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The association between physical activity and bladder cancer: systematic review and meta-analysis

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Background: Physical activity may protect against bladder cancer through several biologic pathways, such as enhanced immune function and decreased chronic inflammation. Physical activity may also indirectly prevent bladder cancer by reducing obesity. A sizeable number of epidemiologic studies have examined the association between physical activity and bladder cancer, but the available evidence has not yet been formally summarised using meta-analysis.

Methods: We performed a systematic literature review and meta-analysis of English-language studies published from January 1975 through November 2013. We followed the PRISMA guidelines and used a random effects model to estimate the summary risk estimates for the association between physical activity and bladder cancer.

Results: A total of 15 studies with 5 402 369 subjects and 27 784 bladder cancer cases were included. High *vs* low levels of physical activity were related to decreased bladder cancer risk (summary relative risk (RR) = 0.85, 95% confidence interval (CI) = 0.74–0.98; $I^2 = 83\%$; *P*-value for heterogeneity across all studies < 0.001). Results were similar for cohort studies (RR = 0.89, 95% CI = 0.80–1.00; $I^2 = 64\%$) and case–control studies (RR = 0.71, 95% CI = 0.43–1.16; $I^2 = 87\%$; *P*-value for difference = 0.108) and they were comparable for women (RR = 0.83, 95% CI = 0.73–0.94; $I^2 = 0\%$) and men (RR = 0.92, 95% CI = 0.82–1.05; $I^2 = 67$; *P*-value for difference = 0.657). Findings were also comparable for recreational (RR = 0.81, 95% CI = 0.66–0.99; $I^2 = 77\%$) and occupational physical activity (RR = 0.90, 95% CI = 0.76–1.0; $I^2 = 76\%$; *P*-value for difference = 0.374), and they were largely consistent for moderate (RR = 0.85, 95% CI = 0.75–0.98; $I^2 = 76\%$) and vigorous activity (RR = 0.80, 95% CI = 0.64–1.00; $I^2 = 87\%$; *P*-value for difference = 0.535).

Conclusions: Physical activity is associated with decreased risk of bladder cancer. Further studies are required to assess the relations of intensity, frequency, duration, and timing in life of physical activity to bladder cancer risk.

During the past 10 years, the incidence rate of bladder cancer has increased by 26% (Jemal *et al*, 2003; Siegel *et al*, 2013). In 2012, approximately 72 570 new cases of bladder cancer were diagnosed in the United States (U.S.) (Siegel *et al*, 2013), and approximately 150 000 new cases were diagnosed in 40 European countries (Ferlay *et al*, 2013). Risk factors for bladder cancer include age, male gender, smoking, exposure to arsenic in drinking water, and occupational exposure to aromatic amines (Bachir and Kassouf, 2012). In addition, obesity appears to modestly increase the risk of bladder cancer (Qin *et al*, 2013).

In contrast, physical activity may protect against bladder cancer. Potential biologic pathways linking increased physical activity to decreased risk of bladder cancer include enhanced immune function, reduced chronic inflammation, increased detoxification of carcinogens, enhanced DNA repair, and modified cell proliferation, differentiation, and apoptosis (Rogers *et al*, 2008). Physical activity may also indirectly prevent bladder cancer by reducing obesity and contributing to body weight maintenance (Koebnick *et al*, 2008).

To date, 15 studies (Severson *et al*, 1989; Brownson *et al*, 1991; Paffenbarger *et al*, 1992; Dosemeci *et al*, 1993; Wannamethee *et al*,

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2001; Tripathi *et al*, 2002; Soll-Johanning and Bach, 2004; Schnohr *et al*, 2005; Holick *et al*, 2007; Koebnick *et al*, 2008; Wilson *et al*, 2008; Yun *et al*, 2008; Lin *et al*, 2010; Parent *et al*, 2011; Sormunen *et al*, 2013) have investigated the association between physical activity and risk of bladder cancer. Seven studies (Paffenbarger *et al*, 1992; Tripathi *et al*, 2002; Schnohr *et al*, 2005; Koebnick *et al*, 2008; Wilson *et al*, 2008; Lin *et al*, 2010; Parent *et al*, 2011) found an inverse relation between physical activity and bladder cancer, two (Wilson *et al*, 2008; Lin *et al*, 2010) of which were statistically significant. In contrast, two studies (Wannamethee *et al*, 2001; Sormunen *et al*, 2013) detected a positive association between physical activity and bladder cancer, one (Wannamethee *et al*, 2001) of which was statistically significant. Six studies (Severson *et al*, 1989; Brownson *et al*, 1991; Dosemeci *et al*, 1993; Soll-Johanning and Bach, 2004; Holick *et al*, 2007; Yun *et al*, 2008) reported a null relation between physical activity and bladder cancer. Despite the availability of a sizeable number of epidemiologic studies and the existence of several plausible biological mechanisms linking increased physical activity to decreased risk of bladder cancer, the evidence has not yet been formally summarised using meta-analysis. Because of this limitation, we performed a comprehensive systematic review and meta-analysis to quantify the relation of physical activity to bladder cancer risk.

MATERIALS AND METHODS

Literature Search. Our systematic review and meta-analysis followed the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines consisting of a checklist including 27 items (Moher *et al*, 2009). We performed a literature search of scientific articles published from January 1975 to November 2013 in the Cochrane Library, EMBASE, MEDLINE, and Web of Science using the following terms for physical activity: ‘physical activity’, ‘motor activity’, ‘exercise’, ‘physical fitness’, ‘endurance training’, ‘sport’, ‘athlete’, ‘sedentary’, ‘sedentary lifestyle’, ‘physical inactivity’, ‘motor inactivity’, ‘recreation’, ‘occupation’, ’walking’, and ‘sitting’. Using an AND operator, we combined those terms with the following terms for bladder cancer outcomes: ‘urinary bladder neoplasms’, ‘bladder cancer’, ‘bladder carcinoma, ‘bladder adenocarcinoma’, and ‘bladder tumour’. Our literature search strategy focused on human research articles written in English language. In addition, we screened the reference lists of the articles to identify further studies.

Studies were included in the meta-analysis if they (1) investigated the association between physical activity and bladder cancer incidence, (2) were observational studies with a cohort or case–control design, (3) published risk estimates such as hazard ratios (HR), odds ratios (OR), relative risks (RR), or standardised incidence ratios (SIR) and 95% confidence intervals (95% CI) or sufficient information to calculate them, and (4) provided age-adjusted or age-matched risk estimates. With the exception of one study of physically active mail carriers (Soll-Johanning and Bach, 2004) and one study of athletes (Sormunen *et al*, 2013), we did not consider occupational cohort studies that were based on record linkage of job titles to bladder cancer because those studies focused on occupational exposure to air pollution.

Two authors (MK, MFL) independently reviewed all identified studies quantifying the association between physical activity and risk of bladder cancer. A detailed overview of our literature search is shown in Supplementary Figure S1.

Our initial literature search yielded 3900 articles, of which 2410 articles remained after a duplicate check. After screening for irrelevant titles ($n=2310$ articles) and abstracts ($n=63$ articles), the remaining 37 manuscripts were reviewed in depth. Subsequently, eight studies were found in the reference lists of the reviewed manuscripts. Of these 45 articles, we excluded 28 articles that investigated the association between job titles and bladder cancer without focusing on physical activity. Further, we removed one article (Pukkala *et al*, 2000) because the results were updated in a subsequent study (Sormunen *et al*, 2013). We also removed one study that focused on physical activity and bladder cancer mortality (Batty *et al*, 2010). Thus, 15 articles were included in the meta-analysis (Severson *et al*, 1989; Brownson *et al*, 1991; Paffenbarger *et al*, 1992; Dosemeci *et al*, 1993; Wannamethee *et al*, 2001; Tripathi *et al*, 2002; Soll-Johanning and Bach, 2004; Schnohr *et al*, 2005; Holick *et al*, 2007; Koebnick *et al*, 2008; Wilson *et al*, 2008; Yun *et al*, 2008; Lin *et al*, 2010; Parent *et al*, 2011; Sormunen *et al*, 2013).

Data extraction. From each study, we extracted the first author’s last name, publication year, location of the study, sample size, number of cases, gender, domains and intensities of physical activity, type of assessment of physical activity, timing in life of physical activity, highest *vs* lowest category of physical activity, risk estimates with corresponding 95% confidence intervals (CI), and adjustment variables.

In four studies (Brownson *et al*, 1991; Dosemeci *et al*, 1993; Wilson *et al*, 2008; Lin *et al*, 2010), the reported risk estimates were based on using the highest level of physical activity as the reference group. For comparability with the other studies, we converted the reported RR to its reciprocal value. In one study (Paffenbarger *et al*, 1992), we calculated the 95% CI using the *P*-value and the RR estimate.

When grouping studies by the potential effect modifying factor ‘component or measure of physical activity’, we created the categories ‘energy expenditure’, ‘activity duration’, ‘activity frequency’, and ‘qualitative assessments’. Assessments of energy expenditure included metabolic equivalents of tasks (METs) per week, kilo joule (kJ)/minute, or weighted physical activity indexes. Activity duration was defined as hours/week or percentage of time spent physically active. Activity frequency was reported as times per week of physical activity. Qualitative assessments of physical activity were based on categories such as ‘sedentary’, ‘light’, ‘moderate’, or ‘high’ physical activity. In one study (Yun *et al*, 2008), physical activity levels were expressed as the combination of activity frequency and duration. For comparability with other studies, we grouped that study into the category ‘activity duration’.

Statistical analysis. We interpreted hazard ratios and odds ratios as estimates of the RR_i. We computed the natural logarithms of those risk estimates $\log(RR_i)$ with their corresponding s.e. $s_i = (\log(\text{upper 95\% CI bound of RR}) - \log(RR))/1.96$ and used a random effects model to determine the weighted average of those $\log(RR_i)$s while allowing for effect measure heterogeneity. We weighted the $\log(RR_i)$s by $w_i = 1/(s_i^2 + t^2)$, where s_i denoted the standard error of $\log(RR_i)$ and t^2 denoted the restricted maximum likelihood estimate of the overall variance (Higgins and Thompson, 2002). Heterogeneity was assessed using Q- and I^2-statistics (Higgins and Thompson, 2002). We examined publication bias using a funnel plot (Egger *et al*, 1997), Egger’s regression test (Egger *et al*, 1997), and Begg’s rank correlation test (Begg and Mazumdar, 1994). *P*-values were considered statistically significant at the 0.05 level. All statistical analyses were conducted in R (R Development Core Team, 2011) using the R-package ‘metafor’ (Viechtbauer, 2010).

The main analysis included one physical activity risk estimate per study. If a study reported risk estimates for men and women separately, we included both risk estimates in the meta-analysis because they were based on independent samples. If a study reported on different domains and/or intensities of physical activity, we included the risk estimate for recreational and vigorous activity.

In a series of subanalyses that were determined *a priori*, we examined the relation of physical activity to bladder cancer risk within categories of study design (cohort study, case − control study), physical activity domain (recreational, occupational),

Table 1. Characteristics of 15 studies on physical activity and bladder cancer risk involved in the meta-analysis.

Authors, Year, Gender	Subjects	Cases	Study geographic region	Domain of PA	Intensity of PA	Timing in life of PA	Relative Risk (95%CI) for high *vs* low PA	Reference group	Exposure definition	Adjustment variables
Cohort studies										
Holick *et al*, 2007										
Men	48 951	502	North America	Recreational	Total	Recent	**1.01 (0.76, 1.34)**	<2.7 MET h/wk	>34.0 MET h/wk	Age, pack-years of cigarette smoking, current smoking status, fluid intake, geographic region in the United States, status and age at menopause (last two among women only), vigorous recreational activity was adjusted for moderate recreational activity
				Recreational	High	Recent	0.99 (0.72, 1.35)	0 MET h/wk	>30.0 MET h/wk	
				Recreational	Moderate	Recent	1.05 (0.80, 1.38)	<0.8 MET h/wk	>10.8 MET h/wk	
Women	76 922	204		Recreational	Total	Recent	**0.91 (0.58, 1.41)**	<2.0 MET h/wk	>21.7 MET h/wk	
				Recreational	High	Recent	0.77 (0.48, 1.24)	0 MET h/wk	>14.9 MET h/wk	
				Recreational	Moderate	Recent	1.07 (0.70, 1.64)	<0.9 MET h/wk	>10.4 MET h/wk	
Koebnick *et al*, 2008										
Men	287 941	1470	North America	Recreational	Total	Recent	**0.87 (0.73, 1.03)**	0 times PA per wk	5 and more times per week PA	Age, race/ethnicity, education, a combination of smoking status, time since quitting for former smokers, and smoking intensity for former and current smokers, family history of any cancer, marital status, intakes of red meat, the combination of fruits and vegetables, total beverages, except alcohol, alcohol, menopausal hormone therapy, use of oral contraceptives and parity (the latter three variables for women only), BMI
Women	183 819	249		Recreational	Total	Recent	**0.78 (0.49, 1.23)**	0 times PA per wk	5 and more times per wk PA	
Paffenbarger *et al*, 1992										
Men and women combined	56 683	58	North America	Recreational	Total	Recent	**0.72 (0.38, 1.35)**	Less than 5 h/wk sports play	5 h/wk or more sports play	Age, sex
Schnohr *et al*, 2005										
Men	15 043	247	Europe	Recreational	High	Recent	**0.83 (0.57, 1.21)**	Low level of PA	Vigorous level of PA	Age, birth cohort, study cohort membership, occupational PA, smoking, education, alcohol consumption
				Recreational	Moderate	Recent	0.98 (0.69, 1.38)	Low level of PA	Moderate level of PA	
Severson *et al*, 1989										
Men	8 006	70	North America	Recreational	Total	Past	**0.78 (0.49, 1.26)**	Mostly sitting	Moderate or heavy physical activity	Age, BMI, cigarette smoking
				Occupational	Total	Past	1.00 (0.54, 1.83)	Mostly sitting	Moderate or heavy physical activity	
Soll-Johanning and Bach, 2004										
Men	14 568	136	Europe	Occupational	Total	Past	**0.98 (0.82, 1.16)**	Copenhagen population	Mail carriers	Age, calendar-period
Sormunen *et al*, 2013										
Men	2448	29	Europe	Occupational	Total	Past	**1.36 (0.97, 1.85)**	General population	Athletes	Age-groups

Table 1. (Continued)

Authors, Year, Gender	Subjects	Cases	Study geographic region	Domain of PA	Intensity of PA	Timing in life of PA	Relative Risk (95%CI) for high *vs* low PA	Reference group	Exposure definition	Adjustment variables
Tripathi *et al*, 2002										
Women	37 459	112	North America	Recreational	Total	Past	**0.66 (0.43, 1.01)**	No regular PA	Yes regular PA	Age, smoking, pack-years of smoking, diabetes, BMI, alcohol, married, occupation lifetime
				Recreational	High	Past	0.73 (0.46, 1.17)	Low physical activity	High physical activity	
				Recreational	Moderate	Past	0.62 (0.38, 1.00)	Low physical activity	Moderate physical activity	
Wannamethee *et al*, 2001										
Men	7588	92	Europe	Recreational	High	Recent	**2.06 (1.08, 3.95)**	No PA to moderate PA	Vigorous PA	Age, cigarette smoking, BMI, alcohol intake, social class
				Recreational	Moderate	Recent	0.90 (0.45, 1.77)	No PA to moderate PA	Moderate-vigorous PA	
Wilson *et al*, 2008										
Men	3 448 108	18,244	Europe	Occupational	High	Past	**0.71 (0.67, 0.76)**	Sedentary PA	Heavy PA	Age, year of diagnosis, urban residence
				Occupational	Moderate	Past	0.75 (0.71, 0.78)	Sedentary PA	Medium PA	
Women	749 576	3,347		Occupational	High	Past	**0.85 (0.75, 0.98)**	Sedentary PA	Heavy PA	
				Occupational	Moderate	Past	0.93 (0.83, 1.04)	Sedentary PA	Medium PA	
Yun *et al*, 2008										
Men	444 963	414	Asia	Recreational	Total	Recent	**0.94 (0.77, 1.15)**	Low leisure-time PA	Moderate-high leisure-time PA	Age, dietary preference, smoking status, amount of alcohol drinking, BMI, employment, fasting blood sugar
Case-control studies										
Brownson *et al*, 1991										
Men	15 309	1,080	North America	Occupational	High	Recent	**0.91 (0.67, 1.25)**	Low physical activity level	High physical activity level	Age, smoking
				Occupational	Moderate	Recent	0.91 (0.77, 1.11)	Low physical activity level	High physical activity level	
Dosemeci *et al*, 1993										
Men	2394	267	Europe	Occupational	High	Consistent PA over time	**1.11 (0.71, 2.00)**	Sedentary energy expenditure index	Active energy expenditure index	Age, socioeconomic status, smoking
				Occupational	Moderate	Consistent PA over time	1.11 (0.77, 1.67)	Sedentary energy expenditure index	Moderate energy expenditure index	
Lin *et al*, 2010										
Men and women combined	1574	779	North America	Recreational	High	Recent	**0.35 (0.26, 0.48)**	< 9 METs	>25 METs	Age, sex, tobacco smoking, energy intake, BMI
				Recreational	Moderate	Recent	0.53 (0.40, 0.70)	< 9 METs	⩾9 – <25 METs	
Parent *et al*, 2011										
Men	1017	484	North America	Recreational	Total	Consistent PA over time	**0.78 (0.59, 1.05)**	Never/not often PA	Often PA	Age, socio-economic status, educational level, ethnicity, respondent status, smoking, BMI, sports and outdoor activities / occupational PA level (mutual adjustment), coffee, beta-carotene, aromatic amines
				Occupational	High	Consistent PA over time	0.63 (0.35, 1.12)	Low long-life PA	High long-life PA	
				Occupational	Moderate	Consistent PA over time	0.85 (0.55, 1.29)	Low long-life PA	Intermediate long-life PA	

Abbreviations: BMI = body mass index; CI = confidence interval; h = hour(s); MET = metabolic equivalent of task; PA = physical activity; RR = relative risk; wk = week(s). The studies are grouped according to cohort and case – control study design. The meta-analysis included only one risk estimate (in bold) per study design, gender, physical activity domain, and activity intensity level.

gender (men, women, men, and women combined), physical activity intensity (moderate, vigorous), component or measure of physical activity (energy expenditure, activity duration, activity frequency, qualitative assessments), timing in life of physical activity (recent, consistent over time, past), type of physical activity assessment (interview, self-reported, by proxy), number of adjustment factors (greater or less than the median), adjustment for body mass index (BMI; yes, no), adjustment for smoking (yes, no), and study geographic region (North America, Europe, Asia).

The number of risk estimates included in the stratified analyses differed for each subanalysis. Subanalyses stratified by study design, gender, component or measure of physical activity, timing in life of physical activity, type of physical activity assessment, number of adjustment factors, adjustment for BMI, adjustment for smoking, and study geographic region included 18 risk estimates. The subanalysis stratified by physical activity domain contained 20 risk estimates, and the subanalysis stratified by activity intensity included 22 risk estimates.

We evaluated potential heterogeneity of the physical activity and bladder cancer relation according to those factors by using random effects meta-analysis regression where we compared the model that included the current factor of interest as a single explanatory variable with the null model that included no explanatory variable.

Dose-response analysis. We employed a fractional polynomial approach (Rota *et al*, 2010) to fit a non-linear dose response meta-analysis using all studies that included a minimum of three physical activity categories (Severson *et al*, 1989; Brownson *et al*, 1991; Dosemeci *et al*, 1993; Wannamethee *et al*, 2001; Tripathi *et al*, 2002; Schnohr *et al*, 2005; Holick *et al*, 2007; Koebnick *et al*, 2008; Wilson *et al*, 2008; Lin *et al*, 2010; Parent *et al*, 2011). For each study, we converted the physical activity cut points to percentile cut points based on the reported physical activity group sizes. Percentiles ranged from 0 to 100, with 0 indicating the lowest physical activity level and 100 indicating the highest physical activity level.

RESULTS

Study characteristics. The main characteristics of the eleven cohort studies (Severson *et al*, 1989; Paffenbarger *et al*, 1992; Wannamethee *et al*, 2001; Tripathi *et al*, 2002; Soll-Johanning and Bach, 2004; Schnohr *et al*, 2005; Holick *et al*, 2007; Koebnick *et al*, 2008; Wilson *et al*, 2008; Yun *et al*, 2008; Sormunen *et al*, 2013) and four case – control studies (Brownson *et al*, 1991; Dosemeci *et al*, 1993; Lin *et al*, 2010; Parent *et al*, 2011) are shown in Table 1. Three studies (Holick *et al*, 2007; Koebnick *et al*, 2008; Wilson *et al*, 2008) presented results stratified by gender, yielding a total of 18 independent risk estimates. A total of 5 402 369 subjects and 27 784 bladder cancer cases were included in the meta-analysis. The majority of risk estimates involved men, were derived from studies located in North America, and were based on recreational activity. Eight studies used self-report questionnaires to assess physical activity, four studies assessed physical activity using an interview, and three studies used information provided by proxy. Five studies used energy expenditure as a measure of physical activity, four studies used data on activity duration, four studies used information on activity frequency, and three studies were based on qualitative measures of physical activity. Eight studies assessed recent physical activity, five studies collected information on past physical activity, and two studies evaluated consistent physical activity over time. The number of adjustment factors in the individual studies ranged between one and fourteen. Eleven studies adjusted for smoking and seven studies adjusted for BMI.

Main analysis. Comparing the highest with the lowest physical activity level, the combined bladder cancer risk estimate was 0.85 (95% CI = 0.74–0.98), with considerable between-study heterogeneity ($I^2 = 83\%$, *P*-value for heterogeneity across all studies < 0.001) (Figure 1). After removal of case – control studies (Brownson *et al*, 1991; Dosemeci *et al*, 1993; Lin *et al*, 2010; Parent *et al*, 2011) and cohort studies that did not control for smoking (Paffenbarger *et al*, 1992; Soll-Johanning and Bach, 2004; Wilson *et al*, 2008; Sormunen *et al*, 2013), the heterogeneity of the data was no longer apparent ($I^2 = 0\%$, *P*-value for heterogeneity = 0.256). No publication bias was demonstrated by Egger's regression test ($P = 0.467$), Begg's rank correlation test ($P = 0.654$), or the funnel plot (Supplementary Figure S2).

Study design. We investigated cohort and case – control studies separately and observed a stronger but statistically non-significant inverse association between physical activity and bladder cancer in case – control studies (RR = 0.71, 95% CI = 0.43–1.16) than in cohort studies (RR = 0.89, 95% CI = 0.80–1.00), although that difference was not statistically significant (*P*-value for difference by study design = 0.108) (Figure 1). Between-study heterogeneity was more pronounced in case – control studies ($I^2 = 87\%$) than cohort studies ($I^2 = 64\%$). There was no heterogeneity in cohort studies that adjusted for smoking ($I^2 = 0\%$, *P*-value for heterogeneity = 0.256), whereas cohort studies that did not adjust for smoking indicated considerable heterogeneity ($I^2 = 88\%$, *P*-value for heterogeneity < 0.001).

Physical activity domain. Both recreational and occupational activities were related to decreased risk of bladder cancer, and the relation with recreational activity was statistically significant (Figure 2). The summary risk estimates for recreational and occupational activity were 0.81 (95% CI = 0.66–0.99, $I^2 = 77\%$) and 0.90 (95% CI = 0.76–1.07, $I^2 = 76\%$), respectively, comparing the highest with the lowest levels of activity (*P*-value for difference by physical activity domain = 0.374).

Gender. When stratifying by gender, the summary risk estimate appeared to be slightly more pronounced in women (RR = 0.83, 95% CI = 0.73–0.94) than men (RR = 0.92, 95% CI = 0.82–1.05) but that difference was not statistically significant (*P*-value for difference by gender = 0.657) (Table 2). We noted sizeable between-study heterogeneity among men ($I^2 = 67\%$) but not among women ($I^2 = 0\%$).

Activity intensity. The magnitude of the inverse relations of moderate and vigorous activity to bladder cancer were comparable, although the summary risk estimate for vigorous physical activity did not reach statistical significance (RR for moderate intensity activity = 0.85, 95% CI = 0.75–0.98, $I^2 = 76\%$; RR for vigorous intensity activity = 0.80, 95% CI = 0.64–1.00, $I^2 = 87\%$; *P*-value for difference by activity intensity = 0.535) (Table 2).

Other factors. No clear pattern of difference regarding the physical activity and bladder cancer relation emerged in analyses stratified by component or measure of physical activity ($P = 0.783$), timing in life of physical activity ($P = 0.962$), type of physical activity assessment ($P = 0.201$), number of adjustment factors ($P = 0.739$), adjustment for BMI ($P = 0.231$), adjustment for smoking ($P = 0.620$), or study geographic region ($P = 0.217$) (Table 2). Three studies (Koebnick *et al*, 2008; Yun *et al*, 2008; Lin *et al*, 2010) examined whether the physical activity and bladder cancer relation was modified by smoking status. We pooled the findings from those studies and did not find a significant difference regarding the relation of physical activity to bladder cancer between current, former, or never smokers (p-difference by smoking status = 0.846).

Dose-response meta-analysis. The dose-response meta-analysis revealed an approximately linear relation between physical activity percentile and bladder cancer risk. The 25th, 50th, and 75th physical activity level percentiles were associated with reductions in

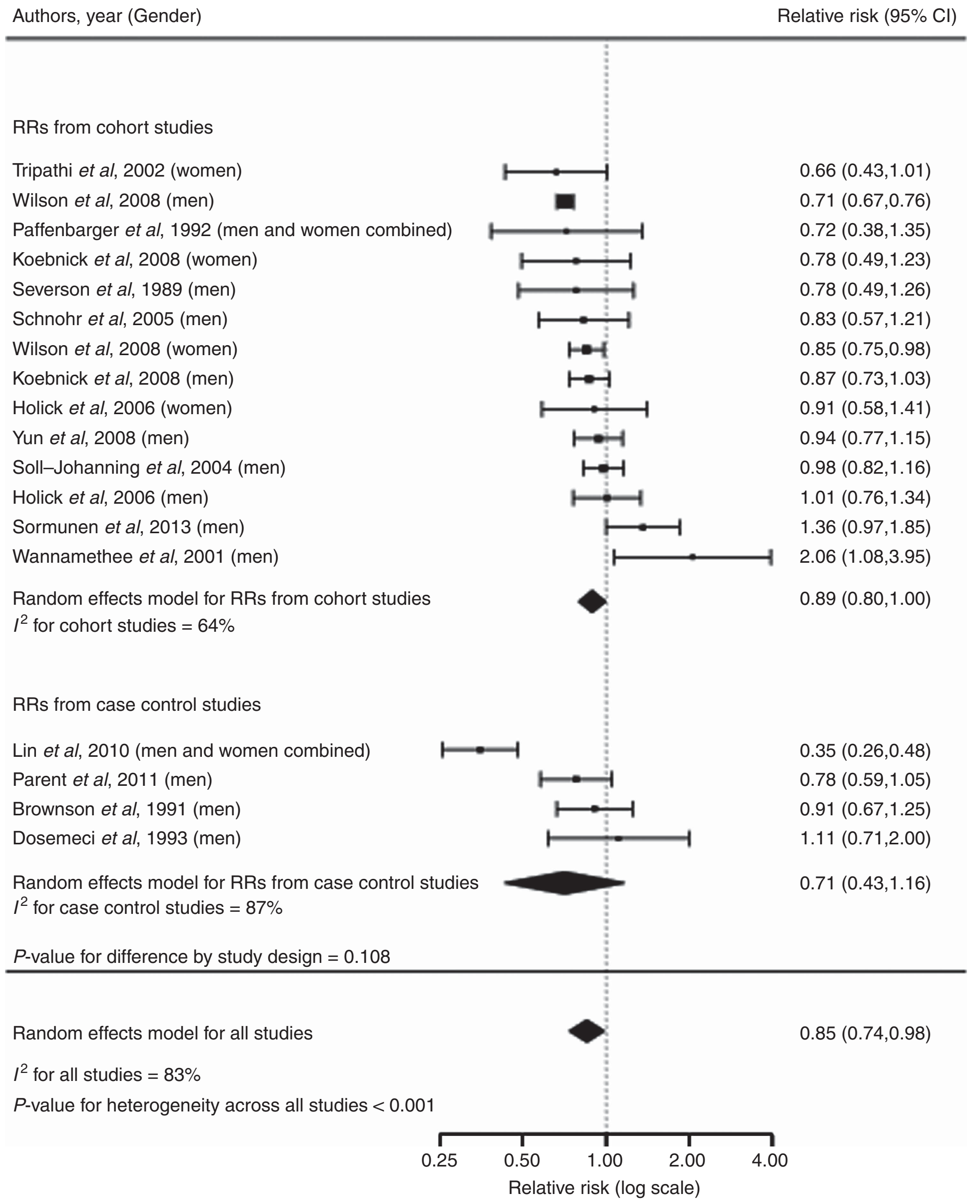

Figure 1. Forest plot quantifying the association between physical activity and bladder cancer risk by study design, including summary risk estimates, I^2 values, and *P*-value for difference by study design and *P*-value for heterogeneity across all studies. The meta-analysis included 18 bladder cancer risk estimates comparing high *vs* low levels of physical activity. The *P*-value for difference was estimated from random effects meta-regression comparing a model that included the stratification variable with the null model that did not include the stratification variable.

bladder cancer risk of 10% (RR = 0.90, 95% CI = 0.83–0.97), 14% (RR = 0.86, 95% CI = 0.77–0.96), and 17% (RR = 0.83, 95% CI = 0.72–0.95), respectively (Figure 3).

We conducted a sensitivity analysis in which we omitted one study at a time from the meta-analysis to examine whether the main finding was influenced by a particular study. Removal of individual studies one at a time did not appreciably change the results. In each case, the risk estimate was well within the CIs of the overall risk estimate.

DISCUSSION

Physical activity and bladder cancer. The findings from this systematic review and meta-analysis show a statistically significant 15% decreased risk of bladder cancer comparing high *vs* low levels of physical activity. Our dose-response meta-analysis suggested a linear association between physical activity percentile and bladder cancer risk. We found no strong evidence that the association between physical activity and bladder cancer varied by study design, gender, physical activity intensity, component or measure of physical activity, timing in life of physical activity, type of physical activity assessment, adjustment factors, or study geographic region.

Although smoking is a well-known bladder cancer risk factor (Bachir and Kassouf, 2012) and is associated with physical activity (Kaczynski *et al*, 2008), adjustment for smoking did not influence the relation of physical activity to bladder cancer in our meta-analysis. This suggests that the mechanisms through which physical activity may protect against bladder cancer are not mediated by the effects of low or no exposure to tobacco smoke among physically active persons. This notion is supported by our finding of no effect modification of the association between physical activity and bladder cancer when we pooled the data from three studies (Koebnick *et al*, 2008; Yun *et al*, 2008; Lin *et al*, 2010)

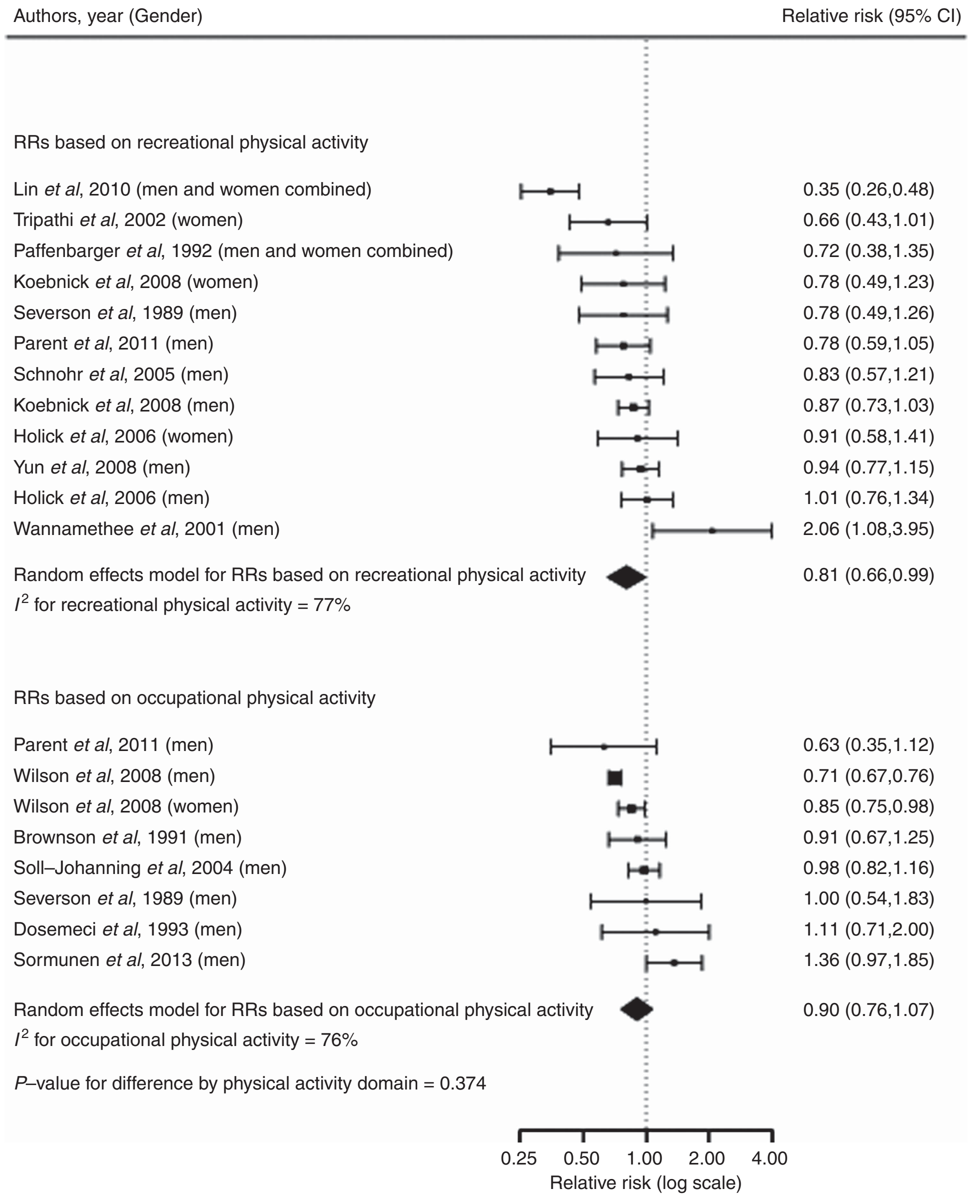

Figure 2. Forest plot quantifying the association between physical activity and bladder cancer risk by domain of physical activity, including summary risk estimates, I^2 values, and *P*-value for difference by physical activity domain. The meta-analysis included 20 bladder cancer risk estimates comparing high *vs* low levels of physical activity. The *P*-value for difference was estimated from random effects meta-regression comparing a model that included the stratification variable with the null model that did not include the stratification variable.

that reported on the association between physical activity and bladder cancer stratified by smoking status.

Two previous studies (Holick *et al*, 2007; Koebnick *et al*, 2008) investigated whether BMI modified the association between physical activity and bladder cancer. One study (Holick *et al*, 2007) reported that BMI did not modify the inverse association between physical activity and bladder cancer, whereas the other study (Koebnick *et al*, 2008) observed a trend of a more pronounced inverse association between physical activity and bladder cancer among lean than among overweight or obese women. This suggests that physical activity and BMI affect bladder cancer risk through distinct biologic pathways. Support for the idea that the apparent protective effect of physical activity on bladder cancer risk is not mediated by healthy body mass among physically active individuals is offered by our finding showing that the magnitude of the risk estimate for physical activity that was adjusted for BMI was similar to the BMI-unadjusted risk estimate.

We did not rely on overall quality scores to stratify risk estimates (Juni *et al*, 1999). Instead, we assessed relevant methodologic aspects of the underlying studies and explored the influence of those study characteristics on the effect size. Previous meta-analyses of physical activity in relation to cancers of the endometrium (Voskuil *et al*, 2007), colon (Boyle *et al*, 2012), pancreas (O'Rorke *et al*, 2010), and prostate (Liu *et al*, 2011) found no influence of the methodological quality of the underlying studies on the magnitude of the summary risk estimate.

Although we noted considerable heterogeneity between studies in our main analysis, such heterogeneity was no longer apparent after removal of case – control studies (Brownson *et al*, 1991; Dosemeci *et al*, 1993; Lin *et al*, 2010; Parent *et al*, 2011) and cohort studies that did not adjust for smoking (Paffenbarger *et al*, 1992; Soll-Johanning and Bach, 2004; Wilson *et al*, 2008; Sormunen *et al*, 2013). Selection and recall bias can be of potential concern in case – control studies and may have contributed to heterogeneity in those studies. It is conceivable that confounding by smoking

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Table 2. Summary risk estimates of high *vs* low physical activity, stratified by selected characteristics

Stratification variable	Number of risk estimates included	Relative risk (95% CI) for high *vs* low physical activity	I^2 (%)	*P*-value for difference
Gender				
Men	12	0.92 (0.82, 1.05)	67	
Women	4	0.83 (0.72, 0.94)	0	0.657
Men and women combined	2	0.48 (0.24, 0.96)	75	
Intensity of physical activity				
Moderate	11	0.85 (0.75, 0.98)	76	
Vigorous	11	0.80 (0.64, 1.00)	87	0.535
Component or measure of physical activity				
Energy expenditure	5	0.76 (0.49, 1.17)	83	
Activity duration	4	0.90 (0.77, 1.05)	0	
Activity frequency	5	0.85 (0.75, 0.97)	0	
Qualitative measures	4	0.92 (0.72, 1.18)	92	0.783
Timing in life of physical activity				
Recent	10	0.84 (0.66, 1.07)	82	
Consistent over time	2	0.85 (0.63, 1.13)	9	
Past	6	0.87 (0.71, 1.06)	84	0.962
Type of physical activity assessment				
Interview	4	0.78 (0.39, 1.56)	91	
Self reported	11	0.84 (0.76, 0.92)	46	
By proxy	3	1.05 (0.79, 1.39)	58	0.201
Number of adjustment factors				
Number of adjustment factors greater than the median (6–14)	7	0.86 (0.77, 0.95)	0	
Number of adjustment factors equal to or lower than the median (1–5)	11	0.88 (0.69, 1.12)	92	0.739
Adjustment for body mass index				
Adjusted for body mass index	8	0.78 (0.58, 1.06)	86	
Not adjusted for body mass index	10	0.91 (0.79, 1.04)	68	0.231
Adjustment for smoking				
Adjusted for smoking	13	0.83 (0.69, 1.01)	75	
Not adjusted for smoking	5	0.90 (0.72, 1.12)	88	0.620
Study geographic region				
North America	10	0.75 (0.62, 0.93)	72	
Europe	7	0.98 (0.79, 1.22)	87	
Asia	1	0.94 (0.77, 1.15)	–	0.217

The *P*-value for difference across strata of selected characteristics was estimated from random effects meta-regression comparing a model that included the stratification variable with the null model that did not include the stratification variable.

may have been partly responsible for the observed heterogeneity in cohort studies.

Biologic mechanisms. The precise biologic mechanisms through which physical activity may prevent bladder cancer have not been elucidated. However, there is evidence that physical activity increases carcinogenic detoxification, promotes DNA repair processes, modifies cell proliferation, differentiation and apoptosis, reduces chronic inflammation, and enhances immune function, factors that are related to carcinogenesis (Rogers *et al*, 2008). Although not supported by our findings, physical activity may indirectly protect against bladder cancer by reducing smoking (Kaczynski *et al*, 2008) and preventing adiposity (Wing, 1999; Shaw *et al*, 2006) and diabetes mellitus (Thomas *et al*, 2006), three bladder cancer risk factors (Hemelt *et al*, 2009; Fang *et al*, 2013; Qin *et al*, 2013).

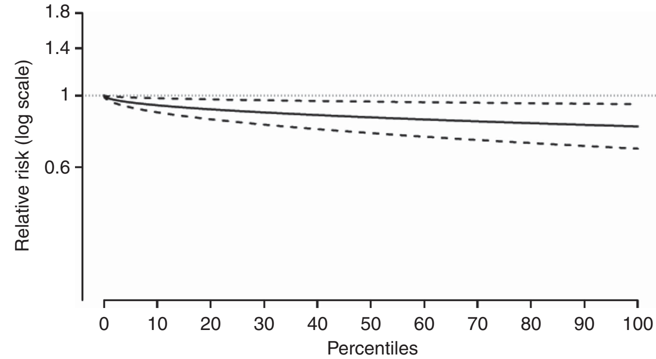

Figure 3. Dose response analysis quantifying the association between increasing percentiles of physical activity and bladder cancer. Analysis includes all studies reporting on three or more physical activity categories.

Strengths and limitations. One asset of the current study is that it represents the first meta-analysis of the association between physical activity and bladder cancer. Apart from that novelty, one strength of our meta-analysis is the large sample size, which enabled us to conduct a wide range of informative subanalyses, including analyses stratified by physical activity domain and gender. We used standardised criteria to identify relevant articles and abstract pertinent data.

One limitation of our meta-analysis is the variation in the definitions of the reference and exposed groups of physical activity in the underlying studies, ranging from 'no physical activity' to 'less than 5 h of vigorous physical activity per week' for the reference group to 'physically active' to '5 h of physical activity per week or more' for the exposed group. However, we addressed that issue in a subanalysis by performing a dose-response meta-analysis that was based on comparable percentiles of the distributions of physical activity in the underlying studies. A further shortcoming of our study is that nearly half the studies included in our meta-analysis presented physical activity risk estimates that were adjusted for BMI, which may have represented a certain degree of statistical over-control because the biological pathways linking increased physical activity to decreased bladder cancer risk may in part be mediated by adiposity.

A number of important research gaps persists regarding the relation of physical activity to bladder cancer. Future studies should identify the precise type, duration, frequency, intensity, and timing in life of physical activity relevant for potential decreased risk of bladder cancer. In addition, studies should employ more comprehensive physical activity questionnaires in combination with objective and standardisable instruments, such as accelerometers. In addition, studies among non-Caucasians are needed to elucidate whether results concerning physical activity and bladder cancer are generalisable to those populations.

CONCLUSION

In conclusion, this meta-analysis suggests that high *vs* low levels of physical activity are associated with a 15% decreased risk of bladder cancer. Further research is needed to assess the specific duration, frequency, and intensity of physical activity needed for bladder cancer risk reduction. In addition, mechanistic studies are required to clarify the aetiologic pathways through which physical activity may prevent bladder cancer.

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