Contemporary Occupational Carcinogen Exposure and Bladder Cancer
A Systematic Review and Meta-analysis

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IMPORTANCE Bladder cancer (BC) is a common disease. Despite manufacturing and legislative changes to workplace hygiene, many BCs still arise through occupational carcinogen exposure.

OBJECTIVE To profile contemporary risks of occupational BC.

DATA SOURCES A systematic review using PubMed, Medline, Embase, and Web of Science was performed in October 2012 (initial review) and May 2014 (final review) and was updated in June 2015.

STUDY SELECTION We identified 263 eligible articles. We excluded reports in which BC or occupation were not the main focus, and those with insufficient case, risk, or confidence interval data. We selected the most recent data from populations with multiple reports.

DATA EXTRACTION AND SYNTHESIS Reports were selected by 2 of us independently. We combined odds ratios and risk ratios (RRs) to provide pooled RRs, using maximally adjusted RRs in a random effects model. Heterogeneity and publication bias were assessed using I² and Beg and Egger tests. Risk estimates were annotated by occupational class using Nordisk Yrkesklassificering, or Nordic Occupational Classification, and International Standard Classifications of Occupations (NYK and ISCO-1958) Codes.

MAIN OUTCOMES AND MEASURES Occupations were profiled by BC incidence and mortality risk over time. After data collection, we detected a sex difference in these profiles and recorded this as a secondary outcome.

RESULTS Meta-analysis revealed increased BC incidence in 42 of 61 occupational classes and increased BC-specific mortality in 16 of 40 occupational classes. Reduced incidence and mortality were seen in 6 of 61 and 2 of 40 classes, respectively. Risk varied with sex and was greatest in men (standardized incidence ratio, 1.03 [95% CI, 1.02-1.03]; P < .001). From the 1960s to the 1980s, there was a steady decline in standardized incidence ratio (SIR) for both sexes. This trend reversed from the 1980s, as in the decade 2000 to 2010 the SIR increased to 113 (95% CI, 1.07-1.19) for men and 1.27 (95% CI, 1.12-1.43) for women. In contrast, mortality risk declined for both sexes from the 1960s to the 1990s. The overall risk of BC mortality was also greater for men (standardized mortality ratio [SMR], 1.32 [95% CI, 1.18-1.48]) than for women (SMR, 1.14 [95% CI, 0.80-1.63]). Limitations include possible publication bias, that reports stratify workers mostly by job title not task, that not all studies adjusted for smoking, and that the population was mostly derived from Western nations.

CONCLUSIONS AND RELEVANCE The profile of contemporary occupations with increased BC risk is broad and differs for incidence and mortality. Currently the incidence seems to be increasing, and this increase is occurring faster in women than men. Improved detection mechanisms and screening are possible reasons for this. Workers with aromatic amine exposure have the highest incidence, while those exposed to polycyclic aromatic hydrocarbons and heavy metals have the greatest mortality.

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Bladder cancer (BC) is the fourth commonest male malignant neoplasm worldwide. Most tumors arise following exposure to exogenous carcinogens that enter the circulation through inhalation, ingestion, or skin contact. The 2 most frequent routes of exposure are through tobacco smoking and occupation. Tobacco smoke is estimated to account for 50% of BCs. The risk varies with sex, smoking history, and type of tobacco. The second commonest exposure to carcinogens is through occupational tasks. This route has been known for many years, includes a genetic interaction with detoxification enzymes and has been reduced through workplace health and safety regulations in most countries. Examples include European Union directives (eg, Council Directives 90/394/EEC and 98/24/EC) and the 2002 Control of Substances Hazardous to Health Regulations in the United Kingdom.

In 1981 Doll and Peto estimated that 10% of BCs arose from occupational exposure. Given the 20- to 30-year latency between exposure and cancer, we expected that workplace legislation has now reduced this rate. Indeed, workplace legislative changes, and that this has led to a change in occupational risk has occurred through social and workplace legislative changes, and that this has led to a change in the workforces at risk for BC. To examine this, we undertook a systematic review and meta-analysis of contemporary reports of occupational exposure and bladder carcinogenesis. We compared these with similar historical reports.

### Methods

#### Data Sources
In October 2012 (initial review) and May 2014 (final review) we searched PubMed, Medline, Embase, and Web of Science for full-text articles published or in press. No time or language limits were applied. We used a variety of terms for occupation and either BC or urothelial-transitional cell carcinoma (eTable 1 in the Supplement). Abstracts of all reports were read and full articles retrieved for those appearing to fulfill selection criteria. Two of us (M.G.K.C. and J.W.F.C.) manually searched reference lists of identified reports and jointly selected reports. We also searched for chemicals implicated as urothelial carcinogens and detailed their industrial use using reference textbooks and data repositories. This analysis is reported using recommended criteria (see PRISMA statement, eTable 2 in the Supplement).

#### Study Selection
Articles were eligible if they reported original data on occupational risk for BC in adults. Reports were rated for sample size, quality of reporting, population descriptions, and study design (preferably case-control design) by 2 of us (M.G.K.C. and J.W.F.C.) independently. We excluded reports in which BC or occupational exposures were not the main focus of analysis, those not reporting or with insufficient data to calculate confidence intervals, and those with missing data. We selected the most recent data from populations with multiple reports. Risk estimates were annotated by occupational class using NYK and ISCO-1958 (Nordisk yrkesskilling, or Nordic Occupational Classification, and International Standard Classifications of Occupations) codes (detailed by Pukkala et al and dates of exposure (taken as the mid-time point of documented exposure interval). Occupational codes were modified to discriminate those commonly reported to be important for BC (eg, public safety and protection workers [code 44]) were stratified into firefighters and policemen; rubber workers were selected from glass, ceramic, tile workers, and others (code 41)).

#### Data Extraction and Synthesis
For meta-analysis, we used articles reporting risk estimates (eg, odds ratio [OR], standardized incidence ratio [SIR], standardized mortality ratio [SMR], or RR) and 95% CIs, or enough information to calculate these. We used adjusted risk estimates to control for other confounders, such as...
tobacco smoking or socioeconomic factors. Meta-analysis of risks was performed using a random effects model using Stata statistical software (version 12.0; StataCorp LP). This model was chosen because we anticipated heterogeneity between studies given the nature of occupational BC reports (eg, there are few with large populations, most have low disease incidences, all are nonrandomized, and most are retrospective in design). We assessed heterogeneity ($I^2$) between studies for each occupation. Incidence and disease-specific mortality (DSM) risk were computed separately. Publication bias was evaluated by visual inspection of funnel plots, Egger linear regression, and Begg rank correlation tests.

Main Outcomes and Measures

Our objective was to evaluate the current risk profile of occupational BC and evaluate the change in risk over time to determine whether social and workplace legislation has changed the face of occupational BC.

The institutional review board of the University of Sheffield waived the requirement for an ethics statement for this work.

Results

Reports of Occupation and BC

We identified 2844 reports, from which we read 697 full articles and selected 263 for systematic review (reporting 31.4 million persons) (Figure 1 and eTable 3 in the Supplement). These articles reported BC risk in 1254 occupations, which were subclassified into the NYK and ISCO-1958 codes for occupational class. While funnel plots suggested symmetry for each comparison, statistical analyses identified potential publication bias for men and incidence data (eFigure 1 in the Supplement). One occupation (racehorse trainers/jockeys) had a single report, while all other occupational classes had multiple estimations of risk (mean [SD], 27 [25]) comparisons per occupation). The highest individual reported incidence risks were for factory workers (RR, 16.6 [95% CI, 2.1-131.3]),20 hairdressers (RR, 13.4 [95% CI, 1.5-48.2]),21 and aircraft/ship’s officers (RR, 11.8 [95% CI, 1.5-95.7]).22 For mortality, the highest reported rates were for chemical (RR, 27.1 [95% CI, 11.7-53.4])23 and dye workers (RR, 8.3 [95% CI, 1.7-24.8]).24 For meta-analysis of risk, we used data from 231 627 cases and 4.76 million controls annotated in 217 articles by occupation (eTable 4 in the Supplement).

BC Risk and Sex and Over Time

Meta-analysis by sex revealed higher incident risks for men (SIR, 1.03 [95% CI, 1.02-1.03]) than women (SIR, 1.00 [95% CI, 0.99-1.01]; $\chi^2 P < .001$), and that this risk varied over time.
(Figure 2A, and eFigure 2A and 2B in the Supplement). From the 1960s to the 1980s, there was a steady decline in SIR for both sexes. This trend reversed from the 1980s, as in the decade 2000 to 2010 the SIR increased to 1.13 (95% CI, 1.07-1.19) for men and 1.27 (95% CI, 1.12-1.43) for women. In contrast, mortality risk declined for both sexes from the 1960s to the 1990s (Figure 2B). The overall risk of BC mortality was also greater for men (SMR, 1.32 [95% CI, 1.18-1.48]) than for women (SMR, 1.14 [95% CI, 0.80-1.63]).

Comparisons of incidence and mortality over time within most occupational classes were limited by cohort heterogeneity or small sample sizes (eTable 5 in the Supplement). Exceptions included several occupations with evidence of reductions or no change in risk over time. For example, reductions in risk over time were apparent for drivers (from a SIR of 1.4 [95% CI, 0.7-3.0] in the 1940s to 0.99 [95% CI, 0.9-1.1] in the 2000s) and mechanics (from an SIR of 1.4 [95% CI, 1.0-1.8] in the 1950s to 1.1 [95% CI, 1.0-1.3] in the 2000s). The reduction in risk for drivers supports the findings of a recent focused meta-analysis.25

BC Incidence and Occupation
Meta-analysis by occupation revealed significantly increased SIR and decreased SIR for BC incidence in 42 of 61 (67%) and 6 of 61 (10%) of the classes, respectively, when compared with the general population (eTable 4, Figure 3). Significant heterogeneity ($F^2$ $P < .05$) between studies was seen in 11 classes, suggesting caution should be exercised when interpreting risk in these occupations. Overall, the highest BC risks were for workers exposed to aromatic amines (tobacco, dye, and rubber workers; hairdressers; printers; and leather workers) and polycyclic aromatic hydrocarbons (PAHs) (chimney sweeps, nurses and midwives, aluminum workers, seamen, and oil/petroleum workers). The lowest risks were seen in agricultural sector workers.

BC Mortality and Occupation
Sufficient data were present to calculate DSM for 40 occupational classes. Of these, 16 of 40 (43%) and 2 of 40 (5%) occupations had significantly elevated or reduced risks of death from BC, respectively (eTable 4 in the Supplement, Figure 3). Many occupations with the highest risks of BC mortality differed from those with the highest risk of BC incidence. The highest rates of mortality occurred in workers exposed to heavy metals and PAHs (metal workers [although there was significant heterogeneity], aluminum workers, electricians, and mechanics), to diesel and combustion products (military and public safety workers) and those exposed to aromatic amines (domestic assistants and cleaners, rubber workers, painters, and hairdressers). Disparities between an increased BC incidence and mortality were seen in oil and petroleum workers, among health care professionals, and in those exposed to textiles and leather.

Chemical Agents and Urothelial Carcinogenesis
We identified 44 agents with a reported role in urothelial carcinogenesis (eTable 6 in the Supplement). These included chemicals with multiple (eg, 2-naphthylamine found in the dye and rubber industry and tobacco smoke) and single exposures (4,4'-methylenebis[2-chloroaniline] [MBOCA]) used in polyurethane production).

Study Limitations
There are several limitations to this work. First, risk was stratified according to occupational title or class rather than tasks. Therefore, risks were averaged among employees, which may have hidden the at-risk subpopulation. Second, we combined cohort and case-control studies, with different control arms. This may have compounded weaknesses within each, and our outcomes were sometimes generated using heterogeneous reports. While control arms differed across most studies, BC is rarely asymptomatic (as shown by the low detection rates found when screening the general population3), suggesting that the control groups were comparable in terms of low BC risk. Analysis between reports revealed significant heterogeneity in those used to combine risks for 11 occupations (eTable 7 in the Supplement). While we used a random effects model for meta-analysis, we should caution regarding the strength of interpretation for these occupations. Third, we were unable to adjust for smoking, the most common carcinogen. Smoking patterns are known to differ with occupational class and so may have contributed to our reported differences. Fourth, time of exposure was estimated as the midpoint of an employment window. Many reports lacked detail of this window, and so we estimated at risk periods. Fifth, most of the reports represented populations in Western nations and hence should be viewed with respect to these. Finally, there was evidence of publication bias (eFigure 1 in the Supplement) when all studies were compared, suggesting a need to caution the strength of our findings.

Discussion
Historical reports identified high risks for exposed individuals. For example, 16% to 19% of workers exposed to 4-amino-biphenyl (4-ABP) and 26% of those exposed to 1-naphthylamine, 2-naphthylamine or benzidine developed BC.26 Our current meta-analysis reveals lower risks for contemporary exposures and that this risk varies between occupations, with sex, and over time, and supports findings from a previous meta-analyses.4 Our data suggest that many occupations still have an elevated risk of BC incidence or mortality, despite improvements in workplace hygiene. As such, occupational BC remains an important public health issue.27,28 Comparisons within each class over time revealed either no change in risk or insufficient studies (number, size, or distribution) to make meaningful comparisons. Exceptions included drivers, whose risk seems to be declining.25

The profile of occupations with elevated incidence and DSM may differ. This may reflect exposure to different carcinogens with cancer-phenotype specificity or occupational health differences. Efforts to reduce the impact on workers should be targeted to occupations at risk of mortality (rather than just incidence), and solutions may be offered from occupations with disparate incidence and mortality risks. For
example, physicians and health care workers (who have elevated incidence rates but lower than expected DSM) may be knowledgeable patients who do not ignore suspicious symptoms and facilitate rapid treatment pathways, whereas dye
workers are in an industry with known risks and receive workplace education or targeted screening.

**Workers Exposed to Aromatic Amines**

Incidence was highest in occupations in which workers were exposed to aromatic amines, namely rubber, plastic, and dye workers, hairdressers, and painters. These are typical workers at risk for occupational BC. For example, since 1949 the potent carcinogen 2-naphthylamine has been restricted within the rubber industry. Urothelial carcinogens within plastic manufacture include 1,1-dichloroethane (used as a solvent and for 1,1,1-trichloroethane production); MBOCA, used as a curing agent in polyurethane production; and 4,4’-methylenedianiline, used to make polyurethane foams or as a hardener in epoxy resins. These latter 2 agents seem to be weaker bladder carcinogens; both were implicated by animal studies, but an exposure report in humans has suggested a low risk. Printing and painting are graded by IARC as 2b (possible carcinogenicity) and 1 (definitive) exposures, respectively, because workers are exposed to aromatic amines and PAHs. Inks and paints are composed of dyes and/or pigments, solvents, and additives for handling, and the balance of these depends on purpose. For example, newspaper presses used mineral oil pigmented with carbon black and benzidine until the 1980s. High-speed rotating presses released an ink mist rich with these carcinogens, which was subsequently linked to lung and BC. Other printing exposures include 4-aminodiphenyl (4-ADP) as a metabolite of indigine/nigrosine dyes (mostly replaced in the 1970s). As printing technology becomes more digital, BC risk is likely to disappear within this industry. A comparison of BC risk in printers recruited from 1953 to 1998 shows a risk reduction from 1.47 (95% CI, 1.19-1.79) to 1.23 (95% CI, 1.17-1.30) (eTable 4 in the Supplement). We calculated that the most recent SIR was now 1.05 (95% CI, 0.72-1.54) (eTable 5 in the Supplement). With regard to painters, our findings reveal limited reduction in risk when compared with a previous study.
meta-analysis using data from 1972 to 2009 (RR, 1.28 [95% CI, 1.15-1.43]). While these findings suggest continued exposure to carcinogenic pigments or solvents (eTable 5 in the Supplement), an in-depth analysis questions a direct link between painters and BC. The main carcinogen for hairdressers is reported to be 4-ABP. This agent has been restricted since the 1970s, and consequently BC risk has fallen from 3.2- to 1.23- to 1.32-fold (eTable 4 in the Supplement or Reulen et al4). Of note, BC risk increases with duration of employment within hairdressers. Textile workers are at increased BC risk from contact with pigments, dyes, and synthetic materials. Specific exposures include 2-naphthylamine, 4-ABP, nitrobenzyl, benzidine, direct black 58, and blue 6. These latter 2 are azo-dyes that release benzidine when metabolized. Leather workers (eg, shoe repairers) are also exposed to leather dust, leather dyes (eg, ortho-toluidine [IARC 1]), adhesives, and polishes.

**Workers Exposed to PAHs**

Bladder cancer mortality risks were highest in occupations with PAH exposures, including those working with metals, aluminum, and glass manufacture, and electrical workers. PAHs are atmospheric pollutants or lubricants sharing a fused aromatic ring pollutants. Their carcinogenicity is graded according to composition (eg, naphthalene [IARC 2b], benzo[a]pyrene [IARC 1]), and exposure. Our analysis suggests that many workers at risk of BC are exposed to PAHs through combustion products and diesel fumes, metal working fluids, and coal tar products. This confirms recent data analyzing this exposure specifically. High PAH exposure occurs during aluminum manufacture when coal tar and/or pitch anodes evaporate during electrolysis to produce benzo[a]pyrene vapor (IARC 1). Our findings (SIR, 1.40) support previous meta-analysis indicating sustained elevated BC risk, despite changes to anode manufacture. Drivers, miners, marine workers, and seamen partly derive their BC risk from the inhalation of diesel exhaust fumes. Diesel fumes contain PAHs and other particles known to have mutagenic effects on the urothelium in a dose-dependent manner. The carcinogenicity of exhaust inhalation may be enhanced by the low volumes of fluid drunk by drivers (to reduce micturition frequency) and the high prevalence of cigarette smoking within these occupations. Seamen and deep sea fishermen are also exposed to solvents, antirust paints, and creosote. The risk of BC within drivers and those exposed to diesel fumes was elevated across the entire cohort but seems to be declining. This observation supports findings of a previous meta-analysis and data from the Swedish Cancer Environment Register.49

Bladder cancer risk in metal, machine, and automobile workers is partly derived from the exposure to mineral oils (as metal-working fluids), solder and/or welding fumes, solvents, paints, and greases. Metal-working fluids are used in cooling, lubricating, and cutting metal. They are colorless, odorous, light alkane mixtures from a nonvegetable (mineral) source (often a distillate of petroleum), and include paraffinic oils (based on n-alkanes), naphthenic oils (based on cycloalkanes), and aromatic oils (aromatic hydrocarbons). Mineral oils are known (IARC 1) carcinogens owing to their high PAH content. Bladder cancer risk increases proportionally with the intensity, duration, and accumulation of exposure and the type of mineral oil: straight (high-risk) vs soluble and/or synthetic fluids (low-risk). The content of metal-working fluids varies with use, storage, and handling. For example, nitrosamine concentration increases with prolonged storage, heating, or pressure. Cutaneous PAH exposure also occurs within nurses and health care workers, who are exposed to coal tar preparations (IARC 1). Coal tar products are reported to be antiseptic, antipruritic, antiparasitic, antifungal, antibacterial, keratolytic, and anticanthemic and are used to treat dermatological conditions. Contemporary medicinal products are thought to be safe and contain less than 5% coal tar. Health care workers are also exposed to various medicinal carcinogens and ionizing radiation.

**Workers Exposed to Tobacco Smoke and Combustion Products**

Recreational sector and bar staff are exposed to the inhalation of environmental tobacco smoke. In many countries, smoking in public and work places is now prohibited, and thus the risks for these staff will decrease in future. As with drivers, the low frequency of micturition in recreational staff increases risk. Firefighters are exposed to various combustion products (particulate matter that can be inhaled) containing carcinogens such as aromatic amines from paint (methoxaniline, methoxybenzylamine, PAHs, and polyhalogenated dibenzodioxins or dibenzofurans from flame-retardants. Heterogeneity of risk among firefighters reflects the fire types attended (industrial, urban, or rural) and use of protective clothing and/or breathing systems.

**Workers With Mixed Exposures**

Many workers are exposed to various carcinogenic substances. For example, petroleum workers are exposed to aromatic amines (benzenes), PAHs (lubricants), diesel exhaust fumes, and petroleum additives, such as alkyl lead. Increasing automation within this industry is reducing petroleum exposure for workers. Chemical workers are exposed to a variety of agents, and so caution must be used when combining these into a single group. The studies used in our analysis tended to define chemical workers as those within chemical synthesis. Carcinogen exposures include chlorination by-products (disinfection agents), MBBOCA, benzidine, and chlorinated hydrocarbons in synthesis of trichloroethane.

**Workers Exposed to Heavy Metals**

Plumbers are exposed to numerous carcinogens, including lead, welding/solder fumes, solvents, tar, greases, and asbestos. Solder and welding fumes contain lead oxide, heavy metals (eg, arsenic, cadmium, chromium, and nickel) and colophony (rosin-based flux containing acetone and carbon monoxide). Bladder cancer risk was highest for plumbers working prior to 1960. In our analysis, plumbing was not statistically significant (95% CI, 0.85-2.38). The concentration of heavy metals in solder has decreased since the 1960s. Electrical workers are exposed to polychlorinated biphenyls used in coolants for electrical transformers and heavy metals (eg, cad-

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mium [IARC grade 1], antimony, and arsenic). Cadmium is used in batteries, as a catalyst, in electroplating (cadmium oxide or sulfate), as a pigment (cadmium sulfide), and as a plastics stabilizer (cadmium stearate). Exposure is usually via inhalation (eg, from soldering). A survey suggested that risk was highest in electrical engineers, electricians, telephone installers and repairers, and telephone linesmen and cable joiners.

Assorted Occupations

Various processes in food preparation expose workers to urothelial carcinogens. These include solvents (including chloroform hexane [IARC 2b carcinogen], isopropanol, and petroleum ether) used to remove animal or vegetable fat from food, food dyes (eg, Sudan red G), preservatives (phenol-derived cresote compounds), and mineral oil exposure from the inks in recycled cardboard packaging. In particular, dry cleaners use nonaqueous solvents (eg, tri- and tetra-chloroethylene [TCE] [IARC 2a]). Bladder cancer risk seems to be related to TCE exposure whether through work or water pollution.

Conclusions

While there have been reductions in occupational BC incidence and mortality, it appears that there may still be many occupations with an elevated incidence or mortality risk. This persists despite improvements in workplace hygiene, although the profile of at-risk occupations has changed over time and may differ for BC incidence and mortality. Efforts to reduce the impact of BC on workers should be targeted to occupations at risk of mortality. Solutions that reduce mortality may be found within occupations with disparate incidence and mortality risks. Recent data suggest that the risk of occupational BC is rising and effecting women more than men. This may be due to an increase in the number of women in the workforce or the emergence of occult carcinogens in occupations predominated by women.

REFERENCES


