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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

TABLE 2. Hazard ratios for total cancer incidence according to daily total physical activity level (n = 79,771), Japan Public Health Center-based Prospective Study, 1995–2004

Quartile of physical activity level (quartile of METs*/day score)	No. of subjects	Person-years of follow-up	Total					Excluding cases diagnosed within first 3 years				
			No. of cases	HR1*,†	95% CI*	HR2‡	95% CI	No. of cases	HR1	95% CI	HR2	95% CI
Men (n = 37,898)					(n = 2,704)					(n = 1,804)		
Lowest	12,966	92,421	921	1.00	Reference	1.00	Reference	604	1.00	Reference	1.00	Reference
Second	7,822	57,957	575	1.00	0.90, 1.10	1.00	0.90, 1.11	381	0.98	0.86, 1.11	0.98	0.86, 1.11
Third	7,579	56,512	574	0.96	0.86, 1.06	0.96	0.86, 1.07	386	0.95	0.83, 1.08	0.95	0.83, 1.08
Highest	9,531	72,841	634	0.87	0.79, 0.96	0.87	0.78, 0.96	433	0.86	0.76, 0.97	0.86	0.76, 0.98
p for trend					0.006		0.005			0.015		0.017
Per 1-MET increase				0.99	0.99, 0.998	0.99	0.99, 0.998		0.99	0.99, 0.999	0.99	0.99, 0.999
Per 10-MET increase				0.93	0.88, 0.99	0.93	0.88, 0.99		0.93	0.87, 0.996	0.93	0.87, 0.997
Women (n = 41,873)					(n = 1,630)					(n = 1,056)		
Lowest	13,277	99,385	569	1.00	Reference	1.00	Reference	368	1.00	Reference	1.00	Reference
Second	10,838	83,644	428	0.92	0.81, 1.04	0.93	0.82, 1.05	290	0.94	0.81, 1.10	0.94	0.81, 1.10
Third	9,663	74,073	350	0.84	0.73, 0.96	0.84	0.73, 0.96	222	0.80	0.68, 0.95	0.79	0.67, 0.94
Highest	8,095	62,284	283	0.83	0.72, 0.96	0.84	0.73, 0.97	176	0.78	0.65, 0.93	0.78	0.65, 0.94
p for trend					0.004		0.007			0.002		0.002
Per 1-MET increase				0.99	0.98, 0.997	0.99	0.98, 0.997		0.98	0.97, 0.995	0.98	0.97, 0.995
Per 10-MET increase				0.89	0.82, 0.97	0.90	0.82, 0.98		0.85	0.77, 0.95	0.85	0.77, 0.95

* MET(s), metabolic equivalent(s); HR, hazard ratio; CI, confidence interval.

† Adjusted for age (stratified, 5-year categories) and area (stratified, 10 public health center areas).

‡ Adjusted for age (stratified, 5-year categories), area (stratified, 10 public health center areas), total energy intake (stratified, quintiles), history of diabetes (no, yes), smoking status (never smoking, past smoking, or 1–19, 20–29, or ≥30 cigarettes/day), alcohol intake status (almost none, occasional, or regular), body mass index (weight (kg)/height (m)^2; <20, 20–<27, or ≥27), and leisure-time sports or physical exercise (<1, 1–2, or ≥3–4 days/week).

in 1995–1999 at age 45–74 years. Initially, at baseline, 133,323 subjects were identified as being in the study population. After excluding 241 persons with non-Japanese nationality (n = 51), duplicate enrollment (n = 4), a late report of emigration occurring before the start of the follow-up period (n = 180), or ineligibility due to an incorrect birth date (n = 6), a population-based cohort of 133,082 subjects was established. After exclusion of the 13,663 persons who had died, moved out of the study area, or been lost to follow-up before the starting point, the remaining 119,419 subjects were considered eligible for the present study. A total of 96,566 subjects responded to the questionnaire, yielding a response rate of 81 percent.

Questionnaire

The questionnaire included items on demographic factors, personal medical history, physical activity, smoking and alcohol drinking, other lifestyle factors, and diet (via a validated food frequency questionnaire containing questions on 138 food items and 14 supplementary questions (13)). Persons who had been diagnosed with cancer before the starting point (n = 2,153) or who had missing data for physical activity-related factors (n = 6,346) or other factors included in the multivariate model (n = 8,296) were excluded. Finally, 79,771 eligible subjects (37,898 men and 41,873 women) were included in the analysis.

Follow-up

Subjects were followed from the starting point until December 31, 2004. 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, 5,271 died, 3,166 moved out of the study area, one withdrew from the study, and 239 (0.3 percent) were lost to follow-up within the follow-up period. Information on the cause of death for deceased subjects was obtained from death certificates (provided by the Ministry of Health, Labour, and Welfare with the permission of the Ministry of Internal Affairs and Communications), on which cause of death is defined according to the *International Classification of Diseases*, Tenth Revision (14). Resident registration and death registration are required by law in Japan, and the registries are believed to be complete.

Incident cancers were identified through notification from the major hospitals in the study area and through data linkage with population-based cancer registries. Death certificates were used as a supplementary information source. The site and histology of each case were coded using the *International Classification of Diseases for Oncology*, Third Edition (15). In our cancer registry system, the proportion of cases for which information was available from death certificates only was 3.7 percent. For the present analysis, the

TABLE 3. Hazard ratios for total cancer incidence according to daily total physical activity level and body mass index or frequency of leisure-time sports or physical exercise (n = 79,771), Japan Public Health Center-based Prospective Study, 1995–2004

Quartile of physical activity level (quartile of METs*/day score)	No. of subjects	Person-years of follow-up	Total			Excluding cases diagnosed within the first 3 years		
			No. of cases	HR*,†	95% CI*	No. of cases	HR†	95% CI
Men (n = 37,898)								
Age (years)								
<60								
Lowest	8,239	61,181	364	1.00	Reference	259	1.00	Reference
Second	5,063	38,860	239	1.00	0.85, 1.18	174	1.00	0.83, 1.22
Third	4,709	36,624	219	0.94	0.79, 1.12	161	0.94	0.77, 1.15
Highest	6,301	49,823	269	0.86	0.73, 1.01	202	0.87	0.72, 1.06
p for trend					0.049			0.135
≥60								
Lowest	4,727	31,240	557	1.00	Reference	345	1.00	Reference
Second	2,759	19,096	336	0.99	0.86, 1.14	207	0.96	0.80, 1.14
Third	2,870	19,887	355	0.97	0.85, 1.11	225	0.96	0.81, 1.14
Highest	3,230	23,018	365	0.87	0.76, 1.00	231	0.85	0.72, 1.01
p for trend					0.051			0.064
p for interaction					0.505			0.976
Body mass index‡								
<20								
Lowest	2,316	15,737	196	1.00	Reference	121	1.00	Reference
Second	1,409	10,180	118	0.93	0.73, 1.17	69	0.85	0.63, 1.16
Third	1,407	10,194	131	0.97	0.77, 1.22	89	1.02	0.77, 1.36
Highest	1,772	13,162	126	0.79	0.63, 1.00	71	0.69	0.51, 0.94
p for trend					0.063			0.031
20–<27								
Lowest	9,081	65,122	632	1.00	Reference	420	1.00	Reference
Second	5,493	40,888	386	0.97	0.86, 1.11	264	0.99	0.83, 1.14
Third	5,325	39,896	397	0.96	0.85, 1.09	263	0.92	0.79, 1.08
Highest	6,779	52,341	451	0.87	0.77, 0.98	324	0.89	0.77, 1.04
p for trend					0.026			0.118
≥27								
Lowest	1,569	11,562	93	1.00	Reference	63	1.00	Reference
Second	920	6,889	71	1.16	0.84, 1.62	48	1.23	0.83, 1.84
Third	847	6,422	46	0.84	0.58, 1.22	34	0.94	0.60, 1.46
Highest	980	7,339	57	0.93	0.66, 1.32	38	0.96	0.63, 1.47
p for trend					0.501			0.713
p for interaction					0.515			0.797
Frequency of leisure-time sports or physical exercise (days/week)								
<1								
Lowest	10,378	74,547	723	1.00	Reference	479	1.00	Reference
Second	6,077	45,423	453	1.02	0.91, 1.15	309	1.01	0.88, 1.17
Third	5,704	42,999	443	1.00	0.88, 1.12	303	0.98	0.85, 1.14
Highest	7,497	57,786	499	0.88	0.79, 0.99	343	0.87	0.75, 1.00
p for trend					0.032			0.044
≥1								
Lowest	2,588	17,875	198	1.00	Reference	125	1.00	Reference
Second	1,745	12,534	122	0.90	0.72, 1.14	72	0.84	0.63, 1.13
Third	1,875	13,513	131	0.84	0.67, 1.06	83	0.84	0.63, 1.12
Highest	2,034	15,055	135	0.78	0.62, 0.99	90	0.82	0.62, 1.09
p for trend					0.034			0.190
p for interaction					0.766			0.566

Table continues

TABLE 3. Continued

Quartile of physical activity level (quartile of METs/day score)	No. of subjects	Person-years of follow-up	Total			Excluding cases diagnosed within the first 3 years		
			No. of cases	HR†	95% CI	No. of cases	HR†	95% CI
Women ($n = 41,873$)								
Age (years)								
<60								
Lowest	7,946	61,385	279	1.00	Reference	184	1.00	Reference
Second	7,053	55,628	261	1.03	0.87, 1.22	184	1.09	0.88, 1.33
Third	6,271	48,932	202	0.90	0.75, 1.08	131	0.86	0.69, 1.08
Highest	5,501	43,242	188	0.95	0.79, 1.15	120	0.91	0.72, 1.14
p for trend					0.419			0.241
≥60								
Lowest	5,331	38,000	290	1.00	Reference	184	1.00	Reference
Second	3,785	28,016	167	0.81	0.67, 0.98	106	0.78	0.61, 0.996
Third	3,392	25,141	148	0.77	0.63, 0.95	91	0.72	0.56, 0.93
Highest	2,594	19,042	95	0.71	0.56, 0.90	56	0.63	0.47, 0.86
p for trend					0.001			0.001
p for interaction					0.667			0.396
Body mass index								
<20								
Lowest	2,896	20,823	116	1.00	Reference	72	1.00	Reference
Second	2,383	17,909	86	0.92	0.68, 1.22	64	1.08	0.76, 1.54
Third	2,096	15,459	69	0.87	0.64, 1.18	45	0.92	0.63, 1.36
Highest	1,598	12,009	47	0.76	0.54, 1.09	35	0.92	0.60, 1.40
p for trend					0.119			0.623
20–<27								
Lowest	8,467	63,889	370	1.00	Reference	238	1.00	Reference
Second	7,117	55,220	283	0.91	0.78, 1.06	190	0.92	0.76, 1.12
Third	6,453	49,990	239	0.82	0.70, 0.97	149	0.76	0.62, 0.93
Highest	5,515	42,597	192	0.81	0.68, 0.97	116	0.73	0.58, 0.92
p for trend					0.009			0.002
≥27								
Lowest	1,914	14,673	83	1.00	Reference	58	1.00	Reference
Second	1,338	10,516	59	1.05	0.74, 1.48	36	0.94	0.61, 1.44
Third	1,114	8,624	42	0.82	0.56, 1.20	28	0.79	0.49, 1.25
Highest	982	7,678	44	0.96	0.65, 1.41	25	0.76	0.46, 1.25
p for trend					0.643			0.223
p for interaction					0.839			0.137
Frequency of leisure-time sports or physical exercise (days/week)								
<1								
Lowest	10,837	81,716	464	1.00	Reference	297	1.00	Reference
Second	8,773	68,595	354	0.95	0.83, 1.10	236	0.96	0.81, 1.14
Third	7,521	58,563	274	0.84	0.72, 0.98	174	0.80	0.66, 0.97
Highest	5,811	45,696	223	0.92	0.78, 1.08	139	0.87	0.70, 1.06
p for trend					0.140			0.065
≥1								
Lowest	2,440	17,670	105	1.00	Reference	71	1.00	Reference
Second	2,065	15,049	74	0.80	0.59, 1.09	54	0.85	0.59, 1.22
Third	2,142	15,510	76	0.81	0.59, 1.09	48	0.74	0.51, 1.08
Highest	2,284	16,587	60	0.61	0.44, 0.84	37	0.55	0.37, 0.83
p for trend					0.003			0.003
p for interaction					0.158			0.105

* METs, metabolic equivalents; HR, hazard ratio; CI, confidence interval.

† Adjusted for age (stratified, 5-year categories), area (stratified, 10 public health center areas), total energy intake (stratified, quintiles), history of diabetes (no, yes), smoking status (never smoking, past smoking, or 1–19, 20–29, or ≥30 cigarettes/day), alcohol intake status (almost none, occasional, or regular), body mass index (weight (kg)/height (m)^2; <20, 20–<27, or ≥27), and leisure-time sports or physical exercise (<1, 1–2, or ≥3–4 days/week).

‡ Weight (kg)/height (m)^2.

earliest date of diagnosis was used in cases with multiple primary cancers diagnosed at different times. A total of 4,334 newly diagnosed cancer cases were identified.

Physical activity levels

The main exposure of interest in the present study was daily total physical activity level. In our questionnaire (see Appendix), subjects were asked about the average amount of time spent per day in three types of physical activity: heavy physical work or strenuous exercise (none, <1 hour, or ≥1 hour), sitting (<3, 3–<8, or ≥8 hours), and standing or walking (<1, 1–<3, or ≥3 hours). The following values were assigned as time scores for each activity: heavy physical work or strenuous exercise—0 for none, 0.5 for <1 hour, and 3 for ≥1 hour; sitting—1.5 for <3 hours, 5.5 for 3–<8 hours, and 7.5 for ≥8 hours; standing or walking—0.5 for <1 hour, 2 for 1–<3 hours, and 8.5 for ≥3 hours. The midpoint of the time range for each category was assigned when minimum and maximum values were presented on the questionnaire, and arbitrary values considered to have the highest validity from the validation study were assigned for the highest category. MET-hours/day were estimated by multiplying the daily time score for each activity by the MET intensity of that activity (16): for heavy physical work or strenuous exercise, 4.5; for standing or walking, 2.0; for being sedentary, 1.5; and for sleep or other passive activity, 0.9. After data were summed across all activities, subjects were grouped by sex into four exposure levels according to quartile of total METs/day score. Because the question on MET calculation incorporated all activities, including occupation, housework, leisure-time sports, etc., a separate question on the frequency of leisure-time sports and physical exercise was not included in the estimation of total physical activity level.

The validity of the total METs/day score was assessed among 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 number of total METs/day for physical activity obtained from the self-report was 33.5 in men and 33.4 in women, while the mean from the 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. Spearman's rank correlation coefficient for the correlation between the total METs/day score and the 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 starting point (i.e., the date of response to the 5-year follow-up questionnaire) to the date of occurrence of any cancer, emigration from the study area, death, or the end of the study period, whichever came first. For subjects who withdrew from the study or were lost to follow-up, the date of withdrawal or the last confirmed date of presence in the study was used as the date of censoring.

Hazard ratios and 95 percent confidence intervals were used to characterize the relative risk of cancer occurrence associated with daily total physical activity level. Daily total physical activity was assessed in quartiles of total METs/day score. The median METs/day value for each quartile was used when the linear association was assessed. To investigate whether the effect on the outcome differed by type of physical activity, we also assessed risk by the frequency of leisure-time sports or physical exercise (≤1–3 days/month, 1–2 days/week, 3–4 days/week, or almost every day), in addition to the amount of time spent per day in heavy physical work or strenuous exercise (none, <1 hour, or ≥1 hour) and in standing or walking (<1, 1–<3, or ≥3 hours). Ordinal values were used to assess linear trends for these variables.

The Cox proportional hazards model was employed to control for potentially confounding factors, namely age at the starting point (5-year categories), area (10 public health center areas), history of diabetes (no, yes), smoking status (never smoking, past smoking, or 1–19, 20–29, or ≥30 cigarettes/day), alcohol intake status (almost none, occasional, or regular), body mass index (weight (kg)/height (m)^2; 14–<20, 20–<27, or ≥27), and total energy intake (in quintiles, estimated by semiquantitative food frequency questionnaire). These variables, obtained from the questionnaire, are either known or suspected risk factors for cancer that have been identified in previous studies. We treated age, area, and total energy intake as strata to allow for a different baseline hazard for each stratum. In testing of the proportional hazards assumption by Schoenfeld residuals and scaled Schoenfeld residuals, we found no violation of proportionality. In addition, we evaluated whether the effect of total physical activity was influenced by age, body mass index, or frequency of leisure-time sports or physical exercise using a test of interaction, by entering into the model multiplicative terms for interaction between the respective factors. Since the effect of total physical activity was significantly influenced by sex (p for interaction $\leq$ 0.001), all analysis were conducted by sex. All statistical analyses were performed using Stata 10 (Stata Corporation, College Station, Texas) (17).

RESULTS

During 599,117 person-years of follow-up (average follow-up period, 7.5 years) for the 79,771 subjects (37,898 men and 41,873 women), 4,334 newly diagnosed cases of cancer (2,704 in men and 1,630 in women), including skin cancer (n = 53; 1.2 percent), were identified and included in the analyses. In men, gastric cancer was the most common cancer (n = 621; 23.0 percent), followed by cancers of the lung (n = 388; 14.3 percent), colon (n = 328; 12.1 percent), and prostate (n = 279; 10.3 percent). In women, breast cancer was the most common (n = 294; 18.0 percent), followed by cancers of the stomach (n = 232; 14.2 percent), colon (n = 228; 14.0 percent), and lung (n = 144; 8.8 percent).

Characteristics of the study subjects according to physical activity level are shown in table 1. The median values in the lowest, second, third, and highest quartiles of total METs/day

TABLE 4. Hazard ratios* for total cancer incidence according to type of physical activity (n = 79,771), Japan Public Health Center-based Prospective Study, 1995–2004

	No. of subjects	Person-years of follow-up	Total			Excluding cases diagnosed within the first 3 years		
			No. of cases	HR†	95% CI†	No. of cases	HR	95% CI
Men (n = 37,898)								
Heavy physical work or strenuous exercise (hours/day)								
None	22,235	161,694	1,670	1.00	Reference	1,093	1.00	Reference
<1	5,165	38,119	324	0.95	0.84, 1.07	229	1.02	0.88, 1.18
≥1	10,498	79,918	710	0.89	0.81, 0.98	482	0.89	0.80, 1.00
p for trend					0.014			0.071
Standing or walking (hours/day)								
<1	8,243	59,839	564	1.00	Reference	369	1.00	Reference
1–<3	9,143	65,023	649	1.04	0.92, 1.17	425	1.04	0.90, 1.21
≥3	20,512	154,869	1,491	0.99	0.89, 1.11	1,010	0.99	0.87, 1.13
p for trend					0.787			0.764
Sitting (hours/day)								
<3	17,251	128,076	1,230	1.00	Reference	821	1.00	Reference
3–<8	17,472	128,067	1,247	0.97	0.89, 1.06	835	0.97	0.88, 1.08
≥8	3,175	23,588	227	1.02	0.87, 1.18	148	0.97	0.80, 1.16
p for trend					0.839			0.599
Leisure-time sports or physical exercise (days/week)								
<1	29,656	220,754	2,118	1.00	Reference	1,434	1.00	Reference
1–2	4,095	30,011	240	0.92	0.80, 1.05	155	0.87	0.74, 1.03
≥3–4	4,147	28,965	346	1.12	0.998, 1.26	215	1.09	0.94, 1.26
p for trend					0.158			0.519
Women (n = 41,873)								
Heavy physical work or strenuous exercise (hours/day)								
None	31,286	238,962	1,266	1.00	Reference	832	1.00	Reference
<1	4,097	30,583	138	0.91	0.76, 1.09	89	0.90	0.72, 1.12
≥1	6,490	49,840	226	0.93	0.80, 1.07	135	0.84	0.70, 1.01
p for trend					0.200			0.043
Standing or walking (hours/day)								
<1	6,077	45,688	259	1.00	Reference	164	1.00	Reference
1–<3	9,828	73,552	410	1.00	0.85, 1.18	266	1.02	0.84, 1.25
≥3	25,968	200,146	961	0.89	0.77, 1.04	626	0.90	0.75, 1.09
p for trend					0.054			0.128
Sitting (hours/day)								
<3	18,981	144,501	724	1.00	Reference	463	1.00	Reference
3–<8	20,184	153,659	785	0.98	0.88, 1.09	509	0.97	0.85, 1.11
≥8	2,708	21,226	121	1.05	0.86, 1.29	84	1.10	0.86, 1.41
p for trend					0.896			0.748
Leisure-time sports or physical exercise (days/week)								
<1	32,942	254,570	1,315	1.00	Reference	846	1.00	Reference
1–2	4,338	31,712	136	0.91	0.76, 1.09	85	0.91	0.73, 1.15
≥3–4	4,593	33,104	179	1.05	0.89, 1.23	125	1.20	0.99, 1.45
p for trend					0.883			0.160

* The model included age (stratified, 5-year categories), area (stratified, 10 public health center areas), total energy intake (stratified, quintiles), history of diabetes (no, yes), smoking status (never smoking, past smoking, or 1–19, 20–29, or ≥30 cigarettes/day), alcohol intake status (almost none, occasional, regular), body mass index (weight (kg)/height (m)^2; <20, 20–<27, or ≥27), heavy physical work or strenuous exercise (none, <1 hour, or ≥1 hour/day), sitting (<3, 3–<8, or ≥8 hours/day), standing or walking (<1, 1–<3, or ≥3 hours/day), and leisure-time sports or physical exercise (<1, 1–2, or ≥3–4 days/week).

† HR, hazard ratio; CI, confidence interval.

TABLE 5. Hazard ratios for incidence of cancer at specific sites according to daily total physical activity level (n = 79,771), Japan Public Health Center-based Prospective Study, 1995–2004

Site (*International Classification of Diseases for Oncology*, Third Edition, code)	Quartile of physical activity level (quartile of METs*/day score)	No. of subjects	Person-years of follow-up	No. of cases	Hazard ratio†	95% confidence interval
Men (n = 37,898)						
Stomach (C16)	Lowest	12,966	92,421	194	1.00	Reference
	Second	7,822	57,957	134	1.10	0.88, 1.37
	Third	7,579	56,512	136	1.10	0.88, 1.37
	Highest	9,531	72,841	157	1.04	0.84, 1.29
	p for trend					0.785
Colon (C18)	Lowest	12,966	92,421	131	1.00	Reference
	Second	7,822	57,957	72	0.83	0.62, 1.11
	Third	7,579	56,512	59	0.65	0.48, 0.89
	Highest	9,531	72,841	66	0.58	0.43, 0.79
	p for trend					<0.001
Rectum (C19–20)	Lowest	12,966	92,421	51	1.00	Reference
	Second	7,822	57,957	41	1.30	0.85, 1.97
	Third	7,579	56,512	35	1.11	0.72, 1.72
	Highest	9,531	72,841	35	0.88	0.57, 1.36
	p for trend					0.464
Liver (C22)	Lowest	12,966	92,421	82	1.00	Reference
	Second	7,822	57,957	32	0.69	0.45, 1.06
	Third	7,579	56,512	44	1.01	0.69, 1.49
	Highest	9,531	72,841	31	0.62	0.40, 0.96
	p for trend					0.062
Pancreas (C25)	Lowest	12,966	92,421	36	1.00	Reference
	Second	7,822	57,957	20	0.90	0.52, 1.57
	Third	7,579	56,512	15	0.67	0.36, 1.24
	Highest	9,531	72,841	16	0.55	0.30, 1.00
	p for trend					0.038
Lung (C34)	Lowest	12,966	92,421	108	1.00	Reference
	Second	7,822	57,957	81	1.22	0.91, 1.63
	Third	7,579	56,512	103	1.44	1.09, 1.90
	Highest	9,531	72,841	96	1.10	0.83, 1.45
	p for trend					0.494
Prostate (C61)	Lowest	12,966	92,421	77	1.00	Reference
	Second	7,822	57,957	68	1.39	1.00, 1.94
	Third	7,579	56,512	63	1.21	0.86, 1.69
	Highest	9,531	72,841	71	1.13	0.82, 1.57
	p for trend					0.644

Table continues

score were 25.45, 31.85, 34.25, and 42.65, respectively, in men and 26.10, 31.85, 34.25, and 42.65, respectively, in women. Men who were more physically active were more likely to report regular drinking, a higher frequency of leisure-time sports or physical exercise, and higher daily mean energy consumption and were less likely to report a history of diabetes mellitus and liver disease. 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 regular drinkers were not significant.

Associations between daily total physical activity level by total METs/day score and total cancer incidence are shown

TABLE 5. Continued

Site (*International Classification of Diseases for Oncology*, Third Edition, code)	Quartile of physical activity level (quartile of METs/day score)	No. of subjects	Person-years of follow-up	No. of cases	Hazard ratio†	95% confidence interval
Women ($n = 41,873$)						
Stomach (C16)	Lowest	13,277	99,385	91	1.00	Reference
	Second	10,838	83,644	53	0.74	0.52, 1.04
	Third	9,663	74,073	54	0.78	0.55, 1.10
	Highest	8,095	62,284	34	0.63	0.42, 0.94
	p for trend					0.020
Colon (C18)	Lowest	13,277	99,385	83	1.00	Reference
	Second	10,838	83,644	58	0.87	0.62, 1.22
	Third	9,663	74,073	48	0.74	0.52, 1.07
	Highest	8,095	62,284	39	0.82	0.56, 1.21
	p for trend					0.198
Rectum (C19–20)	Lowest	13,277	99,385	24	1.00	Reference
	Second	10,838	83,644	24	1.26	0.71, 2.23
	Third	9,663	74,073	16	1.05	0.55, 2.00
	Highest	8,095	62,284	22	1.79	0.99, 3.23
	p for trend					0.077
Liver (C22)	Lowest	13,277	99,385	29	1.00	Reference
	Second	10,838	83,644	19	0.96	0.52, 1.78
	Third	9,663	74,073	19	0.99	0.53, 1.84
	Highest	8,095	62,284	7	0.54	0.23, 1.29
	p for trend					0.248
Pancreas (C25)	Lowest	13,277	99,385	19	1.00	Reference
	Second	10,838	83,644	15	0.98	0.50, 1.95
	Third	9,663	74,073	11	0.83	0.39, 1.76
	Highest	8,095	62,284	13	1.29	0.62, 2.67
	p for trend					0.601
Lung (C34)	Lowest	13,277	99,385	50	1.00	Reference
	Second	10,838	83,644	37	0.90	0.58, 1.38
	Third	9,663	74,073	31	0.90	0.57, 1.42
	Highest	8,095	62,284	26	0.92	0.56, 1.49
	p for trend					0.686
Breast (C50)	Lowest	13,277	99,385	85	1.00	Reference
	Second	10,838	83,644	91	1.24	0.92, 1.66
	Third	9,663	74,073	67	1.02	0.74, 1.40
	Highest	8,095	62,284	51	0.91	0.64, 1.29
	p for trend					0.529

* METs, metabolic equivalents.

† Adjusted for age (stratified, 5-year categories), area (stratified, 10 public health center areas), total energy intake (stratified, quintiles), history of diabetes (no, yes), smoking status (never smoker, past smoker, or 1–19, 20–29, or ≥30 cigarettes/day), alcohol intake status (almost none, occasional, or regular), body mass index (weight (kg)/height (m)^2; <20, 20–<27, or ≥27), and leisure-time sports or physical exercise (<1, 1–2, or ≥3–4 days/week).

in table 2. Upon multivariate adjustment, compared with subjects in the lowest quartile, increased daily total physical activity was significantly associated with a decreased risk of cancer incidence in both men and women. In men, hazard ratios in the second, third, and highest quartiles were 1.00 (95 percent confidence interval (CI): 0.90, 1.11), 0.96 (95 percent CI: 0.86, 1.07), and 0.87 (95 percent CI: 0.78, 0.96), respectively (p for trend = 0.005); in women, they were 0.93

(95 percent CI: 0.82, 1.05), 0.84 (95 percent CI: 0.73, 0.96), and 0.84 (95 percent CI: 0.73, 0.97), respectively (p for trend = 0.007). Our estimates also showed that the risk decreased by 7 percent in men and 10 percent in women with each 10-MET/day increase in physical activity level. The results did not differ substantially after exclusion of early cancer cases—those occurring within 3 years of the starting point—or after further exclusion of subjects with very low physical activity levels (<23 METs/day; 2 percent of subjects), considered to result from poor physical condition. On further estimation of the population attributable fraction (18) from our results, 4.5 percent of cases in men and 5.5 percent of cases in women were considered to have been preventable if the persons in the lowest physical activity category had increased their activity to a higher level.

In both sexes, the degree of risk decrease was attenuated among persons with increasing body mass index. In contrast, it was strengthened among the elderly and among persons who regularly engaged in leisure-time sports or physical exercise; this relation appeared more clearly in women. No significant interaction was observed for age, obesity status, or frequency of leisure-time sports and physical exercise (table 3). No particularly significant associations were identified in analysis by type of physical activity (table 4).

Results from analyses of specific cancer sites are shown in table 5. Significantly decreased risks were observed for colon, liver, and pancreatic cancer in men and for stomach cancer in women. In additional analyses for these cancers stratified by age, body mass index, and frequency of leisure-time sports or physical exercise, larger risk reductions were observed in persons with a lower body mass index, persons with frequent leisure-time sports or physical exercise, and the elderly for female stomach cancer and in persons with lower body mass index and persons with infrequent leisure-time sports or physical exercise for male colon cancer. For male liver and pancreatic cancers, we did not detect any significant difference or tendency in risk between stratified groups. In the analysis of breast cancer, the null association was not influenced by menopausal status.

DISCUSSION

The health benefits of physical activity are well established for certain cancer sites (1, 19), but the extent to which the grand sum of these effects influences total cancer incidence has not been clarified. Of course, any such association depends to some degree on the background population, namely the site distribution of cancers which are strongly or weakly associated with physical activity. According to recent statistics, in Japan the cancer sites with the highest incidence rates are the stomach, followed by the lung, colon, liver, and prostate, for men and the breast, followed by the stomach, colon, uterus, and lung, for women (20). In this large-scale, population-based cohort study of Japanese men and women, we found a significant inverse association between daily total physical activity level and total cancer incidence. To reduce the potential for spurious associations from reverse causation, we excluded all subjects with a history of cancer at the starting point. Moreover, exclusion of early cases (those occurring within 3 years of the starting point) had no substantial effect on the results.

To our knowledge, only two studies have assessed the association between physical activity and total risk of cancer (2, 3); both were carried out in relatively small populations. One, which targeted men only, observed a reduced risk with increased physical activity (2), while the second observed an increased risk with increased nonrecreational physical inactivity (3). Our findings, obtained with a substantially larger sample, accord with those of these previous studies.

Our results showed basically similar risk reductions in men and women. Shephard and Shek (21) suggested that differences between the sexes in benefits associated with regular physical activity are due to the difference in hormonal conditions, which may lead to the failure to adapt activity questionnaires to traditional patterns of physical activity in females. 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 (22). In our questionnaire, rank correlation coefficients for correlation with the 24-hour physical activity record were higher in men than in women. This may have partly resulted from the failure of our questionnaire to suitably account for housework. This type of measurement error may have led to underestimation of the association. Nevertheless, in the present study, a stronger effect of total physical activity among persons who engaged in regular leisure-time sports or physical exercise than among those who did not appears to have been more clearly observed in women. The larger proportion of strenuous work as a fraction of total physical activity in men than in women may be one reason for this discrepancy between men and women.

Our findings also showed that the effect of physical activity was diminished among subjects with a high body mass index, which is accordant with a previous report (3). To a substantial degree, physical activity may affect the risk of cancer by reducing weight and body mass index. We therefore suggest that the effect of physical activity appears less clear in persons with a high body mass index.

By site, our results showed inverse associations for colon, liver, and pancreatic cancer in men and for stomach cancer in women. In our population, we observed a positive association with a high body mass index for colon cancer only (23) and little association for pancreatic cancer (24). A recent evaluation found no association for stomach or liver cancer (1). In addition, nonalcoholic fatty liver disease, an increasingly recognized cause of chronic liver disease across the world, appears to be most strongly associated with central obesity and insulin resistance, and hepatocellular carcinoma has been postulated to arise through the development and progression of nonalcoholic fatty liver disease (25, 26). In the Japanese population, however, most cases of hepatocellular carcinoma are associated with hepatitis virus infection, and attribution to other factors may be small. Therefore, the effect of physical activity on these cancers, if any, appears to be operating not only via any improvement in obesity and related factors but also via other mechanisms.

Discussions on the possible mechanisms by which physical activity protects against cancer remain inconclusive. Various mechanisms have been plausibly associated with various cancers, such as alterations in sex hormones or insulin and insulin-like growth factors, immune modulation, alterations in free radical generation, changes in body fatness, and direct effects on cancer (1, 19, 27–32). Hyperinsulinemia produces an increase in circulating insulin-like growth factor 1, which is thought to play a major role in promoting carcinogenesis, and a decrease in insulin-like growth factor-binding proteins (33). Exercise increases insulin sensitivity and decreases fasting insulin and C-peptide levels (34), which may improve insulin resistance. Exercise-induced changes in the activity of macrophages, natural killer cells, lymphokine-activated killer cells, neutrophils, and regulating cytokines suggest that immunomodulation may contribute to the protective value of exercise (35). Strenuous physical exercise enhances oxygen free radical production, and the increased number of reactive oxygen species that are generated potentially results in damage to lipids, protein, and DNA. The antioxidant defense systems have co-evolved to counteract oxidative damage from oxygen free radicals (24, 36, 37). Moderate physical activity may be of benefit as a means of slowing or stopping the loss of antioxidants, whereas severe exercise might overwhelm the antioxidant system, potentially leading to damage and increased cell mutagenesis (37). Other mechanisms include a decrease in gut transit time, which has beneficial effects on bile content and secretion (1, 38), and have been proposed by site (1).

The major strength of the present study was its prospective design, which enabled us to avoid exposure recall bias. Study subjects were selected from the general population, the sample was large, the response rate to the questionnaire (81 percent) was acceptable for study settings such as this, and the loss to follow-up (0.3 percent) was negligible. Further, the number of exclusions due to missing data on physical activity (7 percent) was not particularly large. Although a difference in the characteristics of subjects with and without missing information had the potential to influence the results, no such difference was seen. In addition, the cancer registry in the study population was of sufficient quality to reduce the possibility of misclassification of the outcome.

In addition to those mentioned above, however, several methodological limitations can be identified. In particular, since assessment of physical activity was based on self-reports, misclassification may have been unavoidable. Nevertheless, because the data were collected before diagnosis, any imprecision is likely to have resulted in underestimation of the association. Changes in physical activity over time may also have caused misclassification, which might have led to underestimation of the association. In addition, some types of cancers or health conditions related to them may have caused low levels of physical activity from the starting point of the study; therefore, we cannot deny the possibility of spurious associations. Further, although adjustment was made for lifestyle factors possibly associated with cancer, unmeasured confounders may not have been controlled. Finally, our results may not be generalizable to populations with a different general lifestyle or a different degree of leanness from the Japanese.

Allowing for these methodological issues, our results suggest that increased daily total physical activity may be beneficial in preventing the development of cancer among Japanese men and women, who are characterized as relatively lean. Further research on the generalizability of our results to other relatively lean populations is warranted.

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APPENDIX

Questions related to physical activity in the 5-year follow-up survey of the Japan Public Health Center-based Prospective Study:

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

Heavy physical work or strenuous exercise	None	$<$1 hour	$\geq$1 hour
Sitting	$<$3 hours	3–$<$8 hours	$\geq$8 hours
Standing or walking	$<$1 hour	1–$<$3 hours	$\geq$3 hours

How often do you participate in sports or physical exercise?

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