarettes/day)	10.2	6.2	19.6	64.0	1.12 (0.97–1.30)
Drinking					
None	57.7	21.5	7.1	13.7	1 (ref.)
Quit	58.4	24.1	4.1	13.4	0.92 (0.65–1.30)
Daily (<1 go[1)])	51.6	20.1	11.3	17.0	1.10 (0.92–1.32)
Daily (≥1 go)	57.6	19.2	8.7	14.5	1.39 (1.15–1.67)
Fruit intake					
≤3–4 times/week	62.5	20.2	6.9	10.4	1 (ref.)
Daily	49.4	23.4	8.6	18.6	0.88 (0.80–0.96)
Raw vegetable intake					
≤3–4 times/week	61.1	20.3	6.9	11.6	1 (ref.)
Daily	49.3	23.8	8.9	18.0	0.92 (0.85–1.01)
Milk intake					
None, occasional	61.6	20.4	7.0	11.0	1 (ref.)
Daily	51.0	23.0	8.5	17.6	0.87 (0.80–0.95)
Dietary restriction					
No	60.4	20.4	7.8	11.5	1 (ref.)
Yes	48.3	24.4	7.6	19.7	0.79 (0.72–0.87)
Salty food					
Dislike	54.0	22.1	8.6	15.4	1 (ref.)
Like	58.2	21.4	7.2	13.3	0.94 (0.86–1.03)
Fatty food					
Dislike	55.2	22.4	7.7	14.7	1 (ref.)
Like	58.0	20.8	7.7	13.5	1.01 (0.92–1.10)
Volume of food intake					
Small	56.6	21.9	7.5	14.0	1 (ref.)
Large	56.5	21.7	7.9	14.0	1.02 (0.94–1.12)
History of stomach cancer screening					
No	60.7	21.5	6.9	10.9	1 (ref.)
Yes	53.8	21.7	8.2	16.3	0.64 (0.59–0.70)

OR, odds ratio; CI, confidence interval.
1) The unit of Japanese sake (1 go is equivalent to 180 ml and contains 28.8 ml of neat alcohol).

Table 3. Multivariable adjusted ORs and 95%CI for breast cancer according to the level of exercise (HERPACC DATA: 1989–2000)

Exercise	None	Occasional	3–4 times/mo	≥2 times/wk	*P* for trend
		OR (95%CI)	OR (95%CI)	OR (95%CI)	
All women	1 (ref.)	0.97 (0.86–1.10)	1.01 (0.83–1.21)	0.81 (0.69–0.94)	0.015
Age (years)					
<50	1 (ref.)	0.93 (0.78–1.11)	1.07 (0.84–1.38)	0.82 (0.64–1.04)	0.201
50–59	1 (ref.)	1.02 (0.81–1.28)	1.02 (0.70–1.47)	0.81 (0.61–1.07)	0.211
≥60	1 (ref.)	1.04 (0.81–1.33)	0.80 (0.50–1.28)	0.83 (0.63–1.09)	0.137
Menopausal status					
Premenopausal	1 (ref.)	0.95 (0.81–1.13)	1.06 (0.83–1.34)	0.80 (0.64–1.00)	0.129
Postmenopausal	1 (ref.)	1.02 (0.86–1.22)	0.95 (0.70–1.30)	0.85 (0.69–1.04)	0.131

OR, odds ratio; CI, confidence interval.
Estimates from multiple logistic regression, including (when appropriate) age, visit year, menopausal status, age at menarche, family history, parity, age at first full-term pregnancy, drinking, intake of fruit, dietary restriction, history of stomach cancer screening, body mass index and occupation.

Table 4. Multivariable adjusted ORs and 95%CI for breast cancer according to the level of exercise (HERPACC DATA: 1989–2000)

Frequency of exercise	Cases (No.)	Referents (No.)	Multivariable adjusted[1) OR (95%CI)	Cases (No.)	Referents (No.)	Multivariable adjusted[1) OR (95%CI)
Menarche			Age≥14			Age<14
None	672	5478	1.00	677	5216	1.00
Occasional	273	2191	0.98 (0.83–1.16)	265	1895	0.97 (0.81–1.16)
3–4 times/mo	73	694	0.97 (0.74–1.29)	100	761	1.05 (0.81–1.36)
≥2 times/wk	169	1498	0.82 (0.67–0.99)	134	1166	0.81 (0.64–1.01)
P value for trend			0.070			0.136
Parity			Parous			Nulliparous
None	1179	9426	1.00	178	1305	1.00
Occasional	458	3538	0.98 (0.86–1.11)	82	569	0.95 (0.69–1.31)
3–4 times/mo	152	1268	1.02 (0.84–1.25)	20	194	0.89 (0.52–1.54)
≥2 times/wk	259	2347	0.79 (0.67–0.93)	46	330	0.93 (0.62–1.39)
P value for trend			0.015			0.648
Family history			Without family history			With family history
None	1273	10289	1.00	85	442	1.00
Occasional	502	3918	0.97 (0.86–1.10)	38	189	0.97 (0.61–1.56)
3–4 times/mo	161	1397	1.03 (0.84–1.25)	12	65	0.76 (0.35–1.66)
≥2 times/wk	284	2562	0.81 (0.69–0.94)	21	115	0.85 (0.47–1.52)
P value for trend			0.021			0.472
Drinking			Non-drinker			Current drinker
None	978	7705	1.00	169	1100	1.00
Occasional	372	2874	0.97 (0.85–1.11)	60	403	0.99 (0.71–1.37)
3–4 times/mo	121	941	1.09 (0.88–1.33)	21	206	0.70 (0.43–1.14)
≥2 times/wk	215	1828	0.81 (0.68–0.95)	38	324	0.73 (0.49–1.08)
P value for trend			0.047			0.062

OR, odds ratio; CI, confidence interval.
1) Estimates from multiple logistic regression, including (when appropriate) age, visit year, age at menarche, menopausal status, family histoy, parity, age at first full-term pregnancy, drinking, intake of fruit, dietary restriction, history of stomach cancer screening, body mass index and occupation.

Discussion

Before drawing conclusions from the present study, certain potential limitations should be considered. One methodological issue is possible bias due to use of hospital-based non-cancer patients as referents. It is possible that there are discrepancies in characteristics as compared to those of the general population. In Japan, outpatients, in general, visit hospitals directly when they have symptoms and/or anxiety about their health. This situation is very different from that in the US, where people visit local general clinics first, and are then referred to hospitals which function as secondary and/or specific facilities for

Table 5. Multivariable adjusted ORs and 95%CI for breast cancer risk according to the level of exercise by body mass index and menopausal status (HERPACC DATA: 1989–2000)

Frequency of exercise	Low BMI (BMI<22)			Medium BMI (BMI: 22–25)			High BMI (BMI≥25)		
	Referents		Multivariable adjusted[1)]	Referents		Multivariable adjusted	Referents		Multivariable adjusted
	No.	(%)	OR (95%CI)	No.	(%)	OR (95%CI)	No.	(%)	OR (95%CI)
Premenopausal women									
None	4399	60.1	1.00	1988	58.7	1.00	757	61.6	1.00
Occasional	1500	20.5	0.89 (0.71–1.11)	730	21.6	1.01 (0.75–1.37)	247	20.1	1.10 (0.68–1.76)
3–4 times/mo	645	8.8	1.09 (0.81–1.49)	274	8.1	1.09 (0.71–1.69)	86	7.0	0.66 (0.29–1.54)
≥2 times/wk	771	10.5	0.75 (0.55–1.02)	393	11.6	1.01 (0.69–1.48)	139	11.3	0.57 (0.28–1.15)
P value for trend			0.160			0.843			0.110
Postmenopausal women									
None	1587	51.0	1.00	1232	48.6	1.00	693	54.4	1.00
Occasional	689	22.2	1.14 (0.85–1.53)	616	24.3	0.89 (0.66–1.19)	302	23.7	1.11 (0.79–1.55)
3–4 times/mo	209	6.7	0.89 (0.53–1.50)	168	6.6	1.04 (0.64–1.69)	72	5.7	0.94 (0.49–1.81)
≥2 times/wk	626	20.1	1.02 (0.74–1.41)	518	20.4	0.71 (0.50–1.01)	208	16.3	0.83 (0.55–1.24)
P value for trend			0.989			0.088			0.405

OR, odds ratio; CI, confidence interval.
1) Adjusted for age, visit year, age at menarche, family history, parity, age at first full-term pregnancy, drinking, intake of fruit, dietary restriction, history of stomach cancer screening and occupation.

Table 6. Adjusted ORs and 95%CI for breast cancer in relation to exercise level stratified by stomach cancer screening history (HERPACC DATA: 1989–2000)

Frequency of exercise	Without screening history				With screening history			
	Cases	Referents	OR1[1)] (95%CI)	OR2[2)] (95%CI)	Cases	Referents	OR1 (95%CI)	OR2 (95%CI)
None	698 (61.0)	4660 (60.7)	1.00	1.00	657 (53.5)	6068 (53.8)	1.00	1.00
Occasional	256 (22.4)	1651 (21.5)	0.97 (0.83–1.13)	0.92 (0.78–1.10)	284 (23.1)	2452 (21.7)	1.00 (0.86–1.16)	1.03 (0.87–1.22)
3-4 times/mo	72 (6.3)	529 (6.9)	0.95 (0.73–1.24)	0.93 (0.69–1.26)	101 (8.2)	930 (8.2)	1.00 (0.80–1.25)	1.07 (0.83–1.36)
≥2 times/wk	119 (10.4)	840 (10.9)	0.73 (0.59–0.91)	0.72 (0.57–0.92)	186 (15.2)	1835 (16.3)	0.82 (0.69–0.97)	0.89 (0.73–1.07)
Total	1145 (100%)	7680 (100%)			1228 (100%)	11285 (100%)		
P value for trend			0.009	0.011			0.047	0.363

OR, odds ratio; CI, confidence interval.
1) Adjusted age and visit year.
2) Estimates from multiple logistic regression, including age, visit year, age at menarche, menopausal status, family history, parity, age at first full-term pregnancy, drinking, intake of fruit, dietary restriction, body mass index and occupation.

further medical treatment. At the Aichi Cancer Center Hospital, we found incident cancer cases to comprise only 16% of all new female outpatients. Among randomly sampled non-cancer outpatients (n=1000) in 1988–1989, only 34% were found to have specific diseases, the most common being benign tumors and/or non-neoplastic polyps (13.1%), mastitis (7.5%), digestive disease (4.1%), benign gynecological disease (4.1%) and so on.[21)] To compare lifestyle characteristics between outpatients and the general population, we conducted a study that included 1231 subjects randomly selected from the Nagoya electoral roll. It was concluded that, with due consideration of age, sex, and season in the analysis, it is feasible to use non-cancer outpatients as referents in epidemiological studies.[22)]

The present study was free of response information bias to the questionnaire, because all data were collected prior to diagnoses. Eligible referents were not matched, because our previous study showed that a large number of outpatients give a steadier estimate.[24)]

The most important methodological issue in the present study was the lack of techniques to measure individuals exercise levels. Currently, the questionnaire is the most widely used measurement method for assessing physical activity in study populations, but many of them are complex and insufficient. It is not easy to assess exposure level to all types of physical activity, e.g., occupational, household and recreational, over the long-term. Furthermore, perceptions of time and intensity of physical activity may also be subjective and individuals may not be able to recall physical activity exactly, especially if they are asked to recall physical activities in several previous years or decades. Simplicity of the questionnaire is indispensable in a large-scale epidemiological study to collect data on many factors, including physical activity. Although the validity and reliability of our HERPACC questionnaire were not investigated as regards physical activity, The Japan Collaborative Cohort Study Group reported that measuring physical activity level with single-item questions may be appropriate for establishing baseline data that reflect long-term physical activity in a large-scale cohort study targeting lifestyle-related diseases.[25)] Therefore, we used a single item in the present questionnaire as an index for physical activity level.

Despite these limitations, we observed a decreased risk of breast cancer for women who regularly exercised for health twice a week or more. We were able to detect greater risk reductions within particular subgroups of the population, including women who were parous, without a family history or nondrinkers. In general, persons performing regular exercise are concerned about maintaining their health, and they usually contrive to have an appropriate lifestyle. Therefore, we should note the net effects of regular exercise with other health-promoting factors with regard to cancer.

The literature regarding the influence of parity and exercise on breast cancer risk are inconsistent. Some studies have found greater risk reductions for parous[6, 26, 27)] or nulliparous[10, 28)] women, while others have found no difference across strata for parity.[29)] In this investigation, we observed risk reduction with exercise twice a week or more among parous but not nulliparous women.

Our study revealed a protective effect for women without a family history. Conversely, Verloop *et al.*[10)] reported that women with a family history of breast cancer who were the most physically active experienced a larger risk reduction than the women without family history. A case-control study in Canada did not detect any modification by family history.[3)]

There have been few reports of any effect modification by drinking status. In the present case, protective effects of exercise were evident among non-drinker and current drinker groups, although statistical significance was lacking for the latter. Some epidemiologic studies have shown a positive association between alcohol consumption and breast cancer risk.[30)] However, the drinking habit would not be expected to be a major risk factor in Japan because the proportion of female drinkers, especially in the older generation, is very small and the amount of alcohol actually consumed is much lower than in Western countries. Our study included only a small number of cases in the current drinker group, so stable risk estimates could not be provided. Before any conclusions can be drawn about the possible influence of drinking on the relation between physical activity and breast cancer risk, further studies are needed.

One of the most important confounding variables in the association between breast cancer and physical activity is body mass. If physically active women are at decreased risk for breast cancer, is it a result of physical activity itself or is it a result of less body mass because of a physically active lifestyle? Links between breast cancer and BMI have been extensively studied, and negative correlations among premenopausal women and positive correlations among postmenopausal women have been the predominant findings.[31–33)] In the present study there was a decreased risk with frequency of exercise among premenopausal women whose BMI was high. On the other hand, no similar risk reduction was observed among postmenopausal obese women despite opponent protection in postmenopausal women with medium BMI level. This might imply that physical activity reduces premenopausal body weight and controls weight gain after menopause, which is known to be associated with breast cancer risk. In some studies, greater risk reductions for active women have in fact been observed for those women whose BMI was low,[9, 10, 34)] while other studies observed the risk to decrease more clearly with obese subjects.[28, 34)] Although there is thus no consistency regarding modification by BMI, it is biologically plausible that physical activity might reduce the risk of breast cancer by decreasing abdominal adiposity. Whatever the case, discussion of body mass in the prevention of breast cancer is important, as it may be the only risk factor that women can readily control.

Although we used a multivariate analysis that included the exercise-related factors, we were unable to adjust for other remaining behaviors, such as caloric intake and maintenance of a healthy lifestyle. Physical activity is a very complex behavior that interacts with other behaviors. Women who take regular exercise were more likely to report dietary restriction and to take part in cancer screening programs. Physically active people in general may practice other healthy lifestyle habits. Therefore, we were concerned that stomach cancer screening history might influence breast cancer indirectly. Stratification of history of stomach cancer screening to adjust the modifying effects of health consciousness allows a more precise assessment of protective effect of exercise twice a week or more, independent of stomach cancer screening history. This result suggested that physical activity could affect breast cancer risk either indirectly through correlated factors or through real biological mechanisms. Several hypothesized mechanisms have been described for the prevention of breast cancer by physical activity[35, 36)]: 1) maintenance of low body fat and moderation of extraglandular estrogen, 2) reduction in number of ovulatory cycles and subsequent diminution of lifetime exposure to endogenous estrogen, 3) enhancement of natural immune function. Although the mechanisms are not well defined, several lines of evidence support the inclusion of low-to-moderate physical activity as a preventive strategy for breast cancer. Physical activity can be self-motivated and self-directed, and can be accomplished with little to no expenditure on equipment.

In summary, the present study confirmed that physical activity, especially exercise for health twice a week or more, reduces the risk of breast cancer. The reduction was particularly notable for parous women, for women without a family history, for non-drinkers, for premenopausal obese women and slightly overweight postmenopausal women. Although the protective effect of physical exercise was restricted to low-risk groups for breast cancer in the present study, our findings may aid preventive measures in Japan. Because primary prevention of breast cancer is currently constrained by the fact that most established risk factors for the disease are not readily modifiable, it is encouraging that physical activity, which is amenable to change through personal choice, may reduce risk. Furthermore, there is a need to develop techniques to measure the type of physical activity (occupational, household and recreational) over the entire lifetime, and other parameters (frequency, intensity and duration). Clearly further studies are needed to define the optimal duration and level of regular exercise for breast cancer prevention in heterogeneous populations.

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