

3. EPIDEMIOLOGY OF BLADDER CANCER

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INTRODUCTION

In the United Kingdom, an estimated 12 900 cases of cancer of the urinary bladder are diagnosed and 5400 deaths from the disease occur each year (1). These account for 7.9% of all new cases of cancer among men and 3.2% of cases among women, as well as 4.4% of cancer deaths among men and 2.4% among women. In the USA, the corresponding figures are about 6.3% of all new cases among men and 2.5% among women, as well as 2.9% of cancer deaths among men and 1.5% among women (2). The lifetime risk of ever being diagnosed with bladder cancer is 3.38% among men in the USA (3). Among women, the lifetime risk is 1.18%. The lifetime risks of dying due to bladder cancer are 0.70% for men and 0.35% for women. More than 80% of bladder cancers diagnosed in the United Kingdom are histologically confirmed (4). Most of these are transitional cell carcinomas (82%); 2% are squamous cell carcinomas and 2.5% are adenocarcinomas.

DESCRIPTIVE FACTORS

International geographic variation

Internationally, incidence rates of bladder cancer among men vary more than 10-fold (4). High rates occur in western Europe and North America; relatively low rates are found in eastern Europe and several areas of Asia (Fig. 3.1). Some of the geographic variation may be the result of differing practices regarding the registration of 'benign' tumours or 'papillomas' as cancer, although rates reported by registries that include these categories are not consistently high compared with rates reported by other registries. The rankings of bladder cancer incidence rates among women are similar to those among men in North America, Oceania, and Asia, although the concordance is less in Europe.

BLADDER CANCER

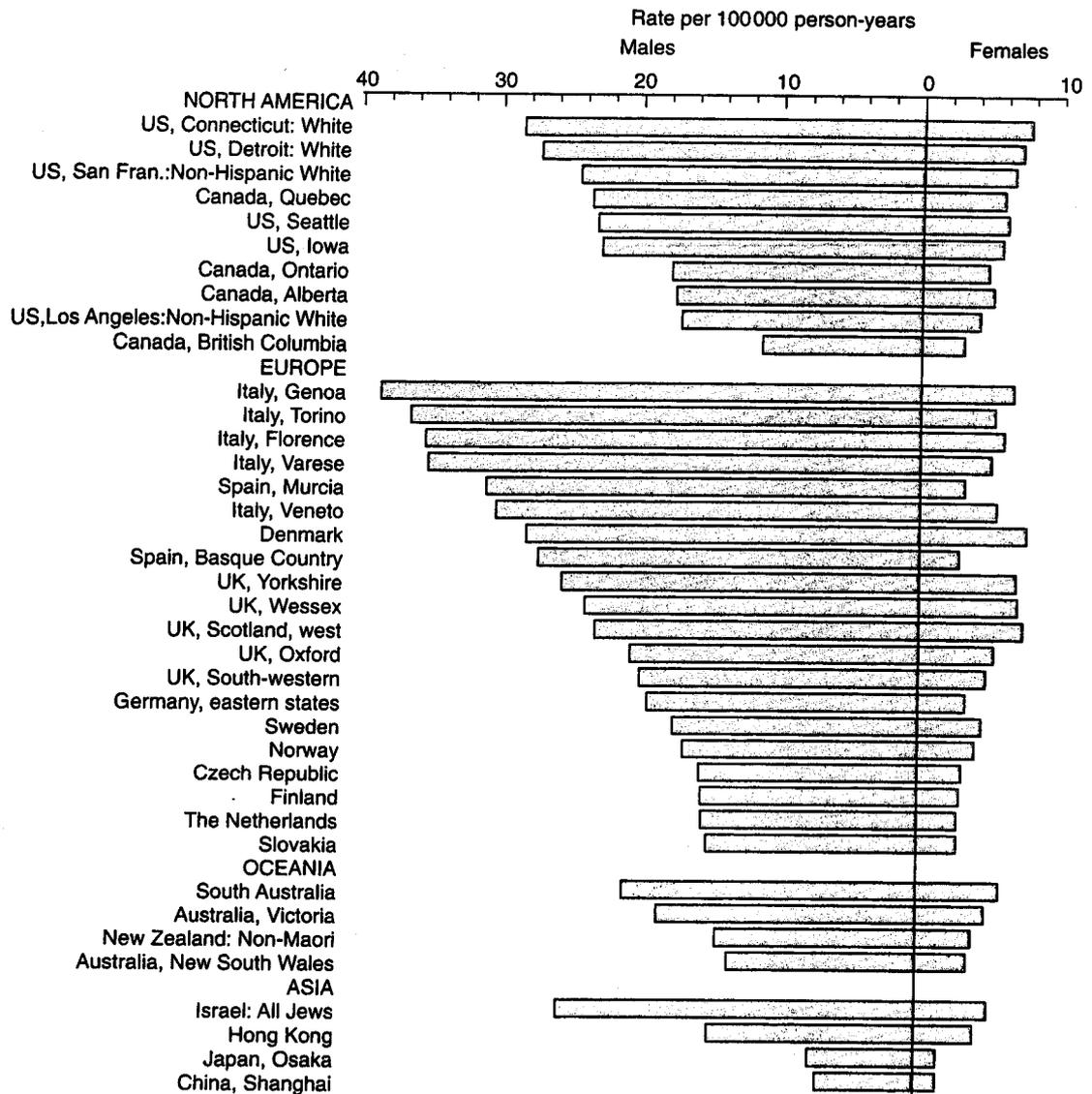


Fig. 3.1 International variation in age-adjusted (world standard) bladder cancer incidence rates per 100 000 person-years by sex, circa 1990

Gender and racial/ethnicity

Cancer of the bladder occurs primarily among white non-Hispanic men (Table 3.1) (5). The incidence rates among white Hispanic and black men in the US are about 50% of that among white non-Hispanics. Rates are lower yet among Asian groups, especially among Filipinos. The male/female rate ratio is 2.6 among black people, at least 3.3 among the other groups shown, and exceeds 4.0 among white non-Hispanics.

Table 3.1

BLADDER CANCER INCIDENCE BY RACIAL/ETHNIC GROUP AND SEX, US SEER PROGRAMME, 1988-92. RATES PER 100 000 PERSON-YEARS, AGE-ADJUSTED BY THE DIRECT METHOD USING THE 1970 US POPULATION STANDARD. BASED ON DATA FROM 11 SEER REGISTRIES (THE STATES OF CONNECTICUT, HAWAII, IOWA, NEW MEXICO, AND UTAH; THE METROPOLITAN AREAS OF ATLANTA, INCLUDING 10 RURAL COUNTIES, DETROIT, LOS ANGELES, SAN FRANCISCO/OAKLAND, SAN JOSE/ MONTEREY, AND SEATTLE/PUGET SOUND) (74)				
Racial/ethnic group	Males		Females	
	Cases	Rate	Cases	Rate
White non-Hispanic	19 594	33.1	6694	8.1
White Hispanic	896	16.7	337	4.5
Black	877	15.2	499	5.8
Japanese	224	13.7	86	4.1
Chinese	202	13.0	69	3.7
Korean	35	10.4	16	NA
Filipino	123	8.3	33	2.1

Age-specific patterns

Incidence rates rise sharply with age, although the increases are less rapid at older ages in some populations (Fig. 3.2). About two-thirds of cases occur among persons age 65 years and older. The geographic differences apparent in the age-adjusted rates generally persist across the entire age range, with little cross-over of the age-specific rates. Excesses among males compared with females become more pronounced with increasing age.

Time trends

Incidence rates of bladder cancer among men have been rising in many areas of the world (6). From the mid-1970s to about 1990, rates increased most notably in several parts of Europe: by more than 40% in Varese, Italy; west Scotland; the eastern states of Germany; and Finland (Fig. 3.3) (4,7-9). The rates of increase in North America have not been as pronounced as in Europe. Increases in incidence rates among women have been less rapid than those among men. In parts of Oceania and Asia, rates have remained relatively low.

The observed increases in incidence may be partly explained by changes in diagnostic practice. The distinction between *in situ*

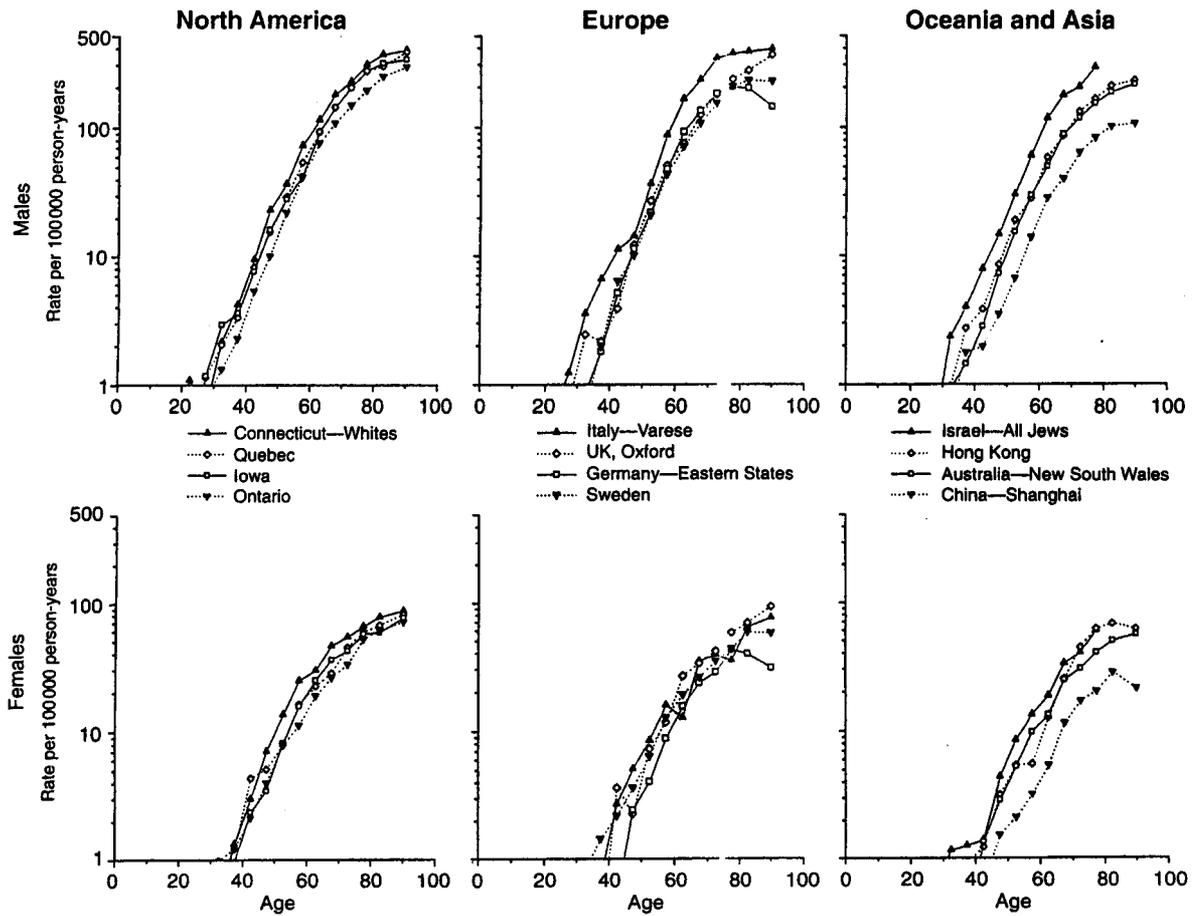


Fig. 3.2 Age-specific incidence rates for bladder cancer in selected regions of North America, Europe, Asia, and Oceania by sex, ca. 1990

and invasive disease may be difficult to make. The proportion of bladder tumours classified as 'carcinoma *in situ*' in the USA increased from less than 1% in 1969–71 to more than 7% about 1980, and considerably more in recent years (10–13). Much of the observed rise in incidence appears to be a result of an increase in the incidence of bladder cancer diagnosed at a localized stage (including *in situ*), with the rate of localized disease rising from 10.3 in 1975–78 to 11.8 in 1982–85 (11). This increase was accompanied, however, by a decrease in the incidence of unstaged bladder cancer (1.7–0.7), suggesting that some of the apparent increase in localized disease was the result of a reduction in the frequency of unstaged cases. Incidence rates of regional- and distant-stage bladder cancer remained virtually constant.

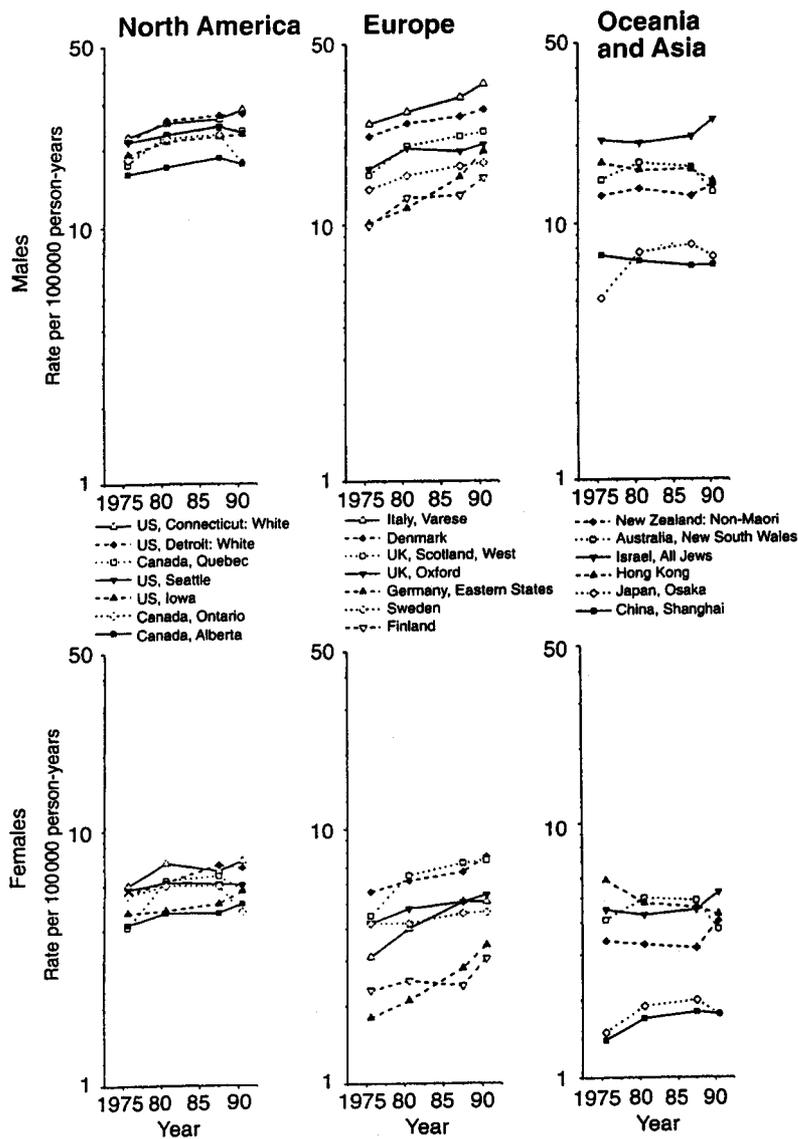


Fig. 3.3 Trends in age-adjusted (world standard) bladder cancer incidence rates in selected regions of North America, Europe, Asia, and Oceania by sex, 1973-77 to 1988-92

Stage of disease and survival

The stage of bladder cancer at diagnosis varies by age, sex, and race. The proportion localized at diagnosis in the USA declines with age from 82% among patients age 40-44 years to 70% among those 70-74 and 61% among those over 84 years (11). During 1986-93, the proportion localized at diagnosis was 76% among white men, 70% among white women, 62% among black men,

and 47% among black women (Table 3.2), with the proportion distant stage ranging from 2 to 13% (3).

Five-year relative survival rates among bladder cancer patients range from 85% for white men to 54% for black women. Stage of disease at diagnosis has a substantial impact on subsequent survival. Among whites, those diagnosed with localized disease have survival rates of 90% or greater, those with regional disease have survival rates of 43–53%, in contrast to those with distant spread whose survival rates are 8% or less. Among cases diagnosed at each stage of disease, white people experience a better prognosis than black people. The relative survival rate also is higher for white men than white women for each stage of disease. Overall, black–white survival differences are only partly explained by differences in stage at diagnosis; racial disparities in survival rates persist after adjustment for stage, histological type, grade, and socio-economic status (14,15). Relative survival rates, adjusted for general population mortality, also vary by age, with higher rates at younger ages and progressively lower rates at older ages.

Table 3.2

STAGE DISTRIBUTION AND 5-YEAR RELATIVE SURVIVAL RATES (%) AMONG BLADDER CANCER PATIENTS BY RACE, SEX, AND AGE, US SEER PROGRAMME, 1986–93 (3)				
	Whites		Blacks	
	Males	Females	Males	Females
Number of cases	20 326	6714	826	441
Stage distribution (%)				
Total	100%	100%	100%	100%
Localized	76	70	62	47
Regional	17	20	24	28
Distant	2	4	6	13
Unstaged	4	6	8	13
Five-year relative survival rate (%) by stage				
Total	85.1	75.1	65.0	53.6
Localized	95.4	90.0	82.0	82.0
Regional	52.6	43.1	37.7	39.0a
Distant	7.9	4.1	5.3	0.0
Unstaged	71.0	50.6	55.2a	32.0a
Five-year relative survival rate (percent) by age at diagnosis				
<45	93.8	90.5	80.0*	NA
45–54	90.8	86.7	77.9*	49.9†
55–64	88.2	83.4	68.5	56.7*
65–74	85.4	73.7	62.8	55.9*
75+	76.6	65.6	47.5*	44.9*

* The standard error of the survival rate is between 5 and 10 percentage points. † The standard error of the survival rate is greater than 10 percentage points.

Survival among patients with bladder cancer has increased over the last several decades. During the period from 1974–76 to 1986–93, 5-year survival increased from 73.7% to 82.5% among white people and from 47.4% to 60.9% among black people (3).

RISK FACTORS

Occupation

Following a number of clinical observations and mortality surveys, the study of occupational causes of bladder cancer gained momentum in the 1950s with the identification of bladder cancer hazards in the British dyestuffs and rubber industries (16,17). During the subsequent four decades, scores of studies have suggested approximately 40 potentially high-risk occupations. Despite this effort, the relations of many of these occupations to bladder cancer risk are unclear. Observed relative risks typically have been less than two, based on a small number of exposed subjects. Further, many reported associations have not been consistently found (18). Strong evidence of increased risk is apparent for very few occupational groups.

Dyestuffs workers and dye users

In 1895, Rehn suggested that men employed in the dyestuffs industry had increased risk of bladder cancer. It was not until 1954, however, that Case showed that dyestuffs workers in England and Wales had a 10–50-fold increased risk of death from bladder cancer due to exposure to two aromatic amines, 2-naphthylamine and benzidine (16). Exposure to a third aromatic amine, 1-naphthylamine, also appeared related to risk, but this elevation may have been caused by contamination with 2-naphthylamine. No excess risk was associated with exposure to aniline.

Two reports based on a cohort of dyestuffs workers in northern Italy (19,20) confirmed the increased risk from exposure to 2-naphthylamine and benzidine. A positive trend in bladder cancer mortality with increasing duration of employment was apparent; observed/expected ratios of 13, 34, and 71 were associated with employment as a dyestuffs worker for 10 years or less, 11–20 years, and more than 20 years, respectively. Dyestuffs workers involved in fuchsin and safranin T manufacturing also experienced high mortality (observed/expected = 62.5), which may have been the result of exposure to two precursors, *o*-toluidine and 4,4'-methylene bis(2-methylaniline). The increased risk among dyestuffs workers has also been observed in case-control studies

(21-26), with relative risks ranging from 1.7 to 8.8. Data from the United Kingdom indicate that bladder cancer risk among dyestuffs workers has been reduced since the introduction of protective measures and the subsequent banning of the industrial use of 2-naphthylamine and benzidine in 1950 and 1962, respectively (21,23).

Studies of the Italian cohort of dyestuffs workers have provided additional information on temporal patterns of risk. First, the mean time from start of exposure to death was 25 years, with a range of 12-41 years. Second, an inverse relationship between age at first exposure and risk was observed; risk was greatest for workers who started before age 25 years (observed/expected = 200.0). Third, a negative trend in relative risk with increasing time since last exposure was observed (19,20).

Users of finished dyes also may have an increased risk of bladder cancer, but the evidence is not as persuasive as that for dyestuffs manufacturing workers. Kimono painters, many of whom ingest benzidine-based dyes by licking the brush, have been found to have seven times the expected rate of bladder cancer. Coarse fishermen who use chrysoidine azo dyes to stain maggot bait have been reported to have an increased risk of bladder cancer (relative risk = 3.0 for fishermen who used bronze dyes for 5 or more years), although a more recent case-control study did not confirm this observation. Canadian dyers of cloth were reported to have a relative risk of 4.6 (26), and British textile dyers with more than 20 years employment had a relative risk of 3.4 (27). Two other studies, however, found no excess risk for dye users (18,28).

Aromatic amine manufacturing workers

Evidence that 2-naphthylamine and benzidine are human bladder carcinogens extends beyond the dyestuffs industry into the chemical industry where these aromatic amines, as well as a third bladder carcinogen, 4-aminobiphenyl, were manufactured (29). A fourfold risk was observed among 2-naphthylamine-exposed chemical workers in the USA (30). The observation of an increased risk of bladder cancer among workers involved in the commercial preparation of 4-aminobiphenyl resulted in the discontinuation of production of this aromatic amine, thus averting its widespread use (29). In a cohort of workers at a benzidine manufacturing facility, an overall excess of bladder cancer cases was apparent (SIR = 343) (31). Risk was greatest among those in the highest exposure category (SIR = 1303); little or no excess was observed for those in the low or medium exposure categories.

Corresponding to the introduction of preventive measures in the plant, a reduction in risk was observed for those first employed in 1950 or later compared with those first employed in 1945-49. In a cohort of benzidine-exposed workers in China, an overall SIR of 25 was reported, with risk ranging from 4.8 for those with low exposure to 158.4 for those with high exposure (32). Risks were elevated for both producers of benzidine (SIR = 45.7), as well as for users of benzidine-based dyes (SIR = 20.9).

Two structural analogues of benzidine, MDA (4,4'-methylene-dianiline) and MBOCA (4,4'-methylene-bis(2-chloroaniline)), are carcinogenic in animals (33), and possibly in humans, as well. MDA, a curing agent for certain resins, was associated with a threefold elevation of proportional mortality from bladder cancer (33). MBOCA, a curing agent used in the manufacture of rigid plastics, has been suggested as the exposure responsible for two non-invasive papillary tumours of the bladder in workers in a MBOCA production plant, although no invasive bladder tumours have been identified in the cohort (34). Manufacturing of another aromatic amine, 4-chloro-*o*-toluidine (4-COT), has been associated with excess bladder cancer mortality in a cohort of chemical workers in Germany (relative risk = 72.7) (35). This large excess in bladder cancer mortality has been confirmed recently in another cohort of German chemical workers exposed to 4-COT (36). In New York State, a cohort of chemical workers exposed to both *o*-toluidine and aniline also experienced elevated risk of bladder cancer (SIR = 360), which was probably attributable to exposure to *o*-toluidine (37).

Rubber workers

Antioxidants containing 2-naphthylamine were used in the rubber and electric-cable manufacturing industries in Great Britain (38). Case observed that the bladder cancer mortality among British rubber workers was twice the expected level (16). This excess was observed only among rubber workers employed before 1950; 2-naphthylamine was withdrawn from use in the British rubber industry in 1949 (39).

Excess risk of bladder cancer also has been reported among rubber workers in the USA (40,41) and Italy (42), although a few studies of rubber workers found no excess (22,23,43,44). The elevation of risk reported in most American studies (45-47) is less than that reported in the British and Italian studies. There was little exposure to 2-naphthylamine in the U.S. rubber industry (45), but many workers were exposed to another antioxidant, which can be metabolized to 2-naphthylamine (29).

Leather workers

An increased risk of bladder cancer among leather workers has been observed in at least 13 studies (23,27,48–59), although no increased risk was observed in three studies of leather tanners (60–62). Most of the positive results are from case-control studies; the relative risk varied from 1.4 to 6.3. The definition of 'leather worker' was not consistent among studies. Some reported increased risks for shoe makers and shoe repairers (53,54,59), whereas others reported elevations for workers in leather products manufacturing (52) or, more broadly, for workers exposed to leather or leather products (23,51,56).

The exposure responsible for the increased risk among leather workers is not known. Cole reported that the excess was associated with jobs that involved finishing and related processes, including cutting and assembling leather pieces (51). In a large case-control study in 10 areas of the USA (56), risk was found to be slightly higher for workers with possible exposure to leather dust compared with other types of leather exposure. In addition to leather dust, leather workers also are exposed to dyes, their solvents, and unreacted intermediates (26). Bladder cancer excesses among Italian leather tannery workers have been linked to exposure to benzidine-based leather dyes. Identification of carcinogens in the leather industry may require chemical analysis of substances encountered in the industry in combination with biological monitoring of workers (56).

Painters

Bladder cancer risk has been elevated among painters in many studies (5,18,22,23,43,51,53,55,59,63–72), although a few studies have suggested no excess risk (23,73). Most of the observed relative risks have been 1.2–1.5. Jensen reported a positive trend in risk with increasing duration of employment (43); painters employed 20 years or more had a relative risk of 4.1. In a large case-control study in the USA (18), painters experienced a 50% increased risk. Among those who started working before 1930, a trend in risk with increasing duration of employment was apparent; the relative risk for such painters employed 10 years or more was 3.0. Painters may be exposed to many known or suspected carcinogens in paints (e.g. benzidine, polychlorinated biphenyls, formaldehyde, and asbestos) and solvents (e.g. benzene, dioxane, and methylene chloride) (74).

Drivers of trucks and other motor vehicles

Excess risk of bladder cancer has been observed frequently among drivers of trucks, buses, or taxi cabs (43,48,65,66,75–85), although

Table 3.3

NUMBERS OF CASES AND CONTROLS AND RELATIVE RISK ACCORDING TO DURATION OF EMPLOYMENT AS A TRUCK DRIVER OR DELIVERYMAN AMONG THOSE FIRST EMPLOYED AT LEAST 50 YEARS BEFORE OBSERVATION. DATA FROM SILVERMAN ET AL. (86). THE TIME OF OBSERVATION WAS THE DATE OF DIAGNOSIS FOR CASES AND THE DATE OF INTERVIEW FOR CONTROLS. MALES WITH UNKNOWN SMOKING HISTORY, DURATION OF EMPLOYMENT, OR DATE STARTED EMPLOYMENT WERE EXCLUDED			
Duration of employment (years)	Cases	Controls	Relative risk*
Never any motor exhaust-related occupation	1353	2724	1.0
<5	74	129	4.2
5-9	32	45	
1.410-24	33	31	2.1
25+	22	19	2.2

(X=3.93; P < 0.0001)
 * Relative to a risk of 1.0 for males never employed in a motor exhaust-related occupation; adjusted for age and smoking.

one Swedish study found no elevation in risk for truck drivers (68). Overall relative risks varied from 1.3 to 2.2. A positive trend in risk with increasing duration of employment was observed for drivers in most studies, with relative risks for long-term drivers ranging from 2.2 to 12.0 (43,65,76,84-86). In the largest study of bladder cancer among truck drivers, the trend in risk by duration of employment was most consistent for those first employed at least 50 years before observation (86) (Table 3.3). Although the specific exposure responsible for the elevation of risk among drivers has not been identified, one likely candidate is motor exhaust. Exhaust emissions contain polycyclic aromatic hydrocarbons (PAHs) and nitro-PAHs, which are highly mutagenic, as well as carcinogenic in laboratory animals (86).

Aluminium workers

Wigle in 1977 suggested that an elevated incidence of bladder cancer among men in the Chicoutimi census division of the Province of Quebec was the result of exposures incurred in the aluminium refining industry (87). Subsequently, increased bladder cancer mortality was observed in three cohort studies of aluminium smelter workers (88-90). The elevated risk in the aluminium industry has been associated with employment in the Soderberg potrooms (relative risk = 2.4) (91-93). Risk increased with increasing duration of employment in this department.

Table 3.4

RELATIVE RISKS PREDICTED FOLLOWING 40 YEARS OF EXPOSURE TO TAR VOLATILES. ASSUMES THAT A MINIMUM OF 10 YEARS ELAPSES BEFORE AN EFFECT OF EXPOSURE OCCURS					
BSM			BaP		
Concentration (mg/m ³)	Relative risk*	95% CI	Concentration (mg/m ³)	Relative risk*	95% CI
1.0	8.1	3.8-17.4	10	10.2	4.6-21.8
0.5	4.5	2.40-9.2	5	5.6	2.8-11.4
0.2	2.42	1.56-4.3	2	2.84	1.72-5.2
0.1	1.71	1.28-2.64	1	1.92	1.36-2.15
0.05	1.35	1.14-1.82	0.5	1.46	1.18-2.04
0.02	1.14	1.06-1.33	0.2	1.18	1.07-1.42
0.01	1.07	1.03-1.16	0.1	1.09	1.04-1.21

* Estimates of risk are relative to a risk of 1.0 for unexposed persons. BSM, benzene-soluble matter; BaP, benzo[*a*]pyrene.
95% CI = 95% confidence interval.

Relative risks were 1.0 for less than 1 year, 1.9 for 1-9 years, 3.0 for 10-19 years, 3.2 for 20-29 years, and 4.5 for 30 years or more (92). Armstrong used historical data on workplace exposures to better quantify exposure-response relationships (Table 3.4) (94).

Coal-tar pitch volatiles emitted from anodes in the Soderberg electrolytic reduction process may be responsible for the observed bladder cancer excess (92). The bladder carcinogens within tar volatiles are unknown, but aromatic amines (particularly 2-naphthylamine) are suspected (94).

Other occupations and exposures

Employment as a machinist has been associated with bladder cancer risk in many studies (18,95), although the increase in risk has not been consistently linked to a specific type of work. Machinists are exposed to mists from oils used as coolants and lubricants in metal machining processes (84,96). Some cutting and lubricating oils contain potentially carcinogenic PAHs (84) and nitrosamines (97).

Increased risk of bladder cancer has also been reported for many other occupational groups: metal workers, printers, chemical workers (other than those involved in manufacturing aromatic amines), hairdressers, dry cleaners, carpenters, construction workers, miners, gas workers, coke plant workers, auto mechanics, petroleum workers, railroad workers, textile workers, tailors, engineers, butchers, clerical workers, cooks and kitchen workers, food processing workers, electricians, gas station attendants,

medical workers, pharmacists, glass processors, nurserymen, photographic workers, security guards and watchmen, welders, sailors, stationary firemen or furnace operators, stationary engineers, paper and pulp workers, roofers, gardeners, bootblacks, and asbestos workers (18,40,98,99). Findings for most of these occupations are not as persuasive as those discussed earlier, and require corroboration.

Strong evidence of human bladder carcinogenicity exists for occupational exposure to certain aromatic amines (29). In addition, many other occupational exposures are suspected of causing bladder cancer, including PAHs (100); diesel engine exhaust (84); leather dust (83); mineral oils (95,101); combustion and pyrolysis products from natural gas and other unspecified substances (83,101); chlorinated solvents (102), particularly those used in dry cleaning (103); creosote (104); herbicides/pesticides (18,22); and asbestos (18). Further research is needed to determine the carcinogenicity of these occupational exposures.

The relation between occupation and bladder cancer risk is dynamic (18). With the elimination of bladder carcinogens from the workplace and the advent of new chemicals, changing worker exposures are generating shifts in 'high-risk occupations.' For example, risks among rubber and leather workers have diminished over time (56,39), whereas new high-risk occupations, such as truck driver and aluminium smelter worker (86,87), have emerged. Thus, occupational bladder cancer continues to be a public health problem, with risks changing over time and from population to population.

TOBACCO

Cigarettes

Cigarette smoking is well-established as a cause of bladder cancer, although the association is not as strong as that observed for smoking and several other cancers. An association between cigarette smoking and bladder cancer has been observed in more than 30 case-control studies and in more than 10 cohort studies (82,105-123). Overall, smokers appear to have two to three times the risk of non-smokers. Data from correlational studies also are consistent with a smoking-bladder cancer association. In the USA, bladder cancer mortality rates at the state level are highly correlated with per capita cigarette sales (124). Birth cohort-specific patterns of bladder cancer incidence and mortality parallel the smoking patterns of those cohorts (125,126).

Risk increases with increasing intensity of smoking (packs per day), with relative risk estimates for moderate to heavy smokers typically ranging from about 2.0 to 5.0, compared with non-smokers (82,105,107–111,113,114,117,121–123). However, the shape of the dose–response curve has varied among the studies. Some have reported a regular gradient in risk with amount smoked, whereas others have reported little change in risk from moderate to heavy smoking levels (82,105,110,113,114,117,122). Duration of smoking has been evaluated less often than intensity, but a regular duration–response relationship has been observed in most studies that investigated the issue (105,107–110,113,114,122,123).

Cessation

Cessation of cigarette smoking has been associated with a 30–60% reduction in bladder cancer risk in many studies (114). However, the pattern of change in risk in relation to time since quitting is less clear (Table 3.5). Four studies suggested that the risk of former smokers who stopped smoking for many years approximates that of non-smokers (110,122,127,128). Other studies indicate that a reduction in risk occurs within the first 2–4 years after stopping, but that risk does not continue to decline with increasing time since quitting (105,107,113,123). In most of these studies, the effect of time since quitting was not adjusted for the effects of age at starting and duration of smoking. Hartge however, estimated relative risk by length of time since quitting among intermittent former smokers (i.e. smokers who quit for at least 6 months, started again, and subsequently quit) with adjustment for age at starting and duration of smoking, as well as age at observation. Among all former smokers, the pattern of risk by time since quitting was weak and inconsistent (Table 3.5). When this analysis was restricted to intermittent former smokers, risk declined 50% within the first 4 years of stopping, but did not continue to decrease with increasing time since quitting. The almost immediate reduction in risk within the first few years after quitting suggests that cigarette smoke contains agents that act at a late stage of bladder carcinogenesis (113).

Filtration

People who smoke unfiltered cigarettes exclusively have been reported to experience about a 35–50% higher risk of bladder cancer than those who smoke filtered cigarettes exclusively (113,129). However, switching to filtered cigarettes does not

Table 3.5

RELATIVE RISKS OF BLADDER CANCER ACCORDING TO TIME SINCE QUITTING SMOKING				
Ref. no.	Years since quitting	Relative risk		Comments
		All smokers	Intermittent smokers	
128	0	2.7		Risks relative to a risk of 1.0 for non-smokers, adjusted for age at observation and race
	1-3	2.9		
	4-6	1.9		
	7-10	1.4		
	11-15	1.6		
	16+	1.1		
133	0	1.0		Risks relative to a risk of 1.0 for current smokers, adjusted for age at observation and lifetime cigarette consumption
	2-15	0.6		
	15+	0.5		
127	0-5	1.7		Risks relative to a risk of 1.0 for non-smokers, adjusted for age at observation
	6-15	1.0		
	16-25	1.1		
	26-35	0.9		
108	0	1.0		Risks relative to a risk of 1.0 for current smokers, adjusted for age at observation and lifetime consumption
	2-15	0.6		
	15+	0.4		
Ref. no.	Years since quitting	Relative risk		Comments
		All smokers	Intermittent smokers	
113	0	1.0	1.0	Includes women; risks relative to a risk of 1.0 for current smokers, adjusted for age at observation, sex, race, duration (all smokers); and age at observation, sex, race, duration, age started (intermittent smokers)
	1	0.9	0.7	
	2-4	0.6	0.5	
	5-9	0.8	0.4	
	10-19	0.7	0.4	
	20+	0.9	0.5	
115	0		1.0	Risks relative to a risk of 1.0 for current smokers or those who stopped less than 2 years before diagnosis/interview, adjusted for age at observation, intensity, duration
	2-4		0.6	
	5-9		0.3	
	10-19		0.2	
	20+		0.2	
137	0		1.0	Risks relative to a risk of 1.0 for current smokers, adjusted for age at observation, duration, intensity
	<3		0.4	
	3-9		0.4	
	10+		0.6	
105	0		1.0	Risks relative to a risk of 1.0 for current smokers, adjusted for age at observation, intensity, duration, education, race, and marital status
	<6		0.7	
	7-12		0.7	
	13+		0.7	
107	0		1.6	Risks relative to a risk of 1.0 for non-smokers, adjusted for age at observation and lifetime cigarette consumption
	>1-<5		1.1	
	>5-<10		0.8	
	10+		1.4	
110	2-4		2.8	Risks relative to a risk of 1.0 for non-smokers, adjusted for age at observation and sex
	5-14		1.9	
	15+		1.0	
122	0		3.1	Risks relative to a risk of 1.0 for non-smokers, adjusted for age at observation
	1-9		1.9	
	10-19		1.5	
	20+		1.2	

Table 3.6

ESTIMATED RELATIVE RISKS OF BLADDER CANCER, ACCORDING TO USE OF FILTERED AND UNFILTERED CIGARETTES, AMONG CURRENT SMOKERS*				
Filtered cigarettes/day	Unfiltered cigarettes/day			
	None*	1-19	20-39	>40
None	2.4 (1.3-4.5)	3.13.6 (1.7-5.6)	(1.8-6.9)	
1-19	1.0 (1.4-4.1)	2.4 (1.3-5.5)	2.7 (0.8-8.5)	2.7
20-39	1.9 (1.1-3.3)	2.1 (1.2-3.7)	3.2 (1.9-5.5)	3.2 (1.5-6.7)
>40	3.0 (1.4-6.5)	2.9 (1.2-7.0)	3.6 (2.0-6.6)	3.9 (2.1-7.1)
<i>No. of cases, controls</i>				
None		87, 56	172, 40	61, 57
1-19	102, 29	165, 122	35, 28	8, 6
20-39	90, 48	100, 68	328, 321	26, 26
≥40	24, 21	16, 15	71, 79	73, 85

appear to reduce the excess risk (107,113,122,129) (Table 3.6). There are several possible explanations for these inconsistent findings. First, people who smoke filtered cigarettes exclusively may have different smoking histories or habits than do people who first smoked unfiltered cigarettes. For example, the latter group may start smoking earlier, or take more puffs of smoke per cigarette. Second, the effect of changing from unfiltered to filtered cigarettes may be quite small, given the small difference between the risk for smokers of only filtered cigarettes and that for smokers of only unfiltered cigarettes. Third, interview data on changing from unfiltered to filtered cigarettes may contain inaccuracies that mask a real, but small, reduction in excess risk. Fourth, smokers of only filtered cigarettes may not, in fact, have a lower risk than smokers of only unfiltered cigarettes; any observed reduction in risk may have been a chance effect.

Inhalation

Cigarette smokers who inhale deeply may have a greater risk than those who do not (107,109,130,131). Morrison observed 30-40% elevation of risk for male cigarette smokers who inhaled deeply compared with those who inhaled somewhat or not at all (132). An association between inhalation and risk has not been observed, however, in some other studies (113,133,134).

Black vs. blond tobacco

Smokers of black tobacco have a risk of bladder cancer two to three times higher than the risk in smokers of blond tobacco (109,115, 119,135–137). Three laboratory observations support this epidemiological observation. First, black tobacco has higher concentrations of aromatic amines, some of which are human bladder carcinogens, than does blond tobacco (137). Second, blood levels of 4-aminobiphenyl haemoglobin adducts, as well as adducts of several other aromatic amines, are higher for smokers of black than of blond tobacco (138). Third, the urine of smokers of black tobacco is more mutagenic than is the urine of smokers of blond tobacco (139,140).

Pipes, cigars, and smokeless tobacco

The roles of pipes, cigars, snuff, and chewing tobacco in the aetiology of bladder cancer are unclear. Evidence of increased risk is strongest for pipe smokers, particularly those who never smoked any other type of tobacco. At least 10 studies have suggested that pipe smokers experience elevated risk compared with non-smokers (relative risks typically ranged from 1.3 to 3.9) (59,108, 116,132–134,141–144), whereas five studies have suggested no association (107,111,122,145,146). A dose-response relationship has been found only rarely, although pipe smokers who inhale deeply do appear to be at greatest risk (133,141).

Weak and inconsistent relationships have been observed between bladder cancer risk and the other forms of tobacco use. For cigars, some studies have been positive (134,141–143), whereas others have shown little or no association (59,78,107,116,133,144–147). In the positive studies, relative risks for cigar smokers compared with non-smokers varied from about 1.3 to 2.5. Risks associated with the use of snuff or chewing tobacco have been assessed in a small number of studies (59,107,133,141,142,145). Of these studies, an increased risk of bladder cancer for snuff users who never smoked cigarettes has been observed in only one (143), and for users of chewing tobacco in only two (142,143).

DIETARY FACTORS

Coffee drinking

An association between coffee drinking and bladder cancer was suggested by a population-based, case-control study conducted in Massachusetts (relative risk = 1.3 for men and 2.5 for women)

(147). Since that report, many studies have evaluated this association. More than 10 studies indicated little or no overall association in either sex (112,121,143,148-155); eight studies were positive for men, but not for women (133,146,156-161); four studies were positive for women, but not for men (162-165); one study was positive for both men and women (78); and six studies suggested an overall positive association, but sex-specific risks were not examined (24,115,118,119,166,167). In most of the studies reported as positive, however, the relative risk of bladder cancer in coffee drinkers compared with non-drinkers has been less than 2. A regular dose-response relationship has been observed only infrequently (78,115,119,146,153,156,157,161), although risk was elevated among drinkers of large amounts of coffee in several studies (121,150,152,159,168,169). The weakness and inconsistency of the observed associations indicate that if coffee is a bladder carcinogen, it is a weak one. Alternatively, associations between coffee drinking and bladder cancer could be the result of residual confounding by smoking (152,159,170). Because cigarette smoking is both an important risk factor for bladder cancer and a strong correlate of coffee drinking, tight control for smoking is required to estimate the bladder cancer risk associated with coffee drinking alone. Although relative risk estimates in nearly all cited studies were adjusted for smoking, adjustment may have been inadequate if smoking categories were too broad. Confounding by smoking also could be introduced by inaccurate recall of smoking habits. In this instance, it might not be possible to control completely the effect of smoking in estimating the risk of bladder cancer associated with coffee drinking.

To avoid residual confounding by smoking, the effect of coffee drinking on bladder cancer risk can be evaluated in lifelong non-smokers. Few studies, however, have had adequate numbers of non-smokers to estimate this risk with reasonable precision. Of these, some indicated no increased risk associated with coffee drinking (133,151,152,156), whereas others suggested an increased risk (118,121,143,149,154,157,159,161,165,166). Of the positive studies that distinguished between men and women in examining the coffee drinking effect, one is positive in both men and women (121), four are positive in men but not in women (149,157,159,161), and one is positive in women but not in men (165).

ARTIFICIAL SWEETENERS

Artificial sweeteners were suggested as potential human bladder carcinogens by the results of animal experiments. The most important evidence was an excess of bladder cancer in rats exposed

to high doses of saccharin *in utero* and weaned to a saccharin-containing diet (171). Saccharin did not induce bladder cancer in rats or other animals fed saccharin only after birth (172).

Epidemiological studies have not substantiated a relationship between artificial sweeteners and bladder cancer. Bladder cancer mortality rates were found not to be elevated among diabetics in the USA (173) or Great Britain (174). The time trend in bladder cancer mortality in England and Wales has not appeared related to saccharin consumption (125). Bladder cancer incidence among the Danish population born during World War II, a group with higher *in utero* saccharin exposure than previous birth cohorts, was not increased in either men or women during the first 30–35 years of life (175).

Several case-control studies have provided data on the relationship between artificial sweeteners and bladder cancer. Results of most studies have been negative (24,115,119,146,148,151,153,163–165,176–182). One study suggested a positive association in men (relative risk = 1.6) (133,183), but there was an inverse association in women (relative risk = 0.6). Moreover, a weak inverse association between use of artificially sweetened beverages and bladder cancer was apparent in both men and women. In a large US population-based, case-control study, the relative risk for subjects who had ever used artificial sweeteners was 1.0 (184). Those who reported very frequent use of artificial sweeteners appeared to have a small elevation in risk, but the dose-response pattern was irregular. A positive association was observed in two study subgroups, white male heavy smokers and non-smoking white females with no known exposure to bladder carcinogens. However, the reason for these associations is uncertain (185,186).

It is difficult to separate the effects of saccharin and cyclamates in the USA and Canada because both substances were used extensively in both countries. Studies conducted in England and Japan, however, pertain primarily to the use of saccharin (170). Results of the latter studies suggested that use of saccharin is not associated with increased bladder cancer risk.

The findings of nearly all studies indicate that the use of artificial sweeteners confers little or no excess risk of human bladder cancer. If, in fact, saccharin is a very weak carcinogen, such a low-level effect may not be detectable in epidemiological studies (185).

ALCOHOL DRINKING

Most studies that have evaluated alcohol drinking as a risk factor for bladder cancer have not supported a positive association (24,59,118,133,146,148,151,155,186,187). Elevated risks related to the consumption of specific types of alcoholic beverages have

been reported in a few studies (78,115,119,163,165,188), but these findings have not been consistent with respect to type of beverage or sex, and regular dose-response relationships have not been apparent. Thus, the positive findings are likely to be the result of chance or residual confounding by smoking.

OTHER DIETARY FACTORS

Of the dietary factors that have been evaluated in relation to bladder cancer, the most consistent evidence supports a protective effect for vegetables and fruits. Relatively high vegetable and fruit consumption has been associated with relatively low risk in most studies (108,118,119,160,167,168,179,189), but not all (190,191). Evidence of a protective effect for vegetables is stronger, however, than that for fruit (192).

The role of other dietary factors in human bladder carcinogenesis less clear. Dietary supplements of natural and synthetic retinoids inhibit bladder carcinogenesis in laboratory animals (193). However, results of epidemiological studies are inconsistent. Increasing intake of foods that contain vitamin A, particularly milk, has been associated with decreasing risk of bladder cancer in four case-control studies (143,160,167,189) and one cohort study (168), but at least two other case-control studies have not supported this relationship (165,194). The use of vitamin A supplements also has been associated with decreased risk (195). Serum levels of retinol, retinol binding protein, and carotenoids do not appear related to risk (179,194,196), although two studies reported a decreased risk associated with increased carotenoid consumption (167,181). In addition, high intake of dietary vitamin C and frequent use of vitamin C supplements were both associated with decreased risk in one study (189).

Increased bladder cancer risk also has been associated with relatively high intake of cholesterol (165), with total fat (18) and saturated fat (190), with fatty meals (108), with fried foods (168,189,195), and with relatively high pork and beef consumption (104). A nearly linear increasing trend in risk with decreasing serum levels of selenium was observed in a nested case-control study in Washington County, Maryland (196).

DRUGS

Analgesics

Heavy consumption of phenacetin-containing analgesics was first linked to cancers of the renal pelvis, ureter, and bladder by a series

of case reports (197). There have been only a few case-control studies in which the relation between use of phenacetin and risk of bladder cancer has been evaluated (198-201). Fokkens reported that Dutch subjects who had a lifetime consumption of at least 2 kg had a relative risk of 4.1 compared with incidental users or non-users (198). McCredie *et al.* found a relative risk of 2.0 in Australian women age 45-85 years who had a lifetime consumption of at least 1 kg (199,200). Piper *et al.* reported a relative risk of 6.5 in US women age 20-44 years who had used phenacetin-containing compounds for at least 30 days in a year (201). Despite these fairly strong associations, a regular gradient in risk with increasing dose was demonstrated only in the Australian study (199). Further study of the relation between phenacetin and bladder cancer will be difficult because most Western countries no longer allow phenacetin-containing analgesics to be sold.

Acetaminophen was assessed as a risk factor in studies in Australia (200) and the US (201,202). Results of these studies suggest that heavy use of acetaminophen-containing analgesics does not increase risk. However, acetaminophen did not become popular until the 1970s. Thus, subjects in the two earlier studies may not have had sufficient time since initial exposure for bladder cancer to develop.

Cyclophosphamide and chlornaphazine

Cyclophosphamide, an alkylating agent that has been used to treat both malignant and non-malignant diseases since the early 1950s, has been linked to risk of bladder cancer in many case reports and case series (203,204). Cyclophosphamide has been shown to produce bladder tumours in both rats and mice (203). Patients with non-Hodgkin's lymphoma who were treated with high doses of cyclophosphamide experienced a sevenfold risk of bladder cancer in a Danish study (205). In the largest non-Hodgkin's lymphoma study to date, Travis and colleagues (206) found that cyclophosphamide-related bladder cancer is dose-dependent, with relative risks of 2.4, 6.0, and 14.5 for patients receiving cumulative doses of less than 20 g, 20-49g, and 50 g or more, respectively. Results of a study of ovarian cancer patients treated with cyclophosphamide indicated a fourfold increased risk of bladder cancer (207). Additional groups of patients, such as long-term survivors of breast cancer who were treated with lower doses of cyclophosphamide as adjuvant chemotherapy, should be studied in order to clarify further the extent of the carcinogenic risk associated with use of this important antineoplastic drug.

In the 1960s, the antineoplastic drug chlornaphazine was linked to the development of bladder cancer (208). Chlornaphazine is

related chemically to 2-naphthylamine. However, this drug was never widely used (209).

UROLOGICAL CONDITIONS

Urinary tract infection

A positive association between urinary bladder infection and risk of bladder cancer has been reported in a number of case-control studies (49,59,133,153,210-212), although two studies found no support for a causal association (213,214). In the USA, Kantor found an increased risk associated with urinary tract infections in both men and women; subjects with a history of at least three infections had a relative risk of 2, compared with those with no infections (211). In addition, bladder infection was more strongly associated with squamous cell than with transitional cell cancer, a striking parallel to the relation between schistosomiasis and squamous cell bladder cancer. The bladder infection/squamous cell carcinoma relationship also is supported by a report of increased risk of squamous cell carcinoma among young female paraplegics, a group with frequent and severe chronic urinary tract infections (53). One weakness, however, in most studies conducted to date is that information on dates of the bladder infections was not obtained. Thus, the occurrence or diagnosis of infections may have been the consequence of early bladder cancer, rather than a cause of the disease.

Urinary stasis

If carcinogens are present in urine, urinary retention or stasis might increase the risk of developing bladder cancer by increasing the duration of contact of the carcinogens with the bladder mucosa (215). Although urinary stasis has not been investigated directly as a risk factor, several findings are consistent with the hypothesis that stasis is related to risk. First, conditions that cause stasis, such as benign prostatic hypertrophy, have been associated with increased risk (210,216,217). It is uncertain, however, whether these conditions preceded the bladder cancer or were related to its diagnosis. Second, infrequent micturition and high urine concentration, both of which increase urine contact with bladder epithelium, were more prevalent in high-risk areas of Israel than in low-risk areas (218). Third, the upper hemisphere of the bladder (dome), which has less contact with urine than the rest of the bladder, is a relatively infrequent site of bladder tumours (215). Fourth, dogs exposed to 2-naphthylamine do not develop tumours in bladders that have not been in contact with

urine (219). Finally, urine itself appears to be a promoter of bladder carcinogenesis in the rat (220,221).

Urine pH

In vitro and animal evidence suggests a role for urine pH in aromatic amine carcinogenesis (222–226). *N*-glucuronides of *N*-hydroxy derivatives of 2-naphthylamine, 1-naphthylamine, and 4-aminobiphenyl are hydrolysed under acidic conditions and can bind to DNA (223). Acidic urine has a similar influence on the hydrolysis of *N*-glucuronides of benzidine and several of its metabolites (227,228). A cross-sectional study of workers exposed to benzidine and benzidine-based dyes showed that acidic urine pH increased benzidine–DNA adduct levels in exfoliated urothelial cells (229). However, the direct influence of urine pH on bladder cancer risk in humans has not been evaluated. Diet is an important determinant of urine pH in the healthy general population (230). In particular, meat, fish, cheese, and grain products contribute to urine acidification, whereas most vegetables and fruits contribute to urine alkalization (230). As discussed earlier, high intake of vegetables and fruits has been consistently associated with decreased bladder cancer risk in epidemiological studies (155,192). Although a role for vegetables and fruits in bladder cancer prevention has been proposed, the effect of vegetables and fruits on urine pH as a modifier of bladder cancer risk needs further evaluation.

SCHISTOSOMA HAEMATOBIMUM

For nearly 90 years it has been thought that *S. haematobium* infection is related to increased risk of bladder cancer (231); results of most studies indicate that this relationship is causal (232,233). The proportional incidence of bladder cancer is high in developing countries where schistosomiasis is endemic (234). The percentage of bladder cancers that are squamous cell tumours is also much higher in endemic areas than it is in non-endemic areas. In Egypt, 70% or more of bladder cancers are squamous cell (234), compared with about 2% in the USA.

Five of six case–control studies indicated that the prevalence of schistosome infection was higher among bladder cancer patients than among controls (235–239). In series of cases from South Africa and Zambia, *S. haematobium* ova were found in higher proportions of patients with squamous cell than with transitional cell tumours (236,240). Bladder tumours have been produced in monkeys infected with *S. haematobium* (241), but these were

transitional cell rather than squamous cell tumours. Squamous metaplasia has been observed in the bladders of hamsters infected experimentally with *S. haematobium* (242).

Several mechanisms by which schistosomiasis infection predisposes to bladder cancer have been suggested. First, chronic inflammation by calcific ova and urinary retention caused by infection might affect the absorption of carcinogens from the urine (243). Second, the urine of patients infected with *S. haematobium* or bacteria might have greater amounts of potentially carcinogenic nitroso compounds than that of non-infected patients (234). Third, the schistosoma antigen might depress the immunocompetence of infected patients (244).

RADIATION

Ionizing radiation causes bladder cancer, although this exposure contributes very little to bladder cancer incidence in the general population. Women who received therapeutic pelvic radiation for dysfunctional uterine bleeding appear to have a two- to fourfold risk of bladder cancer (245,246). In a large, international study of cervical cancer patients treated with radiation, high-dose radiotherapy was associated with a fourfold risk of bladder cancer (247). Higher risks were experienced by women under age 55 years when first treated, compared with those age 55 or older. Risk increased with increasing dose to the bladder. Risk also increased with time since exposure, with the relative risk reaching 8.7 for patients treated at least 20 years earlier.

Radioactive iodine (iodine-131) exposure has also been associated with elevated bladder cancer risk. A threefold risk was found among women who had a thyroid uptake procedure with iodine-131 (153). A cohort of patients treated with high dose iodine-131 for thyroid cancer also experienced excess risk (248).

Follow-up of atomic bomb survivors in Hiroshima and Nagasaki revealed a dose-response relationship between radiation exposure and bladder cancer mortality. Bladder cancer mortality also appeared to be elevated in two groups of workers at nuclear installations in the United Kingdom (249,250), but an excess was not apparent in US nuclear workers (251).

DRINKING WATER AND FLUID INTAKE

An association between by-products of chlorination in drinking water and bladder cancer risk was first suggested by ecological

studies (252), and later by two case-control studies based on death certificates (253).

In seven investigations, detailed information was available on water quality and temporal aspects of exposure. These studies support the association between chlorination by-product levels in drinking water sources and bladder cancer risk. In Washington County, Maryland, residents supplied with chlorinated surface water had higher bladder cancer incidence rates than did those who consumed unchlorinated deep well water (relative risks were 1.8 and 1.6 for men and women, respectively) (254). In a subsequent nested case-control study in Washington County, bladder cancer risk was weakly associated with duration of exposure to municipal water, with a non-significant odds ratio of 1.4 for subjects with more than 40 years of exposure (255). In the NCI study conducted in 10 areas of the USA, risk increased with level of intake of beverages made with tap water (256). The gradient was restricted to subjects with at least 40 years of exposure to chlorinated surface water and was not observed among long-term consumers of non-chlorinated ground water. Among subjects whose residences were served by a chlorinated surface water source for at least 60 years, a relative risk of 2.0 was estimated for heavy consumers compared with low consumers of tap water. In a study in Massachusetts, residents of communities supplied with chlorinated drinking water experienced higher bladder cancer mortality than did those of communities exposed to water containing lower concentrations of chlorination by-products (mortality odds ratio = 1.6) (257). In a Colorado study, years of exposure to chlorinated surface water was significantly associated with increased bladder cancer risk (258). The relative risk for those exposed for more than 30 years to chlorinated surface water was 1.8 compared with subjects with no exposure. In Ontario, Canada, bladder cancer risk increased with both duration and concentration of exposure to chlorination by-products, with an odds ratio of 1.63 for subjects exposed to a trihalomethane level of at least 50 $\mu\text{g/l}$ for 35 or more years (259). In an Iowa study, risk increased with duration of chlorinated-surface water use, with the odds ratio reaching 1.5 for those with at least 60 years of exposure (260). In both the Iowa and Washington County case-control studies, cigarette smoking appeared to enhance the effect of exposure to chlorination by-products. It has been suggested that the effect of chlorination by-products may, in fact, be enhanced by cigarette smoking (261).

A relation between exposure to high levels of arsenic in artesian well water and bladder cancer mortality has been suggested by surveys conducted in an endemic area of chronic arsenic toxicity,

manifested by skin cancer and blackfoot disease in Taiwan (262–264). These findings have been confirmed by ecological studies in Argentina (265) and Chile and by cohort studies in Taiwan (266) and Japan (267). Ingestion of arsenic also has been associated with increased bladder cancer mortality among a cohort of patients treated with Fowler's solution (potassium arsenite) (268). In addition, biological evidence supporting the hypothesis that chronic ingestion of high levels of arsenic is carcinogenic to the bladder is provided by observations of increased micronuclei in exfoliated bladder cells of exposed individuals (269,270). In contrast, the effect of lower levels of arsenic ingestion has received little attention to date (271).

Total fluid intake may be related to bladder cancer risk, but the results have been equivocal. Increased total fluid consumption has been associated with decreased risk (210); with a positive trend in risk (108,150,161,261); and with no excess risk (59,180,260).

HAIR DYES

Three lines of evidence suggest that the use of hair dyes may be associated with increased bladder cancer risk. First, hairdressers and barbers have been reported to be at elevated risk (272,273). Second, findings from mutagenicity tests and animal experiments indicate that some compounds in hair dyes are mutagens and possible bladder carcinogens (274). Third, people who dye their hair appear to excrete dye compounds in their urine (274). Results of several epidemiological studies, however, are negative (274).

FAMILIAL OCCURRENCE

Evidence for familial predisposition to bladder cancer comes mainly from clinical reports, but elevated risks among persons with bladder cancers in close relatives have been identified in a few case-control studies (78,153,275–277). In the largest case-control study to date, familial risks were especially high among those with environmental exposures, such as heavy cigarette smoking, suggesting genetic and environmental interactions. Familial occurrences provide an opportunity to identify genetic markers of susceptibility, including metabolic polymorphisms, pharmacogenetic traits, or oncogene expression.

MOLECULAR EPIDEMIOLOGY

Biological markers have become a focal point of research on bladder cancer aetiology (136,137,278). They include biomarkers of exposure, genetic susceptibility, and disease (i.e. tumour mutations).

BIOLOGICAL MARKERS OF EXPOSURE

Urinary mutagens

Investigations of urinary mutagenicity in relation to bladder cancer have focused on correlating exposure to bladder cancer risk factors with the presence of mutagens in the urine. Cigarette smoking has been found to be associated with mutagenic activity in the urine (279–280). The level of mutagenic activity has been observed to be higher for smokers of black tobacco than for smokers of blond tobacco (139). The relation of urinary mutagenic activity to the tar level of cigarettes is uncertain (140,281). Other risk factors that have been studied in relation to urinary mutagenicity include employment as a rubber worker (282), occupational exposure to benzidine (283), and cyclophosphamide exposure (284). Only one study, however, has attempted to link urinary mutagenicity directly with the risk of bladder cancer: Garner has reported an association of mutagenic urine with bladder cancer in a comparison of cases and controls, but the effect of disease status on the results is not known (285).

HAEMOGLOBIN AND DNA ADDUCTS

Haemoglobin adducts of aromatic amines have been related to cigarette smoking, but the levels of adducts have not yet been related to the occurrence of bladder cancer. Bryant found that smokers have higher levels of haemoglobin adducts of several aromatic amines, including the carcinogens 4-aminobiphenyl and 2-naphthylamine (138). The levels of adducts of 4-aminobiphenyl and 3-aminobiphenyl were correlated with the number of cigarettes smoked per day. Smokers of black tobacco had a higher mean level of haemoglobin adducts of 4-aminobiphenyl, as well as several other aromatic amines, than smokers of blond tobacco (138). Maclure has reported that the levels of the haemoglobin adduct of 4-aminobiphenyl declined after the cessation of smoking (286). Carcinogen–DNA adducts have been identified in human bladder biopsy samples (287,288) and in exfoliated

urothelial cells (288,289), providing new techniques for the identification of human bladder carcinogens. Benzidine-related DNA adducts have been found in exfoliated urothelial cells of benzidine-exposed workers (290).

BIOLOGIC MARKERS OF GENETIC SUSCEPTIBILITY

NAT2 phenotype/genotype

Aromatic amines must be metabolized within the host in order to exert mutagenic or carcinogenic activity (291). For many aromatic monoamines, including those found in tobacco smoke such as 4-aminobiphenyl and 2-naphthylamine, *N*-acetylation appears to be a detoxification pathway, with the acetylated metabolite being excreted into the urine before it can be *N*-oxidized to a reactive form (292). The capacity to *N*-acetylate is polymorphic in humans (292); slow acetylators are homozygotic for a mutated *N*-acetyltransferase gene (*NAT2*), which is responsible for decreased activity (293,294). In 1979, Lower *et al.* proposed that individuals with the slow acetylator phenotype might be at higher risk for aromatic amine-associated bladder cancer (295). This hypothesis was subsequently supported by results from a series of epidemiological studies that, overall, showed that individuals with the slow acetylator phenotype (296,297) or *NAT2* genotype (298–300) are at greater risk of developing bladder cancer. The biological plausibility of these observations is strengthened by reports among smokers that slow acetylators have a higher mean level of the haemoglobin adduct of 4-aminobiphenyl than do rapid acetylators (301). This difference was most pronounced at low exposure levels (302).

Among persons occupationally exposed to aromatic amines, several studies have shown an excess of the slow acetylator phenotype among cases compared with controls (275,292,300,303–305), but the specific aromatic amine exposures were not well characterized. A study in Chinese workers with an increased risk of bladder cancer (32) who were exposed exclusively to benzidine did not demonstrate an excess of slow acetylators among bladder cancer cases, based on both phenotype and genotype analyses (306). In contrast, a study of bladder cancer cases who had been exposed to benzidine in Germany found a non-significant association with the slow acetylation phenotype (307). A cross-sectional study of workers in India who were currently exposed to benzidine and benzidine-based dyes showed that neither *NAT2* genotype or

phenotype influenced exfoliated urothelial cell benzidine–DNA adduct levels and that the predominant adduct was *N*-acetylated (290). These findings suggest that the association between *N*-acetylation and bladder cancer risk may be specific to certain aromatic amines.

Yu suggested that acetylator status may play a part in the racial/ethnic differences in bladder cancer risk (308). They found that the proportion of slow acetylators was highest among whites, intermediate among blacks, and lowest among Asians, closely paralleling the racial/ethnic variation in risk. Acetylator status also has been analysed in relation to the histological grade or the stage at diagnosis of bladder tumours (303,309,310), but the results are inconsistent.

GSTM1 null genotype

Human glutathione *S*-transferase M1 (*GSTM1*) belongs to a family of enzymes that detoxify a spectrum of reactive carcinogenic metabolites, including PAHs, by catalysing their conjugation to glutathione (311). *GSTM1* is encoded by the *GSTM1* gene, and is polymorphic in human populations; deficiency of this enzyme is caused by the homozygous absence of a functional *GSTM1* gene (i.e. null genotype) (312). Nine studies in the general population have found that the *GSTM1* null genotype is associated with elevated risk of bladder cancer (298,313–320), whereas two studies have not detected this association (299,321). Risk estimates have been modest, with most relative risks under 2.0. Two cross-sectional studies have evaluated the influence of *GSTM1* genotype on urine mutagenicity (322) and haemoglobin adducts (323). Hirvonen (322) found that the *GSTM1* null genotype was associated with higher urine mutagenic activity in smokers, which is thought to derive primarily from aromatic amines (323), while Yu (301) reported that the null genotype was associated with higher levels of 3- and 4-aminobiphenyl haemoglobin adducts among both smokers and non-smokers. The exact biological relationship between glutathione *S*-transferase M1 and aromatic amines is uncertain, however, given that glutathione conjugation is not thought to be a major detoxification pathway for these compounds.

Cytochrome P-450 enzymes

Cytochrome P-450A2 (*CYP1A2*) plays an important part in the metabolic activation of several aromatic amines, including 4-aminobiphenyl and 2-naphthylamine, via *N*-oxidation (324).

Susceptibility to aromatic amine-induced bladder cancer may thus vary with an individual's level of CYP1A2. It is unclear, however, whether the activity of this enzyme is determined by genotype and/or by enzyme induction from environmental exposures (e.g. cigarette smoking, dietary factors, and drugs). Higher levels of 4-aminobiphenyl adducts were found in low-level smokers with rapid CYP1A2 activity, particularly among slow acetylators (325). CYP1A2 activity, as measured by 3-demethylation of theophylline, was associated with bladder cancer risk in one study (326), but uncertainty about the validity of the assay, demographic differences between cases and controls, and the potential for disease bias make interpretation of the study findings unclear. Results from case-control studies of CYP2D6 phenotype have been conflicting (327).

TUMOUR MUTATIONS

Understanding the pathogenesis of human bladder cancer at the molecular level has been evolving for a number of years. Bladder cancer appears to arise from a combination of mutations in tumour suppressor genes (e.g. *TP53*, *RB*) and oncogenes (e.g. *H-RAS*, *c-erbB-2*) (328,329). Because bladder tumours are heterogeneous with regard to their molecular characteristics, it has been hypothesized that environmental exposures may have stronger associations with subgroups of tumours defined at the cytogenetic or molecular level. A higher proportion of tumours from bladder cancer cases who smoked contained chromosome 9 alterations compared with non-smoking cases (330). An association between smoking and mutations in the *TP53* gene has been suggested, but not consistently observed across studies (331,332). Occupational exposure to aromatic amines was not associated with either type or frequency of *TP53* mutations in tumour samples in a study by Taylor and colleagues (333).

FUTURE RESEARCH

Bladder cancer is known to be caused by cigarette smoking, occupational exposure to certain aromatic amines, cyclophosphamide, *S. haematobium* infection, chronic ingestion of high levels of arsenic in drinking water, and ionizing radiation. It is likely that phenacetin-containing analgesics also cause the disease. The roles of a number of occupational exposures (e.g. motor exhausts), urinary tract infections, urinary stasis, urine pH, dietary factors,

chlorination by-products in drinking water, chronic ingestion of low/moderate levels of arsenic in drinking water, tobacco products other than cigarettes, and genetic susceptibility deserve further study.

Cigarette smoking accounts for about 50% of bladder cancer among men and 20–30% among women (113,122,334,335). Occupational exposures have been estimated to be responsible for 10–25% of bladder cancer among men (18) and 10% among women (336), yet the exposures responsible for much of occupational bladder cancer remain unknown. Cigarette smoking and occupational exposures, however, explain only a small part of the large male excess risk of bladder cancer (335). Exploration of possible reasons for this male excess, such as gender differences in unidentified environmental risk factors, urination habits, or hormonal (337) and metabolic determinants of risk, should enhance our understanding of the aetiology of bladder cancer.

Finally, the identification of human bladder carcinogens provides an opportunity to conduct interdisciplinary studies that may help to explain the general mechanisms of carcinogenesis. Potentially useful approaches include identification of specific types of DNA adducts in human urothelial cells, evaluation of interactions between human bladder carcinogens and polymorphisms in metabolic genes, and determination of the relationship between exposure to bladder carcinogen and bladder tumour mutations.

UNRESOLVED RESEARCH ISSUES

1. Why do men have a higher risk of bladder cancer than women after all known risk factors have been taken into account?
2. What are the exposures responsible for the increased risks experienced by workers in high-risk occupations, such as painter, leather worker, and truck driver?
3. Do urinary tract infections cause bladder cancer? What role does urinary stasis play in bladder carcinogenesis? Is urine pH an effect modifier of bladder cancer risk?
4. Is chronic ingestion of low/moderate levels of arsenic in drinking water a cause of bladder cancer? Are chlorination by-products in drinking water bladder carcinogens?
5. What is the role of diet in the aetiology of bladder cancer?
6. What is the influence of interindividual variation in carcinogen activation, detoxification, and DNA repair in bladder cancer aetiology?

Key Points

1. In the United Kingdom cancer of the urinary bladder accounts for 7.9% of all new cases of cancer among men and 3.2% of cases among women, as well as 4.4% of cancer deaths among men and 2.4% among women. In the USA, the corresponding figures are about 6.3% of all new cases among men and 2.5% among women, as well as 2.9% of cancer deaths among men and 1.5% among women.
2. Occupational bladder cancer continues to be a public health problem, with risks changing over time and from population to population. With the elimination of bladder carcinogens from the workplace and the advent of new chemicals, risks among rubber and leather workers have diminished over time, whereas new high-risk occupations, such as truck driver and aluminium smelter worker have emerged.
3. Cigarette smoking is well-established as a cause of bladder cancer, although the association is not as strong as that observed for smoking and several other cancers.

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