validated. Our basic measures of physical activity may also introduce confounding of type of physical activity with the intensity of physical activity. Information on occupational physical activity other than walking was not collected, which may be an additional source of exercise [21]. However, the USRT cohort comprises current and former radiologic technologists and current technologists may have similar occupational physical activity levels, suggesting that confounding by occupational activity may be minimal. We also did not collect information about physical activity performed at other ages. Physical activity reported at baseline in this study reflects activity by women who have consistently exercised over their lifetime, as well as activity by women who recently began exercising. Thus, our results may reflect the benefit of long-term exercise or current exercise with no ability to differentiate between these two effects. Another limitation of this study is the moderate amount of missing physical activity data. Some misclassification of menopausal status may be present since we did not have updated information on menopausal status, thus some women who were premenopausal at baseline may have become postmenopausal during the follow-up period. Lack of significant associations may also be due to small numbers of breast cancer cases in some categories of physical activity.

In summary, our results provide modest support that moderate physical activity may protect against breast cancer. Effect modification by MHT use among postmenopausal women suggests that physical activity may reduce risk through hormonal mechanisms. Further epidemiologic and mechanistic research among postmenopausal women is required to clarify the potential hormonal association between physical activity and breast cancer.

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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	女性	( )		( )		( )
年齢	(47.2歳)	[redacted]		( )		前向きコホート
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 Risk of breast cancer according to various measures of physical activity

Exercise variable	Cases	Person-years	Age-adjusted HR	Multivariate[a] HR	Multivariate[a] HR + other activity variables
Strenuous exercise (hours/week)					
Never	460	200,372	1.0	1.0	1.0
<1	160	90,368	0.94 (0.78–1.12)	0.93 (0.78–1.11)	0.93 (0.77–1.11)
1–3	161	75,989	1.06 (0.88–1.27)	1.03 (0.86–1.24)	1.02 (0.85–1.23)
4–9	55	31,415	0.86 (0.65–1.14)	0.83 (0.62–1.10)	0.82 (0.61–1.09)
10+	10	6,312	0.76 (0.41–1.43)	0.76 (0.40–1.42)	0.90 (0.47–1.71)
P_{trend}			0.298	0.196	0.320
Walking/hiking for exercise (hours/week)					
Never	187	82,030	1.0	1.0	1.0
<1	223	110,068	0.96 (0.79–1.17)	0.97 (0.80–1.18)	1.01 (0.82–1.24)
1–3	295	139,260	1.01 (0.84–1.21)	1.02 (0.84–1.22)	1.06 (0.87–1.29)
4–9	143	60,083	1.08 (0.87–1.34)	1.10 (0.88–1.37)	1.16 (0.92–1.46)
10+	16	13,016	0.56 (0.33–0.92)	0.57 (0.34–0.95)	0.63 (0.37–1.07)
P_{trend}			0.264	0.321	0.662
Walking at home or work (hours/week)					
Never	57	20,851	1.20 (0.88–1.63)	1.21 (0.88–1.65)	1.21 (0.88–1.67)
<1	131	58,598	1.0	1.0	1.0
1–3	233	105,771	1.00 (0.81–1.24)	1.01 (0.81–1.25)	1.00 (0.80–1.24)
4–9	177	83,370	0.98 (0.78–1.23)	0.99 (0.79–1.24)	0.97 (0.77–1.23)
10–19	82	41,678	0.92 (0.70–1.21)	0.92 (0.70–1.21)	0.92 (0.69–1.22)
20–39	101	48,537	0.98 (0.76–1.28)	1.00 (0.77–1.29)	0.99 (0.76–1.29)
40+	83	45,652	0.87 (0.66–1.14)	0.88 (0.67–1.16)	0.90 (0.68–1.20)
P_{trend}			0.330	0.401	0.623
Total MET-score					
Q1 (0.0–9.5)	188	79,694	1.0	1.0	
Q2 (11.5–23.0)	181	80,264	1.04 (0.85–1.27)	1.02 (0.83–1.26)	
Q3 (23.5–45.5)	190	84,697	1.03 (0.84–1.26)	1.02 (0.83–1.25)	
Q4 (46.0–96.5)	152	80,381	0.88 (0.71–1.09)	0.87 (0.70–1.08)	
Q5 (≥97.0)	153	79,420	0.92 (0.74–1.14)	0.91 (0.74–1.13)	
P_{trend}			0.170	0.174	

[a] Adjusted for entry age, body mass index, age at menarche, parity, age at first birth, age at menopause, family history of breast cancer, personal history of breast disease, OC use, menopausal hormone therapy, race, smoking, and alcohol consumption

図表掲載箇所	
概 要 (800字まで)	ホルモン補充療法の影響などを考慮しつつ、身体活動と乳がんの発症リスクとの関係を明らかにすること。＜方法＞コホート名：U.S. Radiologic Technologists cohort、対象者数：45631人、追跡期間：8.9年、因子評価方法詳細：直近の前年における週当たりの運動のための歩行/ハイキング（メッツ値：4）と家庭内あるいは勤務中の歩行（メッツ値：3）、高い強度の運動（例：エアロビクス、ジョッギング、水泳：メッツ値：7）の実施回数と実施時間を評価、因子の単位：メッツ時／週、分位毎の身体活動量分位1：0-9.5メッツ・時／週、分位2：11.5-23メッツ・時／週、分位3：23.5-45.5メッツ・時／週、分位4：46-96.5メッツ・時／週、分位5：97メッツ・時／週以上であった。＜結果＞ホルモン補充療法を受けていない閉経女性で、身体活動量と乳がん発症リスクとの関係は、分位1：1、分位2：0.65(0.4-1.08)、分位3：0.64(0.4-1.07)、分位4：0.50(0.3-0.87)、分位5：0.71(0.43-1.17)、であった。閉経前女性あるいはホルモン補充療法を受けている女性ではこのような関係はみられなかった。
結 論 (200字まで)	閉経後の女性では週46メッツ時以上の身体活動が乳がんの発症を予防する（トレンドは有意差無し）。ホルモン補充療法を受けている場合は関係がない。ホルモン療法の有無で、身体活動と乳がん発症との関係は違ってくる可能性がある。
エキスパートによるコメント (200字まで)	ホルモン補充療法がなくとも、身体活動の改善は死のうリスクを減らす可能性が示唆された点で、意義深い。

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Walking Compared With Vigorous Physical Activity and Risk of Type 2 Diabetes in Women
A Prospective Study

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Context Although many studies suggest that physical activity may reduce risk of type 2 diabetes, the role of moderate-intensity activity such as walking is not well understood.

Objectives To examine the relationship of total physical activity and incidence of type 2 diabetes in women and to compare the benefits of walking vs vigorous activity as predictors of subsequent risk of type 2 diabetes.

Design and Setting The Nurses' Health Study, a prospective cohort study that included detailed data for physical activity from women surveyed in 11 US states in 1986, with updates in 1988 and 1992.

Participants A total of 70 102 female nurses aged 40 to 65 years who did not have diabetes, cardiovascular disease, or cancer at baseline (1986).

Main Outcome Measure Risk of type 2 diabetes by quintile of metabolic equivalent task (MET) score, based on time spent per week on each of 8 common physical activities, including walking.

Results During 8 years of follow-up (534 928 person-years), we documented 1419 incident cases of type 2 diabetes. After adjusting for age, smoking, alcohol use, history of hypertension, history of high cholesterol level, and other covariates, the relative risks (RRs) of developing type 2 diabetes across quintiles of physical activity (least to most) were 1.0, 0.77, 0.75, 0.62, and 0.54 (*P* for trend <.001); after adjusting for body mass index (BMI), RRs were 1.0, 0.84, 0.87, 0.77, and 0.74 (*P* for trend = .002). Among women who did not perform vigorous activity, multivariate RRs of type 2 diabetes across quintiles of MET score for walking were 1.0, 0.91, 0.73, 0.69, and 0.58 (*P* for trend <.001). After adjusting for BMI, the trend remained statistically significant (RRs were 1.0, 0.95, 0.80, 0.81, 0.74; *P* for trend = .01). Faster usual walking pace was independently associated with decreased risk. Equivalent energy expenditures from walking and vigorous activity resulted in comparable magnitudes of risk reduction.

Conclusions Our data suggest that greater physical activity level is associated with substantial reduction in risk of type 2 diabetes, including physical activity of moderate intensity and duration.

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STRONG EPIDEMIOLOGIC EVIDENCE suggests that physical activity is associated with reduced risk of type 2 diabetes. In cross-sectional and ecological studies, higher levels of physical activity are associated with lower prevalence of type 2 diabetes.[1,2] Populations who migrate to westernized countries with more sedentary lifestyles have greater risks of type 2 diabetes than their counterparts who remain in their native countries.[2] Populations undergoing westernization in the absence of migration, such as North American Indians[3] and Western Samoans,[4,5] also have experienced increases in obesity and type 2 diabetes. Such studies must be interpreted with caution, however. In cross-sectional studies, it is difficult to establish cause and effect, and in the studies of migrant or westernizing populations, many other factors in addition to physical activity undergo change, including modifications in diet and other lifestyle factors.

More powerful support for the role of physical activity in the prevention of type 2 diabetes has emerged in the past several years from prospective cohort studies.[6-13] Most of these studies, however, did not examine separately the role of moderate-intensity physical activity such as walking vs vigorous activ-

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ity, although increasing evidence supports the beneficial effects of moderate-intensity activity.[14-16] Except for subjects in our own previous report,[7] subjects in these studies have been predominantly male. All have suggested an inverse association between physical activity and diabetes, but there have been discrepancies among studies in terms of the relationship between risk of type 2 diabetes and the frequency and intensity of physical activity. Whether the effects of physical activity on diabetes risk differ between individuals at high vs low risk of type 2 diabetes (ie, the presence or absence of diabetes risk factors) has also been controversial.

In this study, we used detailed and repeated assessments of physical activity to quantify the dose-response relationship between total physical activity and incidence of type 2 diabetes in women. We also examined in detail the potential benefits of walking (the most common form of physical activity in middle-aged and older populations) compared with more vigorous activity.

METHODS

Subjects

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses aged 30 to 55 years residing in 1 of 11 US states responded to mailed questionnaires regarding their medical history and health practices; details have been published elsewhere.[17] The subjects for the present analysis were 70 102 women from this cohort who in 1986 were free from diagnosed diabetes, cardiovascular disease, and cancer (except nonmelanoma skin cancer) and who completed the questions on physical activity in 1986.

Assessment of Physical Activity

A detailed assessment of physical activity was first obtained by questionnaire in 1986 and updated in 1988 and 1992. Subjects were asked the amount of time they spent on average per week on each of the following physical activities: walking; jogging; running; bicycling; calisthenics, aerobics, aerobic dance, or rowing machine use; lap swimming; playing squash or racquetball; and playing tennis. They were also asked about their usual walking pace, specified as easy or casual (less than 3.2 km/h), normal, average (3.2-4.8 km/h), brisk (4.8-6.2 km/h), and very brisk or striding (6.4 km/h or faster). From this information, weekly energy expenditure in metabolic equivalent task–hours (MET-hours) was calculated.[18] Because only 2% of women reported a very brisk or striding pace, we combined brisk and very brisk categories in the analyses of walking pace and diabetes risk. We defined any physical activity requiring 6 METs or greater (a 6-fold or greater increase above resting metabolic rate) as vigorous. These activities included jogging, running, bicycling, performing calisthenics, lap swimming, playing squash or racquetball, and playing tennis. In contrast, walking requires an energy expenditure of only 2 to 4.5 METs, depending on pace, and therefore we considered it to be a moderate-intensity activity.

The reproducibility and validity of the physical activity questionnaire has been described elsewhere.[19] In a representative sample (n = 147) of participants in the Nurses' Health Study II cohort, the 2-year test-retest correlation for activity was 0.59. The correlation between physical activity reported on 1-week recalls and that reported on the questionnaire was 0.79. The correlation between activity reported in diaries and that reported on questionnaires was 0.62. In a separate study on a population aged 20 to 59 years recruited from a university community (n = 103), the correlation between physical activity score on a similar questionnaire and maximum oxygen consumption was 0.54.[20]

Earlier analyses from this cohort had used only a single activity question about number of episodes of vigorous (sweat-inducing) activity per week.[7] These earlier analyses demonstrated an inverse association between such vigorous activity and risk of type 2 diabetes but did not assess the potential role of walking and other moderate-intensity activities. Walking is by far the most prevalent physical activity among older adults[21] and is feasible, accessible, and relatively safe. We undertook the present analyses to examine the relationship between walking and risk of type 2 diabetes.

Diagnosis of Diabetes

A supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy was mailed to women who indicated on any biennial questionnaire that they had been diagnosed as having diabetes. Women reporting a diagnosis of diabetes before 1986 were excluded from these analyses.

A case of diabetes was considered confirmed if at least 1 of the following was reported on the supplementary questionnaire: (1) 1 or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) plus fasting plasma glucose levels of at least 140 mg/dL (7.8 mmol/L) or random plasma glucose levels of at least 200 mg/dL (11.1 mmol/L); (2) at least 2 elevated plasma glucose concentrations on different occasions (fasting levels of at least 140 mg/dL [7.8 mmol/L], random plasma glucose levels of at least 200 mg/dL [11.1 mmol/L], and/or concentrations of at least 200 mg/dL after 2 hours or more shown by oral glucose tolerance testing) in the absence of symptoms; or (3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent).

All women with diabetes in these analyses were at least 40 years old at the time of diagnosis. We excluded 27 cases of type 1 diabetes, 40 women classified as having gestational diabetes only, and an additional 183 cases of self-reported diabetes that did not satisfy all of our criteria for type 2 diabetes. The remaining women who reported new-onset diabetes were classified as having type 2 diabetes and were included in the present analyses.

Because of potential associations between weight and physical activity, no body weight criteria were used in the classification of type of diabetes for these analyses. Our criteria for diabetes classification are consistent with those proposed by the National Diabetes Data Group.[22] The validity of this questionnaire has been verified in a subsample of this study population.[7] Among a random sample of 84 women classified by the questionnaire as having type 2 diabetes, 71 gave permission for their medical records to be reviewed, and records were available for 62. An endocrinologist (J.E.M.) blinded to the information reported on the supplementary questionnaire reviewed the records according to National Diabetes Data Group criteria.[22] The diagnosis of type 2 diabetes was confirmed in 61 (98%) of 62 of the women.[7]

Statistical Analysis

Person-years for each participant were calculated from the date of return of the 1986 questionnaire to the date of confirmed type 2 diabetes, death from any cause, or June 1, 1994, whichever came first. Incidence rates of type 2 diabetes were obtained by dividing number of cases by person-years in each category of physical activity. Relative risks (RRs) were computed as the incidence rate in a specific category of MET score divided by that in the lowest quintile, with adjustment for 5-year age categories. Tests of linear trend across increasing categories of MET were conducted by treating the categories as a continuous variable and assigning the median score for the category as its value. To best represent long-term physical activity levels of individual women and reduce measurement error, we created measures of the cumulative average of MET scores from all available questionnaires up to the start of each 2-year follow-up interval.[23] For example, the 1986 MET score was related to the incidence of type 2 diabetes between 1986 and 1988, and the average of the 1986 and 1988 scores was related to the incidence between 1988 and 1990.

We used pooled logistic regression with 2-year intervals[24] to adjust simultaneously for potential confounding variables including age (5-year interval), smoking status (never; past; current smoking of 1-14, 15-24, and 25 or more cigarettes per day), alcohol consumption (0, 1-4, 5-14, or 15 or more g/d), menopausal status and postmenopausal hormone use, parental history of diabetes, and history of hypercholesterolemia or hypertension at baseline. In additional analyses, we included body mass index (BMI) in quintiles in the model to examine the degree to which the relation with physical activity was mediated through BMI.

RESULTS

A total of 1419 cases of type 2 diabetes were confirmed during 8 years (534 928 person-years) of follow-up, corresponding to an incidence rate of 265 per 100 000 person-years. TABLE 1 shows the distributions of selected characteristics according to quintile of total energy expenditure on physical activity, standardized to the age distribution of the study population. Compared with their sedentary colleagues, physically active women tended to be leaner and were less likely to be current smokers or hypertensive. Dietary intakes of fats and cholesterol did not differ appreciably across quintiles.

There was a progressive reduction in the age-adjusted RR of diabetes with increasing physical activity (TABLE 2). After adjustment for smoking, alcohol use, history of hypertension, and elevated cholesterol level, the RRs across quintiles of total MET-hours per week were 1.0, 0.77, 0.75, 0.62, and 0.54 (*P* for

Table 1. Distribution of Potential Type 2 Diabetes Risk Indicators According to Quintile of Total Physical Activity Score at Baseline (1986)*

	Quintile, MET-Hours per Week (Median)†				
	1 0-2.0 (0.8)	2 2.1-4.6 (3.3)	3 4.7-10.4 (7.7)	4 10.5-21.7 (15.7)	5 ≥21.8 (35.4)
No. of women	13 283	14 564	14 064	13 928	14 263
% of group					
Current smokers	28.3	23.9	19.7	17.4	17.5
History of hypertension	24.8	24.0	22.8	21.5	20.2
History of hypercholesterolemia	11.3	10.9	11.1	11.5	10.1
Family history of diabetes	16.3	17.1	16.1	16.3	15.3
Current postmenopausal hormone use	19.7	21.7	23.4	23.9	24.3
Mean (SD)					
Age, y	52.0 (7.1)	52.2 (7.1)	52.1 (7.2)	52.2 (7.2)	52.2 (7.2)
Alcohol, g/d	6.1 (11.6)	5.8 (10.6)	6.1 (10.2)	6.5 (10.5)	7.1 (10.8)
BMI, kg/m²	24.9 (4.9)	24.5 (4.4)	24.1 (4.0)	23.7 (3.9)	23.4 (3.7)
Waist circumference, cm	80.5 (11.9)	79.2 (10.9)	78.2 (10.4)	77.0 (9.9)	75.4 (9.7)
Saturated fat, % of energy‡	12.2 (2.7)	11.9 (2.5)	11.7 (2.5)	11.5 (2.5)	11.2 (2.6)
Polyunsaturated fat, % of energy‡	6.2 (1.7)	6.1 (1.6)	6.2 (1.6)	6.1 (1.6)	6.1 (1.6)
Trans fat, % of energy‡	1.8 (0.6)	1.7 (0.5)	1.7 (0.5)	1.6 (0.5)	1.5 (0.5)
Dietary cholesterol, mg/4184 kJ‡	154 (50.7)	152 (45.1)	150 (45.0)	149 (43.5)	148 (45.2)

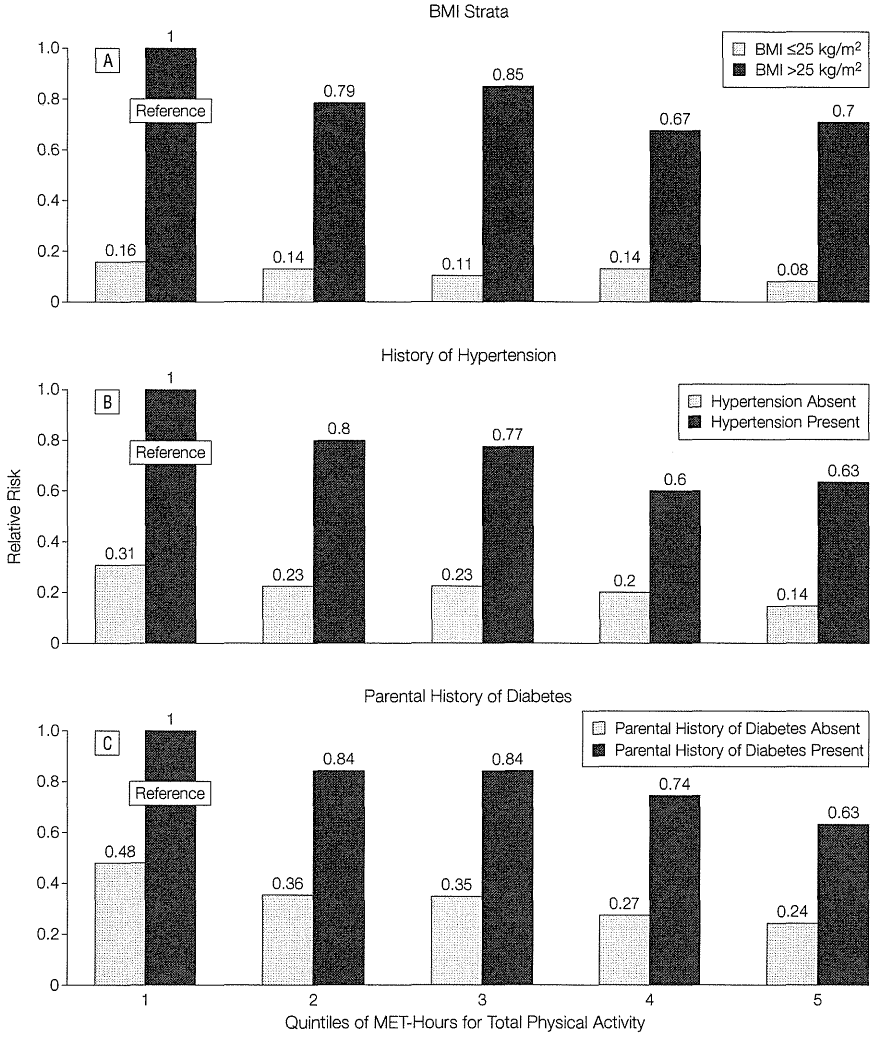
*Percentages and means for variables other than age are standardized according to the age distribution of the overall study group. BMI indicates body mass index; MET, metabolic equivalent task.
†Average time per week spent in each of 8 activities multiplied by the MET value of each activity. The MET value is the energy need per kilogram of body weight per hour of activity divided by the energy need per kilogram of body weight per hour at rest.
‡Per energy intake per day.

Table 2. Relative Risks (95% Confidence Intervals) of Type 2 Diabetes According to Quintile of Total Physical Activity Score From the Nurses' Health Study, 1986-1994*

	Quintile, MET-Hours per Week (Median)					
	1 0-2.0 (0.8)	2 2.1-4.6 (3.3)	3 4.7-10.4 (7.7)	4 10.5-21.7 (15.7)	5 ≥21.8 (35.4)	*P* Value
No. of cases	422	296	287	226	188	
Person-years	108 829	104 467	107 254	107 247	107 131	
Age-adjusted	1.0	0.71 (0.61-0.83)	0.67 (0.57-0.78)	0.52 (0.44-0.61)	0.43 (0.36-0.52)	<.001
Multivariate†	1.0	0.77 (0.66-0.90)	0.75 (0.65-0.88)	0.62 (0.52-0.73)	0.54 (0.45-0.64)	<.001
Additional adjustment for BMI‡	1.0	0.84 (0.72-0.97)	0.87 (0.75-1.02)	0.77 (0.65-0.91)	0.74 (0.62-0.89)	.002

*Computed as cumulative updated average across 1986, 1988, and 1992 (see the "Methods" section). See footnotes to Table 1 for definition of metabolic equivalent task (MET).
†Models included age (5-year category); time period (4 periods); cigarette smoking (never, past, and current smoking of 1-14 or ≥15 cigarettes per day); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, or postmenopausal with current hormone replacement); parental history of diabetes; alcohol consumption (4 categories); history of hypertension; and history of high cholesterol level.
‡BMI indicates body mass index; in quintiles.

Figure. Multivariate Relative Risks of Type 2 Diabetes



Multivariate relative risks of type 2 diabetes according to MET-hours for Total Physical Activity quintile, within strata of body mass index (BMI), history of hypertension, and parental history of diabetes. Adjusted for the same covariates as in Table 2 (BMI not included in the model). See footnotes to Table 1 for definition of metabolic equivalent task (MET).

trend <.001). This inverse gradient remained statistically significant after adjusting for BMI (RRs across quintiles were 1.0, 0.84, 0.87, 0.77, and 0.74; *P* for trend = .002). Adjustment for glycemic load, dietary fiber, and whole grain consumption did not appreciably change the results. The physical activity score was inversely associated with risk of type 2 diabetes in both lean and overweight women, in women with and without a history of hypertension, and in women with and without parental history of diabetes (FIGURE).

To minimize potential bias from subclinical disease, we conducted additional analyses by excluding cases of type 2 diabetes that occurred during the first 2 years of follow-up (1097 cases were included in this analysis). The multivariate RRs across quintiles of physical activity score were 1.0, 0.90, 0.83, 0.72, and 0.61 (*P* for trend <.001). To address the possibility that surveillance may have varied according to physical activity, we performed an analysis restricted to cases reporting at least 1 symptom of diabetes at diagnosis (n = 859 cases, 61% of all cases). Results from this subgroup were not appreciably different from those for the entire cohort (multivariate RRs were 1.0, 0.78, 0.79, 0.59, and 0.55; *P* for trend <.001).

We examined changes in physical activity between 1986 and 1988 in relation to the incidence of diabetes between 1988 and 1994. Compared with women who were consistently sedentary (MET-hours per week ≤2 in both 1986 and 1988), women who were con-

Table 3. Relative Risks (95% Confidence Intervals) of Type 2 Diabetes According to Quintile of MET Score for Walking Among Women Who Did Not Perform Vigorous Activities

	Quintile, MET Score for Walking (Median)†					
	1 ≤0.5 (0)	2 0.6-2.0 (1.7)	3 2.1-3.8 (3.0)	4 3.9-9.9 (7.5)	5 ≥10 (20.0)	*P*
No. of cases	250	205	145	133	111	
Person-years	62977	57069	52872	51277	51406	
Age-adjusted	1.0	0.88 (0.73-1.07)	0.67 (0.55-0.83)	0.62 (0.50-0.77)	0.51 (0.41-0.64)	<.001
Multivariate*	1.0	0.91 (0.75-1.09)	0.73 (0.59-0.90)	0.69 (0.56-0.86)	0.58 (0.46-0.73)	<.001
Additional adjustment for BMI	1.0	0.95 (0.79-1.15)	0.80 (0.65-0.99)	0.81 (0.66-1.01)	0.74 (0.59-0.93)	.01

*Adjusted for the same covariates as in Table 2. See footnotes to Table 1 for definition of metabolic equivalent task (MET). BMI indicates body mass index.

sistently active (MET-hours per week >10.4 in both 1986 and 1988) had the lowest risk of diabetes (RR = 0.59; 95% confidence interval [CI], 0.46-0.75). Women who increased their activity level from 2.1-10.4 MET-hours in 1986 to >10.4 MET-hours in 1988 had a lower risk (RR = 0.71; 95% CI, 0.55-0.93) compared with those who were consistently sedentary.

We examined the association between walking and incidence of type 2 diabetes among participants who reported no physical activity other than walking to determine whether moderate-intensity physical activity (such as walking) has a similar inverse association with risk of type 2 diabetes and to minimize confounding of results by examining vigorous forms of activity. Approximately 47% of women in 1986 reported no vigorous activity, and 60% of all women reported that they walked at least 1 hour per week. There was a strong inverse association between walking score and risk of type 2 diabetes (TABLE 3). The multivariate RRs across quintiles of walking score were 1.0, 0.91, 0.73, 0.69, and 0.58 (*P* for trend <.001). Additional adjustment for BMI attenuated these RRs, but the trend remained statistically significant (*P* = .01). In addition, exclusion of women who reported they were "unable to walk" on the 1990 or 1992 questionnaire (34 cases excluded) did not alter the results. Independent of the number of hours spent on walking, walking pace was also significantly associated with risk of diabetes. Compared with women whose usual walking pace was "easy, casual," multivariate RRs were 0.72 (95% CI, 0.62-0.85) for "normal, average" pace and 0.41 (95% CI, 0.33-0.52) for "brisk" or "striding" pace (TABLE 4).

Table 4. Relative Risk of Type 2 Diabetes According to Usual Walking Pace Among Women Who Did Not Perform Vigorous Activities*

	Usual Walking Pace		
	Easy <3.2 km/h	Normal 3.2-4.8 km/h	Brisk or Very Brisk >4.8 km/h
No. of cases	244	448	133
Person-years	46321	141708	84177
Age-adjusted RR (95% CI)	1.0	0.61 (0.52-0.72)	0.31 (0.25-0.38)
Multivariate RR† (95% CI)	1.0	0.72 (0.62-0.85)	0.41 (0.33-0.52)
Additional adjustment for BMI	1.0	0.86 (0.73-1.01)	0.59 (0.47-0.73)

*The number of cases was less than 844 (Table 3) due to missing values on walking pace. RR indicates relative risk; CI, confidence interval; and BMI, body mass index.
†Adjusted for the same covariates as in Table 2 as well as time spent walking per week.

Approximately 6% of women reported any jogging; 3%, any running; 30%, any biking; 12%, any swimming; 5%, playing any tennis; 27%, performing any calisthenics, aerobics, or aerobic dance; and 0.6%, playing any squash sports. After controlling for nonvigorous and other vigorous activities, the RRs of type 2 diabetes across categories of time spent on calisthenics or aerobics—classified as 0, less than 1 h/wk, and at least 1 h—were 1.0, 0.67 (95% CI, 0.55-0.81), and 0.56 (95% CI, 0.46-0.69), respectively (*P* for trend <.001). In the same model, the multivariate RRs were 0.58 (95% CI, 0.40-0.83) for jogging (any vs none), 0.74 (95% CI, 0.46-1.19) for running (any vs none), 0.79 (95% CI, 0.57-1.10) for tennis (any vs none), 1.14 (95% CI, 0.97-1.34) for swimming (any vs none), and 0.96 (95% CI, 0.85-1.09) for biking (any vs none).

When included simultaneously in the same model as continuous variables, walking and vigorous activity were associated with comparable risk reductions for equivalent energy expenditures. The multivariate RRs associated with a 5 MET-hours per week increase in energy expenditures were 0.95 (0.92-0.98) for vigorous activity and 0.92 (0.88-0.95) for walking.

COMMENT

In this large prospective cohort study, greater leisure-time physical activity level, in terms of both duration and intensity, was associated with reduced risk of type 2 diabetes. The dose-response relationship was consistent in those at low or high risk for diabetes, and remained significant after adjustment for BMI. The inverse association between energy expenditure from walking and risk of type 2 diabetes was similar to that for total physical activity and likewise persisted after controlling for BMI. This finding is reassuring, since walking is a physical activity that is highly accessible, readily adopted, and rarely associated with physical activity–related injury. In addition, we found a strong association between walking pace and risk of type 2 diabetes, even after adjustment for BMI and other known confounders.

Few women engaged in regular vigorous activities. Among the individual vigorous activities, calisthenics or aerobics was associated with the greatest reduction in type 2 diabetes risk. Other vigorous activities, including jogging, running, and playing tennis, were also inversely associated with the risk. Swimming and bicycling were not significantly associated with risk of diabetes. This finding may be due to the highly variable intensity with which these activities may be performed.

Overweight and obese people are less likely to engage in physical activity, because excess body weight may increase the difficulty of physical activity. This self-selection of heavy subjects for lower physical activity levels could account in part for the attenuation of the physical activity–diabetes relationship in regression models that included adjustment for BMI. However, other factors may also be involved in the relationship. Physical activity facilitates weight loss and weight maintenance.[25] Therefore, individuals expending a great deal of energy on physical activity tend to have lower adiposity. Furthermore, the adipose tissue loss resulting from physical activity is often of visceral rather than subcutaneous fat,[26-29] and visceral fat is strongly associated with insulin resistance and the related metabolic syndrome. Leaner individuals have a reduced risk of diabetes.[30-32] To the extent that physical activity causes individuals to have lower BMI, adjustment for BMI in regression models may constitute statistical overcorrection and result in underestimation of the true beneficial effect of physical activity.

It is biologically plausible that physical activity might reduce the risk of type 2 diabetes, because physical activity increases glucose disposal through a number of pathways. Physical activity has independent effects on glucose disposal by increasing both insulin-mediated and non–insulin-mediated glucose disposal.[33] A single bout of physical activity increases insulin-mediated glucose uptake for more than 24 hours.[34] The increased insulin sensitivity occurs because of increased number and activity of glucose transporters (especially the GLUT4 isoform), both in muscle and in adipose tissue.[35,36] Glycogen synthase activity is also increased, resulting in increased glycogen synthesis and increased nonoxidative disposal of glucose.[35,36] In addition to this direct effect on glucose disposal, physical activity results in decreased adipose tissue mass and preserved or increased lean body mass,[25] which also lead to increased insulin sensitivity. Consistent with these metabolic effects, small clinical trials have demonstrated a benefit of physical activity in the prevention of diabetes among people with impaired glucose tolerance.[37,38]

Equivalent energy expenditures from moderate or vigorous activity may confer comparable benefits. In the Insulin Resistance Atherosclerosis Study, both vigorous and nonvigorous activity were significantly associated with insulin sensitivity among 1467 men and women aged 40 to 69 years.[14] Daily walking combined with dietary therapy not only reduced body weight but also improved insulin sensitivity among diabetic patients.[39] Compared with structured aerobic physical activity, moderate-intensity activity had similar benefits on cardiorespiratory fitness and cardiovascular risk factors including blood pressure and lipid levels.[15,16]

Previous prospective studies have been limited but have generally found an inverse relationship between regular physical activity and risk of type 2 diabetes.[6-11,13,40] Few studies, however, have included women or assessed the role of moderate vs vigorous activity. Also, no previous study has provided updated assessments of physical activity. In 4 studies,[6,8,9,13] the risk of type 2 diabetes was shown to decrease with increasing amounts of physical activity, whereas in 3 other studies,[7,10,11] the degree of protection against diabetes was the same in those who exercised the most compared with those who exercised only moderately. In all studies, individuals whose levels of physical activity were moderate were at lower risk of diabetes than were those who were completely sedentary. The studies showing a dose-response relationship tended to have more detailed quantification of the dose of physical activity, as did the present study.

Some limitations of this study deserve attention. Because our "nondiabetic" cohort was not necessarily screened for glucose intolerance, some cases of diabetes may have been undiagnosed. However, when the analyses were restricted to symptomatic cases of type 2 diabetes, the findings were not appreciably altered, suggesting that surveillance bias according to activity level is unlikely. The diagnostic criteria for type 2 diabetes were changed in 1997,[41] such that lower fasting glucose levels (>126 mg/dL [7.0 mmol/L]) would now be considered diagnostic. We used the criteria proposed by the National Diabetes Data Group,[22] because all our cases were diagnosed prior to June 1994. If the new criteria were used, some women in this study classified as being without diabetes would have been reclassified as having diabetes. However, this would not explain our results, because inclusion of those with diabetes in the groups without diabetes would have caused bias toward the null. In addition, our study focused on leisure-time activity. Nonleisure energy expenditure may be also important in the prevention of chronic diseases.[42]

In conclusion, this large prospective study suggests that both walking and vigorous activity are associated with substantial reductions in risk of type 2 diabetes in women. We observed comparable magnitudes of risk reduction with walking and vigorous activity in this cohort, when total energy expenditures were similar. Our findings lend additional support to current guidelines from the Centers for Disease Control and Prevention[43] and the National Institutes of Health[44] that recommend that Americans should accumulate at least 30 minutes of moderate-intensity physical activity on most, but preferably all, days of the week.

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対象の内訳

	ヒト	動物	地 域		研究の種類	
対象	一般健常者	空白		欧米		縦断研究
性別	女性	( )		( )		コホート研究
年齢	40-65	[redacted]		( )		( )
対象数	10000以上			( )		前向きコホート
				( )		( )

調査の方法	質問紙	( )				
アウトカム 予 防	なし	糖尿病予防	な し	なし		( )
アウトカム 維持・改善	な し	な し	な し	なし	(	( )

図 表

Table 2. Relative Risks (95% Confidence Intervals) of Type 2 Diabetes According to Quintile of Total Physical Activity Score From the Nurses' Health Study, 1986-1994*

	Quintile, MET-Hours per Week (Median)					
	1 0-2.0 (0.8)	2 2.1-4.6 (3.3)	3 4.7-10.4 (7.7)	4 10.5-21.7 (15.7)	5 ≥21.8 (35.4)	*P* Value
No. of cases	422	296	287	226	188	
Person-years	108 829	104 467	107 254	107 247	107 131	
Age-adjusted	1.0	0.71 (0.61-0.83)	0.67 (0.57-0.78)	0.52 (0.44-0.61)	0.43 (0.36-0.52)	<.001
Multivariate†	1.0	0.77 (0.66-0.90)	0.75 (0.65-0.88)	0.62 (0.52-0.73)	0.54 (0.45-0.64)	<.001
Additional adjustment for BMI‡	1.0	0.84 (0.72-0.97)	0.87 (0.75-1.02)	0.77 (0.65-0.91)	0.74 (0.62-0.89)	.002

*Computed as cumulative updated average across 1986, 1988, and 1992 (see the "Methods" section). See footnotes to Table 1 for definition of metabolic equivalent task (MET).
†Models included age (5-year category); time period (4 periods); cigarette smoking (never, past, and current smoking of 1-14 or ≥15 cigarettes per day); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, or postmenopausal with current hormone replacement); parental history of diabetes; alcohol consumption (4 categories); history of hypertension; and history of high cholesterol level.
‡BMI indicates body mass index; in quintiles.

図表掲載箇所	P1436, Table2
概 要 (800字まで)	The Nurses' Health Studyにおいて、70102名の女性(40−65歳)を対象に8年間の追跡を行い、総身体活動量やウォーキングが、糖尿病の発症を予防できるかについて検討を行った研究である。身体活動量は、質問票にて、歩行、ジョギング、ランニング、自転車、健康体操、ダンス、ローイングマシン、水泳、スカッシュ、ラケットボール、テニスを週どれくらいするか質問し、メッツ・時/週に換算した。総身体活動が最も少ない群(0.8メッツ・時/週)と比較して、3.3、7.7、15.7、35.4メッツ・時/週有する群は、糖尿病の発症リスクが、それぞれ0.84(95%CI: 0.72-0.97)、0.87(0.75-1.02)、0.77(0.65-0.91)、0.74(0.62-0.89)と有意に減少した。また、高強度身体活動を実施していない集団において、ウォーキングのみの影響を見たところ、ウォーキングの時間が長くなるほど、糖尿病発症のリスクが低下することが示された。またウォーキングのペースが速い群においてもリスク低下が認められた。
結 論 (200字まで)	糖尿病の発症は、総身体活動の量や、高強度身体活動の有無よらずウォーキングの量が多いほど、そのリスクを下げることが示された。
エキスパートによるコメント (200字まで)	糖尿病の罹患予防は、我が国においても重要な課題である。本研究により、身体活動の種別においてその発症リスクとの関連が明確にされており、高強度活動を行わなくとも、中強度身体活動でも予防可能なことが示されており、予防支援のより具体的な方策が示されていると思われる。

担当者 村上晴香

RESEARCH COMMUNICATION

Risk Factors for Multiple Myeloma: Evidence from the Japan Collaborative Cohort (JACC) Study

MMH Khan[1], Mitsuru Mori[1], Fumio Sakauchi[1], Keitaro Matsuo[2], Kotaro Ozasa[3], Akiko Tamakoshi[4] for the JACC Study group

Abstract

This study assessed the association of multiple myeloma (MM) with age, body mass index (BMI, kg/m$_2$), physical activity, occupational history, and medical history for a Japanese cohort of 46,157 men and 63,541 women aged 40-79 years followed during 1988-2003 years. Cox proportional hazard model was mainly used to estimate the age and sex adjusted hazard ratio (HR) of MM including 95% confidence interval (CI) for both sexes. Same model, adjusted for age, was also used for each sex. In total, 98 MM deaths (men=49 and women=49) was observed for both sexes. Higher age groups (60-69 and 70-79 years) experienced significantly higher unadjusted HR of MM than the age group of 40-49 years. Men revealed significantly higher age-adjusted MM than women (HR=1.5; 95% CI=1.0-2.2). For both sexes, higher BMI of ≥30 kg/m$_2$ (HR=2.8; 95% CI=1.0-7.7), walking ≤30 minutes/day (HR=2.0; 95% CI=1.2-3.4), worried about personal relationship in working place (HR=2.3; 95% CI=1.3-4.2), restricted own pace in working place (HR=1.9; 95% CI=1.0-3.4), and history of peptic ulcer (HR=1.7; 95% CI=1.0-2.7) significantly increased age and sex adjusted MM risk. Some of the above-mentioned significant associations became insignificant for age adjusted sex specific analyses. However, these findings should be validated by further epidemiologic studies in Japan before generalization.

Key Words: Risk factors - multiple myeloma - cohort study - Japan

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Introduction

Multiple myeloma (MM) is a hematologic cancer, more specifically a cancer of the plasma cell. Plasma cells that develop from B cells produce different types of proteins called antibodies or immunoglobulins (Ig), abbreviated as IgA, IgD, IgE, IgG, and IgM. These antibodies are important part of the immune system and work with other parts of the immune system to help protect the body from infections and diseases due to germs and other harmful substances (Multiple Myeloma Research Foundation, 2001; National Cancer Institute, 2004). When B cells are damaged, the resulting plasma cells become malignant (called myeloma cells), meaning they continue to divide unchecked and generating more malignant plasma cells. These cells then travel through the bloodstream and gather in the bone marrow, where they damage tissue. Adhesion molecules found on the surface of malignant plasma cells allow them to attach to the bone marrow structural cells (called stromal cells) and can cause myeloma cells to grow. Cytokines (also called chemical messengers) are produced by both myeloma cells and stromal cells, and some cytokines such as interleukin 6 (IL-6) stimulate the growth of myeloma cells and inhibit natural cell death (called apoptosis) (Multiple Myeloma Research Foundation, 2001).

MM is the third most prevalent blood cancer in Japan, after non-Hodgkin's lymphoma and myeloid leukemia (Health and Welfare Statistics Association, 2004). It constituted 0.8% of all cancers worldwide with 86,000 new cases yearly (Parkin et al., 2005), slightly more than 10% of hematologic cancers (Kyle et al., 2003). According to the data of 2004, it constituted 1.2% of all cancer deaths in Japan (Health and Welfare Statistics Association, 2004). Incidence rate vary from 0.4 to 5 per 100,000, and is very rare in persons under age 40. The incidence is high in North America, Australia, New Zealand, northern and western Europe compared with Asian countries. Recently a slow increase in incidence and mortality from MM is observed in most regions of the world (Kyle et al., 1994; Kyle et al., 2003; Parkin et al., 2005) including Japan (Sonoda et al., 2005).

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The reported increased incidences during the past few decades is probably related more to the aging population, and improve diagnostic techniques than to an actual increase (Kyle et al., 1994; McKean-Cowdin et al., 2000; Kyle et al., 2003; Phekoo et al., 2004; Anagnostopoulos et al., 2005). Unfortunately, the etiology of MM remains largely unknown (Multiple Myeloma Research Foundation, 2001; Zaidi and Vesole, 2001; National Cancer Institute, 2004), although epidemiologic researches have shown that people with certain risk factors are more likely than others to develop MM (National Cancer Institute, 2004). For instance, chronic immune stimulation, autoimmune disorders, exposure to ionizing radiation, exposure to certain chemicals, occupational exposure to pesticides or herbicides, and occupational exposure to dioxin are some of the factors that increase the risk of MM (Herrinton et al., 1993; Zejda et al.; 1993; Multiple Myeloma Research Foundation, 2001; Zaidi and Vesole, 2001; National Cancer Institute, 2004; Parkin et al., 2005; Sonoda et al., 2005). Obesity (Brown et al., 2001; National Cancer Institute, 2004) or greater adiposity may increase the risk of MM (Pan et al., 2004; Samanic et al., 2004; Blair et al., 2005) significantly for both men and women (Calle et al., 2003).

Age, race, and gender may also affect MM (Tsuchiya et al., 1994; Multiple Myeloma Research Foundation, 2001; Zaidi and Vesole, 2001; Garcia-Sanz et al., 2004; National Cancer Institute, 2004; Anagnostopoulos et al., 2005). Some other prognostic factors for survival of MM patients are bone marrow plasma cell, hemoglobin, γ_2Microglobulin (γ_2M), bone lesions, serum calcium, low platelet count, serum albumin, serum creatinine, and C-reactive protein (Tsuchiya et al., 1994; Kaneko et al., 2002; Kyle et al., 2003; Garcia-Sanz et al., 2004; Anagnostopoulos et al., 2005; Greipp et al., 2005).

Although various studies have already been conducted worldwide, most of them focused on MM patients only. To our knowledge, negligible studies analyzed the data of a cohort study to identify risk factors for MM, which is particularly true for Japan. Present study has been originated from this background and aimed to identify some of the risk factors for MM by using the nation-wide data from the Japan Collaborative Cohort (JACC) Study.

Materials and Methods

Study Subjects

Details of the study methods that adopted in the baseline and follow-up surveys are explained elsewhere (Ohno and Tamakoshi, 2001). Briefly, the Japan Collaborative Cohort Study (JACC) Study for Evaluation of Cancer Risk (sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan) is a large and nation-wide multicenter prospective cohort study which enrolled 127,477 healthy inhabitants (men=54,032; women=73,445) from 45 municipal areas (6 cities, 34 towns and 5 villages) located in 7 districts (out of 8) of Japan who responded the baseline questionnaire between 1988 and 1990. Number of participants was 12,925 under age 40 years and 3,760 over age 79 years. Most subjects were recruited from the general population or when undergoing routine health checks in the municipalities (Sakauchi et al., 2005). Informed consent for participation was obtained using two strategies either by signing the cover page of the questionnaire (at the individual level which covered majority of the participants) or by explaining the aim of the study and confidentiality of the data (at the group level) to the community leader. For analytical purpose, this study only included the subjects aged between 40 and 79 years at baseline survey. This provided a total of 110,792 subjects (men=46,465; women=64,327), of which 1,904 subjects (men=308; women=786) were again excluded because of past medical history of cancer. Thus, we had a total of 109,698 subjects (men=46,157; women=63,541) for analysis.

At the time of enrollment, the subjects completed a self-administered questionnaire that covered: demographic characteristics such as age, sex, level of education, marital status, place of residence, and occupation; anthropometric measures such as height (cm), weight (kg), and body mass index (BMI, kg/m_2); lifestyle related factors such as smoking, drinking, physical activity (walking, sport activity), dietary habits, sleeping pattern; occupational factors such as kinds of job, sedentary or physical job, shift work, dustiness, noisiness, personal relationship (remain worried or not) in the working place, and restriction about own pace in the working place; and past medical history of several diseases such as history of stroke, hypertension, myocardial infarction, kidney disease, liver disease, gallstone, diabetes mellitus, peptic ulcer, appendectomy and cancer. We analyzed all the above-mentioned factors, but in this paper we reported only the significant variables for both sexes (except the significant factors of dietary habits) namely: age (categories: 40-49, 50-59, 60-69, 70-79), gender (male, female), BMI (<18.5, 18.5-25.0, 25.0-30.0, ≥30.0), walking (≥ 1 hour/day, 30 min to 1 hour/day, <30 minutes/day), worried about personal relationship in the working place (yes, no), restriction about own pace in working place (yes, no), and past medical history of peptic ulcer (yes, no). The same analyses have been done for each sex irrespective of significance level.

Follow-up period and determination of CC death

Follow-up survey was conducted annually until the end of 2003 and 1999 in 42 and 3 areas respectively to determine the vital status of the women using resident registration records available in the respective municipalities. In the most recent data, cause of death was recorded using International Classification of Disease version 10 (ICD-10), where code C90 indicated MM death. All other deaths (except MM deaths) and subjects who alive until the end of follow-up period or who moved out the study areas or lost to follow-up were considered as censored during analysis.

Statistical analysis

Present study analyzed the data (for both sexes, and separately for each sex) by Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, NC). Unadjusted Cox proportional hazard model (PHREG procedure) was used to estimate hazard ratio (HR) of MM mortality including 95% confidence interval (CI) by age groups for both sexes, and specific sex. For both sexes, age adjusted Cox model was applied for estimating the HR of MM mortality by sex and then age and sex adjusted HR for other significant variables. Age adjusted Cox model, for each sex, was also used for all variables. P for trend was reported for the categorical variables of age, BMI, and walking by considering the ordinal values of the categories.

Results

The number of deaths from MM was 98 (49 for each sex) during the follow-up period. For both sexes, the MM mortality rate per 10^5 person-years and the average age at death in years were 6.8 and 72.2 (standard deviation, SD=9.0) respectively. The corresponding figures were 8.3 and 72.4 (SD=8.0) for men, and 5.8 and 72.1 (SD=10.0) for women respectively (not shown).

Distribution of subjects and person-years (only for both sexes), MM deaths, and hazard ratio (HR) for MM including 95% confidence interval (CI) by the selected variables are presented in Table 1. For both sexes, unadjusted HR for MM were about 5 times (HR=5.0; 95% CI=2.4-10.7) and 9 times higher (HR=9.3; 95% CI=4.3-20.3) for the age groups of 60-69 and 70-79 years as compared to the reference age group of 40-49 years. Sex specific analysis also revealed similar results for age. Age adjusted MM was significantly higher for men than women (HR=1.5; 95% CI=1.0-2.2). BMI ≥30 kg/m_2 (HR=2.8; 95% CI=1.0-7.7), walking <30 minutes/day (HR=2.0; 95% CI=1.2-3.4), remaining worried about personal relationship in the working place (HR=2.3; 95% CI=1.3-4.2), restricted own pace in the working place (HR=1.9; 95% CI=1.0-3.4), and having history of peptic ulcer (HR=1.7; 95% CI=1.0-2.7) were significantly associated with age and sex adjusted MM for both sexes. For men, age adjusted HR of MM was significantly higher for those who reported walking <30 minutes/day compared with those group who reported walking ≥1 hour/day. Restricted own pace in the working place was also found to

Table 1. Person-years, Number of Deaths from Multiple Myeloma (MM), Hazard Ratio (HR) of MM including 95% Confidence Intervals (CIs) for Both-sexes, Men and Women by Some Selected Variables of JACC Study, 1988-2003

Variables	Both sexes					Men ‡			Women		
	N§	Person-years	MM Death§	HR	95% CI	MM death§	HR	95% CI	MM death§	HR	95% CI
Age†:											
40-49	27182	384705	8	1.00		4	1.00		4	1.00	
50-59	33680	461014	18	1.90	0.83-4.37	9	2.04	0.63-6.62	9	1.81	0.56-5.87
69-69	33210	420687	42	5.01	2.35-10.67***	23	6.13	2.12-17.74***	19	4.18	1.42-12.29**
70-79	15626	169136	30	9.28	4.25-20.27***	13	9.99	3.24-30.76***	17	9.13	3.07-27.18***
					Trend P<0.0001			Trend P<0.0001			Trend P<0.0001
Sex‡:											
Women	63541	843513	49	1.00							
Men	46157	592028	49	1.51	1.02-2.24*						
BMI‡ (kg/m2) ¶:											
<18.5	6143	73696	5	0.79	0.32-1.98	3	1.02	0.31-3.35	2	0.60	0.14-2.52
18.5-25.0	75398	993125	67	1.00		36	1.00		31	1.00	
25.0-30.0	19824	263996	12	0.72	0.39-1.33	5	0.67	0.26-1.71	7	0.70	0.34-1.75
≥30.0	1752	23041	4	2.79	1.01-7.69*	0	-	-	4	4.11	1.45-11.64**
					Trend P=0.6638			Trend P=0.3515			Trend P=0.1635
Walking/day¶:											
≥1 hr	41868	543504	26	1.00		13	1.00		13	1.00	
30 min-1 hr	16691	211590	12	1.19	0.60-2.36	6	1.23	0.47-3.24	6	1.15	0.44-3.03
<30 min	24600	309040	28	1.99	1.16-3.39*	16	2.25	1.08-4.67	12	1.73	0.79-3.79
					Trend P=0.0130			Trend P=0.0320			Trend P=0.1785
Worried about personal relationship in working place¶:											
No	39134	499567	21	1.00		13	1.00		8	1.00	
Yes	18317	240391	22	2.32	1.27-4.22**	11	1.67	0.75-3.74	11	3.53	1.41-8.79**
Restriction about own pace in working place¶:											
Yes	52117	670727	40	1.00		20	1.00		8	1.00	
No	11539	147181	14	1.87	1.01-3.44*	8	2.15	0.94-4.90	6	1.59	0.64-3.97
Had history of peptic ulcer¶:											
No	79672	1055376	62	1.00		29	1.00		33	1.00	
Yes	15516	198004	22	1.65	1.01-2.71*	12	1.30	0.66-2.55	10	2.20	1.08-4.48*
Total	109698	1435541	98			49			49		

†unadjusted for both sexes, men and women; ‡adjusted for age for both sexes; ¶adjusted for age and sex (for both sexes) and age (for men and women) §total subjects and deaths varied from total due to missing information; ***P<0.001, **P<0.01, *P<0.05

be associated almost significantly with MM (HR=2.2; 95% CI=0.9-4.9; P=0.069). For women, BMI ≥ 30 kg/m_2 (HR=4.1; 95% CI=1.5-11.6), worried about personal relationship in the working place (HR=3.5; 95% CI=1.4-8.8), and having history of peptic ulcer (HR=2.2; 95% CI=1.1-4.5) were significantly associated with age-adjusted MM risk.

Discussion

Present study revealed that the average age at death from MM was around 72 years for each sex and higher age groups (especially 60 years are and above) were associated with significantly higher MM. This means that MM typically occurs in elderly (60+) population, which is also supported by some other studies (Multiple Myeloma Research Foundation, 2001; Zaidi and Vesole, 2001; Kaneko et al., 2002; Kyle et al., 2003; National Cancer Institute, 2004; Phekoo et al., 2004; Shimizu et al., 2004). According to these studies, the average (either mean or median) age of MM patients varied from 65 to 73 years. Several factors such as aging of the population (Kyle et al., 2003), and higher incidence rates in higher age groups for both men and women (Kyle et al., 1994; Kyle et al., 2003; Phekoo et al., 2004) may be associated with higher MM in the elderly population. Combined Japanese data of 2004 indicates that about 83% MM deaths occurred among the people of 65 years and above (Health and Welfare Statistics Association, 2004; Health and Welfare Statistics Association, 2005). Similarly, Phekoo et al. (2004) reported 73% of the MM patients belonged to the age category of 65 years and above in UK. Two percent or less of the MM patients are diagnosed under age 40 (Multiple Myeloma Research Foundation, 2001; Kyle et al., 2003). Phekoo et al (2004) also reported that the incidence rate for both-sexes combined rose steadily with increasing age from 0.14 at age 16 years to 38.4 per 100,000 at age 85+ years. In Japan, death rate from MM per 100,000 population in 2004 was 0.15 for age group 40-44 years, whereas this figure was 15.24 for 75-79 years of age (Health and Welfare Statistics Association, 2004; Health and Welfare Statistics Association, 2005).

Men showed significantly higher MM as compared to women in our study, which may be supported by the higher incidence of MM in men than women (Multiple Myeloma Research Foundation, 2001; Kyle et al., 1994; Kaneko et al., 2002; Kyle et al., 2003; Phekoo et al., 2004). Some studies reported that the incidence rate of MM is significantly higher in men than women (Kyle et al., 1994; Phekoo et al., 2004). Monoclonal gammopathy, a risk factor for hematological malignancies, was also found to be higher in men than women (Ogmundsdottir et al., 2002). The sex differences in MM, particularly the predominance for men at each age cohort, may also be related to a disease-modifying gene on the sex chromosome (Phekoo et al., 2004).

Obese individuals revealed significantly higher HR of MM for both sexes combined. The significant association between obesity and MM is found to be consistent with other studies (Friedman and Herrinton, 1994; Brown et al., 2001; Benjamin et al., 2003; Calle et al., 2003; Pan et al., 2004; Samanic et al., 2004; Blair et al., 2005). The mechanism of linking high BMI to MM is unclear, but some studies suggest that excess caloric intake and obesity may affect immunologic responses (decreased immune response) that are involved in the development of malignancy (Stallone, 1994; Chandra, 1997; Brown et al., 2001). It is reported that the chronic hyperinsulinemic state in obesity reduces the insulin-like growth factor (IGF)-binding protein and increase free IGF-I. Both insulin and IGF-I can stimulate cell proliferation and inhibit apoptosis, thus enhancing tumor development (Gupta et al., 2002; Pan et al., 2004; Samanic et al., 2004). IGF-I also stimulates the proliferation of bone marrow cells (Georgii-Hemming et al., 1996; Ferlin et al., 2000). Another possible mechanism by which excess adiposity may increase the risk of MM is related to the cytokine interleukin 6 (IL-6), which is involved in proliferation and differentiation of both normal and malignant plasma cells. This particular cytokine may increase survival of plasma cells through inhibition of apoptosis (Ferlin et al., 2000; Lauta et al., 2003).

Walking less than 30 minutes per day (an indicator of physical activity) was found to be positively associated with elevated risk of MM for both-sexes, men and women. Unfortunately, the underlying mechanism between physical activity and MM is yet to be known because of scarcity of evidence. However, some speculations could be made in this regard. For example, walking is considered as a common physical activity (Wyatt et al., 2005; Warburton et al., 2006) and less walking may be an indicator of sedentary life style and obesity, which is supported by the other studies (Wyatt et al., 2005; Warburton et al., 2006). Cross-table analysis of our data (not shown) also showed significant association between walking and BMI. Rate of walking <30 minutes/day was highest for the obese subjects and highest for the normal-weight subjects. According to our speculation, reduced weight through physical activity and its associated mechanism mentioned above may partially explain the observed association between MM and walking. However, further studies are recommended to find the answer to: why does walking <30 minutes/day appear as an independent risk factor (HR=1.8; 95% CI=1.0-3.0) even after adjusting for age, sex, and BMI (data not shown)?

MM was found to be significantly higher among the groups of subjects (both-sexes) who reported that "they were worried about personal relationship in working place" and "they were restricted about own pace in working place." Unfortunately, we are unable to report the consistency of the findings as no previous study reported such associations. However, an attempt has been made to explain these associations indirectly. Apparently both groups represent the stressful condition (either psychological or physical) in the working place. Several studies (Zhou et al., 1993; Maes et al., 1998; Cohen et al., 1999; Steptoe et al., 2001; Kiecolt-Glaser and Glaser, 2002; Kiecolt-Glaser et al., 2003) reported that stressors can directly affect the cells of the immune system and modulate the secretion of pro-inflammatory cytokines. For instance, production of IL-6 and other pro-inflammatory cytokines can be directly stimulated by stressful experiences and negative emotions (Zhou et al., 1993; Maes et al., 1998; Kiecolt-Glaser and Glaser, 2002). Overproduction of IL-6 can be linked to the MM as it is involved in proliferation, activation, and differentiation of immune cells or both normal and malignant plasma cells through inhibition of apoptosis (Willenberg et al., 2002; Lauta et al., 2003). As many studies highlighted the linkage between IL-6 and MM, and as the serum analysis is not suitable for the present study, we recommend further studies such as nested case-control study using the data of stored serum of JACC study. According to the present analysis (data not shown), restriction about own pace lost their significance level when we included it with other variables namely age, sex, BMI, and worried about personal relationship in the working place (remained significant).

Peptic ulcer is identified as a significant risk factor for MM, which seems to be inconsistent as one study reported insignificant association between peptic ulcer and MM in Italy (Vineis et al., 1999) and another study reported insignificant association of IgA and IgG with peptic ulcer in USA (Herrinton et al., 1993). However, peptic ulcer was found as a most common disease among MM patients by one study and the authors concluded that prior inflammatory diseases such as gastrointestinal diseases may be implicated in the pathogenesis of the IgA subset of multiple myeloma (Schafer and Miller, 1979). Rosenstock et al. (2003) reported that patients who increased IgG antibodies to Helicobacter pylori infection (seropositive or borderline) significantly increased the risk of developing an ulcer as compared to seronegative.

The main advantage of the present study lies in its prospective design. Cohort study is generally free from recall bias, which is one of the main limitations for case-control studies. Most importantly, to our knowledge, this is the first cohort study which investigated the association of some important factors with MM and hence reported some leading findings in Japan. However, this study may have some limitations. First, small number of deaths may limit the interpretation of the findings due to limited statistical power. Second, in the Cox model we adjusted only the effect of age and sex for both-sexes and we adjusted only age for specific sex, which may not be sufficient. Last but not least limitation may be related to the missing information of the selected variables.

In short, higher age groups (especially after age 60 years) showed significantly risk of MM for both-sexes, men and women. Men experienced significantly higher MM than women. BMI $\geq$30 kg/m_2, walking <30 minutes/day, worried about personal relationship in the working place, restriction about own pace in the working place, and history of peptic ulcer are also appeared as the significant risk factors for MM for both sexes. Finally, all the significant findings of the present study should be validated by further epidemiologic studies in Japan before generalization.

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<tr><td>対象</td><td>一般健常者</td><td>空白</td><td>(　　)</td><td>コホート研究</td></tr>
<tr><td>性別</td><td>男女混合</td><td>(　　)</td><td>(　　)</td><td>(　　)</td></tr>
<tr><td>年齢</td><td>40-79歳</td><td>[redacted]</td><td>(　　)</td><td>前向き研究</td></tr>
<tr><td>対象数</td><td>10000以上</td><td></td><td>(　　)</td><td>(　　)</td></tr>
<tr><td>調査の方法</td><td>質問紙</td><td>(　　)</td><td></td><td></td><td colspan="3"></td></tr>
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図 表

Table 1. Person-years, Number of Deaths from Multiple Myeloma (MM), Hazard Ratio (HR) of MM including 95% Confidence Intervals (CIs) for Both-sexes, Men and Women by Some Selected Variables of JACC Study, 1988-2003

Variables	Both sexes					Men ‡			Women		
	N§	Person-years	MM Death§	HR	95% CI	MM death§	HR	95% CI	MM death§	HR	95% CI
Age†:											
40-49	27182	384705	8	1.00		4	1.00		4	1.00	
50-59	33680	461014	18	1.90	0.83-4.37	9	2.04	0.63-6.62	9	1.81	0.56-5.87
69-69	33210	420687	42	5.01	2.35-10.67***	23	6.13	2.12-17.74***	19	4.18	1.42-12.29**
70-79	15626	169136	30	9.28	4.25-20.27***	13	9.99	3.24-30.76***	17	9.13	3.07-27.18***
					Trend P<0.0001			Trend P<0.0001			Trend P<0.0001
Sex‡:											
Women	63541	843513	49	1.00							
Men	46157	592028	49	1.51	1.02-2.24*						
BMI‡ (kg/m2) ¶:											
<18.5	6143	73696	5	0.79	0.32-1.98	3	1.02	0.31-3.35	2	0.60	0.14-2.52
18.5-25.0	75398	993125	67	1.00		36	1.00		31	1.00	
25.0-30.0	19824	263996	12	0.72	0.39-1.33	5	0.67	0.26-1.71	7	0.70	0.34-1.75
≥30.0	1752	23041	4	2.79	1.01-7.69*	0	-	-	4	4.11	1.45-11.64**
					Trend P=0.6638			Trend P=0.3515			Trend P=0.1635
Walking/day¶:											
≥1 hr	41868	543504	26	1.00		13	1.00		13	1.00	
30 min-1 hr	16691	211590	12	1.19	0.60-2.36	6	1.23	0.47-3.24	6	1.15	0.44-3.03
<30 min	24600	309040	28	1.99	1.16-3.39*	16	2.25	1.08-4.67	12	1.73	0.79-3.79
					Trend P=0.0130			Trend P=0.0320			Trend P=0.1785
Worried about personal relationship in working place¶:											
No	39134	499567	21	1.00		13	1.00		8	1.00	
Yes	18317	240391	22	2.32	1.27-4.22**	11	1.67	0.75-3.74	11	3.53	1.41-8.79**
Restriction about own pace in working place¶:											
Yes	52117	670727	40	1.00		20	1.00		8	1.00	
No	11539	147181	14	1.87	1.01-3.44*	8	2.15	0.94-4.90	6	1.59	0.64-3.97
Had history of peptic ulcer¶:											
No	79672	1055376	62	1.00		29	1.00		33	1.00	
Yes	15516	198004	22	1.65	1.01-2.71*	12	1.30	0.66-2.55	10	2.20	1.08-4.48*
Total	109698	1435541	98			49			49		

†unadjusted for both sexes, men and women; ‡adjusted for age for both sexes; ¶adjusted for age and sex (for both sexes) and age (for men and women) §total subjects and deaths varied from total due to missing information; ***P<0.001, **P<0.01, *P<0.05

図表掲載箇所	P577, Table1
概 要 (800字まで)	本研究は、日本のThe Japan Collaborative Cohort Studyに参加した男女109,698名を対象に15年間の追跡調査を行い、日本人コホートにおける多発性髄膜腫発症のリスク因子を検討したものである。身体活動に関しては、質問紙により1日当たりの歩行時間を尋ね、1時間/日以上、30分−1時間/日、30分/日未満の3群に分類した。男性で1日当たりの歩行時間が1時間以上の集団と比較すると、30分未満の集団で多発性髄膜腫発症リスクが2.25(95%信頼区間:1.08-4.67)と有意に上昇した。女性では身体活動との関連はみられなかった。その他のリスク因子に関しては、男女共に年齢と共に発症リスクが上昇し(Ptrend<0.0001)、BMIが30.0以上の肥満でリスクが上昇した。女性において、職場の人間関係や、消化性潰瘍の有無によりリスクが上昇した。
結 論 (200字まで)	日本人男性において、身体活動(1日当たり1時間以上の歩行)の実施が多発性髄膜炎発症リスクを低下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。我が国のコホート研究で、1日当たり1時間以上の歩行の実施が多発性髄膜炎発症リスクを低下させることを示した点に意義がある。

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Physical activity, obesity, and risk of colon and rectal cancer in a cohort of Swedish men

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ABSTRACT

We investigated the association between physical activity and colorectal cancer risk in a cohort of Swedish men. Information on physical activity was obtained at baseline in 1997 with a self-administered questionnaire from 45,906 men who were cancer-free at enrollment. During a mean follow-up of 7.1 years, 496 cases of colorectal cancer occurred. Leisure-time physical activity was inversely associated with colorectal cancer risk; the multivariate hazard ratio (HR) for 60 min or more per day of leisure-time physical activity compared with less than 10 min per day was 0.57 (95% CI 0.41–0.79; P for trend = 0.001). Results were similar for colon (HR = 0.56; 95% CI 0.37–0.83) and rectal cancer (HR = 0.59; 95% CI 0.34–1.02). Home/housework activity was inversely associated with colon cancer risk (HR = 0.68; 95% CI 0.48–0.96). No association was observed for work/occupational activity. These results support a role of physical activity in reducing the risk of colon and rectal cancer.

1. Introduction

Since Garabrant and colleagues[1] and Husemann and colleagues[2] reported an increased risk of colon and rectal cancer in individuals with a sedentary occupation, many studies have examined the role of physical activity in the etiology of colorectal cancer. In 2002, the International Agency for Research on Cancer concluded that there is sufficient evidence for a cancer-preventive effect of physical activity for colon cancer and inadequate evidence for rectal cancer.[3] Few cohort studies have reported on physical activity and colon cancer by subsite, and the findings are inconsistent.[4–9] Moreover, there is no consensus on the type and critical period of physical activity that might be necessary to reduce colorectal cancer risk.

We therefore examined prospectively the relation between physical activity (leisure-time, housework, and occupational) and risk of colon (overall and by subsite) and rectal cancer in a large population-based cohort of Swedish men. We also report findings on the association of anthropometric variables with colorectal cancer risk.

2. Materials and methods

2.1. *Study population*

The cohort of Swedish men (COSM) began in the autumn of 1997, when all men who were aged 45–79 years and who resided in the Västmanland and Örebro counties of central Sweden received a mailed questionnaire regarding

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