Int. J. Cancer: **108,** 600–605 (2004)

Publication of the International Union Against Cancer

PHYSICAL ACTIVITY AND RENAL CELL CANCER RISK IN A COHORT OF MALE SMOKERS

Somdat MAHABIR[1]*, Michael F. LEITZMANN[2], Pirjo PIETINEN[3], Demetrius ALBANES[2], Jarmo VIRTAMO[3] and Philip R. TAYLOR[1]

[1]*Cancer Prevention Studies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA*
[2]*Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA*
[3]*Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland*

Few studies have examined exercise in relation to risk of renal cell cancer. We examined the association between leisure-time and occupational physical activity and renal cell cancer in a cohort of 29,133 male smokers 50–69 years of age in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study. Physical activity was assessed at baseline using a self-administered questionnaire that inquired about usual level of physical activity during leisure-time and at work during the past year. Cox proportional hazards modeling was used to adjust simultaneously for known or suspected risk factors for renal cell cancer. During 12 years (354,407 person-years) of follow-up, 210 incident cases of renal cell cancer were identified. In age-adjusted analysis, the RRs of renal cell cancer in increasing categories of leisure-time physical activity (light, moderate and heavy) were 1.0, 0.89 (95% CI = 0.67–1.17) and 0.38 (95% CI = 0.15–0.94), respectively (*p*-value for trend = 0.06). After adjustment for body mass index, energy intake, smoking, hypertension, education and fruit and vegetable intake, the multivariate RRs of renal cell cancer in increasing categories of leisure-time physical activity (light, moderate and heavy), were 1.0, 0.89 (95% CI = 0.66–1.19), and 0.46 (95% CI = 0.18–1.13) (*p*-value for trend = 0.12). Occupational physical activity was unrelated to renal cell cancer risk. These data suggest that recreational physical activity may play a role in the prevention of renal cell cancer in men.

Key words: *physical activity; RCC; smokers*

The incidence of renal cell cancer, the most common form of kidney cancer, has been increasing in the United States (US),[1] other Western countries[2,3] and worldwide.[4] In the US, incidence rates for renal cell cancer have risen about 2% per year among the major race groups since 1970.[5] Renal cell cancer also now accounts for approximately 2% of cancers in the US[6] as well as worldwide.[4] Renal cell cancer is more common among men than women and the incidence rates vary more than 10-fold in the world. The highest rates are found in North America and Europe and the lowest in Asia.[4]

The causes of renal cell cancer are poorly understood. Smoking[7,8] and obesity[8] are established risk factors. Several epidemiological studies have reported that obesity is related to an increased risk of renal cell cancer among women and men, although the evidence is stronger for women.[8] Because energy expenditure is an important determinant of weight gain and obesity, physical activity may play a protective role in the development of renal cell cancer. Very few studies have examined the relationship between physical activity and renal cell cancer, however, and in these studies, the association remains unclear. Four case-control studies[9–12] have been reported to date. Of these, one[10] showed an inverse association with occupational physical activity whereas 3[9,11,12] showed no association with either occupational or leisure-time physical activity. Three prospective cohort studies[13–15] have also assessed physical activity in relation to renal cell cancer, and one[14] showed an inverse association with occupational physical activity whereas the others[13,15] showed no association with leisure time physical activity. Of these 7 reported studies, only 4[10–12,15] controlled for body mass and only one[9] accounted for diet as a potential confounding variable.

We examined the relationship between leisure-time and occupational physical activities and risk of renal cell cancer in a large prospective cohort of middle-aged Finnish male smokers, with detailed information on body mass index (BMI), diet and life-style factors.

MATERIAL AND METHODS

Study population

The ATBC study was a randomized, double-blind, placebo-controlled, two-by-two factorial design, primary prevention trial that tested whether alpha-tocopherol (50 mg/day) and beta-carotene (20 mg/day) reduced the incidence of lung cancer in male smokers living in southwestern Finland. The cohort consisted of 29,133 Caucasian males between 50 and 69 years, who smoked 5 or more cigarettes per day at study entry. All subjects were recruited into the trial between 1985–88, and the trial ended on the 30th of April 1993 after 5–8 years of active intervention (median 6.1 years). Participants were randomized to 1 of 4 intervention groups: 50 mg/d alpha-tocopherol; 20 mg/d beta-carotene; 50 mg/d alpha-tocopherol plus 20 mg/d beta-carotene; or placebo. Post-intervention follow-up continued through the Finnish Cancer Registry. Study eligibility was assessed before randomization; subjects who were diagnosed with prior cancer or serious disease limiting long-term participation, as well as those taking supplements of vitamins E, A, or beta-carotene in excess of defined amounts were ineligible for participation. Other details of the ATBC trial have been described previously.[16]

Case identification

Cases were identified through the Finnish Cancer Registry, which provides almost 100% of case ascertainment.[17] The medical records of all potential renal cell cancers were collected from hospitals and pathology laboratories and a study physician reviewed them to confirm the cancer diagnosis.

Grant sponsor: National Cancer Institute; Grant number: N01 CN45165, N01 CN45035.

Somdat Mahabir is supported by the Cancer Prevention Fellowship Program, Office of Preventive Oncology, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD 20892.

*Correspondence to: Cancer Prevention Studies Branch, Center for Cancer Research, National Cancer Institute, 6116 Executive Blvd., Suite 705, MSC 8314, Bethesda, MD 20892-7058. Fax: +301-435-8645. E-mail: mahabirs@mail.nih.gov

Received 25 April 2003; Revised 8 August 2003; Accepted 22 August 2003

DOI 10.1002/ijc.11580

Baseline data collection

At baseline, subjects completed a questionnaire regarding background characteristics and medical history. Physical activity was assessed based on 2 general questions. The first question assessed usual occupational physical activity during the past year: (a) not working; (b) mainly sitting (*e.g.*, watchmaker, radio mechanic, office work at desk); (c) walking quite a lot, but not lifting or carrying (*e.g.*, foreman, shop assistant, light industrial work); (d) walking and lifting (*e.g.*, carpenter, cattle tender, work in engine shop); or (e) heavy physical work (*e.g.*, forestry work, heavy farm work, heavy building and industrial work. The second question assessed leisure time physical activity during the past year: (a) sedentary (*e.g.*, reading, watching television); (b) moderate (*e.g.*, walking, hunting, gardening—all fairly regularly); or (c) heavy (*e.g.*, running, skiing, swimming—all fairly regularly). The participants also completed a self-administered food frequency questionnaire. Height, weight and blood pressure were measured, and a serum sample was drawn and stored at −70°C.

Statistical analysis

We carried out a cohort analysis of the subjects who developed renal cell cancer between 1985–99 (median 12.2 years follow-up) among the 29,133 trial participants. Cox proportional hazards models were used to estimate multivariate adjusted relative risks (RR) and 95% confidence intervals (CI).

In all analyses, sedentary men were used as the comparison group. For occupational physical activity non-workers were kept as a separate category of physical demand because "nonworking" is not well defined in terms of physical activity. Leisure-time and occupational physical activity were mutually adjusted for each other. The variables that constitute the base multivariate model are based on biologic plausibility and are associated with renal cell cancer based on the literature. Any other variable that resulted in a ⩾ 10% change in the beta-coefficients of the physical activity variables of the base model were also included in the final multivariate model.

RESULTS

Baseline characteristics of the study participants according to increasing categories of leisure-time and occupational physical activity are listed in Tables I and II. respectively. For leisure-time physical activity, those who were most active showed lower BMI, fewer cigarettes smoked per day, less years of smoking, less intake of dietary fat and less alcohol consumption. In contrast, they showed higher intake of fruits and vegetables. For occupational physical activity, men who were more active compared to sedentary showed slightly lower BMI, fewer cigarettes smoked per day, less alcohol consumption, less fruits and vegetable intake and had a lower percentage of education. In contrast, they showed higher intakes of total energy and dietary fat.

Table III shows that the age-adjusted RRs for renal cell cancer in increasing categories of leisure-time physical activity (light, moderate and heavy) were 1.0, 0.89 (95% CI = 0.67–1.17) and 0.38 (95% CI = 0.15–0.94) respectively (*p*-value for trend = 0.06). After adjustment for body mass index, energy intake, smoking, hypertension, education, and fruit and vegetable intake, the multivariate RRs of renal cell cancer in increasing categories of leisure-time physical activity (light, moderate and heavy), were 1.0, 0.89 (95% CI = 0.66–1.19), and 0.46 (95% CI = 0.18–1.13) (*p*-value for trend = 0.12). Thus, age-adjustment alone resulted in an approximately 62% decrease risk for renal cell cancer, but this was attenuated to an approximately 54% decrease risk after adjustment for confounders in the multivariate model.

No association for occupational physical activity and risk of renal cancer was found (Table IV). The age-adjusted RR was 1.02 (95% CI = 0.54–1.91) for those in the heavy *vs.* the sedentary group. When adjusted for potential confounding variables using a multivariate model, the RR was 1.08 (95% CI = 0.54–2.15).

We also stratified our sample and examined potential effect modification of the physical activity/renal cell cancer association by age, BMI and number of cigarettes smoked per day. No statistically significant effect modifications were observed (Tables V, VI). Increasing levels of leisure-time physical activity, however, seemed to be more protective against renal cell cancer in those with lower BMIs (≤24 and 25–29) as well as those who smoked less (<15 cigarettes per day) (Table V).

We also combined leisure-time and occupational physical activity into a global index of physical activity and categorized the activity levels as "sedentary, moderate and heavy". In age-adjusted models, the RR for moderate physical activity compared to sedentary was 1.01 (95% CI = 0.76–1.33) and the RR for heavy compared to sedentary was 0.85 (95% CI = 0.59–1.22). In the multivariate model, the RR for moderate *vs.* sedentary was 1.05 (95% CI = 0.75–1.35) and the RR for heavy compared to sedentary was 0.93 (95% CI = 0.64–1.35). There was no interaction with age, BMI or total cigarette smoking.

DISCUSSION

Our study suggests that higher leisure-time physical activity may offer some protection against renal cell cancer. In the age-adjusted analysis, we found a 62% decrease in risk for intensity of leisure time physical activity (RR = 0.38; 95% CI = 0.15–0.94; *p*-value for trend = 0.06) (Table III), but after controlling for confounding variables in the multivariate model, the risk was reduced to 54% (RR = 0.46, 95% CI = 0.18–1.13; *p*-value for trend = 0.12) (Table III). The low number of cases (n = 5) in the highest category of leisure-time physical activity reduced our power to estimate reliably the association with heavy leisure-time activity. Because men with greater recreational physical activity smoked less and consumed less dietary fat and alcohol, but had

TABLE I – BASELINE CHARACTERISTICS ACCORDING TO LEISURE-TIME PHYSICAL ACTIVITY AMONG MALE FINNISH SMOKERS[1]

Characteristic	Leisure time physical activity[2]		
	Light	Moderate	Heavy
Participants (*n*)	12,184	15,191	1,744
Age (years)	57.2 ± 5.1	57.2 ± 5.0	56.9 ± 5.3
Energy (kcal/day)	2,785 ± 806	2,836 ± 771	2,832 ± 782
Body-mass index (kg/m^2)	26.5 ± 4.1	26.1 ± 3.6	25.8 ± 3.2
Years of smoking	36.4 ± 8.3	35.8 ± 8.4	33.8 ± 9.6
Cigarettes smoked/day	21.6 ± 9.2	19.8 ± 8.4	17.6 ± 8.3
Dietary fat (g)[3]	106.6 ± 16.6	105.0 ± 15.9	103.3 ± 16.2
Alcohol (g)[3]	20.3 ± 23.7	16.5 ± 19.4	15.0 ± 18.8
Fruit (g)[3]	81.8 ± 77.8	91.9 ± 78.5	110.0 ± 87.0
Vegetable (g)[3]	151.5 ± 111.6	172.2 ± 113.0	202.3 ± 129.8
Education (% > primary school)	42.4	48.8	8.8

[1]All variables (except age) are standardized to the age distribution of the cohort.–[2]Leisure time physical activity is missing for 14 individuals.–[3]Nutrients are adjusted for total energy intake; dietary variables are available for 93% of the cohort.

TABLE II – BASELINE CHARACTERISTICS OF OCCUPATIONAL PHYSICAL ACTIVITY AMONG MALE FINNISH SMOKERS

Characteristic	Occupational Physical Activity[2]				
	Non-working	Sedentary	Light	Moderate	Heavy
Participants (*n*)	12,321	4,007	5,304	4,808	2,685
Age (years)	60.3 ± 4.8	54.9 ± 3.9	54.9 ± 3.9	54.7 ± 3.8	55.6 ± 4.4
Energy (kcal/day)	2,702 ± 770	2,704 ± 728	2,792 ± 741	3,014 ± 812	3,189 ± 812
Body-mass index (kg/m^2)	26.2 ± 3.9	26.7 ± 3.9	26.3 ± 3.6	26.1 ± 3.7	26.1 ± 3.6
Years of smoking	39.3 ± 8.2	33.4 ± 7.8	33.0 ± 7.9	33.6 ± 7.4	34.0 ± 7.9
Cigarettes smoked/day	19.0 ± 8.3	22.2 ± 9.9	21.2 ± 9.1	21.4 ± 8.5	20.8 ± 8.6
Dietary fat (g/day)[3]	105.7 ± 16.0	105.5 ± 15.5	104.5 ± 15.6	105.1 ± 17.2	108.0 ± 17.7
Alcohol (g/day)[3]	16.8 ± 21.2	21.3 ± 21.7	19.3 ± 20.8	18.8 ± 22.0	14.5 ± 20.1
Fruit (g/day)[3]	87.9 ± 76.6	99.4 ± 84.3	97.6 ± 83.0	82.1 ± 76.9	70.1 ± 72.2
Vegetable (g/day)[3]	149.9 ± 102.9	207.3 ± 130.4	195.9 ± 121.3	158.1 ± 111.9	123.3 ± 92.2
Education (% > primary school)	30.9	30.9	27.3	8.5	2.5

[1]All variables (except age) are standardized to the age distribution of the cohort.–[2]Occupational physical activity is missing for 8 individuals.–[3]Nutrients are adjusted for total energy intake; dietary variables are available for 93% of the cohort.

TABLE III – RELATIVE RISK OF RENAL CELL CANCER IN RELATION TO INTENSITY OF LEISURE-TIME PHYSICAL ACTIVITY AMONG MALE FINNISH SMOKERS*

Variable	Category			*p*-value trend
	Light[1]	Moderate	Heavy	
Cases	98	107	5	
Person-years	125,617	162,696	19,114	
Age-adjusted RR (95% CI)	1 (ref)	0.89 (0.67–1.17)	0.38 (0.15–0.94)	0.06
Multivariate RR (95% CI)[2]	1 (ref)	0.89 (0.66–1.19)	0.46 (0.18–1.13)	0.12

[1]Light is the reference group.–[2]The multivariate model includes the following: age, supplement group, calories, body-mass index, years of smoking regularly, total number of cigarettes smoked per day, smoking inhalation, blood pressure, education level, fruit and vegetable intake and occupational physical activity.

TABLE IV – RELATIVE RISK OF RENAL CANCER IN RELATION TO INCREASING CATEGORIES OF OCCUPATIONAL PHYSICAL ACTIVITY AMONG MALE FINNISH SMOKERS

Variable	Category					*p*-value, trend
	Non-working	Sedentary[1]	Light	Moderate	Heavy	
Cases	91	25	44	34	16	
Person-years	120,746	44,718	59,564	53,273	29,078	
Age-adjusted RR (95% CI)	1.08 (0.68–1.74)	1 (ref)	1.36 (0.83–2.22)	1.14 (0.68–1.92)	1.02 (0.54–1.91)	0.79
Multivariate RR (95% CI)[2]	1.12 (0.67–1.84)	1 (ref)	1.37 (0.82–2.28)	1.24 (0.71–2.15)	1.08 (0.54–2.15)	0.64

[1]Sedentary is the reference group.–[2]The multivariate model includes the following: age, supplement group, body-mass index, calories, blood pressure, years smoking regularly, total number of cigarettes smoked per day, smoking inhalation, education level, fruit and vegetable intake, and leisure-time physical activity. Place of residence, alcohol, serum cholesterol, and dietary fat intake were also included in the model since they produced a greater than 10% change in the beta-coefficients of the base multivariate model.

higher intakes of fruits and vegetables, we cannot exclude the possibility that the apparent protective effect of recreational physical activity on renal cell cancer risk observed in our study was due to residual confounding by a healthy lifestyle. We did not find any association with occupational physical activity and renal cell cancer.

Our study had certain limitations and strengths. Because the cohort consisted exclusively of male smokers, the results may not be generalizable to non-smokers and to women. Data on physical activity was limited; only a small section of the ATBC study questionnaire was devoted to physical activity questions, and respondents were required to recall activity carried out during the past 12 months before study entry. Moreover, there was no information on lifetime physical activity. For example, we were unable to examine whether physical activity early in life potentially affects risk for renal cell cancer. In addition, in our study the time window to the date of cancer diagnoses varied from 1–12 years. Because we do not have updated measures of physical activity, we were unable to address the issue of repeated exposure measures. It is quite possible that participants may have changed their activity habits over time. These features apply to cohort studies in general, however, and are not unique to the current study. Ideally, we would have liked to update our data on physical activity, but the study design did not allow for this opportunity. In Finland jobs are typically held for a number of years or even decades. Thus, our assessment of occupational physical activity likely represents long-term exposure to job-related physical activity. In contrast, it is possible that recreational physical activity varied over time in our study population. Thus, our assessment of recreational physical activity many not have encompassed a long-term exposure period, resulting in measurement error. Such random misclassification of exposure, however, would tend to bias the results toward the null. Moreover, evidence suggests that recreational physical activity tends to track reasonably over time.[18] In addition, most previous large epidemiologic studies on physical activity have used a single assessment of physical activity at baseline, and important associations with heart disease,[18] diabetes[19] and colon cancer[20] have been seen using this approach.

Because physical activity, energy intake and body mass are complementary, 2 of these variables should determine the third, and it would have been appropriate to stratify the responders by 1 of 3 main variables mentioned here. The number of renal cell cancer endpoints in the high physical activity categories was too small, however, to permit desirable stratifications. To address this concern, we created: (*i*) an age-adjusted model [RRs of renal cell cancer in increasing categories of leisure-time physical activity (light, moderate and heavy) were 1.0, 0.89 (95% CI = 0.67–1.17) and 0.38 (95% CI = 0.15–0.94), (*p*-value for trend = 0.06)]; (*ii*)

TABLE V – RELATIVE RISK OF RENAL CANCER IN RELATION TO INTENSITY OF LEISURE-TIME PHYSICAL ACTIVITY IN SUBGROUPS DEFINED BY SELECTED VARIABLES AMONG MALE FINNISH SMOKERS[1]

Variable	Cases (*n*)	Leisure time physical activity			*p*-value, trend	*p*-value, interaction
		Light[2]	Moderate	Heavy		
Age (years)						
≤55	81	1	1.22 (0.76–1.97)	0.81 (0.24–2.70)	0.74	
56–59	46	1	0.70 (0.38–1.28)	—		
>59	83	1	0.73 (0.46–1.16)	0.41 (0.10–1.72)	0.09	0.20
Body-mass index[3]						
≤24	46	1	0.66 (0.35–1.27)	0.27 (0.04–2.06)	0.09	
25–29	126	1	0.83 (0.57–1.20)	0.39 (0.12–1.27)	0.10	
>29	38	1	1.36 (0.69–2.70)	1.05 (0.14–8.14)	0.47	0.09
Cigarettes per day						
<15	61	1	0.54 (0.31–0.92)	0.17 (0.02–1.26)	0.005	
16–24	75	1	0.97 (0.59–1.58)	1.12 (0.39–3.21)	0.98	
≥24	74	1	1.22 (0.75–1.99)	—		0.21

[1]The multivariate models include the following: age, supplement group, body-mass index, calories, blood pressure, years smoking regularly, total number of cigarettes smoked per day, smoking inhalation, education level, fruit and vegetable intake, and occupational physical activity.–[2]Light is the reference group.–[3]Body-mass index is the weight in kilograms divided by height in meters squared.

TABLE VI – RELATIVE RISK OF RENAL CANCER IN RELATION TO INCREASING CATEGORIES OF OCCUPATIONAL PHYSICAL ACTIVITY IN SUBGROUPS DEFINED BY SELECTED VARIABLES AMONG MALE FINNISH SMOKERS*

Variable	Cases (n)	Occupational physical activity					*p*-value, trend	*p*-value, interaction
		Non-working	Sedentary[2]	Light	Moderate	Heavy		
Age (years)								
≤55	81	0.66 (0.28–1.56)	1	1.13 (0.58–2.21)	1.07 (0.53–2.18)	0.93 (0.37–2.32)	0.38	
56–59	46	0.98 (0.38–2.52)	1	1.58 (0.60–4.17)	1.26 (0.43–3.71)	0.63 (0.12–3.24)	0.75	
>59	83	2.11 (0.65–6.93)	1	1.74 (0.43–7.00)	1.21 (0.24–6.15)	2.12 (0.46–9.82)	0.46	0.11
Body-mass index[3]								
≤24	46	1.66 (0.50–5.49)	1	1.71 (0.52–5.62)	1.38 (0.37–5.16)	0.87 (0.15–5.08)	0.58	
25–29	126	1.02 (0.54–1.94)	1	1.28 (0.67–2.43)	1.00 (0.49–2.01)	0.92 (0.38–2.15)	0.94	
>29	38	1.01 (0.33–3.14)	1	1.20 (0.36–3.98)	1.92 (0.58–6.42)	1.92 (0.43–8.62)	0.18	0.31
Number of cigarettes per day								
<15	61	0.86 (0.36–2.04)	1	0.81 (0.3–2.17)	0.53 (0.17–1.70)	0.84 (0.26–2.74)	0.57	
16–24	75	1.12 (0.47–2.65)	1	1.65 (0.71–3.86)	1.28 (0.51–3.21)	0.71 (0.18–2.74)	0.95	
>24	74	1.31 (0.54–3.15)	1	1.58 (0.66–3.76)	1.95 (0.79–4.80)	1.67 (0.55–5.06)	0.25	0.93

[1]The multivariate models include the following: age, supplement group, body-mass index, calories, blood pressure, number of years smoking regularly, total number of cigarettes smoked per day, smoking inhalation, education level, fruit and vegetable intake, and leisure-time physical activity. Place of residence, alcohol, serum cholesterol, and dietary fat intake were also included since they produced a greater than 10% change in the beta-coefficients of the base multivariate model. Values are RR (95% CI).–[2]Sedentary is the reference group.–[3]Body-mass index is the weight in kilograms divided by height in meters squared.

a full multivariate model including age, BMI, calories and other variables [RRs of renal cell cancer in increasing categories of leisure-time physical activity (light, moderate and heavy), were 1.0, 0.89 (95% CI = 0.66–1.19) and 0.46 (95% CI = 0.18–1.13) (*p*-value for trend = 0.12)]; and (*iii*) a multivariate model with all the variables in the full model except BMI [RRs of renal cell cancer in increasing categories of leisure-time physical activity (light, moderate and heavy) were 1.0, 0.88 (95% CI = 0.66–1.16) and 0.44 (95% CI = 0.18–1.09) (*p*-value for trend = 0.09). Therefore, to the extent possible, we believe we have disentangled the effect of physical activity from those of energy intake and BMI.

An advantage of our study is that it is a large prospective cohort with a sizable number of renal cell cancer cases ($n = 210$). Additionally, we had detailed information on many variables such as BMI, smoking, blood pressure and diet, which enabled us to control for potential confounding by these variables. Although our study consisted of all smokers, this can also be considered a unique strength. Because smoking was a common exposure to all subjects, it allowed us to assess the relationship between physical activity and renal cancer in a group that does not generally practice desirable health behaviors. This circumstance should minimize the possibility that physical activity acted as a surrogate index of an overall healthy lifestyle. Smokers are believed to be at increased risk for renal cancer.[7,21] We found that leisure-time physical activity was protective in our cohort of men who smoked an average of 20 cigarettes per day.

We found null results for occupational physical activity and risk for renal cell cancer. It is possible that occupational physical activity may be confounded by occupational exposures that are risk factors for renal cell cancer. For example, a significant dose-response relationship between benzene exposure and renal cell cancer in males has been reported.[22] That study[22] also found an increased risk for renal cancer associated with exposure to coal tar, pitch, asphalt, herbicides, pesticides and vinyl chloride. A Finnish cohort reported a significant excess of renal cell cancer in males with at least 5 years of employment in oil refineries.[23] A large multi-center case-control study[24] conducted in 5 countries found a significant increased risk of renal cell cancer associated with employment in the blast furnace, the iron and steel industry, and exposure to asbestos, dry-cleaning agents, gasoline and other petroleum products. Our study did not collect data on occupational exposures. Another study[25] found increased risk of renal cell cancer with use of anti-hypertensive medications after adjustment for hypertension. In our study, we adjusted for hypertension but did not have data on the use of anti-hypertensive medications. Other possibilities for the null association between occupational physical activity and renal cell cancer risk observed in our study are confounding by other unmeasured lifestyle factors, inadequate assessment of occupational physical activity, limited variability in exposure to occupational physical activity, and chance. Thus, our results regarding occupational physical activity should be interpreted with caution.

Very few studies have assessed physical activity and risk for renal cancer.[9–15] Four of these studies were case-control studies[9–12] and only one found an inverse association with physical activity.[10] That study[10] found an approximately 2.5-fold higher risk in men least active compared to most active at work at age 40 and above, and intensity-dependent trend was evident. That study, however, may have been hampered by selection bias or differential misclassification, as a proportion of the cases (17%) died before interview.

Of the prospective cohort studies of physical activity and renal cell cancer,[13–15] only one[14] found an inverse association with occupational physical activity. That study,[14] however, did not adjust for BMI, smoking or diet. The other studies[13,15] found no evidence of an association between either occupational or leisure-time physical activity and risk of renal cell cancer. The latter study had only 102 cases of renal cancer compared to our study, which had 210 cases of renal cell cancer, suggesting that that study lacked sufficient statistical power to detect a potential association.

Although the causes of renal cell cancer are poorly understood, smoking[7,8] and obesity[8,21] are established risk factors. A number of biological mechanisms explain why physical activity may protect against renal cell cancer. Most importantly, because energy expenditure is an important determinant of the development of weight gain and obesity, it is plausible that physical activity plays a protective role in the development of renal cell cancer. Support for the role of physical activity in the prevention of cancer comes from animal studies of calorie restriction. Data from animal models have shown that calorie restriction protects against tumorigenesis.[26,27] In addition, calorie restriction has been shown to reduce plasma insulin-like growth factor (IGF1).[28] Experimental evidence indicates that IGF-1 plays a role in renal cancer[29] and human renal carcinoma contains more insulin and IGF-1 receptors than adjacent normal kidney tissue.[30] Interestingly, epidemiological studies have reported that patients with diabetes have increased risk of renal cancer.[31] In addition, there is a well-known inverse relationship between exercise and diabetes.[32–34] Other potential mechanisms include modulation of the immune system,[35] and reduction in hypertension,[36] which would represent an intermediate variable, linking increased exercise to decrease risk of renal cell cancer.

To summarize, our study, the largest prospective study of physical activity and renal cell cancer reported to date, suggests a decreased risk of renal cell cancer with increased leisure-time physical activity.

We found that leisure-time physical activity apparently protects against renal cell cancer even beyond its effect on body weight, because the physical activity and renal cell cancer association persisted after adjustment for BMI. In contrast, our data indicated that occupational physical activity is not likely to prevent the incidence of renal cell cancer. Investigations into the mechanisms for the apparent protection provided by physical activity against renal cell cancer should be undertaken.

ACKNOWLEDGEMENT

Our study was supported in part by Public Health Service contracts N01 CN45165 and 45035 from the National Cancer Institute, National Institutes of Health and Human Services.

REFERENCES

1. Chow W-H, Devesa S, Warren J, Fraumeni J. Rising incidence of renal cell cancer in the United States. JAMA 1999;281:1628–31.
2. Black R, Bray F, Ferlay J, Parkin D. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997;33:1075–107.
3. Liu S, Semenciw R, Morrison H, Schanzer D, Mao Y. Kidney cancer in Canada: the rapidly increasing incidence of adenocarcinoma in adults and seniors. Can J Public Health 1997;88:99–104.
4. Parkin D, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827–41.
5. McLaughlin J, Blot W, Devesa S, Fraumeni J. Renal cancer. In: Schottenfeld D, Fraumeni JF. Cancer epidemiology and prevention, 2nd ed. New York: Oxford University Press, 1996. p 1142–55.
6. Landis S, Murray T, Bolden S, Wingo P. Cancer statistics, 1999. CA Cancer J Clin 1999;49:8–31.
7. Yuan J, Castelao J, Gago-Dominguez M, Yu M, Ross R. Tobacco use in relation to renal cell carcinoma. Cancer Epidemiol Biomarkers Prev 1998;7:429–33.
8. Bergstrom A, Hsieh C-C, Lindbald P, Lu C-M, Cook N, Wolk A. Obesity and renal cell cancer: a quantitative review. Br J Cancer 2001;85:984–90.
9. Goodman M, Morgenstern H, Wynder E. A case-control study of factors affecting the development of renal cell cancer. Am J Epidemiol 1986;124:926–41.
10. Lindblad P, Wolk A, Bergstrom R, Persson I, Adami H-O. The role of obesity and weight fluctuations in the etiology of renal cell cancer: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 1994;3:631–9.
11. Mellemgaard A, Engholm G, McLaughlin J, Olsen J. Risk factors for renal-cell carcinoma in Denmark. III. Role of weight, physical activity and reproductive factors. Int J Cancer 1994;2:66–71.
12. Mellemgaard A, Lindbald P, Schlehofer B, Bergstrom R, Mandel J, McCredie M, McLaughlin J, Niwa S, Odaka N, Pommer W. International renal-cell cancer study. III. Role of weight, height, physical activity, and use of amphetamines. Int J Cancer 1995;60:350–4.
13. Paffenbarger R, Hyde R, Wing A. Physical activity and incidence of cancer in diverse populations: a preliminary report. Am J Clin Nutr 1987;45:312–7.
14. Bergstrom A, Moradi T, Lindbald P, Nyren O, Adami H-O, Wolk A. Occupational physical activity and renal cell cancer: a nationwide cohort study in Sweden. Int J Cancer 1999;83:186–91.
15. Bergstrom A, Terry P, Lindblad P, Ahlbom A, Feychting M, Wolk A. Physical activity and risk of renal cell cancer. Int J Cancer 2001;92:155–7.
16. The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. Ann Epidemiol 1994;4:1–10.
17. Korhonen P, Malila N, Pukkala E, Teppo L, Albanes D, Virtamo J. The Finnish Cancer Registry as follow-up source of a large trial cohort. Acta Oncol 2002;41:381–8.
18. Tanasescu M, Leitzmann M, Rimm E, Willett W, Stampfer M, Hu F. Exercise type and intensity in relation to coronary heart disease in men. JAMA 2002;288:1994–2000.
19. Manson J, Rimm E, Stampfer M, Colditz G, Willett W, Krolewski A, Rosner B, Hennekens C, Speizer F. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 1991;338:774–8.
20. Colbert L, Hartman T, Malila N, Limburg P, Pietinen P, Virtamo J, Taylor P, Albanes D. Physical activity in relation to cancer of the colon and rectum in a cohort of male smokers. Cancer Epidemiol Biomarkers Prev 2001;10:265–8.
21. Moyad M. Review of potential risk factors for kidney (renal cell) cancer. Semin Urol Oncol 2001;19:280–93.
22. Hu J, Mao Y, White K, The Canadian Cancer Registires. Renal cell carcinoma and occupational exposure to chemicals in Canada. Occup Med 2002;52:157–64.
23. Pukkala E. Cancer incidence among Finnish oil refinery workers, 1971–1994. J Occup Environ Med 1998;40:675–9.
24. Mandel J, McLaughlin J, Schlehofer B, Mellemgaard A, Helmert U, Lindblad P, McCredie M, Adami H-O. International renal cell cancer study. IV. Occupation. Int J Cancer 1995;61:601–5.
25. McLaughlin J, Chow W-H, Mandel J, Mellemgaard A, McCredie M, Lindblad P, Schlehofer B, Pommer W, Niwa S, Adami H-O. International renal cell cancer study. VIII. Role of diuretics, other antihypertensive medications and hypertension. Int J Cancer 1995;63:216–21.
26. Hursting S, Perkins S, Phang J. Calorie restriction delays spontaneous tumorigenesis in p53-knockout transgenic mice. Proc Natl Acad Sci USA 1994;91:7036–40.
27. Berrigan D, Perkins S, Haines D, Hursting S. Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice. Carcinogenesis 2002;23:817–22.
28. Dunn S, Kari F, French J, Leninger J, Travlos G, Wilson R, Barrett J. Dietary restriction reduces insulin-like growth factor 1 levels, which

modulates apoptosis, cell proliferation, and tumor progression in p53 deficient mice. Cancer Res 1997;57:4667–72.
29. Stadler W, Vogelzang N. Human renal cancer carcinogenesis: a review of recent advances. Ann Oncol 1993;4:451–62.
30. Kellerer M, von-Eye-Corleta H, Muhlhofer A, Capp E, Mosthaf L, Bock S, Petrides P, Harring H. Insulin- and insulin-like growth-factor-I receptor tyrosine-kinase activities in human renal carcinoma. Int J Cancer 1995;62:501–7.
31. Sclehhofer B, Pommer W, Mellemgaard A, Stewart J, McCredie M, Niwa S, Lindblad P, Mandel J, McLaughlin J, Wahrendorf J. International renal cell cancer study. VI. The role of medical and family history. Int J Cancer 1996;66:723–6.
32. American Diabetes Association. Physical activity/exercise and diabetes mellitus. Position statement. Diabetes Care 2003;26:S73–7.
33. Hu F, Leitzmann M, Stampfer M, Colditz G, Willett W, Rimm E. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med 2001;161:1542–8.
34. Chakravarthy M, Joyner M, Booth F. An obligation for primary care physicians to prescribe physical activity to sedentary patients to reduce the risk of chronic health conditions. Mayo Clin Proc 2002; 77:165–73.
35. Woods J, Lowder T, Keylock K. Can exercise training improve immune function in the aged? Ann NY Acad Sci 2002;959:117–27.
36. Ohkubo T, Hozawa A, Nagatomi R, Fujita K, Sauvaget C, Watanabe Y, Anzai Y, Tamagawa A, Tsuji I, Imai Y, Ohmori H, Hisamichi S. Effects of exercise training on home blood pressure values in older adults: a randomized controlled trial. J Hypertens 2001;19:1045–52.