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Original Article

Physical Activity and Bladder Cancer Risk: Findings of the Japan Collaborative Cohort Study

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Purpose The association of physical activity with the risk of bladder cancer remains inconsistent among Asian populations. We aimed to examine the association in a large Japanese cohort.

Materials and Methods In a population-based prospective cohort study, a total of 50,374 Japanese adults aged 40-79 years without a history of cancer or cardiovascular disease who had information on physical activity from self-administrated questionnaires were used for analysis. We performed Cox proportional hazard models to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for incident bladder cancer after adjusting for several potential confounders.

Results During the median 17.5 years of follow-up, 153 incident bladder cancers (116 men and 37 women) were identified. After the multivariable adjustment, HRs (95% CI) of bladder cancer concerning those with recreational sports participation of 1-2 hr/wk, 3-4 hr/wk, and 5 hr/wk and more were 0.67 (0.38-1.20), 0.79 (0.36-1.74), and 0.28 (0.09-0.89), respectively (p for trend=0.017). Compared with mostly sitting at the workplace, occupational physical activity of standing and walking were associated with a lower risk of bladder cancer (HR, 0.53 [95% CI, 0.32 to 0.85]). Hours of daily walking were not associated with the risk. The lower risk of bladder cancer was more evident for recreational sports (HR, 0.33 [95% CI, 0.10 to 1.00]), and for occupational standing and walking activity at work (HR, 0.57 [95% CI, 0.33 to 0.98]) among men.

Conclusion Recreational sports participation and occupational physical activity were inversely associated with the risk of bladder cancer among Japanese, especially in men.

Key words Urinary bladder neoplasms, Exercise, Occupational activity, Japan, Cohort studies, Incidence, Asian population

Introduction

Bladder cancer, the second most common cancer of the urinary system, is the tenth most prevalent cancer worldwide, with 550,000 new cases diagnosed annually [1]. Although bladder cancer is more common in Western countries, it is estimated that Japanese men have the highest bladder cancer incidence rates in Central and Eastern Asia, in which an age-standardized incidence and mortality rate was 9.6/100,000 [2]. While several factors [3] such as cigarette smoking and environmental exposure to aromatic amines have been identified as contributing to the development of bladder cancer, recent studies showed that modifiable lifestyle such as physical activity may also play a role in the incidence of the disease.

Physical activity is linked with a lower risk of developing cardiovascular disease and various types of cancer, including lung cancer [4], breast cancer [5], and colon cancer [6]. It has been proposed that physical activity may generate an anticancer impact by enhancing endogenous antioxidant enzyme systems, reducing chronic inflammation, increasing DNA repair, and decreasing obesity [7]. A meta-analysis including 15 published articles reported high levels of physical activity were associated with a 15% reduced risk of bladder cancer (relative risk [RR], 0.85; 95% confidence interval [CI], 0.74 to 0.98) [8]. However, of these studies, only one was conducted in Asia and the results were not significant (RR, 0.94; 95% CI, 0.77 to 1.15) [9] while Western studies reported inverse associations or null relationships [10,11]. In addition, few studies have separately compared the association of recreational physical activity and occupational physical activity with the risk of bladder cancer [12].

As Asians and Westerners have different lifestyle habits and genetic backgrounds, we consider that it is of crucial

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public health interest to investigate the association of recreational or occupational physical activity with the risk of bladder cancer in the Japanese population through a large prospective cohort study over 15 years of follow-up.

Materials and Methods

1. Study population

This study originated from The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), which commenced in 1988 and enrolled participants until the end of 1990. Detailed information on the JACC study has been described in previous publications [13,14]. Briefly, a total of 110,585 (46,395 men and 64,190 women) participants aged 40 to 79 years were recruited in the study from 45 areas throughout Japan. The baseline characteristics of participants were collected with self-administered questionnaires at enrollment. In this study, we only included 24 study areas where the data on cancer incidence, including the date of diagnosis and primary cancer site could be collected from hospital records or recorded in the cancer registry. Of 52,137 participants with cancer incidence information, we excluded 1,763 participants with previous diagnoses of cancers or cardiovascular diseases, including stroke and coronary heart disease), and a total of 50,374 (21,219 men and 29,155 women) participants were finally included in this study. Ethical approval of all procedures performed in the current study was approved by Osaka University Hospital and Nagoya University research ethics committees.

2. Exposure and covariates

We asked the participants about their information through self-administrated questionnaires at the enrollment including their age, sex, height, weight, smoking status (never smoked, former smoker, current smoker), drinking habits (never drinker, former drinker, current smoker of light-to-heavy alcohol consumption: < 23, 23 to < 46, 46 to < 69, ≥ 69 g ethanol/day), histories of diabetes mellitus, hypertension, cardiovascular diseases, and cancer (yes or no), family history of cancer (yes or no), occupation status (yes or no), television viewing time (television viewing time < 2, 2 to < 3, 3 to < 4.5, ≥ 4.5 hours/day), and physical activities. Body mass index (BMI) was calculated as weight divided by the square of height and further categorized into five quintiles (< 18.5, 18.5 to < 21, 21 to < 23, 23 to < 25, 25 to < 30, ≥ 30 kg/m^2).

Different types of physical activity were collected as follows: (1) sports activity time: (per week): almost none; 1-2 hours; 3-4 hours; more than 5 hours; (2) walking time (indoor, work, home, outdoor, etc.) per day: almost none; about 30 minutes; 30 minutes-1 hour; more than 1 hour; (3) occupational physical activity: mostly sitting; sitting and standing; mostly standing; standing and walking. As the inquiry about occupational physical activity corresponded to the occupation in which the participants had been involved for the longest period including all people who reported occupational physical activity including those who were employees, self-employ part-time workers, or the unemployed at baseline [15]. The validity and reliability of physical activity in this study have been reported previously [16].

3. Bladder cancer ascertainment

Bladder cancer incident cases were ascertained by population-based cancer registries, local major hospital records, and death certificates according to the 10th revision of the International Classification of Diseases (ICD-10). The duration of follow-up ended when one of three dates occurred first: the date of death, the date of moving out from the study area, or the end of 2009. Some study areas discontinued the follow-up survey before 2009 (1994 in one study area, 1997 in two areas, 1999 in one area, 2000 in one area, 2002 in one area, 2003 in one area, 2006 in two areas, and 2008 in two areas).

4. Statistical analysis

Participants' baseline characteristics were compared using the one-way analysis of variance (ANOVA) and Pearson chi-squared (χ^2) tests. We used Cox proportional hazard regression models to calculate the hazard ratios (HRs) and 95% CIs for bladder cancer incidence by different types of physical activity. Model 1 was adjusted for age and sex. Model 2 was further adjusted for the study centers, BMI, smoking status, alcohol drinking status, history of diabetes, history of hypertension, family history of cancer, occupation, as well as television viewing time. Model 3 was further adjusted for sports, walking, and occupational physical activity mutually. Missing data for these covariates were treated as separate categories and their indicators dummy variables were included in the model. The p-value for trend across the sports timing and walking timing categories was calculated using the median value in each category. The p-value for difference among occupational physical activity type was calculated. Stratified analyses were conducted to test the potential modifier according to sex. The p-value for interaction was tested for cross-product terms of sex (men or women). We performed all analyses using SAS ver. 9.4 software (SAS Institute Inc., Cary, NC), and a $p < 0.05$ was treated as statistically significant.

Table 1. Baseline characteristics of participants according to sports activity time

Characteristic	Sports activity time (hr/wk)			
	Almost none	1-2	3-4	≥ 5
No. of participants	33,262	7,059	2,880	2,297
Age (yr)	55.9±9.8	55.5±10.4	58.7±11.0	61.9±10.1
Men	13,305 (39.9)	3,441 (48.7)	1,438 (50.0)	1,208 (52.9)
Body mass index (kg/m²)	22.9±3.0	22.8±2.9	22.8±2.9	22.6±3.0
History of diabetes mellitus	1,160 (3.6)	305 (4.5)	147 (4.8)	129 (4.8)
History of hypertension	6,115 (19.2)	1,286 (19.5)	619 (19.8)	516 (17.9)
Current drinker	13,469 (39.8)	3,450 (47.9)	1,367 (48.8)	1,102 (51.5)
Current smoker	8,076 (24.0)	1,868 (26.0)	769 (27.3)	618 (28.6)
Family history of cancer	836 (2.5)	185 (2.6)	72 (2.5)	65 (2.8)
Job	19,850 (58.0)	4,428 (60.3)	1,482 (54.8)	1,239 (62.9)
Television viewing time (hr/day)	2.7±1.5	2.6±1.4	2.7±1.4	2.8±1.5
Walking				
Almost none	4,177 (14.3)	336 (5.1)	82 (3.3)	51 (2.3)
30 min/day	5,156 (17.7)	1,554 (23.6)	431 (17.5)	171 (7.7)
30-60 min/day	5,513 (19.0)	1,672 (25.4)	684 (27.8)	332 (15.0)
> 1 hr/day	14,299 (49.0)	3,033 (46.0)	1,271 (51.5)	1,664 (75.0)
Occupational physical activity				
Mostly sitting	8,930 (35.0)	2,428 (42.1)	816 (38.1)	578 (30.6)
Sitting and standing	4,116 (16.1)	1,073 (18.6)	385 (18.0)	277 (14.7)
Mostly standing	1,667 (6.5)	360 (6.2)	137 (6.4)	107 (5.7)
Standing and walking	10,793 (42.3)	1,910 (33.1)	804 (37.5)	928 (49.1)

Values are presented as mean±standard deviations or number (%).

Results

Table 1 shows the baseline characteristics of participants according to sports activity time. Compared to the almost non-sports activity group, participants who spent more time on recreational sports activity were more likely to be older, men, thinner, current drinkers, current smokers, and to have jobs, history of diabetes mellitus, family history of cancer, longer walking time, and more active occupational physical activity. Among the 50,374 participants (men and women) aged 40-79 years at baseline enrollment and within the median 17.5 years follow-up period, 153 incident cases of bladder cancer (116 men and 37 women) were identified. The results presented in Table 2 reported the association between different types of physical activity and bladder cancer risk. Compared to respondents with almost no sports activity time, higher sports activity was inversely associated with the risk of bladder cancer in a dose-response manner. The HRs (95% CIs) for bladder cancer risk among those with sports 1-2 hr/wk, 3-4 hr/wk, and ≥ 5 hr/wk were 0.65 (0.37, 1.15), 0.78 (0.36, 1.70), and 0.26 (0.08, 0.85), respectively; p-trend=0.017 after adjusting for confounding factors (Model 2). The results were similar after mutually adjusting for sports, walking, and occupational physical activity in Model 3.

Walking for 30-60 min/day and > 1 hr/day was associated with a reduced risk of bladder cancer after adjusting for age and sex (HR, 0.53 [95% CI, 0.28 to 0.98]; HR, 0.59 [95% CI, 0.36 to 1.00], respectively). However, no association was observed after further adjustment, and the trend across longer time categories did not reach statistical significance (HR, 0.83 [95% CI, 0.44 to 1.54] for those with walking time > 1 hr/day). Compared to lower occupational physical activity- mostly sitting, those with higher occupational physical activity-standing and walking were associated with a reduced risk of bladder cancer (HR, 0.53 [95% CI, 0.32 to 0.85]). Other types of occupational physical activity did not observe significant association (HR, 0.68 [95% CI, 0.37 to 1.25] for sitting and standing, and HR, 1.22 [95% CI, 0.63 to 2.36] for mostly standing).

We further examined the association between a sedentary lifestyle, measured as a television viewing time, and bladder cancer risk in S1 Table, and it showed that shorter television viewing time was not associated with a lower risk of bladder cancer: HR, 0.89 [95% CI, 0.40 to 1.97] for persons with television viewing time < 2 hr/day compared with those ≥ 4.5 hr/day.

The sex-specific associations of different types of physical activity with the risk of bladder cancer was shown in Table

Table 2. HR and 95% CI for the risk of bladder cancer according to different types of physical activities

	Person years	No. of cases	HR (95% CI)		
			Model 1	Model 2	Model 3
Sports					
Almost none	493,962	105	1	1	1
1-2 hr/wk	105,141	18	0.71 (0.40-1.18)	0.65 (0.37-1.15)	0.67 (0.38-1.20)
3-4 hr/wk	41,432	11	0.86 (0.46-1.60)	0.78 (0.36-1.70)	0.79 (0.36-1.74)
≥ 5 hr/wk	32,384	3	0.23 (0.07-0.73)	0.26 (0.08-0.85)	0.28 (0.09-0.89)
p for trend			0.007	0.012	0.017
Walking					
Almost none	64,721	19	1	1	1
30 min/day	108,309	26	0.75 (0.42-1.36)	0.73 (0.36-1.48)	0.80 (0.40-1.63)
30-60 min/day	123,921	21	0.53 (0.28-0.98)	0.70 (0.34-1.40)	0.79 (0.39-1.60)
> 1 hr/day	316,671	61	0.59 (0.36-1.00)	0.73 (0.39-1.34)	0.83 (0.44-1.54)
p for trend			0.098	0.733	0.732
Occupational physical activity					
Mostly sitting	202,232	49	1	1	1
Sitting and standing	87,100	15	0.75 (0.42-1.33)	0.68 (0.37-1.25)	0.68 (0.37-1.25)
Mostly standing	33,964	11	1.24 (0.65-2.39)	1.25 (0.65-2.42)	1.22 (0.63-2.36)
Standing and walking	222,574	38	0.58 (0.38-0.89)	0.53 (0.33-0.86)	0.53 (0.32-0.85)
p difference			0.017	0.024	0.020

Model 1: adjusted for age and sex. Model 2: adjusted further for areas, body mass index, smoking status, drinking status, history of diabetes, history of hypertension, family history of cancer, occupation, as well as television viewing. Model 3: adjusted further for sports, walking, and occupational physical activity mutually. CI, confidence interval; HR, hazard ratio.

3. In the stratified analyses, the inverse association between sports activity and bladder cancer risk was more evident among men than women albeit with no significant interaction (p=0.786). Walking time was not associated with bladder cancer risk among either men or women. A significantly lower risk of bladder cancer with occupational physical activity was observed among men but not among women with no interaction (p=0.430).

Discussion

In this prospective cohort study, we found that longer recreational sports time and occupational physical activity (including standing and/or walking) were associated with a reduced risk of bladder cancer among middle-aged and older Japanese after adjusting for potential confounding factors. We did not observe a significant association between recreational walking time and the risk of bladder cancer.

Our findings were consistent with those reporting an inverse association between physical activity and bladder cancer risk [8,17-19]. A pooled research [19] based on 12 prospective cohort studies including 1.44 million people from United States and Europe showed that compared with a lower level of leisure-time physical activity, a high level of activity had a 13% lower risk of bladder cancer (HR, 0.87 [95% CI, 0.82 to 0.92]). Another research [17] derived from the Women's Health Initiative Study found that total and moderate to vigorous physical activity were associated with a decreased risk of bladder cancer compared to inactive physical activity (HR, 0.74 [95% CI, 0.59 to 0.94]; and HR, 0.76 [95% CI, 0.61 to 0.94], respectively). However, these studies were mainly based on Caucasian populations, which may not be generalizable to Asian populations due to the different lifestyles and genetic background. A Korean study [9] used the health insurance data to investigate the effect of leisure-time physical activity on bladder cancer risk and reported no significant association was found (adjusted RR, 0.94 [95% CI, 0.77 to 1.15]), which was contrary to our results. The inconsistency between that study and our current results may be due to the shorter follow-up time (6 years), and the difference in the definition of physical activity, which did not include occupational physical activity in the study from Korea. Given that work hours are generally longer in Asian populations [20], we consider it is essential to include occupational physical activities in the estimate of overall daily physical activity. To the best of our knowledge, our study is the first to report a significant association between recreational sports and a reduced risk of bladder cancer in the Asian population. Further investigations are needed to verify this finding in other

Table 3. HR and 95% CI for the risk of bladder cancer according to different types of physical activities, stratified by sex

	Person years	No. of cases	HR (95% CI)		
			Model 1	Model 2	Model 3
Sports					
Men					
Almost none	193,205	78	1	1	1
1-2 hr/wk	50,620	15	0.75 (0.43-1.31)	0.74 (0.42-1.29)	0.76 (0.41-1.39)
3-4 hr/wk	20,083	9	0.89 (0.45-1.79)	0.91 (0.46-1.84)	0.86 (0.37-2.02)
≥ 5 hr/wk	16,699	3	0.29 (0.09-0.93)	0.29 (0.09-0.94)	0.33 (0.10-1.00)
p for trend			0.033	0.040	0.057
Women					
Almost none	300,757	27	1	1	1
1-2 hr/wk	54,521	3	0.56 (0.17-1.86)	0.47 (0.14-1.55)	0.28 (0.04-2.13)
3-4 hr/wk	21,349	2	0.77 (0.18-3.27)	0.66 (0.16-2.82)	0.46 (0.06-3.85)
≥ 5 hr/wk	15,686	0	-	-	-
p for trend			0.112	0.069	0.128
Walking					
Men					
Almost none	29,025	16	1	1	1
30 min/day	47,977	18	0.63 (0.32-1.24)	0.56 (0.29-1.11)	0.64 (0.30-1.38)
30-60 min/day	51,112	16	0.50 (0.25-1.00)	0.49 (0.24-0.98)	0.70 (0.33-1.51)
> 1 hr/day	130,512	47	0.57 (0.32-1.00)	0.55 (0.31-0.98)	0.79 (0.41-1.52)
p for trend			0.159	0.162	0.901
Women					
Almost none	35,696	3	1	1	1
30 min/day	60,332	8	1.32 (0.35-5.00)	1.15 (0.30-4.39)	2.45 (0.28-21.45)
30-60 min/day	72,809	5	0.68 (0.16-2.85)	0.62 (0.15-2.59)	1.70 (0.19-15.47)
> 1 hr/day	186,159	14	0.76 (0.22-2.63)	0.77 (0.22-2.70)	1.24 (0.15-10.34)
p for trend			0.420	0.595	0.613
Occupational physical activity					
Men					
Mostly sitting	87,166	38	1	1	1
Sitting and standing	37,789	14	0.92 (0.50-1.70)	0.87 (0.46-1.65)	0.86 (0.45-1.65)
Mostly standing	159,408	8	1.15 (0.54-2.47)	1.15 (0.53-2.49)	1.12 (0.52-2.43)
Standing and walking	105,098	32	0.63 (0.39-1.01)	0.59 (0.35-1.00)	0.57 (0.33-0.98)
p difference			0.187	0.198	0.207
Women					
Mostly sitting	115,065	11	1	1	1
Sitting and standing	49,311	1	0.19 (0.03-1.49)	0.18 (0.02-1.43)	0.18 (0.02-1.50)
Mostly standing	18,024	3	1.55 (0.43-5.56)	1.62 (0.43-6.13)	1.66 (0.43-6.39)
Standing and walking	117,475	6	0.40 (0.15-1.10)	0.42 (0.13-1.35)	0.37 (0.11-1.25)
p difference			0.040	0.064	0.046

Model 1: adjusted for age. Model 2: adjusted further for areas, body mass index, smoking status, drinking status, history of diabetes, history of hypertension, family history of cancer, occupation, television viewing, as well as adjusted for sports, walking, and occupational physical activity, as well as television viewing. Model 3: adjusted further for sports, walking, and occupational physical activity mutually. p-interactions between physical activities and sex for bladder cancer were 0.786 for sports, 0.259 for walking, and 0.430 for occupational physical activity. CI, confidence interval; HR, hazard ratio.

Asian populations.

Despite the biological mechanism connecting physical activity and bladder cancer remains unknown, there have been suggested pathways that may account for the potential association. Physical activity intervention reduces the levels of insulin, which is a mitogenic factor that may stimulate cell proliferation and suppress apoptosis [21]. Meanwhile, insulin may promote tumor cell growth by enhancing circulating insulin-like growth factor-I (IGF-1), which could serve as a stimulus for the growth of preneoplastic and neoplastic cells [22]. A case-control study comparing 154 newly diagnosed bladder cancer patients with the controls showed that higher plasma levels of IGF-1 were associated with an increased risk of bladder cancer (odds ratio, 3.10, [95% CI, 1.43 to 6.70] for the highest versus lowest quartiles of plasma IGF-1) [23]. Furthermore, both animal and human studies [24,25] have reported that inflammatory markers, interleukin-6 may inhibit tumor growth in bladder carcinoma cells. Physical activity may play a role in the suppression of bladder carcinogenesis by increasing the circulating levels of inflammatory markers, which have been linked to cellular transformation, proliferation, angiogenesis, and metastasis [26,27].

In the current study, we also found participants whose occupational physical activity was standing/walking were at a lower risk of bladder cancer. Likewise, previous studies found sedentary types of work with mostly sitting position, such as clerical workers and managers were observed to have a higher risk of bladder cancer [12,28,29]. A study using the Swedish national census and cancer registry-linked data investigated the association of occupation type and occupational physical activity with the risk of incidence of bladder cancer [12]. They corroborated that compared to workers with physically active jobs, those with sedentary jobs showed an increased risk of bladder cancer (HR, 1.40 [95% CI, 1.31 to 1.50] for men; and HR, 1.17 [95% CI, 1.02 to 1.33] for women). We explored whether recreational and occupational physical activities have independent associations by models 2 and 3. The inverse associations of sports and occupational physical activities with the risk of bladder cancer did not change materially.

The strength of the current study is a community-based prospective design and a long follow-up period with an active endpoint confirmation using a cancer registry. Additionally, our study recruited a large number of participants throughout Japan with a high response rate. We collected many potential confounding factors for bladder cancer at baseline enrollment and further adjusted them in the multivariable analyses. However, some limitations of this study should be noted. First, data on physical activity were self-reported which may lead to misreporting; however, the studies found self-reported physical activity was shown to be satisfactory among Japanese [16]. Second, the detailed types and intensities of different physical activities or the duration of sedentary behavior were not collected in this study, which prevented us from analyzing the effect of metabolic equivalents of total activity on bladder cancer. Further studies could explore their association more comprehensively. Third, the data on environmental or occupational exposed to aromatic amines was unavailable in this study. Yet great efforts have been taken to reduce occupational exposure since 1960's in Japan [30]. Additionally, physical activity and other covariates were collected only once at the beginning of the study; thus, alterations in their physical activity that occurred during the follow-up period were unmeasured and may result in misclassification bias. However, the misclassification would be non-differential across different groups, so that the real association would be stronger. Finally, due to the small number of bladder cancers, the results of women should be carefully interpreted.

In conclusion, we used a large prospective cohort study with median 17.5 years of follow-up to examine the association between physical activity and the risk of bladder cancer among Japanese adults. Spending longer time in sports and walking or standing during work were associated with a reduced risk of bladder cancer incidence. More studies are needed to validate the association between physical activity and bladder cancer in other Asian populations.

Electronic Supplementary Material

Supplementary materials are available at the Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

Informed consent was obtained from participants asking their will to participate to the JACC study in the baseline questionnaire. Ethical approval of all procedures performed in the study was approved by Osaka University Hospital (14285-12) and Nagoya University research ethics committees (177).

Author Contributions

Conceived and designed the analysis: An H, Liu K.
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Performed the analysis: An H, Kawasaki R, Tamakoshi A, Iso H.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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