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The contemporary landscape of occupational bladder cancer within the United Kingdom: A meta-analysis of risks over the last 80 years

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Abstract

Importance

Bladder cancer (BC) is a common malignancy that arises through occupational carcinogen exposure. Here we analyse trends in UK to better understand contemporary occupational BC.

Objective

To profile the contemporary risks of occupational BC in the UK.

Materials and methods

Systematic review using PubMed, Medline, Embase and Web of Science was performed in March 2016. We selected reports of British workers in which BC or occupation were the main focus, with sufficient cases or with confidence intervals (CI). We used the most recent data in populations with multiple reports. We combined odds ratios and risk ratios (RRs) to provide pooled RRs of incidence and disease specific mortality (DSM). We tested for heterogeneity and publication bias. We extracted BC mortality from Office of National Statistics death certificates. We compered across regions and with our meta-analysis.

Results

We identified 25 articles reporting risks in 702,941 persons. Meta-analysis revealed significantly increased incidence for 12/37 and DSM for 5/37 occupational classes. Three classes had reduced BC risks. The greatest risk of BC incidence occurred in chemical process (RR 1.87 (1.50-2.34)), rubber (RR 1.82 (1.4-2.38)) and dye workers (RR 1.8, (1.07-3.04)). The greatest risk of DSM occurred in electrical (RR 1.49 (1.19-1.87)) and chemical process workers (RR 1.35 (1.09-1.68)). BC mortality was higher in the North of England, probably reflecting smoking patterns and certain industries. Limitations include the lack of sufficient robust data, missing occupational tasks and no adjustment for smoking.

Conclusion

Occupational BC occurs in many workplaces and the risks for incidence and DSM may differ. Regional differences may reflect changes in industry and smoking patterns. Relatively little is known about BC within British industry, suggesting official data underestimate the disease.

Introduction

Bladder cancer (BC) is the fourth commonest male malignancy worldwide and the 9th commonest cancer within the UK [1]. Whilst the incidence of BC in the UK has reduced in recent years, this cancer still represents the 6th most lethal malignancy in the UK and survival rates appear to be deteriorating, in contrast to most other cancers [2]. The commonest cause of BC is tobacco smoking, which accounts for about 50% of cases [3]. A recent meta-analysis [4] suggests that this is still a significant worldwide health problem despite legislature to prohibit smoking in public places and at work in many Western nations [5]. In the UK, tobacco smoking in public places was prohibited in 2007 and the NHS promotes smoking cessation. However, despite knowledge about the adverse health outcomes of tobacco smoking, approximately 1/5 of the UK population smoked in 2014 [6].

The second commonest cause of BC is occupational exposure to carcinogens [3, 7]. This aetiology is well known and has been subject to health and safety regulations, such as the 2002 Control of Substances Hazardous to Health Regulations in the United Kingdom [8]. In 1981 Doll and Peto estimated that 10% of BCs arose through occupational carcinogen exposure [9]. This attributable fraction was recently re-calculated by the Health and Safety Executive to have reduced to 5-7% in 2010 [10]. This risk calculation mostly uses exposure to recognised carcinogens in known industries. This method excludes poorly controlled, unknown or occult exposures and so may underrepresent the true risks. Evidence of unrecognized carcinogen exposure may be derived from regional BC demographics that mirror industrial differences rather than smoking patterns. For example, in 2011 there were 11.1 new BC cases per 100,000 in England and 8.6 in 100,000 in Northern Ireland [11]. Smoking rates in England and Northern Ireland are similar [6], but there are marked industrial differences [12]. In the South West of England the respective number of persons smoking (% of total population) has reduced from 30% in 2000 to 17.3% in 2013 (the greatest reduction in any region), whilst the incidence of BC has increased from 10% to 12% of the overall UK total (924 to 1075 cases) [11, 13].

We recently reported apparent differences between DSM and BC incidence following occupational exposures using worldwide data [14, 15]. However, heterogeneity in smoking prevalence and industrial patterns between nations may have limited these analyses. This global picture also lacked detail for individual countries. To overcome these issues, we now focus upon a single nation. We aimed to profile occupational BC within the UK and to identify contemporary at risk populations. We hypothesise that this will help identify current carcinogens and will aid better targeting of preventative and screening interventions.

Materials and Methods

Literature Search and Inclusion Criteria

In May 2015 (initial) and March 2016 (updated) two authors independently (MC and JWFC) conducted a systematic search using PubMed, Medline, Embase and Web of Science. We included full-text articles published or in press with no time or language limits applied. We used a variety of search terms for occupation and industry and either BC or urothelial/transitional carcinoma (supp. table 1). Abstracts of all reports were read and full papers retrieved that matched inclusion criteria. The methods used have been described previously [14] and are compliant with PRISMA reporting guidelines (supp. table 2).

Articles were eligible if they reported original data on occupational BC risk in adults working within the UK. Reports were mostly case control or cohort by design and were required to focus on occupational exposures. Reports needed to have sufficient data to calculate confidence intervals (CI). We selected the most recent and maximally adjusted data from study populations with multiple datasets to ensure contemporaneity and to minimise confounding bias (e.g. tobacco smoking, gender, ethnicity or socio-economic group).

Meta-analysis

Risk estimates were annotated by occupational class using Nordisk Yrkesklassficering or Nordic Occupational Classification (NYK), and International Standard Classifications of Occupations (ISCO-1958) classifications [16]. For meta-analysis, we used manuscripts reporting risk estimates (e.g. odds ratio (OR), standardised incidence ratio (SIR), standardised mortality ratio (SMR) or relative risk (RR)) and 95% confidence intervals, or enough information to calculate these.

Meta-analysis was performed using a random effects model using STATA (Vsn. 12.0). This model was chosen as we anticipated heterogeneity between studies given that occupational BC reports are often from large populations with low disease incidences and most reports are retrospective and non-randomised. Heterogeneity was assessed using I^2 between studies for each occupation. Publication bias was evaluated by visual inspection of funnel plots, Egger's linear regression [17] and Begg's rank correlation tests [18].

Calculating regional BC Mortality rates

Age-standardised mortality rates in which BC was identified as the cause of death on the death certificate were calculated for 9 English Government Office Regions (GORs) from 1981 to 2014 using Office of National Statistics data. Prior to 1981 outcomes were collated in Standard regions not equivalent to GORs. Mortality rates were standardized against both a 1976 and 2013 European Standard Population. Regional rates were presented relative to the lowest overall rate.

Results

We identified 2,844 reports from which we read 697 full manuscripts, and selected 25 for full inclusion (figure 1, table 1). The selected manuscripts reported risks in 702,941 persons. These included 111 and 43 groups of workers for BC incidence and DSM, respectively, representing 37 different NYK and ISCO-1958 occupational classes. Most occupational classes had multiple reports of BC risk, including textile workers (n=10 separate reports). Funnel plots suggested symmetry for comparisons. Begg and Egger's tests for publication bias were not significant (supp. figures 1 and 2).

Bladder Cancer Incidence

Chemical process (RR 1.87 (1.50-2.34), rubber (RR 1.82 (1.40-2.38)) and dye workers (RR 1.80 (1.07-3.04)) had the highest significant risks of BC. Other workers at significantly elevated risks occupations were glass workers (RR 1.66 (1.21-2.27)), waiters RR 1.30 (1.01-1.65), healthcare workers RR 1.16 (1.07-1.26), nurses RR 1.15 (1.06-1.25), electrical workers 1.60 (1.09-2.36), smelters 1.55 (1.07-2.25), domestics 1.49 (1.05-2.12) and textile workers 1.74 (1.45-2.08). The highest pooled RR of BC incidence (table 2) was seen in fire fighters (RR 4.30 (95%CI 0.78-23.80)) and beverage workers (RR 2.09 (0.34-12.88)), although these did not reach statistical significance. Three occupations had a statistically significant reduced pooled RR of BC incidence; artistic workers (RR 0.66 (95%CI 0.47-0.92), warehouse workers (RR 0.48 (0.31-0.76) and drivers (RR 0.46 (0.28-0.75).

Disease Specific Mortality

Three occupations had a statistically significant increased risk of DSM (table 3); electrical (RR 1.49 (95%CI 1.19-1.87)), chemical process (RR 1.35 (95%CI 1.09-1.68)) and transport workers (RR 1.15 (95%CI 1.03-1.28)). Other occupations with elevated non-significant risks of DSM included rubber workers RR 1.28 (0.57-2.91), painters RR 1.27 (1.00-1.62), construction workers RR 1.20 (0.79-1.81), military workers RR 1.15 (0.31-4.30) and bartenders RR 1.08 (0.75-1.56). Occupations with lower than expected DSM included clerical workers (RR 0.89 (95%CI 0.89-1.0)) and physicians (RR 0.45 (95%CI 0.31-0.66)) (Figure 2, Supp. Table 4).

Trends over time

Whilst we aimed to look at trends in occupational BC over time, insufficient data prevented this for all occupations.

Geographic trends in mortality from bladder cancer within England

We plotted mortality registrations from BC registered in England from 1974 to 2014 in males and females (Figure 3, see https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/005651numberofdeathsandagestandardisedmortalityrateswherebladdercanceristheunderlyingcauseregionsofenglanddeathsregisteredbetween1974and2014). Whilst changes in geographic regions make comparisons over time difficult, we identified a marked decline in BC mortality in the West Midlands and that in recent years the highest rates were amongst males in the North East and North West. Occupational information was available for a minority of cases with registered BC mortality between 2001 and 2014 (table 4, 16,737/58,495 (28.6%)). Listed occupations included those identified within our meta-analysis, e.g. electrical and transport workers, and those found elsewhere e.g. metal, construction and domestic workers [14, 15].

Discussion

Here we profile contemporary BC within the UK using outcomes in over 700,000 persons and death certificate data. We observed changing demographics of the disease that might reflect manufacturing and legislative changes, and that have implications for efforts to improve workplace safety. Firstly, we found some similarities with previous reports of occupations at risk of BC (e.g. [8]). Historical series reported the highest risks in workers exposed to aromatic amines in rubber, dye and textiles workers. In the UK, many of these were employed around the West Midlands in automobile manufacture and exposed to the rubber anti-oxidant β-naphthylamine (2-naphthylamine) through tyre production. However, our calculated relative risks are lower than previous reports (e.g. RR 1.80 versus 2.90 [19] for dye workers, RR 1.82 versus 3.03 [20] [21] for rubber workers) suggesting robot use in automobile manufacture, replacement of known carcinogens and the geographical relocation of industries has improved safety. Whilst these events may partly explain the absolute and relative decline in BC mortality across the West Midlands (figure 3), smoking rates in this regions are some of the lowest in the UK (around 17%)[6].

Secondly, our findings support previous reports that the industries at risk of BC incidence and mortality can differ [14, 15]. The highest observed DSM rates within our meta-analysis occurred in electrical, chemical and transport workers and were supported by observations from English death certification details (table 4). Within the UK, some of the at risk industries are commonly located in the North (such as chemical manufacture and transport workers (HGV drivers)). As smoking rates are high in the North East and North West (around 19% prevalence [6]), it is likely that the geographic patterns are multifactorial. Some occupations with high DSM are ubiquitous throughout the UK (e.g. electrical workers and painters) and include multiple exposures. Electrical workers are exposed to polycyclic aromatic hydrocarbons through their handling of metals, anode vapour, and soldering fumes. Such occupations make poor choices for targeted screening. In the mean time whilst our findings do not test the role of screening high-risk workers, it seems reasonable to suggest a low threshold for urological assessment in workers within the electrical, chemical, rubber, transport, and metal industries presenting with mixed urinary symptoms. Furthermore, this data will hopefully inform (but is unlikely to change) UK compensation law in the short term, however, it does highlight the pertinence of accurate occupational histories. In addition, patients can be directed towards renumeration services such as the *Industrial injuries and disablement benefits* scheme [22].

Thirdly, our analysis reveals that there are few high quality reports of occupational BC in the UK. For example, we were unable to compare risks over time for all occupations (i.e. to see if changes in legislation had made an impact), and we could not examine DSM in common occupations previously reported to have high mortality rates in other countries or in the UK death certificates (such as metal workers, dry cleaners) [14, 15]. Furthermore, occupational details are unavailable on many British death certificates. This may be due to incomplete recording at the time of death registration or that most deaths occurred in retired workers (and so 'none' was often recorded as their current occupation). As such, our findings suggests that many occupational BCs in the UK are misssed [10]. Nearly all BCs arise following exogenous carcinogen exposure (albeit with some genetic predisposition). As smoking is estimated to be the aetiology for only 50% of BCs, it is plausible that occupational exposures (perhaps using unknown carcinogens, known carcinogens in unknown roles [23] or indirectly through environmental pollution) must contribute to a large proportion of the remaining cancers. Our report suggests the need for further primary research and vigilance by treating physicians to detect these exposures. We were able to observe reductions in BC risk amongst drivers over time (a reduction from RR 0.52 to 0.49 from 1950 to 1990), although data was limited and not statistically significant. This may reflect cleaner diesel fumes [17] or trends in cigarette smoking. Contrary to this, the overall risk profile of occupational BC in the UK does seem to be on a slightly upward trend in risk since the 1950's, with a spike in the 1960s (figure 5).

Conclusions

Here we have profiled contemporary occupational BC in the UK. We found a reduction in incidence risk from previous reported rates and that many occupations continue still have elevated risks. The profile of occupations at risk of BC appears to differ from those at risk of dying from BC. Further work is needed to better understand the contribution of occupational tasks to BC aetiology and to reduce workplace exposures.

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Registration

This initial review was prospectively registered with the Prospero database of systematic reviews (no. CRD42013004927).

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Figure legends

Figure 1. Consort diagram of manuscripts selected in this report.

Figure 2. A Forest plot of the pooled relative risks of new bladder cancer diagnosis (incidence) in British workers 1930 to 2010.

Figure 3. A Forest plot of the pooled relative risks of bladder cancer disease specific mortality (DSM) in British workers 1930 to 2010.

Figure 4. Regional trends in standardized mortality from bladder cancer from 1974 to 2014 in (a). Males and (b). Females. Rates are presented relative to those in South East (lowest). Data were collated in standard regions from 1974 to 1980, then in GOR from 1981-2014. Although aligned for illustrative purposes, these regions are not entriely equivalent. For example, London was included in the South East until 1981, East Anglia was discrete from the East until 1981. Given this, we have plotted relative rates to show trends rather absolute values.

Table 1. Manuscripts included within this meta-analysis.

Publication year	Design	BC cases	Controls/Expected	Total persons	Collection method	Occupational setting	Population	Ref.
1965	Cohort	5		11,499	Gas Board Data	Gas Workers	Gas board staff	[24]
1969	Cohort	10	4	1,400	Personnel Records	Rubber Factory	Residents, Holloway, UK	[21]
1970	Case Control	632	722	1,030	Interview	Assorted	Residents, Leeds, UK	[25]
1975	Cohort	1	1	2,120	Company Records	Chemical Plant Workers	Welsh Plant	[26]
1976	Cohort	37	19	40,867	Census data	Rubber And Cable Making	UK Workers	[27]
1978	Cohort	14		1,500	Death Certificates	Dye Workers	Union members	[28]
1982	Cohort	559		991	Interview	Assorted	Residents, Yorkshire, UK	[19]
1985	Case Control	86	44		Interview	Chemical Dye Workers	Residents, Yorkshire, UK	[29]
1985	Case Control	846	1,403		Interview	Non-Chemical Dye Workers	Residents, Yorkshire, UK	[29]
1987	Cohort	3		255	Census data	Tar Workers	Four distilleries	[30]
1989	Cohort	4		862	Census data	Fertilizer Manufacturers	NHS registry	[31]
1989	Cohort	4		652	Census data	Fertilizer Manufacturers	NHS registry	[31]
1990	Cohort	989	3,658		Questionnaire	Fisherman	Regional BC cases	[32]
1991	Cohort	8		1,253	Union Records	Print Workers	Union members	[33]
1992	Cohort	1,510		2,457	Death Certificates & Census	Assorted	Coastal & Estuarine Locations	[34]
1993	Case Control	27	11	21,358	Service Records	Nuclear Testing Officers	Ministry of Defence staff	[35]
1994	Cohort	29		9,471	Registry & Census Data	Newspaper Workers	Union members	[36]
1996	Cohort	34		5,029	Census Data	Shoe Manufacturers	Workers From 3 Towns In UK	[37]
1997	Cohort	27		20,526	Department Of Health Data	Medical Workers	NHS staff	[38]
1998	Case Control	803	2,135		Questionnaire	Assorted	BC cases	[39]
1999	Cohort	162		119,065	Registry Data	Assorted	Cancer registrations 1981-7	[40]
1999	Cohort	39	37	14,319	Personnel Files	Radiation Workers	Single Plant	[41]
1999	Cohort	679		381,915	Registry Data	Assorted	Cancer registrations 1971-90	[42]
2002	Cohort	181		45,110	National Stats Register	Petroleum Workers	England, Scotland & Wales	[39]
2004	Cohort	115		3,412	Company Records	Rubber Workers	British workers	[43]
2005	Cohort	14		2,689	Registry Data	Quarry Workers	Quarry employees	[44]
2009	Cohort	2		308	Personnel Records	Chemical Workers	MBOCA Plant Workers	[45]

Table 2. Relative risks of BC incidence per Occupational class in British workers

Occupational class	Cases	Controls	No. comparisons	Summary RR	95% CI lower	95% CI upper	I2 (%)	p
Public safety workers - Firefighters	5	2	1	4.30	0.78	23.80		NA
Beverage workers	19	0	2	2.09	0.34	12.88	84.90	0.01
Mix	868	1429	2	1.89	1.14	2.50	0.00	0.40
Chemical process workers	174	159.4	6	1.87	1.50	2.34	4.60	0.39
Rubber workers	609	5174.6	8	1.82	1.40	2.38	75.50	0.00
Dye workers	171	5243	5	1.80	1.07	3.04	67.20	0.02
Textiles	201	67.6	10	1.74	1.45	2.08	0.00	0.87
Glass workers etc.	91	5375.5	6	1.66	1.21	2.27	0.00	0.55
Military personnel	42	20.7	3	1.62	0.55	4.76	77.30	0.01
Electrical workers	70	99.9	4	1.60	1.09	2.36	35.90	0.20
Smelting workers	120	122.2	3	1.55	1.07	2.25	38.00	0.20
Domestic assistants	34	0	1	1.49	1.05	2.12		NA
Hairdressers	22	0	2	1.38	0.70	2.72	0.00	0.39
Waiters	69	0	1	1.30	1.01	1.65		NA
Painters	119	182.2	3	1.30	0.87	2.00	39.00	0.19
Aluminium workers	420	4989	3	1.26	0.93	1.71	53.70	0.12
Technical workers	593	541.8	3	1.26	0.93	1.71	53.70	0.12
Metal workers	65	140	1	1.26	0.90	1.77		NA
Shoe and leather workers	40	52.4	3	1.21	0.37	4.00	81.00	0.05
Printers	54	79.7	3	1.19	0.51	2.78	77.70	0.01
Healthcare workers	618	68	5	1.16	1.07	1.26	0.00	0.55
Nurses	580	0	3	1.15	1.06	1.25	0.00	0.67
Farmers	78	107.1	5	1.13	0.72	1.78	45.60	0.12
Forestry workers	33	48.7	2	1.11	0.51	2.45	66.20	0.09
Miners & Quarry workers	68	72.5	2	1.07	0.77	1.50	0.00	0.90

Laboratory assistants	21	49	1	1.05	0.60	1.85		NA
Mechanics	1080	4226	2	0.95	0.80	1.14	0.00	0.57
Clerical workers	271	372.9	5	0.90	0.60	1.39	77.40	0.00
Bartenders	337	202.3	4	0.88	0.60	1.29	46.30	0.13
Other construction workers	57	115.4	3	0.87	0.62	1.22	0.00	0.48
Sales agents	88	194.5	2	0.83	0.45	1.53	79.80	0.03
Transport workers	342	114	1	0.72	0.47	1.10		NA
Artistic workers	52	232	1	0.66	0.47	0.92		NA
Packers, loaders & warehouse workers	25	97.7	2	0.48	0.31	0.76	0.00	0.44
Drivers	57	143.9	3	0.46	0.28	0.75	47.80	0.15

No. comparisons = number of separate analysis included

I^2 – test for heterogeneity

NA – Statistical analysis not possible as only one comparison

Table 3. Relative risks of BC disease specific mortality (DSM) per Occupational class in British workers

Occupational class	Cases	Controls	No. comparisons	Summary RR	95% CI lower	95% CI upper	I2 (%)	p
Electrical workers	75	0	1	1.49	1.19	1.87		NA
Chemical process workers	86	0	4	1.35	1.09	1.68	0.00	0.84
Rubber workers	53	0	2	1.28	0.57	2.91	78.80	0.03
Painters	65	0	1	1.27	1.00	1.62	0.00	0.00
Other construction workers	267	0	3	1.20	0.79	1.81	85.00	0.00
Military personnel	3	0	1	1.15	0.31	4.30		NA
Transport workers	307	0	1	1.15	1.03	1.28		NA
Waiters & Bartenders	242	0	2	1.08	0.75	1.56	84.80	0.01
Dye workers	14	0	1	1.07	0.51	2.23		NA
Laboratory assistants	39	0	1	1.04	0.72	1.51		NA
Oil & Petroleum workers	181	0	2	1.00	0.86	1.16	0.00	1.00
Smelting workers	32	0	1	1.00	0.71	1.41		NA
Technical workers	374	0	1	1.00	0.91	1.10		NA
Packers, loaders & warehouse workers	109	0	1	0.98	0.82	1.18	0.00	0.00
Farmers	59	0	1	0.97	0.75	1.25		NA
Sales agents	165	0	1	0.96	0.82	1.12		NA
Drivers	73	2.38	2	0.94	0.74	1.18	0.00	0.67
Forestry workers	59	0	1	0.94	0.73	1.22		NA
Miners & Quarry workers	60	0	1	0.93	0.72	1.20		NA
Clerical workers	282	0	2	0.89	0.89	1.00	0.00	0.41
Shoe and leather workers	46	0	3	0.88	0.65	1.20	0.00	0.81
Glass workers etc.	14	0	1	0.87	0.50	1.52	0.00	0.00
Printers	30	0	1	0.87	0.60	1.26	0.00	0.00
Mix	150	171	3	0.78	0.57	1.06	43.20	0.17

Healthcare workers	27	0	2	0.69	0.30	1.56	89.20	0.00
Textiles	10	0	2	0.51	0.25	1.02	0.00	0.94
Physicians	27	0	1	0.45	0.31	0.66	0.00	0.00

No. comparisons = number of separate analysis included

I^2 – test for heterogeneity

NA – Statistical analysis not possible as only one comparison

Table 4. Registry details of occupational description in English cases with BC mortality. Occupations are defined using the Standard Occupation Classification (SOC) from 2010.

Code	SOC 2010 description	n	%
8211	Large goods vehicle drivers	508	3.0%
5223	Metal working production and maintenance fitters	379	2.3%
9233	Cleaners and domestics	376	2.2%
8125	Metal working and machine operatives	365	2.2%
9139	Elementary process plant occupations n.e.c.	323	1.9%
5319	Construction and building trades n.e.c.	321	1.9%
5241	Electricians and electrical fitters	311	1.9%
7111	Sales and retail assistants	303	1.8%
5315	Carpenters and joiners	287	1.7%
4122	Book-keepers, payroll managers and wages clerks	256	1.5%
	Other	13308	79.5%