Obesity, High Energy Intake, Lack of Physical Activity, and the Risk of Kidney Cancer

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Abstract

The authors conducted a population-based case-control study of 810 cases with histologically confirmed incident kidney cancer and 3,106 controls to assess the effect of obesity, energy intake, and recreational physical activity on renal cell and non–renal cell cancer risk in Canada from 1994 to 1997. Compared with normal body mass index (BMI; 18.5 to <25.0 kg/m^2), obesity (BMI, ≥30.0 kg/m^2) was associated with multivariable-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of 2.57 (2.02-3.28) for renal cell cancer and 2.79 (1.70-4.60) for non–renal cell cancer. The OR (95% CI) associated with the highest quartiles of calorie intake was 1.30 (1.02-1.66) for renal cell cancer and 1.53 (0.92-2.53) for non–renal cell cancer. Compared with the lowest quartile of total recreational physical activity, the highest quartile of total activity was associated with an OR (95% CI) of 1.00 (0.78-1.28) and 0.79 (0.46-1.36) for the two subtypes. There were no apparent differences between men and women about these associations. The influence of obesity and physical activity on the risk of renal cell and non–renal cell cancer did not change by age, whereas the effect of excess energy intake was stronger among older people. No significant effect modifications of physical activity on BMI among both genders and of energy intake on BMI among men were observed, with a synergic effect of obesity and high energy intake on renal cell cancer risk found among women. This study suggests that obesity and excess energy intake are important etiologic risk factors for renal cell and non–renal cell cancer. The role of physical activity needs further investigation. (Cancer Epidemiol Biomarkers Prev 2006;15(12):2453–60)

Introduction

The incidence of kidney cancer has been increasing in Canada (1). In 2006, there were an ~4,600 new cases of kidney cancer and 1,550 kidney cancer deaths in Canada (1). From 1992 to 2001, the average annual percentage change in age-standardized incidence for kidney cancer was 0.5 for males and 0.8 for females (1). Similar trends have been observed worldwide (2, 3). Although diagnostic improvements can explain some of the increases, increasing levels of obesity in modern society may have contributed to these trends (4-8). Obesity has become an epidemic (6-8). The rapidly increasing prevalence of obesity is a driving force for the modern epidemic of many chronic diseases, including several cancers (9-11).

More than 80% of kidney cancers arise from the renal parenchyma (renal cell carcinoma), whereas the remainder is from the renal pelvis, which consists mainly of transitional cell carcinoma (12-14). Renal cell carcinoma is one of the cancer sites that have been most consistently observed to be associated with obesity (15, 16). However, there is very little in the literature about the relationship of obesity, energy intake, and physical activity with renal pelvis cancer.

Obesity is caused by increased energy intake and/or decreased energy expenditure. Consequently, it is logical to examine the effects of obesity, high energy intake, and reduced physical activity on the risk of kidney cancer simultaneously. However, previous studies assessing the associations of energy intake and physical activity with the risk of kidney cancer have yielded inconsistent results (15, 17-22). Many previous studies have been hampered by inadequate sample size, especially given the need to adjust for many confounding factors simultaneously and to assess the potential effect modifications of energy intake and physical activity on obesity. The objective of this study was to examine the effects of obesity, energy intake, and recreational physical activity on the risk of kidney cancer, overall and by subtype, and the possible effect modification of energy intake and physical activity on obesity, using data from a large population-based case-control study in Canada.

Materials and Methods

The National Enhanced Cancer Surveillance System. This study was based on data collected by the National Enhanced Cancer Surveillance System (NECSS). NECSS was a multicomponent, collaborative project of Health Canada and the provincial cancer registries. The case-control component included individual data from 21,020 Canadians with 1 of 19 types of cancers and 5,039 population controls ages 20 to 76 years, which were collected between 1994 and 1997 in 8 of the 10 Canadian provinces (Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan). The respective ethics review boards of each province reviewed and approved the study proposal. The current analysis was based on 810 incident cases of kidney cancer and 3,106 controls from all eight provinces, except Ontario, because Ontario did not collect information on duration of each physical activity, which was needed in our calculation of physical activity index.

The population-based provincial cancer registries identified kidney cases through a review of pathology reports. All cases were histologically confirmed incident kidney patients, newly diagnosed between 1994 and 1997 in the seven participating provinces. The cancer registries tried to identify cases as soon as possible after diagnosis to reduce the loss of subjects caused by severe illness and death. The registries

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identified 1,304 kidney cancer cases. Physicians refused consent to contact the cases for 87 (6.7%) subjects, and 130 (10.0%) cases had died before they could be sent questionnaires. Questionnaires were sent to 1,187 cases; 810 cases completed and returned the questionnaires, representing 68.2% of cases who were sent questionnaires and 62.1% of ascertained cases.

The morphologic data were derived from pathology reports and coded using the *International Classification of Diseases for Oncology, Second Edition* (ICD-O-2). The histologic subtypes of kidney cancer were based on ICD-O-2 morphology coding and grouped into two categories: renal cell and non–renal cell.

In NECSS, frequency matching to the overall case group (19 types of cancers) was used to select population controls with similar age and sex distribution, so that there would be at least one control for every case within each sex and 5-year age group for any specific cancer site within each province. The sampling strategy for control selection varied by province, depending on data availability, data quality (completeness and timeliness), and the confidentiality restrictions of provincial databases. Prince Edward Island, Nova Scotia, Manitoba, Saskatchewan, and British Columbia used provincial health insurance plans to get a random sample of the provincial population stratified by age group and sex. More than 95% of Canadians are covered by these public plans, and individuals are excluded only if covered through other federal plans. Newfoundland and Alberta used similar random digit dialing protocols to obtain population samples.

The provincial cancer registries recruited 5,107 subjects without cancer in the seven participating provinces studied and mailed these subjects the same questionnaires as those sent to cases. Questionnaires were returned for 81 (1.6%) controls because of a wrong or old address, and no updated address could be found. A total of 3,106 controls completed and returned questionnaires, representing 60.8% of the ascertained controls.

Data collection. The provincial registries collected data by self-administered questionnaires, with telephone follow-up when necessary for clarification and completeness.

The questionnaires were designed to obtain detailed data on risk factors for cancers. The questionnaires collected information on education, average family income over the last 5 years, marital status, ethnic group, height, weight, physical activity, alcohol consumption, diet (69-item food frequency questions), and vitamin and mineral supplements 2 years before interview. Questionnaires also gathered information about smoking history, menstrual and reproductive history, employment history, residential history, and history of occupational exposure to some specific chemicals.

Assessment of obesity and energy intake. Participants in the study reported their adult height and weight 2 years before interview. As a measure of overweight and obesity, body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. Based on WHO standards, obesity was defined as a BMI of 30 kg/m^2 or more, and overweight was defined as a BMI between 25 and <30 kg/m^2 for both sexes (8). Obesity was further categorized as class I (BMI, 30 to <35), class 2 (BMI, 35 to <40), and class 3 (BMI, $\geq$40).

The questionnaire asked subjects the usual frequency for each of the 69-food items (in specified portion size) 2 years before interview. We calculated weekly intake of calories for each item by multiplying the quantity of each item weekly with the associated calorie value, which is determined from food composition data using the Nutrient Value of Some Common Foods (23). We summed the weekly calorie intake for all 69 items to obtain the total calorie intake.

Assessment of physical activity. The questionnaire gathered information on recreational physical activity 2 years before interview. Respondents were asked, in which seasons, how often and how long per session, on average, they participated in each of the 12 most common types of leisure time physical activity in Canada. Individual activities included walking for exercise, jogging or running, gardening or yard work, home exercise or exercise class, golf, racquet sports, bowling or curling, swimming or water exercise, skiing or skating, bicycling, social dancing, and other strenuous exercise. Respondents indicated their usual frequency of participating in each of the above activities by choosing one of the following categories: never, less than once monthly, one to three times monthly, one to two times weekly, three to six times weekly or every day. Time per session was recorded as <15 min, 15 to 30 min, 31 to 60 min, and >60 min. We estimated the intensity of each activity by assigning a specific metabolic equivalent task (MET) value to each reported activity. The MET values used here were abstracted from the Compendium of Physical Activities (24, 25). A MET is defined as the ratio of the associated metabolic rate for a specific activity compared with the resting metabolic rate (26). One MET is the average seated resting energy cost for an adult and is set at 3.5 mL/kg/min oxygen. A weekly number of MET-hours was derived for each activity by combining frequency, duration, and MET value (intensity) of each activity. The variable used in the analysis was the sum of each category of physical activity.

Statistical analysis. We estimated risks of kidney cancer associated with obesity, energy intake, and recreational physical activity based on odds ratios (OR) and corresponding 95% confidence intervals (95% CI), using unconditional logistic regression with the software package SAS (version 8, SAS Institute, Inc., Cary, North Carolina). Energy intake and total physical activity were categorized into quartiles based on the distribution of the variables in the control population.

Because cases and controls were not directly matched, the methods for identifying cases and controls varied by province, and age is associated with kidney cancer risk; all logistic regression analyses were controlled for province of residence and age to remove the effect of any uneven distribution of these two factors between cases and controls. We used the change-in-point-estimate approach to assess the potential confounding effect of a wide range of factors, including age, educational level, family income adequacy, marital status, alcohol consumption, smoking, BMI, total calorie intake, physical activity, menopausal status, and number of live births. We retained variables in the final models that are considered biologically important, if inclusion of these variables in the models changed the OR estimate in an appreciable degree, regardless of the statistical significance. We adjusted the final multivariate models for age (years, continuous), province of residence, education (years, continuous), total vegetable intake (servings weekly, continuous), smoking pack-years (continuous), and self-reported exposure to pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs (yes and no). BMI, total calorie intake, and physical activity were adjusted to each other. We conducted tests for trends for all models of categorized data by treating the different categories as a single ordinal variable. A total of 15 cases and 55 controls were deleted from the multivariate analyses because of missing values.

Because the risk factors for kidney cancer may differ by subtype, we conducted stratified analysis by subtype of kidney cancer. We also examined whether the risks associated with BMI, total calorie intake, and physical activity vary by age. To assess whether the effects of BMI on kidney cancer risk were modified by calorie intake and physical activity, we did stratified analysis by calorie intake and physical activity.

Results

Data from 810 kidney cancer cases and 3,106 controls were available for analysis. Majority (680) of the 810 kidney cancer cases were renal cell cancer, with non–renal cell cancer cases constitute the remaining 130 cases.

Table 1 shows the distribution of some selected characteristics of kidney cancer cases and controls. For both genders combined, compared with controls, cases were slightly older, had lower education level, tended to have higher total calorie intake, had longer smoking pack-years, were more likely to be ex-smokers or current smokers, and exposed to several chemicals (pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs) than controls. For men and women separately, the distribution of these variables among cases and controls was similar to that for both genders combined, except male cases consumed less vegetable than controls.

Table 2 presents risks of kidney cancer associated with BMI, calorie intake, and recreational physical activity by histology subtype. Obese (BMI, $\geq$30 kg/m^2) people had multivariable adjusted OR (95% CI) of 2.57 (2.02-3.28) for renal cell cancer and 2.79 (1.70-4.60) for non–renal cell cancer, compared with those with a BMI of 18.5 to <25 kg/m^2. Although the numbers of subjects became quite small and the OR estimates became unstable when risk estimates were made according to class of obesity, there were still increasing trends in risk associated with higher obesity class (data not shown). People in the highest quartile of calorie intake had an increased OR (95% CI) of 1.30 (1.02-1.66) for renal cell cancer and 1.53 (0.92-2.53) for non–renal cell cancer. Compared with the lowest quartile of total activity, highest quartile of total activity was associated with multivariable-adjusted ORs (95% CIs) of 1.00 (0.78-1.28) for renal cell cancer and 0.79 (0.46-1.36) for non–renal cell cancer.

Table 3 presents risks of kidney cancer associated with BMI, calorie intake, and recreational physical activity, by gender and by histology subtype. Similar patterns of associations of BMI and calorie intake with renal cell and non–renal cell cancer were observed for both men and women. For women, highest quartile of total activity was associated with a nonsignificant decrease in OR for both renal cell and non–renal cell cancer compared with the lowest quartile of total activity.

We also examined whether the relationships of renal cell and non–renal cell cancer risk with BMI, total calorie intake, and physical activity varied by age group (age, <50, 50 to <65, and $\geq$65 years; Table 4). Risks of renal cell cancer associated with BMI and physical activity did not vary significantly by age; however, the risk associated with total calorie intake was considerably higher among people ages 65 years or older than younger people. Because of the small number of non–renal cell cancer cases, the risk estimates became unstable.

We then assessed the effect of BMI on renal cell and non–renal cell cancer risk, stratified by gender and by calorie intake and total recreational physical activity (Tables 5 and 6). For renal cell cancer, there was no significant effect modification of total physical activity on obesity for both genders and of calorie intake on obesity among men, whereas a higher risk associated with obesity was observed among female subjects

Table 1. Selected characteristics of cases with kidney cancer and controls, NECSS, Canada, 1994-1997

Characteristic	Men			Women			Men and women		
	Cases (n = 446)	Controls (n = 1,642)	P	Cases (n = 364)	Controls (n = 1,464)	P	Cases (n = 810)	Controls (n = 3,106)	P
Age (y), mean (SD)	58.7 (10.6)	57.9 (14.6)	0.22	57.9 (11.3)	56.2 (12.2)	0.013	58.3 (10.9)	57.1 (13.5)	0.008
20-24 (%)	0.2	2.2		0.3	1.3		0.3	1.8	
25-29 (%)	0.0	3.8		0.8	1.6		0.4	2.8	
30-34 (%)	1.8	4.9		2.2	2.5		2.0	3.8	
35-39 (%)	2.7	5.9		5.5	4.1		3.9	5.0	
40-44 (%)	7.4	4.2		3.6	8.1		5.7	6.0	
45-49 (%)	9.2	4.1		9.6	11.5		9.4	7.6	
50-54 (%)	11.9	5.9		14.6	11.6		13.1	8.6	
55-59 (%)	14.8	8.8		14.3	13.5		14.6	11.0	
60-64 (%)	15.0	14.2		15.1	15.4		15.1	14.8	
66-69 (%)	20.0	21.3		17.0	16.2		18.6	18.9	
70-76 (%)	17.0	24.6		17.0	14.3		17.0	19.8	
Province of residence (%)									
Newfoundland	6.3	7.6		7.4	8.0		6.8	7.8	
Prince Edward Island	2.9	5.0		2.5	9.4		2.7	7.1	
Nova Scotia	9.2	20.5		11.3	16.3		10.1	18.5	
Manitoba	12.3	9.5		11.5	10.5		12.0	10.0	
Saskatchewan	9.6	9.0		10.4	8.5		10.0	8.8	
Alberta	25.6	19.9		32.4	19.9		28.6	19.9	
British Columbia	34.1	28.5		24.5	27.5		29.8	28.0	
Educational level (y), mean (SD)	11.4 (3.7)	11.8 (4.0)	0.048	11.5 (3.4)	11.9 (3.2)	0.046	11.5 (3.6)	11.9 (3.7)	0.005
Alcohol drinking (servings/wk), mean (SD)	6.4 (10.5)	6.4 (11.1)	0.94	2.2 (5.3)	2.4 (5.4)	0.44	4.5 (8.8)	4.5 (9.1)	0.99
Total calorie intake (kcals/wk), mean (SD)	14,590 (8,722)	14,047 (5,748)	0.11	13,264 (4,817)	12,896 (7,177)	0.24	13,993 (7,257)	13,505 (6,486)	0.082
Vegetable consumption (servings/wk), mean (SD)	18.3 (9.9)	19.4 (12.4)	0.045	21.5 (15.8)	21.3 (15.8)	0.75	19.8 (12.7)	20.3 (14.1)	0.30
Pack-years, mean (SD)	22.7 (24.3)	21.4 (24.3)	0.33	11.9 (16.2)	9.6 (15.3)	0.013	17.9 (21.7)	15.8 (21.4)	0.019
Smoking status (%)									
Never smoked	24.4	25.6		45.3	48.6		33.8	36.4	
Ex-smoker	52.2	49.7		31.6	31.5		43.0	41.1	
Current smoker	23.3	24.7		23.1	19.9		23.2	22.5	
Chemical exposure (%)*									
Yes	50.9	40.0		12.6	11.8		33.7	26.7	
No	49.1	60.0		87.4	88.2		66.3	73.3	

*Self-reported exposure to pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs.

Table 2. Risk of kidney cancer associated with recreational physical activity, BMI, and energy intake, by histologic subtype, NECSS, Canada, 1994-1997

Variable	Controls (*n*)	Renal cell			Non–renal cell		
		Cases (*n*)	Province- and age- adjusted OR (95% CI)	Multivariable-adjusted* OR (95% CI)	Cases (*n*)	Province- and age- adjusted OR (95% CI)	Multivariable-adjusted* OR (95% CI)
BMI (kg/m^2)							
18.5 to <25	1,399	195	1.00	1.00	39	Ref	Ref
<18.5	63	10	1.13 (0.57-2.26)	1.19 (0.60-2.38)	1	0.54 (0.07-4.03)	0.51 (0.07-3.85)
25 to <30	1,178	314	1.94 (1.60-2.37)	1.89 (1.55-2.32)	57	1.85 (1.22-2.82)	1.85 (1.20-2.84)
≥30	450	157	2.64 (2.08-3.36)	2.57 (2.02-3.28)	32	2.97 (1.82-4.84)	2.79 (1.70-4.60)
P_{trend}			<0.0001				
Total calorie intake (kcals/wk)							
<10,166	774	153	1.00	1.00	30	Ref	Ref
10,166 to <12,762	776	167	1.11 (0.88-1.42)	1.10 (0.85-1.41)	27	0.92 (0.54-1.56)	0.98 (0.57-1.69)
12,762 to <15,895	775	160	1.07 (0.84-1.36)	1.07 (0.83-1.37)	33	1.13 (0.68-1.88)	1.22 (0.72-2.06)
≥15,895	774	199	1.37 (1.08-1.73)	1.30 (1.02-1.66)	40	1.47 (0.90-2.39)	1.53 (0.92-2.53)
P_{trend}			0.018				
Physical activity (MET-hour/wk)							
<6.3	778	169	1.00	1.00	32	Ref	Ref
6.3 to <17.0	776	170	0.95 (0.75-1.21)	0.98 (0.77-1.26)	41	1.13 (0.70-1.83)	1.17 (0.72-1.91)
17.0 to <34.4	776	167	0.91 (0.72-1.16)	0.98 (0.77-1.26)	28	0.76 (0.45-1.29)	0.84 (0.50-1.44)
≥34.4	776	174	0.95 (0.75-1.21)	1.00 (0.78-1.28)	29	0.76 (0.45-1.28)	0.79 (0.46-1.36)
P_{trend}			0.62				

*OR adjusted for age, province, gender, education, smoking pack-years, vegetable intake, and self-reported exposure to pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs. Physical activities, BMI, and total calorie intake are adjusted for each other.

with medium and high calorie intake than those with low calorie intake (the *P* values for interaction between BMI and calorie intake in women were 0.021). For non–renal cell cancer, there was no significant effect modification of total activity and of calorie intake on obesity among both men and women, but the assessment was based on very small samples.

Discussion

Our large population-based study indicated that obesity was associated with an increased risk of renal cell and non–renal cell cancer for both genders. The obesity-related increase in kidney cancer risk remained virtually unchanged after simultaneously adjusted for total energy intake and total recreational physical activity. High calorie intake was also independently associated with an increased risk of renal cell and non–renal cell cancer for both genders, with a magnitude smaller than the association between obesity and renal cell and non–renal cell cancer risk. However, recreational physical activity was not independently related to the risk of renal cell and non–renal cell cancer. The pattern about these associations was similar for renal cell and non–renal cell cancer. The risks associated with BMI and physical activity did not vary by age, but the risk associated with total calorie intake was higher among people ages 65 years or older than younger people. There was a synergic effect of obesity and excess calorie intake on the risk of renal cell cancer among women.

The increased risk of renal cell cancer associated with obesity observed in our study is consistent with most previous

Table 3. Risk of kidney cancer with recreational physical activity, BMI, and energy intake, by sex and by histology subtype, NECSS, Canada, 1994-1997

Men						Women					
Variable	Controls	Renal cell		Non–renal cell		Variable	Controls	Renal cell		Non–renal cell	
		Cases	OR (95% CI)*	Cases	OR (95% CI)*			Cases	OR (95% CI)*	Cases	OR (95% CI)*
BMI (kg/m^2)											
18.5-<25	621	84	1.00	17	1.00	18.5 to <25	778	111	1.00	22	1.00
<18.5	19	3	1.46 (0.41-5.13)	0	—	<18.5	44	7	1.13 (0.49-2.60)	1	—
25-<30	755	209	2.05 (1.55-2.72)	34	1.71 (0.93-3.11)	25 to <30	423	105	1.68 (1.24-2.27)	23	1.81 (0.98-3.35)
≥30	236	79	2.57 (1.80-3.66)	18	3.22 (1.59-6.50)	≥30	214	78	2.56 (1.82-3.58)	14	2.23 (1.09-4.55)
*P*trend			<0.0001		0.001	P_{trend}			<0.0001		0.017
Total calorie intake (kcals/wk)											
<10,503	410	83	1.00	16	1.00	<9,784	365	65	1.00	15	1.00
10,503 to <13,289	409	90	1.14 (0.81-1.61)	12	0.95 (0.43-2.11)	9,784 to <12,344	365	85	1.36 (0.94-1.97)	15	1.06 (0.50-2.26)
13,289 to <16,672	409	102	1.32 (0.93-1.87)	17	1.45 (0.68-3.10)	12,344 to <15,107	366	65	1.00 (0.68-1.48)	11	0.80 (0.35-1.81)
≥16,672	410	100	1.35 (0.93-1.95)	25	2.50 (1.18-5.30)	≥15,107	365	89	1.42 (0.99-2.05)	19	1.49 (0.72-3.04)
P_{trend}			0.085		0.008	P_{trend}			0.19		0.39
Physical activity (MET-hour/wk)											
<6.4	411	86	1.00	16	1.00	<6.1	366	78	1.00	16	1.00
6.4 to <19.1	410	96	1.11 (0.80-1.55)	20	1.28 (0.64-2.55)	6.1 to <15.2	366	83	1.02 (0.71-1.46)	20	1.12 (0.56-2.27)
19.1 to <37.4	410	84	0.99 (0.70-1.40)	13	0.84 (0.39-1.79)	15.2 to <31.4	366	82	1.12 (0.78-1.62)	13	0.76 (0.35-1.66)
≥37.4	411	110	1.21 (0.86-1.69)	21	1.18 (0.58-2.39)	≥31.4	366	61	0.80 (0.54-1.18)	11	0.63 (0.28-1.43)
P_{trend}			0.39		0.43	P_{trend}			0.39		0.17

*OR adjusted for age, province, education, smoking pack-years, vegetable intake, and self-reported exposure to pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs. Physical activities, BMI, and total calorie intake are adjusted for each other.

Table 4. Risk of kidney cancer associated with recreational physical activity, BMI, and energy intake, by age group (years), NECSS, Canada, 1994-1997

Histologic subtype	Variable	Age, <50			Age, 50 to <65			Age, ≥65		
		Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*
Renal cell	BMI (kg/m^2)									
	18.5 to <25	51	443	1.00	74	466	1.00	70	490	1.00
	<18.5	4	23	2.06 (0.65-6.55)	5	13	2.33 (0.79-6.87)	1	27	0.26 (0.03-1.95)
	25 to <30	62	270	1.80 (1.16-2.81)	134	394	2.14 (1.54-2.96)	118	514	1.62 (1.16-2.26)
	≥30	26	100	1.90 (1.09-3.29)	80	187	2.80 (1.92-4.07)	51	163	2.30 (1.51-3.51)
	P_{trend}			0.004			<0.0001			<0.0001
	Total calorie intake (kcals/wk)									
	<10,166	34	208	1.00	72	272	1.00	47	294	1.00
	10,166 to <12,762	40	192	1.27 (0.74-2.16)	68	265	0.92 (0.62-1.36)	59	318	1.15 (0.75-1.76)
	12,762 to <15,895	32	210	0.99 (0.57-1.71)	74	277	0.96 (0.65-1.42)	54	288	1.16 (0.74-1.80)
	≥15,895	38	227	1.09 (0.64-1.87)	81	250	1.05 (0.71-1.55)	80	298	1.70 (1.13-2.56)
	P_{trend}			0.99			0.75			0.011
	Physical activity (MET-hour/wk)									
	<6.3	34	185	1.00	72	262	1.00	63	331	1.00
	6.3 to <17.0	38	216	1.01 (0.59-1.72)	71	271	0.94 (0.63-1.38)	61	289	1.09 (0.73-1.64)
	17.0 to <34.4	32	194	0.84 (0.48-1.48)	77	296	0.99 (0.67-1.45)	58	286	1.04 (0.69-1.56)
	≥34.4	40	244	0.92 (0.53-1.59)	75	237	1.08 (0.73-1.61)	59	295	1.04 (0.68-1.59)
	P_{trend}			0.64			0.63			0.91
Non–renal cell	BMI (kg/m^2)									
	18.5 to <25	11	443	1.00	15	466	1.00	13	490	1.00
	25 to <30	13	270	1.84 (0.78-4.32)	24	394	1.97 (1.00-3.87)	20	514	1.70 (0.80-3.58)
	≥30	7	100	2.97 (1.08-8.15)	11	187	1.85 (0.81-4.22)	14	163	3.86 (1.69-8.80)
	P_{trend}			0.028			0.088			0.002
	Total calorie intake (kcals/wk)									
	<10,166	5	208	1.00	14	272	1.00	11	294	1.00
	10,166 to <12,762	7	192	1.83 (0.55-6.09)	11	265	0.80 (0.34-1.85)	9	318	0.75 (0.30-1.88)
	12,762 to <15,895	9	210	2.08 (0.66-6.58)	13	277	0.90 (0.40-2.03)	11	288	1.03 (0.41-2.56)
	≥15,895	10	227	2.19 (0.70-6.88)	13	250	1.03 (0.45-2.33)	17	298	1.72 (0.76-3.86)
	P_{trend}			0.18			0.89			0.12
	Physical activity (MET-hour/wk)									
	<6.3	5	185	1.00	9	262	1.00	18	331	1.00
	6.3 to <17.0	13	216	1.98 (0.67-5.85)	17	271	1.80 (0.76-4.25)	11	289	0.62 (0.27-1.39)
	17.0 to <34.4	7	194	1.26 (0.38-4.23)	11	296	1.07 (0.42-2.70)	10	286	0.65 (0.28-1.47)
	≥34.4	6	244	0.78 (0.22-2.74)	14	237	1.43 (0.58-3.53)	9	295	0.60 (0.25-1.41)
	P_{trend}			0.38			0.79			0.23

*OR adjusted for age, province, gender, education, smoking pack-years, vegetable intake, and self-reported exposure to pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs. Physical activities, BMI, and total calorie intake are adjusted for each other.

studies (15, 16, 18, 27-36). A meta-analysis estimated a summary relative risk of 1.07 (95% CI, 1.05-1.09) per 1-kg/m^2 increase in BMI in both men and women (16). This association was confirmed in a Netherlands Cohort Study on Diet and Cancer consisting of 120,852 men and women ages 55 to 69 years: relative risk, 1.07 (95% CI, 1.02-1.12) per 1-kg/m^2 increase in BMI (15). Most studies have observed an association between BMI and renal cell cancer in both men and women, although a few studies have found the association confined to men (33) or women (35, 36) and several studies included only men (34) or only women (18).

We found a positive association between renal cell cancer risk and high calorie intake for both genders. This finding is consistent with an international study (multicenter, population-based case-control study) on the association between diet and renal cell cancer risk with a sample of 1,185 incident pathologically confirmed cases (698 men and 487 women) and 1,526 controls (915 men and 611 women) frequency-matched to cases by sex and age (19). After adjustment for age, sex, study center, BMI, and smoking, the investigators found a statistically significant positive association between total energy intake and renal cell cancer (relative risk, 1.7; 95% CI, 1.4-2.2 for the highest versus lowest quartile; ref. 19). A population-based case-control study of 351 cases and 340 controls, which was included in the above international study, also observed a positive association between the risk of renal cell cancer and total energy intake (17). On the other hand, two cohort studies failed to find an association between high energy intake and renal cell cancer risk (15, 18). Although the sample size of the two cohort studies are quite large: 120,852 men and women (9.3 years of follow-up) in the Netherlands Cohort Study (15) and 35,192 postmenopausal (predominantly White) women (8 years of follow-up) in the Iowa Surveillance, Epidemiology, and End Results Register Study (18), the incident renal cell cancer cases were 275 and 62, respectively, in the two cohort studies, only a fraction of renal cell cancer cases in our study and the international diet and renal cell cancer study (19).

Our study did not find a significant association between physical activity and renal cell cancer risk, although there was a nonsignificant decrease in risk associated with higher level of recreational physical activity among women. This is in line with previous studies (15, 20, 21, 29, 36, 37). Two studies also found no association with occupational physical activity (22, 38). However, a large Swedish cohort study (39) and a case-control study (40) observed that occupational physical activity was inversely associated with renal cell cancer in men but not in women, and a small Finnish cohort study (41) found a nonsignificant association of kidney cancer risk with occupational physical activity. Another cohort study on male smokers also observed a nonsignificant relation of kidney cancer risk with leisure time physical activity (22). The measurement of physical activity is rather difficult in epidemiologic studies, and few measurement methods have been appropriately validated (42). As was the case in many previous studies of kidney cancer and physical activity, our study only examined recreational activities; the failure to include occupational and incidental physical activities introduced some degree of nondifferential misclassification that may have contributed to our failure to note an effect.

Table 5. Risk of kidney cancer associated with BMI by total caloric intake (kcals/wk; tertiles), Canada, 1994-1997

BMI (kg/m^2)	Low caloric intake			Medium caloric intake			High caloric intake			$P_{interaction}$
	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	
Women										
Renal cell										
<25.0	51	280	1.00	32	273	0.63 (0.39-1.02)	35	269	0.76 (0.48-1.21)	0.021
25.0 to <30.0	34	133	1.39 (0.84-2.31)	36	153	1.27 (0.77-2.09)	35	134	1.46 (0.89-2.40)	
≥30.0	17	72	1.25 (0.66-2.36)	25	61	2.51 (1.40-4.50)	36	81	2.56 (1.54-4.24)	
P_{trend}			0.32			0.004			0.0002	
Non–renal cell										
<25.0	7	280	1.00	7	273	2.81 (0.70-11.32)	9	269	3.56 (0.84-15.15)	0.99
25.0 to <30.0	6	133	2.86 (0.75-10.87)	9	153	3.09 (0.79-12.14)	8	134	6.23 (1.63-23.76)	
≥30.0	4	72	4.56 (0.92-22.54)	4	61	9.11 (2.20-37.73)	6	81	7.19 (1.69-30.66)	
P_{trend}			0.05			0.003			0.002	
Men										
Renal cell										
<25.0	27	221	1.00	31	205	1.37 (0.77-2.42)	29	213	1.42 (0.78-2.59)	0.62
25.0 to <30.0	63	249	2.22 (1.34-3.66)	64	266	2.06 (1.23-3.46)	81	237	3.52 (2.07-5.96)	
≥30.0	25	70	3.43 (1.80-6.54)	22	72	2.65 (1.38-5.07)	32	94	3.55 (1.91-6.58)	
P_{trend}			<0.0001			0.0006			<0.0001	
Non–renal cell										
<25.0	3	221	1.00	7	205	1.08 (0.37-3.19)	7	213	1.39 (0.50-3.84)	0.52
25.0 to <30.0	10	249	2.17 (0.66-7.12)	9	266	2.10 (0.74-5.95)	15	237	2.16 (0.74-6.28)	
≥30.0	4	70	2.15 (0.58-7.95)	7	72	2.51 (0.68-9.21)	7	94	2.87 (0.91-9.07)	
P_{trend}			0.19			0.079			0.045	

*OR adjusted for age, province, education, total recreational physical activity, vegetable intake, smoking pack-years, and self-reported exposure to pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs.

We observed similar pattern between renal cell carcinoma and non–renal cell cancer about the relation to obesity, total energy intake, and physical activity, with positive independent associations with obesity and total energy intake. Because of the rareness of non–renal cell cancers, studies on non–renal cell cancer are sparse in the literature. Only two published studies have been found that have examined the association of obesity with renal pelvis cancer (34, 43), which observed no association. To our knowledge, there was no published study that assessed the relationship of the risk of non–renal cell cancer to total energy intake and physical activity.

The mechanisms for the link of kidney cancer risk with obesity, energy intake, and physical activity are complex (5, 44). Several hypotheses have been proposed for the underlying association. The first is through insulin-like growth factor-I (IGF-I; ref. 5). It has been observed that obese persons have higher IGF-I levels (45) and IGF-I can stimulate cell proliferation and inhibit apoptosis, both of which have been reported to be associated with tumor growth (46). High energy intake has been shown to increases IGF-I levels (46), but the effect of physical activity on IGF-I levels has not been observed consistently (45). The second mechanism has to do with the process of lipid peroxidation (47). Lipid peroxidation by-products can react with renal cell DNA to form adducts, which may result in mutations. Increased lipid peroxidation has been observed in obese subjects, and exercise can reduce lipid

Table 6. Risk of kidney cancer associated with BMI, by total recreational physical activity (MET-hour/wk; tertiles), Canada, 1994-1997

BMI (kg/m^2)	High physical activity			Medium physical activity			Low physical activity			$P_{interaction}$
	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	Cases	Controls	OR (95% CI)*	
Women										
Renal cell										
<25.0	34	302	1.00	46	285	1.47 (0.91-2.37)	38	235	1.67 (0.99-2.80)	0.17
25.0 to <30.0	37	132	2.33 (1.38-3.93)	32	138	1.88 (1.10-3.23)	36	153	2.36 (1.37-4.06)	
≥30.0	22	53	3.56 (1.89-6.71)	20	63	2.73 (1.44-5.18)	36	98	3.85 (2.21-6.72)	
P_{trend}			<0.0001			0.001			<0.0001	
Non–renal cell										
<25.0	6	302	1.00	11	285	2.12 (0.76-5.92)	6	235	1.44 (0.45-4.62)	0.82
25.0 to <30.0	5	132	1.96 (0.56-6.86)	7	138	2.15 (0.69-6.69)	11	153	3.73 (1.30-10.69)	
≥30.0	2	53	2.00 (0.37-10.97)	5	63	3.68 (1.04-12.98)	7	98	3.63 (1.15-11.47)	
P_{trend}			0.29			0.048			0.006	
Men										
Renal cell										
<25.0	36	231	1.00	20	217	0.56 (0.31-1.02)	31	192	1.03 (0.60-1.76)	0.91
25.0 to <30.0	78	247	1.77 (1.13-2.77)	64	257	1.61 (1.02-2.54)	67	251	1.73 (1.09-2.75)	
≥30.0	25	66	2.04 (1.11-3.74)	22	73	2.00 (1.07-3.73)	32	97	2.29 (1.31-4.00)	
P_{trend}			0.008			0.002			0.0007	
Non–renal cell										
<25.0	8	231	1.00	5	217	0.63 (0.20-1.98)	4	192	0.53 (0.15-1.87)	0.91
25.0 to <30.0	9	247	0.94 (0.35-2.50)	10	257	1.07 (0.41-2.81)	15	251	1.52 (0.61-3.82)	
≥30.0	5	66	1.98 (0.61-6.46)	9	73	3.44 (1.23-9.65)	4	97	1.06 (0.29-3.83)	
P_{trend}			0.36			0.036			0.370	

*OR adjusted for age, province, education, total energy intake, vegetable intake, smoking pack-years, and self-reported exposure to pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs.

peroxidation (47). Obesity has also been shown to be associated with the risk of hypertension and diabetes, both of which increase the risk of renal cell cancer (5, 34, 43, 48). Other potential mechanisms underlying the association between obesity and kidney cancer risk include higher estrogen level; elevated cholesterol level and down-regulation of low-density lipoprotein receptor; immune system dysfunction and dysregulation; and lower levels of vitamin D (5).

Limitations of our study should not be overlooked. Self-reported weight could introduce misclassification in the measurement of BMI (6), but the tendency of underreporting of weight by obese people would be nondifferential and tends to attenuate the estimates. Recall bias is possible among cases in their responses to questions on physical activity after a few months of cancer diagnoses. Another limitation is that we could not assess the effect of all physical activity because we did not collect information on incidental physical activity and we did not have a good summary estimate of occupational physical activity. Hypertension is an established risk factor for renal cell cancer, independent of obesity but correlated with obesity (5, 14, 31, 34, 43). We could not assess the influence of hypertension either as potential confounder or as an effect modifier because information on the history of hypertension was not available. The food frequency questionnaire inquired only 69 food items, and therefore, by not capturing all the foods Canadians consumed, should have modestly underestimated total energy intake. Again, however, the resulting misclassification should have been nondifferential. The diagnoses of histologic subtypes of kidney cancer were done by pathologists in the respective provinces rather than by a single expert pathologist; therefore, errors of histologic subtypes were possible. However, the proportion of renal cell to non–renal cell cancer in our study is comparable with the literature (13, 14, 34).

In summary, our population-based study shows that obesity and excess energy intake were important etiologic risk factors of kidney cancer, although recreational physical activity was not independently related to the risk of kidney cancer. Our study also suggests that these associations were similar between renal cell and non–renal cell cancer. Further investigations are warranted to confirm our results and to clarify the underlying mechanisms for these associations.

Appendix A. The Canadian Cancer Registries Epidemiology Research Group

The Canadian Cancer Registries Epidemiology Research Group comprises a principal investigator from each of the provincial cancer registries involved in the National Enhanced Cancer Surveillance System: Bertha Paulse, M.Sc., B.N., Newfoundland Cancer Foundation; Ron Dewar, M.A., Nova Scotia Cancer Registry; Dagny Dryer, M.D., Prince Edward Island Cancer Registry; Nancy Kreiger, Ph.D., Cancer Care Ontario; Erich Kliewer, Ph.D., CancerCare Manitoba; Diane Robson, B.A., Saskatchewan Cancer Foundation; Shirley Fincham, Ph.D., Division of Epidemiology, Prevention, and Screening, Alberta Cancer Board; and Nhu Le, Ph.D., British Columbia Cancer Agency.

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