Table 1—*Baseline characteristics of men according to cardiorespiratory fitness levels (quartiles)*

Characteristic	All men	Q_1 (lowest)	Q_2	Q_3	Q_4 (highest)	*P*
n	4,745	1,184	1,178	1,187	1,196	
Vo_{2max} (ml · kg^{-1} · min^{-1})	41.0 ± 7.9	32.4 ± 3.1	38.0 ± 2.5	42.4 ± 3.0	51.1 ± 6.2	<0.001*
Age (years)	31.4 ± 5.0	31.6 ± 4.9	31.2 ± 4.9	31.5 ± 5.0	31.2 ± 5.0	0.158*
BMI (kg/m^2)	22.9 ± 2.5	24.3 ± 2.7	22.9 ± 2.3	22.3 ± 2.4	22.0 ± 2.1	<0.001*
Systolic blood pressure (mmHg)	125.4 ± 11.6	129.0 ± 11.1	126.4 ± 11.5	124.4 ± 11.5	121.8 ± 11.2	<0.001*
Diastolic blood pressure (mmHg)	72.7 ± 9.0	75.7 ± 8.8	73.1 ± 8.8	72.0 ± 9.0	70.1 ± 8.4	<0.001*
Current smokers (%)	67.2	69.6	71.3	66.0	62.1	<0.001†
Current drinkers (%)	69.1	69.1	71.2	69.8	66.7	0.118†

Data are means ± SD, unless otherwise specified. *ANOVA; †Kruskal-Wallis test.

start of the submaximal exercise test to assess smoking and alcohol intake.

Cardiorespiratory fitness test
Subjects underwent a submaximal exercise test on a cycle ergometer to assess cardiorespiratory fitness. The exercise test consisted of three 4-min progressively increasing exercise stages. The initial exercise loads for subjects in the 20- to 29-, 30- to 39-, and 40- to 45-year age-groups were 600, 525, and 450 kpm, respectively. Heart rate was calculated from the R-R interval on an electrocardiogram, and 85% of their age-predicted maximal heart rate (220 − age [years]) was set as the target heart rate. The exercise load was increased by 225 kpm for each stage among all age-groups until heart rates during the course of the exercise reached the target heart rate or until completion of the third stage. Based on the exercise rate during the last 1 min of the final stage completed and the heart rate obtained from the last 10 s of exercise, Vo_{2max} was estimated using Åstrand-Ryhming Nomogram (9) and Åstrand's Nomogram correction factors (10).

Diagnosis of type 2 diabetes
The development of type 2 diabetes was based on any one of the following three diagnostic parameters. First, the serum glucose levels exceeded 11.1 mmol/l (200 mg/dl) 2 h after an oral glucose tolerance test, conducted in men with urinary glucose detected at a follow-up annual health examination. Second, the participants themselves reported current therapy with hypoglycemic medication (insulin or oral hypoglycemic agent) when they were interviewed at the subsequent health examination. Third, fasting blood glucose tests have been adopted since 1988. The criteria for fasting blood glucose levels for the diagnosis of type 2 diabetes were based on the American Diabetes Association's diagnostic guidelines published in 1997 (11).

Subjects contributed person-years of follow-up until the first of the following events: development of diabetes (n = 280), death (n = 42), or completion of the study (including 143 men lost to follow-up because of retirement).

Statistical analysis
We categorized men into quartiles depending on age-specific (20–24, 25–29, 30–34, 35–39, and 40–45 years) distributions of estimated Vo_{2max}. We used Cox proportional hazards models (12) to study the relationship between cardiorespiratory fitness and incidence of type 2 diabetes, adjusted for age, BMI, systolic blood pressure, family history of diabetes, smoking status (nonsmokers, 1–20 cigarettes per day, or ≥21 cigarettes per day), and alcohol intake (none, 1–45 g per day, or ≥46 g per day). Relative risks (RRs) for incidence of type 2 diabetes and 95% CI were obtained by using the group with the lowest estimated Vo_{2max} as the reference category. We tested proportionality assumptions and found no evidence of violation. All statistical analyses were conducted using SPSS 11.0J for Windows (Chicago, IL).

RESULTS— During a 14-year follow-up period that included 64,434 person-years of observation, 280 men developed type 2 diabetes. The average

Table 2—*Adjusted RRs for incidence of type 2 diabetes by potential risk factors*

Variable	Participants	RR*	95% CI	*P*
BMI				
1st tertile	1,578	1.00 (Referent)	—	—
2nd tertile	1,585	1.90	1.20–3.02	0.006
3rd tertile	1,582	4.60	3.01–7.02	<0.001
Age (single year)	4,745	1.07	1.04–1.10	<0.001
High blood pressure				
<140/90 mmHg	4,194	1.00 (Referent)	—	—
≥140/90 mmHg	551	1.73	1.31–2.28	<0.001
Family history				
No	3,709	1.00 (Referent)	—	—
Yes	1,036	3.57	2.82–4.51	<0.001
Smoking status				
None	1,555	1.00 (Referent)	—	—
1–20/day	1,829	1.22	0.91–1.63	0.185
≥21/day	1,361	1.27	0.94–1.71	0.119
Alcohol intake				
None	1,462	1.00 (Referent)	—	—
1–45 g/day	3,020	1.59	1.16–2.17	0.004
≥46 g/day	263	1.68	1.03–2.76	0.039

*Adjusted for cardiorespiratory fitness level and all items in the table.

Table 3—*RRs of incidence of type 2 diabetes according to cardiorespiratory fitness levels*

	Cardiorespiratory fitness levels, quartiles				
	Q_1 (lowest)	Q_2	Q_3	Q_4 (highest)	*P* for trend
n	1,184	1,178	1,187	1,196	
Person-years of follow-up	15,730	16,038	16,252	16,415	—
Number of cases	128	72	47	33	—
Age-adjusted RR (95% CI)	1.00 (Referent)	0.56 (0.42–0.75)	0.35 (0.25–0.50)	0.25 (0.17–0.37)	<0.001
Multivariate RR* (95% CI)	1.00 (Referent)	0.78 (0.58–1.05)	0.63 (0.45–0.89)	0.56 (0.37–0.84)	0.001

*Adjusted for age, BMI, systolic blood pressure, family history of diabetes, smoking status, and alcohol intake.

age of subjects was 31.4 ± 5.0 years at baseline. Table 1 shows the physical characteristics at the baseline of this study according to cardiorespiratory fitness levels. Men in the highest cardiorespiratory fitness group had the lowest levels of BMI, systolic blood pressure, and diastolic blood pressure. The highest cardiorespiratory fitness group also had the lowest prevalence of current smoking.

Table 2 shows the relationship between potential risk factors estimated by Cox proportional hazards model. Men in the higher BMI groups had greater RRs for type 2 diabetes than men in the lowest BMI group. In addition, older age, high blood pressure, a family history of diabetes, and alcohol intake significantly increased the risk of type 2 diabetes.

There were progressively lower age-adjusted RRs of type 2 diabetes across cardiorespiratory fitness levels (Table 3). After further adjustment for BMI, systolic blood pressure, family history of diabetes, smoking status, and alcohol intake, there remained an inverse association between type 2 diabetes risk and cardiorespiratory fitness (for trend, $P = 0.001$). Overall, men in the highest fitness group had a 44% lower risk of type 2 diabetes when compared with men in the lowest fit quartile.

Cardiorespiratory fitness level was estimated from heart rate obtained during the submaximal exercise test. The heart rate obtained during the submaximal exercise test may be influenced by premeasurement cigarette smoking (13), and cigarette smoking is known to be an independent risk factor for the development of type 2 diabetes (14). Therefore, we investigated the RRs for developing type 2 diabetes by categorizing the subjects as "smokers" or "nonsmokers." Inverse associations between cardiorespiratory fitness and type 2 diabetes were observed in the two smoking status groups (Table 4).

CONCLUSIONS — In this study, we prospectively investigated the relationship between cardiorespiratory fitness level and the development of type 2 diabetes among Japanese, in whom obesity is less common and insulin secretion capacity smaller than that among Caucasians. Our results show that low cardiorespiratory fitness was associated with higher risk for the development of type 2 diabetes in Japanese men, as has been shown in Caucasian groups. To our knowledge, only two prospective studies have been conducted on the relationship between cardiorespiratory fitness level and the incidence of type 2 diabetes (7,8). Lynch et al. (7) reported that Finnish men with a higher cardiorespiratory fitness level, measured using a bicycle ergometer, had a significantly lower risk of developing type 2 diabetes over the 4-year follow-up period. In a study of U.S. men with the study group consisting primarily of Caucasian men, Wei et al. (8) found a significant inverse relationship between cardiorespiratory fitness (measured by treadmill time) and the incidence of type 2 diabetes.

Although cardiorespiratory fitness is a highly objective parameter, it is not readily measured. Therefore, few studies have investigated the relationship between cardiorespiratory fitness and the incidence of type 2 diabetes. However, several studies have examined the relationship between physical activity as determined through questionnaire surveys and the incidence of type 2 diabetes (15–25). All of the studies of physical activity, conducted primarily among Caucasians, have reported an inverse relationship between physical activity level and the incidence of type 2 diabetes. Only one study on physical activity and type 2 diabetes in a Japanese population has been reported, and the investigators showed that leisure-time physical activity contributes to the prevention of type 2 diabetes even when it is performed only one time per week (25). There are plausible mechanisms that link low cardiorespiratory fitness to risk of type 2 diabetes; for example, individuals with low cardiorespiratory fitness have

Table 4—*RRs of incidence of type 2 diabetes among smokers and nonsmokers according to cardiorespiratory fitness levels*

	Cardiorespiratory fitness levels, quartiles				
	Q_1 (lowest)	Q_2	Q_3	Q_4 (highest)	*P* for trend
Smokers (*n*)	824	840	783	743	
Multivariate RR* (95% CI)	1.00	0.70 (0.49–1.00)	0.67 (0.44–1.00)	0.58 (0.35–0.95)	0.012
Nonsmoker (*n*)	360	338	404	453	
Multivariate RR† (95% CI)	1.00	1.02 (0.59–1.74)	0.56 (0.28–1.10)	0.53 (0.26–1.10)	0.036

*Adjusted for age, BMI systolic blood pressure, family history of diabetes, smoking status, and alcohol intake; †adjusted for age, BMI, systolic blood pressure, family history of diabetes, and alcohol status.

high insulin resistance. This was demonstrated by Sato et al. (6), who showed that there is a positive relationship between the rate of glucose metabolism and Vo_{2max}. Additionally, Ivy and Kuo (26) reported that individuals with lower cardiorespiratory fitness levels have fewer glucose transporters compared with those more fit.

The laboratory measurement of cardiorespiratory fitness is a strength of our study, even with the submaximal exercise protocol we used. Previous studies assessing the estimated precision of the nomogram used in this study have shown that the measured values of Vo_{2max} are closely correlated with the estimated values with our protocol (27). In addition, we used values obtained in oral glucose tolerance tests and fasting blood glucose levels as objective measures of the study outcome, type 2 diabetes. Another strength is that this was a prospective cohort study in a Japanese population; previous studies investigating the relationship between cardiorespiratory fitness and the development of type 2 diabetes were limited to Caucasian populations. The incidence of type 2 diabetes differs among ethnic populations, and the association may also be different in various ethnic groups.

Several limitations of this study need to be discussed. The subjects are not representative of the entire Japanese population but were men employed in a large metropolitan company. In addition, we excluded men without a submaximal exercise test at baseline. However, this limits the generalizability of the study but not its validity. Another limitation is that cardiorespiratory fitness was based on data obtained at the baseline examination, and possible changes in cardiorespiratory fitness level were not taken into account during the follow-up period. However, not accounting for changes would only dilute the true association between physical fitness and the risk of developing diabetes. Further research will be necessary to investigate the relationship between changes in cardiorespiratory fitness and the development of type 2 diabetes.

In conclusion, our results showed a strong inverse relationship between cardiorespiratory fitness and the development of type 2 diabetes. This relationship was independent of age, BMI, family history of type 2 diabetes, alcohol intake, and smoking status. We conclude that maintaining a high cardiorespiratory fitness level may contribute to the prevention of type 2 diabetes.

Acknowledgments— This study was supported in part by U.S. National Institute on Aging Grant AG06945 (to S.N.B.).

We thank the Tokyo Gas Health Promotion Center physicians and staff for assistance with data collection and Ayumi S. for secretarial support.

References

1. Health and Welfare Statistics Association: Current status of national health and welfare (In Japanese). *J Health Welfare Stat* 48:93–94, 2001
2. Kadowaki T, Miyake Y, Hagura R, Akanuma Y, Kajinuma H, Kuzuya N, Takaku F, Kosaka K: Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 26: 44–49, 1984
3. Wasada T, Arii H, Kuroki H, Saeki A, Katsumori K, Saito S, Omori Y: The relationship between insulin resistance and insulin secretiosn in japanese subjects with borderline glucose intolerance. *Diabetes Res Clin Pract* 30:53–57, 1995
4. Fujimoto WY, Leonetti DL, Bergstrom RW, Kinyoun JL, Stolov WC, Wahl PW: Glucose intolerance and diabetic complications among Japanese-American Women. *Diabetes Res Clin Pract* 13:119–130, 1991
5. Zimmer P, Alberti KGMM, Shaw J: Global and societal implications of the diabetes epidemic. *Nature* 414:782–787, 2001
6. Sato Y, Iguchi A, Sakamoto N: Biochemical determination of training effects using insulin clamp technique. *Horm Metab Res* 16:483–486, 1984
7. Lynch J, Helmrich SP, Lakka TA, George AK, Cohen RD, Salonen R, Salonen JT: Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med* 156:1307–1314, 1996
8. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Lee CD, Blair SN: The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med* 130:89–96, 1999
9. Åstrand PO, Ryhming I: A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. *J Appl Physiol* 7:218–221, 1954
10. Åstrand I: Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand* 49:45–60, 1960
11. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Position Statement). *Diabetes Care* 20: 1183–1197, 1997
12. Cox DR: Regression models and life-tables. *J R Stat Soc (B)* 34:187–220, 1972
13. Vogel JA, Gleser MA: Effect of carbon monoxide on oxygen transport during exercise. *J Appl Physiol* 32:234–239, 1972
14. Nakanishi N, Nakamura K, Matsuo Y, Suzuki K, Tatara K: Cigarette smoking and risk for impaired fasting glucose and type 2 diabetes in middle-aged Japanese men. *Ann Intern Med* 133:183–191, 2000
15. Helmrich SP, Ragland DR, Leung RW, Paffenbarger Jr RS: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152, 1991
16. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991
17. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer RE: A prospective study of exercise and incidence of diabetes among U.S. male physicians. *JAMA* 268:63–67, 1992
18. Lipton RB, Liao Y, Cao G, Cooper RS, McGee D: Determinants of incident non-insulin-dependent diabetes mellitus among blacks and whites in a national sample. *Am J Epidemiol* 138:826–839, 1993
19. Helmrich SP, Ragland DR, Paffenbarger RS Jr: Prevention of non-insulin-dependent diabetes mellitus with physical activity. *Med Sci Sports Exerc* 26:824–830, 1994
20. Gurwitz JH, Field TS, Glynn RJ, Manson JE, Avorn J, Taylor JO, Hennekens CH: Risk factors for non-insulin-dependent diabetes mellitus requiring treatment in the elderly. *J Am Geriatr Soc* 42:1235–1240, 1994
21. Burchfiel CM, Sharp DS, Curb JD, Rodriguez BL, Hwang LJ, Marcus EB, Yano K: Physical activity and incidence of diabetes: the Honolulu Heart Program. *Am J Epidemiol* 141:360–368, 1995
22. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin-dependent diabetes in middle aged British men. *BMJ* 310: 560–564, 1995
23. Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE: Walking compared with vigorous physical activity and risk of type 2 diabetes in women. *JAMA* 282:1433–1439, 1999
24. Wannamethee SG, Shaper AG, Alberti KGMM: Physical activity, metabolic factors, and the incidence of coronary heart disease and type 2 diabetes. *Arch Intern Med* 160:2108–2116, 2000

25. Okada K, Hayashi T, Tsumura K, Suematsu C, Endo G, Jujii S: Leisure-time physical activity at weekends and the risk of type 2 diabetes mellitus in Japanese men: the Osaka Health Survey. *Diabet Med* 17:53–58, 2000
26. Ivy JL, Kuo CH: Regulation of GLUT4 protein and glycogen synthase during muscle glycogen synthesis after exercise. *Acta Physiol Scand* 162:295–304, 1998
27. Siconolfi SF, Cullinane EM, Carleton RA, Thompson PD: Assessing VO2max in epidemiologic studies: modification of the Åstrand-Ryhming test. *Med Sci Sports Exerc* 14:335–338, 1982

論文名	Cardiorespiratory fitness and the incidence of typr 2 diabetes
著 者	Sawada SS, Lee IM, Muto T, Matuszaki K, Blair SN.
雑誌名	Diabetes Care
巻・号・頁	26 10 2918-22
発行年	2003
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/14514602

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	男性	( )		( )		( )
年齢	(31.4歳)	[redacted]		( )		前向きコホート
対象数	1000～5000			( )		( )

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

図 表

Table 3—*RRs of incidence of type 2 diabetes according to cardiorespiratory fitness levels*

	Cardiorespiratory fitness levels, quartiles				
	Q_1 (lowest)	Q_2	Q_3	Q_4 (highest)	P for trend
n	1,184	1,178	1,187	1,196	
Person-years of follow-up	15,730	16,038	16,252	16,415	—
Number of cases	128	72	47	33	—
Age-adjusted RR (95% CI)	1.00 (Referent)	0.56 (0.42–0.75)	0.35 (0.25–0.50)	0.25 (0.17–0.37)	<0.001
Multivariate RR* (95% CI)	1.00 (Referent)	0.78 (0.58–1.05)	0.63 (0.45–0.89)	0.56 (0.37–0.84)	0.001

*Adjusted for age, BMI, systolic blood pressure, family history of diabetes, smoking status, and alcohol intake.

図表掲載箇所	
概 要 (800字まで)	＜目的＞日本人で2型糖尿病発症リスクと全身持久力との関係を明らかにすること。＜方法＞コホート名：東京ガスコホート、対象者数：4745人、追跡期間：14年、因子評価方法詳細：最大下の自転車エルゴメーター運動試験：20-29歳は600, 30-39歳は525, 40-45歳は450kpmからスタート. 4分後とに225kpmずつ負荷が増加. 最大心拍数の85%をtarget HRとした. 最大酸素摂取量の推定値に基づき, 20-24, 25-29, 30-34, 35-39, 40-45歳ごとに, 体力を4分位に分類した。全身持久力の単位：ml/kg/minであった。各分位毎の全身持久力は、分位1：32.40ml/kg/min未満、分位2：32.5-38ml/kg/min、分位3：38.1-42.4ml/kg/min、分位4：51.1ml/kg/min以上であった。＜結果＞全身持久力と糖尿病罹患リスクとの関係は、分位1：1、分位2：0.78(0.58-1.05)、分位3：0.63(0.45-0.89)、分位4：0.56(0.37-0.84)であった。
結 論 (200字まで)	低体力男性(32.4ml/kg/min未満)の2型糖尿病発症のリスクは, 51-75%上位者よりも有意に高かった。
エキスパートによるコメント (200字まで)	全身持久力と2型糖尿病発症との関係を日本人男性で初めて明らかにした貴重な研究である。

担当者 宮地元彦

Long-Term Trends in Cardiorespiratory Fitness and the Incidence of Type 2 Diabetes

Susumu S. Sawada, PHD[1,2]
I.-Min Lee, MD, SCD[3,4]
Hisashi Naito, PHD[2]
Jun Noguchi, MD, PHD[1]
Koji Tsukamoto, MD, PHD[1]
Takashi Muto, MD, PHD[5]
Yasuki Higaki, PHD[6]
Hiroaki Tanaka, PHD[6]
Steven N. Blair, PED[7,8]

OBJECTIVE — Whereas single assessments of cardiorespiratory fitness have been shown to predict lower incidence of type 2 diabetes, there are no data on long-term trends in fitness and risk. We investigated the relationship between long-term trends in fitness and the incidence of type 2 diabetes.

RESEARCH DESIGN AND METHODS — A cohort of 4,187 Japanese men free of diabetes completed annual health checkups and fitness tests for estimated maximal oxygen uptake at least four times over 7 years (1979–1985). We modeled the trend in fitness over 7 years for each man using simple linear regression. Men were then divided into quartiles based on the regression coefficient (slope) from the model. During the follow-up period (1985–1999), 274 men developed diabetes. Hazard ratios (HRs) and 95% CIs for the incidence of diabetes were obtained using the Cox proportional hazards model.

RESULTS — Men in the lowest quartile of the distribution decreased in fitness over the 7 years (median slope −1.25 ml/kg/min), whereas men in the highest quartile increased in fitness (median slope 1.33 ml/kg/min). With adjustment for age, initial fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes and use of the lowest quartile, the HRs (95% CI) for the second through fourth quartiles were 0.64 (0.46–0.89), 0.40 (0.27–0.58), and 0.33 (0.21–0.50), respectively ($P_{trend} < 0.001$).

CONCLUSIONS — These results indicate that the long-term trend in fitness is a strong predictor of the incidence of type 2 diabetes in Japanese men.

Diabetes Care 33:1353–1357, 2010

Type 2 diabetes is a global problem with devastating human, social, and economic impact. Today >240 million people worldwide are living with diabetes. Each year another 7 million people develop diabetes. Thus, the prevention of type 2 diabetes is an important public health priority (1).

It is well known that physical inactivity is one of the primary causes of type 2 diabetes (2,3). Previous cohort studies also have shown a strong inverse relationship between cardiorespiratory fitness and the incidence of type 2 diabetes (4–7). However, these studies considered only once or twice measures of fitness level at baseline as the exposure. There are no data on long-term trends in activity or fitness as they relate to the risk of developing type 2 diabetes. Several randomized controlled trials of lifestyle, including physical activity, healthful diet, and weight reduction, in relation to type 2 diabetes over a period of years, have shown that such lifestyle changes decrease the incidence of developing type 2 diabetes among individuals with impaired glucose tolerance (8–10). No data are available from individuals at usual risk. This study was thus designed to investigate the relationship between long-term trends in fitness and the incidence of type 2 diabetes using a cohort study design among nondiabetic Japanese men.

RESEARCH DESIGN AND METHODS

Participants were employees of the Tokyo Gas Company that supplies natural gas to the Tokyo area. All employees received annual health checkups and completed a health questionnaire in accordance with the Industrial Safety and Health Law. Employees are required by law to participate.

The participants for this study were 5,984 male employees who had participated in an annual health checkup and annual submaximal exercise tests in 1985. Among these men, 335 were excluded because they were found at the health checkup to have at least one of the following: diabetes ($n = 102$), cardiovascular disease including hypertension ($n = 228$), tuberculosis ($n = 3$), or gastrointestinal disease ($n = 9$). For the present study, we also required participants to have at least four submaximal exercise tests in the previous 7 years (1979–1985). This excluded 1,462 men, leaving 4,187 men, who were followed until June 1999 for the development of type 2 diabetes.

Cardiorespiratory fitness test

Participants underwent a submaximal exercise test on a cycle ergometer to assess fitness. This test consisted of two to three progressively increasing 4-min exercise stages. The initial exercise loads were 600, 525, and 450 kilopond meter/min for participants aged 20–29, 30–39, and 40–49 years, respectively. Heart rate was

From the [1]Health Promotion Center, Tokyo Gas Co., Tokyo, Japan; the [2]Department of Exercise Physiology, School of Health and Sports Science, Juntendo University, Chiba, Japan; the [3]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; the [4]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; the [5]Department of Public Health, Dokkyo Medical University School of Medicine, Tochigi, Japan; the [6]Laboratory of Exercise Physiology, Faculty of Sports and Health Science, Fukuoka University, Fukuoka, Japan; the [7]Department of Exercise Science, University of South Carolina, Columbia, South Carolina; and the [8]Department of Epidemiology and Biostatistics, University of South Carolina, Colombia, South Carolina.
Corresponding author: Susumu S. Sawada, s-sawada@tokyo-gas.co.jp.
Received 4 September 2009 and accepted 25 February 2010. Published ahead of print at http://care.diabetesjournals.org on 9 March 2010. DOI: 10.2337/dc09-1654.

Table 1—*Baseline characteristics by cardiorespiratory fitness trend*

Characteristic	All men	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
n	4,187	1,047	1,048	1,046	1,046	
Median regression coefficient or slope (ml/kg/min)	−0.04 (−6.41 to 6.19)	−1.25 (−6.41 to −0.77)	−0.40 (−0.77 to −0.04)	0.32 (0.04–0.73)	1.33 (0.73–6.19)	<0.001
Age (years)	32.0 ± 4.3	31.4 ± 4.0	32.2 ± 4.0	32.6 ± 4.2	32.0 ± 4.9	<0.001
Initial cardiorespiratory fitness (1979), predicted Vo_{2max} (ml/kg/min)	40.0 ± 6.9	45.3 ± 6.7	40.5 ± 5.5	38.1 ± 5.6	36.3 ± 6.3	<0.001
BMI (kg/m^2)	23.0 ± 2.5	22.9 ± 2.5	23.1 ± 2.5	23.0 ± 2.6	22.9 ± 2.5	0.237
Systolic blood pressure (mmHg)	125.5 ± 11.7	125.8 ± 11.3	125.9 ± 11.8	125.6 ± 11.9	124.5 ± 11.7	0.020
Diastolic blood pressure (mmHg)	72.9 ± 8.9	72.9 ± 8.9	72.9 ± 9.3	73.6 ± 8.8	72.2 ± 8.8	0.004
Current smokers (%)	68.1	70.1	71.3	67.5	63.5	0.003
Current drinkers (%)	71.1	71.2	71.4	73.0	69.0	0.178
Family history of diabetes (%)	23.5	21.9	25.2	25.1	21.7	0.083

Data represent median (range), mean ±SD, or %.

calculated from the R-R interval on an electrocardiogram, and 85% of the age-predicted maximal heart rate (220 − age [years]) was set as the target heart rate. The exercise load was increased by 225 kilopond meter/min for each stage among all age-groups, until heart rates during the course of the exercise reached the target heart rate or until the completion of the third stage. Maximal oxygen uptake (Vo_{2max}) was estimated using the Åstrand-Ryhming nomogram (11) and the Åstrand age correction factors (12).

First, we used a simple linear regression of Vo_{2max} against time to assess the individual regression coefficient (slope) of fitness over 7 years. Next, all participants were divided into quartiles based on the slope from their individual model. Initial fitness levels in 1979 were estimated using the regression line.

Diagnosis of type 2 diabetes

The annual health checkup included measurement of height, body weight, and blood pressure and a urinary glucose test. Fasting plasma glucose tests have been used since 1988.

During 1985–1999, participants were followed for the development of type 2 diabetes, which was based on any one of the following three diagnostic parameters: *1*) plasma glucose levels exceeded 11.1 mmol/l (200 mg/dl) 2 h after an oral glucose tolerance test, conducted in men with urinary glucose detected at a follow-up annual health checkup, *2*) participants themselves reported current therapy with hypoglycemic medication (insulin or oral hypoglycemic agent) when they were interviewed at their health checkup, or *3*) fasting plasma glucose levels were >7.0 mmol/l (126 mg/dl).

Statistical analysis

We first compared baseline characteristics of participants according to quartiles of the fitness trend using one-way ANOVA for continuous variables and a χ^2 test for categorical variables as appropriate. We used Cox proportional hazards models to estimate the hazard ratios (HRs) of the incidence of type 2 diabetes. We adjusted for age, initial fitness level (continuous Vo_{2max}), BMI (continuous variable), systolic blood pressure (continuous variable), cigarette smoking (nonsmokers, 1–20 cigarettes/day, and ≥21 cigarettes/day), alcohol intake (none, 1–45 g/day, and ≥46 g/day), and a family history of diabetes (present or not) in a

Table 2—*Adjusted HR for incidence of type 2 diabetes by potential risk factors at baseline (1985)*

Variable	Participants	HR (95% CI)	*P* value	P_{trend} value
Age (years)				
22–30	1,614 (38.5)	1.00 (referent)	—	
31–35	1,497 (35.8)	1.20 (0.89–1.62)	0.241	0.018
36–40	1,076 (25.7)	1.45 (1.06–1.99)	0.019	
Initial (1979) cardiorespiratory fitness (ml/kg/min)				
<35.0	961 (23.0)	1.00 (referent)	—	
35.0–39.9	1,213 (29.0)	0.88 (0.66–1.18)	0.386	0.003
40.0–44.9	1,083 (25.9)	0.72 (0.50–1.02)	0.065	
≥45.0	930 (22.2)	0.50 (0.31–0.81)	0.005	
BMI (kg/m^2)				
<21.0	949 (22.7)	1.00 (referent)	—	
21.0–22.9	1,299 (31.0)	1.45 (0.84–2.48)	0.180	<0.001
23.0–24.9	1,125 (26.9)	2.52 (1.51–4.20)	<0.001	
≥25.0	814 (19.4)	5.34 (3.23–8.82)	<0.001	
Systolic blood pressure (mmHg)				
<120	1,209 (25.4)	1.00 (referent)	—	
120–129	1,317 (26.2)	1.32 (0.92–1.90)	0.135	0.001
130–139	1,248 (22.7)	1.30 (0.91–1.86)	0.149	
≥140	413 (25.7)	2.17 (1.46–3.23)	<0.001	
Cigarette smoking				
None	1,336 (31.9)	1.00 (referent)	—	
1–20/day	1,609 (38.4)	1.20 (0.89–1.61)	0.224	0.151
≥21/day	1,242 (29.7)	1.25 (0.92–1.69)	0.150	
Alcohol intake				
None	1,209 (28.9)	1.00 (referent)	—	
1–45 g/day	2,731 (65.2)	1.64 (1.20–2.24)	0.002	0.008
≥46 g/day	247 (5.9)	1.59 (0.96–2.62)	0.071	
Family history of diabetes				
No	3,204 (76.5)	1.00 (referent)	—	
Yes	983 (23.5)	3.26 (2.57–4.14)	<0.001	

Data are *n* (%) unless otherwise noted. *Adjusted for all items in the table.

multivariate model. A family history of diabetes was defined as the known presence of family members with diabetes in any of three generations, as determined by self-report on the health questionnaire. The proportionality assumption of the model was tested using a log-minus-log plot; no evidence of violation was found. All analyses were performed using SPSS 15.0J for Windows (SPSS, Chicago, IL).

RESULTS — The mean age of the participants was 32.0 years (range 22–40 years) at baseline. The mean ± SD number of fitness tests during 7 years was 6.0 ± 0.96. The time between the first and last fitness test in each single individual was 6.5 ± 0.73 years. The median follow-up time was 14 years, with a total of 56,749 man-years of observation. During follow-up, 274 participants developed type 2 diabetes. There were 42 deaths, and 143 participants were lost to follow-up due to retirement.

Table 1 shows the baseline characteristics of men in each fitness trend quartile. Men in the lowest fitness trend quartile (quartile 1) decreased their average Vo_{2max} from 45.3 to 36.6 ml/kg/min (median slope −1.25 ml/kg/min) between 1979 and 1985, whereas men in the highest fitness trend quartile (quartile 4) increased their average Vo_{2max} from 36.3 to 45.6 ml/kg/min (median slope 1.33 ml/kg/min) over the same time. There was an inverse relationship across categories with regard to initial fitness levels. The men in the lowest fitness trend quartile had the highest level of fitness in 1979, whereas those in the highest fitness trend quartile had the lowest level of fitness. The men in the highest quartile were more likely to have lower systolic and diastolic blood pressure and a lower rate of smoking compared with those in the lowest quartile.

Table 2 shows the relationship between potential risk factors and type 2 diabetes risk. Men with higher initial fitness had lower HRs for type 2 diabetes than men in the lower initial fitness group. In addition, older age, high BMI, high systolic blood pressure, alcohol intake, and a family history of diabetes all significantly increased the risk of type 2 diabetes.

Table 3 shows the HRs for type 2 diabetes by fitness trend quartiles, with the lowest quartile used as the referent. There were progressively lower age-adjusted HRs of type 2 diabetes across fitness trend quartiles. After further adjustment for initial fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes, there re-

Table 3—*HRs of incidence of type 2 diabetes, according to quartiles of cardiorespiratory fitness trend*

Variable	Slope (ml/kg/min)	Participants	Man-years of follow-up	No. cases diabetes	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)*
Quartile 1	−1.25 (−6.41 to −0.77)	1,047	14,114	75	1.00 (referent)	1.00 (referent)
Quartile 2	−0.40 (−0.77 to −0.04)	1,048	14,152	82	1.03 (0.75–1.41)	0.64 (0.46–0.89)
Quartile 3	0.32 (0.04–0.73)	1,046	14,212	64	0.77 (0.55–1.07)	0.40 (0.27–0.58)
Quartile 4	1.33 (0.73–6.19)	1,046	14,271	53	0.65 (0.46–0.93)	0.33 (0.21–0.50)
					$P_{trend} = 0.005$	$P_{trend} < 0.001$

Data are means (range) unless otherwise indicated. *Adjusted for age, initial cardiorespiratory fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes.

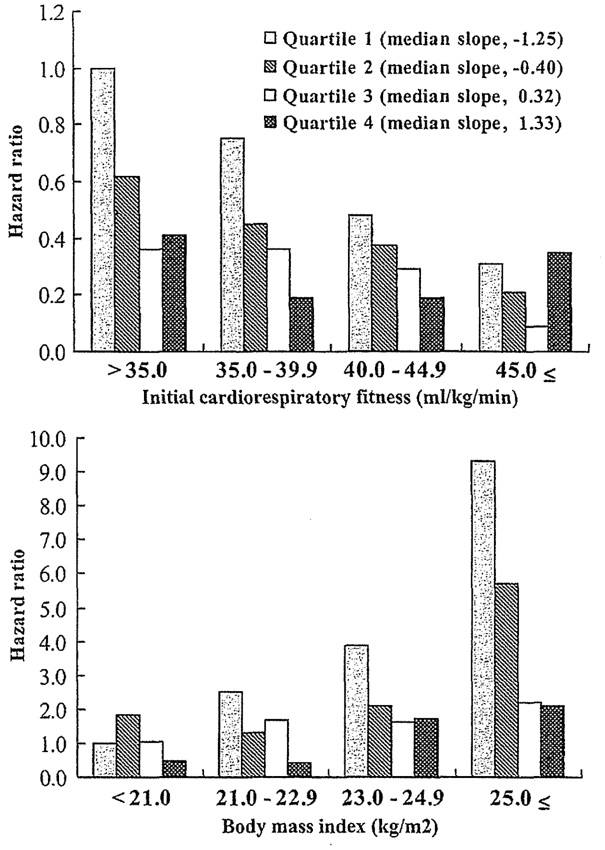

Figure 1—*HRs for incidence of type 2 diabetes associated with quartiles of cardiorespiratory fitness trend, among men categorized by initial (1979) cardiorespiratory fitness level* (top) *or baseline (1985) BMI* (bottom). *HRs were adjusted for age, systolic blood pressure, cigarette smoking, alcohol intake, a family history of diabetes, and BMI* (top) *or initial cardiorespiratory fitness level* (bottom).

mained a strong inverse association between type 2 diabetes risk and fitness trend quartiles ($P_{trend} < 0.001$). Men in the highest quartile of fitness trend had an ~70% lower risk of developing type 2 diabetes compared with men in the lowest quartile.

We next investigated the HRs of type 2 diabetes associated with quartiles of fitness trend, among men classified according to their initial fitness levels in 1979. (Fig. 1). The inverse gradient for diabetes across long-term trends in fitness categories was generally observed for all levels of fitness in 1979, except for men in the highest category of initial fitness (≥45.0 ml/kg/min). We also investigated the HRs of type 2 diabetes among men with different levels of BMI at baseline (1985). Again, there generally was an inverse gradient for diabetes risk across long-term trends in fitness categories for all BMI categories except the lowest.

CONCLUSIONS— In this study, we prospectively investigated the relationship between long-term trends in fitness and the incidence of type 2 diabetes in nondiabetic Japanese men. There was a strong inverse relationship between long-term trends in fitness and the incidence of type 2 diabetes, with men increasing their fitness over a 7-year period having lower risks than men with decreasing fitness over the same span.

The observed association is biologically plausible, because physical activity or fitness is a strong independent predictor of lower type 2 diabetes incidence rates (2,3). Physical activity or fitness may prevent and delay type 2 diabetes by improving glucose levels, reducing adiposity, increasing muscle mass and the GLUT4 in muscle tissues, and reducing insulin resistance (13,14).

The major strength of this study is the objective measurement of fitness, repeated over time. Fitness, an objective marker of daily physical activity, is a stronger predictor of morbidity or mortality than self-reported physical activity (15). Teräslinna et al. investigated the relationship, among 31 subjects, between measured Vo_{2max} and estimated Vo_{2max} using the Åstrand-Ryhming nomogram and correction factors used in the present study, obtaining a correlation coefficient of 0.92 (16). Furthermore, we used values obtained in oral glucose tolerance tests or fasting blood glucose levels as objective measures of the study outcome, type 2 diabetes.

Individuals at high risk of type 2 diabetes, such as those with impaired glucose tolerance or obesity, have been studied in randomized controlled trials of lifestyle, including physical activity and type 2 diabetes (8–10). However, there are no data in low-risk populations. In addition, most of the data have been in Caucasian subjects. Type 2 diabetes is a global problem; thus, data are needed not only in high-risk populations but also in low-risk populations and in other racial/ethnic groups.

One limitation of the present study is that subjects may not be representative of the entire Japanese population and women were not included. Nonetheless, this study provides important and valid information on Japanese male workers. Another limitation is that possible changes in fitness levels were taken into account between 1979 and 1985 but not during the follow-up period, 1985–1999. However, not accounting for changes during the latter period would probably dilute the true association between fitness and the risk of developing diabetes.

In conclusion, this cohort study showed a strong inverse relationship between long-term trends in fitness and the development of type 2 diabetes in Japanese men. This relationship was independent of age, initial fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes. Thus, regular physical activity, which is associated with an increase or preservation of fitness, should be promoted by health professionals, because it decreases the risk of type 2 diabetes, in addition to decreasing the risks of many chronic diseases (17).

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

We thank the study participants and the Tokyo Gas Health Promotion Center physicians and staff for assistance with data collection. We also thank Benjamin Howe for helpful comments and Ayumi Sawada for secretarial assistance.

References

1. Silink M. UN resolution 61/225: a gift to the diabetes world. Pract Diab Int 2007; 24:387–388
2. LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. J Appl Physiol 2005;99:1205–1213
3. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 2007;30:744–752
4. Lynch J, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R, Salonen JT. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. Arch Intern Med 1996;156:1307–1314
5. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Lee CD, Blair SN. The association between fitness and impaired fasting glucose and type 2 diabetes mellitus in men. Ann Intern Med 1999;130:89–96
6. Sawada SS, Lee IM, Muto T, Matuszaki K, Blair SN. Cardiorespiratory fitness and the incidence of type 2 diabetes: prospective study of Japanese men. Diabetes Care 2003;26:2918–2922
7. Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR Jr, Liu K. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. JAMA 2003;290:3092–3100
8. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
9. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346: 393–403
10. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20: 537–544
11. Åstrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol 1954;7:218–221
12. Åstrand I. Aerobic work capacity in men and women with special reference to age. Acta Physiol Scand Suppl 1960;49:1–92
13. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med 1998;49:235–261
14. Ivy JL, Zderic TW, Fogt DL. Prevention and treatment of non-insulin-dependent diabetes mellitus. Exerc Sport Sci Rev 1999;27:1–35
15. Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 1996;276:205–210
16. Teräslinna P, Ismail AH, MacLeod DF. Nomogram by Åstrand-Ryhming as a predictor of maximum oxygen intake. J Appl Physiol 1966;21:513–515
17. Kesaniemi YK, Danforth E Jr, Jensen MD, Kopelman PG, Lefèbvre P, Reeder BA. Dose-response issues concerning physical activity and health: an evidence-based symposium. Med Sci Sports Exerc 2001; 33:S351–S358

論文名	Long-term trends in cardiorespiratory fitness and the incidence of type 2 diabetes						
著者	Sawada SS, Lee IM, Naito H, Noguchi J, Tsukamoto K, Muto T, Higaki Y, Tanaka H, Blair SN.						
雑誌名	Diabetes care						
巻・号・頁	33	6	1353-1357				
発行年	2010						
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/20215460						
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	男性	( )		( )		( )
	年齢	(32歳)	[redacted]		( )		前向きコホート
	対象数	1000～5000			( )		( )
調査の方法	実測	( )					
アウトカム	予防	なし	糖尿病予防	なし	なし		( )
	維持・改善	なし	なし	なし	なし	(	( )

図表

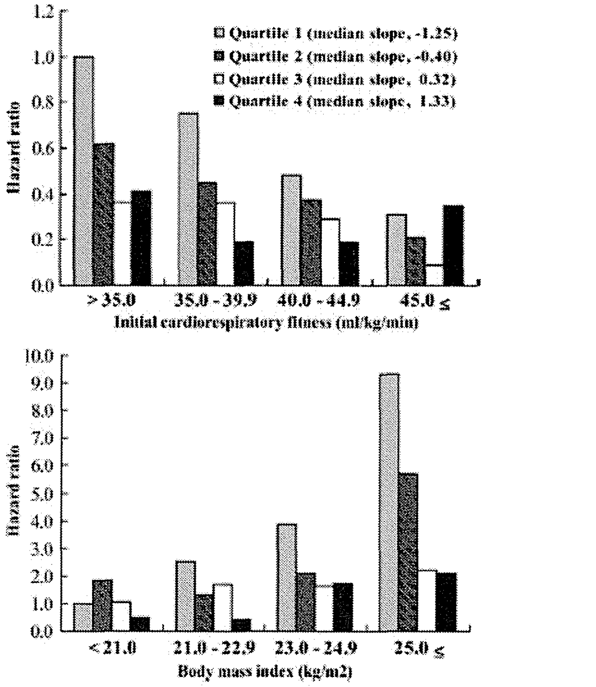

Figure 1—*HRs for incidence of type 2 diabetes associated with quartiles of cardiorespiratory fitness trend, among men categorized by initial (1979) cardiorespiratory fitness level (top) or baseline (1985) BMI (bottom). HRs were adjusted for age, systolic blood pressure, cigarette smoking, alcohol intake, a family history of diabetes, and BMI (top) or initial cardiorespiratory fitness level (bottom).*

図表掲載箇所	
概要 (800字まで)	＜目的＞労働者の糖尿病罹患率に体力と一要素である全身持久力との関係を縦断的に検討すること。さらに、7年以上の間の全身持久力の変化と将来の糖尿病発症との関係を明らかにすること。＜方法＞コホート名：東京ガスコホート、対象者：4187人の糖尿病でない男性労働者、追跡期間：1985年から1999年までの14年間、因子とそのの単位：全身持久力＝最大酸素摂取量(ml/kg/min)、因子評価方法詳細：オストランドとレイミングの最大下自転車エルゴメータテスト、アウトカム：糖尿病の発症、分析方法：ベースラインから7年以上の間の持久力の変化から、4つの分位に分ける。＜結果＞ベースラインの全身持久力(ml/kg/min)は、分位1：-34.9、分位2：35-39.9、分位3：40-44.9、分位4：45-であった。ベースラインでの持久力が高いほど糖尿病の発症が有意に低かった。7年間の持久力の減少が最も大きい分位の最大酸素摂取量の平均減少量は、-1.25 ml/kg/min、減少が最も少ない分位では逆に1.33ml/kg/min増加した。減少量で見た分位2の相対危険度は、0.64(0.46-0.89)、0.40(0.27-0.58)と0.33(0.21-0.50)であった。＜結論＞全身持久力が高いほど、全身持久力の経年低下が小さいほど、将来の糖尿病発症リスクが低かった。
結論 (200字まで)	全身持久力が高いほど、全身持久力の経年低下が小さいほど、将来の糖尿病発症リスクが低かった。
エキスパートによるコメント (200字まで)	全身持久力と糖尿病発症との関係は複数のコホート研究ですでに明らかとなっているが、持久力の経年変化と発症との関係を明らかにし、体力の維持増進がと生活習慣病予防に重要であることを示した研究として貴重である。

担当者　宮地元彦

Cardiorespiratory Fitness and Cancer Mortality in Japanese Men: A Prospective Study

SUSUMU S. SAWADA[1], TAKASHI MUTO[2], HIROAKI TANAKA[3], I-MIN LEE[4,5], RALPH S. PAFFENBARGER, JR.[6], MUNEHIRO SHINDO[2], and STEVEN N. BLAIR[7]

[1]Tokyo Gas Health Promotion Center, Tokyo, JAPAN; [2]Department of Public Health, School of Medicine, Juntendo University, Tokyo, JAPAN; [3]Department of Sport Science, Fukuoka University, Fukuoka, JAPAN; [4]Department of Epidemiology, Harvard School of Public Health, Boston, MA; [5]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [6]Division of Epidemiology, Stanford University School of Medicine, Palo Alto, CA; and [7]The Cooper Institute, Dallas, TX

ABSTRACT

SAWADA, S. S., T. MUTO, H. TANAKA, I-M. LEE, R. S. PAFFENBARGER, JR., M. SHINDO, and S. N. BLAIR. Cardiorespiratory Fitness and Cancer Mortality in Japanese Men: A Prospective Study. *Med. Sci. Sports Exerc.*, Vol. 35, No. 9, pp. 1546–1550, 2003. **Purpose:** Limited data are available on the relationship between cardiorespiratory fitness and cancer mortality. We evaluated the cardiorespiratory fitness and risk of cancer mortality in Japanese men **Methods:** A total of 9039 men (19–59 yr) who were given a submaximal exercise test and a health examination between 1982 and 1988 and were followed for mortality up to 1999. Cardiorespiratory fitness was measured using a cycle ergometer test, and maximal oxygen uptake was estimated. **Results:** The mean follow-up period was slightly more than 16 yr, producing a total of 148,491 person-years of observation. There were 231 deaths, with 123 deaths due to cancer. Relative risk (RR) and 95% confidence interval (95%CI) for cancer mortality were obtained using the Cox proportional hazards model. Taking into consideration age, systolic blood pressure, body mass index, smoking habit, and alcohol habit and using the lowest physical fitness group as the reference, the RR (95% CI) for increasing quartiles of fitness were 0.75(0.48–1.16), 0.43(0.25-0.74) and 0.41(0.23-0.74); $P < 0.001$ for trend. **Conclusion:** Low cardiorespiratory fitness is associated with cancer mortality in Japanese men. **Key Words:** ALCOHOL DRINKING, COHORT STUDY, EPIDEMIOLOGY, MAXIMAL OXYGEN UPTAKE, SMOKING

The rate of cancer mortality by organ varies largely from country to country. For example, the most common types of fatal cancers for U.S. males are lung cancer, prostate cancer, and colon cancer (16). For Japanese men, the most common fatal cancers are stomach cancer, lung cancer, and liver cancer (16). It is thought that such differences are caused by differences in genetic factors, as well as differences in the environment and lifestyle.

Numerous epidemiological studies have been undertaken since 1980 to examine the link between physical activity and cancer, with many showing an inverse gradient between physical activity and cancer mortality (11–12,19). Such results carry an important message for public health, because they suggest that physical activity may reduce the risk of cancer, a leading cause of death in many countries. However, most of these studies involved Western populations; relatively few involved Asians. Additionally, most studies investigated physical activity. There have been only four studies in which cardiorespiratory fitness, an objective index of physical activity, was examined, and the subjects in all four studies were from Western countries, three of which were from the same cohort (1,5,10,14). Thus, to provide more information, we conducted a prospective study of healthy Japanese males, to examine whether low cardiorespiratory fitness may be a risk factor for cancer mortality in this population.

METHODS

Subjects. Personnel working at the Tokyo Gas Company, which provides and sells gas in metropolitan Tokyo, were enrolled in the present study. The number of personnel in the Tokyo Gas Company was 12,899 (female: 921 and male: 11,978) at the end of March 1982 when the study was instituted. The ratio of blue-collar to white-collar workers was approximately 6:4.

Subjects included in the present study were 9039 healthy male (19–59 yr) workers (exclusion criteria are described below) who participated in periodic health examination and submaximal exercise test during a 7-yr period from 1982 to 1988. Female workers were excluded because of the small number.

Address for correspondence: Susumu S. Sawada, Ph.D., Tokyo Gas Health Promotion Center, Tokyo, 1-5-20 Kaigan, Minato-ku, Tokyo 105-8527, Japan; E-mail: s-sawada@tokyo-gas.co.jp.
Submitted for publication May 2002.
Accepted for publication April 2003.

0195-9131/03/3509-1546
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/01.MSS.0000084525.06473.8E

Clinical examination. All subjects received annual health examinations in accordance with the Industrial Safety and Health Law. The health examinations included a measurement of height, body weight, visual acuity, and blood pressure; a chest x-ray; and a urinary protein and glucose test. Height and weight were measured on a standard physician's scale, and body mass index was calculated (weight in kilograms divided by the square of height in meters). Blood pressure was measured by the auscultatory method with a mercury sphygmomanometer, diastolic pressure being recorded as the disappearance of sound. Persons who were diagnosed as having cancer, cardiovascular disease, diabetes mellitus, gastrointestinal disease, and tuberculosis based on the health examination ($N = 1162$) were excluded from the present study to prevent the influence of these diseases and medication use on the assessment of cardiorespiratory fitness. A submaximal exercise test was performed on a different day from the routine health examination. In addition, the subjects were given an interview on the day of submaximal exercise test to check for the presence or absence of asthma, liver disease, kidney disease, bone fractures, torsional deformity of the lumbar spine, lower back pain, and neuralgia. If the subjects had any one of these conditions, they also were excluded from the test ($N = 1777$). A self-administered questionnaire was conducted before the start of the submaximal exercise test to assess the individual's smoking habit and alcohol habit. Subjects underwent an exercise test on a cycle ergometer. The exercise test consisted of two to three 4-min progressively increasing exercise stages. The initial loads for subjects in 19–29, 30–39, 40–49, and 50–59 yr of age were 600 kpm, 525 kpm, 450 kpm, and 375 kpm, respectively. Heart rate was calculated from the R-R interval on an electrocardiogram, and 85% of their age-predicted maximal heart rate (220 − age [years]) was set as the target heart rate. The load was increased by 225 kpm for each stage among all age groups, until heart rates during the course of the exercise reached the target heart rate or until the completion of the third stage. Based on the work rate obtained from the last 1 min of the final stage and heart rate obtained from the last 10 s, maximal oxygen uptake ($\dot{V}O_{2max}$) was estimated using Åstrand-Rhyming Nomogram (3) and Åstrand's Nomogram correction factors (2).

Mortality surveillance. We followed the cohort for mortality to June 30, 1999. The mean follow-up period was slightly more than 16 yr (range: 15–205 months), and the total follow-up experience for the cohort was 148,491 person-years of observation. A total of 231 deaths, with 123 due to cancer, were identified in the cohort during follow-up. This included deaths from lung cancer (31 cases), stomach cancer (22 cases), liver cancer (16 cases), colon cancer (8 cases), esophagus cancer (7 cases), and rectum cancer (6 cases). The proportions of site-specific cancer mortality were similar to those among Japanese men in a survey conducted by Japan's Ministry of Health (9). We ascertained mortality in two ways. Death occurring during employment at the Tokyo Gas Company was available from the company ($N = 124$). For those who died after retirement, death was identified based on a members list kept by Tokyo Gas Retiree Office ($N = 107$). Individuals retired from the company have access to a variety of welfare services for a minimal membership fee, paying this membership fee to the secretariat every year. Because the Office collects this annual fee from members every year, the secretariat has contact annually with the member. This allows proper follow-up of every person. Furthermore, to ascertain causes of death among members, when a member dies, the secretariat talks to the next of kin to determine the cause of death. This was the list employed in this study to identify causes of death. Based on this information, the underlying cause of death was classified according to the *International Classification of Diseases*, Tenth Revision. Persons who had survived until the end of the study had follow-up time censored at the termination of the study (June 30, 1999); 311 persons (3.4%) who did not belong to the Tokyo Gas Retiree Office had follow up time censored at the time they retired from Tokyo Gas Company.

Data analysis. Data obtained from the first submaximal exercise test during the 7-yr study period provided information on baseline levels of cardiorespiratory fitness. We categorized men into fourths depending on age-specific (19–29, 30–39, 40–49, and 50–59 yr of age) distributions of estimated $\dot{V}O_{2max}$. We used Cox proportional hazards models to study the relationship between cardiorespiratory fitness and cancer mortality, adjusted for age, systolic blood pressure, body mass index, smoking habit (nonsmoker, 1–19 cigarettes·d^{-1}, 20 or more cigarettes·d^{-1}), and alcohol habit (none, 1–45 g·d^{-1}, $\geq$ 46 g·d^{-1}) (6). Relative risks for cancer mortality with the 95% confidence intervals were obtained by using the group with the lowest estimated

TABLE 1. Baseline characteristics of survivors and decedents, 1982–88.*

Characteristic	Survivors ($N = 8808$)	Decedents ($N = 231$)	Cancer Decedents ($N = 123$)
Age (yr)	35.8 (9.1)	45.8 (9.2)†	46.4 (8.3)†
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})	37.1 (6.9)	33.3 (6.6)†	32.8 (5.6)†
Body mass index (kg·m^{-2})	22.7 (2.5)	22.7 (2.8)	22.9 (2.8)
Systolic blood pressure (mm Hg)	124.3 (12.1)	125.1 (12.8)	123.7 (12.7)
Diastolic blood pressure (mm Hg)	73.4 (10.8)	77.1 (10.0)†	76.5 (10.4)†
Current smokers (%)	63.5	69.3	71.5
Current drinkers (%)	72.7	72.3	74.0

$\dot{V}O_{2max}$, maximal oxygen uptake.
* Data are given as means (SD) except where noted.
† $P < 0.05$ for the comparison with the survivors by t-test.

TABLE 2. Baseline characteristics of men according to cardiorespiratory fitness levels (quartiles), 1982–88.*

Characteristic	Q_1 (Lowest) (N = 2473)	Q_2 (N = 2309)	Q_3 (N = 2197)	Q_4 (Highest) (N = 2060)	P
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})	29.8 (3.3)	35.0 (2.8)	38.9 (3.0)	45.9 (5.5)	
Age (yr)	36.8 (8.9)	36.0 (9.3)	36.0 (9.1)	35.2 (9.7)	< 0.001
Body mass index (kg·m^{-2})	24.1 (2.6)	22.8 (2.3)	22.0 (2.2)	21.5 (2.2)	< 0.001
Systolic blood pressure (mm Hg)	127.0 (12.0)	124.8 (11.8)	123.2 (12.0)	121.7 (12.1)	< 0.001
Diastolic blood pressure (mm Hg)	76.1 (10.3)	74.0 (10.7)	72.4 (10.6)	70.9 (10.9)	< 0.001
Current smokers (%)	64.0	64.9	64.2	61.3	0.072
Current drinkers (%)	73.1	73.8	71.4	72.5	0.287

$\dot{V}O_{2max}$, maximal oxygen uptake.
* Data are given as means (SD) except where noted.

$\dot{V}O_{2max}$ as the reference category. We tested proportionality assumptions and found no evidence of violation. We used a χ^2 test for categorical comparisons of the data. Differences in the means of continuous measurements were tested by t-test and analysis of variance. The Statistical Package for the Social Science (version 10.0 J) was used for statistical analysis (SPSS, Inc., Chicago, IL). All probability values provided are from two-sided tests, and values of $P < 0.05$ were considered statistically significant.

RESULTS

Table 1 shows baseline characteristics of survivors, decedents, and men who died of cancer. Survivors were younger than decedents and had higher levels of cardiorespiratory fitness. Diastolic blood pressure was lower among survivors.

Table 2 shows baseline characteristics of individuals according to cardiorespiratory fitness levels. Men who were more fit tended to have better clinical risk factor profiles, but there was little difference in smoking or drinking habits across fitness levels.

Table 3 shows the relative risks for cancer mortality by fitness levels, with the lowest fitness level as the referent. We observed an inverse dose-response trend across fitness levels for cancer mortality. After adjusting for potential confounders, the group with the highest cardiorespiratory fitness had a 59% lower risk of cancer mortality than the group with the lowest cardiorespiratory fitness.

The level of cardiorespiratory fitness used in the present study was assessed by $\dot{V}O_{2max}$ that was estimated from heart rates obtained during submaximal exercise. Heart rate during exercise is reportedly influenced by cigarette smoking before measurement (20). In this study, because $\dot{V}O_{2max}$ was expected to decrease with increased heart rate as a result of premeasurement smoking, relative risks for cancer death also were calculated by dividing the subjects into those who smoked and those who did not (Table 4). Former smokers did demonstrate a higher risk of death from cancer than never smokers, but not to a significant degree. Due to the rather small margin of this difference, both former smokers and never smokers were analyzed as part of the same group.

These analyses also suggest that a low cardiorespiratory fitness is a risk factor for cancer death, irrespective of smoking status.

The fact that preexisting disease at baseline may decrease $\dot{V}O_{2max}$ had to be considered to ameliorate this possible influence on the relationship between low cardiorespiratory fitness and cancer death. Therefore, we calculated relative risks for cancer death using data obtained within 6 yr and after 6 yr from the start of the study. Relative risks for cancer mortality within 6 yr and from 6 yr onward were similar and did not differ substantially from the primary analyses (data not shown).

DISCUSSION

The present study provides results similar to those in studies conducted among Western populations, suggesting that high cardiorespiratory fitness reduces the risk of cancer mortality among the Japanese, where patterns of site-specific cancer mortality differ.

There have only been four reports from longitudinal investigations of the relationship between cardiorespiratory fitness and cancer incidence or mortality. Arraiz et al. (1) used the step test to assess cardiorespiratory fitness and investigated the relationship between these results and cancer mortality. These researchers noted a dose-response relationship, in which the relative risk of cancer mortality was progressively lower across cardiorespiratory fitness categories. None of the relative risks were statistically significant, possibly due to the relatively short follow-up. Blair et al. (5) investigated the relationship between a maximal treadmill exercise test and all-cause mortality, cardiovascular disease

TABLE 3. Relative risks of cancer mortality, according to cardiorespiratory fitness levels (quartiles), 1982–99.

	Cardiorespiratory Fitness Levels (Quartiles)				
	Q_1 (Lowest) (N = 2473)	Q_2 (N = 2309)	Q_3 (N = 2197)	Q_4 (Highest) (N = 2060)	P for Trend
No. of cancer deaths	50	36	20	17	
Age-adjusted cancer death rate (10,000 person-years)	12.4	9.4	5.5	5.0	
Age-adjusted RR (95% CI)	1.00	0.79 (0.51–1.21)	0.46 (0.28–0.78)	0.44 (0.25–0.76)	<0.001
Multivariate RR* (95% CI)	1.00	0.75 (0.48–1.16)	0.43 (0.25–0.74)	0.41 (0.23–0.74)	<0.001

RR, relative risk; CI, confidence interval.
* Adjusted for age, BMI, systolic blood pressure, alcohol habit, smoking habit.

TABLE 4. Relative risks of cancer mortality among smokers and non smokers, according to cardiorespiratory fitness levels (quartiles), 1982–99.

	Cardiorespiratory Fitness Levels (Quartiles)				
	Q_1 (Lowest)	Q_2	Q_3	Q_4 (Highest)	P for Trend
Smokers	(N = 1582)	(N = 1498)	(N = 1411)	(N = 1262)	
No. of cancer deaths	33	29	14	12	
Age-adjusted cancer death rate (10,000 person-years)	12.8	11.7	6.0	5.8	
Multivariate RR* (95% CI)	1.00	0.92 (0.55–1.53)	0.46 (0.24–0.87)	0.46 (0.23–0.93)	0.005
Never or former smokers	(N = 891)	(N = 811)	(N = 786)	(N = 798)	
No. of cancer deaths	17	7	6	5	
Age-adjusted death rate (10,000 person-years)	12.4	9.4	5.5	5.0	
Multivariate RR† (95% CI)	1.00	0.41 (0.17–1.00)	0.38 (0.14–0.99)	0.31 (0.11–0.89)	0.017

RR, relative risk; CI, confidence interval.
* Adjusted for age, BMI, systolic blood pressure, alcohol habit, smoking habit.
† Adjusted for age, BMI, systolic blood pressure, alcohol habit.

mortality, and cancer mortality, and reported a significant inverse gradient across fitness groups for all outcomes. Moreover, Kampert et al. (10) verified the relationship between cardiorespiratory fitness and cancer mortality in this cohort by expanding the total person-years of the study with extended mortality surveillance, finding a strong and significant inverse gradient for cancer death across fitness categories. Oliveria et al. (14) investigated the relationship between a maximal treadmill exercise test and the incidence of prostate cancer, and reported a significant inverse gradient by fitness levels.

There are several possible mechanisms through which maintaining a high level of cardiorespiratory fitness may aid cancer prevention. First, physical activity may inhibit DNA oxidation and prevent cancer cell initiation (17), despite the increase in free radicals that accompanies an increase in energy consumption caused by physical activity. Second, cancer cell promotion may be inhibited by immune functions (for example, NK cell activity) enhanced by cardiorespiratory fitness (15,21). Third, excess secretion of insulin, a cancer cell promoter, may be inhibited as a result of improved insulin sensitivity resulting from physical activity (13). An increase in GULT4, a glucose transporter, has been attributed to physical activity, with the possible effect of enhancing insulin sensitivity (7). It also has been reported that muscle contraction itself may be a stimulus for glucose intake into skeletal muscles (8), which then suggests the possibility that physical activity may correct hyperinsulinism, thereby preventing cancer cell proliferation. Although the extent and type of the mechanisms involved in cancer prevention need further identification and investigation, it appears that various mechanisms may interact in a complex manner.

A strength of the present study is the objective measurement of cardiorespiratory fitness. Previous reports on the estimated accuracy of the Åstrand-Rhyming Nomogram used in the present study indicate a high correlation between actual measurements and estimates of $\dot{V}O_{2max}$ ($r = 0.94$) (18). In comparison with the level of physical activity estimated from questionnaire, cardiorespiratory fitness is more objective (4,10) and thus may have less misclassification on the exposure of interest. This study also involves large sample of Japanese subjects, and no previous study has examined cardiorespiratory fitness and cancer among Asians. It is important to continue investigating cancers where rates of mortality by organ differ significantly among different nationalities and ethnic groups.

This study has limitations due to the fact that the cause of death was reported in an interview with the next of kin, leading to a possible misclassification of the cause of death. However, it is assumed that in most cases attending physicians directly informed the next of kin of the cause of death; therefore, this may not be a major limitation. We obtained death certificates for a nonrandom sample on 117 of the subjects (50.6%) and found that in only five cases (4.3%) did the cause of death given by the next of kin differ from that shown on the death certificate. This study has also been limited by the fact that we did not measure cancer incidence, an additional factor that inhibited this study is the small number of cases, which makes it impossible to analyze the cancers according to their developed sites. Subjects also were employees of a single, urban company and may not be representative of Japanese in general.

Although many studies have shown that certain kinds of food may reduce risk of cancer mortality (22), we did not have information on diet at baseline; thus, we cannot rule out the possibility of confounding between diet and cardiorespiratory fitness. It is possible that those who maintain a high level of cardiorespiratory fitness might have had more healthy diet habits than low-fit persons. Therefore, the results of present study might have been overestimated. Cardiorespiratory fitness was based on data obtained at the baseline examination, and possible changes in cardiorespiratory fitness level were not taken into account during the follow-up period. Further research will be necessary to investigate the relationship between changes in cardiorespiratory fitness and cancer morality.

In conclusion, the present study indicates that low cardiorespiratory fitness is associated with cancer mortality in Japanese men.

We thank the Tokyo Gas Health Promotion Center physicians and staff for assistance with data collection, and S. Ayumi for secretarial support.

Dr. Blair's participation in the study was supported in part by a grant from the U.S. National Institute on Aging (AG06945).

REFERENCES

1. ARRAIZ, G. A., D. T. WIGLE, and Y. MAO. Risk assessment of physical activity and physical fitness in the Canada health survey mortality follow-up study. *J. Clin. Epidemiol.* 45:419–428, 1992.
2. ÅSTRAND, I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol. Scand.* 49:45–60, 1960.
3. ÅSTRAND, P. O., and I. RYHMING. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. *J. Appl. Physiol.*. 7:218–21, 1954.
4. BLAIR, S. N., H. W. KOHL III, C. E. BARLOW, R. S. PAFFENBARGER Jr., L. W. GIBBONS, and C. A. MACERA. Changes in physical fitness and all-cause mortality. *JAMA* 273:1093–1098, 1995.
5. BLAIR, S. N., H. W. KOHL III, R. S. PAFFENBARGER Jr., D. G. CLARK, K. H. COOPER, and L. W. GIBBONS. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA* 262:2395–2401, 1989.
6. COX, D. R. Regression models and life-tables. *J. R. Stat. Soc. (B)* 34:187–220, 1972.
7. GOODYEAR, L. J., M. F. HIRSHMAN, and E. S. HORTON. Exercise-induced translocation of skeletal muscle glucose transporters. *Am. J. Physiol.* 261:E795–E799, 1991.
8. HAYASHI, T., J. F. P. WOJTASZEWSKI, L. J. GOODYEAR. Exercise regulation of glucose transport in skeletal muscle. *Am. J. Physiol.* 273:E1039–1051, 1997.
9. HEALTH AND WELFARE STATISTICS ASSOCIATION. Current Status of National Health and Welfare. (In Japanese). *J. Health Welfare Statistics* 47:52–95, 2000.
10. KAMPERT, J. B., S. N. BLAIR, C. E. BARLOW, and H. W. KOHL III. Physical activity, physical fitness, and all-cause and cancer mortality: a prospective study of men and women. *Ann. Epidemiol.* 6:452–457, 1996.
11. LEE, I.-M., and R. S. PAFFENBARGER, Jr. Physical activity and its relation to cancer risk: a prospective study of college alumni. *Med. Sci. Sports Exerc.* 26:831–837, 1994.
12. LEE, I.-M., R. S. PAFFENBARGER, Jr., and C.-C. HSIEH. Physical activity and risk of developing colorectal cancer among college alumni. *J. Natl. Cancer Inst.* 83:1324–1329, 1991.
13. MAYER-DAVIS, E. J., R. D'AGOSTINO, A. J. KARTER, S. M. HAFFNER, M. J. REWERS, M. SAAD, and R. N. BERGMAN. Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* 279:669–674, 1998.
14. OLIVERIA, S. A., H. W. KOHL III, D. TRICHOPOULOS, and S. N. BLAIR. The association between cardiorespiratory fitness and prostate cancer. *Med. Sci. Sports Exerc.* 28:97–104, 1996.
15. PEDERSEN, B. K., and H. ULLUM. NK cell response to physical activity: possible mechanisms of action. *Med. Sci. Sports Exerc.* 26:140–146, 1994.
16. PISANI, P., D. M. PARKIN, F. BRAY, and J. FERLAY. Estimates of the worldwide mortality from 25 cancers in 1990. *Int. J. Cancer* 83:870–873, 1999.
17. RADAK, Z., T. KANEKO, S. TAHARA, et al. The effect of exercise training on oxidative damage of lipids, proteins, and DNA in rat skeletal muscle: evidence for beneficial outcomes. *Free Radic. Biol. Med.* 27:69–74, 1999.
18. SICONOLFI, S. F., E. M. CULLINANE, R. A. CARLETON, and P. D. THOMPSON. Assessing $\dot{V}O_{2max}$ in epidemiologic studies: modification of the Åstrand-Ryhming test. *Med. Sci. Sports Exerc.* 14:335–338, 1982.
19. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Physical activity and health: a report of the Surgeon General. Atlanta, GA: U.S. Dept of Health and Human Services, 1996, pp.112–124.
20. VOGEL, J. A., and M. A. GLESER. Effect of carbon monoxide on oxygen transport during exercise. *J. Appl. Physiol.* 32:234–239, 1972.
21. WOODS, J. A., and J. M. DAVIS. Exercise, monocyte/macrophage function, and cancer. *Med. Sci. Sports Exerc.* 26:147–156, 1994.
22. WORLD CANCER RESEARCH FUND/AMERICAN INSTITUTE FOR CANCER RESEARCH. Food, nutrition and the prevention of cancer. Washington DC: American Institute for Cancer Research 1997, pp. 362–500.

論文名	Cardiorespiratory fitness and cancer mortality in Japanese men: a prospective study.
著 者	Sawada SS, Muto T, Tanaka H, Lee IM, Paffenbarger RS Jr, Shindo M, Blair SN.
雑誌名	Med Sci Sports Exerc.
巻・号・頁	35(9) 1546-50
発行年	2003
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/12972875

対象の内訳

	ヒト	動物
対象	一般健常者	空白
性別	男性	( )
年齢	19-59歳	
対象数	5000～10000	空白

地 域	国内
	( )
	( )
	( )
	( )

研究の種類	縦断研究
	コホート研究
	( )
	前向き研究
	( )

調査の方法: 実測 (自転車エルゴメータ)

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 3. Relative risks of cancer mortality, according to cardiorespiratory fitness levels (quartiles), 1982–99.

	Cardiorespiratory Fitness Levels (Quartiles)				
	Q_1 (Lowest) (N = 2473)	Q_2 (N = 2309)	Q_3 (N = 2197)	Q_4 (Highest) (N = 2060)	P for Trend
No. of cancer deaths	50	36	20	17	
Age-adjusted cancer death rate (10,000 person-years)	12.4	9.4	5.5	5.0	
Age-adjusted RR (95% CI)	1.00	0.79 (0.51–1.21)	0.46 (0.28–0.78)	0.44 (0.25–0.76)	<0.001
Multivariate RR* (95% CI)	1.00	0.75 (0.48–1.16)	0.43 (0.25–0.74)	0.41 (0.23–0.74)	<0.001

RR, relative risk; CI, confidence interval.
* Adjusted for age, BMI, systolic blood pressure, alcohol habit, smoking habit.

図表掲載箇所: P1548, Table3

概 要 (800字まで)

東京ガスの勤労者9039名(男性、19－59歳)を対象に、平均16年間の追跡調査を行い、体力とがんによる死亡との関連について検討を行った論文である。体力は、自転車エルゴーメータを用いた漸増負荷試験により行い、Astrand Rhyminig Nomogramにて推定の最大酸素摂取量を算出した。最大酸素摂取量が最も低かった群(29.8ml/min/kg)は、最大酸素摂取量が平均35.0, 38.9, 45.9ml/mi/kgであった群と比較して、がんによる死亡のリスクが、0.75(0.48-1.16), 0.43(0.25-0.74), 0.41(0.23-0.74)のリスク低下を示した。

結 論 (200字まで)

日本人男性において、体力を高く保つことで、がんによる死亡のリスクが低下することが示された。

エキスパートによるコメント (200字まで)

日本人男性において、このような体力とがんによる死亡との関連が明らかになったことは非常に意義深いことであり、今後、日本において、健康増進のための体力アップを推進していく上で重要な科学的根拠となりえた研究である。

担当者 村上晴香

EDITOR'S CHOICE

Physical activity, cardiorespiratory fitness and the incidence of type 2 diabetes in a prospective study of men

John C Sieverdes,[1] Xuemei Sui,[1] Duck-chul Lee,[1] Timothy S Church,[2] Amanda McClain,[1] Gregory A Hand,[1] Steven N Blair[1,3]

[1]Department of Exercise Science, University of South Carolina, Columbia, South Carolina, USA
[2]Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA
[3]Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, South Carolina, USA

Correspondence to:
Dr Xuemei Sui, University of South Carolina, 921 Assembly Street, Columbia, SC 29210, USA; msui@mailbox.sc.edu

Accepted 3 July 2009
Published Online First 26 July 2009

ABSTRACT

Objective To assess the independent and joint associations between self-reported physical activity (PA) and objectively measured cardiorespiratory fitness (CRF) from a maximal treadmill exercise test and the development of type 2 diabetes mellitus in a large cohort of men.

Methods Participants for the current analysis were 23 444 men aged 20–85 years free of cardiovascular disease (CVD), cancer or diabetes at baseline. Incident diabetes were identified from mail-back surveys. Cox regression analysis was used to estimate hazard ratios (HRs), 95% confidence intervals (CIs) and diabetes incidence rates (per 10 000 man-years) according to exposure categories.

Results During an average of 18 years of follow-up, 589 incident cases of diabetes were identified. After adjusting for age, examination year, survey response pattern, body mass index, smoking, drinking, fasting glucose, chronic diseases and family history of CVD or diabetes, the walking/jogging/running (WJR) and sport/fitness groups had a 40% and 28% lower risk of developing diabetes compared with the sedentary men, respectively (both $p < 0.05$). For CRF, diabetes incidence rates were 31.9, 14.5 and 6.5 for low-, moderate- and high-fitness groups, respectively. After adjustment for the above covariables, moderate and high CRF had a 38% and 63% lower risk of developing diabetes compared with the low CRF group (p trend<0.0001).

Conclusion Our findings showed a lower risk of developing diabetes for men who participated in a WJR programme or sport/fitness activity, compared with those who were sedentary. Higher levels of fitness were associated with an inverse gradient of incident diabetes.

Type 2 diabetes is a major public health problem. The American Diabetes Association (ADA) reported in 2006 that 9.3% of the US population have diabetes, where 2.8% were undiagnosed.[1] The 2007 estimated direct and indirect cost of diabetes in the US was $178 billion in medical expenses, lost productivity and disability. People with diagnosed diabetes have medical expenditures that are approximately 2.3 times higher per year than those without.[2] Mounting evidence has suggested that physical activity (PA) or cardiorespiratory fitness (CRF) has protective influences on hyperglycaemia[3] and incident diabetes.[3–17] The significance of the evidence has led several organisations, including the American Heart Association, the ADA and the US Department of Health and Human Services to include PA in their recommendations and guidelines.[18 19]

Studies have shown that participation in PA produces multiple health benefits and is inversely associated with incident diabetes.[4 7–12 14] This is inclusive for all activity levels from moderate[6] to vigorous (eg, brisk walking to running).[7] While most studies have been based on self-reported PA, self-reported measures correlate only modestly with objective measures obtained using criterion methods.[20–24] Thus, the true effects of PA on diabetes may not have been fully captured. To overcome the shortcomings of previous studies, we need to examine not only the self-reported PA but also objective exposures such as CRF.[22 25] CRF, an objective reproducible measure that reflects the functional consequences of recent PA habits, disease and genetics,[26] may have different effects on the incidence of diabetes.

Previous studies have reported an inverse association between the fitness level and incident diabetes.[3 4 8 10 15–17] However, very few prospective epidemiological studies have simultaneously examined both CRF and PA and incident diabetes in adults.[16 27] Because CRF and PA are correlated only modestly, more studies are needed to examine the interaction of PA and CRF on incident diabetes to explain these protective influences. Therefore, we set forth to assess the independent and joint associations between PA and CRF and the development of type 2 diabetes mellitus in a large cohort of men from the Aerobics Center Longitudinal Study (ACLS).

METHODS

Participants

The ACLS is a prospective epidemiological study of the health effects of PA and fitness. Data were obtained from a population of patients at the Cooper Clinic, a preventive medicine clinic in Dallas, Texas, USA. Participants came to the clinic for periodic preventive health examinations and for counselling regarding diet, exercise and other lifestyle factors associated with increased risk of chronic disease. Participants thus were volunteers, were not paid and were not recruited specifically to the study, as would be the case for a clinical trial. Many were sent by their employers for the examination, some were referred by their physicians, and others were self-referred. Participants for the current analysis were 23 444 men aged 20–85 years who completed a clinical examination during 1970–2003 and had no history of known cardiovascular disease (CVD) or cancer. They also reported no physician diagnosis of diabetes, were not taking insulin and had a fasting blood glucose of <126 mg/dl at baseline. The men were predominantly white, well educated and from middle to upper socio-economic strata. All participants provided written consent to participate in the examination and in the follow-up research. The study protocol was reviewed and approved annually by the Cooper Institute Institutional Review Board.

Clinical examination

The comprehensive health evaluation was completed following a minimum 12 h fast and has been described in detail elsewhere.[28 29] Briefly, information pertaining to personal and family health histories, personal health habits and demographic information was obtained from standardised medical history questionnaires. Body mass index (BMI) was calculated from measured height and weight as kg/m^2. Resting blood pressure was recorded as the first and fifth Korotkoff sounds using auscultation methods.[30] An antecubital venous blood sample was obtained, and plasma concentrations of lipids and glucose were determined with standardised automated bioassays at the Cooper Clinic Laboratory, which participated in and met quality control criteria of the Centers for Disease Control and Prevention Lipid Standardization Program. Hypertension was defined as a resting blood pressure of 140/90 mm Hg or greater, or a history of physician diagnosis. Hypercholesterolaemia was defined as a total cholesterol of 240 mg/dl or greater. Personal history of CVD (myocardial infarction or stroke), information on smoking habits (never, former or current smoker), alcohol intake (drinks per week), family (from parents and siblings, ie, first-degree relatives) history of CVD or diabetes, and PA habits (sedentary, walking/jogging/running (WJR) and sport/fitness activity) were obtained from a standardised questionnaire.

Physical activity

PA status was categorised into three mutually exclusive groups according to the usual type of PA reported in the last 3 months.[31 32] Sedentary individuals were those participants who answered 'no' to all activity questions (walking, jogging, running, bicycling, swimming, racquet sports and other strenuous sports). WJR participants were those who answered 'yes' to the question, 'Have you participated in a walk/jog/run programme in the last 3 months?'; and 'no' to the other activities. Sport/fitness activity participants were those who answered 'no' to the walk/jog/run question, but 'yes' to a series of questions about participation in racquet sports, cycling, swimming, or other strenuous sports (football, basketball, softball, etc).

Cardiorespiratory fitness

We assessed CRF with a symptom-limited maximal treadmill exercise test using a modified Balke protocol.[28 33] The treadmill test began with the patient walking 88 m/min at 0% grade. At the end of the first minute, the elevation was increased to 2% and thereafter increased 1% per minute until the 25th minute. For those who were able to continue past 25 min, the treadmill speed was increased by 5.4 m/min for each min after the 25th. Exercise duration on this protocol is highly correlated with measured maximal oxygen uptake in men (r=0.92).[34] The test end point was volitional exhaustion or termination by the supervising physician. Maximal metabolic equivalents (METs, 1 MET=3.5 ml O_2 uptake/kg/min) were estimated from the final treadmill speed and grade.[35] Previous ACLS reports have shown that low CRF is an independent predictor of mortality and non-fatal disease.[15 28 29] We defined low, moderate and high CRF exposures according to the lowest 20%, the next 40% and the upper 40%, respectively, of the age-specific distribution of treadmill duration in the overall ACLS population.[15] We used the above approach to maintain consistency in our study methods and because a widely accepted clinical categorisation of CRF does not exist.

Morbidity surveillance

The incidence of diabetes was ascertained from responses to mail-back health surveys in 1982, 1986, 1990, 1999 and 2004. The aggregate survey response rate across all survey periods in the ACLS is ≈ 65%. Non-response bias is a concern in epidemiological studies. This issue has been investigated in the ACLS[36] and found not to present a major source of bias. Baseline health histories and clinical measures were similar between responders and non-responders, and between early and late responders.[36] The end point was defined as a participant report of a physician diagnosis of diabetes and has been described in detail elsewhere.[8 15 37] We previously verified the accuracy of self-reported, physician-diagnosed diabetes in this cohort and observed a 92% agreement between reported events and medical record review.[15] Our methods of case ascertainment are similar to those used in other established epidemiological studies on diabetes.[16 38 39] Though we cannot verify that the participants had type 2 rather than type 1 diabetes due to the self-report nature, based on the current literature, >90% of adults with diabetes are estimated to have type 2 diabetes.[40]

Statistical analysis

Baseline characteristics of the population were estimated by PA and CRF categories. Differences in covariates were tested using ANOVA tests for continuous variables and χ^2 tests for categorical variables. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs), 95% confidence intervals (CIs) and diabetes incidence rates (per 10 000 man-years) according to exposure categories. Multivariable analyses included controls for baseline measures: age (in years), BMI (kg/m^2), smoking status (never, former or current smoker), alcohol intake (drinks per week), fasting glucose (mg/dl), medical conditions (the presence or absence, separately measured, of hypertension or hypercholesterolaemia) and family history of CVD or diabetes (present or not for each). We also constructed indicator variables (yes/no) for each survey period to account for differences in survey response patterns in order to reduce the influence of ascertainment bias.[15 41] To standardise for surveillance period and length of follow-up, we entered these variables, as well as the year of the baseline examination, into our analyses as covariables. Cumulative hazard plots grouped by exposure suggested no appreciable violations of the proportional hazards assumption. Next, we examined the joint effects of PA (sedentary, WJR and sport/fitness) and CRF (low, moderate and high) on incident diabetes. For this analysis, we created nine activity–fitness combination categories. We compared the effect of each combination of activity and fitness status (sedentary–low; sedentary–moderate; sedentary–high; WJR–low; WJR–moderate; WJR–high; sport/fitness–low; sport/fitness–moderate; and sport/fitness–high) with the referent group (sedentary–low). Finally, we conducted Cox regression analyses of CRF stratified by baseline glucose levels (fasting glucose <100 mg/dl and 100–125 mg/dl) to assess whether the associations were stronger in particular subgroups. All p values were calculated assuming two-sided alternative hypotheses; p values <0.05 were taken to indicate statistically significant comparisons. All analyses were performed using SAS statistical software, version 9.1 (SAS, Cary, North Carolina).

RESULTS

Tables 1 and 2 show the baseline characteristics of the participants by PA and CRF, respectively. In table 1, sedentary men in general had a lower fitness and higher BMI, were more likely to be current smokers, and had more unfavourable lipid profiles and CVD risk factors, such as hypercholesterolaemia or high blood pressure, than those in the WJR or Sport/Fitness groups. In table 2, participants with lower CRF values tended to be younger, were less active and were more likely to have hypercholesterolaemia or hypertension.

During an average 18 years of follow-up and 424 336 man-years of observation, 589 incident cases of diabetes were identified. Table 3 shows the relative risk of diabetes across PA and CRF groups. The incidence rates were 20.1, 9.6 and 12.4 across the sedentary, WJR and sport/fitness groups, respectively. After adjusting for age, examination year and survey response pattern, the WJR and sport/fitness groups had a 56% and 40% lower risk of developing diabetes compared with the sedentary men, respectively (both p<0.05). Further adjusting for BMI, smoking, drinking, fasting glucose, hypercholesterolaemia, hypertension and family history of diabetes or CVD did not change the associations significantly. After additional adjusting for CRF, the WJR group remained at a lower risk of diabetes than the sedentary group. The sport/fitness group was no longer significantly different from the sedentary group, but still showed a 19% reduction in diabetes risk.

For CRF, diabetes incidence rates were 31.9, 14.5 and 6.5 across low, moderate and high-fitness groups. This presented an inverse gradient of incident diabetes across the incremental CRF groups (p trend <0.0001). After adjustment for the covariables in Model 2, the moderate and high CRF groups had a 38% and 63% lower risk of developing diabetes compared with the low CRF group (p trend <0.0001). Additional adjusting for PA did not change the inverse association between CRF and diabetes.

Next, we examined the joint associations of PA (sedentary, WJR and sport/fitness activity) and CRF (low, moderate and high) on the risk of diabetes (figure 1). The results show the age- and examination year-adjusted diabetes incidence rates per 10 000 man-years among the nine activity–fitness combination categories. The lowest event-rate was the category consisting of high CRF and the sport/fitness PA group. Sedentary and low-fitness men had more than a sixfold higher risk of diabetes compared with high-fitness men who participated in sports/fitness activities. The adjusted incident rate was inversely related to CRF within each of the PA groups (all p trend <0.0001). There was no association between WJR or sport/fitness activity group and outcome within any of the fitness groups, compared with the sedentary men (all p>0.05).

Finally, we examined the influence of baseline fasting glucose on the association between fitness and diabetes risk (figure 2). There was an inverse gradient for the risk of diabetes across levels of fitness in normal glucose (<100 mg/dl) (p_{trend}=0.008) and impaired fasting glucose (IFG: 100–125 mg/dl) (p_{trend}<0.001) groups. Among men with normal glucose, risk was lower in the moderate- (HR 0.53 (95% CI 0.33 to 0.84)) and high- (HR 0.45 (95% CI 0.26 to 0.81)) CRF groups. In individuals with IFG, risk was lower in both the moderate- (HR 0.70 (95% CI 0.53 to 0.92)) and high- (HR 0.43 (95% CI 0.29 to 0.63)) CRF groups.

DISCUSSION

Our primary findings indicate that both CRF and PA are inversely associated with the risk of developing diabetes. The inverse association between fitness and incident diabetes was strong, even after adjustment for PA. We also found that doing any PA, including walking/jogging/running, or any sport-related fitness activity, is protective. Our findings confirm previous reports that both CRF and PA are independent factors for diabetes in men.[13] We previously reported that low fitness is a risk factor for diabetes in men.[8 42] Since the ACLS concurrently measured objective fitness and self-reported subjective PA, this allowed us to evaluate these exposures separately and jointly.

Our findings are also consistent with other large epidemiological studies that examined CRF and diabetes risk.[8 15 27 39] Sawada *et al* reported in a cohort study of 4747 Japanese men, aged 20–40 at baseline, in which 280 developed type 2 diabetes. An inverse association of incident type 2 diabetes (p trend <0.001) was shown across incremental quartiles of CRF.[39] Lynch *et al* studied 897 middle-aged Finnish men, aged 42–60, in a 4-year prospective study. Forty-six cases of diabetes were identified from 2 h postload glucose concentrations. CRF was assessed by respiratory gas exchange on a maximal bicycle ergometry test. They reported that those in the lowest quartile compared with the highest quartile had a fivefold higher risk of diabetes after adjustment for confounding factors.[27] Overall, these studies, including our own, show a strong inverse association between CRF and diabetes incidence.

Previous studies, including the Alumni of the University of Pennsylvania Study, the Nurses' Health Study, the US Physicians' Health Study, the British Regional Heart Study and the Population Sample from Northeast Finland, have all shown an inverse association between moderate or high intensity PA and the risk of type 2 diabetes.[6 10] One exception is with the Japanese study by Okada *et al*.[11] where 444 of the 6013 Japanese men developed type 2 diabetes. This may be attributed to the fact that they were studying leisure-time activity on the weekends instead of more frequent bouts throughout the week. Even so, men who engaged in PA at least once a week had a 25% lower risk of developing diabetes compared with those who exercised less often. More bouts of exercise during the weekend reduced the risk further.[11] In our study, the WJR and sports groups were not differentiated by intensity, and the risk of type 2 diabetes was similar in the two groups. In the US Physicians Health Study, 21 271 men aged 40–84 were followed for 5 years. Men who exercised vigorously at least once a week had a 29% lower risk of diabetes compared with those who exercised less than once a week. Our findings correlate with previous findings that participation in PA has a protective effect on developing type 2 diabetes.

It is true that engaging in PA will influence CRF to improve health.[43] Therefore, looking at both PA and CRF together needs attention. Data on joint associations of PA and CRF on diabetes are scant.[16] Lynch *et al*. reported that PA and CRF independently protected people from developing diabetes when they performed 40 min or more of PA at or above 5.5 METS.[27] In the Canadian Physical Activity Longitudinal Study (PALS), 709 men and 834 women were followed for about 15 years. They