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Malignant tumors of the kidney account for about 2% of all new cancer cases and deaths each year in the United States, making this site the twelfth most common cancer (Boring et al, 1994). Data from the Surveillance, Epidemiology and End Results (SEER) program for ICD-189 (renal and urinary tract cancers other than bladder) for the years 1975–1985 show that renal parenchyma (renal cell) cancer accounts for 70% of the total, renal pelvis cancer 15%, ureter cancer 8%, urethra cancer 4%, and other sites about 3% (Devesa et al, 1990). Nearly all renal cell cancers are adenocarcinomas, whereas the vast majority of cancers of the renal pelvis, ureter, and urethra are transitional cell carcinomas. Wilms' tumor (nephroblastoma), an embryonal neoplasm, is reviewed in the chapter on childhood cancer.

The etiology of kidney cancer remains enigmatic for the most part, except for renal pelvis and ureter cancers, the majority of which are related to cigarette smoking. In this review, information on renal cell cancer will be presented separately, whenever possible, from data on renal pelvis and ureter cancers. In many descriptive and some analytical studies, however, the available data pertain to all kidney cancers combined and do not permit further analyses by site.

## DEMOGRAPHIC PATTERNS

### *Incidence in the United States*

Incidence rates for renal cell cancer have risen about 2% per year among the four major race/sex groups since 1970 (Fig. 53–1), based on data from five U.S. registries (Devesa et al, 1987; Devesa et al, 1990). Increases have been more rapid among blacks than whites, resulting in a recent shift in excess from among whites to among blacks (Kosary and McLaughlin, 1993). Age-adjusted rates among whites, blacks, and Hispanics during 1975–1985 were similar, although elevated rates were

found among American Indian women, based on small numbers (Table 53–1). Alaskan natives have also been reported to have increased rates of renal cell cancer (Lanier et al, 1980). Rates among Asians of both sexes were about half those of other racial groups. With the exception of American Indians, rates among men are more than twice those among women. Incidence rates of renal cell cancer rise with increasing age before plateauing around age 70 (Fig. 53–2). The recent excess among blacks is less apparent at older ages compared to younger ages, whereas the excess among males is most notable at ages 50 years and older (Fig. 53–2).

For cancers of the renal pelvis, rates rose almost 3% per year during the 1970s and less rapidly thereafter (Fig. 53–1). There is a suggestive decrease in rates among blacks starting in the late 1970s, but the numbers involved are small. Rates among white men for these cancers are 2.5 times those among white women, black men, and Hispanic men, whereas the rates for Asians are intermediate (Table 53–1).

### *International Patterns*

Figure 53–3 presents kidney cancer rates from selected cancer registries around the world, as reported in Volume 6 of *Cancer Incidence in Five Continents* (Parkin et al, 1992). The rates, shown here in descending order within continent among men, vary more than 10-fold. Incidence is highest in Bas-Rhin, France, with relatively high rates in several Scandinavian countries, and other parts of northern Europe, but not England and Wales. The lowest rates are reported in India, among Chinese and Japanese populations, and in areas of Central and South America.

Many registries provide data separately for renal cell and renal pelvis cancers (using the fourth digit level of the International Classification of Diseases). The incidence of renal cell cancer is elevated in several areas of

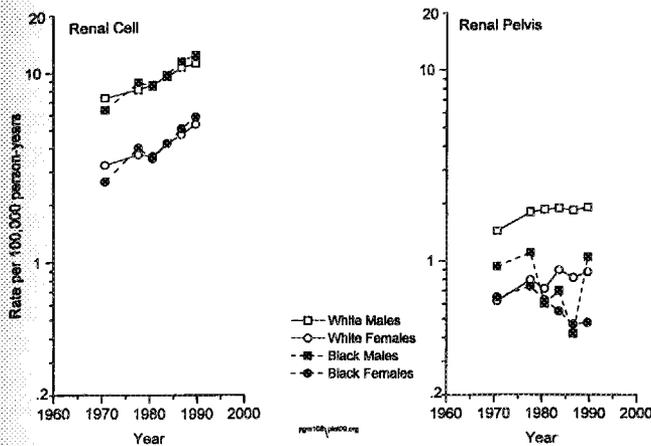


FIG. 53-1. Trends in age-adjusted (1970 standard) incidence of renal cell cancer and renal pelvis cancer in five geographic areas of the United States (Atlanta, Detroit, San Francisco, Connecticut, Iowa) by race and sex, 1969-1990. (Based on data from the Third National Cancer Survey, the Connecticut Tumor Registry, and the SEER Program.)

northern Europe; the rates for renal pelvis cancer appear high in Switzerland, Denmark, and among U.S. whites (Fig. 53-3). The proportion specified as renal pelvis cancer varies considerably by registry. This may partly reflect variations in reporting and classification, as well as actual differences in cancer rates. In certain rural parts of Bulgaria, Yugoslavia, and Romania, rates for renal pelvis and ureter cancers are exceptionally high because

TABLE 53-1. Incidence Rates\* for Cancers of the Renal Parenchyma, Renal Pelvis, and Ureter, by Racial/Ethnic Group and Sex, SEER Program, 1975-1985

	Males		Females	
	No.	Rate	No.	Rate
<b>Renal parenchyma<sup>a</sup></b>				
Whites (9 SEER areas)	7717	8.42	4307	3.69
Blacks (9 SEER areas)	677	8.62	379	3.78
Hispanics (New Mexico)	130	7.91	67	3.70
American Indians (New Mexico)	24	8.43	19	5.85
Asians (San Francisco and Hawaii) <sup>b</sup>	163	4.26	64	1.70
Native Hawaiians	29	5.73	14	2.42
<b>Renal pelvis and ureter</b>				
Whites (9 SEER areas)	2564	2.85	1421	1.14
Blacks (9 SEER areas)	77	1.04	69	0.71
Hispanics (New Mexico)	17	1.14	15	0.85
Asians (San Francisco and Hawaii) <sup>b</sup>	58	1.67	34	0.84

\*Rates per 100,000 person-years, age-adjusted using 1970 U.S. standard.

<sup>a</sup>Transitional, papillary, and squamous cell cancers of the kidney (ICD 189.0) are grouped with renal pelvis tumors.

<sup>b</sup>Includes Japanese, Chinese, Filipino.

Source: Unpublished SEER data; Devesa et al, 1990.

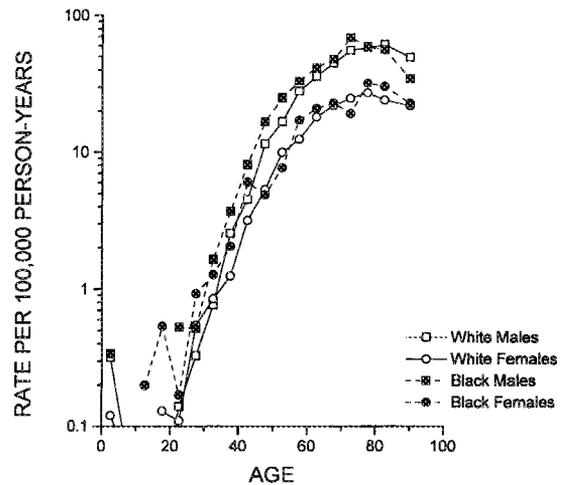


FIG. 53-2. Age-specific incidence of renal cell cancer in the United States by race and sex, 1986-1990. (Based on Kosary and McLaughlin, 1993.)

of a predisposing condition called Balkan nephropathy, which is endemic in these areas (Stoyanov et al, 1978). In general, the descriptive patterns for cancer of the renal pelvis (and ureter) resemble those of bladder cancer more than renal cell cancer (Devesa et al, 1990).

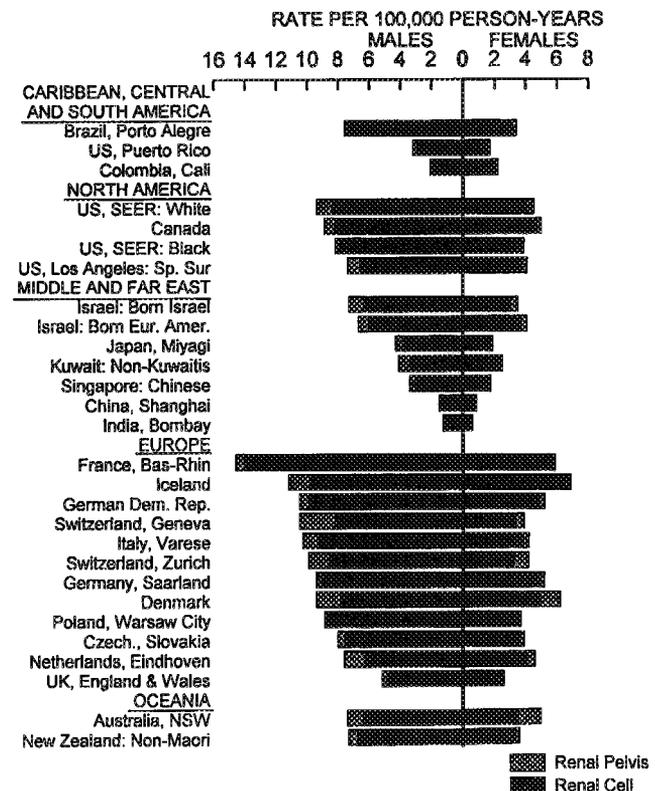


FIG. 53-3. International variation in age-adjusted (world standard) incidence of total kidney cancer, renal cell cancer, and cancers of the renal pelvis and ureter by sex, 1983-1987. (Based on Parkin et al, 1992.)

## Survival

The prognosis of patients diagnosed with kidney cancer has improved in recent times, with 5-year relative survival rates increasing from 36% to 39% in the early 1960s to over 50% in the 1980s (Axtell et al, 1976; National Cancer Institute, 1989; Kosary and McLaughlin, 1993). Table 53-2 presents 5-year relative survival rates by site, race, and sex. Survival rates are generally better for cancers of the renal pelvis than renal cell cancer for men; for women, the rates are similar. Blacks tend to have poorer survival rates for renal cell cancer, although they have better rates for renal pelvis cancer.

## Urbanization and Socioeconomic Factors

Mortality and incidence rates for kidney cancer are generally higher in urban than rural areas in the United States, England and Wales, and Norway and Denmark (McLaughlin and Schuman, 1983; Muir et al, 1987). The urban-rural differential is mainly among men, and probably reflects past levels of cigarette smoking. The pattern is influenced also by the greater availability of medical care and diagnostic services in urban than rural areas.

Kidney cancer mortality statistics from the United States and other countries have shown no clear relation with educational achievement (McLaughlin and Schuman, 1983). Case-control studies of renal cell cancer have not indicated an effect of social class variables such as education (Wynder et al, 1974; Armstrong et al, 1976; McLaughlin et al, 1984; Goodman et al, 1986; McCredie et al, 1988; Talamini et al, 1991; Maclure and Willett, 1990; McCredie and Stewart, 1993; Kreiger et al, 1993), although studies in Oklahoma (Asal et al, 1988a) and Denmark (Mellemgaard et al, 1994a) have reported an inverse trend with education. In a recent case-control study from France, patients were significantly better educated than the control subjects (Benhamou et al, 1993). Except for the new study

from Australia (McCredie and Stewart, 1993), investigations of renal pelvis and ureter cancers have also reported no major differences in education between patients and control subjects (Armstrong et al, 1976; McCredie et al, 1982, 1983a,b; McLaughlin et al, 1983; Jensen et al, 1988; Ross et al, 1989; McLaughlin et al, 1992c). When available, kidney cancer data have shown little relation to income level (McLaughlin and Schuman, 1983), although one correlation study reported a weakly positive association (Blot and Fraumeni, 1979).

## RENAL CELL CANCER

Virtually all information on risk factors for renal cell cancer has come from case-control studies (Table 53-3). These studies have been conducted in a number of countries, including the United States, Canada, England, Australia, Italy, Finland, France, Denmark, and China; the studies ranged in size from 64 cases and 197 controls to 690 cases and 707 controls.

## Cigarette Use

Although results from case-control studies are not entirely consistent, a convincing relation between cigarette smoking and renal cell cancer has emerged (Wynder et al, 1974; McLaughlin et al, 1984; Yu et al, 1986; Brownson, 1988; McCredie et al, 1988; La Vecchia et al, 1990; Maclure and Willett, 1990; McLaughlin et al, 1992a; McCredie and Stewart, 1992a; Kreiger et al, 1993; Mellemgaard et al, 1994a). Cohort studies also support this association (McLaughlin and Schuman, 1983), with the most recent and largest study, a 26-year follow-up of U.S. veterans (719 kidney cancer deaths), showing a strong dose-response relation (McLaughlin et al, 1990). The relative risks among smokers from case-control and cohort studies range from 1.2 to 2.3, although a small chart-review study in the 1960s reported a five-fold increase in risk (Bennington and Laubscher, 1968). A number of the case-control studies have demonstrated a dose-response relation in men (Wynder et al, 1974; McLaughlin et al, 1984; Yu et al, 1986; Brownson, 1988; McCredie et al, 1988; La Vecchia et al, 1990; Maclure and Willett, 1990; McLaughlin et al, 1992a; McCredie and Stewart, 1992a; Kreiger et al, 1993; Mellemgaard et al, 1994a) as well as in women (Wynder et al, 1974; McLaughlin et al, 1984; Yu et al, 1986; La Vecchia et al, 1990; Maclure and Willett, 1990; McLaughlin et al, 1992a; McCredie and Stewart, 1992a; Kreiger et al, 1993), with risks for heavy smokers ranging from 2.0 to 3.0. Use of hospital controls or small sample size is the likely explanation for the absence of a statistically significant cigarette as-

TABLE 53-2. *Five-Year Relative Survival Rates (percent) for Cancer of the Renal Parenchyma and Renal Pelvis, by Race and Sex, SEER Program, 1983-1989*

	Males Rate	Females Rate
Renal parenchyma		
Whites	58	59
Blacks	50	55
Renal pelvis		
Whites	62	55
Blacks	71	57

Source: Kosary and McLaughlin, 1993.

TABLE 53-3. *Published Case-Control Studies of Renal Cell Cancer*

<i>Authors</i>	<i>Year</i>	<i>Source of Controls</i>	<i>Number of Cases/Controls</i>	<i>Location</i>
Bennington and Laubacher	1968	hospital	100/190	Washington
Wynder et al	1974	hospital	202/394	3 U.S. cities
Armstrong et al	1976	hospital	106/106	England
Kolonel	1976	hospital	64/197	New York
McLaughlin et al	1984	population	495/697	Minneapolis
Yu et al	1986	neighborhood	160/160	Los Angeles
Goodman et al	1986	hospital	267/267	6 U.S. cities
Brownson	1988	cancer registry	326/978	Missouri
Asal et al	1988a	hospital/population	315/313/336	Oklahoma
McCredie et al	1988	population	360/985	New South Wales
Sharpe et al	1989	urologic patients	164/161	Montreal
La Vecchia et al	1990	hospital	131/394	Northern Italy
Maclure and Willett	1990	population	410/605	Boston
Talamini et al	1991	hospital	240/665	Northern Italy
Partanen et al	1991	population	338/484	Finland
McCredie and Stewart	1992a,b	population	489/523	New South Wales
McLaughlin et al	1992a	population	154/157	Shanghai
Kreiger et al	1993	population	518/1381	Ontario
Finkle et al	1993	medical plan	191/191	Los Angeles
Benhamou et al	1993	hospital	196/347	France
Mellemgard et al	1994a,b,c,d	population	368/396	Denmark
Hiatt et al	1994	medical plan	257/257	San Francisco
Chow et al	1994a,b	population	690/707	Minnesota

sociation in some case-control studies (Schwartz et al, 1961; Armstrong et al, 1976; Kolonel, 1976; Goodman et al, 1986; Asal et al, 1988a; Talamini et al, 1991; Benhamou et al, 1993). The moderate risk of renal cell cancer associated with cigarette smoking would be difficult to detect in a small study and could easily be obscured with the use of control subjects who have an elevated prevalence of smoking.

The risk associated with cigarette smoking has been shown to decline significantly with years of cessation (McLaughlin et al, 1984). More recent studies in Italy and Australia have confirmed the effect of cessation (LaVecchia et al, 1990; McCredie and Stewart, 1992a). Population-based attributable risks indicate that between approximately 30% and 37% of the renal cell cancers among men and 14% to 24% among women could be due to cigarette smoking (McLaughlin et al, 1984; McCredie and Stewart, 1992a). A recent study has reported a suggestive association of passive smoking with renal cell cancer (Kreiger et al, 1993).

### **Drugs**

Although heavy use of phenacetin-containing drugs has been clearly linked to renal pelvis tumors (International Agency for Research on Cancer [IARC], 1987), an as-

sociation has been reported also for renal cell cancer (McLaughlin et al, 1984, 1985; Maclure and MacMahon, 1985; McCredie et al, 1988; McLaughlin et al, 1992a; Kreiger et al, 1993). Confounding does not explain the association, because the studies adjusted for cigarette smoking and the use of other types of analgesics. These studies revealed no increased risk associated with aspirin or acetaminophen, but a cohort study of retirees reported a significant six-fold increased risk for daily aspirin use (Paganini-Hill et al, 1989). This finding is preliminary, because it was based on nine cases, apparent only among men, and not adjusted for prior use of phenacetin-containing analgesics, relative weight, or smoking habits. A new large-scale population-based case-control study in an area of the world known for heavy analgesic consumption confirmed the relation of phenacetin to renal cell cancer, but found no evidence that aspirin increases the risk of renal cell cancer (McCredie et al, 1993). In the same study, a link with acetaminophen analgesics was suggested. In the large Canadian study an association was also observed for phenacetin use but none with acetaminophen (Kreiger et al, 1993). The recent large-scale study in Minnesota observed no relation with regular use or duration of use for aspirin, acetaminophen, or phenacetin (Chow et al, 1994a), however, in Denmark, women who were heavy

users of phenacetin had a significant five-fold risk of renal cell cancer (Mellempgaard et al, 1994b). This study observed no significantly increased risk for aspirin or acetaminophen users. Linked-registry studies of patients with diseases that require treatment with analgesics have reported increased risks of renal cell cancer, although the type of analgesic was unknown and control of confounding factors was not possible (Mellempgaard et al, 1992b; Gridley et al, 1993; Lindblad et al, 1993).

Diuretic use has been associated with a five-fold increase in the risk of renal cell cancer among women (Yu et al, 1986). Adjustment for blood pressure status made little difference, because both hypertensives and non-hypertensives were at elevated risk. This finding was confirmed by a larger case-control study, although the excess risk was confined to nonhypertensive women (McLaughlin et al, 1988). Recent cohort studies have also linked renal cell cancer with diuretic use (Fraser et al, 1990; Grove et al, 1991; Mellempgaard et al, 1992a; Lindblad et al, 1993). The recent Australian study did not confirm the association with diuretics, but rather found an increased risk with nondiuretic antihypertensive medications (McCredie and Stewart, 1992b). One screening study of prescription drug-cancer associations did not observe a significantly elevated risk (Selby et al, 1989). But recent medical records-based case-control studies using prescription data from patients' charts have found three- to four-fold increased risks among women after adjustment for known confounders, including hypertension (Finkle et al, 1993; Hiatt et al, 1994). It is noteworthy that animal studies have linked hydrochlorothiazide and furosemide, the most commonly used diuretics, with tubular cell adenomas and adenocarcinomas of the kidney in rats and hepatocellular tumors in mice (Lijinsky and Reuber, 1987; National Toxicology Program, 1989a,b). Moreover, these compounds act on the renal tubules (Laski, 1986), the site of origin for renal cell cancers. In the United States, the use of diuretics increased by 40% between 1975 and 1984 and is especially common among the elderly (Baum et al, 1988). Future analytical studies of renal cell cancer should strive to clarify the role of diuretics, because an association, if causal, would have major public health implications as a result of the widespread use of these drugs (National Center for Health Statistics, 1987, 1993).

Although estrogens have induced renal cell carcinomas in laboratory animals, particularly Syrian golden hamsters, there is little epidemiological evidence supporting an association in humans (McLaughlin and Schuman, 1983; Newsom and Vurgin, 1987). Weakly positive findings have been reported for menopausal estrogen use (Asal et al, 1988b; McLaughlin et al, 1992a; McCredie and Stewart, 1992b) and oral contraceptives

(McLaughlin et al, 1992a; Kreiger et al, 1993). The relation in humans between hormone-related variables and renal cell cancer remains unclear.

### **Coffee, Alcohol, and Other Beverages**

Although correlation studies have suggested a relation between the distribution of kidney cancer and per capita consumption of coffee (Shennan, 1973; Armstrong and Doll, 1975), the finding has not been confirmed by case-control studies of renal cell cancer, when adjustment is made for the confounding effect of cigarette use (Wynder et al, 1974; Armstrong et al, 1976; McLaughlin et al, 1984; Asal et al, 1988a; McCredie et al, 1988; Maclure and Willett, 1990; Talamini et al, 1991; Partanen et al, 1991; Kreiger et al, 1993; Benhamou et al, 1993; Mellempgaard et al, 1994a; Chow et al, 1994b). However, two studies have suggested a positive association. A two-fold risk in both sexes combined was associated with use of decaffeinated coffee without dose-response relation (Goodman et al, 1986), while an increased risk for regular coffee use was seen among women only, again with no dose-response relation (Yu et al, 1986). On the other hand, results from a cohort study in Norway, an area of heavy coffee intake, showed a significant inverse trend, with consumers of seven or more cups having one fourth the risk of those drinking two or fewer cups daily (Jacobsen et al, 1986). Overall, the results from analytical studies indicate that coffee consumption does not increase the risk of renal cell cancer.

Correlation studies have also reported a relation between per capita intake of alcohol and kidney cancer mortality (Breslow and Enstrom, 1974; Hinds et al, 1980). Analytical studies of renal cell cancer do not support these findings, with cases and controls consuming similar amounts of alcohol (Wynder et al, 1974; Armstrong et al, 1976; McLaughlin et al, 1984; Goodman et al, 1986; Yu et al, 1986; Brownson, 1988; Asal et al, 1988a; Maclure and Willett, 1990; Talamini et al, 1991; Kreiger et al, 1993; Benhamou et al, 1993; Chow et al, 1994b). The recent Danish case-control study observed a statistically significant inverse association of alcohol consumption with renal cell cancer risk (Mellempgaard et al, 1994a). Moreover, cohort studies of alcoholics and brewery workers have reported no excess mortality from kidney cancer (Schmidt and De Lint, 1972; Pell and Alonzo, 1973; Monson and Lyon, 1975; Jensen, 1979; Schmidt and Popham, 1981; Adami et al, 1992).

An increased risk among tea drinkers has been reported in a few studies of renal cell cancer, particularly among women (McLaughlin et al, 1984; Goodman et al, 1986; Asal et al, 1988a). Also, a mortality follow-up of 20,000 London men revealed a dose-response relation between tea consumption and kidney cancer mor-

tality (Kinlen et al, 1988). Although some teas have been found to be mutagenic (Uyeta et al, 1981) and contain tannins that appear carcinogenic in laboratory animals (IARC, 1976), the etiologic significance of these findings is not clear.

### **Diet**

Correlation studies in the 1970s pointed to an association of kidney cancer mortality with per capita consumption of fat and protein (Wynder et al, 1974; Armstrong and Doll, 1975). Case-control studies of renal cell cancer, however, have found relatively few significant differences in dietary factors (Armstrong et al, 1976; Yu et al, 1986; McLaughlin et al, 1984; McCredie et al, 1988; Maclure and Willett, 1990; Talamini et al, 1991; Kreiger et al, 1993). However, elevated risks have been reported with consumption of meat (McLaughlin et al, 1984; Maclure and Willett, 1990; Kreiger et al, 1993), milk (McCredie et al, 1988), and margarine and oils (Talamini et al, 1991). Reduced risks have been observed with increased intake of vegetables (Maclure and Willett, 1990; McLaughlin et al, 1992a), carrots (Talamini et al, 1991), and fruits (McLaughlin et al, 1992a). Recently, an association with high dietary protein consumption independent of fat and caloric intake has been shown (Chow et al, 1994b). There may be some biologic plausibility to a high protein diet affecting risk of renal cell cancer, because animal studies have shown protein intake can induce renal tubular hypertrophy (Smith et al, 1993).

### **Occupation**

Unlike bladder cancer, the most common tumor of the urinary tract, renal cell cancer is not generally considered an occupationally associated tumor. However, asbestos has been linked to kidney cancer in several studies. Two cohort studies, one of insulators (Selikoff et al, 1979) and one of asbestos products workers (Enterline et al, 1987), reported significantly elevated mortality rates for kidney cancer. An association between asbestos exposure, mostly from work in shipyards, and renal cell cancer was suggested in a Boston-area case-control study (Maclure, 1987). There is some evidence from autopsy surveys and animal studies that asbestos fibers can be deposited in the kidney (Smith et al, 1989). Most case-control studies of renal cell cancer have found no association with asbestos exposure (McLaughlin et al, 1984; Yu et al, 1986; Goodman et al, 1986; Asal et al, 1988b; Brownson, 1988; Partanen et al, 1991), although their power to detect risks for asbestos exposure is generally low because of the small number of exposed workers. However, case-control studies from Australia

(McCredie and Stewart, 1993) and Denmark (Mellemgaard et al, 1994d) observed elevated risks for self-reported exposure to asbestos.

Coke-oven workers exposed to high levels of polycyclic aromatic hydrocarbons have been reported to be at increased risk for kidney cancer (Redmond et al, 1972), although this finding is based on small numbers (eight deaths), with no clear evidence of a dose-response or duration-of-employment effect (Redmond, 1983). Two recent case-control studies observed little excess risk for coke-oven workers (McCredie and Stewart, 1993; Mellemgaard et al, 1994c). More general exposure to hydrocarbons was linked to renal cell cancer in two small case-control studies (Sharpe et al, 1989; Kadmani et al, 1989), but was not associated with risk in a large case-control study in Finland (Partanen et al, 1991).

Cadmium exposure was estimated from employment, food, and cigarettes, and linked to renal cell cancer in a case-control study from Roswell Park Memorial Institute in New York (Kolonel et al, 1976). Subsequent case-control studies and occupational cohort investigations have shown no relation between cadmium exposure and renal cancer (McLaughlin et al, 1984; Elinder et al, 1985; Thun et al, 1985; Yu et al, 1986; Brownson, 1988; Asal et al, 1988b; McCredie and Stewart, 1993). Although inorganic lead has induced renal tumors in laboratory animals, there is little epidemiological evidence of an association in humans (IARC, 1987). However, a recent update of lead smelter workers did detect an excess mortality from kidney cancer (including renal pelvis and ureter cancers) (Steenland et al, 1992). It is not clear, however, how many of the nine deaths were caused by transitional cell tumors, and the kidney cancer excess was not clearly related to duration of exposure.

Proportional mortality studies have suggested that laundry and dry cleaning workers may be at increased risk for kidney cancer (Blair et al, 1979; Katz and Jowett, 1981; Duh and Asal, 1984; Brown and Kaplan, 1987), and case-control studies of renal cell cancer in Oklahoma (Asal et al, 1988b) and Australia (McCredie and Stewart, 1993) indicated an excess risk among dry cleaners. However, a recent large-scale cohort study of these workers showed no increased mortality from kidney cancer (Blair et al, 1990). Dry cleaners have been exposed to a large number of chemicals, notably tetrachloroethylene, which has produced hepatocellular carcinomas in laboratory animals (IARC, 1987).

It has been suggested that kidney cancers occur excessively among oil refinery workers (Savitz and Moure, 1984). A case-control study of renal cell cancer in Oklahoma reported an excess risk associated with employment in petroleum refining work (Asal et al, 1988b). Recent reviews of cohort studies of petroleum refinery

workers find little or no evidence of an excess risk of kidney cancer (Wong and Raabe, 1989; IARC, 1989).

Gasoline came under suspicion as a risk factor for renal cell cancer when male rats exposed long-term to vapors of unleaded gasoline developed a significant excess of renal cancers (MacFarland et al, 1984). As a result of this finding, a number of epidemiological studies examined the effect of gasoline exposure. In a case-control study of renal cell cancer in Minnesota, service station attendants experienced a slight upward trend in risk with duration of employment (McLaughlin et al, 1985b). No association with gasoline was observed in case-control studies in New York (Domiano et al, 1985), Los Angeles (Yu et al, 1986), or Australia (McCredie and Stewart, 1993). Exposure to aviation and jet fuels was related to kidney cancer risk in a case-control screening study of occupational exposures and cancers (Siemiatycki et al, 1987), but a later cohort study of aviation maintenance workers showed no association with risk (Spirtas et al, 1991). Case-control studies in Finland (Partanen et al, 1991) and Denmark (Mellemgaard et al, 1994c) have reported a significant association with gasoline exposure. However, studies of gasoline-exposed workers in the petroleum industry have not found an association (McLaughlin, 1993). In addition, recent nested case-control and cohort studies of gasoline exposure among industry workers have not observed a significantly increased risk of kidney cancer (Poole et al, 1993; Wong et al, 1993; Rushton, 1993; Schnatter et al, 1993).

Several other occupational associations have been reported. One cohort study found newspaper pressmen at elevated risk for kidney cancer (Paganini-Hill et al, 1980), although the association has not been confirmed (Alderson, 1986; McCredie and Stewart, 1993; Mellemgaard et al, 1994d). Swedish lumberjacks were reported at increased risk for kidney cancer in a pilot study of forestry workers (Edling and Granstam, 1980), but a nationwide survey of renal cell cancer incidence and occupation in Sweden showed no increased risk in this particular industry (McLaughlin et al, 1987). The same survey found an excess risk among health care workers, including physicians. An elevated risk of renal cell cancer among truck drivers was reported in a Missouri case-control study (Brownson, 1988), and more recently in Denmark (Mellemgaard et al, 1994d). A link between renal cell cancer and exposure to polychlorinated biphenyls was suggested when a cluster of three cases occurred among electric power utility workers (Shalat et al, 1989). Inorganic arsenic has been linked to kidney cancer, although mainly through drinking water in one area of Taiwan (Bates et al, 1992). Architects were reported to be at excess risk for renal cell cancer (Lowry et al, 1991), although no other reports support this observation (McLaughlin et al, 1992b). Another

study has reported that paperboard printing workers have an elevated risk (Sinks et al, 1992).

### **Obesity**

Virtually every study that has examined body weight and renal cell cancer has observed a positive association. Earlier studies noted the association primarily in women (Whisenand et al, 1962; Wynder et al, 1974; Lew and Garfinkel, 1979; McLaughlin et al, 1984), but more recent studies have found an effect in both sexes, although it is usually more pronounced in women (Whittemore et al, 1985; Yu et al, 1986; Goodman et al, 1986; Asal et al, 1988a; Maclure and Willett, 1990; McCredie and Stewart, 1992b; McLaughlin et al, 1992a; Kreiger et al, 1993; Benhamou et al, 1993; Mellemgaard et al, 1994c). One study reported that the association was primarily for weight gained in later adulthood (McLaughlin et al, 1984), but other studies have not supported this finding (Yu et al, 1986; Asal et al, 1988a). A linked-registry study of Danish patients discharged with a diagnosis of obesity reported significantly elevated risks for renal cell cancer in both sexes (Mellemgaard et al, 1991).

The mechanism responsible for the obesity effect is unclear. Because the association with renal cell cancer is most pronounced in women, it is believed that obesity may act by promoting hormonal changes, such as increased levels of endogenous estrogens. Although estrogens induce renal cancer in certain laboratory animals (Newsom and Vurgin, 1987), there is scant epidemiological evidence linking hormone-associated variables to renal cell cancer. Obesity may also predispose to arterionephrosclerosis, which may, in turn, render the renal tubules more susceptible to carcinogenesis. Moreover, obesity is sometimes treated with diuretics, which are under evaluation as a potential risk factor.

### **Radiation**

Ionizing radiation appears to increase the risk of renal cell cancer, especially among patients treated for ankylosing spondylitis and cervical cancer, but the effects are weak (Land, 1986; Boice et al, 1988). An increased risk has also been described among patients receiving radium 224 for bone tuberculosis and ankylosing spondylitis (Spiess et al, 1989). In one case-control study, significantly more female patients than control subjects reported receiving diagnostic or therapeutic radiation (Asal et al, 1988b).

### **Hemodialysis**

Among patients undergoing renal dialysis, there is an increased incidence of acquired cystic disease of the kid-

ney, which predisposes to renal cell cancer, especially in men (Ishikawa, 1987). Although the carcinogenic mechanism is uncertain, some aspect of the uremic process appears involved.

### Genetic Susceptibility

There have been several reports of familial clustering of renal cell cancer. Cohen and colleagues (1979) described a family with an inborn chromosomal defect and renal cell cancer affecting seven members of three generations. The pattern of tumors suggested an autosomal dominant mode of inheritance. Surveillance of remaining family members uncovered bilateral renal cancers in three young women, who were treated with surgical resection. The cytogenetic defect in lymphocytes was a balanced reciprocal translocation between chromosomes 3 and 8, with breakpoints determined at bands 3p14.2 and 8q24.1 (Wang and Perkins, 1984). This constitutional rearrangement prompted cytogenetic and molecular studies of tumor cells in unselected patients with renal cell cancer, which have consistently revealed deletions of distal chromosome 3p (Kovacs et al, 1988; Zbar et al, 1987). These findings have been extended by molecular studies of von Hippel-Lindau disease (featuring angiomas of the retina and cerebellum), an autosomal dominant condition that predisposes to renal cell cancer. The gene for this disorder has been linked to *c-raf-1* on chromosome 3p25 (Seizinger et al, 1988). Recent work has cloned and characterized the tumor suppressor gene for von Hippel-Lindau disease (Latif et al, 1993).

These observations, taken together, suggest that the origins of renal cell cancer may involve several tumor suppressor genes on the short arm of chromosome 3. This concept has been further extended by studies of the

nonheritable form of renal cell cancer (Gnarra et al, 1994). However, hereditary papillary renal cell cancer, a rare histologic subtype, may not be linked to chromosome 3 (Zbar et al, 1994). The role of developmental defects in renal cell cancer is suggested also by reports of associated renal anomalies, including polycystic kidneys (McFarland et al, 1972) and horseshoe kidneys (Blackard and Mellinger, 1968). In addition, an excess frequency of polymastia or supernumerary nipples has been noted with renal cell cancer (Goedert et al, 1981; Asal et al, 1988b), as well as with various renal anomalies (Pellegrini and Wagner, 1983).

### CANCERS OF THE RENAL PELVIS AND URETER

As with renal cell cancer, the identification of risk factors for renal pelvis and ureter cancers has come mainly from case-control studies, summarized in Table 53-4. As a result of the relative infrequency of renal pelvis and ureter tumors, these studies are typically smaller than those for renal cell cancer, ranging in size from 27 to 502 cases.

#### Cigarette Use

Case-control studies have generally reported smoking-related risks that are higher than those for renal cell cancer or bladder cancer (Schmauz and Cole, 1974; Armstrong et al, 1976; McCredie et al, 1982, 1983a,b; McLaughlin et al, 1983; Jensen et al, 1988; Ross et al, 1989; McLaughlin et al, 1992c; McCredie and Stewart, 1992a). The risks for smokers are 2.5 to 7 times those for nonsmokers, with heavy smokers having risks of five- to 11-fold. This variation in reported risks proba-

TABLE 53-4. *Published Case-Control Studies of Renal Pelvis and Ureter Cancers*

Authors	Year	Source of Controls	Number of Cases/Controls	Location
Schmauz and Cole	1974	population	17 renal pelvis 10 ureter/451	Massachusetts
Armstrong et al	1976	hospital	33 renal pelvis/33	England
McCredie et al	1982	friend/clinic	67 renal pelvis/84/96	New South Wales
McCredie et al	1983a	population	29 renal pelvis 36 ureter/307	New South Wales
McCredie et al	1983b	population	31 renal pelvis/400	New South Wales
McLaughlin et al	1983	population	74 renal pelvis/697	Minnesota
Jensen et al	1988	hospital	76 renal pelvis 20 ureter/294	Denmark
Ross et al	1989	neighborhood	121 renal pelvis 66 ureter/187	Los Angeles
McLaughlin et al	1992c	population	308 renal pelvis 194 ureter/496	3 areas in United States
McCredie and Stewart	1992a,b	population	147 renal pelvis/523	New South Wales

bly reflects the relatively small number of cases in most of the studies. In the largest study of these cancers, cigarette smokers had a 3.2-fold risk, with current smokers at a 4.4-fold risk (McLaughlin et al, 1992c). Cessation of smoking for 10 years or longer reduced the risks for these tumors 60% to 70% relative to current smokers (McLaughlin et al, 1992c). Similar reductions in risk were seen among quitters in Australia (McCredie and Stewart, 1992a). This steep decline in risk suggests that smoking affects a relatively late stage in carcinogenesis, thus making it possible for smoking cessation to lower the risk for these tumors. Population-based attributable risk estimates for cigarette smoking and renal pelvis and ureter cancers in the United States have suggested that 70% to 82% of the cases among men and 37% to 61% among women are due to smoking (McLaughlin et al, 1983; McLaughlin et al, 1992c). Results from Denmark indicate that smoking accounts for 56% of the cases of renal pelvis and ureter cancers among men and 40% among women (Jensen et al, 1988). In Australia, 46% of the cases among men and 35% among women are attributable to cigarette smoking (McCredie and Stewart, 1992a). Thus, cigarette smoking appears to be the strongest risk factor for these tumors and accounts for the majority of cases in most areas of the world.

### Drugs

The relation between heavy use of phenacetin-containing analgesics and cancers of the renal pelvis, ureter, and bladder is well established (IARC, 1980, 1987). Case reports and clinical surveys starting in the mid-1960s and continuing through the 1970s linked phenacetin use to analgesic nephropathy, and an accompanying excess of renal pelvis cancer (Hultengren et al, 1965). In a series of case-control studies in New South Wales, Australia, where analgesic abuse is relatively common, McCredie and colleagues (1982, 1983a,b, 1993) reported three- to 12-fold increased risks for renal pelvis and ureter cancers among men and women using phenacetin analgesics. In the United States, where analgesic abuse is relatively uncommon (Murray and Goldberg, 1978), two case-control studies were limited by the small number of exposed subjects. In the Minnesota study of renal pelvis cancer, long-term use (over 3 years) of phenacetin was related to an eight-fold risk for men and a four-fold risk for women (McLaughlin et al, 1985a). In the Los Angeles study, the risk for renal pelvis and ureter cancers was only slightly elevated after use of phenacetin analgesics over 30 consecutive days (Ross et al, 1989). In Denmark, use of phenacetin-containing analgesics was associated with risks of 2.4 among men and 4.2 among women after adjustment for use of other analgesics, cigarettes, and occupation (Jen-

sen et al, 1989). Phenacetin has also been shown to induce urinary tract tumors in laboratory animals (Nakanishi et al, 1982; IARC, 1987). In future studies, detection of risk for phenacetin use may be difficult, because phenacetin was removed from analgesics in most industrial countries starting in the late 1960s.

There are some limited data suggesting that acetaminophen, a relatively recent addition to over-the-counter analgesics, may increase risk of renal pelvis cancer. Acetaminophen is the major metabolite of phenacetin (Hinsen, 1981). Although a few clinical and experimental findings have linked heavy acetaminophen intake with renal papillary necrosis (Nanra, 1983), the primary lesion of analgesic nephropathy, a population-based case-control evaluation of this condition in Australia showed no association (McCredie and Stewart, 1988). Results of animal studies have been mixed, with two studies suggesting carcinogenic effects (Flaks and Flaks, 1983; Flaks et al, 1985) and two being negative (Hiraga and Fujii, 1985; Amo and Matsuyama, 1985). The Minnesota case-control study of renal pelvis cancer reported a positive association with acetaminophen, although only a few patients took acetaminophen-containing analgesics exclusively (McLaughlin et al, 1983, 1985a). In Australia, no increase in risk was observed for cancer of the renal pelvis among acetaminophen users, but a significant 2.5-fold increase in risk was found for ureter cancer (McCredie and Stewart, 1988). In a larger and more recent Australian study, acetaminophen use was not related to risk (McCredie et al, 1993). The Los Angeles case-control study reported a two-fold risk for acetaminophen use, but again, the number of users was small. Use of acetaminophen-containing analgesics in the United States did not become widespread until the mid-1970s—hence it may be too early to detect tumors with long latency periods and the number of exclusive users of these products may be too small to evaluate risks presently. Moreover, heavy users of acetaminophen products were often past users of phenacetin-containing analgesics, further confounding the association (McLaughlin et al, 1985a).

Experimental, clinical, and most epidemiological studies have shown no relation between aspirin intake and cancers of the renal pelvis or ureter (Emkey, 1983; Patierno et al, 1989; Armstrong et al, 1976; McCredie et al, 1982, 1983a,b; McLaughlin et al, 1985a). One study, however, has reported a significant two-fold risk for aspirin use, with the excess mainly among women with renal pelvis tumors (Ross et al, 1989). The Danish study also reported a significant association among women who took aspirin, which the authors attributed to prior or concomitant phenacetin use (Jensen et al, 1989). By contrast, the recent Australian study found aspirin use associated with a decreased risk of renal pelvis cancer (McCredie et al, 1993).

Overall, the available evidence on analgesics indicates a causal relation between phenacetin intake and cancers of the renal pelvis and ureter. Evidence for acetaminophen is weak, but suggestive because of its biochemical resemblance to phenacetin. The relatively recent introduction of this widely used analgesic warrants close monitoring for possible carcinogenic effects. The limited positive findings for aspirin probably reflect confounding by earlier phenacetin use or a chance event, but further study appears indicated.

### **Coffee, Alcohol, and Other Beverages**

There are few data to indicate that coffee or alcohol is related to renal pelvis and ureter cancers (Armstrong et al, 1976; McLaughlin et al, 1983; Ross et al, 1989). One study found a 15-fold increased risk for drinkers of over seven cups of coffee per day, but this observation was based on two cases (Schmauz and Cole, 1974). Another study reported a significant inverse relation between coffee intake and risk of renal pelvis cancer (Armstrong et al, 1976). No case-control differences have been observed for alcohol consumption (Armstrong et al, 1976; McLaughlin et al, 1983; Ross et al, 1989). An excess risk has been reported among heavy consumers of tea, particularly women, which may deserve further study (McLaughlin et al, 1983).

### **Occupation**

There are few occupational associations for renal pelvis and ureter cancers because of their relative rarity and frequent inclusion with renal cell cancers in occupational cohort studies. Early case reports linked renal pelvis and ureter tumors with exposure to dyes (Macalpine, 1947; Poole-Wilson, 1969). A significant excess of employment in the leather industry was reported in Massachusetts (Schmauz and Cole, 1974), but was not confirmed in the British case-control study, which included an area with a concentration of boot and shoe manufacturing (Armstrong et al, 1976). Case-control studies in Australia (McCredie et al, 1982) and the United States (McLaughlin et al, 1983) have revealed no significant occupational associations. However, in the U.S. study, significant increases in risk were associated with exposure to high-risk materials such as coal, natural gas, and mineral oils (McLaughlin et al, 1983). In the recent Australian case-control study, employment in the dry cleaning, iron and steel, and petroleum refining industries was related to an increased risk (McCredie and Stewart, 1993). The Danish case-control study found significantly increased risks for employment in the chemical, petrochemical, and plastics industries, and for exposures to coal and coke, and to asphalt and tar (Jen-

sen et al, 1988). A record-linkage survey of occupation and cancer incidence in Denmark found significantly elevated risks for renal pelvis and ureter cancers in a number of industries, including forestry and logging; slaughtering, preparing and preserving meat; and printing and publishing (Olsen and Jensen, 1987). A Swedish record-linkage study reported a significant excess risk among machinists and plumbers (McLaughlin et al, 1987), but adjustment for smoking was not possible in either Scandinavian survey. Although the available data are limited, the work-related risks observed for cancers of the renal pelvis and ureter resemble the occupational associations that are more clearly established for bladder cancer.

### **Radiation**

The carcinogenic influence of ionizing radiation appears stronger for the renal pelvis and ureter than the renal parenchyma. The effect is seen especially in cervical cancer patients treated with radiation (Boice et al, 1988). Renal pelvis cancer has also been a consequence of Thorotrast administration during retrograde pyelography (Verhaak et al, 1965).

### **Multicentric Tumors**

Transitional epithelial tumors of the lower urinary tract have a tendency to arise at multicentric sites, due partly to shared risk factors such as smoking (Kantor and McLaughlin, 1985). This pattern suggests the need for screening patients with renal pelvis and ureter cancers (eg, urinary cytology) for new tumors arising along the urinary tract, including the bladder.

### **PREVENTIVE MEASURES**

It may be possible to prevent—through elimination of cigarette smoking—the majority of renal pelvis and ureter cancers and a smaller fraction of renal cell cancers. Hence, measures aimed at persuading current smokers to quit and encouraging nonsmokers, particularly young people, not to start should have a substantial impact on subsequent renal cancer incidence and mortality. The exclusion of phenacetin from analgesic products, an action already taken by most Western countries, should contribute to a reduction of renal tumors. Further research into the environmental and genetic determinants of renal cancer will augment the means of primary prevention and target high-risk groups for screening aimed at early detection and treatment.

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