

Update of a meta-analysis on lung cancer and welding

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Objectives This study is an update, over the period 1954–2004, of a previous meta-analysis completed in 1994. It was aimed at assessing lung cancer risk among welders, while addressing heterogeneity, publication bias, and confounding issues.

Methods Combined relative risks (CRR) and their variances were calculated using fixed and random effects models. Heterogeneity was tested using the Q statistic. The publication bias was estimated using funnel plots, and Egger's regression and partially controlled by excluding studies with positive reporting bias.

Results The literature provided 60 studies eligible for the meta-analysis. No heterogeneity was observed. The fixed effect CRR for all of the welders and all of the studies was 1.26 (95% CI 1.20–1.32) after partial control of publication bias. No difference was observed according to welding activities. Smoking did not appear to be a marked confounder in the relationship between lung cancer and welding, but the effect of asbestos could not be assessed.

Conclusions The meta-analysis showed a 26% excess of lung cancer for welders without any difference according to welding activities.

Key terms epidemiologic study; heterogeneity; publication bias; stainless steel.

Following the publication of the IARC Monograph on the carcinogenic effects of exposure to chromium, nickel, and welding (1), we published a meta-analysis of epidemiologic studies on lung cancer among welders (2). The study covered the period 1954–1994, was aimed at assessing the relationship between lung cancer and welding activities, in particular welding stainless steel, which generates exposure to chromium and nickel compounds, and welding in shipyards, which is likely to be associated with asbestos exposure (1).

This meta-analysis, which showed a 30% to 40% increase in the relative risk of lung cancer among welders as compared with rates in the general population, found no excess lung cancer risk among shipyard and stainless steel welders when compared with mild steel welders (2). Another outcome of the meta-analysis was the difficulty to assess the relative importance of smoking and concomitant exposure to asbestos as possible confounding factors (2).

Our present report is an update of the previous meta-analysis throughout the period 1954–2004. It takes a closer look at the issues of study heterogeneity and publication biases in light of recent methodological

developments (3–6). Another aim was to investigate further the comparison of shipyard, stainless steel, and mild steel welders and improve the assessment of confounding due to smoking.

Study population and methods

Selection of studies

A search was conducted of the literature using the Medline, Toxline, and NIOSHTIC2 databases and the keywords “welding & cancer”, “welding & mortality”, “welding & respiratory tract neoplasm”, “welder & cancer”, “lung & cancer & occupational & epidemiology”, “respiratory tract neoplasm & occupational & case control study”.

The abstracts of the several hundred papers thus selected were screened for their potential interest. The selected papers were read extensively and complemented by the references quoted therein. Finally a total of 80 potentially interesting studies were thus included.

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On the basis of the detailed assessment, 20 papers were excluded according to the following systematic exclusion criteria: (i) if later updates were available (7–20), (ii) if it was a mortality statistic (21) and a cancer morbidity study was available (22), (iii) the papers republished data (23, 24) that were already available elsewhere (25, 26), (iv) the metal welded was atypical (lead) or the welders were resistance welders (27, 28), and (v) the description of the welder population was insufficient (29).

The largest industry-based cohort study was the multicentric IARC study, which included large historical subcohorts from nine European countries (30, 31). Due to the fact that five of these subcohorts (ie, Finland, France, Germany, Norway, Sweden) had been separately published or updated (26, 32–35), the IARC study itself was excluded from the database of the meta-analysis. However, in order to avoid losing the information provided by the four other unpublished subcohorts (ie, Denmark, England, Italy, Scotland), we extracted the relevant data on these subcohorts from the IARC study report (30) and included them in the database.

Data collection

The following three subcategories of welders were considered: shipyard, mild steel, and stainless steel welders. When no information as to the welding type was available, a generic nonspecific welding category was created.

For each study, data on the observed number of lung cancer cases, relative risk and their 95% confidence intervals (95% CI) were abstracted and selected by consensus of the authors, along with data on potential sources of heterogeneity (study design, country and year of publication, welding activity). The relative risks obtained from case-control studies (population-based and cohort-nested case-control studies) were either mortality odds ratios (MOR) or incidence odds ratios (IOR). Those published in cohort mortality studies were standardized mortality ratios (SMR) or proportional mortality ratios (PMR), and they were standardized incidence ratios (SIR) in cancer incidence studies. For some cohort studies that provided internal relative risks, we denoted incidence rate ratios (IRR) or mortality rate ratios (MRR) as relevant (35–37). When a study provided more than one effect measure, the authors extracted what they considered the “best estimate” [ie, odds ratios adjusted for smoking and other confounders instead of crude odds ratios in case-control studies, and internal relative risks (IRR and MRR) (internal references) or odds ratios (nested case-control study) instead of SMR or SIR values in industrial cohort-based studies.

We abstracted all published relative risks referring to dose-response relationships according to the following surrogates: duration of exposure or other quantitative parameters. However, dose-response relationships were not addressed in the meta-analysis since, depending on the study, relative risks for graded welding exposure were either lacking or given using different surrogates.

In an attempt to take into account publication bias, we considered the fact that, depending on the study design, some results may have been published because they revealed a positive association between lung cancer and welding. This bias is likely to occur in population-based studies, in particular in cases of record linkage, which provide numerous relative risks calculated for many effects in many occupational groups. In most of these studies, which were set up to generate hypotheses, the authors reported only positive associations. For our present study, code B (ie, biased) was assigned to a study whenever the authors indicated that only “statistically significant relative risks” or only relative risks “higher than a given value” were reported. Consequently, the other studies were considered as a group without positive reporting bias. Exclusion of the studies with a mentioned positive reporting bias could partially control for publication bias.

All available smoking information was abstracted from the papers. Some of the studies, mainly population based case-control studies and nested case-control studies, provided smoking-adjusted odds ratios. Conversely, due to a lack of data, most of the cohort studies did not take smoking into account. However, some cohort studies used Axelson’s method (38) to assess the confounding risk ratio (39) due to smoking. Using this information, we calculated an estimate of the smoking adjusted SMR values or SIR values by dividing the reported SMR values or SIR values by the confounding risk ratio derived using Axelson’s method.

Statistical analysis

Combined relative risks (CRR) were calculated using fixed and random effects models. The variance and the precision (defined as the inverted variance w_i) of given study i were calculated on the assumption that the log-transformed relative risks followed a Gaussian distribution. The logarithms of the CRR values were computed as an average of the log-transformed relative risks, weighted by their precision for the fixed effect and their random-effect weights w_i for the random effect estimate. The precision of the CRR values is the sum of the respective weights (3–4).

To test heterogeneity, we used the standard Q statistic (3–4). The potential sources of heterogeneity that were addressed were study design and welding categories (as in our previous meta-analysis), study countries, publication years, types of relative risks, mortality or morbidity endpoints, and analytical approaches to control for smoking.

To assess the effect of publication bias, we constructed funnel plots which are a scatterplot of the LnRR_i versus their precision w_i (6). Publication bias was revealed by asymmetry of the funnel plot (6). To measure this funnel plot asymmetry, we used a linear regression approach (the so-called Egger regression) by regressing the standardized coefficients ($\text{LnRR}/\text{se}(\text{LnRR})$) against $1/\text{se}(\text{LnRR})$ (6). In the absence of publication bias, the regression line runs through the origin. The intercept of the regression line provides a measure of the funnel plot asymmetry, the larger its deviation from zero the more pronounced the asymmetry (6).

All of the analyses were repeated with restriction on the set of studies without positive reporting bias.

Results

Description of the studies

The complete listing of the included studies (22, 25–26, 30–37, 40–88) is given in table 1. These studies examined populations in 14 different countries, most of the studies having been conducted in the United States (26 studies) and Europe (26 studies), of which 12 were from Nordic countries. The numbers of studies according to years of publication were 21 studies between 1954–1985, 17 studies between 1986–1993, and 22 studies after 1993. Altogether 24 (40 %) new studies had not been included in the former meta-analysis.

Table 1. Relative risks and 95% confidence intervals (95% CI) according to study design and welding category. [All = all welding categories, SY = shipyard welding, MS = mild steel welding, SS = stainless steel welding, B = only positive associations were reported, Y = not included in our previous meta-analysis (2)]

Study	Country	Welding category	Observed number ^a	Relative risk ^b	95% CI	Bias	New study ^c
<i>Morbidity and mortality statistics</i>							
Enterline et al, 1963 (40)	United States	All	34	SMR 0.92	0.64–1.29		
Menck et al, 1976 (41)	United States	All	48	SMR 1.37	1.01–1.82	B	
Decoufle et al, 1978 (42)	United States	All	11	MOR 0.85	0.50–1.50		
Population census, 1978 (43)	United Kingdom	All	246	SMR 1.51	1.33–1.71	B	
Gottlieb et al, 1980 (44)	United States	All	8	MOR 3.50	0.73–16.70	B	
Petersen et al, 1980 (45)	United States	All	37	PMR 0.99	0.61–1.40		
Milne et al, 1983 (46)	United States	All	5	MOR 1.31	0.43–3.59		
Gallagher et al, 1983 (47)	Canada	All	74	PMR 1.45	1.15–1.83	B	
Sjögren et al, 1986 (22)	Sweden	All	193	SIR 1.30	1.12–1.50		
Firth et al, 1993 (48)	New Zealand	All	200	MOR 1.40	1.21–1.61	B	Y
Milham et al, 1997 (49)	United States	All	267	PMR 1.31	1.16–1.50	Y	
Burnett et al, 1997 (50)	United States	All	1097	PMR 1.24	1.18–1.30	B	Y
Andersen et al, 1999 (51)	Nordic countries	All	650	SIR 1.23	1.14–1.33		Y
<i>Population based case-control studies</i>							
Breslow et al, 1954 (52)	United States	All	14	IOR 7.18	1.62–31.74	B	
Blot et al, 1978 (53)	United States	SY	11	IOR 0.70	0.32–1.41		
Blot et al, 1980 (54)	United States	SY	11	MOR 0.9	0.4–2.3		
Gérin et al, 1984 (55)	Canada	MS	2	IOR 1.2	0.1–9.4	B	
		All	12	IOR 2.4	1.0–5.4	B	
		SS	10	IOR 3.3	1.2–9.2	B	
Buiatti et al, 1985 (56)	Italy	All	7	IOR 2.8	0.9–8.5	B	
Kjuus et al, 1986 (57)	Norway	All	28	IOR 1.9	0.9–3.7	B	
	Norway	SS	16	IOR 3.3	1.2–9.3	B	
Schoenberg et al, 1987 (58)	United States	All	38	IOR 1.19	0.75–1.88		
	United States	SY	33	IOR 2.5	1.1–5.5		
Lerchen et al, 1987 (59)	United States	SY	6	IOR 2.2	0.5–9.1	B	
	United States	All	19	IOR 3.2	1.4–7.4	B	
Benhamou et al, 1988 (60)	France	All	18	IOR 1.42	0.79–2.88	B	
Ronco et al, 1988 (61)	Italy	All	6	MOR 2.93	0.87–9.82		
Zahm et al, 1989 (62)	United States	All	29	IOR 1.2	0.7–2.1		
Hull et al, 1989 (63)	United States	SS	34	IOR 0.9	0.5–1.8		
	United States	MS	56	IOR 1.6	0.8–3.1		
	United States	SY	37	IOR 1.7	0.9–3.1		
Morabia et al, 1992 (64)	United States	All	18	IOR 1.5	0.8–2.7	B	
Finkelstein et al, 1995 (65)	Canada	All	18	MOR 1.07	0.57–1.91	Y	
de Stefani et al, 1996 (66)	Uruguay	All	18	IOR 1.4	0.7–2.8	Y	

(continued)

Table 1. Continued.

Study	Country	Welding category	Observed number ^a	Relative risk ^b	95% CI	Bias	New study ^c
Van Loon et al, 1997 (67)	Netherlands	All	63	IOR 0.86	0.46–1.58	Y	
Jöckel et al, 1998 (25)	Germany	All	233	IOR 1.25	0.94–1.65	Y	
Pezzoto et al, 1999 (68)	Argentina	All	11	IOR 1.1	0.4–3.1	Y	
Gustavson et al, 2000 (69)	Sweden	All	99	IOR 1.44	1.08–1.92	Y	
Matos et al, 2000 (70)	Argentina	All	5	IOR 1.6	0.4–6.2		Y
<i>Industrial cohort studies</i>							
Dunn et al 1968 (71)	United States	All	49	SMR 1.05	0.78–1.39		
Ott et al, 1976 (72)	United States	All	2	SMR 1.00	0.11–3.61	Y	
Redmond et al, 1981 (73)	United States	All	14	SMR 1.51	0.82–2.53		
Beaumont et al, 1981 (36)	United States	SY	50	MRR 1.28	0.89–1.84		
Polednak et al, 1981 (74)	United States	SS	7	SMR 1.24	0.5–2.55		
	United States	All	17	SMR 1.50	0.87–2.39		
	United States	MS	10	SMR 1.75	0.84–3.22		
McMillan et al, 1983 (75)	United Kingdom	SY	5	PMR 1.04	0.34–2.43		
Fletcher et al, 1984 (76)	United Kingdom	All	8	SMR 1.46	0.62–2.88		
Newhouse et al, 1985 (77)	United Kingdom	SY	26	SMR 1.13	0.80–1.57		
Rinsky et al, 1988 (78)	United States	SY	41	MOR 1.13	0.76–1.68		
Tola et al, 1988 (32)	Finland	SY	27	SIR 1.15	0.76–1.67		
	Finland	MS	14	SIR 1.35	0.74–2.26		
Merlo et al, 1989 (79)	Italy	SY	16	SMR 1.67	0.95–2.71		
Simonato et al, 1991 (30–31)	Italy	SS	1	SMR 0.76	0.02–4.21		
	England	SS	7	SMR 1.01	0.40–2.08		
	Italy	All	3	SMR 1.11	0.23–3.26		
	Scotland	SS	7	SMR 1.40	0.56–2.88		
	Italy	SY	2	SMR 1.46	0.18–5.28		
	Denmark	MS	7	SMR 1.50	0.60–3.09		
	Denmark	All	30	SMR 1.57	1.06–2.23		
	Denmark	SS	23	SMR 1.62	1.03–2.44		
Moulin et al, 1993 (33)	France	SY	3	SMR 0.91	0.19–2.67		
	France	SS	3	SMR 0.92	0.19–2.69		
	France	All	19	SMR 1.24	0.75–1.94		
	France	MS	9	SMR 1.59	0.73–3.02		
Danielsen et al, 1993 (80)	Norway	SY	9	SIR 2.50	1.14–4.75		
Park et al, 19994 (81)	United States	All	7	MOR 2.73	1.20–6.30	Y	
Lauritsen et al, 1996 (26)	Norway	MS	26	MOR 1.3	0.8–2.1	Y	
	Norway	All	46	MOR 1.5	1.0–2.4	Y	
	Norway	SS	20	MOR 1.5	0.8–2.6	Y	
Danielsen et al, 1996 (82)	Norway	SS	6	SIR 1.03	0.38–2.26	Y	
	Norway	All	50	SIR 1.33	0.99–1.76	Y	
Austin et al, 1997 (83)	United States	All	7	MOR 0.76	0.28–2.10	Y	
Stern et al, 1997 (84)	United States	All	92	PMR 1.23	0.99–1.51	Y	
Milatou-Smith et al, 1997 (34)	Sweden	MS	2	SMR 0.41	0.05–1.48	Y	
	Sweden	SS	6	SMR 1.64	0.60–3.58	Y	
Danielsen et al, 1998 (85)	Norway	SY	10	SIR 1.55	0.74–2.84	Y	
de Silva et al, 1999 (86)	United States	All	4	SMR 1.10	0.30–2.81	Y	
Becker et al, 1999 (35)	Germany	SS	28	MRR 1.30	0.80–2.12	Y	
Danielsen et al, 2000 (87)	Norway	SY	9	SIR 1.27	0.58–2.42	Y	
Puntoni et al, 2001 (88)	Italy	SY	33	SMR 1.61	1.11–2.26	Y	
Steenland et al, 2002 (37)	United States	MS	108	MRR 1.22	0.93–1.59		Y

^a Observed numbers of lung cancer cases (case–control studies), lung cancer deaths (mortality studies), lung cancer diagnoses (cancer incidence studies).

^b Relative risks and 95% CI abstracted from the IARC report (30).

There were 13 population surveys, 20 case–control studies, and 27 industry-based cohorts, of which 4 included a nested case–control study. Some studies that provided results for more than one welding category may have contributed to several welding categories. This possibility led to 83 relative risks extracted from the published papers. The distribution of the relative risks was 28 SMR values, 6 PMR values, 9 SIR values, 24 IOR values, 13 MOR values, and 3 MRR values.

Most of the relative risks (44 of 83 = 53%) provided information on nonspecific welding categories, smaller numbers (17, 9, and 13 relative risks) concerned shipyard, mild steel, and stainless steel welding, respectively. For five studies (26, 30, 33, 55, 74), relative risks concerning the category nonspecific welders were excluded from the CRR calculation whenever all of the subgroups of the same populations (ie, shipyard, mild steel, or stainless steel welders) were already included in the calculation.

A positive reporting publication bias (ie, studies coded B) was identified for 6 (46%) of 13 relative risks in the population surveys and for 11 (41%) of the 27 relative risks in population-based case-control studies, whereas no such bias was detected in the cohort studies (0 of 43 studies) (table 1). With regard to smoking, the high proportion of adjusted relative risks provided by the case-control studies [19 (70%) of 27] contrasted with the low proportions observed in the population surveys [2 (15%) of 13] and the cohort studies [6 (14%) of 43].

When the observed numbers, relative risks, and 95% confidence intervals were considered according to study designs and welding category, it appeared that the greatest numbers of observed cases were obtained in the population surveys [6 (46%) of 13 with 200 or more lung cancer cases among the welders]. This result contrasted

with the study size of the case-control and cohort studies, in which most of the observed numbers of cases were below 100. Another contrast is that the population surveys provided results on the nonspecific welding category only, whereas several case-control or cohort studies could assess lung cancer risks according to shipyard, mild steel, or stainless steel welding separately.

Meta-analysis

Figure 1 and table 2 show the effect of the selection bias. In the total database a significant funnel plot asymmetry, as computed from the Egger regression, was detected. When studies with a positive reporting bias were excluded, the overall CRR decreased from 1.28 (95% CI 1.24–1.32) to 1.26 (95% CI 1.21–1.32). In addition, the studies with a positive reporting bias were

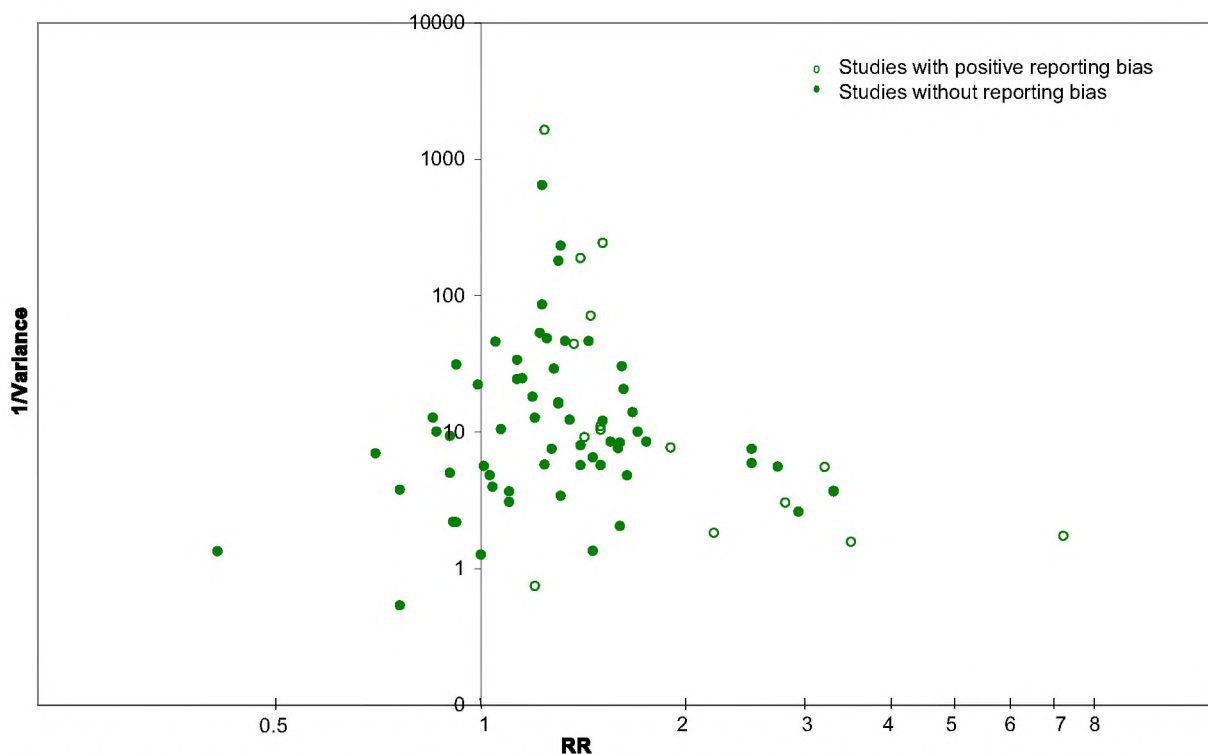


Figure 1. Funnel plot of the precision versus relative risk (RR) on a logarithmic scale [Y axis: precision = (variance)⁻¹; X axis: RR (CRR = 1.26)].

Table 2. Meta-analysis considering publication bias. ^a (CRR = combined relative risks, 95% CI = 95% confidence interval)

Type of study	Number of relative risks	Fixed effects		Random effects		Q statistic	P-value	Egger regression	
		CRR	95% CI	CRR	95% CI			Intercept	95% CI
Biased ^a	16	1.30	1.25–1.36	1.50	1.32–1.70	32.3	0.006	1.40	0.83–1.972
Unbiased ^b	61	1.26	1.20–1.32	1.26	1.20–1.32	41.3	0.97	0.06	–0.25–0.43
All studies	77	1.28	1.24–1.32	1.28	1.24–1.32	75.0	0.51	0.30	0.02–0.62

^a Papers indicating that only positive associations are reported.

^b Papers without any indication of selective reporting (ie, "unbiased results").

heterogeneous, and, when they were excluded, the asymmetry in the funnel plot, as assessed by the Egger regression, virtually disappeared. All further description is therefore restricted to the studies without this positive reporting bias.

Table 3 presents the results according to study design and endpoints, types of relative risks, and welding categories. The meta-analysis using fixed and random effect models led to similar and significantly elevated CRR values for the case-control and cohort studies, 1.27 (95% CI 1.11–1.46) and 1.29 (95% CI 1.19–1.40), respectively (table 3). The CRR was slightly lower for the population surveys (1.24, 95% CI 1.17–1.31). The mortality and morbidity studies gave similar estimations for the CRR. Similarly, the CRR values did not differ according to the type of relative risks, except for the MOR values, which provided a lower CRR value (1.21, 95% CI 0.99–1.48). The CRR values for the welding subgroups were similar (1.32 for shipyard and mild steel welders and 1.31 for stainless steel welders). The CRR was smaller (1.24) for the nonspecific welding category. No heterogeneity was detected according to study design, types of relative risk, and welding category.

Countries and years of publication were also tested as to whether they could be sources of heterogeneity. The results were lower when the studies published in North America were considered versus those published in northern Europe or in other countries [CRR 1.22 (95% CI 1.13–1.32) using random and fixed effects for North America, CRR 1.27 (95% CI 1.20–1.35) for north European studies and CRR 1.30 (95% CI 1.14–1.49) for all other countries]. Three periods were defined for the

years of publication, each of them including approximately one-third of the relative risks. The CRR values using fixed or random effects did not differ [CRR 1.09 (95% CI 0.96–1.24) for 1954–1985, 1.34 (95% CI 1.21–1.48) for 1986–1993, and 1.27 (95% CI 1.20–1.34) for 1994–2004]. No trend according to years of publication was thus detected, but the CRR of the first period was significantly lower than the overall CRR.

Among the 13 studies that had no reporting bias and provided tobacco adjusted relative risks, 11 reported relative risks higher than unity (22, 25, 26, 35, 58, 61–62, 66, 68–70). When crude and adjusted relative risks were available, it appeared that no or only slight confounding due to smoking was detected (25–26, 61, 69–70). The results were similar for the cohort studies that used Axelson's method (34, 37, 79–80, 82, 87). The CRR values were higher for the studies with adjustment for tobacco smoking (1.29, 95% CI 1.17–1.43) than for those without adjustment (1.24, 95% CI 1.17–1.30), the finding indicating that the lung cancer excesses could not be only due to smoking.

Discussion

The aim of our present meta-analysis was to improve our previous one (2) by including a greater number of studies and improving the methods used to address between-study heterogeneity and publication bias. We thus included 24 studies providing 28 relative risks that had not been included earlier. This rather large number is

Table 3. Meta-analysis considering potential sources of heterogeneity (only for studies without any indication on result reporting (ie, "unbiased results"). (CRR = combined relative risks, 95% CI = 95% confidence interval, IOR = incidence odds ratio, SIR = standardized incidence ratio, MOR = mortality odds ratio, SMR = standardized mortality ratio)

	Number of relative risks	Fixed effects		Random effects		Q statistic	P-value
		CRR	95% CI	CRR	95% CI		
Population surveys	7	1.24	1.17–1.31	1.23	1.15–1.32	6.9	0.33
Case-control studies	16	1.27	1.11–1.46	1.27	1.11–1.46	13.0	0.60
Cohort studies	38	1.29	1.19–1.40	1.29	1.19–1.40	20.6	0.99
Exposure							
Unspecified	26	1.24	1.18–1.31	1.24	1.18–1.31	18.4	0.82
Shipyards	16	1.32	1.16–1.51	1.32	1.16–1.51	14.3	0.50
Mild steel	8	1.32	1.10–1.59	1.32	1.10–1.59	3.51	0.83
Stainless steel	11	1.31	1.06–1.61	1.31	1.06–1.61	3.83	0.95
Morbidity studies	22	1.26	1.19–1.34	1.26	1.19–1.34	15.4	0.80
Mortality studies ^a	35	1.25	1.14–1.37	1.25	1.14–1.37	24.1	0.90
IOR	13	1.28	1.11–1.47	1.28	1.11–1.47	10.3	0.59
SIR	9	1.26	1.18–1.34	1.26	1.18–1.34	5.0	0.75
MOR	10	1.21	0.99–1.48	1.21	0.98–1.49	9.5	0.39
SMR	22	1.26	1.11–1.43	1.26	1.11–1.43	14.4	0.85
Other	7	1.26	1.15–1.38	1.26	1.15–1.38	1.9	0.93

^a Except studies providing proportional mortality ratio.

due to the fact that, after the IARC multicentric study published at the beginning of the 1990s (30–31), efforts have been made in industrialized countries to set up several epidemiologic studies specifically aimed at assessing lung cancer risks of stainless steel versus mild steel welders and at improving methods for taking smoking into account.

Our present meta-analysis failed to detect substantial heterogeneity since the CRR values were similar according to the different potential sources of heterogeneity. A possible exception was the low CRR for the studies published before 1984. This low figure was primarily due to three population surveys in the United States (40, 42, 45), whose relative risk estimates were lower than one and based on MOR and PMR values.

The results of a meta-analysis may be biased if the probability of publishing a study is influenced by the results (3, 6, 89). In particular, finding increased risks may increase the chances of publication and thus result in an overestimation of CRR values. A publication bias was detected in this meta-analysis using a funnel plot and Egger regression. Our strategy to control for this publication bias consisted in excluding studies identified as having a positive reporting bias. Despite the loss of power due to study exclusion, and even if this method probably underestimates publication bias, we considered that this approach led to a better effect estimate. This strategy seemed effective, as no publication bias, as assessed by Egger's regression, was detected after the exclusion of B-coded studies.

According to our present meta-analysis, the estimate of lung cancer risk among welders, as compared with nonwelders, was 1.26. Another main outcome was that the CRR values were similar for mild steel and stainless steel welders. These results do not support the hypothesis that stainless steel welders are at higher lung cancer risk than mild steel welders, despite their probable exposure to chromium and nickel compounds in welding fumes. This finding agrees with the results of our previous meta-analysis (2), as well as with the conclusions of the large multicentric European study (30–31) and with the IARC monograph on lung cancer among welders (1).

A few studies, mostly industrial cohorts, investigated the existence of a dose–response relationship, but most of them used different dose surrogates. It was therefore impossible to compute dose-related CRR values. The multicentric European study included a large cohort of 11 092 welders from nine European countries (30–31). The cohort was followed for mortality and cancer incidence. An ad hoc job-exposure matrix was developed to assess exposure to chromium (metal, trivalent, hexavalent) and nickel (90). This study failed to detect any dose–response relationship between lung cancer occurrence and cumulative exposure to hexavalent

chromium or nickel (31). In 14 other studies, employment duration as a welder was used as a quantitative exposure estimate, but the time periods used differed between the studies. In six papers, the results for the welders with >20 years of exposure were available (18, 24, 26, 33, 37, 66). Four of them showed an SMR above one, but none of them reached significance. Van Loon et al (67) built a “cumulative probability of exposure” that combines the probability of exposure and exposure duration in three categories. They found a statistically significant dose–response relationship (trend $P=0.03$), but this trend disappeared after adjustment for smoking and other occupational exposures. Gustavsson et al (69), applying a job-exposure matrix, calculated a cumulative dose but failed to demonstrate any relationship, as did Jöckel et al (25) using an index based on an estimation of the lifetime number of welding hours. In fact, only three studies reported a significant dose–response relationship. Two of them (36, 80) were conducted among shipyard welders and suggested a possible confounding by asbestos exposure.

On the whole, despite some positive results, the data are too limited to reach a conclusion about a dose–response relationship between welding and lung cancer risk.

Another outcome of our present meta-analysis is that shipyard welders have lung cancer CRR values that are similar to those of other welders (table 3). This observation confirms the previous result of the IARC study (31). However, this result is surprising, as several authors considered asbestos exposure to be more likely to have occurred in shipyards than in factories (2, 91, 92). This conclusion raises the question of the extent to which asbestos exposure among welders could explain the lung cancer excesses. The use of asbestos protection devices (blanket, aprons, gloves, etc) was common among welders, so that welding is considered an occupation for which asbestos exposure is likely to have occurred (31, 91, 92). This assumption is confirmed by the fact that significant excesses of mesothelioma have been reported for several cohorts of welders (21, 22, 31, 35, 51, 75, 82, 91, 92). However, some case–control studies have reported that asbestos-adjusted odds ratios remained elevated (10, 23, 25, 67).

In our present meta-analysis, it was impossible to evaluate the part played by exposure to asbestos with respect to lung cancer excess, as the information available from the reviewed epidemiologic studies was too poor to be used in the calculation of the CRR values.

Smoking is a major risk factor to be considered in epidemiologic studies focused on lung cancer risk. Some population surveys in the United States have suggested that welders may smoke more than the general male population (93–95), so that smoking could act as a confounder. Unfortunately, the information on smoking is

very often lacking in the selected studies. The only direct evidence against a strong role of smoking comes from the case-control studies, which did not find substantial changes in the relative risks after adjustment. The adjusted CRR values seemed to confirm this observation. A residual confounding can however not be ruled out.

In conclusion, our meta-analysis showed a 26% excess of lung cancer for welders and little heterogeneity between the studies once the positive reporting bias was accounted for. No difference between mild steel and stainless steel welders could be shown. This risk cannot be explained by confounding by smoking. The precise role of asbestos could however not be assessed.

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