下山直人, 他	研究プロジェクト② がん疼痛に対する代替療法・支持療法	緩和医療学	10(3)	11-6	2008
下山直人	緩和医療の現状と今後の展望	東京都医師会雑誌	61(4)	75-9	2008

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
山本精一郎		日本乳癌学会	乳癌診療ガイドライン 5. 疫学・予防	金原出版	東京	2008	
高橋秀徳, 下山直人	癌性疼痛と疼痛緩和	中川和彦	Cancer Treatment Navigator	メディカルレビュー社	東京	2008	272-3
下山恵美, 下山直人	疼痛管理	神田善伸	造血幹細胞移植の基礎と臨床（上巻）	医薬ジャーナル社	東京	2008	299-302
下山直人, 他	疼痛の メカニズム	東原正明	癌緩和ケア	振興医学出版社	東京	2008	6-9
岩瀬哲, 黒田佑次郎		リンパ浮腫診療ガイドライン作成委員会	リンパ浮腫診療ガイドライン	金原出版	東京	2009	
黒田佑次郎, 岩瀬哲	がん医療における緩和ケア -Overview	北原規 相羽恵介	化学放射線療法プラクティカルガイド	何山堂	東京	2009	73-82

Ⅳ. 研究成果の刊行物・別刷

Circ J 2008; **72:** 1563 – 1568

Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC)

— Rationale, Design, and Population Characteristics —

Japan Arteriosclerosis Longitudinal Study (JALS) Group*

Background The Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC) is a pooled study based on individual participant data from existing prospective cohort studies in Japan. Its purpose was to consider associations between risk factors and cardiovascular disease (CVD) outcomes, as well as differences between subgroups, defined by age, gender or geographical region, which could not be detected in the smaller samples.

Methods and Results Individual records for 66,691 participants in 21 cohort studies were pooled, accounting for a total of 575,628 person-years. From this data, there were 409 deaths attributed to stroke and 169 deaths attributed to coronary heart disease (CHD). Total stroke and CHD events were 1,478 and 178, respectively. Of the 1,424 total stroke events with a reported stroke subtype, 975 were classified as ischemic, 267 as hemorrhagic, and 178 as subarachnoid hemorrhage.

Conclusion The JALS-ECC collected data from existing cohort studies covering a diverse Japanese population, which has provided information about the effects of modifiable factors on the risks of the CVD. Such information should provide a reliable basis for establishing prevention strategies. (*Circ J* 2008; **72:** 1563 – 1568)

Key Words: Cohort study; Coronary heart disease; Meta-analysis; Stroke

Many of the epidemiological studies that have been conducted in Japan are internationally accepted as studies that have a unique perspective;[1–12] however, except for a few of them, the studies are either small in size or short in follow-up duration. Consequently, the small numbers of cardiovascular events recorded in individual studies have limited the strength of the evidence provided by any single study. Therefore, most studies cannot provide precise evidence about associations between risk factors and disease outcomes, nor can they reliably assess differences among subgroups defined by age, gender, or geographical region.

The Japan Arteriosclerosis Longitudinal Study (JALS) involves cohort studies conducted in Japan and consists of 2 different collaborative pooling projects based on individual participant data: the JALS with a common protocol, and the JALS with a meta-analysis of existing cohorts, which is called the Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC).[13] The difference between these 2 studies is the method of standardizing measurements. Their common purpose is to clarify the following: (1) associations between risk factors and cardiovascular disease (CVD) outcomes; (2) risk factors and prevention strategies of CVDs nationwide; and (3) differences among subgroups defined by age, gender, or geographical region that cannot be detected from any single cohort study. The collaborating investigators expect that both studies, together with an assessment of homogeneity and heterogeneity among cohorts, will provide reliable evidence for an epidemiological hypothesis. The JALS-ECC is the precedent to the JALS and its principal aim is to propose a hypothesis and proper statistical methods for the JALS in progress by analyzing individual data. This paper describes the rationale, study design, and methods of the JALS-ECC.

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Methods

Study Design

Study Eligibility Cohort studies were eligible for inclusion if they satisfied the following criteria: (1) subjects were Japanese; (2) prospective cohort study; (3) at least 3,000 person-years of follow-up; (4) data included date of birth (or age), gender, height, weight, blood pressure, and total cholesterol recorded at baseline; and (5) data included date of death or the age at death (for death from stroke or coronary heart disease, at least) recorded during follow-up.

Principal Risk Factors The JALS group requested individual participants' data from the collaborating investigators: date of baseline survey, date of birth or age at baseline, gender, height, weight, history of CVDs, blood pressure (systolic and diastolic), total cholesterol, high-density lipoprotein-cholesterol (HDL-C), triglycerides, smoking and drinking habits. Data were requested not only from the baseline examination, but also from any subsequent examinations during follow-up in order to examine and control the effects of regression dilution bias.[14]

Principal Outcomes Individual participants' data were requested on the occurrence of any of the following out-

Table 1 Principal Outcomes in JALS-ECC

Events	*ICD-9 codes*	*ICD-10 codes*
Cardiovascular diseases		
Ischemic heart diseases	*410*	*I21–I23*
All cerebrovascular disease	*430, 431, 433, 434, 436*	*I60, I61, I63, I64*
Ischemic stroke	*433, 434*	*I63*
Hemorrhagic stroke	*431*	*I61*
Subarachnoid hemorrhage	*430*	*I60*
Total death		

JALS-ECC, Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine; ICD-9, 9th Revision of the International Classification Diseases (–1994); ICD-10, 10th Revision of the International Classification Diseases (1995–).

Table 2 Baseline Characteristics of the Population in the JALS-ECC, 1985–2005

Regions	*Cohort name*	*Cohort size, n*	*Follow-up mortality, start-end (year)*	*Follow-up (months)*		*Follow-up morbidity, start-end (year)*	*Follow-up (months)*		*Female (%)*	*Age (years)*					
										Male			*Female*		
				Mean	*SD*		*Mean*	*SD*		*Mean*	*SD*	*Min-Max*	*Mean*	*SD*	*Min-Max*
Community-based															
Hokkaido	*Tannno/ Soubetsu*	2,066	1991–1999	66.1	30.1	1991–1999	66.1	30.1	56.1	60.5	10.9	25–91	59.8	10.5	22–83
Akita 1		6,484	1988–2003	167.4	36.4	1988–2000	141.7	27.2	64.9	58.5	11.9	27–93	56.8	11.2	22–94
Akita 2	*Ikawa*	2,595	1985–1999	128.8	29.5	1985–1999	128.8	29.5	56.4	56.1	10.9	40–88	56.1	10.7	40–88
Iwate	*Ohasama*	3,114	1990–2001	125.5	26.6	1990–2001	125.5	26.6	60.9	57.9	12.9	26–89	57.0	11.8	34–87
Ibaraki	*Kyowa*	4,479	1985–1999	120.6	30.7	1985–1999	120.6	30.7	57.2	54.7	9.4	40–83	54.9	9.6	40–83
Niigata	*Tokamachi*	8,480	1993–2003	93.8	31.5	1993–2003	93.8	31.5	66.9	59.5	12.8	28–92	57.3	12.0	29–93
Toyama	*Oyabe*	5,197	1988–1998	119.5	20.3	1988–1998	119.5	20.3	68.8	58.8	11.7	23–89	56.0	11.1	22–89
Wakayama		1,365	1989–1999	114.9	29.7	–	–	–	54.5	59.8	9.5	40–80	60.5	9.9	40–80
Osaka	*Yao, Minami-takayasu*	3,855	1985–1998	114.7	42.7	1985–1998	114.7	42.7	65.2	56.1	11.1	40–84	52.9	10.7	40–87
Shiga 1	*Shigaraki*	2,934	1992–2004	115.0	28.0	1992–2001	87.2	21.9	58.9	56.5	13.7	29–88	56.6	14.1	29–94
Shiga 2		1,138	1999–2002	35.2	6.0	1999–2002	35.2	6.0	58.5	72.7	6.5	60–93	74.7	7.6	45–99
Hiroshima	*Hiroshima*	2,222	1992–2001	70.9	22.0	1992–2000	43.5	23.3	71.3	70.6	8.0	60–93	72.8	7.8	60–96
Kochi	*Kahoku*	779	1992–2003	108.6	37.7	–	–	–	60.3	77.4	5.5	64–94	76.1	5.1	64–92
Ehime	*Ohzu*	5,301	1996–2003	66.1	12.6	1996–2003	66.1	12.6	66.1	62.3	12.6	22–95	58.0	14.1	20–94
Fukuoka 1	*Hisayama*	757	1990–2000	118.4	19.5	1990–2000	118.4	19.5	60.5	61.0	10.3	42–87	60.7	10.1	42–91
Fukuoka 2	*Tanushimaru*	1,920	1999–2003	44.9	3.7	1999–2003	44.9	3.7	58.6	63.5	10.9	40–94	62.0	11.0	40–95
Kumamoto		2,465	1999–2003	50.7	2.9	1999–2003	50.7	2.9	30.0	47.1	4.2	40–55	46.8	4.3	40–55
Work-site based															
Tokyo		801	1995–2001	69.4	7.3	1995–2001	69.4	7.3	25.5	50.5	7.9	35–67	51.1	6.5	36–68
Toyama		7,057	1990–2002	126.4	37.7	1990–2002	126.4	37.7	37.7	38.0	9.9	18–65	36.3	10.2	18–64
Aichi		2,810	1997–2001	31.8	10.6	1997–2001	31.8	10.6	0.0	51.0	6.7	34–70	–	–	–
Osaka		872	1985–2005	127.1	49.6	1985–2005	127.1	49.6	12.4	41.0	12.1	20–70	32.6	12.3	19–63
Total		66,691	1985–2005	99.9	49.0	1985–2005	93.4	45.1	55.5	54.2	13.8	18–95	56.3	13.5	18–99

Abbreviation see in Table 1.

comes: nonfatal stroke, nonfatal myocardial infarction (MI), cause-specific cardiovascular death, and all-cause mortality (Table 1). Details of the diagnostic criteria used for the definition of major cardiovascular events and data on the completeness of follow-up were also collected. All outcomes were classified, after recoding when necessary, according to the 9th revision of the International Classification of Diseases until the end of 1994, and according to the 10th revision of the International Classification of Diseases from the beginning of 1995![15] For any study that did not use this classification system, events were re-coded by the Coordinating Center staff members.

Data Management

All data were submitted electronically from collaborating investigators, and were checked by staff at the JALS Coordinating Center. The reports of completeness and consistency were referred back to the collaborating investigators for review and confirmation. When data queries arose, the Collaborating Center staff members and collaborating investigators discussed and resolved the problems. The process of the correction was kept on record and it was checked periodically in the Coordinating Center.

The data provided for inclusion in the JALS-ECC are held in strict confidence by the Coordinating Center. The data from each cohort study remain the property of the principal investigators of that study and will not be used for any presentation or publication without the permission of the Steering Committee. Permission to submit each cohort's data to the JALS Coordinating Center was obtained from each institute's ethical review board.

Statistical Analysis Plan

Collected individual follow-up data will be expanded into person-year type data, taking age changes into account. The expanded data will then be aggregated by gender, cohort, and age category. All analyses will be done by gender. Hazard ratios of risk factors and their confidence intervals will be calculated using the Poisson regression model for each event. Potential confounding factors and effect modifiers will included in the model. Heterogeneity in the effect of risk factors among cohorts will be assessed using the

Table 3 Number of Fatal Events in Each Study, JALS-ECC 1985–2005

Study	n	Total						Male						Female					
		All	Stroke				CHD	All	Stroke				CHD	All	Stroke				CHD
			Total	Isch	Hemo	SAH			Total	Isch	Hemo	SAH			Total	Isch	Hemo	SAH	
Community-based																			
Hokkaido	2,066	138	20	5	8	7	13	82	10	4	6	0	5	56	10	1	2	7	8
Akita 1	6,484	1,120	–	–	–	–	–	595	–	–	–	–	–	525	–	–	–	–	–
Akita 2	2,595	379	21	11	5	3	2	219	8	5	1	1	1	160	13	6	4	2	1
Iwate	3,114	384	57	27	18	12	21	241	37	20	13	4	16	143	20	7	5	8	5
Ibaraki	4,479	402	39	20	11	6	31	244	20	13	5	1	17	158	19	7	6	5	14
Niigata	8,480	424	44	14	16	13	5	238	21	9	7	5	3	186	23	5	9	8	2
Toyama	5,197	479	69	38	16	14	27	264	35	23	7	5	16	215	34	15	9	9	11
Wakayama	1,357	198	15	9	4	1	11	117	6	4	2	0	5	81	9	5	2	1	6
Osaka	3,855	283	25	16	2	7	6	166	14	11	1	2	6	117	11	5	1	5	0
Shiga 1	2,934	281	–	–	–	–	–	171	–	–	–	–	–	110	–	–	–	–	–
Shiga 2	1,135	90	13	11	2	0	1	46	7	7	0	0	1	44	6	4	2	0	0
Hiroshima	2,222	467	48	29	15	3	21	175	15	9	5	1	8	292	33	20	10	2	13
Kochi	776	301	31	11	7	4	26	157	8	1	3	0	12	144	23	10	4	4	14
Ehime	5,300	189	–	–	–	–	–	114	–	–	–	–	–	75	–	–	–	–	–
Fukuoka 1	757	88	12	4	4	4	1	53	5	3	0	2	1	35	7	1	4	2	0
Fukuoka 2	1,920	38	5	3	1	1	–	20	4	3	1	0	0	18	1	0	0	1	0
Kumamoto	2,465	1	–	–	–	–	–	1	0	0	0	0	0	0	0	0	0	0	0
Work-site based																			
Tokyo	801	4	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0
Toyama	7,057	105	7	1	4	2	3	85	7	1	4	2	3	20	0	0	0	0	0
Aichi	2,810	7	2	0	0	2	0	7	2	0	0	2	0	0	0	0	0	0	0
Osaka	872	15	1	0	1	0	1	14	1	0	1	0	1	1	0	0	0	0	0
Total	66,676	5,393	409	199	114	79	169	3,013	200	113	56	25	95	2,380	209	86	58	54	74

All, all-cause mortality; Isch, ischemic stroke; Hemo, hemorrhagic stroke; SAH, subarachnoid; CHD, coronary heart disease; –, no data available. Other abbreviation see in Table 1.

Table 4 Number of Nonfatal Events in Each Study, JALS-ECC 1985–2005

Study	n	Total					Male					Female				
		Stroke				CHD	Stroke				CHD	Stroke				CHD
		Total	Isch	Hemo	SAH		Total	Isch	Hemo	SAH		Total	Isch	Hemo	SAH	
Community-based																
Hokkaido	2,066	75	59	7	9	75	41	34	6	1	10	34	25	1	8	5
Akita 1	6,484	280	185	55	40	280	138	103	27	8	–	142	82	28	32	–
Akita 2	2,595	106	67	24	15	106	56	38	11	7	9	50	29	13	8	6
Iwate	3,114	210	151	40	18	210	107	83	18	5	–	103	68	22	13	–
Ibaraki	4,479	125	69	32	24	125	62	43	11	8	30	63	26	21	16	17
Niigata	8,480	–	–	–	–	–	–	–	–	–	19	–	–	–	–	11
Toyama	5,197	143	90	30	22	143	69	51	12	6	–	74	39	18	16	–
Wakayama	1,357	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Osaka	3,855	66	36	17	13	66	35	19	13	3	15	31	17	4	10	7
Shiga 1	2,934	71	54	10	7	71	32	27	1	4	10	39	27	9	3	4
Shiga 2	1,135	3	3	0	0	3	2	2	0	0	–	1	1	0	0	–
Hiroshima	2,222	77	64	8	2	77	23	20	3	0	6	54	44	5	2	6
Kochi	776	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ehime	5,300	95	76	13	5	95	52	48	3	1	7	43	28	10	4	3
Fukuoka 1	757	45	29	11	5	45	14	9	3	2	8	31	20	8	3	7
Fukuoka 2	1,920	24	18	4	2	24	18	14	3	1	6	6	4	1	1	1
Kumamoto	2,465	3	2	1	0	3	3	2	1	0	3	0	0	0	0	0
Work-site based																
Tokyo	801	1	1	0	0	1	2	1	1	0	3	0	0	0	0	1
Toyama	7,057	86	61	14	13	86	65	44	12	10	16	21	17	2	3	2
Aichi	2,810	9	7	0	2	9	9	7	0	2	12	0	0	0	0	0
Osaka	872	5	3	1	1	5	5	3	1	1	6	0	0	0	0	0
Total	66,676	1,424	975	267	178	230	733	548	126	59	160	692	427	142	119	70

Abbreviations see in Tables 1,3.

mixed-effect Poisson regression model. The effects of regression dilution will be assessed and adjusted by proposed methods using repeat measurements of risk factors data. All analyses will be done using SAS version 9.13 (SAS Institute Inc, Cary, NC, USA) and PROC GENMOD will be used for the Poisson regression.

Results

Individual records for 66,691 participants in 21 cohort studies were included in this study, with 82.7% of the participants from community-based cohorts and 17.3% from work-site based cohorts (Table 2). The mean follow-up

Table 5 Baseline Summary Statistics for Studies Included in JALS-ECC 1985–2005

Cohort	Blood pressure					Total cholesterol (mg/dl)		HDL-C (mg/dl)		LQC	Triglyceride (mg/dl)		Blood glucose (mg/dl)			
	SBP		DBP		Device								Fasting		Casual	
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD
Community-based																
Hokkaido	132.7	21.5	77.9	10.6	SP	193.3	33.1	54.3	13.9	CDC	134.0	92.3	93.4	20.8	–	–
Akita 1	132.6	18.9	78.4	11.0	SP	188.0	35.5	–	–	–	119.0*	73.1	–	–	106.7*	23.5
Akita 2	134.7	19.6	81.4	11.2	SP	188.8	32.3	59.6	14.1	CDC	132.0	86.1	119.6	29.4	135.3	44.1
Iwate	130.4	16.9	73.4	11.2	OC	195.8	36.7	51.7*	13.8	CDC	–	–	–	–	–	–
Ibaraki	136.7	19.7	81.5	11.7	SP	194.7	37.0	58.1*	13.9	CDC	157.4	106.8	124.5	36.3	130.6	42.1
Niigata	127.1	18.5	73.3	10.8	SP	197.0	35.5	56.6	14.3	OTH	138.0	94.6	–	–	–	–
Toyama	126.5	19.9	75.5	11.2	RZ	194.0	36.2	47.1	11.7	OTH	128.6	79.4	–	–	–	–
Wakayama	–	–	–	–		197.9*	34.4	50.4*	13.2	–	114.4*	71.5	–	–	–	–
Osaka	132.2	20.2	79.7	11.7	SP	203.7	35.7	60.3*	13.4	CDC	138.4	89.9	108.0	23.1	130.6	38.5
Shiga 1	132.0	19.7	78.0	11.8	SP	193.2	34.7	56.1	14.2	CDC	131.8	86.9	–	–	107.7	34.1
Shiga 2	145.4*	18.4	77.3*	10.2	OC	193.9*	35.4	48.6*	12.6	CDC	105.6*	54.5	–	–	–	–
Hiroshima	136.1	21.5	78.1	11.4	SP	215.3	38.3	52.5	14.6	CDC	149.7	85.0	–	–	112.9	41.7
Kochi	143.7	22.4	78.8	12.1	OC	191.8	36.4	49.2	14.4	CDC	119.4	61.7	–	–	112.0	30.0
Ehime	129.9	18.7	76.2	10.9	SP	205.6	38.0	59.7	15.8	CDC	120.5	76.0	95.8	19.0	105.9	29.9
Fukuoka 1	133.0	21.5	77.9	10.6	SP	209.5	37.7	52.5	11.8	OTH	115.8	88.1	98.0	20.5	107.1	21.7
Fukuoka 2	133.6	20.8	78.8	11.6	SP	199.8	34.6	55.8	14.0	–	113.7	83.4	97.8	20.1	–	–
Kumamoto	126.8	17.2	79.9	11.3	SP	207.1	36.4	57.4	15.0	CDC	145.3	139.7	103.5	23.5	–	–
Work-site based																
Tokyo	124.5	17.4	81.8	11.7	OC	244.6	18.7	55.2	17.1	OTH	–	–	–	–	–	–
Toyama	118.5	14.6	71.0	11.8	SP	190.5	35.3	53.3	13.1	OTH	103.5	64.4	92.7	13.1	–	–
Aichi	129.4	19.0	79.2	12.0	SP	206.9	33.7	53.5	13.7	OTH	132.2	92.8	97.6	20.6	–	–
Osaka	121.4	17.8	74.8	12.6	SP	186.6	31.3	58.5*	11.7	CDC	147.5	89.3	100.0	14.8	111.1	27.3

*Data available for less than 50% of all of participants.
SBP, systolic blood pressure; DBP, diastolic blood pressure; Device, measuring device; HDL-C, high-density lipoprotein-cholesterol; LQC, lipids quality control; SP, sphygmomanometers; CDC, CDC CRMLN; OC, automatic device cuff-oscillometric; RZ, random-zero sphygmomanometers; OTH, other quality control program. Other abbreviations see in Tables 1,3.

Table 6 Data on Smoking and Drinking Habits, JALS-ECC 1985–2005

Cohort	Smoking habit				Drinking habit				
	Current /Non	Current /Ex/Non	No. per day (cont.)	No. per day <20,≥20	Current /Non	Current /Ex/Non	No. per day (cont.)	No. per day <1,1–2,2–3, ≥3*	Conversion to ethanol
Community-based									
Hokkaido	○	○	–	–	○	○	–	–	–
Akita 1	○	–	○	○	○	–	○	○	▲
Akita 2	○	○	○	○	○	○	○	○	○
Iwate	○	○	–	–	○	○	–	–	–
Ibaraki	○	○	○	○	○	○	○	○	○
Niigata	○	○	–	–	○	–		–	–
Toyama	○	–	○	○	○	–	○	○	▲
Wakayama	○	○	○	○	○	○	○	○	○
Osaka	○	○	○	○	○	○	○	○	○
Shiga 1	○	○	○	○	○	○	○	○	○
Shiga 2	○	○	–	○	○	–	–	–	–
Hiroshima	○	–	○	○	–	–	–	–	–
Kochi	○	○	–	○	○	–	–	○**	▲
Ehime	○	○	–	○	○	○	–	○	○
Fukuoka 1	○	○	–	○	○	○	○	○	○
Fukuoka 2	○	○	–	○	○	○	–	○	▲
Kumamoto	○	○	○	○	○	○	○	○	○
Work-site based									
Tokyo	○	○	○	○	○	○	○	○	○
Toyama	○	○	–	○	○	○	○	○	○
Aichi	○	○	○	○	○	–	–	○	▲
Osaka	○	○	○	○	○	○	○	○	▲

*Units of "gou" (traditional Japanese unit of measurement, by volume, corresponding to 23 g of ethanol). 1 gou 180 ml of sake; **<3, ≥3 ("gou"/day).
▲=Data on frequency per week (or month) not available.
cont., continuous. Other abbreviations see in Tables 1,3.

period was 93.4 months. During a total of 575,628 person-years, there were 409 deaths attributed to stroke and 169 deaths attributed to CHDs; total stroke and CHD events were 1,478 and 230, respectively (Table 3). Of the 1,424 total stroke events with reported stroke subtype information, 975 were classified as ischemic, 267 as hemorrhagic and 178 as subarachnoid hemorrhage (Table 4).

Table 5 is a summary of the data on exposures. Data for baseline height, weight, and blood pressures were available for all participants, and for total cholesterol, HDL-C, and triglycerides from 95.5%, 67.2%, and 76.5% participants, respectively. Blood pressure was measured in each cohort using standard or random-zero sphygmomanometers and automatic devices based on the cuff-oscillometric method.

Table 6 shows the current smoking and drinking habits of the cohorts. All cohort studies included current cigarette smoking status. Eighteen studies additionally recorded "non-smoker" or "ex-smoker" for non-smokers, and 16 studies recorded the number of cigarettes smoked per day. Twenty studies asked about current drinking status and 12 studies additionally recorded "non-drinker" or "ex-drinker" for non-drinkers.

Discussion

The JALS-ECC is a meta-analysis of 21 prospective cohort studies that had enrolled a total of 66,691 subjects. It is the largest study in Japan investigating the morbidity and mortality of CVD as the study outcomes.

Pooling projects of epidemiological studies of CVD, namely the Asia Pacific Cohort Studies Collaboration (APCSC)[16] and the Prospective Studies Collaboration (PSC), have been published previously.[17] Those studies reported the association between risk factors and CVD in the Asian and Pacific populations. The APCSC also revealed the homogeneity in relative risks, although the absolute risk for stroke and the absolute risk for CHD in the Asian population were different.[18–24] Those differences could be attributed to lifestyle differences, such as nutrition and physical activity; however, the APCSC did not look at those parameters. Lifestyle differences could also account for the differences seen in absolute risks in domestic CVD epidemiological studies in Japan. The difference in absolute risk of stroke and the absolute risk of CHD between urban vs rural areas and northern vs southern areas has been reported.[3,6,12,25–27] In addition, previous Japanese studies did not focus attention on geographical differences, with most large-scale studies lumping many areas together as 1 cohort or conducting studies in 1 area,[1,2,28,29] whereas JALS covers a diverse Japanese population and, as such, should enable an in-depth analysis of the differences among subgroups defined by age, gender, or geographical area.

To assure the accuracy and precision of combining data from various cohort studies for this project, consistency in the definitions of outcome and measurement of risk factors was required. Most studies used the standard definitions for CHDs based on the criteria from the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study.[30] For example, MI was defined according to clinical features, characteristic electrocardiogram changes, and marked elevations in blood levels of cardiac enzymes. Most studies also reported stroke diagnoses based on typical clinical features and characteristic changes on computed tomography and/or magnetic resonance imaging brain scans using either the criteria from the MONICA study[30] or the WHO.[31] Studies that used definitions other than these have their definitions reported elsewhere.[12,32]

Most laboratories that measured lipids participated in some type of quality control program, such as the US Cholesterol Reference Method Laboratory Network (CRMLN) of the Centers for Disease Control and Prevention (CDC).[33] It seems reasonable to integrate this data and correlate lipid measurements with outcomes, but the present JALS-ECC study did not conduct a strict standardization of lipids measurements and outcomes. Conversely, data on smoking and drinking habits, and medical history were based on self-reported or administered questionnaires, making it difficult to combine data and determine objective outcomes, which is a limitation of this study.

In conclusion, the JALS-ECC project succeeded in collecting valuable data from existing cohort reports, which provided information about the effects of modifiable factors on the risks of the CVD. Such information should provide a reliable basis for establishing prevention strategies.

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References

1. Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, et al; NIPPON DATA80 Research Group. Cigarette smoking as a risk factor for stroke death in Japan. *Stroke* 2004; **35:** 1836–1841.
2. Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Ohnishi H, et al; The NIPPON DATA90 Research Group. Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. *Circ J* 2006; **70:** 954–959.
3. Kita Y, Okayama A, Ueshima H, Wada M, Choudhury SR, Bonita R, et al. Stroke incidence and case fatality in Shiga, Japan 1989–1993. *Int J Epidemiol* 1999; **28:** 1059–1065.
4. Okamura T, Nakamura K, Kanda H, Hayakawa T, Hozawa A, Murakami Y, et al; Health Promotion Research Committee, Shiga National Health Insurance Organizations. Effect of combined cardiovascular risk factors on individual and population medical expenditures: A 10-year cohort study of national health insurance in a Japanese population. *Circ J* 2007; **71:** 807–813.
5. Takeuchi H, Saitoh S, Takagi S, Ohnishi H, Ohhata J, Isobe T, et al. Metabolic syndrome and cardiac disease in Japanese men: Applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program-Adult Treatment Panel III to Japanese men: The Tanno and Sobetsu Study. *Hypertens Res* 2005; **28:** 203–208.
6. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: The Hisayama study. *Stroke* 2003; **34:** 2349–2354.
7. Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, et al. Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. *Diabetologia* 2004; **47:** 2137–2144.
8. Kitamura A, Iso H, Sankai T, Naito Y, Sato S, Kiyama M, et al. Alcohol intake and premature coronary heart disease in urban Japanese men. *Am J Epidemiol* 1998; **147:** 59–65.
9. Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, et al. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation* 1989; **79:** 503–515.
10. Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, et al. How many times should blood pressure be measured at home for better prediction of stroke risk?: Ten-year follow-up results from the Ohasama study. *J Hypertens* 2004; **22:** 1099–1104.
11. Kodama K, Sasaki H, Shimizu Y. Trend of coronary heart disease and its relationship to risk factors in a Japanese population: A 26-year follow-up, Hiroshima/Nagasaki study. *Jpn Circ J* 1990; **54:** 414–421.
12. Morikawa Y, Nakagawa H, Naruse Y, Nishijo M, Miura K, Tabata M, et al. Trends in stroke incidence and acute case fatality in a Japanese rural area: The Oyabe study. *Stroke* 2000; **31:** 1583–1587.
13. Ohashi Y, Ueshima H, Harada A. Japan Arteriosclerosis Longitudinal Study. *Nippon Rinsho* 2006; **64**(Suppl 6): 112–115 (in Japanese).
14. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart diseases. Part 1: Prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335:** 756–774.
15. World Health Organization. International classification of diseases and related health problems, 10th revision, Version for 2007. Available at: http://www.who.int/classifications/apps/icd/icd10online; accessed December 18, 2007.
16. Asia Pacific Cohort Studies Collaboration. Determinants of cardiovascular disease in the Asian Pacific region: Protocol for a collaborative overview of cohort studies. *CVD Prev* 1999; **2:** 281–289.
17. Prospective Studies Collaboration. Age-specific relevance of usual

blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360:** 1903–1913.

18. Asia Pacific Cohort Studies Collaboration. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. *Circulation* 2004; **110:** 2678–2686.
19. Asia Pacific Cohort Studies Collaboration. Blood pressure indices and cardiovascular disease in the Asia Pacific region: A pooled analysis. *Hypertension* 2003; **42:** 69–75.
20. Asia Pacific Cohort Studies Collaboration. Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region. *Circulation* 2005; **112:** 3384–3390.
21. Asia Pacific Cohort Studies Collaboration. Smoking, quitting, and the risk of cardiovascular disease among women and men in the Asia-Pacific region. *Int J Epidemiol* 2005; **34:** 1036–1045.
22. Asia Pacific Cohort Studies Collaboration. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care* 2003; **26:** 360–366.
23. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens* 2003; **21:** 707–716.
24. Feigin V, Parag V, Lawes CMM, Rodgers A, Suh I, Woodward M, et al. Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: An overview of 26 cohorts involving 306620 participants. *Stroke* 2005; **36:** 1360–1365.
25. Public Health Bureau, Ministry of Health and Welfare. Kokumin Eiyo no Genjyo (The National Nutrition Survey, 2003). Tokyo: Daiichi Shupppan, 2006 (in Japanese).
26. Public Health Bureau, The Ministry of Health and Welfare. A report of the National Survey on Circulatory Disorders 2000. Tokyo: Public Health Bureau, The Ministry of Health and Welfare, 2002 (in Japanese with English abstract).
27. Iso H, Shimamoto T, Kitamura A, Iida M, Komachi Y. Trends of cardiovascular risk factors and diseases in Japan: Implications for primordial prevention. *Prev Med* 1999; **29:** S102–S105.
28. Tamakoshi A, Yoshimura T, Inaba Y, Ito Y, Watanabe Y, Fukuda K, et al. JACC Study Group. Profile of the JACC study. *J Epidemiol* 2005; **15**(Suppl): S4–S8.
29. Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, et al. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: The Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation* 2006; **113:** 195–202.
30. WHO MONICA project. MONICA manual, revised edn. Geneva: Cardiovascular Diseases Unit, WHO, 1990.
31. World Health Organization. Cerebrovascular diseases: Prevention, treatment, and rehabilitation. Technical Report Series No. 469. Geneva: World Health Organization, 1971.
32. Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, et al. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation* 1989; **79:** 503–515.
33. Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. *J Atheroscler Thromb* 2003; **10:** 145–153.

Appendix 1

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JALS のデザイン論文の訂正です。Total CHD のイベント数に誤りがありました。

Table 4. Number of Non-fatal events in each study, JALS-ECC, 1985-2005

		Total					Male					Female				
		Stroke				CHD	Stroke				CHD	Stroke				CHD
Study	n	Total	Isch	Hemo	SAH		Total	Isch	Hemo	SAH		Total	Isch	Hemo	SAH	
Community based																
Hokkaido	2,066	75	59	7	9	15	41	34	6	1	10	34	25	1	8	5
Akita1	6,484	280	185	55	40	-	138	103	27	8	-	142	82	28	32	-
Akita2	2,595	106	67	24	15	15	56	38	11	7	9	50	29	13	8	6
Iwate	3,114	210	151	40	18	-	107	83	18	5	-	103	68	22	13	-
Ibaraki	4,479	125	69	32	24	47	62	43	11	8	30	63	26	21	16	17
Niigata	8,480	-	-	-	-	30	-	-	-	-	19	-	-	-	-	11
Toyama	5,197	143	90	30	22	-	69	51	12	6	-	74	39	18	16	-
Wakayama	1,357	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Osaka	3,855	66	36	17	13	22	35	19	13	3	15	31	17	4	10	7
Shiga1	2,934	71	54	10	7	14	32	27	1	4	10	39	27	9	3	4
Shiga2	1,135	3	3	0	0	-	2	2	0	0	-	1	1	0	0	-
Hiroshima	2,222	77	64	8	2	12	23	20	3	0	6	54	44	5	2	6
Kochi	776	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ehime	5,300	95	76	13	5	10	52	48	3	1	7	43	28	10	4	3
Fukuoka1	757	45	29	11	5	15	14	9	3	2	8	31	20	8	3	7
Fukuoka2	1,920	24	18	4	2	7	18	14	3	1	6	6	4	1	1	1
Kumamoto	2,465	3	2	1	0	3	3	2	1	0	3	0	0	0	0	0
Work-site based																
Tokyo	801	1	1	0	0	4	2	1	1	0	3	0	0	0	0	1
Toyama	7,057	86	61	14	13	18	65	44	12	10	16	21	17	2	3	2
Aichi	2,810	9	7	0	2	12	9	7	0	2	12	0	0	0	0	0
Osaka	872	5	3	1	1	6	5	3	1	1	6	0	0	0	0	0
Total	66,676	1,424	975	267	178	230	733	548	126	59	160	692	427	142	119	70

Abbreviations see in Tables 1, 3.

Daily Total Physical Activity Level and Premature Death in Men and Women: Results From a Large-Scale Population-Based Cohort Study in Japan (JPHC Study)

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PURPOSE: The impact of daily total physical activity level on premature deaths has not been fully clarified in non-Western, relatively lean populations. We prospectively examined the association between daily total physical activity level (METs/day) and subsequent risk of all-cause mortality and mortalities from cancer, heart disease, and cerebrovascular disease.

METHODS: A total of 83,034 general Japanese citizens ages 45–74 years who responded to the questionnaire in 1995–1999 were followed for any cause of death through December 2005. Mutlivariate-adjusted hazard ratios were calculated with a Cox proportional hazards model controlling for potential confounding factors.

RESULTS: During follow-up, a total of 4564 deaths were recorded. Compared with subjects in the lowest quartile, increased daily total physical activity was associated with a significantly decreased risk of all-cause mortality in both sexes (hazard ratios for the second, third, and highest quartiles were: men, 0.79, 0.82, 0.73 and women, 0.75, 0.64, 0.61, respectively). The decreased risk was observed regardless of age, frequency of leisure-time sports or physical exercise, or obesity status, albeit with a degree of risk attenuation among those with a high body mass index. A significantly decreased risk was similarly observed for death from cancer and heart disease in both sexes, and from cerebrovascular disease in women.

CONCLUSION: Greater daily total physical activity level, either from occupation, daily life, or leisure time, may be of benefit in preventing premature death.

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KEY WORDS: Physical Activity, Population-Based, Cohort Study, Mortality

INTRODUCTION

To date, a number of studies have reported the health benefits of physical activity, including a reduction in the risk of premature death (1–4) as well as in the risk of major causes of death, such as cardiovascular disease (2, 5) and cancer at some sites (6, 7). Physical activity is now regarded as one of the most important targets for the prevention of premature death and other adverse health outcomes (8). Physical activity has been assessed using various types of activity category, such as leisure and nonleisure time activity, physical exercise or sports, and nonexercise activity, such as occupational and household work. However, the need for comprehensive evaluation of these physical activities in the aggregate, particularly with regard to nonexercise physical activity, has been recognized (9).

From a public health point of view, as well as to clarify which type of physical activity has the strongest impact, it is important to estimate the impact of overall physical activity level on major outcomes, whether exercise or nonexercise and leisure time or nonleisure time. This in turn requires a quantitative approach to the assessment using a common scale for each activity, such as metabolic equivalent (MET). In addition, evidence from populations with a similar general lifestyle background is indispensable. Relatively few studies have assessed total physical activity using

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Selected Abbreviations and Acronyms

MET = metabolic equivalent
JPHC Study = Japan Public Health Center Study
ICD-10 = *International Classification of Disease, 10th Version*
HR = hazard ratio
95% CI = 95% confidence intervals

such a common quantitative scale (10–16), however, and those which have were conducted in Western populations. Evidence on physical activity and premature death in other populations is limited (16–19), particularly in Japanese (18, 19), with only two studies reported to date, one based on simple assessment of physical activity at work and the second on walking only. Thus, few studies have reported the effect of total physical activity on mortality in non-Western populations (16).

Here, we examined the association between daily total physical activity and mortality in the Japan Public Health Center-based Prospective Study (JPHC Study). Our main purposes were to estimate the impact of overall physical activity, including both exercise and nonexercise physical activities, on premature death, in other words, death before reaching the natural life span of Japanese, whose life expectancy is one of the highest in the world, at 79 years in men and 85 years in women by a 2005 life table using data from the Japanese Ministry of Health, Labour and Welfare. We also aimed to obtain epidemiologic evidence of this issue using a common quantitative scale for the assessment of any type of physical activity, from a population characterized as non-Western and relatively lean.

METHODS

Study Population

The JPHC Study was conducted in two cohorts, one initiated in 1990 (Cohort I) and the other in 1993 (Cohort II), which targeted all registered Japanese inhabitants in 11 public health center areas ages 40–59 years in Cohort I and 40–69 years in Cohort II at the beginning of each baseline survey. The details of the study design have been provided elsewhere (20). The study protocol was approved by the Institutional Review Board of the National Cancer Center, Japan (approval no.: 13–21).

The subjects of the present study were JPHC study subjects who responded to a 5-year follow-up self-administered questionnaire in 1995–1999 at ages 45–74 years. Initially at baseline, 140,420 subjects were identified as the study population. During the study period, a total of 258 subjects were found to be ineligible and excluded because of non-Japanese nationality (n = 51), duplicate enrollment (n = 4), late report of emigration occurring before the start of the follow-up period (n = 197), or incorrect birth date (n = 6). As a result, a population-based cohort of 140,162 subjects was established. After excluding 3,839 persons who had died, moved out of Japan, or were lost to follow-up before the start point, the remaining 136,323 subjects were considered eligible as the study population of the present study. A total of 103,791 subjects responded to the questionnaire, yielding a response rate of 76%.

Questionnaire

The questionnaire included items on demographics, personal medical history, physical activity, smoking and alcohol drinking status, other lifestyle factors, and diet via a validated food frequency of 138 food items and 14 supplementary questions (21). Those who reported a history of cancer, stroke, or myocardial infarction which had the potential to reduce physical activity (n = 5776), or had missing data for physical activity-related questions (n = 6351) or for other questions included in the multivariate model (n = 8630) were excluded. Finally 83,034 eligible subjects (39,183 men and 43,851 women) were included in the analysis.

Follow-Up

Subjects were followed from the start point (date of response to the 5-year follow-up questionnaire) until December 31, 2005. Residence status, including survival, was confirmed through the residential registry. Inspection of the resident registry is available to anyone under the resident registration law. Among the study subjects, 25 moved out of Japan, 1 withdraw participation, and 248 (0.3%) were lost to follow-up within the follow-up period. Information on the cause of death was obtained from the death certificate, provided by the Ministry of Health, Labour, and Welfare with the permission of the Ministry of Internal Affairs and Communications, in which cause of death is defined according to the *International Classification of Disease, 10th Version* (ICD-10) (22). Resident and death registration are required by law in Japan and the registries are believed to be complete.

The outcome of the present study was defined as all-cause mortality, including the three major causes of death in Japanese, namely cancer (ICD-10: C00-C97), heart disease (ICD-10: I20-I52), and cerebrovascular disease (ICD-10: I60-I69). During the study period, we identified 4564 deaths (3098 men and 1466 women), including 2044 deaths from cancer (1359 men and 685 women), 521 from heart disease (373 men and 148 women), and 453 from cerebrovascular disease (281 men and 172 women).

Physical Activity Levels

The main exposure of interest in the present study was daily total physical activity level. In our questionnaire (Appendix), subjects were asked about the average time spent per day on three types of physical activity, i.e., heavy physical

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work or strenuous exercise (none, <1 h, ≥1 h); sedentary activity (<3 h, 3–8 h, ≥8 h); and walking and standing (<1 h, 1–3 h, and ≥3 h). The following values were assigned as time scores for each activity; heavy physical work or strenuous exercise: 0 for none, 0.5 for <1 h, 3 for ≥1 h; sedentary activity: 1.5 for <3 hours, 5.5 for 3–8 h, and 7.5 for ≥8 h; and walking or standing: 0.5 for <1 h, 2 for 1–3 h, and 8.5 for ≥3 h. The midpoint of time range for each category was assigned when both minimum and maximum values were presented, and arbitrary values considered to have the highest validity from the validation study was assigned for the highest category. MET hours/day was estimated by multiplying the time score spent at each activity/day by its MET intensity (23): heavy physical work or strenuous exercise (4.5), walking or standing (2.0), sedentary (1.5), and sleep or others (0.9). After summing across all activities, subjects were grouped into four exposure levels by quartile of total METs/day by sex.

The validity of the total METs/day score was assessed using 108 eligible samples (53 men and 55 women) derived from 110 original volunteer subjects from the cohort using 4-day, 24-hour physical activity records (Sunday or another day off plus three weekdays) in two different seasons, namely harvesting and one other season in a single year. The mean of total METs/day for physical activity obtained from the self-report was 33.5 in men and 33.4 in women, whereas that from the mean of 24-hour physical activity record was 39.5 in men and 40.8 in women. Energy expenditure estimated in METs showed little difference by area. The Spearman's rank correlation coefficient between the total METs/day score and physical activity records was 0.46 when the average of two seasons was taken (men, 0.53; women, 0.35).

Analysis

The number of person-years in the follow-up period was counted from the start point, i.e., date of response to the 5-year follow-up questionnaire, until the date of death, date of emigration from Japan, or end of the study period, whichever came first. For subjects who withdraw from or were lost to follow-up, the date of withdrawal and the last confirmed date of presence, respectively, were used as the date of censor.

Hazard ratios (HR) and 95 % confidence intervals (95% CIs) were used to describe the relative risk of all-cause mortality associated with daily total physical activity level. Daily total physical activity was assessed by quartile of total METs/day score. The median METs/day value for each quartile was used when linear association was assessed. To investigate whether the effect on outcome differed by type of physical activity, we also assessed risk by the frequency of leisure-time sports or physical exercises (≤1–3 times per month, 1–2 times per week, 3–4 times per week, almost every day) in addition to the time spent per day for heavy physical work or strenuous exercise (none, <1 h, ≥1 h) and walking or standing (<1 h, 1–3 h, ≥3 h). Ordinal values were used to assess linear trends for these variables. We included a variable on the frequency of leisure-time sports or physical exercises and occupation in the model since this was not considered in calculating METs scores, although it was associated with physical activity level. The Cox proportional hazards model was used as a control for potential confounding factors, namely age at start point (5-year age categories), area (11 public health center areas), occupation (full-time agriculture/forestry/fishery, full-time salaried/self-employed/professional, multiple occupations, full-time housework/retired/unemployed), history of diabetes (no, yes), smoking status (never, past, current), alcohol intake status (almost none, occasional, regular), body mass index (14 to <20, 20 to <27, ≥27), and total energy intake (quintiles estimated by semi-quantitative food frequency questionnaire). These variables, obtained from the questionnaire, are either known or suspected from previous studies as risk factors for premature death.

Occupation, smoking status, alcohol intake frequency and body mass index were treated as strata to allow for a different baseline hazard for each stratum. Testing of the proportional hazards assumption by Schoenfeld and scaled Schoenfeld residuals found no violation of proportionality. In addition, we evaluated whether the effect of total physical activity was influenced by sex, age, body mass index, and frequency of leisure-time sports or physical exercise using a test of interaction by entering into the model multiplicative interaction terms between each factors. Because the effect of total physical activity was significantly influenced by sex (p for interaction = 0.004), all analyses were conducted by sex. Stata 10 (Stata Corporation, College Station, TX) (24) was used to perform statistical analyses.

RESULTS

During 725,071 person-years of follow-up (average follow-up period: 8.7 years) for 83,034 subjects (39,183 men and 43,851 women), a total of 4,564 deaths (3,098 men and 1,466 women) were identified and included in the analyses.

Characteristics of the study subjects according to physical activity level are shown in Table 1. The total METs/day scores for four groups, namely the lowest, second, third, and highest, were 25.45, 31.85, 34.25, and 42.65 in men and 26.10, 31.85, 34.25, and 42.65 in women, respectively. Occupationally, a greather proportion of those with full-time agriculture/forestry/fishery and lower proportion with full-time housework/unemployed/retired were observed with increased physical activity level in both sexes. Men who were more physically active were more likely to report current smoking, regular drinking, a greater frequency of

TABLE 1. Baseline characteristics of the study subjects according to physical activity level in the JPHC Study (n = 83,034)

	METs/day*			
	Lowest	Second	Third	Highest
Men (n = 39,183)				
Number of subjects	13,498	8,117	7,804	9,764
Quartile median of METs/day	25.45	31.85	34.25	42.65
(Range)	(21.60–27.10)	(27.25–31.85)	(32.40–36.05)	(36.25–46.25)
Age, years (mean ± SD)	56.1 ± 7.9	56.1 ± 7.6	56.6 ± 7.7	55.9 ± 7.4
Occupation (%)				
Full-time agriculture/forestry/fishery	11.4	16.5	19.9	26.9
Full-time salaried/self-employed/professional	72.5	69.1	64.9	57.7
Multiple occupations	3.5	6.5	6.9	12.3
Full-time housework/unemployed/retired	12.6	7.9	8.3	3.1
Body mass index (mean)	23.67	23.61	23.54	23.46
History of diabetes mellitus (%)	9.7	8.4	8.0	7.4
Current smokers (%)	47.7	47.0	47.4	49.0
Regular drinkers (≥1/week) (%)	65.9	68.5	68.5	71.4
Leisure-time sports or physical exercise (≥3–4/week) (%)	8.8	10.9	13.0	12.3
Total energy intake (age-adjusted mean, kcal/day)	2,042.8	2,140.9	2,171.2	2,302.8
Women (n = 43,851)				
Number of subjects	13,870	11,321	10,215	8,445
Quartile median of METs/day	26.10	31.85	34.25	42.65
(range)	(21.60–27.10)	(27.25–31.85)	(32.75–34.25)	(35.45–46.25)
Age, years (mean ± SD)	56.9±8.2	56.1±7.5	56.1±7.6	55.8±7.3
Occupation (%)				
Full-time agriculture/forestry/fishery	12.9	16.4	14.5	29.7
Full-time salaried/self-employed/professional	65.8	67.6	67.0	56.5
Multiple occupations	2.2	3.1	2.9	6.3
Full-time housework/unemployed/retired	19.1	12.8	15.8	7.4
Body mass index (mean)	23.53	23.38	23.33	23.44
History of diabetes mellitus (%)	4.7	3.7	3.4	3.8
Current smokers (%)	6.3	6.0	6.0	5.9
Regular drinkers (≥1/week) (%)	13.7	14.2	14.3	14.0
Leisure-time sports or physical exercise (≥3–4/week) (%)	9.5	9.7	11.7	15.0
Total energy intake (age-adjusted mean, kcal/day)	1,841.8	1,887.0	1,884.2	1,972.1

*Metabolic equivalent (MET)s/day = sum of the score for reported time per day spent in each physical activity multiplied by the MET value for each activity.

leisure-time sports or physical exercise, and higher daily mean energy consumption and less likely to report a history diabetes mellitus. No difference in body mass index was observed between groups by physical activity level. In women, similar trends were observed except that the differences in the proportion of current smokers and regular drinkers were not significant.

Associations between daily total physical activity level by total METs/day scores and all-cause and cause-specific mortalities are shown in Table 2. On multivariate adjustment, compared with subjects in the lowest quartile, increased daily total physical activity level was significantly associated with a decreased risk of all-cause mortality both in men (second highest, HR, 0.79 [95% CI, 0.71–0.87]; third highest, 0.82 [0.74–0.91]; highest, 0.73 [0.66–0.81], p for trend < 0.001) and in women (second highest, 0.75 [0.66–0.85]; third highest, 0.64 [0.56–0.74]; highest, 0.61 [0.52–0.73], p for trend < 0.001).

The results did not substantially differ after exclusion of early deaths occurring within 3 years of the start point, nor on further exclusion of subjects with very low physical activity levels less than 23 METs/day (4% of subjects) considered to be the result of poor physical condition (data not shown). Furthermore, inclusion of those who reported a history of cancer, stroke, or myocardial infarction resulted in a similar risk tendency: in men, second highest, 0.78 (0.72–0.86), third highest, 0.78 (0.71–0.86), highest, 0.72 (0.66–0.80), p for trend < 0.001; and in women, second highest, 0.76 (0.67–0.86); third highest, 0.64 (0.56–0.74); highest, 0.60 (0.51–0.70), p for trend < 0.001.

A significantly decreased risk for death from cancer and from heart disease was similarly observed in both sexes. A decreased risk for death from cerebrovascular disease was significant only in women. Decreased risk was equally observed regardless of age or frequency of leisure-time sports or physical exercise. When analyzed by obesity status, a decreased risk tendency was observed, but this was attenuated in the group with a body mass index of 27 or above. No significant effect modification was observed for age, obesity status, or frequency of leisure-time sport and physical exercises (data not shown).

TABLE 2. HRs and 95% CIs of all-cause and major specific-cause mortality according to daily total physical activity level by METs/day score quartiles (n=83,034)

			Total					Excluding deaths with first 3 years*		
Quartile (median for METs/day)	Number of subjects	Person-years	Number of deaths	HR1	(95%CI)	HR2	(95%CI)	Number of deaths	HR2	(95% CI)
Men (n = 39,183)										
All			(n = 3,098)					(n = 2,309)		
Lowest	13,498	112,789	1,249	1.00	(reference)	1.00	(reference)	889	1.00	(reference)
Second	8,117	70,212	590	**0.76**	**(0.68–0.83)**	**0.79**	**(0.71–0.87)**	450	**0.82**	**(0.74–0.93)**
Third	7,804	67,876	618	**0.79**	**(0.71–0.87)**	**0.82**	**(0.74–0.91)**	473	**0.86**	**(0.77–0.97)**
Highest	9,764	86,469	641	**0.67**	**(0.61–0.74)**	**0.73**	**(0.66–0.81)**	497	**0.77**	**(0.69–0.87)**
p for trend				**<0.001**		**<0.001**			**<0.001**	
Cancer (ICD10: C00-C97)			(n = 1,359)					(n = 996)		
Lowest	13,498	112,789	502	1.00	(reference)	1.00	(reference)	353	1.00	(reference)
Second	8,117	70,212	286	0.92	(0.79–1.06)	0.92	(0.80–1.07)	206	0.91	(0.77–1.09)
Third	7,804	67,876	284	0.89	(0.77–1.03)	0.89	(0.77–1.04)	217	0.94	(0.79–1.11)
Highest	9,764	86,469	287	**0.76**	**(0.66–0.88)**	**0.80**	**(0.68–0.93)**	220	**0.83**	**(0.69–0.99)**
p for trend				**<0.001**		**0.003**			**0.041**	
Heart diseases (ICD-10: I20-I52)			(n = 373)					(n= 275)		
Lowest	13,498	112,789	155	1.00	(reference)	1.00	(reference)	106	1.00	(reference)
Second	8,117	70,212	77	0.77	(0.59–1.02)	0.84	(0.64–1.11)	63	0.99	(0.72–1.36)
Third	7,804	67,876	62	**0.62**	**(0.46–0.83)**	**0.68**	**(0.50–0.92)**	45	**0.69**	**(0.48–0.99)**
Highest	9,764	86,469	79	**0.63**	**(0.48–0.82)**	**0.72**	**(0.54–0.96)**	61	0.78	(0.56–1.09)
p for trend				**<0.001**		**0.015**			0.076	
Cerebrovascular diseases (ICD-10: I60-I69)			(n = 281)					(n = 211)		
Lowest	13,498	112,789	99	1.00	(reference)	1.00	(reference)	74	1.00	(reference)
Second	8,117	70,212	53	0.85	(0.61–1.18)	0.89	(0.64–1.25)	44	0.98	(0.67–1.43)
Third	7,804	67,876	64	1.04	(0.76–1.43)	1.11	(0.81–1.53)	45	1.04	(0.71–1.51)
Highest	9,764	86,469	65	0.85	(0.62–1.16)	0.95	(0.68–1.32)	48	0.93	(0.63–1.36)
p for trend				0.417		0.927			0.737	
Women (n = 43,851)										
All			(n=1,466)					(n=1,134)		
Lowest	13,870	121,030	648	1.00	(reference)	1.00	(reference)	496	1.00	(reference)
Second	11,321	100,918	350	**0.70**	**(0.62–0.80)**	**0.75**	**(0.66–0.85)**	277	**0.76**	**(0.66–0.88)**
Third	10,215	90,696	274	**0.61**	**(0.53–0.70)**	**0.64**	**(0.56–0.74)**	215	**0.65**	**(0.55–0.77)**
Highest	8,445	75,082	194	**0.54**	**(0.46–0.64)**	**0.61**	**(0.52–0.73)**	146	**0.60**	**(0.49–0.72)**
p for trend				**<0.001**		**<0.001**			**<0.001**	
Cancer (ICD10: C00-C97)			(n=685)					(n=538)		
Lowest	13,870	121,030	263	1.00	(reference)	1.00	(reference)	209	1.00	(reference)
Second	11,321	100,918	175	0.84	(0.70–1.02)	0.87	(0.72–1.06)	139	0.87	(0.70–1.08)
Third	10,215	90,696	149	**0.79**	**(0.64–0.96)**	**0.81**	**(0.66–0.996)**	119	0.81	(0.64–1.01)
Highest	8,445	75,082	98	**0.65**	**(0.52–0.82)**	**0.69**	**(0.54–0.88)**	71	**0.62**	**(0.47–0.82)**
p for trend				**<0.001**		**0.001**			**0.001**	
Heart diseases (ICD-10: I20-I52)			(n=148)					(n=102)		
Lowest	13,870	121,030	73	1.00	(reference)	1.00	(reference)	51	1.00	(reference)
Second	11,321	100,918	32	**0.61**	**(0.40–0.93)**	0.71	(0.46–1.08)	23	0.73	(0.44–1.21)
Third	10,215	90,696	23	**0.49**	**(0.31–0.79)**	**0.55**	**(0.34–0.89)**	16	**0.54**	**(0.30–0.95)**
Highest	8,445	75,082	20	**0.52**	**(0.32–0.86)**	0.69	(0.41–1.17)	12	0.58	(0.30–1.12)
p for trend				**0.001**		**0.035**			**0.027**	
Cerebrovascular diseases (ICD-10: I60-I69)			(n=172)					(n=131)		
Lowest	13,870	121,030	76	1.00	(reference)	1.00	(reference)	55	1.00	(reference)
Second	11,321	100,918	42	0.72	(0.49–1.06)	0.74	(0.50–1.08)	34	0.78	(0.50–1.21)
Third	10,215	90,696	31	**0.58**	**(0.38–0.88)**	**0.60**	**(0.39–0.92)**	25	0.64	(0.39–1.04)
Highest	8,445	75,082	23	**0.56**	**(0.35–0.89)**	0.64	(0.39–1.04)	17	0.63	(0.36–1.11)
p for trend				**0.003**		**0.019**			**0.049**	

HR1: Adjusted for age (5-year age categories), area (11 PHC areas).
HR2: Adjusted for age (5-year age categories), area (11 PHC areas), occupation (stratified, full-time agriculture/forestry/fishery, full-time salaried/self-employed/professional, multiple occupations, full-time housework/retired/unemployed), history of diabetes (no, yes), smoking status (stratified, never, past, current), alcohol intake status (stratified, almost none, occasional, regular), body mass index (stratified, 14 to <20, 20 to <27, ≥27), total energy intake (quintiles) and leisure-time sports or physical exercise (<1 day/week, 1–2 days/week, ≥3–4 days/week).
*Exclusion of early deaths occurring within 3 years of the start point was done to reduce the effect of cases of poor physical condition which were considered to have been preceded by long-term inactivity.

When analyzed by type of physical activity (Table 3), both increased heavy physical work or strenuous exercise and walking or standing hours were significantly associated with a decreased risk of all-cause mortality. The decreased risk with increased frequency of leisure-time sports or physical exercise was observed more clearly in men than in women.

DISCUSSION

In this large-scale population-based prospective study of Japanese men and women, we found a significant inverse association between daily total physical activity level and all-cause mortality. Decreased risk was observed in both men and women. On analysis by type of physical activity, the decreasing trend was observed in both those with increased heavy physical work or strenuous exercises and those with longer walking or standing hours; and was also observed regardless of age, frequency of leisure-time sports or physical exercise or obesity status, despite some risk attenuation among those with a high body mass index. Decreased risk was also observed for major causes of mortality. High energy intake is considered associated with obesity and inactivity and was included in the model to control these effects to the greatest extent possible to see the effect of total physical activity level clearly. Since age range at the starting point was 45–74 years, which is less than life expectancy in both sexes, most deaths during the follow-up period occurred prematurely. To reduce the potential for spurious associations from reverse causation, namely that fatal diseases reduce physical activity, we excluded early deaths occurring within 3 years from the start point, but observed similar results. Furthermore, decreased risk was equally observed regardless of the frequency of leisure-time sports or physical exercise. Our results suggest that increased total physical activity level, either from occupation, daily life, or leisure time, helps in preventing premature death.

Although a number of studies have supported the health benefits of physical activity on all-cause mortality, only a few have assessed the association by daily total physical activity using a common activity scale such as MET (10–16). Our findings accord with these previous studies, notwithstanding that they were conducted in populations with general lifestyle possibly different from ours. In particular, although those with low physical activity levels have been reported to be typically more obese than those with higher levels in western populations (10, 11, 25, 28), no such tendency was observed in our population, nor also in a Chinese population (16). This suggests that the balance of contribution of the effects of physical activity on premature death may differ between non-Western, relatively lean populations and Western populations, namely that the indirect

TABLE 3. HRs* and 95%CIs of all-cause mortality according to type of physical activity (n = 83,034)

	Men (n = 39,183)					Women (n = 43,851)				
	Number of subjects	Person-years	Number of deaths	HR	(95%CI)	Number of subjects	Person-years	Number of deaths	HR	(95%CI)
Heavy physical work or strenuous exercise										
Non	23,026	195,805	2,076	1.00		32,779	290,280	1,208	1.00	
<1 h/day	5,415	46,711	299	**0.77**	**(0.68–0.88)**	4,335	37,629	103	0.83	(0.68–1.02)
≥1 h/day	10,742	94,830	723	**0.88**	**(0.80–0.96)**	6,737	59,816	155	**0.80**	**(0.67–0.96)**
p for trend				**0.001**					**0.004**	
Walking or standing hours										
<1 h/day	8,499	72,049	806	1.00		6,254	54,807	315	1.00	
1–3 h/day	9,601	80,288	767	**0.90**	**(0.81–0.99)**	10,410	90,763	423	**0.86**	**(0.74–0.99)**
≥3 h/day	21,083	185,009	1,525	**0.80**	**(0.73–0.88)**	27,187	242,154	728	**0.64**	**(0.55–0.73)**
p for trend				**<0.001**					**<0.001**	
Sedentary activities										
<3 h/day	17,667	152,673	1,331	1.00		19,651	173,068	648	1.00	
3–8 h/day	18,223	156,183	1,445	1.02	(0.95–1.11)	21,404	189,268	704	0.95	(0.85–1.06)
≥8 h/day	3,293	28,491	322	**1.18**	**(1.04–1.35)**	2,796	25,389	114	1.10	(0.82–1.25)
p for trend				**0.036**					0.698	
Leisure-time sports or physical exercise										
<1 day/week	30,526	264,625	2,547	1.00		34,239	306,097	1,221	1.00	
1–2 days/week	4,377	37,299	231	**0.75**	**(0.65–0.86)**	4,733	40,481	96	**0.69**	**(0.56–0.85)**
≥3–4 days/week	4,280	35,422	320	**0.78**	**(0.69–0.88)**	4,879	41,147	149	0.87	(0.73–1.03)
p for trend				**<0.001**					**0.008**	

*Model includes age (5-year age categories), area (11 PHC areas), occupation (stratified, full-time agriculture/forestry/fishery, full-time salaried/self-employed/professional, multiple occupations, full-time housework/retired/unemployed), history of diabetes (no, yes), smoking status (stratified, never, past, current), alcohol intake status (stratified, almost none, occasional, regular), body mass index (stratified, 14 to <20, 20 to <27, ≥27), total energy intake (quintiles), heavy physical work or strenuous exercise (none, <1 h, ≥1 h), sedentary activity (<3 h, 3–8 h, ≥8 h), walking or standing hours (<1 h, 1–3 h, ≥3 h), and leisure-time sports or physical exercise (<1 day/week, 1–2 days/week, ≥3–4 days/week).

effect of physical activity via a reduction in body mass index may be relatively greater in Western than non-Western populations.

Results showed a basically similar risk reduction in the two sexes, although to a somewhat stronger degree in women, and in this regard are consistent with previous studies (1, 4, 25). In addition, we observed significant effect modification between physical activity and sex. This suggests the existence of different mechanisms for the association between physical activity and premature death, additional to difference in the content of total physical activity between men and women. Methodologically, it is commonly noted that men are more likely to be physically active in their jobs and women are more likely to be involved in housework (1). In our questionnaire, rank correlation coefficients with the 24-h physical activity record were greater in men than in women, which may have partly resulted from a lack of detailed questions related to housework in our questionnaire, and a subsequent misclassification of physical activity; any failure of the questionnaire to suitably account for housework may thus lead to greater measurement errors in total physical activity in women than in men. This type of measurement error may have led to the underestimation of association.

Because of the structure of our questionnaire, we were unable to clearly distinguish components of the effect of physical activity level and were unable to assess the role of specific sports, even though we could assess the effect of physical activity by intensity type, i.e., strenuous, sedentary, and walking and standing. This is one of the limitations of the present study. Questions on occupation and the frequency of sports activity were not used to estimate METs, although total physical activity level would be explained in part by them. We instead included these variables in the model to control for undetected lifestyle characteristics, such as income and religious participation etc., which may affect the association, notwithstanding the lack of the information in the present study. Analysis stratified by the frequency of leisure-time sports or physical exercise suggested that risk reduction with increased daily total physical activity may be expected regardless of the frequency of leisure-time sports or physical exercise. Although identification of the components of physical activity which affect premature death is clearly important to our understanding of the etiology and mechanism of the outcome, this was not the primary purpose of our study; rather, we focused on the effect of total physical activity volume.

Discussions on the possible mechanisms by which physical activity protects against premature death remain inconclusive. Among difficulties, the reported risk reduction by physical activity is a grand sum of the impacts of various causes of death. Various mechanisms have been plausibly associated with cardiovascular disease and cancer, such as improvements in glucose tolerance, lipid profile, blood pressure, fibrinolytic activity and hemostatic function; (5, 26–34) and decreases in oxidative stress have been associated with aging and inflammation levels (35–37), respectively. Physical activity may also enhance various psychosocial determinants of healthy life conditions (11), although the biological mechanisms of these are yet to be addressed.

The major strength of the present study is its prospective design, which avoids exposure recall bias. Other strengths include the following: study subjects were selected from the general population, study size was large, response rate to the questionnaire (76%) was acceptable for study settings such as this, and the proportion of losses to follow-up (0.3%) was negligible. In addition, death registration in Japan is complete, and conducted in accordance with standard requirements of the World Health Organization.

In addition to those mentioned already, however, several other methodological limitations can also be identified. In particular, assessment of physical activity was based on self-reports. Although accuracy was validated, misclassification may have been unavoidable. However, because the data were collected before death, any imprecision is likely to have resulted in the underestimation of association. Changes in physical activity over time also cause misclassification, which might have lead to underestimation of the association. Further, although adjustment was made for lifestyle factors possibly associated with premature death, unmeasured confounders may not have been controlled. For instance, subjects with a history of arthritis and muscular-skeletal diseases or diabetes might experience a change in physical activity that might in turn affect their outcome. In our study, we did not collect information on arthritis or other musculoskeletal diseases and, thus, any effect of such conditions may not have been fully controlled. Further, although exclusion due to missing data for physical activity (6%) was not particularly large, the characteristics of subjects with and without missing information differed: those with missing information tended to be characterized by a high proportion of full-time housework/unemployed/retired in both men (32%) and women (46%) compared with those without missing information (8% in men and 14% in women). This difference may have the potential to influence the results. Finally, our results may not be generalizable to populations with a different general lifestyle to Japanese.

Allowing for these methodological issues, our results suggest that greater daily total physical activity levels, either from occupation, daily life, or leisure time, may be of benefit in preventing premature death among Japanese men and women. The findings of the present study should be of great use in health policy planning.

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REFERENCES

1. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? Med Sci Sports Exerc. 2001;33(6 Suppl):S379–399.
2. Erlichman J, Kerbey AL, James WP. Physical activity and its impact on health outcomes. Paper 1: The impact of physical activity on cardiovascular disease and all-cause mortality: An historical perspective. Obes Rev. 2002;3:257–271.
3. Katzmarzyk PT, Janssen I, Ardern CI. Physical inactivity, excess adiposity and premature mortality. Obes Rev. 2003;4:257–290.
4. Oguma Y, Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and all cause mortality in women: a review of the evidence. Br J Sports Med. 2002;36:162–172.
5. Wannamethee SG, Shaper AG. Physical activity and cardiovascular disease. Semin Vasc Med. 2002;2:257–266.
6. Lee IM. Physical activity and cancer prevention—data from epidemiologic studies. Med Sci Sports Exerc. 2003;35:1823–1827.
7. International Agency for Research on Cancer. Weight and physical activity. IARC Handbook of Cancer PreventionVolume 6Lyon: IARC Press; 2002.
8. World Health Organization. Global strategy on diet, physical activity and health. Geneva: World Health Organization; 2004.
9. Sesso HD. Invited commentary: a challenge for physical activity epidemiology. Am J Epidemiol. 2007;165:1351–1353.
10. Manini TM, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M, et al. Daily activity energy expenditure and mortality among older adults. JAMA. 2006;296:171–179.
11. Crespo CJ, Palmieri MR, Perdomo RP, Mcgee DL, Smit E, Sempos CT, et al. The relationship of physical activity and body weight with all-cause mortality: Results from the Puerto Rico Heart Health Program. Ann Epidemiol. 2002;12:543–552.
12. Lee IM, Paffenbarger RS Jr. Associations of light, moderate, and vigorous intensity physical activity with longevity. The Harvard Alumni Health Study. Am J Epidemiol. 2000;151:293–299.
13. Dorn JP, Cerny FJ, Epstein LH, Naughton J, Vena JE, Winkelstein W Jr, et al. Work and leisure time physical activity and mortality in men and women from a general population sample. Ann Epidemiol. 1999;9:366–373.
14. Weller I, Corey P. The impact of excluding non-leisure energy expenditure on the relation between physical activity and mortality in women. Epidemiology. 1998;9:632–635.
15. Sherman SE, D'Agostino RB, Cobb JL, Kannel WB. Physical activity and mortality in women in the Framingham Heart Study. Am Heart J. 1994;128:879–884.
16. Matthews CE, Jurj AL, Shu XO, Li HL, Yang G, Li Q, Gao YT, Zheng W. Influence of exercise, walking, cycling, and overall nonexercise physical activity on mortality in Chinese women. Am J Epidemiol. 2007;165:1343–1350.
17. Lam TH, Ho SY, Hedley AJ, Mak KH, Leung GM. Leisure time physical activity and mortality in Hong Kong: Case-control study of all adult deaths in 1998. Ann Epidemiol. 2004;14:391–398.
18. Menotti A, Blackburn H, Kromhout D, Nissinen A, Adachi H, Lanti M. Cardiovascular risk factors as determinants of 25-year all-cause mortality in the seven countries study. Eur J Epidemiol. 2001;17:337–346.
19. Fujita K, Takahashi H, Miura C, Ohkubo T, Sato Y, Ugajin T, et al. Walking and mortality in Japan: the Miyagi Cohort Study. J Epidemiol. 2004;14(Suppl 1):S26–32.
20. Tsugane S, Sobue T. Baseline survey of JPHC study—design and participation rate. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol. 2001;11(6 Suppl):S24–29.
21. Tsubono Y, Takamori S, Kobayashi M, Takahashi T, Iwase Y, Iitoi Y, et al. A data-based approach for designing a semiquantitative food frequency questionnaire for a population-based prospective study in Japan. J Epidemiol. 1996;6:45–53.
22. World Health Organization. International classification of diseases and health related problem, 10th revision. Geneva: World Health Organization; 1990.
23. Ainsworth BE, Bassett DR Jr, Strath SJ, Swartz AM, O'Brien WL, Thompson RW, et al. Comparison of three methods for measuring the time spent in physical activity. Med Sci Sports Exerc. 2000;32(9 Suppl):S457–464.
24. Stata Corporation. Stata Statistical Software, version 10. College Station, TX: Stata Corporation; 2007.
25. Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P. The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged Finnish men and women. Int J Obes (Lond). 2005;29:894–902.
26. Dunn AL, Marcus BH, Kampert JB, Garcia ME, Kohl HW 3rd, Blair SN. Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: A randomized trial. JAMA. 1999;281:327–334.
27. Andersen RE, Wadden TA, Bartlett SJ, Zemel B, Verde TJ, Franckowiak SC. Effects of lifestyle activity vs structured aerobic exercise in obese women: a randomized trial. JAMA. 1999;281:335–340.

28. Thune I, Njolstad I, Lochen ML, Forde OH. Physical activity improves the metabolic risk profiles in men and women: The Tromso Study. Arch Intern Med. 1998;158:1633–1640.

29. Marrugat J, Elosua R, Covas MI, Molina L, Rubies-Prat J. Amount and intensity of physical activity, physical fitness, and serum lipids in men. The MARATHOM Investigators. Am J Epidemiol. 1996;143:562–569.

30. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, Saad M, et al. Intensity and amount of physical activity in relation to insulin sensitivity: The Insulin Resistance Atherosclerosis Study. JAMA. 1998;279:669–674.

31. King AC, Haskell WL, Young DR, Oka RK, Stefanick ML. Long-term effects of varying intensities and formats of physical activity on participation rates, fitness, and lipoproteins in men and women aged 50 to 65 years. Circulation. 1995;91:2596–2604.

32. Szymanski LM, Pate RR. Effects of exercise intensity, duration, and time of day on fibrinolytic activity in physically active men. Med Sci Sports Exerc. 1994;26:1102–1108.

33. Rauramaa R, Li G, Vaisanen SB. Dose-response and coagulation and hemostatic factors. Med Sci Sports Exerc. 2001;33(6 Suppl):S516–520.

34. Hardman A. Physical activity and cardiovascular risk. J Cardiovasc Risk. 1995;2:285–288.

35. Goto S, Radak Z, Nyakas C, Chung HY, Naito H, Takahashi R, Nakamoto H, Abea R. Regular exercise: An effective means to reduce oxidative stress in old rats. Ann N Y Acad Sci. 2004;1019:471–474.

36. Chung HY, Kim HJ, Kim JW, Yu BP. The inflammation hypothesis of aging: Molecular modulation by calorie restriction. Ann N Y Acad Sci. 2001;928:327–335.

37. Pedersen BK, Toft AD. Effects of exercise on lymphocytes and cytokines. Br J Sports Med. 2000;34:246–251.

APPENDIX. QUESTIONS RELATED TO PHYSICAL ACTIVITY IN 5-YEAR FOLLOW-UP SURVEY OF THE JPHC STUDY

How long on average do you engage in the following activities each day?

Physical labor or sports	None	Less than 1 h	More than 1 h
Sitting	Less than 3 h	3–8 h	More than 8 h
Standing or walking	Less than 1 h	1–3 h	More than 3 h

How often do you participate in sports or physical exercise?

Almost never	1–3 days a month	1–2 days a week	3–4 days a week	Almost every day

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Original Contribution

Daily Total Physical Activity Level and Total Cancer Risk in Men and Women: Results from a Large-scale Population-based Cohort Study in Japan

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The impact of total physical activity level on cancer risk has not been fully clarified, particularly in non-Western, relatively lean populations. The authors prospectively examined the association between daily total physical activity (using a metabolic equivalents/day score) and subsequent cancer risk in the Japan Public Health Center-based Prospective Study. A total of 79,771 general-population Japanese men and women aged 45–74 years who responded to a questionnaire in 1995–1999 were followed for total cancer incidence (4,334 cases) through 2004. Compared with subjects in the lowest quartile, increased daily physical activity was associated with a significantly decreased risk of cancer in both sexes. In men, hazard ratios for the second, third, and highest quartiles were 1.00 (95% confidence interval (CI): 0.90, 1.11), 0.96 (95% CI: 0.86, 1.07), and 0.87 (95% CI: 0.78, 0.96), respectively (*p* for trend = 0.005); in women, hazard ratios were 0.93 (95% CI: 0.82, 1.05), 0.84 (95% CI: 0.73, 0.96), and 0.84 (95% CI: 0.73, 0.97), respectively (*p* for trend = 0.007). The decreased risk was more clearly observed in women than in men, especially among the elderly and those who regularly engaged in leisure-time sports or physical exercise. By site, decreased risks were observed for cancers of the colon, liver, and pancreas in men and for cancer of the stomach in women. Increased daily physical activity may be beneficial in preventing cancer in a relatively lean population.

cohort studies; exercise; Japan; neoplasms; physical fitness

Abbreviations: CI, confidence interval; MET(s), metabolic equivalent(s).

A number of investigators have reported beneficial effects of physical activity on the risk of cancer at certain specific sites, and physical activity is now regarded as an important target for cancer prevention. The second report of the World Cancer Research Fund/American Institute for Cancer Research recently concluded that all forms of physical activity protect against some cancers, including colon cancer, postmenopausal breast cancer, and endometrial cancer, in relation to or independently of weight gain, overweight, and obesity (1).

To date, however, the association between physical activity and total cancer risk has been relatively poorly investigated. Given that exercise and physical activity probably affect cancer development at different sites via the same mechanism or closely similar mechanisms, at least to some degree, it is reasonable to assess the preventive effect of physical activity not only on cancer at specific sites but also on all cancers in aggregate. Further, from a public health point of view, an understanding of the preventive effect of physical activity on total cancer risk will provide concrete

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TABLE 1. Baseline characteristics of study subjects according to daily total physical activity level (n = 79,771), Japan Public Health Center-based Prospective Study, 1995–2004

Characteristic	Quartile of physical activity level (quartile of METs*/day score)†			
	Lowest	Second	Third	Highest
Men (n = 37,898)				
No. of subjects	12,966	7,822	7,579	9,531
Quartile median value (METs/day score)	25.45 (21.60–27.10)‡	31.85 (27.25–31.85)	34.25 (32.40–36.05)	42.65 (36.25–46.25)
Mean age (years)	56.7	56.4	56.9	56.1
Mean body mass index§	23.66	23.62	23.56	23.49
History of diabetes mellitus (%)	10.1	8.6	8.3	7.6
History of liver disease (%)	3.7	2.9	2.7	2.6
Current smoking (%)	47.2	46.9	47.2	48.8
Regular alcohol drinking (≥1 day/week) (%)	64.6	68.0	68.1	71.0
Regular leisure-time sports or physical exercise (≥3–4 days/week) (%)	9.0	10.8	13.1	12.0
Mean total energy intake¶ (kcal/day)	2,040.8	2,141.5	2,168.6	2,299.5
Women (n = 41,873)				
No. of subjects	13,277	10,838	9,663	8,095
Quartile median value (METs/day score)	26.10 (21.60–27.10)	31.85 (27.25–31.85)	34.25 (32.75–34.25)	42.65 (35.45–46.25)
Mean age (years)	57.3	56.4	56.5	56.0
Mean body mass index	23.58	23.41	23.40	23.49
History of diabetes mellitus (%)	5.0	3.8	3.5	3.9
History of liver disease (%)	1.3	1.3	1.5	1.0
Current smoking (%)	5.9	5.8	5.6	5.5
Regular alcohol drinking (≥1 day/week) (%)	12.8	13.4	13.7	13.2
Regular leisure-time sports or physical exercise (≥3–4 days/week) (%)	9.4	9.7	11.5	14.6
Mean total energy intake¶ (kcal/day)	1,840.3	1,886.4	1,882.3	1,972.2

* METs, metabolic equivalents.
† Sum of the scores for reported amount of time per day spent in each physical activity multiplied by the MET value for each activity.
‡ Numbers in parentheses, range.
§ Weight (kg)/height(m)^2.
¶ Adjusted for age.

clues in estimating the effect of physical activity measures in health policy planning. For the latter case, evidence from populations with similar general lifestyle backgrounds is indispensable. Evidence for an association between physical activity and total cancer risk is limited (2–10), however; most studies have targeted mortality (4–10) rather than incidence (2, 3) and have been carried out in Western populations (2–8). Evidence from other populations is sparse (9, 10).

Here, we examined the association between daily total physical activity and risk of all types of cancer in the Japan Public Health Center-based Prospective Study. Our main purpose was to estimate the magnitude of the effect of overall physical activity, including exercise and nonexercise physical activities, on total cancer risk among Japanese, a population characterized as non-Western and relatively lean. To date, physical activity has been assessed using various types of activity categories, such as leisure-time and non-leisure-time activity, physical exercise or sports, and nonexercise activities, such as occupational activity and household work. However, given recognition of the need for comprehensive evaluation of these physical activities in the aggregate, particularly with regard to nonexercise physical activity (11), here we attempted a quantitative approach to assessment using a common scale for all activities (namely, metabolic equivalents (METs)) to estimate the effect of total physical activity level.

MATERIALS AND METHODS

Study population

The Japan Public Health Center-based Prospective Study was started in 1990–1994. It targeted all registered Japanese inhabitants in 11 public health center areas who were aged 40–69 years at the beginning of the baseline survey (12).

The study protocol was approved by the institutional review board of the National Cancer Center, Japan. In the present analysis, one public health center area was excluded, since data on cancer incidence were not available.

The participants in the present study were subjects in the Japan Public Health Center-based Prospective Study who responded to a self-administered 5-year follow-up questionnaire