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Can habitual physical activity contribute to reducing the health burden of renal cancer?

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Abstract

The aim of this review was to assess the influence of habitual physical activity upon the risk of developing renal cancer. Some benefit might be anticipated through favourable effects of exercise upon immune function, oxidative stress, obesity, and the resulting modulation of hormones influencing the growth of cancerous cells. A systematic search of the Ovid/Medline data-base from 1996 to August 20th 2016 was supplemented by a review of reference lists and personal files. A total of 27 unique cohort and case-control studies were found, many covering both occupational and leisure activity. No papers pointed to any increase of risk for individuals with an active lifestyle, but only 6 of 13 cohort and 6 of 14 case-control studies showed any statistically significant association between greater physical activity and lower risk. Moreover, even in these articles, benefit was usually confined to a specific subset of the original sample identified post-hoc. The overall weighted risk ratio for active individuals was 0.88 in cohort and 0.93 in case-control studies, but risk ratios became 0.96 and 0.94 on omitting analyses that did not include important co-variates such as obesity and smoking. This suggests that habitual physical activity reduces the risk of renal cancer largely through a modulation of these variables. Problems that must be addressed in future investigations of this topic include finding populations that include an adequate number of cases of renal cancer, making a better (and preferably objective) categorization of physical activity, and handling the influence of co-variates in a more systematic fashion. There is also scope for prospective trials in humans, and further studies in animal models of renal carcinoma.

Key words: Carcinogenesis, Habitual activity, Kidneys, Leisure activity, Occupational activity

Introduction

In adults, some 90% of renal cancers are parenchymal adenocarcinomas, often described as renal cell cancers, and around 10% are transitional cell tumours of the renal pelvis. However, in children, the most common cancer is a nephroblastoma (Wilms tumour); this condition accounts for only about 1% of all renal tumours, and will not be discussed here.

The incidence of renal cell cancer varies substantially from one country to another. In British Colombia, the incidence of renal parenchyma tumours is about 6.5/100,000 in men and 3.2/100,000 in women, with corresponding figures of 0.6 and 0.3/100,000 for the rarer lesions of the renal pelvis (Chow, Dong, & Devesa, 2010). In the U.S. and Europe, the incidence ranges quite widely, from 3 to 15/100,000 in men, and from 3 to 7/100,000 in women, depending in part on the ethnic make-up of the region studied (Curado et al., 2007). The economic impact of

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renal tumours is substantial. In 2009, the added additional annual health cost for each elderly U.S. patient with renal cancer was U.S.$ 11,169 (Shih et al., 2011), and there is a corresponding interest in preventive measures that could attenuate this health burden.

Known risk factors for renal parenchymal adenocarcinomas include cigarette smoking (Hunt, van der Hel, McMillan, & Brennan, 2005), obesity (Chow et al., 1996) hypertension (Choi et al., 2010), and type 2 diabetes mellitus (Behrens & Leitzmann, 2013). An increase of habitual physical activity can make a substantial contribution to a reduction in the risk of some types of cancer, most notably for tumours of the colon. One recent systematic review concluded that regular physical activity might also reduce the risk of renal tumours by as much as 20% (Behrens & Leitzmann, 2013). Certainly, some indirect impact would be anticipated from an enhancement of overall lifestyle, with control of smoking and obesity, but other more direct effects could apossibly arise through a modulation of immune function and hormone levels. The objectives of the present paper were to assess current knowledge on this topic through a systematic search of the literature relating renal cancer to habitual physical activity incurred at work and in leisure time, to look critically at recent assessments of the benefits from physical activity, and to find pointers to wards future more definitive research on this topic.

Methods

The Ovid/Medline data base was searched systematically from 1996 to August 20th, 2016, without restriction of language (Table 1). The MeSH terms used were "carcinoma, renal cell" (20,784 hits) versus "physical activity" (194,891 hits), "exercise" (115,064 hits), "physical exertion" (12,389), "physical fitness" (15,624 hits), or "sports" (104,935 hits), with a total of 244,604 unique hits for the various indicators of habitual physical activity. The combination of the 2 searches yielded 36 hits, of which 19 had sufficient apparent relevance to justify review of the entire article. Twelve of these reports described human epidemiological studies relating the incidence of renal cancer to habitual physical activity. A search of reference lists and personal files added a further 18 titles, for a total of 30 articles relating the risk of renal cell and/or renal pelvic cancer to occupational activity (3), leisure activity 15), or a combination of occupational and leisure activity (12). Twenty-eight of these articles (including 2 studies of the same population [Mellemgaard, Engholm, & McLaughlin (1994), Mellemgaard et al. (1995)] referred to renal cell cancer, one study was of renal pelvic cancer (Wilson et al., 2008), and one study included data for both types of tumour [Pan, DesMeules, & Morrison, 2006).

Table 1. *Summary of Ovid/Medline search process, 1996 to August 20th, 2016.*

Step	Operation	Finding
1	MeSH term "Carcinoma, renal cell"	20, 784 hits
2	MeSH term "Physical activity"	194,891 hits
3	MeSH term "Exercise"	115,064 hits
4	MeSH term "Physical exertion"	12,389 hits
5	MeSH term "Physical fitness"	15,624 hits
6	MeSH term "Sports"	104,935 hits
7	2, 3, 4, 5, OR 6	244,604 hits
8	1 AND 7	36 hits
9	Articles reviewed in detail	19
10	Cohort & case-control studies	12
11	Articles gleaned from personal files & reference lists	18
12	10 + 11	30 reports*

1 report is on renal pelvic tumours only, 2 reports are based on differing subject numbers from the same population, and 1 report groups State-wide data..

Given the limited total number of reports, all were evaluated, although the quality of the information provided was evaluated critically in terms of sample size, the number of renal tumours included in any given study, the quality of the physical activity assessment, the introduction of important co-variates (particularly smoking, obesity, hypertension and type 2 diabetes mellitus) into the analyses, and the variance of the estimated effect. All ratios have been adjusted to show the risk associated with an active versus a sedentary lifestyle. The characteristics of the samples tested, the definition of renal cancer (incidence or death), the method of identifying active individuals (heavy occupational work, patterns of active leisure or sedentary behaviour, active transportation or attained levels of aerobic fitness), the timing of activity assessments (recent, or over the likely period of carcionogenesis), and the choice of co-variates were judged too heterogeneous to merit a formal meta-analytic analysis of the findings.

Results

Renal pelvic cancers.

There are only 2 published reports concerning physical activity and the risk of renal pelvic cancers (Pan et al., 2006; Wilson et al., 2008). The first of these investigations found no association of renal pelvic cancer with the reported volume of leisure activity, assessed in MET-h/wk. The second report (Wilson et al., 2008) was based on quite a large sample (1,014 pelvic cancers in men and 360 in women) drawn from workers employed in 1960 and/or 1970. Data were adjusted for age and year of diagnosis, and a significant decrease of risk was seen in men with active employment [a standardized incidence ratio of 0.66 (95% confidence limits 0.50-0.88)]. Moreover, the risk for both sexes was increased among those employed in specific trade categories, including sedentary work, indoor work, the machine/electronics industry, and (in men) shop and construction metal industries.

Cohort studies of renal parenchymal cell cancers

Thirteen cohort studies and 1 state-wide correlational analysis (Colli et al., 2009) have examined the incidence of deaths from renal cell cancer in relation to reported habitual physical activity [or in one instance, to an estimate of attained aerobic fitness (Thompson et al, 2008)](Table 2).

Bergström et al., (1999) conducted an 18-year prospective study of a large sample of Swedes (3.28 million men and 3.35 million women), noting diagnoses of renal cell cancer in relationship to a 4-level categorization of occupational activity. A substantial number of renal tumours (3,291) was seen over this period. In the men, a significant decrease of risk with a dose-response relationship was observed in those with physically more demanding jobs [a relative risk of 0.80 (0.65-0.98) after adjusting for socio-economic status, area of residence and year of follow-up]. However, (perhaps because of lesser job demands or a confounding of data by demanding domestic physical activity), a heavy occupational energy expenditure provided no protection against renal cancer in the women, with a relative risk of 1.25 (0.79-1.96) in the more active individuals. Bergström, Terry, & Lindblad, (2001) also followed 17,241 twin pairs for a period of 20 years. In this sample, they accumulated only 102 cases of renal cell cancer. They introduced smoking, body mass index and hypertension as co-variates in their second study, and with this adjustment of the data they observed no evidence of any decrease of risk with an active occupation [relative risk 1.25 (0.63-2.50)] or active leisure [relative risk 1.67 (0.83-3.33) in either men or women.

Choi, Jee, Sull, & Nam (2005) followed a sample of 576,562 men initially aged 30 to > 60 years for a total of 6 years. This yielded 92 deaths from renal cancer. The prime focus of the study was on hypertension rather than exercise, and there was a substantial increase of relative risk with a high blood pressure (2.43). However, the risk for exercisers (as classified only by a simple "yes" vs. "no" response) was not significant [0.9 (CI 0.6-1.4)]. In addition to weakness in the assessment of physical activity, this calculation apparently included no co-variates.

Colli et al. (2009) compared the state-wide incidence of renal cancer with the state-wide prevalence of physical inactivity, as reported in the NHANES survey. The 2 indices were significantly correlated in both men ($r = 0.48$, $p < 0.001$) and women ($r = 0.31$, $p = 0.04$).

George et al. (2011) accumulated a substantial sample of 1206 cases of renal cell cancer after following 300,000

Table 2. *Association between high level of habitual physical activity and the risk of developing renal parenchymal and pelvic cancers as seen in cohort studies.*

Author	Sample	Cases and Findings	Comments
Bergström et al. (1999)	3.28 million men, 3.35 million women working in 1960 or 1970, 19-year follow up	2704 cases in men, 587 cases in women. 4-level classification of occupational activity, SIR of sedentary 1.19, 1.18 (M), 0.92, 0.86 (F), high/very 0.91, 0.92 (M), 1.10,1.08 (F); effects of active occupation significant in men [0.80 (0.65-0.98)] but not in women [1.25 (0.79-1.96].	Few women had active jobs. Data adjusted for age, SES and year of follow-up
Bergström et al. (2001)	17,241 twin-pairs, 20 yr follow-up, mean age at diagnosis 71.8 yr	102 cases of renal cell cancer, RR unrelated to occupation [1.25 (0.63-2.50)] or leisure [1.67 (0.83-3.33)]	Data adjusted for age, smoking, BMI, hypertension
Choi et al. (2005)	576,562 men age 30 - >60 yr followed for 6 years	92 deaths from renal cancer; hypertension gave RR of 2.43; risk for exercisers ("yes" vs. "no) 0.9 (0.6-1.4)	Prime focus of experiment on hypertension rather than exercise. Apparently no co-variates.
Colli et al. (2009)	State-wide incidence of renal cancer vs. inactivity as seen in NHANES survey	Incidence of renal cancer in a given State significant inverse correlation with habitual activity in that State for both men (r = - 0.48, p <0.001) and women (r = - 0.31, p = 0.04)	State-wide grouping of data does not match that of any other analysis
George et al. (2011)	300,000 adults aged ~ 63 yr, followed for 10 yr	1206 cases of renal cell cancer versus time spent sitting watching TV or videos (<1 vs. >7 h/day), HR 1.04 (0.72-1.52) or total sitting time (<3 vs. >9 h/day) HR 0.89 (0.71-1.15)	Data adjusted for age, sex, race, diabetes, smoking, alcohol consumption, diet, energy intake
Mahabir et al. (2004)	29,133 male smokers aged 50-69 yr	210 cases of renal cell cancer seen over 12-year follow-up. Vigorous leisure activity gave RR of 0.46 (0.18-1.13), p = 0.12, no effect of occupational activity [RR 1.08 (0.54-2.15)]. RR 0.38 if adjusted only for age	Dose-related effect of leisure activity. Data adjusted for age, energy intake, BMI, smoking, blood pressure, diet, occupational or leisure activity
Moore et al. (2008)	482,386 adults, age ~ 62 yr; 8.2 yr follow-up	1,238 cases of renal cancer, RR current highest vs. lowest leisure activity) 0.77 (0.64-0.9), as adolescent 0.82 (0.68-1.00); heavy work vs. sitting 0.84 (0.57-1.22)	Data adjusted for age, sex, BMI
Nicodemus et al. (2004)	34,637 women initially aged 55-69 yr, followed for 15 years	124 cases of renal cancer; RR with age-adjusted data vigorous activity 0.37 (0.14-0.99) but benefit not significant with moderate activity, not seen in multivariate model	Data adjusted for age, body mass, waist/hip ratio, alcohol consumption, HRT, live births. Central adiposity a major risk factor.
Paffenbarger et al. (1987)	Retrospective data on 56,683 university alumni, 35-70 yr ago	53 cases of renal cancer, >5h/wk sports vs. <5h/wk, 0.95 (confidence limits estimated from p value =0.47-1.94)	Birth year only
Setiawan et al. (2007)	161,126 adults, 8.3 year follow-up,	220 cases in men, 127 cases in women, significant dose-related trend to reduction of risk with physical activity (METS/day) in women only; RR third quartile 0.52 (0.31-0.89); fourth quartile 0.66 (0.40-1.10), p for trend = 0.027. In men, 1.09 (0.75-1.58)	Relative risk of renal cell cancer in obesity: 1.76 (M), 2.27 (F), with hypertension 1.42 (M), 1.58 (F), current smokers 2.3 (M), 1.7 (F)

Author	Sample	Cases and Findings	Comments
Thompson et al. (2008)	16-yr follow up of 18,858 men with pre-diabetes or diabetes attending Aerobics Center, Dallas, TX.	31 deaths from renal tumours; in those with at least moderate aerobic fitness, HR for renal tumour death 0.91(0.46-2.68)	Data adjusted for age, examination year, smoking, alcohol consumption, body mass index, fasting glucose and previous history of cancer
van Dijk et al. (2004)	Case-cohort study, 120,852 adults initially aged 55-69 yr, 9.3 year follow-up	275 histologically confirmed cases of renal cell cancer (179 m, 96 F). Energy intake unrelated to risk. RR occupational activity (>12 vs. < 8 kJ/min) 0.82 (0.46-1.47), non-occupational in men 30-60 min/d [0.52 (0.30-0.91)], ns with longer activity [0.74 (0.44-1.23) or in women [1.13 (0.56-2.29)]	Data adjusted for age, smoking, energy intake, BMI. High BMI a risk in both sexes.
Washio et al. (2013)	Approximate 20-yr follow-up of 46,395 M, 64,190 F.	Kidney cancer deaths in relation to sports involvement (n =65) > 3 h/wk vs. <1h/wk) HR 0.64 (0.30-1.37) and walking (n = 66) >60 min/d vs. <30 min/d HR 0.57 (0.32-1.00) (p for trend 0.039)	Data adjusted for age & sex
Yun et al. (2008)	446,927 Korean men aged 40->60 yr	395 renal tumours RR moderate/high vs. low leisure activity [1.01 (0.83-1.23)], non-smokers 0.94 (0.68-1.30), smokers 1.02 (0.78-1.32)	Data adjusted for age, diet, smoking, alcohol consumption, BMI and fasting blood sugar
Renal pelvic cancer			
Wilson et al. (2008)	Individuals employed in 1960 or 1970	1014 (M), 360 (F) cancers of renal pelvis; SIRs significantly decreased with physically demanding work [men 0.66 (0.50-0.88)], and for both sexes employment in specific trades	Data adjusted for age, year of diagnosis

BMI = body mass index; CI = confidence interval; HR = hazard ratio; HRT + hormone replacement therapy. METs = metabolic equivalents; NHANES = National health & nutrition examination survey (U.S.). OR = odds ratio; RR = relative risk; SES = socio-economic status; SIR = standardized incidence ratios.

adults for 10 years. In contrast to other investigators, they focussed upon sedentary behaviour rather than habitual physical activity. After adjusting data for age, sex, race, diabetes, smoking, alcohol consumption, diet and energy intake, they calculated hazard ratios for the time spent sitting watching television or videos (<1 vs. >7 h/day) and for the total sitting time (<3 vs. >9 h/day), but they found no significant decrease in the risk of renal cancer among the less sedentary individuals, with respective risk ratios of [1.04 (0.72-1.52)] and [0.89 (0.71-1.15)]. One issue with this study is the inclusion of energy intake as a co-variate. Inevitably, this would have claimed some of the variance that would otherwise have been attributed to physical activity.

A 12-year follow-up of 29,133 male smokers found 210 cases of renal cell cancer (Mahabir, Leitzman, & Pietinen, 2004). The risk was unrelated to occupational activity [risk ratio 1.08 (0.54-2.15)], but was strongly related to reported leisure activity, with a dose-related risk ratio of 0.46 (0.18-1.13) favouring the most active individuals in a multivariate analysis.

Moore et al. (2008) questioned 482,386 adults about their leisure activity, both currently and as an adolescent. During an 8.2-year follow-up, a substantial 1,238 of their sample developed a renal cancer. After adjusting data for age, sex, body mass index, height, ethnicity, smoking, diabetes, protein intake, and hypertension, risk was reduced both with frequent current leisure activity [RR 0.77 (0.64-0.92)] and with frequent leisure activity as an adolescent [0.82 (0.68-1.00)].

Nicodemus et al. (2004) followed a sample of 34,637 women for 15 years, accumulating 124 cases of renal cancer. Most of the group reported little physical activity, but nevertheless in an age-adjusted analysis a strong inverse relationship was seen between renal cancer and vigorous leisure activity [relative risk 0.37 (0.14-0.99)]. Relative weight was a major risk factor, and after including this and other co-variates in the model, leisure activity no longer had a significant effect upon the incidence of renal cancer (data not shown).

Paffenbarger et al. (1987) made a retrospective survey of records for 56,683 university alumni over a period of up to 70 years, looking at the incidence of fatal or non-fatal renal cancer in relation to participation in sport while attending university (>5h/week vs. <5h/week). Their sample included 53 renal tumours, and the relative risk in the more active group was 0.95 (0.47-1.94). However, the only co-variate introduced into this analysis was the individual's birth age, and no information was available on the activity patterns of the subjects after they had left university.

Setiawan et al. (2007) completed a prospective study of 161,126 adults over a period averaging 8.3 years, finding 220 cases of renal cancer in men and 127 cases in women. A multivariate analysis demonstrated that substantial relative risks of renal cell cancer were associated with current smoking [2.3 (M), 1.7 (F)], obesity [1.76 (M), 2.27 (F)] and hypertension [1.42 (M), 1.58 (F)]. Questionnaire estimates of physical activity (MET/day), classified by quartiles, also showed a significant inverse relationship to cancer risk in women [the relative risk for the third quartile was 0.52 (0.31-0.89) and that for the fourth quartile was 0.66 (0.40-1.10)], with a dose-related trend (p = 0.027). In contrast, a physically active lifestyle conferred no significant benefit in the men [relative risk for 4th quartile 1.09 (0.75-21.58)]. The authors of this report suggested that the sex difference in response might reflect in part some residual confounding of data by the effects of obesity (which were greater in the women than in the men).

Thompson et al. (2008) examined relationships between a treadmill prediction of aerobic fitness (here considered as a surrogate of habitual aerobic activity) and the risk of dying from various types of cancer in 18,858 men with pre-diabetes or diabetes who were attending the Aerobics Fitness Center in Dallas, TX. Over an average 16.4 year follow-up, this series included 33 deaths from renal tumours, and data adjusted for age, examination year, smoking, alcohol consumption, body mass index, fasting glucose and previous history of cancer showed no significant reduction of risk in those who had achieved at least a moderate level of fitness [(hazard ratio 0.91 (0.45-2.68)].

The cohort study of van Dijk et al. (2004) followed 120,852 adults over a period of 9.3 years. They found 275 histologically-confirmed cases of renal cell cancer over this period. Risk was unrelated to energy intake, but in the men there was a substantial inverse relationship of risk to reported leisure activity. The effect was largest in those taking 30-60 minutes of such activity per day, with a relative risk of 0.52 (0.30-0.91) relative to those who were inactive. There was no evidence of a dose-response gradient, and indeed effects were smaller and non significant in those reporting longer periods of active leisure (at 90 min/d, the relative risk for the men was 0.74 (0.44-1.23), and the risk tended to an increase in the most active women [relative risk 1.13 (0.56-2.29). Moreover, the male participants in this study showed no statistically significant benefit from a higher average rate of occupational energy expenditure [>12 vs. < 8 kJ/min, 0.82 (0.46-1.47)].

In a study focussed primarily upon the effects of cigarette smoking, Washio et al. (2013) followed a sample of 46,395 men and 64,190 women for approximately 20 years, accumulating 88 deaths from kidney cancer. Information was also obtained on sport involvement and daily walking. A non-significant trend favoured those practicing sport for >3 hours/week versus those involved in sport for less than 1 hour/week [hazard ratio 0.64 (0.30-1.37)], while there was statistically significant benefit from walking >60 minutes/day versus <30 minutes/day [hazard ratio 0.57 (0.32-1.00)(p for trend = 0.039)]. Unfortunately, although these ratios were adjusted for age and sex, they were not co-varied for smoking habits or other important variables.

Yun et al. (2008) examined data for 446,927 Korean men aged from 40 to over 60 years. After adjusting data for age, diet, smoking, alcohol consumption, body mass index and fasting blood sugar, the relative risk in those with moderate or high levels of leisure activity did not differ from those with a low level [relative risk 1.01 (0.83-1.23). Data were also sorted by smoking habits; in non-smokers the relative risk was 0.94 (0.68-1.30), and in smokers it was 1.02 (0.78-1.32).

In summary, many cohort investigations have examined quite large samples and followed subjects prospectively over quite long periods; nevertheless, many studies have accumulated only a small number of cases of renal cancer, limiting the likelihood of definitive conclusions. Only 6 of the 13 cohort studies found any relationship between renal cancer and leisure or occupational activity (Bergström, Moradi, & Lindblad, 1999; Moore, Chow, & Schatzkin, 2008; Nicodemus, Sweeney, & Folsom, 2004; Setiawan, Stranm, & Nomura, 2007; van Dijk, Schouten, & Kiemeney, 2004; Washio et al., 2013). Moreover, the 95% confidence limits of any apparent benefits were broad, and even in these reports, the positive findings were limited to sub-groups determined post-hoc [men only (Bergström et al., 1999), benefit not seen in a subsequent study with co-variates (Bergström et al., 2001); benefit seen in leisure but not occupational activity (Moore et al., 2008); benefit not seen after multivariate analysis (Nicodemus et al., 2004); benefit seen in women only (Setiawan et al. 2007); benefit limited to leisure activity and seen only with moderate, but not with prolonged activity (van Diyjk et al., 2004); and benefit seen with walking but not with sports involvement (Washio et al., 2014). The 13 studies totalled 7241 cases of renal cancer, and a simple weighting of data by case numbers showed an average risk ratio of 0.88 in the more active individuals. Omitting 5 studies with few co-variates (Bergström et al., 1999; Choi et al., 2005; Nicodemus et al., 2004; Paffenbarger et al., 1987); Washio et al., 2013), the risk ratio for active individuals (0.96) approached unity. In 7 occupational studies, the average risk for active individuals was again 0.88, but omitting one study without co-variates, the risk ratio rose to 0.98. In the leisure studies, the weighted average for all reports was 0.91, or 0.93 on omitting 4 studies with limited allowance for co-variates.

Case-control studies of renal parenchymal cell cancers

There have been at least 14 unique case-control studies that have included data on the risks of renal cancer in relation to occupational or leisure-time physical activity.

Brownson, Chang, & Davis (1991) made a general survey of cancers in relation to occupational classifications among 17,174 male cancer cases in Missouri. Their sample included 449 individuals with renal tumours. The control group was drawn, somewhat surprisingly, from other individuals with cancer rather than healthy individuals, although cancers of the colon were excluded from the control group. After adjusting data only for age and smoking habits, there was no significant difference in the standardized incidence ratio of renal cancer between those whose occupation demanded a high level of physical activity and those whose occupational activity was low [relative risk 0.77 (0.50-1.11)].

Chiu et al. (2006) compared 406 cases of renal cancer aged 64-68 years with 2,434 controls. In the women, the odds ratio of developing renal cancer among those who reported that they exercised at least once per day versus those who took leisure exercise less than once per month was 0.40 (0.19-0.83), but frequent leisure activity had no significant influence on the risk of renal tumours in the men [odds ratio 0.83 (0.48-1.43)]. There was a substantial risk associated with a high body mass index, but apparently little interaction between body mass index and reported habitual physical activity.

Goodman, Morgernstern, & Wynder (1986) studied 189 men and 79 women who had developed renal cancer with age, sex and race-matched hospital controls. They made a 3-level categorization of leisure activity, ranging from participation in strenuous sports to inactive, and also categorized occupational activity. The risk of renal cell cancer was strongly related to the individual's body mass index, but appeared to be unrelated to either active leisure

Table 3. *Association between high level of habitual physical activity and the development of renal parenchymal cancer as seen in case-control studies.*

Author	Sample	Cases and Findings	Comments
Brownson et al. (1991)	17,174 male cancer patients.	449 renal cases, controls cancer at other sites except colon. No reduction of risk of renal cancers in those with active occupations; OR moderate activity 1.2 (0.9-1.5), low activity 1.3 (0.9-2.0); RR for physically demanding occupation 0.77 (0.50-1.11)	Data adjusted for age and smoking
Chiu et al. (2006)	Age 64-68 yr, 1660 M, 829 F.	406 cases, 2434 controls. OR of cancer with exercise >1/day vs. <1/month 0.40 (0.19-0.83) in women (p = 0.1 for trend), 0.83 (0.48-1.43, ns) in men	Substantial effect from BMI, but little interaction between physical activity and BMI. Data adjusted for smoking, energy intake, hypertension, family history, diet, educational attainment
Goodman et al. (1986)	Age 20-80 yr, 378 M, 156 F.	189 M, 79 F cases of renal cell carcinoma vs. hospital controls. Strenuous sports vs. inactive, OR 1.14 (0.65-2.05) in men, 1.11 (0.44-2.97) in women. Occupational activity also unrelated to risk of cancer 0.88 (0.48-1.55) in men, 1.20 (0.41-4.06) in women	BMI is associated with cancer in both sexes. Controls matched for age, sex, race & hospital.
Hu et al. (2008)	Age 20 to >70 yr, 6177 subjects	617 M & 521 F with renal cancer, 5,039 matched population controls. Questions on frequency, duration & season of 12 common categories of moderate & of strenuous leisure activity. Most active moderate OR 0.86 (0.67-1.10), Most active strenuous OR 0.90 (0.71-1.14)	Residential area
Lindblad et al. (1994)	Age 20-79 yr, 1035 subjects	Structured interviews of 207 M, 172 F cases of renal cell cancer. High activity at work reduced risk in men (significant at age 30, 40 yr), but not in women. Men showed dose-response effect, greatest if related to physical activity at age 40 years [OR 0.37 (0.16-0.89), p = 0.008], OR for women 0.75 (0.20 -2.86). Leisure activity unrelated to risk in either men or women (data not shown).	Body mass and BMI weak risk factors in men, but important in women. Data adjusted for age, sex, educational attainment, smoking, BMI, amphetamine use, weight cycling
Mellemgaard et al. (1994)	Age 20-79 yr, 764 subjects	Questionnaire on activity at work and leisure. No effect of physical activity on cancer risk	Relative weight was an important risk factor
Mellemgaard et al. (1995)	Age 20-79 yr, 4041 subjects	1732 cases, 2309 controls; 5-level classification of both occupational & leisure activity at age 20 and at age 40. No significant effect of either occupational activity, [in men 1.11 (0.71-1.67 in women 1.67 (0.91-3.33)] or leisure activity [in men 1.11 (0.56-2.50), in women 1.67 (0.71-3.33)]	Data adjusted for age, BMI, smoking. Amphetamine associated with increased risk in men. BMI risk factor in women, less in men
Menezes et al. (2003)	Ages 20-79 yr, 933 subjects	Cases (173 M, 133 F) & matched controls. RR highest vs. least vigorous physical activity M 0.72 (0.42-1.23), F 0.40 (0.22-0.75); moderate activity M 0.49 (0.27-0.89), F 1.05 (0.55-2.00)	Data adjusted for age, BMI, smoking. In men, greatest effect from vigorous activity as an adolescent.
Paffenbarger et al. (1992)	College records from 35-70 yr ago. 51,977 men, 4706 women, cases matched with non-athletic peers	29 cases of renal cancer. RR of renal cancer (0.95) unrelated to former participation in university sports teams	Controls matched for age, sex & birth year.

Author	Sample	Cases and Findings	Comments
Pan et al. (2006)	Aged 20-76 yr. 3908 subjects	446 M, 364 F cases, 3106 controls. Recreational physical activity [>37 (M), >31 (F) vs. <6 MET-h/wk] 2 years earlier. OR 1.21(0.86-1.69) in men, 0.80 (0.54-1.18) in women, ns; also no effect on non-renal cell cancer	Data adjusted for age, province, educational attainment, BMI, total energy intake, smoking, diet, industrial chemicals. Large risk associated with high BMI.
Parent et al. (2011)	Age ~ 59 yr, 710 subjects	177 cases of renal cancer, 533 population controls. OR: high occupational activity 0.84 (0.38-1.89); leisure activity "often" vs. "never/not often" 1.11 (0.76-1.64); overall activity 1.02 (0.70-1.49)	Data adjusted for age, SES, ethnicity, smoking, BMI, and other confounders
Pukkala et al. (1992)	Comparison of 1449 physical education & 8619 language teachers, aged 20->75 yr.	15 cases of renal cancer. SIR 0.39 (0.01-2.15) in physical education teachers, 1.33 (0.73-2.23) in language teachers, RR = 0.29	No co-variates
Spyridopoulos et al. (2009)	Aged 22-83 yr. 350 subjects	70 cases, 280 age & sex-matched controls Physical exercise >90 min/d vs.0 min chi^{2}p <0.001[RR0.62 (0.48-0.82)]	Data adjusted for age & sex
Tavani et al. (2007)	Age ~ 62 yr. 2301 subjects	767 cases, 1534 controls. Occupational activity (high vs. low) reduces risk at all ages from 15-60 years [OR 0.71 (0.55-0.92) p <0.01). No effect of leisure activity (hr/wk) [OR 1.03 (0.78-1.36)].	Data adjusted for age, sex, BMI, smoking, alcohol consumption, hypertension, study centre
Xiao et al. (2014)	Ages 20 - 79 yr. Histologically confirmed cases vs. general population controls. 2452 subjects	Whites 856 cases, 712 controls; blacks 361 cases, 523 controls. Data on occupational & leisure activity & active transportation, total activity score for 20s and 50s. No significant effect in blacks. For whites, total activity (highest vs. lowest) in 20s OR 0.74 (0.50-1.10), p for trend = 0.06; in 50s, OR 0.67 (0.41-1.05) (p for trend 0.12). For blacks, OR in 20s 0.88 (0.52-1.47), in 50s 0.97 (0.54-1.72)	Data adjusted for study centre, age, sex, educational attainment, smoking, family history of cancer

BMI = body mass index; CI = confidence interval; HR = hazard ratio; HRT + hormone replacement therapy. METs = metabolic equivalents; OR = odds ratio; RR = relative risk; SES = socio-economic status; SIR = standardized incidence ratios.

pursuits [relative risk 1.14 (0.65-2.05) in men, 1.11 (0.44 (0.44-2.97) in women] or occupational physical activity [0.88 (0.48-1.55) in men, 1.20 (0.41-4.06) in women].

In a study that focussed primarily on diet and fibre intake, Hu et al. (2008) compared the reported leisure activities of 617 men and 521 women with renal cancer against the responses of 5,039 age and sex-matched controls. The data were adjusted for age, sex, and residential area only. Questions were asked about the frequency, duration and seasonality of 12 common categories of moderate and of strenuous physical activity. The odds ratio of renal cancer for those with the greatest volume of moderate activity was 0.86 (0.67-1.10), and for those with the greatest volume of strenuous activity (>55 min/week) it was 0.90 (0.71-1.14).

Lindblad et al. (1994) conducted a case-control study that compared renal cell cancer in 207 men and 172 women with findings in 353 controls. A structured interview found a strong inverse and dose-related relationship between relative risk and a 4-level classification of job activity in men, the greatest benefit being associated with vigorous physical activity at the age of 40 years [an odds ratio of 0.37 (0.16-0.89)]. In the men, significant benefit was also associated with the demands of occupation at the age of 30 years. However, occupational activity had no significant impact upon the relative risk of renal cancer in women [odds ratio 0.75 (0.20-2.86)], and leisure activity was said to show no association with the risk of renal cancer in either sex (although the data were not presented).

Mellemgaard et al. (1994) compared 368 histologically-verified cases of renal cancer with 396 controls. They found an association between the incidence of such tumours and relative weight, but no relationship to physical activity either at work or in leisure time. The following year, Mellemgaard et al. (1995) looked at a much larger series of 1,732 cases and 2,309 controls, making a 5-level classification of both occupational and leisure activity at the ages of 20 and 40 years. However, after adjusting data for age, body mass index and smoking, risk ratios showed no significant effect of either occupational [in men 1.11 (0.71-1.67 in women 1.67 (0.91-3.33)] or leisure activity [in men 1.11 (0.56-2.50), in women 1.67 (0.71-3.33)]. Nevertheless, the use of amphetamine was associated with a substantial increase of risk in men.

Menezes et al. (2003) compared 173 male and 133 female cases of renal cancer with matched controls. After adjustments for age, body mass index and smoking habits, reports of strenuous leisure activity were associated with a relative risk of 0.40 (0.22-0.75) in women. However, no reduction of risk was seen among those reporting only moderate physical activity [1.05 (0.55-2.00)]. In the men, both total recreational activity and moderate physical activity yielded risk ratios of 0.49 (0.27-0.89), with the greatest effects being seen from physical activity undertaken as an adolescent. However, any benefit associated with participation in vigorous activity was smaller and not statistically significant [0.72 (0.42-1.23)].

Paffenbarger, Lee, & Wing (1992) examined relationships between fatal and non fatal cancers and prior membership of sports teams in a sample of 56,683 university alumni. There were only 29 cases of renal cancer in this series, and these incidents bore no relationship to the rather tenuous measure of habitual physical activity provided by affiliation to an athletic team as a young adult (a relative risk 0.95 among those who engaged in more than 5 hours of sport per week while at university). Two specific problems with this investigation are that participation in many sports is influenced by body build, and that by middle-age, many of those who were athletes in their youth have become less active and more obese than their "non-athletic" peers (Montoye, Van Huss, Olson, Pierson, & Hudec, 1957).

Pan et al. (2006) compared 810 individuals aged 20-76 years who developed renal cancers with 3,106 controls. Data were adjusted for age, province of residence, educational attainment, body mass intake, total energy intake, smoking, diet, and any exposure to toxic industrial chemicals. A high body mass index was associated with a large increase of risk of renal cancer. Recreational activity was estimated in MET-h/week, ranging from <6 to >37 in men and <6 to >31 in women. The odds ratios for renal cell carcinoma were 1.21(0.86-1.69) and 0.80 (0.54-1.18) for active men and women respectively. Data were also obtained for non-renal cell carcinomas; these were unrelated to the volume of leisure activity.

Parent, Rousseau, & El Zein (2011) reported data for 177 cases of renal cancer aged ~ 59 years and 533 population controls. Data were adjusted for age, socio-economic status, ethnicity, smoking, body mass index, and other potential confounders. The odds ratio for those facing heavy energy demands at work was 0.84 (0.38-1.89). A simple classification of leisure activity ("often" vs. "never/not often") showed no evidence of benefit from physical activity, with an odds ratio of 1.11 (0.76-1.64) for active individuals; further,a combination of occupational and leisure activity did not enhance prognosis [odds ratio 1.02 (0.70-1.49)].

Pukkala et al. (1992) compared the experience of 1,449 physical education teachers with that of 8,619 language teachers. On various measures, the typical physical education teacher had a demonstrably more active lifestyle than the language teachers. The standardized incidence ratio of renal cancer for the physical education teachers was 0.39 (0.01-2.15), whereas that for the language teachers was 1.33 (0.73-2.23), a risk ratio of 0.29, although confidence limits were also broad, since the entire study included only 15 individuals with a renal cancer.

In an article that focussed on leptin levels, Spyridopoulos et al. (2009) examined the minutes per day spent in "physical exercise" between 70 cases of renal cancer and 280 age and sex-matched controls. A chi2 comparison between those taking no activity versus those taking > 90 min/d found a significant advantage in the latter group ($p < 0.001$).

Tavani et al. (2007) studied 767 individuals with renal tumours and 1,534 controls, looking at both occupational and leisure activity as reported for various ages from 15 to 60 years. After controlling for body mass index, smoking, alcohol consumption, hypertension and study centre, a beneficial effect was associated with occupational activity, irrespective of the age when it was undertaken [odds ratio 0.71 (0.55-0.92) $p < 0.01$) $p < 0.01$), but no effect of leisure activity was observed [OR 1.03 (0.78-1.36)].

Xiao et al. (2014) drew a distinction between "white" and "black" subjects, comparing the habitual physical activity of 1217 histologically confirmed cases with that of 1225 population controls when in their 20s and in their 50s. Data were obtained on occupational and leisure activity and on active transportation. After adjustment of the data for study centre, age, sex, educational attainment, smoking habits and family history of cancer, no significant effects of physical activity were seen in the blacks. However, in the whites there was a suggestion of a positive trend for those with a high total activity score both in their 20s [OR 0.74 (0.50-1.10), p for trend = 0.06] and in their 50s [OR 0.67 (0.41-1.05), p for trend = 0.12]. Further, significant benefit was associated with tranportation-related activity in the 20s, and with leisure-time activity in the 50s.

Many of the case-control studies suffer the disadvantage of including relatively few cases of renal cancer. Of 14 unique case-control studies, only 6 showed a statistically significant advantage to an active group, and as with cohort studies this was generally in a sub-group of the data [women only (Chiu, Gapstur, & Chow, 2006), men only, and at work but not in leisure (Lindblad, Wolk, & Bergström, 1994), in men and women, but a greater benefit for moderate than for vigorous activity (Menezes, Tomlinson, & Kreiger, 2003), a large but non-significant advantage of standardized incidence ratio based on a very small sample (Pukkala, Poskiparta, & Apter, 1992), benefit from occupational but not leisure activity (Tavani, Zucchetto, & Dal, 2007)], and benefit in white but not in black individuals (Xiao et al., 2014). In all, the case-control studies included 7410 cases of renal cell carcinoma, with a weighted average risk for an active lifestyle of 0.93. Omitting 5 studies with limited co-variance adjustment, the risk ratio increased marginally to 0.94. The weighted average for the occupational studies was 0.98, or 0.99 omitting 3 studies with limited co-variates; likewise, the average for leisure studies was 0.98, and omitting 4 reports with limited co-variates it was 1.01.

Discussion

The data on a possible association between renal cancer and physical activity are as yet not entirely convincing. Although no studies have produced evidence that physical activity significantly augments the risk of renal tumours, a trend to reduced risk has been found in only 6 of 13 cohort and 6 of 14 case/control studies; moreover, in most instances statistically significant benefit has been limited to a sub-group of the total sample.

The meta-analysis of Behrens and Leitzmann (2013) suggested that the risk of renal cell cancer in active individuals was 0.88 (0.79-0.97) relative to those with a low level of habitual activity, and restricting their analysis to papers that they judged of high quality, the risk ratio became 0.78 (0.66-0.92). The number of relevant studies has now increased from the 19 identified by Behrens and Leitzmann (2013) to a total of 27, but the additional research has not greatly modified the overall picture, with overall weighted risk ratios for active individuals averaging 0.88 in cohort and 0.93 in case-control studies. Interpretation of this small apparent advantage must be tempered by the fact that it largely disappears when the analysis is restricted to studies that include important co-variates such as obesity and smoking. Presumably. much of the reduction in risk observed in the unrestricted data base reflects an interaction between regular physical activity and these variables. All conclusions must still be accepted cautiously. Although more than 14,000 cases of renal cancer have now been studied, many individual reports are based on relatively few cases, leading to broad confidence limits and limiting the possibility of demonstrating statistically significant benefit from physical activity. Moreover, measurements of physical activity have often been weak, and some samples have included very few individuals who were vigorously active, either at work or in their leisure hours. One study was based on attained aerobic fitness (Thompson et al., 2008), but as yet no investigators have made objective measurements of habitual physical activity using personal monitors such as a pedometer or accelerometer, and there have been no human prospective trials looking at risks in groups assigned to known and differing physical activity programmes.

Perhaps the biggest issue to resolve in future investigations is an appropriate handling of co-variates. Body mass index and obesity are recognized risk factors (Chow et al., 1996; Setiawan et al., 2007) and many studies have included one or both of these items, sometimes along with total energy intake, as co-variates in their analyses. However, these parameters are correlated with physical activity, and they inevitably claim some of the variance that would otherwise be attributable to habitual physical activity, reducing the likelihood of finding a statistically significant effect for this last variable.

Many questionnaires have assessed recent physical activity, and it could be argued that this was not the period when carcinogenic change was occurring. However, the timing of reports does not seem a major criticism of existing studies. Several investigators have looked specifically at differences in response, depending on the age when the exercise was undertaken. Mellemgaard et al. (1994) found no effect, whether subjects were active at 20 or 40 years of age, and Tavani et al. (2007) found a similar reduction of risk from occupational activity at all ages from 15-60 years. Moore et al. (2008) also found benefit from physical activity both as an adolescent and as an adult. Lindblad et al. (1994) compared responses at various ages, finding the largest effect from activity that was undertaken at 40 years of age.

Many of the occupational assessments refer to the period 1920-1980, when the energy expenditures required in "heavy" industry were still relatively high, and men in sedentary jobs were less likely to compensate for a lack of activity at work by deliberate leisure-time exercise. However, other risks associated with heavy occupations may have clouded findings, particularly an exposure to toxic industrial chemicals (Pesch et al., 2000) such as solvents and metals (very few investigators co-varied for this risk) and a greater prevalence of cigarette smoking among heavy industrial workers. Cigarette smoking is a major risk factor for renal tumours (Setiawan et al., 2007), and it is difficult to eliminate its effect by co-variance analysis. Demanding occupations commonly require 5-6 hours of moderate intensity activity, performed 5 days per week; in contrast, leisure activity is of shorter duration but higher intensity. Moreover, most of the leisure studies to date have focussed upon aerobic activity, whereas occupational tasks sometimes include resistance-type activity. However, as previously noted by Behrens and Leitzmann (2013), we saw no major differences in risk ratios between occupational and leisure studies.

There is as yet little agreement on the relative impact of differing intensities, frequencies and overall volumes of physical activity. A few reports have found a dose-response gradient, associating the largest reduction of risk with the greatest amount of physical activity, however measured. Thus Lindblad et al. (1994) observed (but only in men) a graded decrease of risk with greater physical demands of occupation (p for a trend = 0.03). Mahabir et al. (2004) also found the largest effect at the highest of 3 levels of leisure activity (p for trend = 0.12). Moore et al. (2008) distinguished 5 gradations in the frequency of leisure activity, and in the women (but not in the men) there was a significant trend, with the greatest reduction of risk in those taking activity more than 5 times/week. Finally, Chiu et al. (2006) graded the frequency of activity (from less than once/month to more frequently than daily); in their study, the risk of renal cancer was lowest in those taking the most frequent activity, but risks were inconsistently greater among those reporting activity at frequencies of 2-6 times/week to less than once per month. In other investigations, the lowest risk has been associated with less than the maximal volume of activity. In contrast, Menezes et al. (2003) linked the greatest benefit with a large volume of moderate as opposed to vigorous physical activity, and although Setiawan et al. (2007) found a dose-response gradient in women (p for trend = 0.027), the greatest reduction of risk was for individuals in the third quartile of the leisure activity volume continuum. Finally, van Dijk et al. (2004) graded non-occupational activity in terms of its duration (from < 30 to > 90 minutes/day), and in their study, the greatest benefit was seen among those taking 30-60 minutes of leisure activity per day.

There are a number of potential mechanisms for benefit that merit further research. These include the general mechanisms associated with the prevention of carcinoma at other body sites, such as enhanced immune surveillance and a reduction of oxidative stress and chronic inflammation (Pialoux, Brown, & Leigh, 2009; Shephard & Shek, 1995). Those who choose active leisure pursuits are also less likely to be smokers (Hunt et al., 2005) and exercise would tend to reduce body mass (Chow et al., 1996) with a lesser endogenous synthesis of cancer-promoting hormones such as oestrogen and insulin-like growth factor I (IGF-I)(Solomon, Haus, & Kelly, 2009). Finally, regular physical activity reduces hypertension; a high blood pressure is associated with renal carcinogenesis (Setiawan et al., 2007), although it is unclear which is cause and which effect (Stojanovic, Goldner, & Ivkovic, 2009).

There has as yet been little attempt to examine the impact of physical activity in animal models. Kato et al. (2011) induced renal cancer in male rats by the administration of ferric nitrilotriacetate. In the short-term, the condition of the rats was worsened by exercise, but over a 40 week period treadmill running (8 m/min, 0% slope for 30 minutes, 5 days/week) led to significant decreases in the number of microcarcinomas, karyomegalic cells and degenerative renal tubules.

Conclusions

There is little evidence that regular physical activity increases the risk of renal cancer, and 12 of 27 unique studies have reported some reduction of risk in active individuals, although usually this has been seen only in a specific sub-set of the overall subject-sample. The overall weighted risk ratio for an active lifestyle is 0.88 in cohort and 0.93 case-control studies, similar to the conclusions drawn by Berhens and Leitzmann (2013) for a smaller group of 19 reports. However, a large part of this apparent benefit disappears on excluding studies that do not co-vary for obesity and smoking, suggesting that any reduction of risk arises from an interaction between habitual physical activity and these variables. There remains a need for further studies of adequate sample size, using objective techniques to provide more reliable information on physical activity patterns at various times during the lifecycle, with careful handling of co-variates such as body mass index, obesity and total energy intake. There is also scope for further animal experimentation, and for prospective trials where subjects are assigned to carefully determined and contrasting levels of daily energy expenditure. For the present, we can affirm that exercise does not increase the likelihood of developing renal tumours, but most of any preventive value of regular physical activity probably arises indirectly, through an action upon obesity and smoking behaviour.

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