30.3 Bladder Cancer

Avima M Ruder, Tania Carreón, Elizabeth M Ward, Paul A Schulte, William Halperin

It is well documented that the etiology of bladder cancer involves environmental risk factors. Occupational risks may account for 21–27% of bladder cancers among men in the United States,[1,2] an estimated 40,000 cases in 2001,[3] and 11% among the estimated 15,000 cases in women in 2001.[3,4]

Occupational exposure to aromatic amines has been known to cause bladder cancer since Rehn identified the first few cases in workers in the new organic chemical industry in 1895.[5] Since that time, numerous occupations and specific substances have been associated with an increased risk of bladder cancer (Tables 30.3.1 and 30.3.2). Beyond the certainties that specific aromatic amines have been demonstrated to be human occupational bladder carcinogens and that a broad range of occupations are at risk of bladder cancer, a well-informed approach to the prevention and management of bladder cancer depends on appreciating various controversies involved in its primary and secondary prevention and treatment. The reader is referred to a report of a national conference held in 1989[6] to delineate these issues. Many of these controversies, such as the relevance to human bladder cancer of findings from animal studies, the line between benign and malignant tumors, the appropriate screening regimen for workers exposed to bladder carcinogens, and whether early detection is worthwhile, remain relevant more than a decade later.

In addition to incidence and survival differences by social class, race, and gender,[7] new developments in understanding inherited risk factors, such as acetylator status and intermediate biomarkers, influence understanding of etiology, prevention and management.

ETIOLOGY

Epidemiology

Bladder cancer is the eighth most common neoplasm worldwide. An estimated 261,000 new cases of bladder cancer occur each year, with four-fifths of the cases occurring in men.[8] Incidence rates of bladder cancer vary about 10-fold, with higher rates in Western Europe and North America, and lower rates in Eastern Europe and several Asian countries.[9]

Cigarette smoking accounts for 47% of bladder cancer among men and 37% among women; smokers have twice the risk of non-smokers.[3] The contributions of coffee drinking and alcohol consumption to bladder cancer are equivocal. The World Health Organization estimates that bladder cancer cases can be subdivided into two broad categories based on etiology. (1) Those caused by tobacco and industrial carcinogens are predominantly transitional cell carcinomas and are common in industrialized countries. 2) Those due to bilharzia, human papilloma virus, and schistosomiasis infection[10,11] are more likely to be squamous cell carcinomas and are found chiefly in subtropical and tropical countries. Thus, both types are, in principle, preventable.[12]

Bladder cancer is historically the neoplastic disease most strongly linked to occupational exposure to chemicals. Several occupations have been suspected to increase the risk of bladder cancer, but strong associations only exist for dye workers, aromatic amine manufacturing workers, leather workers, rubber workers, painters, truck drivers, and aluminum workers.[13] Table 30.3.1 presents the epidemiologic studies of occupational associations. Occupational exposures to chemicals such as arylamines, polycyclic aromatic hydrocarbons and other industry-related agents may explain some of the risk associated with these occupations.[14] Some of the relative risks for exposed workers are substantially higher than the two-fold increased risk for smokers. Table 30.3.2 includes specific chemicals or processes classified by IARC as carcinogenic to the human or canine bladder, combined with data on working populations potentially at risk. Over 200 chemicals have been confirmed as rodent bladder carcinogens; however, rodent bioassays do not appear to be a good model for human bladder cancer[15] (see 'Animal studies' section below).

A relationship between bladder cancer and exposure to chemical dyes was first established in 1895.[5] In the late 1930s, oral administration of the industrial arylamine 2-naphthylamine was shown to induce bladder cancer in dogs.[16] In 1954, Case et al. reported a 20-fold excess of bladder cancer in arylamine-exposed individuals, compared to the general population of England and Wales.[17] Since then, the most investigated bladder carcinogens have been 2-naphthylamine, benzidine, and 4-aminobiphenyl. Several studies have reported increased risks of bladder cancer in workers exposed to 2-naphthylamine and 4-aminobiphenyl, and have been reviewed elsewhere.[18]

One newly recognized factor that may have an occupational component is fluid intake. In a study of about 50,000 men, it was observed that drinking more fluids was associated with a significantly decreased rate of bladder cancer.[19] These results are consistent with the urogenous contact hypothesis, which proposed that the level of DNA adducts to 4-aminobiphenyl (a carcinogenic amine) could be decreased by increased fluid intake.[20,20a] Occupations that have exposure to carcinogens and limit the workers' ability to drink liquids could be at risk.

There is no known distinctive histologic feature for occupational bladder cancer. However, in some heavily exposed cohorts, cases regularly occur at ages 15 years younger than the median age at diagnosis of the general population,[17,21] in which the rate of bladder cancer increases substantially with age. Usually, the interval from first exposure to onset of symptoms is decades long; however, occupational cases have occurred surprisingly early after exposure, which substantiates the argument that cases with only a few years of latency may be occupationally induced. It has been estimated that the latency for chemically induced bladder cancer ranges from 4 to 45 years.[21,22]

Occupation /Industry	Study site, type, population	Increased morbidity relative risk	Increased mortality relative risk (95% CI)	Controlled for (95% CI)	Reference
Aluminum smelterers (10 yrs)	Canada, NCC, men	3.9 (1.6–9.6)*		smoking	Armstrong et al., 1986[58]
Armed services	Canada, CC, men	1.8 (1.2–2.7)			Howe et al., 1980[59]
Auto workers (>10 yrs)	US, CC, African-American men	4.7 (1.7–10.7)		age, smoking	Silverman et al., 1989[1]
Butchers	Sweden, CC, men	1.3 (1.0–1.6)			Malker et al., 1987[60]
Carpenters	US, CC, men	11.1 (3.3–37.0)		current smokers	Schumacher et al., 1989[61]
Carpenters	US, CC, white men	1.4 (1.1–1.8)		smoking	Silverman et al., 1989[2]
Chemical mfg. workers	UK, CC, men	2.2 (1.7–3.0)			Boyko et al., 1985[62]
Chemical mfg. workers	US, C, white men	2.6 (1.1–6.4)*		age	Schulte et al, 1985[63]
	US, C, African-American men	5.0 (2.2–11.3)*		age	
Chemical workers†	Sweden, CC, men	1.3 (1.1–1.5)			Malker et al., 1987[60]
Chemical workers	US, CC, white women	2.1 (0.9–5.1)*		smoking	Silverman et al., 1990[4]
Clerical workers	UK, CC, men	1.5 (1.1–1.9)			Cartwright, 1982[64]
Clerical workers	China, CR, men	1.3 (1.0–1.7)			Zheng et al., 1992[65]
Clerical workers (>10 yrs)	US, CC, African-American men	2.9 (1.2–6.2)		age, smoking	Silverman et al., 1989[1]
Construction workers	US, CC, white men	1.6 (1.1–2.5)*		smoking	Silverman et al., 1989[2]
Construction workers	US, C, Latino men		PMR 1.6 (0.9–2.8)		Schultz & Loomis, 2000[66]
Crafts workers	China, CR, women	1.2 (1.0–1.4)			Zheng et al., 1992[65]
Dental technicians	Sweden, CC, men	2.5 (1.3–4.3)			Malker et al., 1987[60]
Drivers	Argentina, CC, men	5.3 (2.3–12.2)			Iscovich et al., 1987[67]
Drivers	Denmark, CC	1.6 (1.1–2.3)*		sex, age, smoking	Jensen et al., 1987[68]
Drivers†	US, CC, white men	1.2 (1.1–1.4)*		smoking	Silverman et al., 1989[1,2]
Drivers, railroad	Germany, CC, men	3.0 (1.2–8.8)			Claude et al., 1988[69]
Drivers, taxi	US, CC, white men	6.3 (1.6–29.3)*		age, smoking	Silverman et al., 1986[87]
Drivers, truck	US, CC, white men	2.1 (1.4–4.4)*		age, smoking	Silverman et al., 1983[88]
Drivers, truck	Germany, CC, men	1.8 (1.1–2.8)*			Claude et al., 1988[69]
Drivers, truck	US, CC, white men	1.5 (1.1–2.0)		age, smoking	Silverman et al., 1986[87]
Drivers, truck	UK, CC, men		PMR 2.0 ($P<0.05$)		Baxter & McDowall, 1986[70]
Dry cleaners	US, CC, African-American men	2.8 (1.1–7.4)			Silverman et al., 1989[1]
Dry cleaners	US, C, African-American men		5.1 (1.4–13.1)	age	Ruder et al., 2001[71]
Dye mfg. workers	China, C, men	11.1 (3.6–25.9)		non-smokers	Bi et al, 1992[72]
		31.5 (20.4–46.4)		smokers	
			17.5 (7.5–34.5)	age	
Dye mfg. workers	UK, CC, men	3.5 (2.2–5.3)			Cartwright, 1982[64]
Dye mfg. workers	UK, CC, men	2.6 (1.8–3.7)		age, smoking	Boyko et al., 1985[62]
Dye mfg. workers	US, C, white men		5.2 (1.4–13.2)	age, exposure (azo dyes only)	Sathiakumar & Delzell, 2000[73]
Dyers, printers, textile ind.	US, CC, white men	4.4 (1.2–16.8)		smoking	Silverman et al., 1989[2]
Dye workers†	Canada, CC, men	4.1 (2.9–5.5)		latency ≥ 8 yrs	Risch et al., 1988[74]
Dye workers	Russia, C, men	3.9 (2.7–6.0)	2.8 (1.9–3.9)	age	Bulbulyan et al., 1995[75]
Dye workers	Russia, C, women	8.6 (4.6–80.0)	3.1 (1.5–5.7)	age	Bulbulyan et al., 1995[75]
Fabricators, assemblers, hand workers	US, C, African-American men		PMR 1.6 (0.9–2.9)		Schultz & Loomis, 2000[66]
Fabricators, etc.	US, Latino men		PMR 2.8 (1.0–7.9)		
Farm workers (field crops, vegetables)	Europe, CC, women	1.8 (1.0–3.1) *		age, smoking	't Mannetje et al., 1999[85]
Farm workers (nurseries)	Canada, CC, men	5.5 (1.2–51.1)			Howe et al., 1980[59]
Food counter workers	US, white men	2.6 (1.4–5.1)		age, smoking	Schoenberg et al., 1984[76]
Food counter workers	US, CC, white men	1.4 (0.9–2.1)*		smoking	Silverman et al., 1989[2]
Guards	Canada, CC, men	4.0 (1.3–16.4)			Howe et al., 1980[59]
Guards	Germany, CC, men	3.5 (1.2–9.9)*			Claude et al., 1988[69]
Janitors and cleaners	US, CC, white men	3.5 (1.6–7.7)		age, alcohol, smoking	Brownson et al., 1987[77]
Janitors	Germany, CC, men	3.5 (1.2–9.9)*			Claude et al., 1988[69]
Laborers in mfg. ind.	US, CC, white men	12.3 *			Silverman et al., 1989[2]
Laborers in metal ind.	US, African-American women		PMR 4.2 (1.1–16.8)		Schulz & Loomis, 2000[66]
Leatherworkers	US, CC, men	6.3 (3.1–11.3)*			Decoufle, 1979[78]
Leatherworkers	US, CC, women	4.4 (1.2–12.1)			Decoufle, 1979[78]
Lumber jacks	US, CC, white men	1.3 (1.0–1.5)*		smoking	Silverman et al., 1989[2]
Machine operators, tenders	US, C, Latino men		PMR 1.7 (1.0–3.1)		Schultz & Loomis, 2000[66]
Machinists	Sweden, CC, men	1.2 (1.1–1.3)			Malker et al., 1987[60]

Table 30.3.1 Occupations associated with increased risk of bladder cancer

Occupation /Industry	Study site, type, population	Increased morbidity relative risk	Increased mortality relative risk (95% CI)	Controlled for (95% CI)	Reference
Machinists, metal	Canada, CC, men	2.7 (1.1–7.6)			Howe et al., 1980[59]
Machinists†	US, CC, white men	1.3 (1.0–1.7)		smoking	Silverman et al., 1989[2]
Mail sorting clerks	Europe, CC, women	4.4 (1.0–19.5)		age, smoking	't Mannetje et al., 1999[85]
Mfg. workers	China, CR, women	1.2 (1.0–1.5)			Zheng et al., 1992[65]
Mfg. checkers, examiners, and inspectors	US, CC, white men	1.4 (1.1–1.8)*		smoking	Silverman et al., 1989[2]
Mfg. checkers	US, CC, white women	1.5 (1.0–2.3)		smoking	Silverman et al., 1990[4]
Mechanics	US, CC, white men	3.5 (1.4–9.1)		age, alcohol, smoking	Brownson et al., 1987[77]
Mechanics	Spain, CC, men	1.8 (1.2–2.7)		smoking, other jobs	Gonzalez et al., 1989[89]
Mechanics†	US, CC, white men	1.2 (1.0–1.4)		smoking	Silverman et al., 1989[2]
Mechanics, auto	US, CC, white men	10.2 (2.1–68.6)		smoking	Silverman et al., 1989[2]
Mechanics & repairers	US, C, Latino men		PMR 1.6 (0.7–3.7)		Schultz & Loomis, 2000[66]
Metal workers†	US, CC, white men	1.2 (1.0–1.4)		smoking	Silverman et al., 1989[2]
Metal workers	China, CR, men	1.4 (1.0–2.0)			Zheng et al., 1992[65]
Metal workers	Europe, CC, women	1.9 (1.1–3.6)*		age, smoking	't Mannetje et al., 1999[85]
Metal workers	US, women	1.4 (1.0–1.9)		smoking	Silverman et al., 1990[4]
Mining machine ops	US, CC, white men	2.9 (1.1–7.5)		age, alcohol, smoking	Brownson et al., 1987[77]
Mining workers	Germany, CC, men	2.0 (1.2–3.3)*			Claude et al., 1988[69]
Painters	Switzerland, C, men	1.7 (1.0–2.7)	2.1 (1.0–3.9)		Guberan et al., 1988[79]
Painters	Denmark, CC	2.5 (1.1–5.7)*		sex, age, smoking	Jensen et al., 1987[68]
Painters, artistic	US, CC, C, men	2.5 (1.1–5.7)*	PMR 3.5 (2.1–5.7)	smoking (incidence)	Miller et al., 1986[80]
Painters	US, CC, white men	1.5 (1.2–2.0)*		smoking	Silverman et al., 1989[2]
Painters	US, C, white men	1.2 (1.1–1.4)*		age	Steenland & Palu, 2000[81]
Paper pulp workers†	Sweden, CC, men	1.1 (1.0–1.3)			Malker et al., 1987[60]
Pesticide mfg. workers	Europe, C, men	35 (14–66)		smoking	Popp et al., 1992[82]
Petroleum processors†	US, CC, white men	2.4 (1.1–5.5)		smoking	Silverman et al., 1989[2]
Printers	Sweden, CC, men	1.2 (1.0–1.3)			Malker et al., 1987[60]
Printers	UK, CC, men	3.1 (1.4–6.8)			Cartwright, 1982[64]
Printers	US, CC, white men	2.1 (1.0–4.3)		smoking	Silverman et al., 1989[2]
Print machine operators	US, CC, white men	3.1 (1.1–8.9)		age, alcohol, smoking	Brownson et al., 1987[77]
Produce graders, packers	US, CC, white men	3.2 (1.1–9.3)		smoking, educ.	Silverman et al., 1989[2]
Precision prod. workers	US, C, African-American women		PMR 1.8 (1.0–3.3)		Schultz & Loomis, 2000[66]
Professional specialists	US, C, African-American men		PMR 1.4 (1.0–1.9)		Schultz & Loomis, 2000[66]
Rubber & plastics workers	China, CR, men	2.1 (1.2–3.4)			Zheng et al., 1992[65]
Rubber additive workers†	US, C	3.6 (1.9–6.3)			Ward et al., 1991[90]
Rubber processing workers	US, CC, white women	4.5 (1.1–21.9)		smoking	Silverman et al., 1990[4]
Salespeople	US, C, Asian men		PMR 2.1 (0.8–5.6)		Schultz & Loomis, 2000[66]
Salespeople, service, construction industries	US, CC, white men	2.2 (1.2–4.1)*		smoking	Silverman et al., 1989[2]
Salespeople	US, CC, white women	2.5 (1.0–6.0)*		smoking	Silverman et al., 1990[4]
Salespeople	Europe, CC, women	2.6 (1.0–6.9) 4.8 (1.2–18.7) (≥ 10 yrs)		age, smoking	't Mannetje et al., 1999[85]
Services, personal	US, Asian women		PMR 5.3 (1.6–16.8)		Schulz & Loomis, 2000[66]
Switchboard ops > 10 yrs)	Europe, CC, women	8.1 (2.1–32.0)		age, smoking	't Mannetje et al., 1999[85]
Tailors	Germany, CC, men	2.7 (1.1–6.6)			Claude et al., 1988[69]
Tailors	Canada, CC, men	3.9 (1.3–14.2)		latency≥ 8 yrs	Risch et al., 1988[74]
Tailors, dressmakers	Europe, CC, women	1.4 (1.0–2.1)		smoking	't Mannetje et al., 1999
Technicians	US, C, African-American women		PMR 1.8 (0.8–3.8)		Schultz & Loomis, 2000[66]

ble 30.3.1 (Cont'd) Occupations associated with increased risk of bladder cancer

Occupation /Industry	Study site, type, population	Increased morbidity relative risk	Increased mortality relative risk (95% CI)	Controlled for (95% CI)	Reference
Telephone & telegraph ops	US, CC, white men	1.9 (0.9–4.0)*		smoking	Silverman et al., 1989[2]
Textile workers	Spain, CC, women	6.4 (1.3–30.0)		smoking, other jobs	Gonzalez et al., 1989[89]
Textile workers	Spain, CC, men	1.9 (1.1–3.1)		smoking, other jobs	Gonzalez et al., 1989[89]
Textile workers	Denmark, CC	1.7 (1.1–2.4)		sex, age, smoking	Jensen et al.. 1987[68]
Textile workers†	Italy, CC, women	1.9 (0.9–4.2)			Maffi & Vineis, 1986[86]
Tobacco processors	Europe, CC, women	3.1 (1.1–9.3)		age, smoking	't Mannetje et al., 1999[85]
Turners (lathe operators)	UK, CC, men	1.5 (1.2–1.8)			Cartwright, 1982[64]
Turners (lathe operators)	Germany, CC, men	2.3 (1.0–5.6)*			Claude et al., 1988[69]
Upholsterers	Germany, CC, men	2.7 (1.1–6.6)			Claude et al., 1988[69]
Weavers	Germany, CC, men	2.7 (1.1–6.6)			Claude et al., 1988[69]
Weavers	Spain, CC, men	3.5 (1.3–9.3)		smoking, other jobs	Gonzalez et al., 1989[89]
Weavers	Spain, CC, women	21.2 (1.5–298)		smoking, other jobs	Gonzalez et al., 1989[89]
Weavers	US, CC, white men	3.5 (1.3–9.3)		smoking	Silverman et al., 1989[2]
Welders	Canada, CC, men	2.8 (1.1–8.8)			Howe et al., 1980[59]
Welders, oxyacetylene	Italy, C, men		3.7 (1.2–8.6)	age	Merlo et al., 1989[83]

Only occupations explicitly mentioned in a study are included. Study types: CC (case-control), C (cohort), NCC (nested case-control), CR (linkage of case registry and census data)
* Dose–response demonstrated
† Higher risks were found for some subcategories of workers

Table 30.3.1 (Cont'd) Occupations associated with increased risk of bladder cancer

Based on mortality data from England and Wales, it was estimated that bladder cancer due to occupational exposures was responsible for half of the rate difference between high and low social classes because these exposures are concentrated in blue-collar jobs.[23] However, no evidence was provided associating the blue-collar jobs with exposure to bladder carcinogens.

Metabolic polymorphisms and bladder cancer

Interindividual variation is common for many metabolic enzymes. In some cases, the variability has been attributed to inherited polymorphisms.[24] Phenotypic and genotypic tests have shown that variation in xenobiotic metabolizing enzymes is associated with cancer risk and may have an influence on human susceptibility to genotoxic agents.

A limited number of studies of bladder cancer genetic susceptibility in populations exposed occupationally to arylamines has been published.[25–29] The results of a meta-analysis of all studies of acetylation status and bladder cancer in the general population suggest that certain groups with the NAT2 slow-acetylation phenotype are at greater risk of bladder cancer.[30] Additional studies are needed to establish if individuals could be at higher risk of bladder cancer given the presence of certain alleles that make them more susceptible. In the workplace, various metabolic polymorphisms could be acting in combination with occupational toxicants to produce risk. For occupational bladder cancer, polymorphic genotypes in the *NAT* (N-acetyltransferase) and *GST* (glutathione S-transferase) families of genes have been explored. Their joint effect, together with the effect of other genotypes, has not yet been investigated. Moreover, the metabolic differences between monoarylamines and diarylamines, such as benzidine, warrant careful attention to the specific compounds to which each worker is exposed.

Animal models

Use of animal models to predict human bladder carcinogens has been problematic. Rats and mice are not susceptible to bladder cancer by most aromatic amines, including some highly potent occupational carcinogens. For aromatic amines, the Syrian hamster and dog were found to be better predictors for human bladder cancer than mice or rats, but this may not necessarily be the case for other chemical classes.[15] There has been considerable debate about the relevance to human bladder cancer of bladder tumors associated with urinary calculi in mice or rats or calcium phosphate-containing precipitates in rats. The International Agency for Research on Cancer (IARC), which has a formal program for identification of carcinogenic hazards to humans, has issued a consensus report on this subject.[31] Based on this consensus report, the IARC monograph program has recently classified saccharin in Group 3 (not classifiable as to carcinogenicity in humans) because the mechanism through which it is thought to cause bladder cancer in rats, formation of a calcium phosphate-containing precipitate, is not relevant to humans.[32]

Numerous classes of genotoxic chemicals have been identified as bladder carcinogens in rodents and some of these have been identified in humans, most notably, aromatic amines, nitrosamines, and cyclophosphamide. In contrast, non-genetoxic chemicals appear to be highly specific with regard to species strain, diet, agent, dose, and mechanism.

Compound name [variant name]	CAS#	IARC group	Source(s)	Potentially exposed occupations, numbers*
Aluminum (production)	7429–90–5†	1	Boffetta	al production workers
Arsenic & arsenic compounds	7440–38–2	1	Wilbourn	arsenical pesticide manufacturing workers; pesticide users
Auramine dye manufacturing	492–80–8†	1	Boffetta	dye mfg. workers
Benzidine	92–87–5	1	Boffetta	1,554 (NOES)
Benzidine-based dyes		2A	IARC 29;	28,442 (NOES)
Direct Black 38 [2,7-Naphthalenedisulfonic acid, 4-amino-3- ([4'-((2,4-diaminophenyl)azo) (1,1'-biphenyl)-4-yl]azo)-5-hydroxy-6-(phenylazo)-disodium salt]	1937–37–7		IARC Supp 7	dye manufacturing workers; dye-using workers – 44,500 (BLS)
Direct Blue 6 [2,7-Naphthalenedisulfonic acid, 3,3'-[(1,1'-biphenyl)- ((4,4'-diylbis(azo)]bis(5-amino-4-hydroxy)-, tetrasodium salt]	2602–46–2			
Benzidine, 3,3'-dichloro-	91–94–1	2A	Wilbourn	
4-Biphenylamine [4-Aminobiphenyl]	92–67–1	1	Boffetta; Wilbourn	
Chemotherapy agents				
Chlornaphazine [(N,N-Bis(2-chloro-ethyl)-2-naphthylamine)]	494–03–1	1	Wilbourn	pharmaceutical mfg. workers, oncology nurses, pharmacists
Cyclophosphamide [2H-1,3,2-Oxazaphosphorine, 2-(bis(2-chloroethyl) amino)tetrahydro, 2-oxide]	50–18–0	1		27,171 (NOES)
Coal-tar pitches	65996–93–2	1	Wilbourn; Boffetta	roofers – 142,600 (BLS)
Coal tars	65996–89–6	1	Wilbourn; IARC Supp 7	roofers – 142,600 (BLS)
Diesel engine exhaust	various	2A	Wilbourn	truck drivers – 2,500,000+ (BLS)
p-Dimethylaminoazobenzene [Brilliant yellow]	60–11–7	2B	Wilbourn	dye-using workers – 44,500 (BLS)
Magenta dye manufacture	632–99–5†	1	Boffetta	dye mfg. workers
4,4'-Methylene bis (2-chloroaniline) [MOCA]	101–14–4	2A	Wilbourn	
Mineral oils, untreated and mildly treated	various	1	Wilbourn	metal machinists – 1 million+ (BLS)
2-Naphthylamine	91–59–8	1	Boffetta	275 (NOES)
Phenacetin [p-Acetophenetidide]	62–44–2	2A	Wilbourn	17,658 (NOES) pharmaceutical mfg.
Analgesic mixtures containing phenacetin	various	1	Wilbourn	workers, oncology nurses, pharmacists
Rubber industry (certain occupations)	various†	1	Boffetta	rubber additives workers
Tobacco smoke		1	Wilbourn	‡
p-Chloro-o-toluidine	95–69–2	2A	IARC, 2000; Wilbourn	
o-Toluidine [o-Aminoazotoluene]	97–56–3	2A	IARC, 2000; Wilbourn	rubber additives workers & dye workers

An RTECS search for substances associated with bladder tumors produced the original list, adapted from Ruder et al., 1990.[84]
IARC classifications are adapted from Wilbourn et al. 1999[15] and Boffetta et al 1997.[23] Updates through Monograph 84 by the authors of this chapter. IARC ratings: 1, definite human bladder carcinogen; 2A, probable human bladder carcinogen. Compounds rated by Wilbourn et al.[15] as canine bladder carcinogens are included, but not those rated as exclusively rodent bladder carcinogens.
* Estimated numbers are from two sources: 1. (NOES) Chemical-specific numbers of workers potentially exposed are from the 1981–1983 National Occupational Exposure Survey. Note that all these workers would be reaching > 20 years latency about 2001–3; 2. (BLS) Estimates of numbers of workers in occupational categories are from the Bureau of Labor Statistics 1999 National Occupational Employment and Wage Estimates (http://stats.bls.gov/oes). These data do not consider turnover among employees, which would lead to a greater number of persons exposed than is suggested by estimates from specific points in time.
† These manufacturing processes involve exposure to a number of chemicals.
‡ No study to date has linked passive smoking to bladder cancer; several have found no association.

Table 30.3.2 Known and suspected human bladder carcinogens and estimated numbers of potentially exposed US workers

Use of molecular and genetic mechanism information may be helpful in identifying possible mechanisms involved for these non-genotoxic chemicals and, therefore, can be important for a rational evaluation of human risk.

CLINICAL ASPECTS

Pathology

Transitional cell carcinomas (TCC) are graded by the World Health Organization histologically by the degree of abnormality of the tissues[33] and staged by the American Joint Committee on Cancer – Union Internationale Contre le Cancer by the extent to which they have spread.[34] One problem in the pathology of bladder tumors is the somewhat ambiguous line between the benign and the malignant, distinguishing between a papilloma, a papillary tumor with delicate fibrovascular stroma covered by a layer of epithelial cells indistinguishable from normal bladder mucosa, and a papillary carcinoma. This distinction should be viewed as a region where borders shift between pathologists, between institutions, and given the circumstances, even successive biopsies of the patient.

Some so-called benign papillomas display effects of inflammation and reactive or regenerative conditions so that they are classified by some pathologists as anaplastic, although most of them do not behave as malignant tumors. To make the situation more complicated, some papillary tumors do become aggressive. Robinson and Hall[33] summarized the results of several studies: about 2–5% of 'benign' papillomas progress to carcinoma. The use of biochemical, molecular and genetic characteristics of cells is beginning to provide pathologists with a way to reduce these uncertainties. Strong associations of various markers with progression, invasiveness, and metastatic potential may provide a way to distinguish between pathologic subtypes of bladder cancer in the future.[35]

Therapy

Strategies for diagnosis and therapy of occupational bladder cancer do not differ from those for bladder cancer resulting from non-occupational etiologies. A comprehensive guide to current treatment options by stage and grade has been assembled by the National Cancer Institute.[36] Treatment strategies do not appear to differ by histological type. Occupational bladder cancer does have a public health component: putative bladder carcinogens and high-risk populations that need to be followed with screening have been identified when exceptional cases of bladder cancer (i.e., in young non-smokers) were diagnosed.

Survival

The survival of patients with bladder cancer depends on the grade of anaplasia of the tumor and the stage of tumor invasion at time of diagnosis. SEER 1992–1997 5-year survival rates range from 94.5% for localized disease in white males to 0% for distant disease in African-American males. At each stage, women fare more poorly than men (except African-American women with distant disease) and African-Americans more poorly than whites. From 1974 to 1997 overall survival has improved from 48% to 65% in African-Americans and from 74% to 82% in whites. During the same period, incidence increased slightly overall from 14.6 to 16.7/100,000, in men from 25.6 to 29.0, and in women from 6.3 to 7.4.[37]

Survival also appears to depend on social class and race, which, of course, are somewhat correlated. A review of five studies on bladder cancer survival found about a 20% discrepancy overall between higher and lower income patients.[38] African-Americans are less likely than whites to develop bladder cancer; however, once diagnosed, African-Americans experience poorer survival: 64% 5-year survival vs. 82% for whites.[3]

PREVENTION

Techniques for early detection

Cytoscopy is effective in identifying visible tumors in the bladder. A cytoscope is a slender tube with a lens and a light that is inserted through the urethra, allowing the physician to visually inspect the urethra and bladder. Cytoscopy is invasive and not employed for asymptomatic individuals.[39]

Urine cytology is the accepted technique for detection of bladder cancer in asymptomatic individuals. Urine cytology microscopically identifies the presence of abnormal, malignant cells, which are shed into the urine of patients with bladder cancer.[39] Cytologic screening for bladder cancer has a sensitivity of about 70% and a specificity of 90–95%, depending on the grade and stage of the tumor,[40] which is comparable to screening tests for cervical cancer, breast cancer, and colon cancer.[41] Bladder cytology is effective in detecting preclinical stages of aggressive tumors and is substantially less effective in detecting low-grade tumors. There is widespread agreement that superficial well-differentiated papillary tumors rarely can be diagnosed definitively from voided urine cytology. In summary, cytology may be used to detect aggressive tumors, but these tumors may be advanced by the time they are discovered by this method. Cytology is less effective for low-grade tumors, which, although they are less aggressive, it would be desirable to find.[42]

The greatest determinant of the sensitivity of urine cytology is the level of cytopathologist expertise. Ancillary techniques have been tested to improve the sensitivity of urine cytology. Of the large variety of methods, the most promising techniques appear to be DNA flow cytometry and image analysis for the detection of nuclear aneuploidy. Other sensitive methods include immunocytochemistry to detect the presence of antigens that are commonly expressed in neoplastic urothelium but not in the normal urothelium, such as the Lewis X antigen, and immunohistochemical analysis for the detection of p53 overexpression.[43]

Hematuria screening, by urinalysis or by dipstick – a positive reaction for blood on urine-reagent-strip testing of asymptomatic people[44] – may be a more effective method than cytology for detecting low-grade early stage bladder tumors. The dilemmas with testing for hematuria are: (1) although almost all bladder tumors eventually cause hematuria, an infrequent examination may not be adequately sensitive, and (2) hematuria due to bladder cancer may be intermittent.[45] Although more frequent examinations increase the sensitivity of the test for bladder cancer, this method decreases the specificity of the test because it will detect other, non-malignant conditions causing hematuria, including cystitis, kidney disease, and urinary calculi.[3] The debate then focuses on the predictive value of a positive test result for hematuria or the probability that a positive test result will reflect bladder cancer rather than another problem. It has been suggested that 5–10% of patients with hematuria have bladder cancer and 10–20% have some other serious urinary tract disease. As a condition becomes more prevalent in a population, the predictive value of a positive test increases. Exposure of an individual to an occupational carcinogen, as well as the individual's age and other risk factors for bladder cancer, should ensure a higher underlying prevalence of bladder cancer and thus increase the predictive value of a screen for hematuria.[45] The American Urological

Association recommends that asymptomatic microhematuria be evaluated only when associated with a risk (such as occupational exposure to carcinogens) of disease.[46]

Tests of genetic factors are now being developed or assessed for evaluation of risk factors for bladder cancer. In addition to variations in metabolic phenotypes such as *N*-acetyltransferase, there are other genetic factors and acquired factors, such as recessive alleles for oncogenes, mutated tumor suppressor genes, and growth factors, that may place individuals at increased risk for bladder cancer independent of occupational exposure.[47] These genetic factors could add to any occupational risks for bladder cancer or multiply those risks. It is likely that the rapid pace of research will result in the identification of new predictive or prognostic markers in the near future.

A number of new techniques are being tested for use in bladder cancer screening. Most markers appear to have an advantage over urine cytology in terms of sensitivity, especially for detecting low-grade superficial tumors. However, most markers tend to be less specific than cytology, yielding more false-positive results. This scenario is more common in patients with concurrent bladder inflammation or other benign bladder conditions. A summary of the sensitivity, specificity and limitations of these methods is presented in Table 30.3.3.

The nuclear matrix protein (NMP) 22 test detects and measures urinary levels of a particular NMP called NuMA (nuclear mitotic apparatus). The NMP22 assay appears to be useful only to monitor, with high accuracy, for recurrence in patients with a past history of bladder cancer.[48]

The bladder tumor antigen (BTA) test detects the presence of a bladder tumor antigen in the urine of patients with bladder cancer. The BTA stat and the BTA trak assays are qualitative and quantitative assays, respectively. Both detect a human complement factor H-related protein in the urine, and both accurately identify two-thirds of patients with bladder cancer. Both are limited because of the high number of false-positive reactions compared to urine cytology in low-grade bladder tumors.[39]

The fibrin and fibrinogen degradation products (FDP) test is positive in two-thirds of patients with bladder cancer. The FDP test detects the degradation product of an extravascular fibrin clot produced by tumors. It is more sensitive than urine cytology and has a high specificity.[49]

Telomerase is an essential enzyme for cellular immortality and tumorigenesis. The telomeric repeat amplification protocol assay for telomerase in exfoliated cells can be used as a tumor marker. However, the low stability of telomerase in urine affects test sensitivity.[50] Inflammatory cells and stem cells have telomerase activity, and may be the source of false-positive tests.

Hyaluronic acid is a glycosaminoglycan that promotes tumor metastasis. High levels are detectable in the urine of patients with bladder cancer. Patients with high-grade TCC have elevated urinary hyaluronidase activity. A combination of both tests (HA-HAase test) yields a higher sensitivity than the sensitivity of individual tests,[51] but it has no better sensitivity than urine cytology for detecting low-grade lesions.

Recently, detection of survivin in urine has been suggested as a predictive molecular marker of bladder cancer. Survivin is an enzyme inhibitor of apoptosis that is selectively overexpressed in human cancers, but undetectable in most normal adult tissues. In a patient series, the sensitivity of the urine survivin test for new or recurrent bladder cancer was 100%, and the specificity was 90–100%, depending on the population tested.[52]

Test batteries

Combining tests can increase their sensitivity and specificity.[41] Series testing is used to increase specificity and reduce the number of false-positive results. Parallel testing is used to increase sensitivity and reduce the number of false-negative results. A new US/European research consortium wants to create a simple, cost-effective, non-invasive diagnostic test to replace cytoscopy and cytology, initiating multicenter trials to find which of seven molecular markers, alone or in combination, is the most accurate detector of bladder cancer.[53]

Screening programs

There are two reasons for screening a population exposed to a known or suspect bladder carcinogen. First, individu-

Test	Sensitivity	Specificity	Limitations
Urine cytology	17–70%	90–95%	Poor criteria to identify low-grade TCC*
BTA test	29–40%	68–91%	Low detection of grade I TCC. Poorer predictive value than urine cytology
BTA stat test	67–87%	40–70%	High false positive with gross hematuria, prostate cancer, BCG
BTA trak test	72%	43–48%	High false positive with UTI, stones, instrumentation
NMP22	48–80%	64–80%	High false positive with gross hematuria
FDP test	40–68%	80–96%	High false positive with gross hematuria
Telomerase	70–86%	60–90%	False negatives with gross hematuria, false positives with inflammation, complicated assay not widely available
HA-HAase test	90–92%	80–84%	No detection of grade I TCC

Modified from Brown, 2000[43]
* Abbreviations: BCG = bacillus Calmette-Guérin, BTA = bladder tumor antigen, FDP = fibrin/fibrinogen degradation products, HA-HAase = hyaluronic acid/hyaluronidase, NMP = nuclear matrix protein, TCC = transitional cell carcinoma, UTI = urinary tract infection

Table 30.3.3 Sensitivity and specificity of non-invasive bladder tumor markers als may be screened so that their tumors can be detected early when they are more readily treated, resulting in less morbidity and higher survival rates. This type of screening is for the personal benefit of the individuals. The second rationale for screening is to detect disease in a population at the earliest time possible in order to ensure that more primary methods of disease prevention, such as engineering controls and use of personal protective devices, are effectively incorporated to prevent exposure.[54] The two motivations should be kept in mind in appreciating a consensus view that was reached at the 1989 conference on screening for bladder cancer in high-risk groups. For populations exposed to known carcinogens at high levels, cytologic examination and testing for hematuria was recommended at 6-month intervals. The rationale for including hematuria was to ensure the acceptability of the screening program by ensuring that low-grade tumors would be detected that otherwise may be missed by cytology.

For low-exposure groups, as may be found in patients suffering from conditions as a result of environmental exposures, cytology was recommended 2 years after the first exposure, then every 5 years thereafter. For a suspect carcinogen, at high-exposure levels, cytology was recommended every 6 months, as well as measurement of hematuria to detect low-grade tumors. The argument for detecting low-grade tumors, even though there may be limited personal benefit for the individual because most such tumors are less aggressive, was to provide information that exposure had not been adequately controlled. The panel was not enthusiastic about any recommendations for a suspect carcinogen at low levels of exposure.[55]

When weighing the benefits of a strategy of early detection, be it for the personal benefit of the worker or for the benefit of the workforce, it is necessary to consider the extent to which false-positive findings will be involved. A screening modality that leads to a disproportionate number of unnecessary follow-up and diagnostic procedures may not be cost effective or personally desirable. Moreover, the lengthening of the lead time, although possibly providing an extended opportunity for therapeutic intervention, also could provide a longer period of anxiety and distress for the worker.[54]

In contrast to the recommendations of the bladder cancer conference consensus panel, the US Preventive Services Task Force concluded that there was insufficient evidence that hematuria and cytology screening improved the prognosis for those found to have cancer, even within high-risk groups.[56] If the efficacy of hematuria and cytology screening is not established, then in monitoring high-risk populations, cystoscopy should be reserved as a diagnostic test in individuals who had positive results on cytology and hematuria. However, it should be remembered that in at least one high-risk group, the MBOCA cohort, bladder cancer was diagnosed in two individuals who had had negative hematuria by dipstick and cytology screening.[57] Perhaps the non-invasive screening batteries now under development will end this dilemma.

SUMMARY

Despite substitution and process changes to prevent or reduce worker exposure, a substantial number of workers continue to be exposed to bladder carcinogens. Much larger numbers have been exposed to bladder carcinogens in the past. Some of these workers may still be at risk for bladder cancer. Improved screening options for high-risk groups, as well as better treatment options, should continue to improve survival and quality of life for these individuals.

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Textbook of Clinical Occupational and Environmental Medicine

Second Edition

Edited by

Linda Rosenstock MD MPH
Dean, School of Public Health
Professor of Medicine and Environmental Health Sciences
University of California, Los Angeles
Los Angeles, CA
USA

Mark R Cullen MD
Professor of Medicine and Public Health Director
Occupational and Environmental Medicine Program
Yale University School of Medicine
New Haven, CT
USA

Carl Andrew Brodkin MD MPH
Clinical Associate Professor of Medicine and
Environmental and Occupational Health Sciences
University of Washington
Seattle, WA
USA

Carrie A Redlich MD MPH
Professor of Medicine
Occupational and Environmental Medicine Program
and Pulmonary Critical Care Section
Yale University School of Medicine
New Haven, CT
USA

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