ABSTRACT

Purpose: To examine kidney cancer incidence and mortality patterns since 1969 in Canada.
Method: Linear regression of the log rates was used to estimate secular trends by age group and sex, and age-period-cohort models were fitted to examine changes in kidney cancer and renal adenocarcinoma incidence rates.
Results: A substantial increase in incidence rates was observed among those 35 years and older, with average increases of 2.5% or more annually for both sexes. Age-period-cohort modelling suggested that much of this increase resulted from a period effect. Changes in mortality were much more modest, especially among those aged 0-34, for whom mortality rates actually declined by an average of 4.2% and 5.4% annually for males and females respectively.
Conclusions: Kidney cancer incidence rates have increased significantly, especially renal adenocarcinoma among adults and seniors. Diagnostic improvements and increasing levels of obesity in the Canadian population may have contributed to these trends.

ABRÉGÉ

Objectif : Étudier l'incidence du cancer du rein et les tendances de la mortalité au Canada depuis 1969.
Méthode : La régression linéaire des logarithmes de taux a été utilsée pour estimer les tendances générales en fonction des groupes d'âge et de sexe. Des modèles de cohorte par âge ont été ajustés en vue d'étudier la variation des taux d'incidence du cancer du rein et de l'adénocarcinome rénal.
Résultats : L'étude a révélé une augmentation importante du taux d'incidence chez les personnes âgées de 35 ans et plus. L'augmentation moyenne est de 2,5 % par an ou plus pour les deux sexes. Cette modélisation semble indiquer que l'augmentation des taux est due avant tout à un effet lié à des périodes. Les variations des taux de mortalité étaient beaucoup moins importantes, surtout chez les personnes âgées de 0 à 34 ans. Dans cette tranche d'âge, le taux de mortalité a diminué en moyenne de 4,2 % par an chez les hommes et de 5,4 % par an chez les femmes.
Conclusions : Les taux d'incidence du cancer du rein ont augmenté de façon significative, surtout ceux de l'adénocarcinome rénal chez les personnes d'âge moyen et les personnes âgées. Il est possible que de meilleures méthodes diagnostiques et un accroissement de l'obésité dans la population canadienne aient influé sur les tendances observées.

Kidney Cancer in Canada: The Rapidly Increasing Incidence of Adenocarcinoma in Adults and Seniors

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Although cancers of the kidney, renal pelvis and ureter are relatively uncommon, i.e., accounting for less than 2% of all cancers worldwide, incidence and mortality rates have been rising steadily in almost every country. Considerable international variations are observed, with a ten-fold difference in incidence, the lowest occuring in Asian populations, and the highest in Scandinavia and Canada as well as in American Caucasians.[1] Approximately 80% of primary kidney cancers are renal cell carcinomas of the renal parenchyma; most are adenocarcinomas. The remaining are primarily renal pelvis cancers, most of which are transitional cell carcinomas. Wilm's tumour is a malignant tumour of the kidney which occurs primarily in young children.[2,3]

Kidney cancer accounts for about 3% of all new cancers diagnosed in Canada, currently making this site the sixth most common cancer among men and the eighth among women.[4] The average annual percentage change in age-standardized incidence (1984-1991) is 2.5% for males and 2.3% for females. In 1996, there will be an estimated 4,050 new cases of kidney cancer and 1,350 deaths; 60% of new cases and deaths occur among men.[4]

This study was conducted to identify the incidence and mortality patterns of kidney cancer since 1969 in Canada, to determine the relative contributions to the observed increases of age, period and cohort by using an age-period-cohort Poisson regression model, and to discuss some possible risk factors.

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METHODS

Data source

Incidence data were obtained from the National Cancer Incidence Reporting System (NCIRS) of Statistics Canada, which collected data from provincial and territorial cancer registries from 1969-1991. In this paper, incidence data for Canada exclude Quebec, due to a change in registration procedures in Quebec starting in 1981. Mortality statistics were derived from data obtained from the Vital Statistics Section of the Canadian Centre for Health Information of Statistics Canada. Annual population estimates were obtained from the Demography Division of Statistics Canada. The study period was 1969 through 1991 for incidence and 1969 through 1993 for mortality.

Kidney cancer was coded using the 9th revision of the International Classification of Diseases (ICD)[5] rubric 189. Kidney cancer was defined to include malignant neoplasms of the kidney and other and unspecified urinary organs, i.e., ICD-9 rubrics 189.0 to 189.9. Histology was classified using the International Classification of Diseases for Oncology,[6] i.e., was categorized as transitional cell (ICDO 8120, 8123, 8130), adenocarcinoma (ICDO 814-838), Wilm's (ICDO 8960-8962), other (ICDO 801-998) and unknown (ICDO 800, 999). Provinces for which comparable histology data were available for the full study period included British Columbia, Saskatchewan and Ontario.

Statistical analysis

Age-standardized incidence and mortality rates for kidney cancer using the world population as standard were calculated. As a visual inspection indicated that a linear

model provided a good fit, trends starting from 1969 to 1991 for incidence and from 1969 to 1993 for mortality were modelled using a linear regression on the logarithm of the annual rates, of which secular trends were tested by using t-test. In the linear regression model, ß is the estimated coefficient and the average annual percent change is derived from [exp (ß)-1]x100. The period rates for initial and final three years, relatively more stable, were used to compare the difference across the study periods.

Incidence rates from 1969 to 1991 were plotted for four 5-year periods and one 3-year period as the sum of annual incidence frequencies among 5-year age intervals (35-39 years to 80-84 years) to demonstrate the difference in the time periods of diagnosis. Age-period-cohort analysis of incidence rates of kidney cancer and its main subtype, adenocarcinoma, were based on categorized data from the 10 age groups and the 5 time periods of diagnosis. Thus, a total of 14 overlapping, 10-year birth cohorts (1884-1893 to 1949-1958) were created. Each case diagnosed with cancer in a given 5-year age group and 5-year or 3-year time period of diagnosis was assigned to only one 10-year birth cohort, though the cohort intervals overlap.[7] Age-period-cohort models and various submodels were fitted with standard Poisson assumptions.[8,9] The parameters of the models were estimated by means of the maximum likelihood method through the SAS procedure GENMOD.[10]

TABLE I
Average Annual Percent Change (Standard Error) of Kidney Cancer Incidence and Mortality Rates per 100,000, Canada*

	Incidence Rate			Mortality Rate		
	1969/71	1989/91	Annual % Change	1969/71	1991/93	Annual % Change
Males						
0-34	0.69	0.74	0.23 (0.62)	0.19	0.09	-4.17 (0.99)‡
35-64	10.77	17.44	2.51 (0.21)‡	5.67	5.55	0.18 (0.17)
65+	37.12	65.58	2.83 (0.21)‡	25.60	30.81	0.88 (0.20)‡
All ages	6.37	10.46	2.53 (0.16)‡	3.67	3.93	0.44 (0.12)‡
Females						
0-34	0.65	0.71	1.35 (0.56)	0.26	0.07	-5.42 (1.40)‡
35-64	5.22	9.23	2.85 (0.33)‡	2.61	2.50	0.14 (0.30)
65+	17.57	31.77	3.13 (0.28)‡	11.84	14.35	1.06 (0.21)‡
All ages	3.25	5.53	2.80 (0.23)‡	1.80	1.82	0.37 (0.30)

* For incidence, Quebec data were excluded from Canadian data. Rates were standardized to the World Population.
† p≤0.05, ‡ p≤0.01

RESULTS

Secular trends

Table I presents the 3-year period rates and the average annual percent change in kidney cancer incidence and mortality rates during the study period among both men and women ages 0-34, 35-64 and 65 or older. A substantial increase in incidence was observed only for the adult and senior groups, with an average increase of 2.5% or more annually for both males and females in the 35-64 and 65+ age groups. The average annual percent change in mortality rates for all age groups was much more modest than was observed for incidence rates. Graphing annual age-specific rates for 10-year age groups starting with 35 years and for all ages on a semi-log scale further demonstrates the rapidly increasing trends in incidence for men and women (Figure 1).

Figure 2 shows temporal trends in the age-standardized incidence rates by histology for all ages for males and females, respectively in the three available provinces. The incidence rates in adenocarcinoma increased greatly during the period 1969-1971 to 1989-1991, with average annual increases of 5.1% and 4.5% for

TABLE II
Analysis of Age-period-cohort Models for Incidence of Kidney Cancer and its Subtype, Renal Adenocarcinoma, in Canada (ex. Quebec), 1969-1991

Models	Effect	df	Kidney Cancer Deviance	Kidney Cancer χ^2	Kidney Cancer p-value	Adenocarcinoma Deviance	Adenocarcinoma χ^2	Adenocarcinoma p-value
Male								
Age-period-cohort	Goodness-of-fit	24	16.45		ns	24.06		ns
	P|A, C	3		8.40	0.0384		9.44	0.0240
	C|A, P	12		12.04	0.4423		17.60	0.1283
Age-period	Goodness-of-fit	36	28.49		ns	41.66		ns
	P|A	4		529.57	0.0001		489.07	0.0001
Age-cohort	Goodness-of-fit	27	24.85		ns	33.50		0.1811
	C|A	13		533.21	0.0001		497.24	0.0001
Age	Goodness-of-fit	40	558.06		0.0001*	530.74		0.0001*
Female								
Age-period-cohort	Goodness-of-fit	24	27.99		ns	28.02		ns
	P|A, C	3		16.00	0.0011		17.55	0.0005
	C|A, P	12		25.13	0.0142**		10.43	0.5784
Age-period	Goodness-of-fit	36	53.12		0.0328	38.45		ns
	P|A	4		404.60	0.0001		309.53	0.0001
Age-cohort	Goodness-of-fit	27	43.99		0.0207	45.57		0.0141
	C|A	13		413.73	0.0001		302.41	0.0001
Age	Goodness-of-fit	40	457.73		0.0001*	347.98		0.0001*

* Significant lack of fit
** p-value for corresponding overdispersion model is 0.1075. The cohort effect is attributed to Period-cohort interaction, i.e., the period effect is not consistent across all age groups.

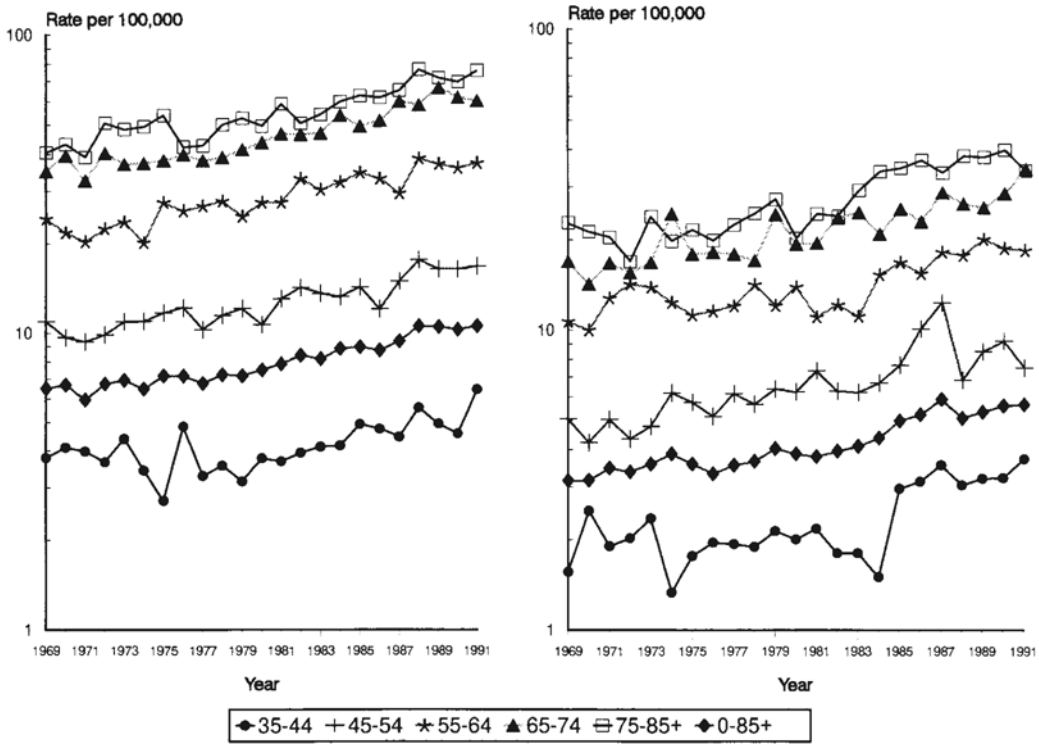

Figure 1. Age-specific incidence rates for 10-year age groups from 35 years old and age-standardized rates for all ages per 100,000 of kidney cancer are plotted anually on semi-logarithmic scales in males (left) and females (right) in Canada (ex. Quebec), 1969 to 1991.

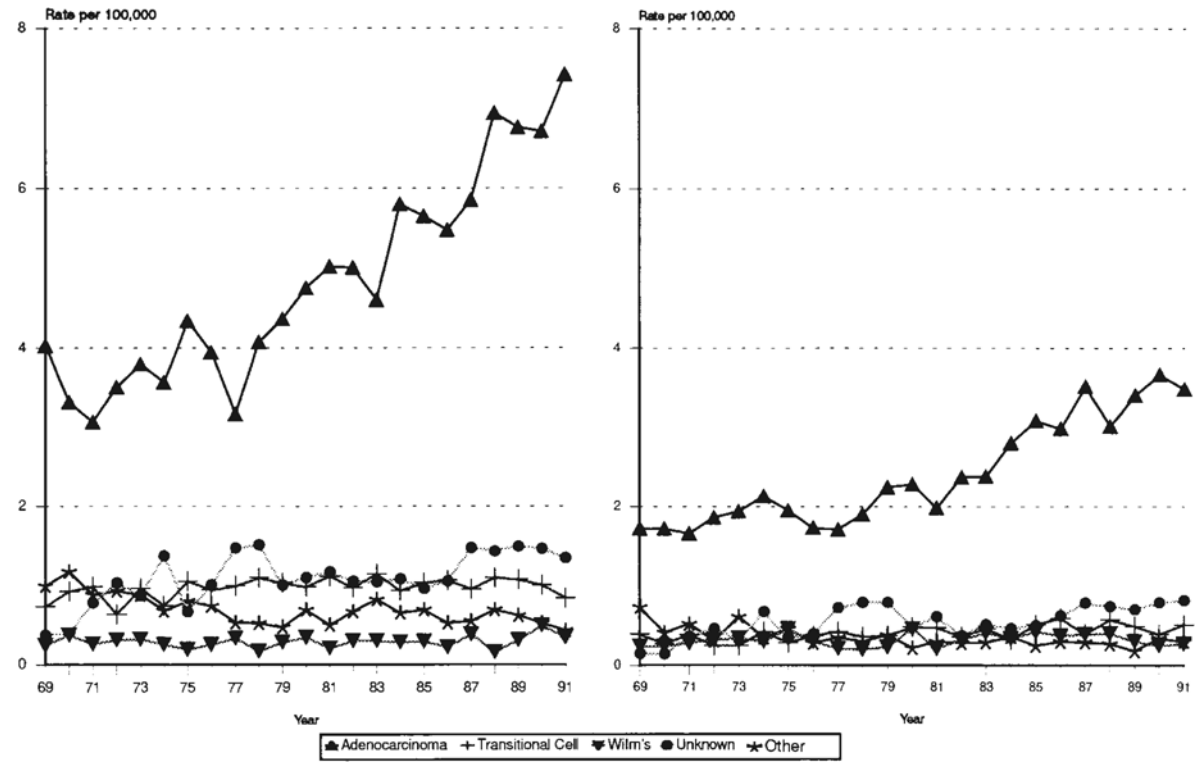

Figure 2. Standardized incidence rates of kidney cancer by histologic type for all ages per 100,000 in males (left) and females (right) of British Columbia, Saskatchewan and Ontario, 1969 to 1991.

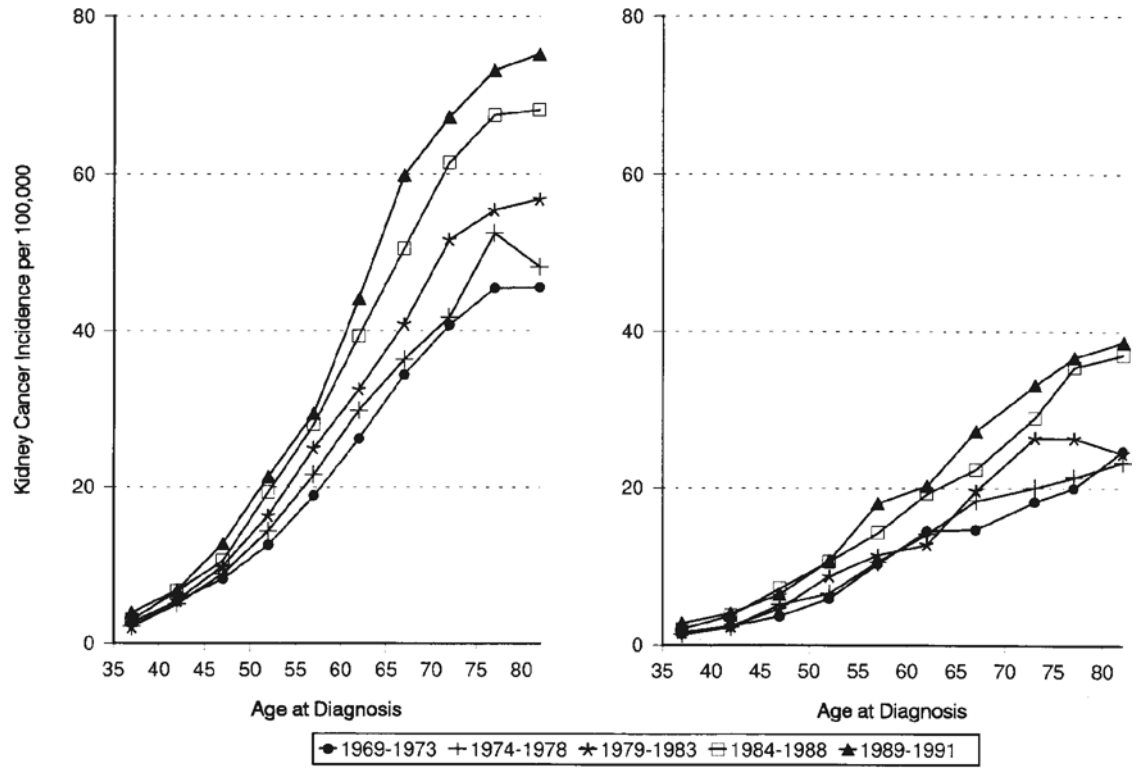

Figure 3. Age-specific incidence rates per 100,000 of kidney cancer are plotted for each diagnosis period among males (left) and females (right) in Canada (ex. Quebec). The rates are plotted at the midpoints of the 5-year age intervals.

males and females respectively. Transitional cell and Wilm's tumours did not change significantly. As a consequence, the proportion which were adenocarcinomas increased from 54% of all cases during the period 1969-71 to 65% during the period 1989-91 (data not shown).

Period effects

The temporal trends in age-specific incidence of kidney cancer from ages 35 to 84 differed among periods of diagnosis for both men and women (Figure 3). For both sexes, rates increased in almost every age group over time, with larger increases noted with increasing age.

The full age-period-cohort models and various sub-models were fitted for kidney cancer and renal adenocarcinoma for ages 35 to 84 years for both males and females (Table II). The goodness-of-fit statistics for all full models are not significant, indicating that the data patterns are reasonably explained by the models based on the Poisson assumption. Although the goodness-of-fit statistics for age-cohort models are not significant either, the addition of birth cohort in all full age-period-cohort models did not significantly improve the fit of the models compared to models with age and period only, and the models with age and period of diagnosis fit better than models with age and cohort. Therefore, the age-period model is preferable for either kidney cancer or renal adenocarcinoma, suggesting that a positive period effect could have had an impact on the incidence trends.

TABLE III
Period Relative Risks (95% Confidence Intervals) of Kidney Cancer in Canada (ex. Quebec) and Renal Adenocarcinoma in Bristish Columbia, Saskatchewan and Ontario Diagnosed at Ages 35 to 84 Years, 1969 to 1991

Period of Diagnosis	Kidney Cancer		Adenocarcinoma	
	Men	Women	Men	Women
1969-1973	1.00	1.00	1.00	1.00
1974-1978	1.07 (1.01-1.13)	1.06 (0.98-1.15)	1.08 (0.99-1.18)	1.05 (0.93-1.18)
1979-1983	1.22 (1.16-1.29)	1.20 (1.12-1.29)	1.36 (1.25-1.48)	1.26 (1.12-1.41)
1984-1988	1.43 (1.36-1.50)	1.52 (1.43-1.63)	1.71 (1.58-1.85)	1.76 (1.59-1.96)
1989-1991	1.63 (1.55-1.72)	1.72 (1.61-1.85)	2.00 (1.83-2.17)	1.98 (1.78-2.21)

Using the period 1969-1973 as the reference, large increases in both kidney cancer and renal adenocarcinoma have been observed (Table III). For kidney cancer, incidence rates in 1989-1991 were 163% and 172% higher than in 1969-1973 for males and females respectively. For adenocarcinoma, rates were 200% and 198% higher for men and women respectively.

DISCUSSION

Increases in kidney cancer mortality were much smaller than those observed for incidence. This pattern is similar to that observed in the U.S.[11] In our study, most of the increase in incidence of kidney cancer was attributable to adenocarcinoma; other histologies were relatively stable. The increase appeared to be greater with advancing age, with a significant period effect of diagnosis for both males and

females. No significant birth cohort effect in age-period-cohort models was noted. The observed increase in incidence may be explained by changes in patterns of detection and surveillance and/or changing patterns of exposure to new or pre-existing risk factors.

Since the 1970s, the introduction of ultrasonography (US) and computed tomography (CT) diagnostic imaging has led to dramatic advances in detection, diagnosis, and subsequent treatment of kidney masses.[12-14] The improved diagnostic ability afforded by US and CT as well as the widespread application of these procedures has led to both the intentional and incidental detection of small asymptomatic renal masses that would not otherwise have been detected at that time.[15,16] The resulting lead time bias may explain in part the increasing survival time for kidney cancer patients.[17,18] Transitional cell carcinoma, which often presents as haematuria, is less likely to be an incidental finding.[19] The use of US and CT imaging would be expected to contribute to a positive period effect for adenocarcinoma incidence, but not transitional cell carcinoma incidence.

Changes in the incidence in renal adenocarcinoma may be partly attributable to changing patterns of exposure to risk factors. Cigarette smoking appears to be a risk factor for renal cell carcinoma, but the association is much weaker and less consistently observed than the association with transitional cell carcinoma, with a recent case-control study reporting an odds ratio of 7.2 for long-term smokers. In 1966, 54% of all Canadian males and 29% of all Canadian females above age 15 were active smokers. By 1991, the prevalence of smoking had declined to 26% for both sexes.[20] The downturn in smoking may not have contributed appreciably to the changing adenocarcinoma incidence rates, but may help explain the stable incidence rates of the transitional cell carcinoma during the study period.

Another risk factor reported in virtually all studies of kidney cancer is obesity. The risk of renal cell carcinoma increases with level of body mass index (BMI), and the association is stronger among women than men.[21,22] Recently, a case-control study of risk factors for renal cell carcinoma conducted in Ontario reported that men and women in the upper 25% quartile of BMI had a two-fold increased risk, resulting in attributable risk percents of 17% and 26% for men and women respectively.[23] This association was also noted in China, a country with low rates of obesity.[24] In Denmark, the overall risk of renal cell carcinoma among obese individuals was increased in both sexes, while risk of cancer of renal pelvis was not different from that of the Danish population in general.[25] In Canada, the prevalence of obesity, as defined by BMI > 27 for both sexes, increased from 22% among men and 14% among women aged 20-64 in 1985 to 28% and 19% in 1991.[20]

Approximately 30-50% of patients on long-term dialysis develop acquired cystic disease, and up to 6% of these patients with acquired cystic disease develop renal cell carcinoma.[3] The association between dialysis and renal cell carcinoma has resulted in a recommendation for frequent CT scan screening for this population.[26] Incidence rates of haemodialysis and peritoneal dialysis increased to 4.9 and 2.9 per 100,000 respectively in 1993 from 2.5 and 1.9 per 100,000 in 1981 in Canada (world population-based age-standardized rates).[27] However, the increasing dialysis population is likely to have contributed in only a minor way to the period effect noted for renal adenocarcinoma incidence.

Abuse of phenacetin has been causally linked to transitional cell carcinoma of the renal pelvis.[28,29] Long-term use of phenacetin-containing analgesics has also been associated with an increased risk of renal cell carcinoma.[30-32] However, the use of phenacetin as a component of analgesic preparations has been banned in Canada since the mid-1970s. Although the latency of renal cell or transitional cell carcinoma due to phenacetin is unknown, phenacetin use is unlikely to have contributed appreciably to recent increases in kidney cancer incidence.

In conclusion, there has been a significant increase in the incidence of kidney cancer among both sexes ages 35 or greater since 1969. The incidence of adenocarcinoma, the most common histology of kidney cancer, has risen steadily and continues to do so, while the incidence of transitional cell carcinomas and Wilm's tumour has been stable. Diagnostic improvements leading to the detection of tumours at earlier stages, and to a much lesser extent increasing levels of obesity in the Canadian population are suspected contributors to the rapidly increasing trends. Declines in cigarette smoking prevalence may be related to the stable incidence of transitional cell carcinoma.

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REFERENCES

1. Coleman MP, Estève J, Damiecki P, et al. (Eds.) Kidney and other urinary organs. In: *Trends in Cancer Incidence and Mortality.* IARC Scientific Publications No. 121. Lyon: International Agency for Research on Cancer, 1993;577-99.
2. Higginson J, Muir CS, Munōz N. (Eds.) Kidney and renal pelvis. In: *Human Cancer: Epidemiology and Environmental Causes*. Cambridge: Cambridge University Press, 1992;425-30.
3. Richie JP. Neoplasms of the genitourinary tract. In: Holland JF, Bast RC, Kufe DW, et al. (Eds.) *Cancer Medicine,* 3rd Edition, Vol. 2. London: 1993;1529-38.
4. National Cancer Institute of Canada (NCIC). Canadian Cancer Statistics. 1996. Toronto: NCIC, 1996;15-46.
5. World Health Organization. International Classification of Diseases, 1975 Revision, Vols. 1 and 2. Geneva: WHO, 1977.
6. World Health Organization. International Classification of Diseases for Oncology. Geneva: WHO, 1976.
7. Davis DL, Dinse GE, Hoel DG. Decreasing cardiovascular disease and increasing cancer among whites in the United States from 1973 through 1987—good news and bad news. *JAMA* 1994;271:431-37.
8. Clayton D, Schifflers E. Models for temporal variation in cancer rates, I: Age-period and age-cohort models. *Stat Med* 1987;6:449-67.
9. Clayton D, Schifflers E. Models for temporal variation in cancer rates, II: Age-period-cohort models. *Stat Med* 1987;6:469-81.
10. SAS Institute Inc. SAS/STAT Software: Changes and enhancements through release 6.11. Cary, NC; 1996.
11. Gloeckler Ries LA, Miller BA, Hankery BF, et al. (Eds.) SEER Cancer Statistics Review 1973-1991. Bethesda, MD: National Institutes of Health, 1994;203-15.
12. Smith SJ, Bosniak MA, Megibow AJ, et al. Renal cell carcinoma: Earlier discovery and increased detection. *Radiology* 1989;170:699-703.

13. Tosaka A, Ohya K, Yamada K, et al. Incidence and properties of renal masses and asymptomatic renal cell carcinoma detected by abdominal ultrasonography. *J Urol* 1990;144:1097-99.
14. Aso Y, Homma Y. A survey on incidental renal cell carcinoma in Japan. *J Urol* 1992;147:340-43.
15. Lanctin HP, Futter NG. Renal cell carcinoma: Incidental detection. *Can J Surg* 1990;33:488-90.
16. Rousseau T, Peyret C, Zerbib M, et al. Circumstances of the detection of kidney cancer. Current part of accidental discoveries. *J Urol* (Paris) 1994;100:189-95.
17. Homma Y, Kawabe K, Kitamura T, et al. Increased incidental detection and reduced mortality in renal cancer—recent retrospective analysis at eight institutions. *Int J Urol* 1995;2:77-80.
18. Sasaki Y, Homma Y, Hosaka Y, et al. Clinical and flow cytometric analyses of renal cell carcinomas with reference to incidental or non-incidental detection. *Jpn J Clin Oncol* 1994;24:32-36.
19. Bennington, JL. Cancer of the kidney-etiology, epidemiology, and pathology, *Cancer* 1973;32:1017-22.
20. Statistics Canada. Health Status of Canadians: Report of the 1991 General Social Survey. Ottawa: Statistics Canada, 1994;77-154.
21. Benhamou S, Lenfant MH, Ory-Paoletti C, et al. Risk factors for renal-cell carcinoma in a French case-control study. *Int J Cancer* 1993;55:32-36.
22. Yu MC, Mack TM, Hanisch R, et al. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. *JNCI* 1986;77:351-56.
23. Kreiger N, Marrett LD, Dodds L, et al. Risk factors for renal cell carcinoma: Results of a population-based case-control study. *Cancer Causes Control* 1993;4:101-10.
24. Mclaughlin JK, Gao YT, Gao RN, et al. Risk factors for renal-cell cancer in Shanghai, China. *Int J Cancer* 1992;52:562-65.
25. Mellemgaard A, Møller H, Olsen JH, et al. Increased risk of renal cell carcinoma among obese women. *JNCI* 1991;83:1581-82.
26. MacDougall ML, Welling LW, Wiegmann TB. Renal adenocarcinoma and acquired cystic disease in chronic hemodialysis patients. *Am J Kidney Dis* 1987;9:166-71.
27. Canadian Institute for Health Information. Canadian Organ Replacement Register, 1993 Annual Report. Don Mills, Ontario: CIHI, 1995;109-12.
28. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, some pharmaceutical drugs. Lyon: IARC, 1980;24:135-61.
29. Ross RK, Paganini-Hill A, Landolph J, et al. Analgesics, cigarette smoking, and other risk factors for cancer of the renal pelvis and ureter, *Cancer Res* 1989;49:1045-48.
30. Mclaughlin JK, Blot WJ, Mehl ES, et al. Relation of analgesic use to renal cancer: Population-based findings. *Natl Cancer Inst Monogr* 1985;69:217-22.
31. McCredie M, Ford JM, Stewart JH. Risk factors for cancer of the renal parenchyma. *Int J Cancer* 1988;42:13-16.
32. Maclure M and MacMahon B. Phenacetin and cancers of the urinary tract. *N Engl J Med* 1985;313:1479.

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