論文名	Physical activity, white blood cell count, and lung cancer risk in a prospective cohort study
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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	43-86歳	[redacted]		( )		前向き研究
	対象数	1000～5000			( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	な し	な し	ガン予防	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表

Table 2. HR and 95% CI of lung cancer according to physical activity levels and inflammatory markers

	No. cases	Person-years*	HR (95% CI)†	P_{trend}†	HR (95% CI)‡	P_{trend}‡
Episodes of sweat-inducing activities/wk						
0	105	36,753	1		1	
1-3	10	10,862	0.44 (0.23-0.85)		0.45 (0.23-0.87)	
≥4	19	9,611	0.75 (0.45-1.24)	0.08	0.76 (0.46-1.26)	0.09
City blocks walked/d						
0	73	25,117	1		1	
1-11	44	19,633	0.93 (0.63-1.37)		0.92 (0.62-1.35)	
≥12	17	12,292	0.53 (0.31-0.90)	0.03	0.52 (0.30-0.89)	0.02
Flights of stairs climbed/d						
0-1	44	17,715	1		1	
2-5	60	20,224	1.53 (1.02-2.29)		1.53 (1.02-2.29)	
>5	30	19,254	0.84 (0.52-1.36)	0.58	0.86 (0.53-1.40)	0.67
Total physical activity index (kcal/wk)§						
0-174	65	18,531	1		1	
175-874	38	19,120	0.72 (0.47-1.09)		0.72 (0.48-1.09)	
≥875	31	19,358	0.55 (0.35-0.86)	0.01	0.56 (0.35-0.87)	0.01
Heart rate (30 s)						
21-33	27	12,065	1		1	
34-42	70	33,925	0.93 (0.59-1.46)		0.95 (0.60-1.49)	
>42	37	11,235	1.30 (0.80-2.16)	0.27	1.25 (0.75-2.09)	0.35
WBC tertile ($\times 10^3/\mu L$)						
<6.4	16	19,605	1		—	
6.4-7.9	50	19,421	2.74 (1.53-4.90)		—	
≥8	68	18,019	2.81 (1.58-5.01)	0.001	—	
Albumin tertile (g/dL)						
<4.6	52	19,307	1		—	
4.6-4.8	51	20,321	1.02 (0.69-1.52)		—	
≥4.9	31	17,427	0.85 (0.54-1.34)	0.52	—	

*Total person-years for cases and noncases in category of activity.
†Models are adjusted for age, sex, pack-years of smoking, time since smoking cessation, body mass index, alcohol intake, and education.
‡Models are adjusted for all variables in †, plus WBC count.
§Kilocalories per week from city blocks walked, flights of stairs climbed, and sweat-inducing activities (see Materials and Methods).

図表掲載箇所	P2716, Table2
概 要 (800字まで)	本研究は、アメリカのウィスコンシン州で行われた国民調査に参加した男女4,831名を対象に平均12.8年間の追跡調査を行い、身体活動量と肺がん発症の関連を検討したものである。身体活動については、1日当たり何ブロック(12ブロック=1マイル)歩いているか、1日当たり何度階段を使用するか、1週間当たり汗をかくような身体活動を何回行うかを尋ね、1ブロック/日を56kcal/週、階段1回は28kcal/週、汗をかくような活動1回を266kcalとし、合計消費カロリー数を総身体活動量とした。週当たり12ブロック以上の歩行を行う集団は、全く行わない集団と比較すると、肺がん発症リスクが0.52(95%信頼区間:0.30-0.89)と有意に低下した。汗をかくような活動を週当たり1-3回行う集団で、全く行わない集団と比較すると、肺がん発症リスクが0.45(0.23-0.87)と低下した。また総身体活動量が174kcal/週未満の集団と比較すると、875kcal/週以上で発症リスクが0.56(0.35-0.87)と有意に低下した(Ptrend=0.01)。また、喫煙者で総身体活動量が多い集団で肺がん発症リスクが量反応的に低下し(Ptrend=0.02)、同様に男性で総身体活動量が多い集団で発症リスクが低下した(Ptrend=0.01)。非喫煙者や喫煙経験者、または女性における関連はみられなかった。また、全身性炎症を示すマーカである白血球数が低い集団と比較すると、高い集団で肺がん発症リスクが2.81(1.58-5.01)と量反応的に上昇した(Ptrend=0.001)。
結 論 (200字まで)	アメリカ人コホートにおいて、身体活動量と白血球数は独立して肺がん発症リスクに関連していることが明らかとなった。特に、男性または喫煙者において、肺がんリスクに対する身体活動の保護効果が明らかとなった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に用いられた研究の1つである。肺がんは日本においてがんによる死因の第1位であり、肺がんを予防することは重要な課題である。非喫煙者や女性においては、身体活動と肺がんのリスクとの間に関連は認められなかったものの、喫煙者において、身体活動量が多いものほど肺がんのリスク低下が認められており、特に喫煙者に対する身体活動の奨励を行う重要性が示唆された。

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Leisure-Time Physical Activity in Pregnancy and Risk of Postpartum Depression: A Prospective Study in a Large National Birth Cohort

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Objective: To explore the association between physical activity during pregnancy and postpartum depression (PPD) in a large, prospective cohort.

Method: Exposure information from the Danish National Birth Cohort, a large, prospective cohort with information on more than 100,000 pregnancies (1996–2002), was linked to the Danish Psychiatric Central Register and the Danish Register for Medicinal Product Statistics for data on clinically identified cases of depression up to 1 year postpartum. A total of 70,866 women from the Danish National Birth Cohort were included in the analyses. Duration, frequency, and type of physical activity were assessed by a telephone interview at approximately week 12 of gestation. Admission to hospital due to depression (PPD-admission) and prescription of an antidepressant (PPD-prescription) were treated as separate outcomes.

Results: Through linkage to national registers, we identified 157 cases of PPD-admission and 1,305 cases of PPD-prescription. Women engaging in vigorous physical activity during pregnancy had a lower risk of PPD-prescription compared to women who were not physically active (adjusted odds ratio, 0.81; 95% CI, 0.66–0.99). No association was observed between physical activity and PPD-admission; but, in women who were underweight prior to pregnancy, physical activity was associated with increased risk of PPD-admission.

Conclusions: Our data are compatible with a protective effect of vigorous physical activity, but not for other measures of physical activity, against postpartum depression requiring antidepressant therapy. No protective effect could be detected on PPD leading to hospitalization.

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Depression is an illness of serious public health concern, estimated by the World Health Organization to account for 4.4% of the global burden of disease.[1] Depression in the postpartum period is of particular interest, since it may damage the relationship between mother and child during a period of extraordinary vulnerability, with both short- and long-term consequences.[2–4]

The term *postpartum depression* (PPD) refers to a depressive episode that begins in or extends into the postpartum period[5]; the condition has been estimated to afflict 5% to 15% of all childbearing women.[6,7] There is little evidence that physiologic changes connected to pregnancy and childbirth are the basis for the disorder,[2] and there is some dispute as to whether PPD is a specific psychiatric entity. Some studies have found the incidence of depression postpartum to be the same as in other life periods,[8,9] while others find the rate of onset of depression to be elevated following childbirth.[5,10]

Several studies have shown past psychopathology and low social support to be strongly associated with PPD, while modifiable behavioral factors have not received similar attention. In nonpregnant populations, one such modifiable behavioral factor, physical activity, has been shown to be inversely associated with depression.[11–13] Although findings have not been consistent,[14,15] there seems to be a broad consensus that physical activity is advantageous for general well-being. The purpose of this study was to investigate the association between physical activity during pregnancy and PPD in the Danish National Birth Cohort.

METHOD

The Danish National Birth Cohort is a nationwide study covering 101,046 pregnancies and with more than 90,000 women enlisted. All pregnant women living in Denmark between 1996 and 2002 and fluent in Danish were eligible for recruitment, which took place at the first antenatal visit to the general practitioner, (at roughly weeks 6–10 of gestation). In short, the data collection comprised a recruitment form at inclusion and 4 computer-assisted telephone interviews lasting 10 to 15 minutes, administered at weeks 12 and 30 of gestation and when the child was 6 and 18 months old, roughly. The rate of participation among women who were invited to the study was 60%, and it has been estimated that 35% of all eligible pregnant women entered the cohort, which is described in detail elsewhere.[16,17]

In this study, we primarily used data from the recruitment form and the telephone interview conducted in gestation week 12. Information on admissions to hospital and prescriptions for antidepressants were obtained from the Danish Psychiatric Central Register, which includes all admissions to psychiatric hospitals and to psychiatric wards in general hospitals,[18] and the Register of Medicinal Product Statistics, which contains information on all medicinal products sold by prescription in Denmark.

Measures of Physical Activity

Detailed information on leisure-time physical activity (hereafter referred to as *physical activity*) was obtained from the telephone interview. The women were asked, "Now that you are pregnant, do you engage in any kind of exercise?" and, if they responded positively to this question, they were asked about type, frequency, and duration of each activity session. Answers on type of activity were classified in the following predefined categories: special gymnastics/aerobics for pregnant women, aerobics/gymnastics, dancing, cycling, fast walking, jogging/orienteering, ball games, swimming, use of fitness/health centers, badminton, tennis, horseback riding, and "other" (a text variable for any activities not covered by the predefined types of activity). Women were asked to report walking and bicycling for transport if it made them sweaty and short of breath.

With the purpose of exploring different dimensions of physical activity, we defined 4 different measures of physical activity in our analytic approach based on the information described above.

First, in order to test whether there was an effect of any versus no physical activity on PPD, we categorized women according to the general question on physical activity.

Second, we defined 6 groups according to total time of physical activity to investigate whether increasing duration, regardless of the other dimensions of physical activity, was associated with decreasing risk of PPD.

Third, we categorized women according to the intensity of their physical activity to investigate whether engagement in higher intensity physical activity had an effect on PPD, regardless of duration of activity. Here we made use of the concept of metabolic equivalents (METs [$\text{kcal}\cdot\text{kg}^{-1}$ body $\text{weight}\cdot\text{hour}^{-1}$]), which allows the classification of types of physical activity by rate of energy expenditure. The MET score of a specific type of activity is defined as the ratio between a person's metabolic rate when engaged in that specific activity and the resting metabolic rate. Metabolic equivalent scores range from 0.9 (sleeping) to 18 (running at 10.9 mph).[19] The applied MET scores were our estimation based on the compendium by Ainsworth et al.[20] We defined *vigorously active women* as those reporting at least 25% of their total time in physical activity to be spent in activity of a higher intensity (> 6 METs) and *moderately active women* as those who spent less than 25% of their total physical-activity time in high intensity activity.

Fourth, we investigated whether energy expenditure in physical activity was associated with PPD. Intensity, duration, and frequency of physical activity were combined into 1 measure of physical activity. For each woman, we calculated total MET hours/week by summing the activity-specific products of MET score and duration (h/wk) over all activities reported. Total MET h/wk were divided into quartiles.

Outcome Measures

Women who were admitted to psychiatric hospitals and psychiatric wards due to depression were identified using the Danish Psychiatric Central Register. A case of *PPD-admission* was defined as a person admitted to a hospital or an outpatient contact with a diagnosis of a depressive episode (*International Classification of Diseases, Tenth Revision* [*ICD-10*], codes F320–F329). Information on antidepressants purchased with a prescription in a pharmacy was obtained from the Register of Medicinal Product Statistics. A case of *PPD-prescription* was defined as a person who filled a prescription for antidepressant medication (Anatomical Therapeutic Chemical Classification System code beginning with N06A).[21] Information on first admission and first prescription during a period of 1 year following childbirth was used to account for cases of PPD-admission and PPD-prescription, respectively.

Covariates Used for Analyses and Supplementary Analyses

Previous studies of PPD have identified several risk factors for the disease; based on these, we identified a priori and included as covariates age, parity, pre-pregnancy body mass index, alcohol intake during pregnancy, smoking during pregnancy, occupation, level of attained education, home ownership, marital status, and social support (a measure combining information on whether the woman has anyone besides a partner to talk with in confidentiality, whether she has help with practical matters, whether she has help economically, and the frequency of contact with family members). We also included history of previous depression as a covariate; this measure was obtained by combining data from the telephone interview, the Danish Psychiatric Central Register, and the Register of Medicinal Product Statistics. A woman was considered to have a history of previous depression if she (1) stated in the interview that she had previously suffered from depression, (2) had been admitted to hospital with a diagnosis of depression before, or (3) had previously filled a prescription for antidepressant medication.

For supplementary analyses, we constructed 2 measures of physical activity based on information from both

Table 1. Distribution of Participants, ORs for PPD-Admission,[a] and ORs for PPD-Prescription[b] by Measures of Physical Activity in Gestation Week 12 (N = 70,866)

			PPD-Admission					PPD-Prescription				
			No. of	Crude		Adjusted[d]		No. of	Crude		Adjusted[d]	
Measure	N	%[c]	Cases	OR	95% CI	OR	95% CI	Cases	OR	95% CI	OR	95% CI
Physical activity												
Not physically active	44,372	62.6	98	Reference	...	Reference	...	886	Reference	...	Reference	...
Active	26,494	37.4	59	1.01	0.73–1.39	1.10	0.79–1.53	419	0.79	0.70–0.89	0.90	0.79–1.02
Intensity												
Not physically active	44,372	62.6	98	Reference	...	Reference	...	886	Reference	...	Reference	...
Moderately active[e]	17,466	24.7	43	1.12	0.78–1.60	1.20	0.83–1.72	297	0.85	0.74–0.97	0.94	0.82–1.08
Vigorously active[f]	9,028	12.7	16	0.80	0.47–1.36	0.88	0.52–1.52	122	0.67	0.56–0.81	0.81	0.66–0.99
Duration (h/wk)												
Not physically active	44,372	62.6	98	Reference	...	Reference	...	886	Reference	...	Reference	...
0–1	5,091	7.2	12	1.07	0.59–1.95	1.19	0.65–2.17	84	0.82	0.66–1.03	0.93	0.73–1.17
> 1–2	9,425	13.3	20	0.96	0.59–1.56	1.09	0.67–1.77	145	0.77	0.64–0.92	0.92	0.77–1.11
> 2–3	5,023	7.1	8	0.72	0.35–1.48	0.78	0.38–1.62	66	0.65	0.51–0.84	0.75	0.58–0.98
> 3–5	4,412	6.2	10	1.03	0.54–1.97	1.07	0.56–2.07	73	0.83	0.65–1.05	0.91	0.71–1.18
>5	2,543	3.6	9	1.61	0.81–3.18	1.54	0.77–3.07	51	1.00	0.76–1.34	0.98	0.73–1.32
MET score (MET h/wk)												
Not physically active	44,372	62.6	98	Reference	...	Reference	...	886	Reference	...	Reference	...
0–5	6,771	9.6	16	1.07	0.63–1.82	1.22	0.71–2.07	104	0.77	0.62–0.94	0.87	0.70–1.08
> 5–8	6,475	9.1	14	0.98	0.56–1.72	1.09	0.62–1.92	104	0.80	0.65–0.98	0.97	0.79–1.21
> 8–15	6,835	9.6	11	0.73	0.39–1.36	0.78	0.41–1.46	97	0.71	0.57–0.87	0.79	0.63–0.99
> 15	6,413	9.1	18	1.27	0.77–2.10	1.31	0.79–2.19	114	0.89	0.73–1.08	0.97	0.79–1.19

[a]A person admitted to a hospital or an outpatient contact with a diagnosis of a depressive episode (*ICD-10*, codes F320–F329).
[b]A person who filled a prescription for antidepressant medication (Anatomical Therapeutic Chemical Classification System code beginning with N06A).
[c]Percentage within variable.
[d]Adjusted for maternal age, parity, pre-pregnant body mass index, alcohol intake, smoking, occupation, education, home ownership, marital status, social support, and history of previous depression.
[e]*Moderately active* defined as reporting less than 25% of total time in physical activity to be vigorous activity.
[f]*Vigorously active* defined as reporting at least 25% of total time in physical activity to be vigorous activity.
Abbreviations: MET = metabolic equivalent, OR = odds ratio, PPD = postpartum depression.

pregnancy interviews; first, we categorized women as not physically active at weeks 12 and 30, physically active at weeks 12 and 30, or changed activity level during pregnancy. Second, women were categorized in the same way according to intensity of physical activity at weeks 12 and 30. Furthermore, for supplementary analyses, we used information on work-related physical activity (whether the woman reported her job to be "sedentary/varying at own wish" or whether she had to "walk/stand for the most part") and self-reported eating disorders.

Statistical Methods

The Danish National Birth Cohort enrolled 91,827 women, with some women contributing more than 1 pregnancy. We used data from the first singleton pregnancy each woman contributed to the cohort, yielding a study population of 85,338 women. Of these, 89% participated in the first telephone interview in first or second trimester; 92% of respondents had nonmissing values for all covariates included in the analyses. Thus, data from 70,866 women were included in our analyses. Logistic regression was used to model risk of PPD-admission and PPD-prescription. Risk estimates are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Chi square tests were used to test bivariate associations. The 4 measures of exposure were treated as categorical variables, and all covariates were included in the adjusted model. We used SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina) for all statistical analyses.

RESULTS

During pregnancy, 37% of participants reported engaging in some type of physical activity (Table 1). Of the active women, approximately one-third were vigorously active, and less than 4% reported duration of physical activity of more than 5 hours/wk. The most frequently reported activities were swimming, cycling, aerobics, and walking (data not shown). The number of cases of PPD-admission was 157 (0.2%), and there were 1,305 cases of PPD-prescription (1.8%).

Table 2 shows associations of selected maternal characteristics with physical activity, PPD-admission, and PPD-prescription. Being physically active was strongly associated with all the demographic, socioeconomic, and behavioral characteristics shown in Table 2. For both PPD-admissions and PPD-prescriptions, there were more cases among single women, smokers, women with poor social support, and women of low socioeconomic status. Furthermore, there were more cases of PPD-prescription among underweight and overweight women; PPD-prescription was most frequent in the oldest age group, whereas PPD-admission was most frequent among young women.

Table 2. Participants Distributed by Maternal Characteristics According to Any Physical Activity in Gestation Week 12, PPD-Admission and PPD-Prescription (N = 70,866)

Characteristic	Total N	Total %[a]	Physical Activity No. Active	Physical Activity %[b]	Physical Activity P Value[c]	PPD-Admission No. Cases	PPD-Admission %[b]	PPD-Admission P Value[c]	PPD-Prescriptions No. Cases	PPD-Prescriptions %[b]	PPD-Prescriptions P Value[c]
Maternal age, y											
< 25	6,906	10	2,406	35	< .001	41	0.6	< .001	148	2.1	.01
25–35	53,677	75	20,642	38		146	0.3		941	1.8	
> 35–40	9,209	13	3,080	33		25	0.3		188	2.0	
> 40	1,074	2	366	34		3	0.3		28	2.6	
Parity											
Nulliparous	35,042	49	15,756	45	< .001	115	0.3	.24	615	1.8	.09
Parous	35,824	51	10,738	30		100	0.3		690	1.9	
Marital status											
Single	1,434	2	500	35	.05	10	0.7	< .01	64	4.5	< .001
Cohabiting	69,432	98	25,994	37		205	0.3		1,241	1.8	
Smoking											
Nonsmoker	51,786	73	20,730	40	< .001	127	0.3	< .001	730	1.4	< .001
Occasional smoker	9,300	13	3,379	36		41	0.4		230	2.5	
Daily smoker	9,780	14	2,385	24		47	0.5		345	3.5	
Alcohol intake											
≤ 1 drink/wk	54,973	78	20,048	36	< .001	172	0.3	.39	1,028	1.9	.29
> 1 drink/wk	15,893	22	6,446	41		43	0.3		277	1.7	
Pre-pregnant body mass index											
< 18.5	3,170	4	1,020	32	< .001	9	0.3	.51	68	2.2	.03
18.5–25	48,119	68	18,752	39		139	0.3		842	1.8	
> 25	19,577	28	6,722	34		67	0.3		395	2.0	
Occupation											
White-collar worker	26,203	37	10,964	42	< .001	47	0.2	< .001	346	1.3	< .001
Skilled worker	13,267	19	4,710	36		31	0.2		189	1.4	
Unskilled worker	15,694	22	4,884	31		47	0.6		191	2.4	
Students	8,080	11	3,569	44		41	0.3		272	1.7	
Unemployed	7,622	11	2,367	31		49	0.6		307	4.0	
Education											
> 4 years post secondary	5,268	7	2,334	44	< .001	12	0.2	< .001	62	1.2	< .001
2–3 years post secondary	20,179	29	8,544	42		48	0.2		305	1.5	
Vocational training	25,024	35	8,391	34		72	0.3		475	1.9	
High school	10,532	15	4,555	43		25	0.2		141	1.3	
< 10 years of school	9,863	14	2,670	27		58	0.6		322	3.3	
Home ownership											
Home owner	50,497	71	18,338	36	< .001	126	0.3	< .001	864	1.7	< .001
Renter	20,369	29	8,156	40		89	0.4		441	2.2	
Social support											
Good	61,654	87	23,667	38	< .001	172	0.3	< .01	1,056	1.7	< .001
Poor	9,212	13	2,827	31		43	0.5		249	2.7	
History of previous depression											
No	67,245	95	25,271	38	< .001	120	0.2	< .001	691	1.0	< .001
Yes	3,621	5	1,223	34		37	1.0		614	17.0	

[a]Percentage (columns) of women distributed by covariate.
[b]Percentage (rows) of active/cases within level of variable.
[c]Chi square test for overall differences between active/not active, cases/noncases.

Table 1 shows crude and adjusted ORs for PPD-admission and PPD-prescription, with women reporting no physical activity as the reference group. Overall, there was no effect of physical activity on risk of PPD-admission. Vigorously active women had a 12% lower risk of PPD-admission, and women exercising more than 5 hours/wk had a 50% higher risk of PPD-admission, but neither of these findings was statistically significant.

Regarding PPD-prescription, we found that physically active women had a lower risk of PPD-prescription, with an OR of 0.79 (95% CI, 0.70–0.89); however, this association was attenuated after adjustment for covariates (OR, 0.90; 95% CI, 0.79–1.02). Vigorously active women had a decreased risk of PPD-prescription, with an adjusted OR of 0.81 (95% CI, 0.66–0.99). Furthermore, women exercising 2 to 3 hours/wk had a 25% decreased risk of PPD-prescription compared to women who were not physically active, just as physical activity corresponding to 8 to 15 MET h/wk was associated with a 20% lower risk of PPD-prescription, whereas ORs for the other groups ranged from 0.87 to 0.97 with confidence intervals containing unity.

In supplementary analyses, we found that underweight women were at higher risk of PPD-admission if they reported any physical activity (adjusted OR, 8.69; 95% CI, 1.37–55.28). Risks were similarly elevated for measures of physical activity based on duration, intensity, and METs (Table 3). Including a history of previous eating disorders as a covariate in the analyses did not attenuate the higher

Table 3. Adjusted[a] OR for PPD-Admission and PPD-Prescription by Measures of Physical Activity in Gestation Week Stratified by Pre-Pregnant Body Mass Index

	PPD-Admission						PPD-Prescription					
	Underweight		Normal Weight		Overweight		Underweight		Normal Weight		Overweight	
Measure	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Physical activity												
Not physically active	Reference	...	Reference	...	Reference	...	Reference	...	Reference	...	Reference	...
Active	8.69	1.37–55.28	0.93	0.62–1.42	1.22	0.67–2.22	1.03	0.58–1.82	0.90	0.77–1.05	0.88	0.69–1.10
Intensity												
Not physically active	Reference	...	Reference	...	Reference	...	Reference	...	Reference	...	Reference	...
Moderately active[b]	8.12	1.17–56.40	1.03	0.65–1.63	1.33	0.69–2.57	0.90	0.48–1.72	0.95	0.80–1.13	0.92	0.71–1.20
Vigorously active[c]	11.37	0.73–176.63	0.74	0.37–1.46	1.00	0.38–2.61	1.52	0.61–3.83	0.79	0.62–1.01	0.78	0.54–1.14
Duration (h/wk)												
Not physically active	Reference	...	Reference	...	Reference	...	Reference	...	Reference	...	Reference	...
0–1	50.96	4.01–648.46	0.97	0.44–2.14	1.00	0.30–3.32	0.90	0.29–2.74	0.93	0.69–1.24	0.94	0.61–1.45
> 1–2	NA[d]	NA[d]	1.06	0.59–1.90	1.10	0.45–2.66	1.83	0.83–4.03	0.92	0.74–1.16	0.83	0.58–1.18
> 2–3	NA[d]	NA[d]	0.79	0.34–1.83	0.78	0.18–3.29	0.41	0.09–1.81	0.80	0.58–1.08	0.72	0.43–1.21
> 3–5	16.01	0.9–284.41	0.70	0.28–1.77	1.72	0.60–4.95	0.60	0.14–2.64	0.92	0.68–1.25	0.96	0.60–1.54
> 5	59.21	NA[d]	1.11	0.44–2.78	2.05	0.61–6.92	1.34	0.43–4.20	0.94	0.65–1.36	1.04	0.58–1.84
MET score (MET h/wk)												
Not physically active	Reference	...	Reference	...	Reference	...	Reference	...	Reference	...	Reference	...
0–5	16.88	1.03–278.13	0.86	0.41–1.81	1.79	0.78–4.11	0.90	0.33–2.46	0.90	0.69–1.16	0.79	0.53–1.19
> 5–8	11.68	0.70–195.29	1.32	0.71–2.48	0.26	0.04–1.90	1.91	0.79–4.66	0.95	0.73–1.24	0.92	0.62–1.37
> 8–15	NA[d]	NA[d]	0.76	0.36–1.59	0.79	0.24–2.60	0.53	0.16–1.82	0.83	0.63–1.07	0.75	0.49–1.14
> 15	30.27	2.63–347.73	0.84	0.41–1.71	2.20	0.95–5.07	1.08	0.42–2.73	0.94	0.73–1.21	1.08	0.72–1.60

[a]Adjusted for maternal age, parity, alcohol intake, smoking, occupation, education, home ownership, marital status, social support, and history of previous depression.
[b]*Moderately active* defined as reporting less than 25% of total time in physical activity.
[c]*Vigorously active* defined as reporting at least 25% of total time in physical activity.
[d]Effect measure could not be estimated due to small numbers.
Abbreviations: OR = odds ratio, MET = metabolic equivalent, NA = not available, PPD = postpartum depression.

risk of PPD-admission among underweight women who were physically active (data not shown). For women who maintained the same level of activity at gestation weeks 12 and 30, findings were similar to the main analysis; indeed, women who were vigorously active at both measurements had a lower risk of PPD-prescription compared to the main analysis (adjusted OR, 0.67; 95% CI, 0.48–0.93) (Table 4). Stratifying by work-related physical activity did not alter the findings of the main analysis (data not shown).

DISCUSSION

Principal Findings

In this large cohort of Danish women, one-third of the study participants reported engaging in physical activity at 12 weeks' gestation. Being physically active did not reduce the risk of being admitted to a hospital due to depression in the first year following childbirth; indeed, in underweight women, physical activity appeared to be a strong risk factor for hospitalization due to depression in the postpartum period. Women who were vigorously active had a 20% lower risk of being prescribed an antidepressant within 1 year postpartum compared with women who were not physically active.

Comparison With Existing Data

This study is, to our knowledge, the first prospective cohort study to address the association between physical activity and PPD on a large scale. A recent review of 11 randomized controlled trials found a beneficial effect of physical activity on depression,[22] and another found physical activity to have a positive effect on mild to moderate depression in general populations.[23] However, a third review concluded that, due to lack of good quality research, the effectiveness of exercise in reducing symptoms of depression could not be determined.[24]

Two randomized controlled trials have examined therapeutic effects of physical activity on depression in the postpartum period: in the first, walks 3 times a week were combined with a social support group and compared to standard care; in the second, walks 3 times a week were compared with a social support group. Both studies showed significantly lower levels of depressive symptomatology in the intervention group compared to the control group.[25,26]

Table 4. Distribution of Participants, OR for PPD-Admission, and OR for PPD-Prescription by Measures of Physical Activity in Gestation Weeks 12 and 30 Combined (N = 70,866)

			PPD-Admission					PPD-Prescription				
			No. of	Crude		Adjusted[b]		No. of	Crude		Adjusted[b]	
Measure	N	%[a]	Cases	OR	95% CI	OR	95% CI	Cases	OR	95% CI	OR	95% CI
Physical activity, weeks 12 and 30												
Not physically active	33,802	48	75	Reference	...	Reference	...	680	Reference	...	Reference	...
Active	12,536	18	23	0.83	0.52–1.32	0.92	0.57–1.49	177	0.70	0.59–0.82	0.84	0.71–1.01
Changed activity level, weeks 12–30	24,528	35	59	1.08	0.77–1.53	1.09	0.77–1.54	448	0.91	0.80–1.02	0.94	0.82–1.06
Intensity, weeks 12 and 30												
Not physically active	33,802	48	75	Reference	...	Reference	...	680	Reference	...	Reference	...
Moderately active[c]	5,591	8	16	1.29	0.75–2.22	1.43	0.82–2.48	84	0.74	0.59–0.93	0.86	0.68–1.10
Vigorously active[d]	3,700	5	3	0.37	0.12–1.16	0.41	0.13–1.31	41	0.55	0.40–0.75	0.67	0.48–0.93
Changed activity level, weeks 12–30	27,773	39	63	1.02	0.73–1.43	1.04	0.74–1.46	500	0.89	0.80–1.00	0.94	0.83–1.07

[a]Percentage within variable.
[b]Adjusted for maternal age, parity, pre-pregnant body mass index, alcohol intake, smoking, occupation, education, home ownership, marital status, social support, and history of previous depression.
[c]*Moderately active* defined as reporting less than 25% of total time in physical activity as vigorous activity.
[d]*Vigorously active* defined as reporting at least 25% of total time in physical activity as vigorous activity.
Abbreviations: OR = odds ratio, PPD = postpartum depression.

In a controlled trial, women suffering from PPD were allocated alternately into an experimental group doing 3 group sessions of gentle stretching exercises a week or a control group receiving standard care, and a beneficial effect was found for the experimental group.[27] It is, however, difficult to separate any effects of physical activity from the psychological or social effect of being in the intervention group in the trials mentioned here.

Strengths and Limitations

Major strengths of this study include its prospective design, size, and the utilization of unique Danish national registers.

However, the use of register data on antidepressants as a measure of PPD implies that cases of PPD-prescription in this study do not necessarily fulfill the *DSM-IV* diagnostic criteria for PPD. A further limitation of this outcome measure might be that this type of medication can be prescribed on indications other than depression. However, in Denmark, antidepressants can be obtained only by a prescription from a medical doctor, and regulation and surveillance of the use of medication is quite strict. All prescriptions are kept in a central registry and can be linked to the relevant physician and patient for relevant authorities to check in accordance with official guidelines.

Another limitation inherent in the study is the intrinsic difficulty in accurately assessing something as complex as physical activity in an observational setting, particularly in a study population of the present size. We focused on activity in leisure time since this may be more modifiable than work-related physical activity and, as such, a more obvious target for disease prevention. The questions on physical activity were similar to those used in other studies of pregnant women[28] and were modified from the Minnesota Leisure-Time Physical Activity Questionnaire.[29] In the telephone interview, women were asked about physical activity in the period prior to the interview, and we therefore believe that there is relatively little error due to poor recall. We also believe the woman's reporting on physical activity in gestation week 12 was a reasonable representation of her habitual level of physical activity, although activity levels have been shown to decline during pregnancy.[28,30] By the time of the second interview, which took place in the third trimester, the pregnancy itself was likely to have influenced her level of physical activity to an extent that may be highly variable between individuals, so we chose a priori to use information from gestation week 12 as our main exposure. Even so, our findings remained largely unchanged after combining the measure of exposure with information on physical activity at gestation week 30; interestingly, a stronger protective effect regarding PPD-prescription was observed for women who maintained their level of vigorous physical activity at gestation week 30.

The prospective study design reduces the chance that depression may have influenced the level of physical activity, making "reverse causality" an unlikely explanation for the associations that we observed. However, women who experienced symptoms of depression prior to or early in pregnancy may have had less energy to engage in physical activity, and, in order to take this into account, we adjusted for history of previous depression in our analyses. As a sensitivity analysis, we excluded women with a history of previous depression, but the central estimate was essentially unchanged after the exclusion (data not shown).

The analyses presented in Table 1 represent a relatively large number of tests, as we used 4 different exposures and 2 different outcome measures to assess the association between physical activity and PPD. However, all these analyses were decided upon a priori, and our findings are thus not a result of explorative analyses. Therefore, we did not correct for multiple testing but are aware that the lower risk of PPD-prescription for women who were vigorously active would not be statistically significant had we, for example, corrected by the (quite conservative) Bonferroni method.

Outcome

Information on outcome was extracted from 2 unique registers available for research in Denmark: the Danish Psychiatric Central Register and the Register of Medicinal Product Statistics. Recently, the point prevalence of major depression in Denmark was estimated to be 3.3%; of these cases, only 13% were currently under treatment by a physician.[31] Our measures of outcome yielded very low rates of PPD (0.2% and 1.8%), and it can be argued that only severe cases of PPD are detected by our case definitions. An outcome measure based on a validated self-report measure of PPD, such as the Edinburgh Postnatal Depression Scale,[32] would most likely have yielded a higher rate of PPD. However, the comprehensive data collection in the Danish National Birth Cohort may have caused depressed women to drop out of the cohort, and our use of register-based data bypassed this particular problem.

Taking into account that hospitalization is a serious life disruption for a new mother and her infant, the rate of PPD-admission in this study may reflect cases of postpartum psychosis rather than PPD. Postpartum psychosis afflicts 1 to 2 per 1,000 women postpartum,[6] which is comparable to the rate of PPD-admission in our study. It is interesting that, in a cross-cultural review of studies on postpartum mental illness, Kumar[6] argues that depression and psychosis may have distinct etiologic patterns. According to Kumar, the etiology of PPD is predominantly psychosocial, with rates of PPD varying greatly between cultures, whereas rates of postpartum psychosis are stable, pointing to an endogenous etiology for psychoses, possibly triggered by the physiology of childbirth.[6] In this study, PPD-admission and PPD-prescription had different associations with physical activity and with some of the covariates, and this may be taken to support Kumar's notion that the 2 outcomes represent 2 distinct etiologic entities.

Suggested Mechanisms

Several biologic and psychosocial pathways have been hypothesized to mediate an antidepressive effect of physical activity. The different mechanisms by which this effect is achieved are poorly understood since studies have not been conducted specifically to address this issue.[33]

Physical activity has been shown to be positively associated with changes in self-esteem[34] and body image,[35] while negative self-evaluations have been shown to be related to depression.[33] We found surprisingly high risks of PPD-admission in underweight women who were physically active in pregnancy, which was not explained by a self-reported measure of eating disorders. This subgroup may be particularly vulnerable to pregnancy-related body changes and limited possibilities of exercising postpartum, potentially resulting in negative self-evaluations or less self-esteem and, thus, increased risk of depression.

From our findings, it can be speculated that a certain intensity of activity is required for an antidepressive effect to occur. This is supported by trials that have found a negative association between physical activity of vigorous intensity and depression, but no effect of light/moderate intensity physical activity against depression,[15,36,37] and this may point in the direction of a biologic response mechanism. Several different mechanisms have been suggested here as well. The endorphin hypothesis proposes that physical activity produces changes in endorphin concentrations and binding in the brain, thereby affecting mood.[33] Another hypothesis suggests that a decreased rate of neurogenesis contributes to depression, and that physical activity increases the synthesis of new neurons in the adult brain, alleviating depressed mood.[38]

Studies showing associations between physical activity and depression at baseline, but not prospectively, indicate that the relationship between the 2 may be largely correlational and not causal; this was also the conclusion of a recent study investigating causality in the association between physical activity and depression.[39] It is possible that a common psychological vulnerability may underlie both lower levels of physical activity and a higher risk of depression. Another plausible explanation for the inverse association between vigorous physical activity and PPD-prescription found in this study is that physical activity in pregnancy is an indicator of better general health. Even though our results were robust to adjustment for a history of previous depression, we cannot exclude the possibility that women who have the energy to perform strenuous exercise in pregnancy may have greater mental and physical resources and, thus, are at decreased risk of depression postpartum.

Perspectives

Findings from this large, prospective cohort of pregnant women are, in part, consistent with evidence from previous randomized controlled trials suggesting that vigorous physical activity may be associated with lower risk of depression. For the more severe cases of depression, those resulting in hospitalization of the woman, we did not find any association with physical activity in pregnancy. It is not possible, based on these data, to discern whether an association between vigorous physical activity and PPD reflects causal effects or is merely correlational in nature.

Underweight women who were physically active during pregnancy were at higher risk of PPD, and this finding needs to be tested in other large, prospective cohorts, which are now emerging in several other countries.

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Denmark; and Unit for Nutrition Research, Faculty of Food Science and Nutrition, University of Iceland and Landspitali-University Hospital, Reykjavík (Dr Halldorson).
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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

論文名	Leisure-time physical activity in pregnancy and risk of postpartum depression: a prospective study in a large national birth cohort
著　者	Strom Marin, et al.
雑誌名	Journal of clinical psychiatry
巻・号・頁	70　12　1707-1714
発行年	2009
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/20141710

対象の内訳		ヒト	動物	地　域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		デンマーク		コホート研究
	性別	女性	(　　)		(　　)		(　　)
	年齢	歳:75%、35-40	[redacted]		(　　)		前向きコホート
	対象数	10000以上			(　　)		(　　)
調査の方法	実測	(　　)					
アウトカム	予　防	なし	なし	なし	なし		(　　)
	維持・改善	な し	な し	な し	心理的指標改善	(　　)	(　　)

図　表

Table 4. Distribution of Participants, OR for PPD-Admission, and OR for PPD-Prescription by Measures of Physical Activity in Gestation Weeks 12 and 30 Combined (N = 70,866)

			PPD-Admission					PPD-Prescription				
			No. of	Crude		Adjusted[b]		No. of	Crude		Adjusted[b]	
Measure	N	%[a]	Cases	OR	95% CI	OR	95% CI	Cases	OR	95% CI	OR	95% CI
Physical activity, weeks 12 and 30												
Not physically active	33,802	48	75	Reference	...	Reference	...	680	Reference	...	Reference	...
Active	12,536	18	23	0.83	0.52–1.32	0.92	0.57–1.49	177	0.70	0.59–0.82	0.84	0.71–1.01
Changed activity level, weeks 12–30	24,528	35	59	1.08	0.77–1.53	1.09	0.77–1.54	448	0.91	0.80–1.02	0.94	0.82–1.06
Intensity, weeks 12 and 30												
Not physically active	33,802	48	75	Reference	...	Reference	...	680	Reference	...	Reference	...
Moderately active[c]	5,591	8	16	1.29	0.75–2.22	1.43	0.82–2.48	84	0.74	0.59–0.93	0.86	0.68–1.10
Vigorously active[d]	3,700	5	3	0.37	0.12–1.16	0.41	0.13–1.31	41	0.55	0.40–0.75	0.67	0.48–0.93
Changed activity level, weeks 12–30	27,773	39	63	1.02	0.73–1.43	1.04	0.74–1.46	500	0.89	0.80–1.00	0.94	0.83–1.07

[a]Percentage within variable.
[b]Adjusted for maternal age, parity, pre-pregnant body mass index, alcohol intake, smoking, occupation, education, home ownership, marital status, social support, and history of previous depression.
[c]*Moderately active* defined as reporting less than 25% of total time in physical activity as vigorous activity.
[d]*Vigorously active* defined as reporting at least 25% of total time in physical activity as vigorous activity.
Abbreviations: OR = odds ratio, PPD = postpartum depression.

図表掲載箇所	
概　要 (800字まで)	<目的>大規模な前向きコホートで、妊娠と産後うつ病(PPD)と身体活動との間の関連を探索すること。<方法>100,000人以上の妊娠(1996年から2002年)に関する情報を持つデンマーク国立出生コホートからの露出情報は、デンマーク精神疾患統計登録にリンクされていた。デンマーク国立出生コホートから70866人の出産女性のデータを分析に含めた。身体活動の持続時間、頻度、およびタイプは妊娠約12週での電話インタビューにより評価した。産後うつ病と、抗うつ薬の処方あるいは入院を、アウトカムとした。<結果>国の登録システムとの連携を通じて、我々は産後うつ-入院157例と産後うつ薬処方の1305例を同定した。妊娠中に活発な余暇身体活動に従事する女性は不活動な女性と比較して、うつ薬処方のリスクが低かった(補正オッズ比、0.81、95%CI、0.66から0.99)。このような関連は身体活動と産後うつ入院の間に観察されなかった、しかし、妊娠前にやせだった女性で、身体活動は、産後うつ入院のリスク増加と関連していた。
結　論 (200字まで)	抗うつ薬治療を必要とする産後うつに対して、活発な余暇身体活動による予防効果を持つことを示唆している。しかし、この予防効果は、産後うつ入院では見られなかった。
エキスパートによるコメント (200字まで)	妊産婦も産後のうつを予防するために適度の身体活動が必要であることを示す、興味深い研究である。

担当者　　宮地元彦

Effect of Physical Activity on Breast Cancer Risk: Findings of the Japan Collaborative Cohort Study

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Abstract

Purpose: **This study aimed to examine prospectively the association between physical activity and breast cancer risk in a non-Western population.**
Methods: **We analyzed data from the Japan Collaborative Cohort Study, which included 30,157 women, ages 40 to 69 years at baseline (1988-1990), who reported no previous history of breast cancer, and provided information on their walking and exercise habits. The subjects were followed prospectively from enrollment until 2001 (median follow-up period, 12.4 years). Breast cancer incidence during this period was confirmed using records held at population-based cancer registries. The Cox proportional hazards model was used to estimate the hazard ratio (HR) for the association of breast cancer incidence with physical activity.**
Results: **During the 340,055 person-years of follow-up, we identified 207 incident cases of breast cancer. The most physically active group (who walked for ≥1 hour per day and exercised for ≥1 hour per week) had a lower risk of breast cancer (HR, 0.45; 95% confidence interval, 0.25-0.78) compared with the least active group after adjusting for potential confounding factors. The inverse association of exercise on breast cancer was stronger among those who walked for ≥1 hour per day than those who walked for <1 hour per day (P = 0.042). These results were not significantly modified by menopausal status or body mass index (BMI).**
Conclusions: **Our analysis provided evidence that physical activity decreased the risk of breast cancer. Walking for 1 hour per day and undertaking additional weekly exercise both seemed to be protective against breast cancer, regardless of menopausal status or BMI.** (Cancer Epidemiol Biomarkers Prev 2008;17(12): 3396–401)

Introduction

Since the early 1990s, breast cancer has been the most commonly diagnosed cancer, even among Japanese women (1). The continuous increase in breast cancer incidence during recent decades has been an important public health concern in Japan, and there has been growing interest in physical activity as a means of primary prevention. Worldwide, numerous epidemiologic studies have reported associations between physical activity and cancer risk, with most observing a protective effect. Reviews published in 2002 concluded that there was sufficient evidence to support the role of physical activity in preventing breast cancer (2, 3). A systematic review published in 2007 (4) showed a decreased relative risk (<0.8) associated with leisure activities in 8 of 17 cohort studies (5-12), whereas the remaining 9 reported no association (13-21). Three more-recent cohort studies supported the risk reduction (22-24), whereas one found no evidence of a protective effect of physical activity on breast cancer (25). In addition to the 20% to 40% overall risk reduction of breast cancer among the more physically active women (2), the effects of menstrual characteristics, obesity, use of sex hormones, hormone-receptor status, and immune function have also been discussed in previous reports (24, 26, 27). However, these have been based on data from Western populations, and to our knowledge there have been no prospective reports from Asia. Different factors might influence Asian populations, as their characteristics (such as breast cancer incidence, physical activity, and body size) tend to differ from those of Western populations. Here, we analyzed data from a large-cohort study, the Japan Collaborative Cohort (JACC) Study, to examine the relationship between physical activity and breast cancer with a particular emphasis on the interactions with other risk factors, such as menopausal status and obesity.

Materials and Methods

Study Population. The present analysis was based on data from the JACC Study. This prospective cohort study evaluated the cancer risk associated with lifestyle factors

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among the Japanese population. At baseline (1988-1990), 110,792 subjects (46,465 men and 64,327 women), ages 40 to 79 y, were enrolled from 45 areas throughout Japan. All of the participants were subsequently followed up for all-cause mortality. Of the women in the baseline cohort, 34,086 lived in the 22 areas where data on both cancer incidence and physical activity were available. The JACC Study has been described in detail elsewhere (28, 29). Informed consent for participation was obtained from all individuals, with the exception of those in a few study areas where informed consent was provided at the group level, after the aims and data confidentiality had been explained to community leaders. The Ethics Board of Nagoya University School of Medicine, Japan, approved the JACC Study protocol.

Physical Activity Assessment. A self-administered questionnaire was used to obtain information on physical activity at baseline (30). The items covered included amount of time spent walking, amount of time spent exercising, and physical activity at the work place. Time spent walking daily was classified into three categories (<30 min, 30-59 min, and ≥1 h), as was time spent exercising (never or seldom, 1-2 h/wk, ≥3 h/wk). The validity of the estimates of time spent participating in sports and leisure activities was examined in a sample of the baseline subjects, suggesting that measuring physical activity level with the single-item question may be appropriate for establishing baseline data that reflect long-term physical activity in a large-scale cohort study (30, 31). We did not analyze the metabolic equivalent intensity, because of a lack of information on the strength of the exercise.

Other Variables. Information on additional potential breast cancer risk factors, such as family history, body mass index (BMI), tobacco and alcohol use, age at menarche, marital status, parity, age at birth of first child, menopausal status, and hormone use, was collected via the baseline questionnaire.

Follow-up and Identification of Breast Cancer Cases. The study participants were followed up from the time of enrollment until 2001, excluding five areas in which they were halted earlier. During this period, population registry data from each municipality were used to ascertain the residential and vital status of the participants. In Japan, the registration of death is required by the Family Registration Law, theoretically providing complete mortality data. Breast cancer incidence was confirmed mainly through the records of the population-based cancer registries in each area. During the study period, only 1,189 (3.9%) of the subjects were lost to follow-up due to moving out of the given study areas. The proportion of death-certificate-only cases was 6.3% (13 of 207). The mortality-to-incidence ratio for breast cancer was 0.26 (50 of 194) in the cohort covered by the cancer registries, which was within the range calculated using the available data from population-based cancer registries in Japan (0.20-0.30; ref. 32). We expect 37.4 breast cancer incidence cases who cannot be found from the cancer registries. The present analysis excluded 246 women who reported a previous diagnosis of breast cancer and 3,683 women who did not provide information on physical activity at baseline. Thus, a total of 30,157 women were included in the present analysis.

Statistical Analysis. For all participants, the person-years of follow-up was calculated as the time from enrollment until the diagnosis of breast cancer, death from any cause, moving out of the study area, or the end of follow-up, whichever occurred first. For the breast cancer cases ascertained by death-certificate-only, the person-years of follow-up were calculated from the time of enrollment until the time of death from breast cancer. Those individuals who died from causes other than breast cancer (n = 2,518) or who moved out of the study areas were treated as censored cases. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of breast cancer incidence with physical activity. We evaluated the relationship using two models: an age-adjusted model (using 5-y age groups), and a multivariable model with adjustments for age, BMI (<22.0 kg/m^2, 22.0-23.9 kg/m^2, 24.0-25.9 kg/m^2, ≥26.0 kg/m^2, or unknown), alcohol drinking (never, past, current, or unknown), age at menarche (<15 y, 15-16 y, ≥17 y, or unknown), education level (attended school until the age of <16 y, 16-18 y, ≥19 y, or unknown), parity (nulliparous, 1 birth, 2-3 births, ≥4 births, or unknown), age at birth of first child (<22 y, 22-23 y, 24-25 y, ≥26 y, or unknown), use of exogenous female hormone (yes, no, or unknown), family history of breast cancer in a first-degree relative (yes, no, or unknown), menopausal status (premenopausal or postmenopausal), and menopausal age for postmenopausal women (<45 y, 45-49 y, ≥50 y, or unknown). In this study, those who provided menopausal age or who were at the average age at menopause, i.e., ≥49 y at baseline, were treated as postmenopausal women, and only those who were <49 y without information of menopausal age were treated as premenopausal women. Each "unknown" category included 5% to 9% of all women. All analyses were stratified by six study areas (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu). Trend tests were done for category-based scores, which were assessed by allocating values ranging from 1 to 3 to each individual according to the selected physical activity variables.

To estimate the interaction of time spent walking and time spent exercising, we recategorized the subjects into four groups using the following cutoff points for physical activity: daily walking for <1 h or ≥1 h, and weekly exercising for <1 h or ≥1 h. Furthermore, the HR for the most active group (those who walked for ≥1 h/d and exercised for ≥1 h/wk) compared with the other groups was estimated according to menopausal status and BMI (<24 or ≥24 kg/m^2), and we examined the interaction between physical activity and these factors (Table 5). We used a BMI of 24 kg/m^2 instead of 25 kg/m^2 as a cutoff point for overweight. That was because there were only 47 cases for BMI ≥24 kg/m^2, which were too few to discuss interaction. For instance, we estimated the two HRs for physical activity among women who were premenopausal and postmenopausal at baseline, and then the P value for the interaction term of menopausal status and physical activity was calculated to test the difference between these HRs. We repeated the analysis after excluding the initial 2 y of follow-up, during which 37 cases of breast cancer were diagnosed. All of the P values were two-sided, with P < 0.05 indicating statistical significance. All of the analyses were done with SAS version 9.1 (SAS Institute, Inc.).

Table 1. Baseline characteristics associated with age in the JACC Study

Characteristics	Age group				Total
	40-49 y	50-59 y	60-69 y	70-79 y	
Number, *n* (row %)	7,561 (25.1)	9,361 (31.0)	9,098 (30.2)	4,137 (13.7)	30,157 (100.0)
Time spent walking per day					
Never or seldom, *n* (%)	868 (11.5)	1,013 (10.8)	807 (8.9)	403 (9.7)	3,091 (10.2)
Around 30 min, *n* (%)	1,393 (18.4)	1,650 (17.6)	1,794 (19.7)	876 (21.2)	5,713 (18.9)
30-59 min, *n* (%)	1,584 (20.9)	1,989 (21.2)	1,945 (21.4)	956 (23.1)	6,474 (21.5)
≥1 h, *n* (%)	3,716 (49.1)	4,709 (50.3)	4,552 (50.0)	1,902 (46.0)	14,879 (49.3)
Time spent exercising per wk					
Never or seldom, *n* (%)	5,890 (77.9)	7,365 (78.7)	6,591 (72.4)	2,842 (68.7)	22,688 (75.2)
1-2 h, *n* (%)	1,176 (15.6)	1,298 (13.9)	1,412 (15.5)	617 (14.9)	4,503 (14.9)
3-4 h, *n* (%)	338 (4.5)	399 (4.3)	572 (6.3)	306 (7.4)	1,615 (5.4)
≥5 h, *n* (%)	157 (2.1)	299 (3.2)	523 (5.7)	372 (9.0)	1,351 (4.5)

NOTE: Mean (SD) or %, calculated for participants with complete physical activity data.

Results

The average age at baseline was 57.6 ± 10.1 years, and the median follow-up time was 12.4 years. During the 340,055 person-years of follow-up, we identified 207 incident cases of breast cancer. The annual incidence of breast cancer in the cohort per 1,000 women was 0.61. Table 1 shows the distributions of physical activity according to age. Time spent walking was distributed similarly in the four age groups, with ~50% of the subjects walking for ≥1 hour per day. By contrast, for time spent exercising and physical activity at the work place, the older the subjects, the more physically active they tended to be. Regardless of the age group, more than two thirds of the participants never or seldom exercised.

Table 2 presents the risk of breast cancer in relation to physical activity. After adjusting for potential confounding factors, the HR was marginally decreased among those who walked for ≥1 hour per day (HR, 0.73; 95% CI, 0.53-1.01). However, those who exercised for ≥3 hours per week were not statistically decreased (HR, 0.85; 95% CI, 0.51-1.40). The *P* value for the linear trend of time spent walking was 0.043, which indicated that the dose-response effect of time spent walking and breast cancer risk was significant. The adjusted HR for those who walked for ≥1 hour compared with the rest of the women was significantly different (HR, 0.70; 95% CI, 0.53-0.93), although that for those who exercised for ≥3 hours per week was not significant (HR, 0.83; 95% CI, 0.59-1.16).

To investigate the joint effect of walking and exercise, we recategorized the data using the following cutoff points for physical activity: daily walking for <1 hour and exercising for <1 hour per week. Table 3 shows the mean values and distributions of risk factors for breast cancer according to the walking and exercise time categories. The subjects who walked and exercised more tended to be older and to drink more alcohol. The BMI values did not significantly differ between categories (range, 22.7-22.8 kg/m^2).

Table 4 shows the HRs of breast cancer associated with the joint effect of time spent walking and time spent exercising. The most physically active group (those who walked for ≥1 hour per day and exercised for ≥1 hour per week) had a lower risk of breast cancer (HR, 0.45; 95% CI, 0.25-0.78) compared with the least active group after adjusting for potential confounding factors. A significant interaction (P = 0.042) was observed between time spent walking and time spent exercising, meaning that the combined effect of exercise and walking on breast cancer was significant.

The HR of the most physically active group compared with the rest of the women was estimated for the subgroups according to menopausal status and BMI in Table 5, to examine the effects modification of these factors on the association between physical activity and breast cancer onset. The marginal inverse association was

Table 2. HR of breast cancer associated with physical activity in the JACC study

Physical activity	Cases	Person-years	Age adjusted	Multivariate*
			HR (95% CI)	HR (95% CI)
Time spent walking per day				
<30 min	69	96,752	1.00 (Reference)	1.00 (Reference)
30−59 min	56	71,411	1.14 (0.71 − 1.84)	1.13 (0.80 − 1.61)
≥1 h	82	171,892	0.70 (0.51 − 0.97)	0.73 (0.53 − 1.01)
P for trend			0.021	0.043
Time spent exercising per week				
Never or seldom	161	255,829	1.00 (Reference)	1.00 (Reference)
1−2 h	29	51,043	0.87 (0.59 − 1.30)	0.83 (0.56 − 1.23)
≥3 h	17	33,183	0.87 (0.53 − 1.45)	0.85 (0.51 − 1.40)
P for trend			0.45	0.33

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 3. Baseline characteristics associated with physical activity in the JACC study

Characteristics	Time spent exercising <1 h/wk		Time spent exercising ≥1 h/wk	
	Time spent walking per day		Time spent walking per day	
	<1 h	≥1 h	<1 h	≥1 h
Number, *n* (row %)	11,864 (39.3)	10,824 (35.9)	3,414 (11.3)	4,055 (13.4)
BMI, mean ± SD (kg/m^2)	22.8 ± 3.2	22.7 ± 3.0	22.8 ± 3.0	22.7 ± 2.9
Age at baseline, mean ± SD, y	57.5 ± 10.3	56.8 ± 9.6	58.5 ± 10.3	59.2 ± 10.4
Age at menarche, mean ± SD, y	14.8 ± 1.8	14.9 ± 1.8	14.8 ± 1.8	14.9 ± 1.8
Age at birth of first child, mean ± SD, y	25.2 ± 3.3	25.0 ± 3.3	25.1 ± 3.2	24.9 ± 3.1
Age at menopause, mean ± SD, y	48.7 ± 4.8	48.6 ± 4.6	48.8 ± 4.7	48.9 ± 4.5
Age of the end of education, mean ± SD, y	16.6 ± 2.1	16.5 ± 2.1	16.9 ± 2.2	16.7 ± 2.1
Postmenopausal, *n* (%)	8,946 (75.4)	8,176 (75.5)	2,657 (77.8)	3,225 (79.5)
Nulliparous, *n* (%)	612 (5.2)	387 (3.6)	142 (4.2)	163 (4.0)
Not married, *n* (%)	223 (2.0)	120 (1.2)	65 (2.1)	42 (1.1)
Exogenous female hormone use, *n* (%)	580 (5.4)	474 (4.8)	191 (6.2)	207 (5.7)
Family history of breast cancer,* *n* (%)	191 (1.6)	159 (1.5)	63 (1.9)	65 (1.6)
Current smoker, *n* (%)	606 (5.6)	556 (5.7)	133 (4.3)	183 (5.0)
Current drinker, *n* (%)	2,594 (23.1)	2,447 (24.0)	906 (27.9)	1,122 (29.4)

NOTE: Mean (SD) or %, calculated for participants with complete physical activity data.
*In a first-degree relative.

observed in each subgroup, and no significant interaction was observed. This suggests that the inverse association was not modified by these factors. Similar results were found after excluding the initial 2 years of follow-up, during which 37 cases of breast cancer were diagnosed.

Discussion

Our prospective analysis of the relationship between physical activity and breast cancer in Japanese women revealed a significant inverse association. In particular, the combined effect of walking and exercise was stronger than that expected based on the individual effects. Moreover, the combined protective effect of walking and exercise was not modified significantly by menopausal status or BMI. This suggests that physical activity has a protective effect regardless of menopausal status or weight. Previous studies of Western populations have provided convincing evidence of an inverse association between physical activity and breast cancer risk (2, 3), as supported by a recent systematic review (4). Adding more recent cohort studies (22-25), 10 of 21 showed a significantly decreased breast cancer risk associated with physical activity. Despite the comparatively lower incidence of breast cancer in Japan (1), an inverse association between physical activity and breast cancer incidence has also been observed, which was consistent with the findings of previous case-control studies in Japan (33-35).

The present study showed an interactive effect of walking and exercise. This could be explained in several ways. For instance, multiple types of exercise might work more effectively than a single type of exercise, the effect of physical activity might be quadratic, or walkers might tend to exercise more intensely. Whatever the reason, our results indicate that walking for ≥1 hour per day should initially be recommended, and additional weekly exercise should be undertaken to improve the protective effect against breast cancer.

In the present study, menopausal status and BMI did not affect the relationship between physical activity and breast cancer. Of the two, the modifying effect of menopausal status is the more controversial. Among the previous cohort studies that have analyzed this association according to menopausal status, only two have observed a significantly decreased breast cancer risk among premenopausal women (11, 22), and the evidence is weaker among premenopausal women (5, 10, 17). This difference might be partly due to the way in which menopause has been treated in the analyses. All of the studies, including the present one, reporting a protective effect of physical activity among premenopausal women have used only baseline menopausal status and have not updated this measure. By contrast, a study that found no association did update the menopausal status (19), and menopause was included as one of its end points.

Compared with menopausal status, the effect modification of BMI on the association between physical

Table 4. HR of breast cancer associated with physical activity in the JACC study

Physical activity		Cases	Person-years	Age adjusted	Multivariate*
Time spent walking (h/d)	Time spent exercising (h/wk)			HR (95% CI)	HR (95% CI)
<1	<1	93	130,279	1.00 (Reference)	1.00 (Reference)
≥1	<1	68	125,550	1.18 (0.79 – 1.77)	1.13 (0.75 – 1.69)
<1	≥1	32	37,885	0.76 (0.56 – 1.04)	0.82 (0.60 – 1.12)
≥1	≥1	14	46,342	0.42 (0.24 – 0.74)	0.45 (0.25 – 0.78)
P for interaction				0.035	0.041

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 5. HR of breast cancer among the most physically active group compared with the rest of the women by subgroup of menopausal status and BMI in the JACC study

Subgroup	Age adjusted	Multivariate*
	HR (95% CI)	HR (95% CI)
Menopausal status		
Premenopausal	0.14 (0.02 - 0.97)	0.13 (0.02 - 0.91)
Postmenopausal	0.53 (0.29 - 0.96)	0.53 (0.29 - 0.96)
P for interaction	0.524	0.528
BMI (kg/m^2)		
<24	0.43 (0.20 - 0.91)	0.42 (0.19 - 0.90)
≥24	0.45 (0.18 - 1.10)	0.44 (0.18 - 1.09)
P for interaction	0.940	0.949

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

activity and breast cancer risk has been more consistent, as previous studies have failed to show general effects (5, 6, 8-10, 13, 14, 16, 18, 19, 21). These findings suggest that the effect of physical activity is independent of menopausal status (despite the possibility of a less precise effect among premenopausal women) and BMI. Therefore, the recommendation to undertake physical activity to prevent breast cancer does not need to be altered according to differences in these factors.

A major strength of the present study is its prospective design, which might avoid the recall bias that is possible in case-control studies. Moreover, information on other risk factors for breast cancer was included, and potential confounding factors were controlled for in the analyses when examining the association.

Our study had some limitations that should be considered when interpreting the results. First, because we used only a simple questionnaire at baseline, neither metric equivalent nor updated values were available to evaluate physical activity. In general, assessing physical activity in epidemiologic studies is difficult, which might explain the heterogeneous results observed across studies of its association with breast cancer (36). Although it is possible that the reported levels might have overestimated or underestimated the actual physical activity, the information was collected before diagnosis and should not have differed according to the end point status. Thus, the misclassification of physical activity in the present study for both reasons is nondifferential. It means the estimated HRs tend to be close to the null, and true HRs should be smaller due to the misclassification. In addition, because more than two thirds of the women in our cohort never or seldom exercised, we expect less serious misclassification. Second, updated information on menopausal status was lacking, which could modify the relationship between physical activity and breast cancer. Thus, from an etiologic viewpoint, the misclassification of menopausal status at the onset of breast cancer should be important. However, from the viewpoint of cancer prevention, the menopausal status at cancer onset is comparatively less important, and the HR could be naturally interpreted for premenopausal women at baseline. Third, misclassification of menopausal status at baseline should also be considered. However, the point estimate of the HR among premenopausal women was smaller than that among postmenopausal women, which could not be explained from misclassification. In addition, the results were not essentially changed when we removed women who were 47 to 50 years old from the premenopausal group. More studies are needed of premenopausal women in larger subjects.

In summary, our analysis provided evidence that physical activity decreased the risk of breast cancer among Japanese women. Another encouraging finding of this study is that the effect of physical activity on breast cancer risk is not modified by menopausal status and BMI. We recommend walking for 1 hour per day along with additional weekly exercise to protect against breast cancer, regardless of menopausal status and BMI.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Appendix 1. The Japan Collaborative Cohort Study Group

The present members of the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Aichi Medical University School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Institute of Community Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Yutaka Inaba, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences Graduate School; Dr. Hiroshi Suzuki, Niigata University Graduate School of Medical and Dental Sciences; Dr. Hiroyuki Shimizu, Gifu University School of Medicine; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, Nagoya City University Graduate School of Medical Sciences; Dr. Yoshinori Ito, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Kenji Wakai, Nayoga University Graduate School of Medicine; Dr. Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. Takesumi Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. Akira Shibata, Kurume

University School of Medicine; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; Dr. Hideo Shio, Moriyama Municipal Hospital; Dr. Yoshiyuki Ohno (former chairman of the study group), Asahi Rosai Hospital; Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research; Dr. Toshio Kuroki, Gifu University; and Dr. Kazuo Tajima, Aichi Cancer Center Research Institute.

The past investigators of the study group were listed in ref. 28 except for the following eight members (affiliations are those at the time they participated in the study): Dr. Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr. Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr. Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Tsutomu Hashimoto, Wakayama Medical University; Dr. Teruo Ishibashi, Asama General Hospital; and Dr. Katsuhiro Fukuda, Kurume University School of Medicine.

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対象の内訳		ヒト	動物	地 域	国内	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	女性	( )		( )		( )
	年齢	57.6±10.1歳			( )		前向き研究
	対象数	10000以上			( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	なし	なし	ガン予防	なし	( )	( )
	維持・改善	なし	なし	なし	なし	( )	( )

図 表

Table 2. HR of breast cancer associated with physical activity in the JACC study

Physical activity	Cases	Person-years	Age adjusted HR (95% CI)	Multivariate* HR (95% CI)
Time spent walking per day				
<30 min	69	96,752	1.00 (Reference)	1.00 (Reference)
30–59 min	56	71,411	1.14 (0.71 – 1.84)	1.13 (0.80 – 1.61)
≥1 h	82	171,892	0.70 (0.51 – 0.97)	0.73 (0.53 – 1.01)
P for trend			0.021	0.043
Time spent exercising per week				
Never or seldom	161	255,829	1.00 (Reference)	1.00 (Reference)
1–2 h	29	51,043	0.87 (0.59 – 1.30)	0.83 (0.56 – 1.23)
≥3 h	17	33,183	0.87 (0.53 – 1.45)	0.85 (0.51 – 1.40)
P for trend			0.45	0.33

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 4. HR of breast cancer associated with physical activity in the JACC study

Physical activity: Time spent walking (h/d)	Time spent exercising (h/wk)	Cases	Person-years	Age adjusted HR (95% CI)	Multivariate* HR (95% CI)
<1	<1	93	130,279	1.00 (Reference)	1.00 (Reference)
≥1	<1	68	125,550	1.18 (0.79 – 1.77)	1.13 (0.75 – 1.69)
<1	≥1	32	37,885	0.76 (0.56 – 1.04)	0.82 (0.60 – 1.12)
≥1	≥1	14	46,342	0.42 (0.24 – 0.74)	0.45 (0.25 – 0.78)
P for interaction				0.035	0.041

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

図表掲載箇所	P3398, Table2, P3399, Table4
概 要 (800字まで)	本研究は、日本のThe Japan Collaborative Cohort (JACC) Studyに参加した女性30,157名を対象に平均12.4年間の追跡調査を行い、身体活動と乳がん発症リスクの関連を検討したものである。質問紙によって、1日当たり歩行に費やす時間、週当たりの運動実施時間を尋ねた。歩行時間を、30分/日未満、30-59分/日、60分/日以上の3群に、運動実施時間を、ほとんどなし、1-2時間/週、3時間/週以上の3群に分類した。乳がん発症リスクにおける歩行時間の延長にはリスク減少傾向がみられたものの、有意な差はみられなかった。同様に運動実施時間についても有意な差はみられなかった。次に、歩行時間と運動時間の複合効果を検討するために、歩行時間1時間/日未満かつ運動時間1時間/週未満の集団(最も不活動な集団)と比較すると、歩行時間1時間/日以上かつ運動時間1時間/週以上の集団(最も活動的な集団)では乳がん発症リスクが0.45(95%信頼区間:0.25-0.78)と有意に減少することが明らかとなった(Pinteraction=0.041)。
結 論 (200字まで)	日本人の中年女性コホートにおいて、活動的でいることは閉経状態や肥満度に関わらず乳がん発症リスクを減少させることが明らかとなった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に用いられた研究の1つである。日本人を対象に、かつ大規模に乳がんの発症と身体活動との関連を検討しており、非常に重要な研究である。歩行時間と運動実施時間を各々単独に乳がん発症との関連を検討した場合には、関連は認められていないが、複合的に検討することで歩行時間が長く運動を実施していることで乳がんのリスクが下がることが示された。今後は総身体活動量との関係や、他の身体活動のドメインとの関連についても詳細に検討されることが期待される。

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Time spent walking and risk of colorectal cancer in Japan: The Miyagi Cohort Study

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Higher levels of physical activity have been consistently associated with a lower risk of colon cancer in earlier epidemiological studies. The specific benefits of walking, however, remain relatively unexplored. In 1990, 20 519 men and 21 469 women in Japan completed a self-administered questionnaire including a question on time spent walking per day. During 7 years of follow-up, 260 cases of colorectal cancer were documented in 305 790 person-years. We used the Cox proportional hazards regression model to estimate the relative risk of incident cancer (colorectal, colon, and rectal) according to three levels of walking. Time spent walking was inversely associated with risk of colorectal cancer incidence in men. Compared with men who walked 0.5 h or less per day, the multivariate relative risks were 1.06 (95% confidence interval 0.72–1.57) for men who walked between 0.5 and 1 h per day, and 0.57 (95% confidence interval 0.38–0.83) for men who walked 1 h or more per day (*P* for trend = 0.003). Time spent walking per day was associated with a lower risk of colon cancer in Japanese men but not in women, and there was no association between time spent walking and the risk of rectal cancer. *European Journal of Cancer Prevention* 16:403–408 © 2007 Lippincott Williams & Wilkins.

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Keywords: colorectal cancer, incidence, prospective cohort study, time spent walking

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Introduction

Colorectal cancer is one of the most common cancers in western people (Parkin *et al.*, 2002). In Japan, the incidence rate has increased in recent years (Parkin *et al.*, 2002), following Japan's westernization over the past few decades. The comprehensive review issued by the World Cancer Research Fund/American Institute of Cancer Research in 1997 noted a close link between physical activity and the risk of colorectal cancer (World Cancer Research Fund/American Institute for Cancer Research, 1997). The review convincingly stated that physical activity would afford substantial protective effects against colon cancer. The reviewers also noted that the relationship between physical activity and rectal cancer was unclear. Previous studies of colon cancer have focused primarily on occupational and leisure physical activities (Thune and Furberg, 2001; Parkin *et al.*, 2002; Slattery *et al.*, 2003), and there have been no reports on the effectiveness of usual daily activities.

Walking is one of the most common forms of moderate-intensity physical activity among middle-aged and older people (US Department of Health and Human Services, 1996). In contrast to earlier guidelines that recommended vigorous exercise to reduce the risk of cardiovascular disease (American College of Sports Medicine, 1986), a recent prospective study demonstrated that daily walking, as well as vigorous exercise, substantially reduced the incidence of cardiovascular events (Manson *et al.*, 2002). Furthermore, prospective cohort studies of the effect of walking found that daily walking improved all cause mortality rates (Hakim *et al.*, 1998; Fujita *et al.*, 2004), and lowered the incidence of coronary heart disease (Manson *et al.*, 1999), stroke (Hu *et al.*, 2000), type 2 diabetes (Hu *et al.*, 1999), hypertension (Hayashi *et al.*, 1999), dementia (Abbott *et al.*, 2004) and cognitive malfunctions (Weuve *et al.*, 2004). Although many studies have shown that vigorous exercise improved the incidence rate of colorectal cancer, to our knowledge, only two studies have prospectively explored the effects of walking alone for colorectal cancer. These studies failed to demonstrate any benefit of walking on the risk of colorectal cancer (Wannamethee *et al.*, 2001; Chao *et al.*, 2004).

The purpose of the present paper was to investigate the association between the amount of time spent walking each day and the risk of colorectal cancer, using a validated, single-item, self-administered questionnaire on walking (Tsubono *et al.*, 2002) in a large, Japanese, population-based, prospective cohort study.

Methods

Study cohort

We have reported the design of this prospective cohort study in detail elsewhere (Fukao *et al.*, 1995; Nakaya *et al.*, 2005). Briefly, from June to August 1990, we delivered a self-administered questionnaire on various health habits to 51 921 study participants (25 279 men and 26 642 women) who were aged 40–64 years and lived in 14 municipalities in Miyagi Prefecture in northern Japan. The questionnaires were delivered to and collected from the participants' residences by members of health promotion committees appointed by the municipal governments. Usable questionnaires were returned by 47 605 persons (22 836 men and 24 769 women), yielding a response rate of 91.7%.

The study protocol was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine. We considered the return of self-administered questionnaires signed by the participants to imply their consent to participate in the study.

Exposure data

For the assessment of time spent walking, the questionnaire asked 'How long do you walk each day on average for the recent 1 year?' and the participants were asked to choose one of the three options: 0.5 h or less per day, between 0.5 and 1 h per day and 1 h or more per day.

We conducted a validation study for the questionnaire assessment of time spent walking (Tsubono *et al.*, 2002), in which 106 participants (51 men and 55 women, mean age 61.7 years) in the study distinct completed the questionnaire five times at 3-month intervals. Along with the first through the fourth questionnaire surveys, pedometer measurements were conducted for 3 consecutive days (a total of 12 days). The sex and age-adjusted mean daily numbers of walking steps counted by the pedometer were 5857, 7047 and 7621 for the three categories of walking questions in the fifth questionnaire, and there were significant linear associations with all of the five questionnaire measurements.

Follow-up

We used population registries in the 14 municipalities to ascertain the vital and residential status of the participants from 1 June 1990 to 31 December 1997. We identified incident cases of colorectal cancer by computerized record linkage with the Miyagi Prefectural Cancer Registry, which covers the study area (Takano and Okuno, 1997).

Of the 47 605 participants who responded to the questionnaire, we excluded those who had incomplete responses in walking information ($n = 4507$). We also excluded 1110 participants who had prevalent cancer ascertained either by self-reports in the questionnaire or by records of the cancer registry. Consequently, 41 988 participants (20 519 men and 21 469 women) with 260 incident cases of colorectal cancer were included in this analysis. Among men, 166 colorectal cancer cases were diagnosed, and there were 94 cases diagnosed in women.

We counted person-years of follow-up for each participant from 1 June 1990, until the date of diagnosis of cancer, date of emigration outside the study districts, date of death or the end of the study period (31 December 1997), whichever occurred first. A total of 308 425 person-years resulted. We discontinued follow-up of participants who emigrated from the study municipalities because of logistical limitations; hence, 1481 participants (3.5% of the analytic cohort) were lost to follow-up during the study period.

Statistical analysis

We used Cox proportional-hazards regression model to estimate relative risk of cancer incidence according to categories of time spent walking per day and to adjust for potentially confounding variables, using SAS version 8.2 statistical software package (SAS Inc., Cary, North Carolina, USA).

We considered the following variables as potential confounders: age in years; alcohol consumption (never drank alcohol, drank in the past, currently drinking); cigarette smoking (never smoked, smoked in the past, currently smoking 1–19 cigarettes per day, or currently smoking 20 or more cigarettes per day); body mass index in kg/m^2 (18.4 or lower, 18.5–24.9 or 25.0 or higher); family history of colorectal cancer (presence or absence); education (in school until age 15 years or younger, or age 16 years or older); sports or exercise (almost never, between 1 and 2 h/week, between 3 and 4 h/week, and 5 h or more per week) and consumption frequencies of meats, green or yellow vegetables and oranges (almost daily, 3 to 4 times per week, 1 to 2 times per week, or 1 to 2 times per month or less often). For women, we also included menopausal status (before menopause, after menopause).

We repeated all analyses after excluding colorectal cancer cases diagnosed during the first two years of follow-up. We also conducted stratified analyses to examine whether the association between the risk of colorectal cancer incidence and time spent walking per day was modified by these variables. P values for testing statistical significance of linear trends were calculated by treating the categories of time spent walking as continuous variables. All P values were two-tailed.

Results

Table 1 outlines the characteristics of the study participants by levels of time spent walking per day. Among men, 30.9% reported that they walked 0.5 h or less per day (the lowest category), 23.6% reported that they walked between 0.5 and 1 h per day (the middle category), and 45.5% reported that they walked 1 h or more per day (the highest category). Corresponding proportions among women were 29.6, 24.8 and 45.6%, respectively. Men who walked 1 h or more per day tended to be older, less obese, have less education and consume green or yellow vegetables and fruits more frequently than those who walked 0.5 h or less per day. Women who walked 1 h or more per day were older, less likely to drink alcohol and tended to consume green or yellow vegetables more frequently than those who walked 0.5 h or less per day.

Table 2 presents relative risk of colorectal cancer according to categories of time spent walking per day for men and women separately. The relationship between risk of colorectal cancer incidence and categories of time spent walking was remarkable only for men. Among men, age-adjusted analysis showed a significant inverse relationship between time spent walking per day and risk of colorectal cancer incidence (P for trend = 0.004). The risk of colorectal cancer incidence among the highest category was 39% lower than in the lowest category. These results remained basically unchanged after multivariate adjustment and after exclusion of cancer cases diagnosed within the first 2 years of follow-up (P for trend = 0.005). The inverse association with time spent walking was limited to colon cancer. In women, there was no association between time spent walking per day and risk of colorectal, colon, or rectal cancer incidence. These results remained basically unchanged after the stratified

Table 1 Baseline characteristics of study participants by time spent walking per day

	Men			Women		
	Time spent walking per day (h)			Time spent walking per day (h)		
Characteristics	≤ 0.5	0.5–1.0	1.0 ≤	≤ 0.5	0.5–1.0	1.0 ≤
No. of participants	6348	4845	9326	6354	5317	9798
Mean age, years (SD)	50.2 (7.6)	51.3 (7.7)	52.4 (7.5)	50.5 (7.6)	52.2 (7.5)	52.7 (7.2)
Smoking (%)						
Never	17.9	18.6	19.2	87.6	89.8	89.3
Past	20.0	22.2	18.6	2.3	1.8	2.0
Current (1–19 cigarettes per day)	13.8	15.0	15.2	6.2	5.5	5.9
Current (20 ≤ cigarettes per day)	48.3	44.2	47.0	3.9	2.9	2.8
Alcohol drinking (%)						
Never	16.6	14.4	15.8	69.6	72.2	73.4
Past	7.7	7.1	7.0	4.6	3.9	3.8
Current	75.7	78.5	77.2	25.8	23.9	22.8
Body mass index in kg/m^2 (%)						
<18.5	2.2	1.9	2.0	3.0	2.4	2.6
18.5–24.9	67.8	69.5	72.5	65.9	65.3	66.9
25.0 ≤	30.0	28.5	25.5	31.2	32.3	30.5
Family history of colorectal cancer						
Yes	1.6	1.8	1.2	1.9	1.7	1.4
Education (%)						
≤ 15	35.4	34.4	46.1	36.9	37.0	41.5
16 ≤	64.6	65.6	53.9	63.1	63.0	58.5
Beef consumption (%)						
≤ 1–2 times per month	83.3	83.1	84.9	87.1	87.6	88.7
1–2 times per week	14.1	14.5	12.1	10.8	10.5	9.4
3–4 times per week	2.1	1.9	2.3	1.6	1.3	1.3
Almost every day	0.5	0.5	0.7	0.5	0.6	0.6
Green vegetables consumption (%)						
≤ 1–2 times per month	17.9	14.1	13.5	9.8	7.1	8.5
1–2 times per week	38.0	36.2	32.6	32.6	29.8	27.1
3–4 times per week	28.0	30.3	30.9	34.9	36.8	35.0
Almost every day	16.1	19.4	23.0	22.7	26.3	29.4
Carrot or pumpkin consumption (%)						
≤ 1–2 times per month	31.3	27.1	26.4	14.3	10.7	11.2
1–2 times per week	39.5	40.0	38.1	36.3	33.9	32.0
3–4 times per week	21.6	23.9	24.8	33.0	37.1	35.2
Almost every day	7.6	9.0	10.7	16.4	18.3	21.6
Orange consumption (%)						
≤ 1–2 times per month	31.9	27.4	28.7	16.0	13.6	16.5
1–2 times per week	31.4	32.3	27.6	21.0	21.3	20.5
3–4 times per week	21.0	24.0	24.0	27.5	27.6	26.5
Almost every day	15.7	16.3	19.7	35.5	37.4	36.5
Exercise (%)						
Almost never	79.4	61.8	73.1	86.1	72.4	76.5
1–2 h/week	15.2	22.5	13.7	10.9	18.3	13.2
3–4 h/week	3.6	10.2	5.2	2.3	6.2	4.8
≤ 5 h/week	1.8	5.5	8.0	0.7	3.1	5.5