REVIEW

Risk of bladder cancer in foundry workers: a meta-analysis

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To clarify the inconsistent reports of bladder cancer risk in foundry workers, a meta-analytic review of epidemiological studies was undertaken. Summary risk estimates (SRE) were calculated from 40 systematically extracted results. Weakly increased risks were observed overall, with an SRE of 1.11. Twenty three selected study results with better exposure information yielded an SRE of 1.16. This weak increase in risk is consistent with estimates obtained from dose-response trends of PAH exposures in aluminium smelter workers. Summary estimates did not vary substantially with exposure quality, study design, control for smoking, or when limiting the meta-analysis to large study results. Exposure-response findings showed significantly increased risks of about 1.6 to 1.7 after 20 or more years of employment, but this was based on few studies. Occupation specific SREs showed a 40–50% increased risk among moulders, casters, and unskilled foundry labourers. There was limited evidence that bladder cancer risk correlated with lung cancer risk, which is a more established risk among foundry workers. The small increased risk observed is prone to bias and confounding. Further studies of dose-response trends would greatly aid in determining whether this observed association is causal.

Foundry operations involve moulding and coremaking (usually using sand mixed with various binders), melting and alloying of metal, pouring the metal (primarily iron or steel) into moulds, shake-out of the cooled moulds, fettling, and finishing which involves grinding or welding of the pieces. Rolling mill operations are occasionally included among foundry jobs, where long shapes such as I-beams, tubes, or wires are produced using machines that process the heated metal through a series of rollers. Conditions in most foundries are generally dirty. Workers have potential for exposure to silica or other mineral dust, metal fumes and dust, binding agents (tar, coal, or other organic chemicals that polymerise), pyrolysis products that can include carcinogenic polycyclic aromatic hydrocarbons (PAH),[1] and oil mist in rolling mill operations.[2] Total airborne PAH exposures in foundries are well below the 1990 ACGIH and European exposure limit of 200 $\mu g/m^3$.[3]

Reports of aromatic amine concentrations in foundries were not found in the literature, but these compounds are likely to be formed during moulding when urethane resins are heated, and when phenol containing binders are combined with nitrogen containing compounds like urea, ethanolamine, hexamethylene-tetraamine, and ammonium salts. Furthermore, the naphthalene in sand additives (coal powder, pitch) can react on heating to give rise to naphthylamines.[4] Bladder cancer has been persuasively associated with aromatic amine exposure in dye workers, aromatic amine manufacturers, and rubber workers.[5] There is also evidence that a number of other occupational groups experience an increased bladder cancer risk, including aluminium smelter workers exposed to coal tar pitch volatiles.[6] Non-occupational risk factors for bladder cancer include genetics (for example, acetylator status), gender, smoking habit,[7] and diet.[8]

While foundry workers appear to experience an increased risk of lung cancer, the evidence for bladder cancer has been more equivocal.[9] This report is an analysis of the level of epidemiological evidence currently available on the association between bladder cancer and foundry exposures.

METHODS

To evaluate the human evidence for bladder cancer risk in foundry workers, a search of MedLine with MeSH for the years 1980–2001 was conducted using the following search string: "((bladder or urothelial or urinary) and cancer) and (occupation or foundry) and eng:la and human:mh". This resulted in 135 hits. These references were manually searched for relevant papers in the English language literature. Recent articles in occupational and epidemiology journals were also scanned for relevant articles. Finally, the reference sections of relevant papers were scanned for additional post-1980 study results with information on cancer risks among foundry workers. The somewhat arbitrary search for literature from 1980 onward was undertaken in order to collect studies that are more likely to be of higher quality, and because many older studies have been superseded by more recent follow ups. Published studies were used as they are

Abbreviations: PAH, polycyclic aromatic hydrocarbon; PMR, proportional mortality ratio; PR, pooled ratio; RR, relative risk; SIR, standardised incidence ratio; SMOR, standardised mortality odds ratio; SMR, standardised mortality ratio; SPMR, standardised proportional mortality ratio; SRE, summary risk estimate

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likely to be more reliable than unpublished reports. Use of English language reports avoided translation problems.

Each study was rated on a five point scale as to the quality of the exposure information related to the effect estimate used in subsequent analyses, as follows: poor exposure information (likely substantial exposure in other occupations and processes in addition to foundry exposures); fair exposure information (inclusion of broad industry groups such as metal refining and processing, where foundry exposures are prevalent but other exposures are probable); moderate exposure information (results based on occupations with known foundry exposure such as furnace, forge, foundry, rolling mill workers for longest or last held job); good exposure information (results based on duration or person-years of foundry exposures); and excellent exposure information (results based on estimation of foundry dust or chemical exposure levels).

Tables of extracted information were constructed by one author (RG). For cohort studies, the following were recorded: length of follow up; size and nationality of study group; additional information such as type of foundry work, race, and exposure durations; cancer site; effect measure (standardised mortality ratio (SMR) or standardised incidence ratio (SIR)); point estimate of risk with 95% CI; number of cases the point estimate is based on; exposure quality rating; and other information such as whether smoking was controlled, lung cancer rates, and comments on exposure.

For surveillance studies (linkage studies of occupation and disease) similar information was recorded, but instead of length of cohort follow up, the duration of mortality or cancer experience recorded in the linkage study was used. Also, the effect measures included the following: SIR; SMR; proportional mortality ratio (PMR); standardised proportional mortality rate (SPMR); standardised mortality odds ratio (SMOR); and relative risk (RR).

For case-control studies, extracted information included: whether the study was population or hospital based; number of cases and controls; description of cases and controls; type of exposure analysed, duration of exposure if available; any lag period used; odds ratio (OR) and 95% CI; number of cases with the exposure; exposure quality rating; factors adjusted for; and comments on exposures. Effect estimates from studies that only presented separate results by gender, race, or occupational subgroup were pooled so that one result for each study could be used in calculating overall summary risk estimates

Results for nine cohort,[4 10–17] 14 surveillance,[18–31] and 22 case-control studies[32–53] were found to be relevant. Other studies were collected that provided no useable information. Two cohort studies[54 55] and five surveillance studies[56–60] do not present data for foundry workers because results were not remarkable or of interest, or the number of cases were too small or possibly zero. Results from six case-control studies of bladder cancer[61–66] are not useful as exposure groupings were too general. These studies were noted in an attempt to monitor for the presence of publication bias.

The effect estimate chosen from the studies reflected a balance between results based on the best exposure information (or the subgroup of interest), the most cases, as well as results with the least bias and confounding. When several studies were available for the same or overlapping groups, one result was chosen from the latest update or expansion of previous studies.

Two methods were used to pool data. For cohort and surveillance studies, observed and expected cancers were added, respectively, to yield pooled observed/expected ratios (PR). The 95% confidence intervals (CI) were calculated assuming a Poisson distribution for the observed cases in the observed/expected ratio. The PR summary estimates do not include case-control results. The other method was a variance based procedure that follows a fixed effect model.[67 68] Each study effect estimate was weighted according to the inverse variance (weight = $1/SE^2$) calculated from the 95% CI using $SE = \ln(RR/CI_{low})/1.96$. The summary risk estimate (SRE) was calculated as the sum of the weighted natural log of the effect estimates divided by the sum of their weights, $\sum(W \times \ln RR)/\sum W$. This weight was also used for statistical tests of heterogeneity using the chi-square statistic, $\chi^2 = \sum W(\ln RR_{SRE} - \ln RR)$. A p value for the chi-square statistic less than 0.1 was chosen to indicate heterogeneous study results. The 95% CI for the SRE was determined using the summary variance (Var_{SRE}) from all studies ($1/\sum W$), as follows: 95% CI = $\exp(\ln RR_{SRE} \pm 1.96 \times Var_{SRE})$. For an SRE that was heterogeneous, the 95% CIs were adjusted[69] so that Var_{SRE} was increased by the chi-square statistic divided by its degrees of freedom (the number of results minus 1), $Var_{SRE} \times (\chi^2/df)$.

RESULTS

None of the studies used in this review were rated as having excellent exposure information. After eliminating studies with poor or fair exposure information, there remained six cohort studies,[4 10–13 17] 10 surveillance studies,[19 20 23 25–31] and eight case-control studies[32 38 41–43 50–52] with moderate or good exposure information.

Table 1 presents summary risk estimates (SRE) for results from all studies, as well as only from studies with better exposure information. Efforts were made to avoid counting results more than once, especially from the Nordic countries. For example, the recent large Nordic surveillance study[18] was used for the "all studies" SRE, but results from earlier surveillance studies[19 21 25] were used for the "better exposure quality" SRE as these studies reported results more specifically for foundry workers. Nevertheless, since the coverage of these surveillance studies is so large, it is possible that other cohort studies from the Nordic countries included some of these workers,[4 10 12 13] so the potential for double counting exists when combining cohort and surveillance results. It is also likely that there was overlap between two cohort studies of Danish foundry workers[4 13] and a larger cohort study,[10] although the population definition, outcome measure, and comparison groups were different.

The heterogeneity test results for the cohort studies in table 1 indicate there is significant heterogeneity. The reason for the heterogeneity among the cohort studies is apparent from the forest plot of studies with better exposure information in fig 1. It is clear that the smaller study by Hansen[4] is unusually increased compared to the rest of the field. When this outlier study is removed from the analysis, the cohort study results are quite homogeneous. The heterogeneity p value of 0.003 for the better exposure quality cohort studies changes to 0.66 and the SRE changes from 1.23 to 1.16 (95% CI 0.98 to 1.37). The overall SRE for all study types with better quality exposure information also changes from 1.17 to 1.16 (95% CI 1.06 to 1.26) with a heterogeneity p value of 0.45.

It is unclear why this single study result is so unusually high. The study showed a lung cancer SMR of 137 that was increased to a level consistent with other findings among foundry workers, but which was not statistically significant. This study followed a small group of skilled moulders in Danish metal foundries and found six bladder cancer deaths resulting in a ninefold increase in the SMR. The large follow up study of Danish foundry workers[10] probably included all (or at least most) of the workers in the study of skilled moulders[4] (Eva S Hansen, Panum Institute, personal communication, 2001). Therefore the study with the outlier result can reasonably be deleted from the SRE calculations. The larger study found a bladder cancer SIR of 114 based on 32 cancers in moulding, oven, casting, crane, and shake-out areas which included both skilled and non-skilled workers.

An SRE was calculated for studies that controlled for the confounding effects of smoking. None of the cohort or

Table 1 Summary risk estimates for bladder cancer and foundry exposures

Study group	Variance based SRE*	95% CI*	Heterogeneity test p value	Pooled observed/ expected estimate	95% CI*
All studies					
Cohort	1.22	0.92 to 1.62	p=0.001 (8df)*	1.17 [181]†	1.01 to 1.35
Surveillance	1.11	1.04 to 1.19	p=0.33 (10df)	1.11 [838]	1.04 to 1.19
Case-control	1.08	0.98 to 1.20	p=0.10 (20df)		
Total group	1.12	1.05 to 1.19	p=0.06 (40df)	1.12 [1019]	1.05 to 1.19
Cohort‡	1.16	0.99 to 1.36	p=0.90 (7df)	1.14 [175]†	0.98 to 1.32
Total group‡	1.11	1.05 to 1.17	p=0.30 (39df)	1.11 [1013]	1.04 to 1.18
Studies with better quality exposure information					
Cohort	1.23	0.89 to 1.69	p=0.003 (5df)	1.18 [152]	1.00 to 1.38
Surveillance	1.11	0.99 to 1.24	p=0.34 (9df)	1.10 [328]	0.98 to 1.23
Case-control	1.31	1.08 to 1.59	p=0.38 (7df)		
Total group	1.17	1.05 to 1.31	p=0.02 (23df)	1.12 [480]	1.02 to 1.22
Cohort ‡	1.16	0.98 to 1.37	p=0.66 (4df)	1.14 [146]	0.96 to 1.34
Total group‡	1.16	1.06 to 1.26	p=0.45 (22df)	1.11 [474]	1.01 to 1.21
Large studies with better quality exposure information (standard error <0.3)					
Total group	1.13	1.04 to 1.24	p=0.25 (9df)	1.10 [435]	1.00 to 1.21
Total group results by control for smoking					
All studies, smoking control	1.11	0.96 to 1.29	p=0.07 (15df)		
Better studies, smoking control	1.40	1.15 to 1.72	p=0.78 (4df)		
Better studies, no smoking control	1.46	1.19 to 1.77	p=0.61 (4df)		
Total group results for better exposure quality studies by outcome measure					
Mortality‡	1.20	1.02 to 1.41	p=0.54 (11df)	1.17 [164]	1.00 to 1.36
Incidence	1.14	1.04 to 1.26	p=0.28 (10df)	1.08 [310]	0.96 to 1.21

*SRE, summary risk estimate; CI, confidence interval; df, degrees of freedom.
†Number of observed cancers.
‡Excluding the results of Hansen.[4]

surveillance studies directly controlled for smoking. The SRE for the 16 case-control studies was 1.11 (95% CI 0.96 to 1.29) but results were heterogeneous (p = 0.07). The five case-control studies with better exposure information were homogeneous, with an SRE of 1.40 (95% CI 1.15 to 1.72). This was not much lower than the SRE of 1.46 calculated for these studies when four results were not adjusted for smoking. Integration of results for studies with mortality or incidence outcome measures were similar. Mortality studies gave slightly higher results, while both types of studies showed weak but statistically significant increased risks. Two cohort studies[13 15] and two case-control studies[34 46] measured urothelial cancer rates (which includes kidney cancer). Removal of these studies from summary estimates had no appreciable effect: the all studies SRE was 1.10 (95% CI 1.03 to1.18); and the better quality SRE was 1.15 (95% CI 1.06 to1.25). Similarly, SRE results limited to studies of only iron/steel foundries showed essentially no change (data not shown).

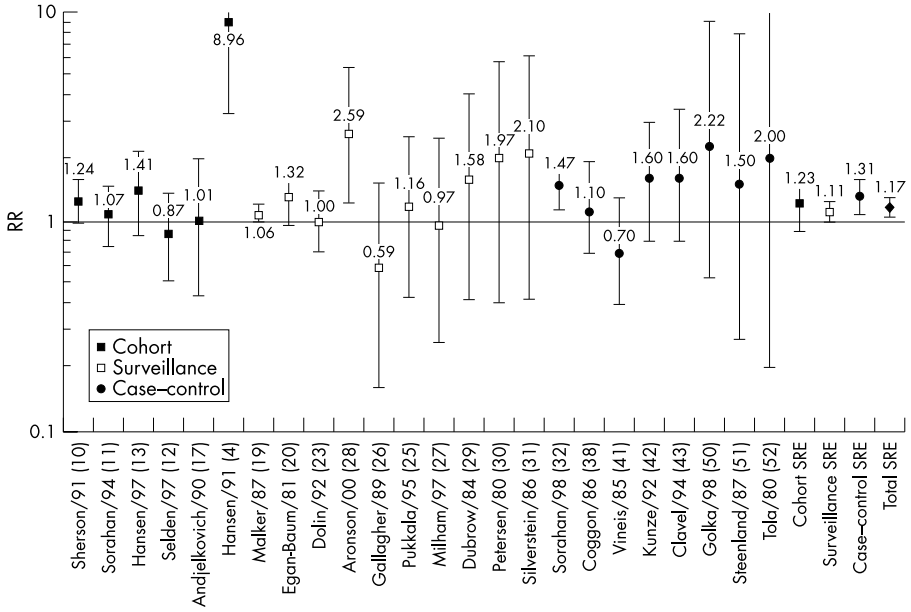

Figure 1 Forest plot of studies on bladder cancer with better foundry exposure information. Individual study and summary risk estimate values are marked, and the high/low limits indicate 95% CIs.

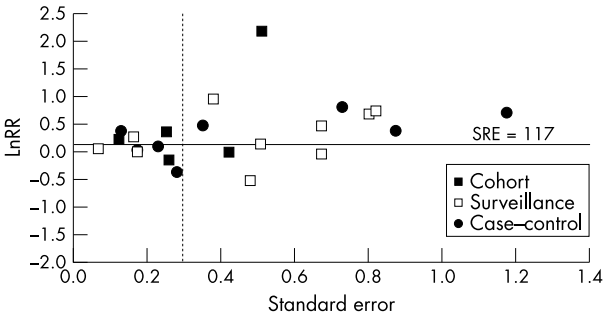

Figure 2 Funnel plot for studies with better exposure information. A symmetrical plot would have points lying within a straight cone pointing to the left. The dotted line at standard error 0.3 indicates the demarcation between large and small studies used in further analyses.

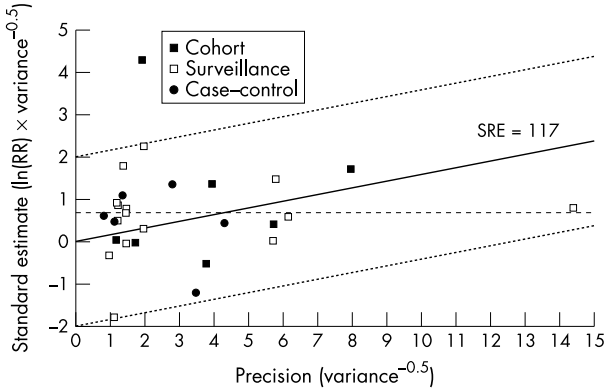

Figure 3 Radial plot of study results with better quality exposure information. The solid line is the regression through the origin where the exponentiated slope gives the summary risk estimate, 1.17. The dotted lines are two standard deviations above and below the central trend. The dashed line is the regression with floating intercept. The intercept value is 0.68 which is not statistically significantly different from zero (p = 0.10).

Iron and steel foundries are by far the most common, so few study results could be dropped in this analysis.

In order to address the question of whether publication bias is present, funnel plots were constructed for all studies, and for the better exposure quality studies.[70] The plot axes used for the better exposure quality studies in fig 2 were lnRR versus standard error.[71] Figure 2 suggests there is some asymmetry arising from a lack of small studies with lowered relative risks. A more objective analysis of funnel plot asymmetry is provided by regression analysis of the radial plot (fig 3). This is a scatter plot of the study's standard estimate (ln(RR) × 1/variance) versus study precision (1/variance). The regression line for the radial plot determines whether the intercept is significantly different from zero, and hence whether funnel plot asymmetry is present and therefore publication bias is likely.[72] Such an analysis indicates that the funnel plot for both the total group of studies (intercept p = 0.39), and those with better exposure information (intercept p = 0.10 but increases to 0.22 when excluding Hansen[4]) were not significantly asymmetric. This graphical display is also useful for comparing estimates with different precision.[73] The plot indicates that the one study of moulders previously identified as an outlier was more than 4 standard deviations from the central trend line (the exponentiated slope of which is equal to the SRE) of 1.17. Two other small study results were close to 2 standard deviations (dotted lines) from the central trend. These were the high relative risk of Aronson *et al*,[28] also for moulders (3.1 based on four deaths), and the low relative risk of Gallagher *et al*[26] for metal furnace workers (0.21 based on one death).

As the sensitivity of the radial plot method for detecting asymmetry is limited, a sensitivity analysis was conducted by removing the smaller study results with standard errors greater than 0.3. These small studies are most prone to publication bias. The remaining large studies included four cohort, three surveillance, and three case-control studies. The SRE for this group was 1.13 (95% CI 1.04 to 1.24), which was only slightly lower than the whole group of studies with better exposure information.

Several studies reported relative risks of bladder cancer after increasing durations of exposure, three of which were for work in foundries. A large cohort mortality study of male Danish foundry workers indicated that employment durations of 20 or more years resulted in an increased risk of bladder cancer.[10] Similarly, in a case-control study of male German foundry workers, a raised risk was observed after 30 years of employment as a foundry worker.[42] An incidence study in Sweden found no dose-response trend or increased bladder cancer risks among aluminium foundry workers.[12] The results for mixed foundry workers[10 42] are combined in table 2. The SRE is significantly raised after 20 or more years of employment in this industry. Similar types of products and exposures are experienced in aluminium foundry workers, although for some exposures, concentrations may be reduced as a result of the lower melt temperature of aluminium compared to iron.[12] When all three studies are combined, a statistically significant dose-response trend is still discernible, with a statistically significant 60% elevation in relative risk after more than 20 years of employment. A number of other results are generally uninformative for gauging whether there is an exposure-response trend in foundry workers, because of the broad exposure categories used.[34–37]

Several studies reported relative risks for a variety of subgroups among foundry workers. The following subgroups

Table 2 Dose-response results for studies with better exposure information

	Male Danish foundry workers (10)*		Male German foundry workers (42)†		Male Swedish aluminium foundry workers (12)‡		Summary risk estimate for ref. (10, 42)		Summary risk estimate for ref. (10, 12, 42)	
Years§	SMR¶	95% CI¶	OR¶	95% CI**	SIR¶	95% CI	SRE¶	95% CI	SRE	95% CI
<10	0.83 [14]††	0.46 to 1.40	1.1 [6]	0.3 to 5	0.87 [12]	0.45 to 1.52	0.87 [20]	0.5 to 1.5	0.87 [32]	0.6 to 1.3
10–19	0.97 [11]	0.48 to 1.73	1.6 [9]	0.6 to 9	0.92 [4]	0.25 to 2.36	1.15 [20]	0.7 to 2.0	1.11 [24]	0.7 to 1.9
20–29	1.72 [20]	1.05 to 2.66	1.2 [7]	0.4 to 4	0.83 [3]	0.17 to 2.40	1.62 [27]	1.0 to 2.5	1.61 [51]	1.2 to 2.3
≥30	1.65 [17]	0.96 to 2.65	3.0 [4]	0.4 to 11			1.72 [21]	1.0 to 2.9		
							trend p (2 sided) = 0.05		trend p (2 sided) = 0.02	

*Dose-response trend for lung cancer also found in this cohort (SMR range 0.99–1.85).
†Dose-response trend for bladder cancer not statistically significant.
‡Lung cancer risk significantly elevated in short term workers (2.1) but suggestive dose-response in longer term workers (range 0.8 to 1.4).
§Duration of employment in years.
¶SMR, standardised mortality ratio; CI, confidence interval; OR, odds ratio; SIR, standardised incidence ratio; SRE, summary risk estimate.
**Crude confidence intervals were calculated using Fisher's exact test.
††Number of cases in square brackets.

Table 3 Summary risk estimates in five occupational subgroups of foundry workers

Occupational subgroup (reference number)	Effect measure	Effect estimate	95% CI*	Number of cases
Moulders				
Moulders, oven, casters, crane, shake-out (10)	SIR*	1.14†	0.81 to 1.61	32
Core room (10)	SIR	1.02	0.28 to 2.61	4
Moulder/coremaker (23)	SMR*	1.72	0.79 to 3.27	9
Skilled moulders (4)	SMR	8.96†	3.29 to 19.49	6
Moulder/coremaker (26)	PMR*	1.46	0.30 to 4.27	3
Metal moulders (27)	PMR	0.97	0.26 to 2.48	4
Moulders (28)	RR*	3.08	1.15 to 8.23	4
Metal moulders (29)	sMOR*	2.1	0.43 to 6.14	3
Metal moulders (30)	PMR	1.97	0.41 to 5.76	3
Moulders (43)	OR*	3.9	0.4 to 35	4
Moulders (49)	OR	0.8	0.2 to 2.4	5
Metal moulder (36)	OR	0.4	0.1 to 1.7	2
	SRE*:	1.44	1.00 to 2.06	
		Heterogeneity p=0.02 (11df)		
	Best SRE*:	1.47	0.99 to 2.2	
		Heterogeneity p=0.52 (9df)		
Furnacemen, heaters				
Moulders, oven, casters, crane, shake-out (10)	SIR	1.14†	0.81 to 1.61	32
Metal furnacemen (23)	SMR	1.38	0.55 to 2.84	7
Metal heaters (22)	PMR	1.33	0.61 to 2.53	9
Metal furnace workers (26)	PMR	0.21	0 to 1.15	1
Furnacemen/metal heaters (28)	RR	0.71	0.1 to 5.09	1
Metal heaters (35)	OR	1.9	0.4 to 8.7	5
Furnacemen, smeltermen, pourers (36)	OR	0.6	0.1 to 2.2	3
Melters/reheaters (43)	OR	1.5	0.1 to 17	2
Smelting furnacemen (43)	OR	0.7	0.2 to 3.7	3
Heaters (46)	OR	3.0	0.3 to 29	3
Heaters (smokers) (53)	OR	8.4	0.77 to 92.2	2
	SRE:	1.14	0.87 to 1.50	
		Heterogeneity p=0.51 (10df)		
	Best SRE:	1.15	0.74 to 1.77	
		Heterogeneity p=0.42 (9df)		
Rolling mill operators				
Forge, hammer, roller, finisher (22)	PMR	1.01†	0.7 to 1.42	33
Rolling tube mill (23)	SMR	0.24	0.01 to 1.34	1
Other metal mill (26)	PMR	1.26	0.54 to 2.48	8
Rolling mill (28)	RR	3.54	0.88 to 14.2	2
Forge, hammer, roller finisher (35)	OR	1.4†	0.6 to 3.4	11
Rolling mill (43)	OR	0.6	0.1 to 3.7	2
Drawers, extruders (43)	OR	1.0	0.1 to 7.1	2
Hot rollers (48)	OR	0.8	0.3 to 2.2	10
Mill machine operator (53)	OR	1.1	0.3 to 4.4	3
	SRE:	1.09	0.83 to 1.43	
		Heterogeneity p=0.75 (8df)		
	Best SRE:	1.15	0.73 to 1.80	
		Heterogeneity p=0.60 (6df)		
Casters				
Moulders, oven, casters, crane, shake-out (10)	SIR	1.14†	0.81 to 1.61	32
Casters (43)	OR	3.6	0.7 to 18	7
Iron casters (32)	OR	1.47	1.13 to 1.90	133
Furnace/smelt/pourer (36)	OR	0.6	0.1 to 2.2	3
	SRE:	1.34	1.09 to 1.65	
		Heterogeneity p=0.32 (3df)		
	Best SRE:	1.48	1.14 to 1.91	
		Heterogeneity p=0.35 (2df)		
Fettlers and finishers				
Finishing (10)	SIR	0.93	0.42 to 1.76	9
File, polish, sand, buff (22)	PMR	0.95	0.61 to 2.53	19
Fettler, metal dresser (23)	SMR	0.24	0.01 to 1.34	1
Forge, hammer, roller, finish (35)	OR	1.4†	0.6 to 3.4	11
	SRE:	0.99	0.70 to 1.41	
		Heterogeneity p=0.69 (3df)		
	Best SRE:	0.93	0.63 to 1.36	
		Heterogeneity p=0.70 (2df)		
General foundry labourers				
Unspecified foundry (10)	SIR	2.83	1.14 to 5.84	7
Unskilled foundry (13)	SMR	1.41	0.86 to 2.17	19
Labourer—foundry (23)	SMR	1.15	0.42 to 2.52	6
Foundry n.e.c. (29)	sMOR	0.90	0.02 to 5.0	1
Labourer (53)	OR	0.9	0.3 to 2.8	4
	Best SRE:	1.43	0.99 to 2.07	
		Heterogeneity p=0.51 (4df)		

*CI, confidence interval; SIR, standardised incidence ratio; SMR, standardised mortality ratio; PMR, proportional mortality ratio; RR, relative risk; SMOR, standardised mortality odds ratio, OR, odds ratio; SRE, summary risk estimate; Best SRE, summary risk estimate without results marked with †.
†Studies removed from analysis for Best SRE.

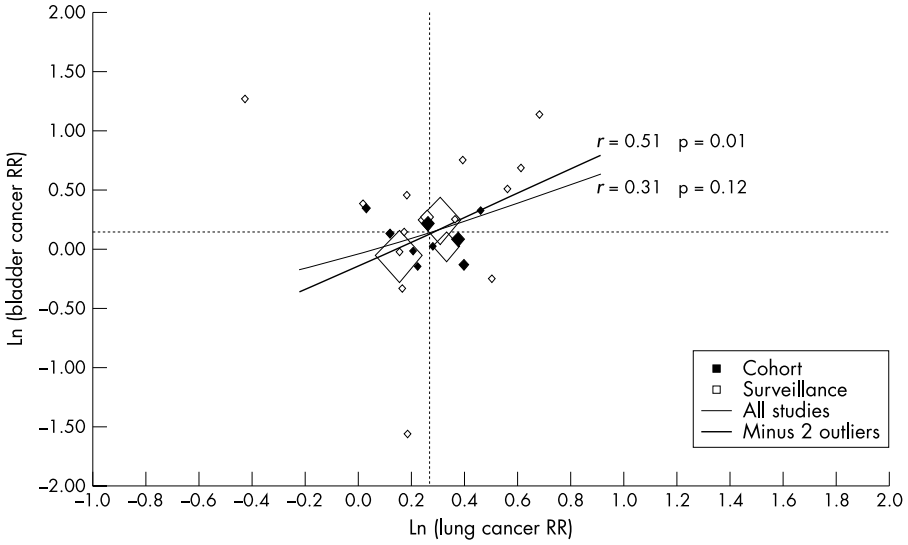

Figure 4 Weighted linear regression of bladder cancer RR on lung cancer RR in foundry workers. The dotted lines indicate the weighted means for bladder (RR = 1.15) and lung cancer relative risks (RR = 1.31). Data point sizes are proportional to the weight of the study result.

were listed in a few studies so that results could be combined: moulders; furnacemen and heaters; rolling mill operators; casters; fettlers and finishers; and general foundry labourers. Table 3 presents summary results for these six subgroups of foundry workers. The SRE for moulders (1.44; 95%CI 1.00 to 2.06) indicates significant heterogeneity (p = 0.02), as a result of the outlier result for Danish skilled moulders.[4] When this group is removed, as well as the Danish cohort,[10] since it also includes foundry workers other than moulders, the SRE becomes 1.47 (95% CI 0.99 to 2.2), with no indication of heterogeneity (p = 0.52). The SRE for furnacemen and heaters was 1.14 (95% CI 0.87 to 1.50). Again, the Danish study includes results for foundry workers other than oven workers.[10] Removal of this study resulted in a best SRE that was not much changed (SRE = 1.15; 95% CI 0.74 to 1.77). The SRE for rolling mill operators is also not substantially increased (SRE = 1.09; 95% CI 0.83 to 1.43). When two results[22 35] for the broad group "forge, hammer, roller, finisher" are removed, the best SRE is 1.15 (95% CI 0.73 to 1.80). There were only four results for casters, which was strongly influenced by a large case-control study.[32] The SRE increased from 1.34 to 1.48 (95% CI 1.14 to 1.91) after removing the result for the broad occupational group.[10] There were also few results for fettlers and finishers, and results generally showed no increased risk. When one result for "forge, hammer, roller, finisher"[35] was removed, the best SRE for fettler/finishers is 0.93 (95% CI 0.63 to 1.36). The SRE for unskilled and general foundry labourers (1.43; 95% CI 0.99 to 2.07) is based on all listed studies. While the unspecified foundry[10] and foundry not elsewhere classified[29] groups may have contained some skilled workers, these groups would likely be primarily made up of general labourers. Although the result from Danish foundry workers[10] is substantially higher than other results, the statistical test for heterogeneity is negative (p = 0.51).

Increased lung cancer risks have been consistently reported in foundry environments.[9] Under the assumption that the exposures in foundry environments which increase the risk of lung cancer will also contribute to elevations in bladder cancer risk, the correlation between these cancers was investigated. Nine cohort and 17 surveillance study results reported risks for both lung and bladder cancer in foundry workers. A variety of functions were tested, with the weighted linear regression of relative risk giving the best fit. The study weight used was the weight (1/variance) calculated for bladder cancer. The results presented in fig 4 show that the regression analysis of all results was not statistically significant and had a Pearson's correlation coefficient (r) of 0.31. This correlation coefficient is highly sensitive to outliers, and in their presence may give misleading results. Two extreme values are clearly identifiable in fig 4. When these are removed, the regression analysis was statistically significant (p = 0.01), and produced a higher correlation coefficient (r = 0.51). So, for example, when the lung cancer relative risk is 1.31 (the observed weighted mean value for lung cancer), the bladder cancer relative risk will be 1.15. In spite of the clustering of the observed lung cancer relative risks between 1.1 and 1.6, a correlation appears to be discernible. An r value of 0.51 (r^2 = 0.26) implies that 26% of the variation in bladder cancer relative risk can be explained by lung cancer relative risk. Nevertheless, this result is sensitive to stray values, and confounding as a result of smoking may play a role in this correlation.

DISCUSSION

The results of this meta-analysis suggest that there is a weak association between foundry work and bladder cancer. The approximately 16% increased risk observed was statistically significant, and did not vary substantially with the quality of exposure information, with study design, or with control for smoking. Results from the largest cohort, surveillance, and case-control studies were consistent with this summary risk estimate. This result is likely to apply primarily to male iron/steel foundry workers since they make up the majority of study subjects.

While this association does not appear to have been significantly influenced by publication bias, nevertheless, such a small increased risk is susceptible to confounding and bias. Five case-control studies with better exposure information controlled for the effects of smoking as well as age. None directly controlled for other risk factors such as fluid intake (coffee, chlorinated water), diet, racial mix, genetic factors, socioeconomic status, and other exposures. Many of these factors are only weakly associated with bladder cancer,[7] and most are unlikely to be related to foundry work. But the possibility that biases and confounding explain partially or totally the excess risk observed cannot be ruled out completely. Although the majority of study results comes from the Nordic countries, the United States, and the United Kingdom, the use of findings from 14 countries provides a good cross section of results from around the world. While study results were retrieved and extracted in a systematic fashion, rating

exposure quality occasionally required a more subjective assessment. A sample of seven studies were rated independently by a certified industrial hygienist. After consultation, in no case did the quality score change. Minor misclassifications were not likely to substantially change results since the summary effect estimates for all studies and better quality exposure studies are quite similar.

The potential for exposure to aromatic amines and the finding of increased concentrations of urinary β-naphthylamine in foundry workers[3] provide suggestive evidence of a biologically plausible mechanism for an excess bladder cancer risk. This confirmed bladder carcinogen may be formed during detoxification reactions within the body, or it may have been absorbed from the working environment. Urinary PAH metabolites and blood PAH-DNA adducts have also been found to be increased in foundry workers,[3 74–77] although smoking and charcoal broiled food consumption may be confounders.[74] The levels of PAH exposure among subgroups of foundry occupations can vary substantially.[1 3 78 79] Nevertheless, a rough average of measurements of PAH exposures in foundry occupations is around 10 μg/m³ total PAH or 0.05 μg/m³ benzo(a)pyrene.[3 74–82] Exposures tend to be higher in earlier periods, especially in coke oven workers[82] and in foundries that use coal tar pitch as a moulding sand additive,[1 83] and lower in more recent exposure assessments.[76] These averages are in keeping with the classification of iron foundries as generally being a low exposure environment from the standpoint of PAH exposure.[84]

To put this rough average PAH exposure in perspective, it can be compared to findings of bladder cancer risk associated with PAH exposures in aluminium smelter workers. Studies in Quebec have shown a linear relation between cumulative PAH exposure and bladder cancer risk.[85 86] For example, an average exposure to total PAH in aluminium smelters of 200 μg/m³ over 40 years (not counting exposures 10 years before the cancer) gave a bladder cancer relative risk of about 2.4. At the lower exposures typical of foundry workers, 10 μg/m³ over 40 years, the relative risk would be about 1.07. Similarly, a 40 year exposure to 2 μg/m³ benzo(a)pyrene, a level observed among aluminium smelters, results in a bladder cancer relative risk of 2.8, while 40 years of exposure at levels more typical of foundry operations, 0.05 μg/m³, results in a relative risk of 1.05 for bladder cancer. This extrapolation of results from the aluminium smelter industry to foundry PAH exposures is consistent with the findings reported here; if an elevation of bladder cancer risk occurs in most foundry environments as a result of PAHs, it is likely to be quite small.

A counter argument can be made that foundry PAH exposures may not be an important bladder cancer risk factor. Support for this argument comes from the experience of coke oven workers who experience high exposures to PAHs, and show an increased lung cancer risk, but do not appear to suffer an increased risk of bladder cancer.[9] Therefore, it is possible that risks do not follow PAH exposure, but some other contaminant. Clues to other important risk factors were investigated by looking at bladder cancer risks among subgroups of foundry workers with different exposure environments. No increased risk was observed among fettlers and finishers. These workers are involved in knocking out the cast part from the mould, grinding or blasting operations to clean the pieces, and welding operations to rectify defects. This produces primarily exposure to crystalline silica dust and metal fumes and dust.[87] Some studies record the highest foundry PAH exposures in the shake-out and fettling operations,[1 78] and the lowest in finishing workers.[78] A more recent report shows a non-detectable level of carcinogenic PAH exposures in shake-out and finishing workers, but a high urine β-naphthylamine concentration in finishing workers.[3] These somewhat conflicting exposure measurements would nonetheless suggest an increased risk might be expected in these workers, while none is observed.

A weakly increased risk of 15% was observed in furnacemen and rolling mill operators, similar to the overall SRE. Furnacemen melt and refine the metal that is eventually poured (cast) into the moulds. Other than the heat and gases such as carbon monoxide and sulphur dioxide, potential exposures include metal fumes, crystalline silica, limestone dust, PAHs, fluorides, and asbestos.[1] Rolling mill operators also work in hot environments, and may in addition be exposed to oil mist.[2] High PAH exposures were found in meltman and pourer occupations,[78] but another study found only low PAH concentrations in melting operations.[1] Melters had urine β-naphthylamine concentrations that were not significantly different from controls, but melters and casters did have increased carcinogenic PAH exposures in a recent study.[3] Rolling mill workers have low PAH exposures, and have been used as a reference group for PAH biomarkers in steel foundry workers.[82]

There were few study results for casters, which show a modest overall elevation of about 45%. One can expect exposure to large amounts of pyrolysis products in these workers, including nitrosamines and aromatic amines from thermal decomposition of nitrogen containing resins. Melting and pouring operations are often described together,[1 2 87] although the furnace section can be in a separate area from the foundry.[87] It is therefore possible that an increased risk for casters is obscured in results for furnacemen and heaters because of low risks among the larger number of furnacemen who do no casting.

Results for moulders and unskilled labourers also showed a modest elevation in relative risk of about 45% which was borderline statistically significant. Moulding and coremaking operations involve exposure to crystalline silica, solvents, and a variety of binders (such as urethane, furan, melamine, and phenolformaldehyde resins), some of which (coal tar pitch) may contain PAHs. Measurement of PAH exposures indicates that moulders, and especially machine moulders,[3] can experience high PAH exposures.[1 78 84] General foundry labourers have potential for exposure to all the agents present in a foundry. Although no specific monitoring results are available for general labourers, area sample results can show some of the highest levels of PAHs in foundries.[78]

Depending on the size and layout of individual foundries, exposures among all subgroups of foundry workers may overlap to some extent. Furthermore, exposure will vary according to unique processes in individual foundries. It is therefore not surprising that a clear picture of a bladder risk gradient with certain job titles does not emerge. The limited evidence available presents suggestive evidence that exposures encountered by foundry moulders, casters, and general foundry labourers may contribute to a modest bladder cancer risk. But further studies that measure risk in relation to exposure data would be needed before accepting this suggestion.

Two out of three studies found an increase of risk with increasing employment duration.[10 12 42] The study showing no dose-response trend was in an aluminium foundry which may have lower exposures than most mixed metal foundries where iron/steel predominates.[12] The SRE for these three studies indicates a statistically significant increased risk of about 60% after 20 or more years of employment in foundry environments.

Weighted regression analysis of the correlation between bladder cancer relative risk estimates in studies that also reported lung cancer relative risks showed a fair degree of correlation. For both diseases however, the increased relative risks were small and therefore prone to confounding by mutual risk factors, especially smoking.

In summary, this systematic review has found consistent evidence of a very weak but statistically significant association between foundry exposures and bladder cancer. The possibility that such small increased relative risks stem from bias or confounding cannot be ruled out. Nevertheless, the association is biologically plausible because foundry environments

are dirty by nature, and a number of contaminants have been associated with bladder cancer risk. A weak overall effect of PAH exposure is consistent with findings from the aluminium smelting industry, although evidence of unusually high PAH exposure in foundries, such as in past processes that used coal tar pitch instead of coal powder,[1] could give rise to higher bladder cancer risks. There is suggestive evidence that workers in some processes, such as moulders, casters, or general labourers, experience modest elevations in bladder cancer risk. The available dose-response information is also suggestive, but inadequate to determine whether a trend exists. Similarly, the correlation of bladder cancer relative risk with that for lung cancer suggests workplace exposures may contribute to both.

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