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Original article

Hazardous Substances

Meta-analysis of occupational exposures in the rubber manufacturing industry and risk of cancer

Mathieu Boniol,[1,2] Alice Koechlin[1,2] and Peter Boyle[1,2]*

[1]University of Strathclyde Institute of Global Public Health, Lyon Ouest Ecully, France and [2]International Prevention Research Institute, iPRI, Lyon, France

*Corresponding author. International Prevention Research Institute, 95 Cours Lafayette, 69006 Lyon, France. E-mail: peter.boyle@i-pri.org

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Abstract

Background: Occupational exposures in the rubber manufacturing industry showed an increased risk of cancer and have been classified as a group 1 carcinogen, largely from studies on workers employed before 1950s. Cancer sites considered as causally associated are bladder, lung and stomach, and leukaemia. Recent studies did not report an increased risk of cancer.

Methods: A meta-analysis was conducted on observational studies published until April 2016 on occupational exposures in the rubber manufacturing industry and risk of cancer. Case-control and cohort studies were included. Random effect models were used. Heterogeneity and publication bias were evaluated. Stratified analyses were conducted on study characteristics.

Results: The literature search identified 46 cohorts and 59 case-control studies. An increased risk was found for bladder cancer [standardised incidence ratio (SRR) = 1.36; 95% confidence interval (CI) 1.18, 1.57], leukaemia (SRR = 1.29; 95% CI 1.11, 1.52), lymphatic and haematopoietic system (SRR = 1.16; 95% CI 1.02, 1.31) and larynx cancer (SRR = 1.46; 95% CI 1.10, 1.94). For lung cancer, a borderline statistically significant increased risk was identified (SRR = 1.08; 95% CI 0.99, 1.17). No association was found for stomach cancer (SRR = 1.06; 95% CI 0.95, 1.17). In stratified analyses, risks of cancer were not increased for workers employed after 1960 for bladder cancer (SRR = 1.06; 95% CI 0.66, 1.71), lung cancer (SRR = 0.94; 95% CI 0.68, 1.29) or leukaemia (SRR = 0.92; 95% CI 0.62, 1.36).

Conclusions: Risk of bladder cancer, lung cancer, leukaemia and larynx cancer were increased among workers in rubber industry. Evidence of elevated risks was no longer seen for bladder cancer, lung cancer or leukemia among workers first employed after 1960.

Key words: Rubber, occupational exposure, cancer, meta-analysis

Key Messages

- Pooling results from 105 observational studies, occupational exposure to the rubber manufacturing industry increases the risk of bladder cancer, lung cancer, leukaemia and larynx cancer. The previously reported association with stomach cancer could not be confirmed.
- Recently employed workers in rubber manufacturing industry do not seem to be at risk of cancer.
- These reassuring results for recently employed workers require to be confirmed by other follow-up studies.

Introduction

Occupational exposures in the rubber manufacturing industry have been considered since 1982 as carcinogenic to humans and have been classified as group 1 by the International Agency for Research on Cancer.[1,2] This classification was based mainly on observational studies on workers mostly employed before the 1960s, with some studies showing an increased risk of bladder cancer, leukaemia, stomach cancer, lung cancer and lymphoma. The IARC monographs also reported limited evidence of association for oesophagus, larynx and prostate cancers.

Two compounds are largely involved in production of tyre and rubber goods:[3,4] 1,3-butadiene and benzene, both of which are established as carcinogens to humans.[5] The production of tyre and rubber goods involves the use of hundreds of different chemical compounds.[2] Several of them are known carcinogens. In addition, several by-products can result from vulcanization and other processes, concerning which effects of exposures are not known. This industry was therefore emblematic of potential exposures confirmed or suspected as carcinogenic to humans. As no clear single carcinogen could be identified as causing the increased risk of cancer, the IARC maintained in its successive evaluations that the whole sector of rubber manufacturing industry was carcinogen to humans.[1,2]

The rubber manufacturing industry has undergone radical technological changes since the 1950s, entailing major reductions in rubber dust[6] and fume exposure and the removal of known carcinogenic agents. The re-analysis of a mortality study conducted in the British rubber industry, covering the period 1967–76, showed that initially increased risk of bladder cancer could be no longer observed in men not exposed to known carcinogens.[7] More recently, a multicentric study in Europe on 38 457 workers employed since 1975, with nearly a million person-years, showed no increased risk of cancer mortality for bladder cancer, leukaemia, lung cancer, stomach cancer or non-Hodgkin's lymphoma.[8] Recent studies[8–10] have suggested that risk of cancer has decreased in recently employed workers.

Previous meta-analyses and systematic reviews reported slightly conflicting results. Wheeras Kogevinas *et al.* 1998[11] reported that risks were elevated for bladder cancer, lung cancer and leukaemia, Alder *et al.* (2006)[12] only reported increased risk for cohort studies. In addition, none of these reviews enabled stratified evaluation of risks according to different study characteristics.

The present study reports data from a meta-analysis on observational studies on occupational exposures in the rubber manufacturing industry and risk of cancer.

Methods

A systematic review of observational studies reporting risk of any site of cancer associated with occupational exposures in the rubber manufacturing industry was performed. This meta-analysis was carried out following PRISMA guidelines.[13] Our study focused on IARC's definition for occupational exposure to rubber manufacturing industry. It therefore includes factories producing tyres and general rubber goods including processes of re-treading; these manufactures use natural or synthetic rubber, mostly a mixture of both.

Searches were conducted in Pubmed up to April 2016. Only articles published in English were included. The literature search strategy consisted initially of extraction of articles from the systematic reviews of Alder *et al.* (2006)[12] and Kogevinas *et al.* (1998).[11] An additional literature search in Pubmed was conducted separately for case-control and cohort studies with a combination of keywords listed in Supplementary material (available as Supplementary data at *IJE* online). Abstracts and titles of each reference from this search were initially screened by one author for further evaluation of the full text. The full text of each article from the literature search and the two reviews of Alder *et al.* (2006) and Kogevinas *et al.* (1998) were assessed by two researchers.

Case-control studies and cohort studies were considered as eligible designs. Studies using a proportionate mortality ratio approach were excluded because of the important risk of bias from such design.[14]

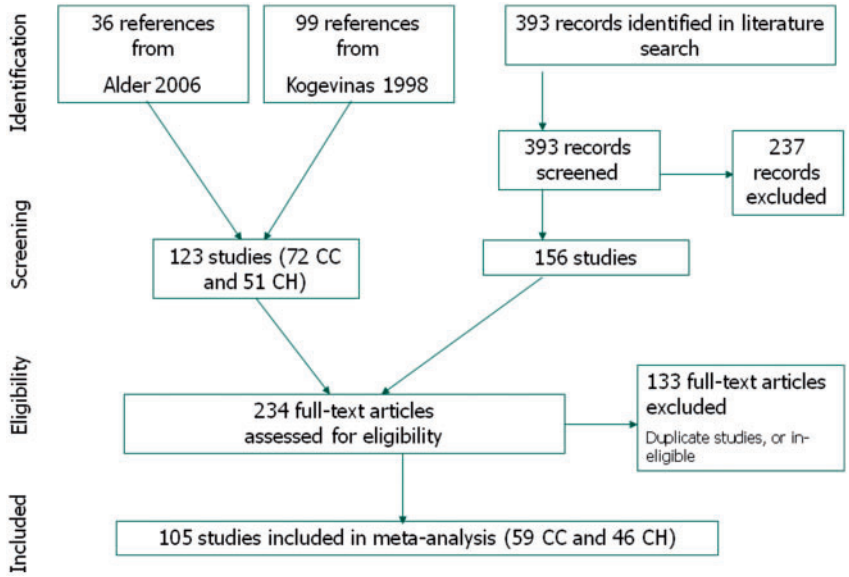

Figure 1. Flow chart of literature search of observational studies on occupational exposure to rubber industry and risk of cancer.

For each study, data on risk, description of the study, cancer sites and characteristics of exposure were extracted from cohort and case-control studies with a standard data abstraction template. All extractions were double-checked by another researcher to minimize data extraction errors.

Relative risks (RRs), odds ratios (ORs), standardised mortality ratios (SMRs) or standardised incidence ratios (SIRs) and their 95% confidence intervals (CIs) were directly extracted from the publications when available or computed from the number of cases, controls and person-years reported. All metrics of risks, i.e. RR, OR, SMR or SIR, were considered as equivalent and no correction was applied.

Summary relative risks were pooled using a random effect model.[15] The 95% confidence intervals of summary estimates were calculated using a t-distribution. Heterogeneity between studies was evaluated with the Cochrane Q and Higgins' I^2 statistics.[16] Publication bias was assessed with Macaskill,[17] Begg[18] and Egger[19] tests and through visual inspection of funnel plots. The trim-and-fill method was applied when significant publication bias was identified from at least one of these tests.

A series of stratified analyses were performed to investigate if summary relative risks differed by gender, study design, outcome being incidence or mortality, type of industry, investigating studies with recently employed workers after 1960 and after 1970, and investigating workers with the longest duration of employment. In addition, meta-regressions were conducted to test whether risks from studies on recently employed workers (after 1960) were lower than those from other studies.

As sensitivity analysis, the meta-analysis was replicated in a leave-one-out analysis testing the impact of excluding each study.

The meta-analysis was conducted with R software (version 3.0.1, GNU General Public License, 2013) and package metafor.[20]

Results

From Alder[12] (36 references) and Kogevinas[11] (99 references), 123 unique references were identified. From the literature search, a total of 393 references were found, out of which 156 were selected from title and abstract for further evaluations of the full-length article. From these two lists of references, after exclusion of duplicate studies and studies not eligible (such as studies using proportionate mortality ratio), 46 cohorts and 59 case-control studies were selected for analysis (Figure 1). Characteristics of selected studies are described in Tables S1 and S2, available as Supplementary data at *IJE* online. Excluded articles and reasons for exclusion are given in Tables S3 and S4, available as Supplementary data at *IJE* online.

The most investigated cancer sites were bladder (54 studies), lung (50 studies), colorectum (48 studies) and stomach (34 studies), and leukaemia (39 studies). Overall, when pooling risks for each site, an increased risk associated with occupational exposures in the rubber manufacturing industry was found for bladder cancer (SRR = 1.36; 95% CI 1.18, 1.57), leukaemia (SRR = 1.29; 95% CI 1.11, 1.52), lymphatic and haematopoietic systems not otherwise specified (SRR = 1.16; 95% CI 1.02, 1.31) and larynx cancer (SRR = 1.46; 95% CI 1.10, 1.94) (Figure 2). Results for lung cancer showed a borderline statistically significant increased risk with an SRR of 1.08 (95% CI 0.99, 1.17) but with a large degree of heterogeneity between studies ($I^2 = 71\%$). Risk of stomach cancer was not

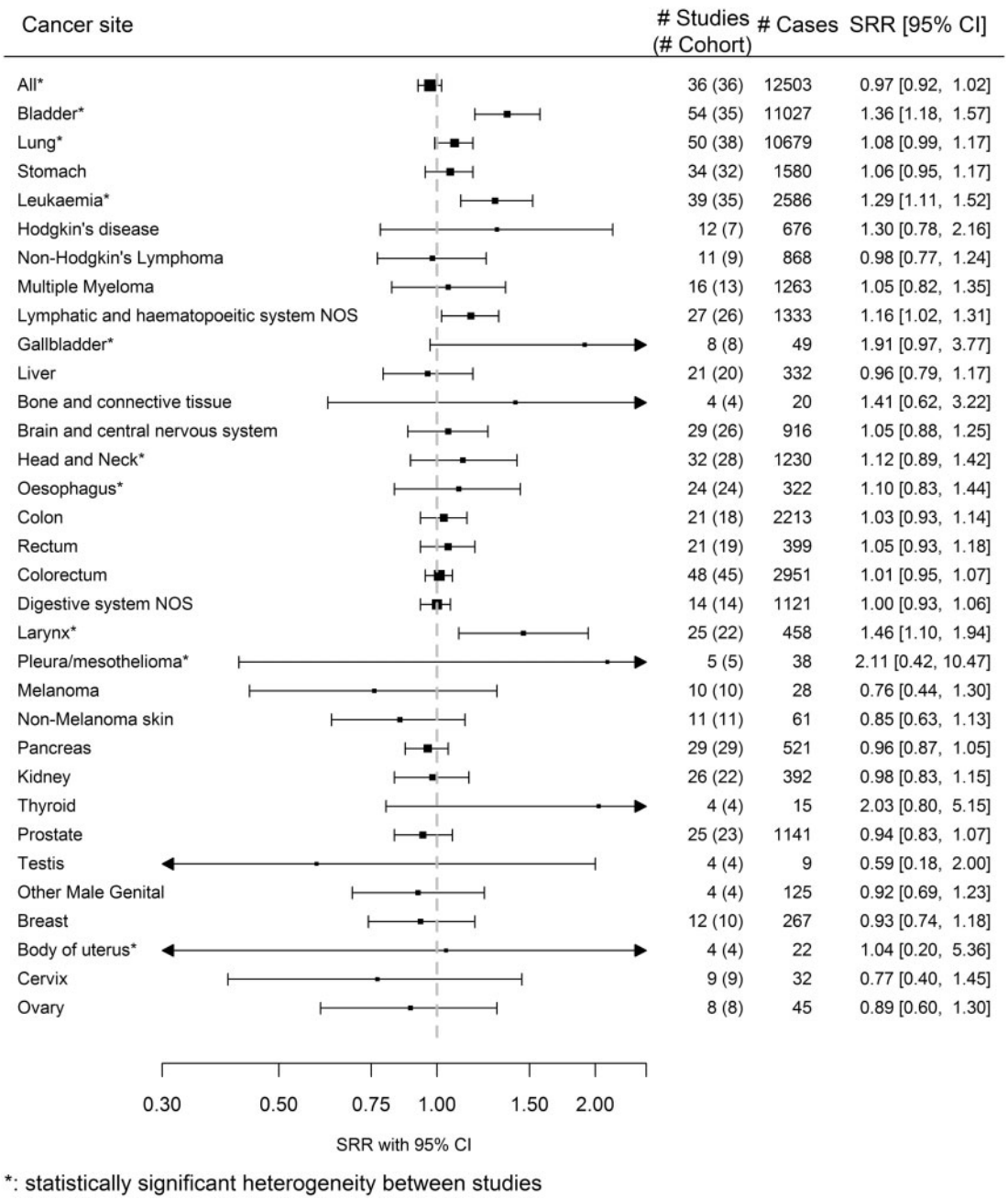

Figure 2. Results of meta-analysis on occupational exposure to rubber industry and risk of cancer, results presented for each cancer site.

raised in workers in the rubber manufacturing industry with an SRR of 1.06 (95% CI 0.95, 1.17) and low heterogeneity ($I^2 = 25\%$). Risk estimates remained low for most cancer sites, and only two sites had an SRR greater than 2 (although with wide confidence interval): pleura with a large degree of heterogeneity ($I^2 = 83\%$) and thyroid cancer with no heterogeneity ($I^2 = 0\%$).

A suspicion of a publication bias was found for bladder cancer from Egger and Macaskill tests, whereas no indication could be found with the Begg test or from funnel plot inspection (Supplementary Figure 5, available as Supplementary data at *IJE* online). Egger and Macaskill testing suggested the presence of publication bias for lung cancer and leukaemia. No evidence of publication bias was found for stomach cancer. Visual inspection of the funnel plots did not confirm a systematic directional publication bias for these sites (Supplementary Figure 5). When applying the trim-and-fill method, the risks of bladder cancer, lung cancer and leukaemia were not changed. Three missing articles were identified of the right side for bladder cancer with a 'corrected' SRR = 1.38 (95% CI 1.20, 1.59). For lung cancer, one missing article was found on the left side

Table 1. Results of stratified meta-analysis on occupational exposure to rubber manufacturing industry and risk of bladder cancer

Analysis	Studies	SRR	95% CI		I^2
Main	54	1.36	1.18	1.57	57%
Study design:					
Cohort studies	35	1.32	1.08	1.60	67%
Case-control studies	19	1.43	1.20	1.71	4%
Gender:					
Men	43	1.26	1.09	1.45	43%
Women	10	2.23	1.39	3.60	0%
Mortality/incidence:					
Cancer mortality	29	1.24	1.01	1.54	56%
Cancer incidence	30	1.42	1.19	1.7	53%
Type of industry:					
Tyre industry	17	1.19	0.95	1.48	0%
General rubber goods industry	12	1.19	0.93	1.51	0%
Employment characteristics:					
Hired after 1960	8	1.06	0.66	1.71	0%
Hired after 1970	6	0.81	0.40	1.64	0%
With the longest duration of employment	7	1.45	0.98	2.13	0%

Table 2. Results of stratified meta-analysis on occupational exposure to rubber manufacturing industry and risk of lung cancer

Analysis	Studies	SRR	95% CI		I^2
Main	50	1.08	0.99	1.17	71%
Study design:					
Cohort studies	38	1.06	0.98	1.16	76%
Case-control studies	12	1.24	0.90	1.71	15%
Gender:					
Men	40	1.05	0.96	1.14	75%
Women	14	1.18	1.00	1.39	0%
Mortality/incidence:					
Cancer mortality	35	1.05	0.87	1.15	78%
Cancer incidence	20	1.29	1.11	1.50	16%
Type of industry:					
Tyre industry	20	1.05	0.91	1.20	70%
General rubber goods industry	13	1.14	0.95	1.37	47%
Employment characteristics:					
Hired after 1960	10	0.94	0.68	1.29	70%
Hired after 1970	6	0.98	0.58	1.65	83%
With the longest duration of employment	10	0.94	0.68	1.29	70%

with a 'corrected' SRR = 1.07 (95% CI 0.99, 1.16). For leukaemia, five missing articles were estimated on the right side with a "corrected" SRR = 1.37 (95% CI 1.17, 1.61).

When splitting results of the 54 studies on bladder cancer by study characteristics (Table 1), risks remained in the same order of magnitude for each subgroup. A few studies were conducted in workers recently employed and showed lower risks: SRR = 1.06 (95% CI 0.66, 1.71) and SRR = 0.81 (95% CI 0.40, 1.64) for workers recently employed either after 1960s (eight studies) or after 1970 (six studies), respectively. The lower risk after 1960 was also observed in the meta-regression, although not statistically significantly different than risk before 1960 ($P = 0.12$).

Stratified analyses for lung cancer also did not show major differences in risk estimates and also suggested lower risk estimates for recently employed workers, with SRRs of 0.94 and 0.98 for workers employed after 1960s (10 studies) and after 1970s (six studies), respectively (Table 2). Risks from studies on recently employed workers (after 1960) were lower than in other studies

Table 3. Results of stratified meta-analysis on occupational exposure to rubber manufacturing industry and risk of stomach cancer

Analysis	Studies	SRR	95% CI		I^2
Main	34	1.06	0.95	1.17	25%
Study design:					
Cohort studies	32	1.05	0.94	1.16	24%
Case-control studies	2	NA	NA	NA	NA
Gender:					
Men	26	1.08	0.97	1.20	25%
Women	10	0.96	0.62	1.48	0%
Mortality/incidence:					
Cancer mortality	29	1.06	0.95	1.18	25%
Cancer incidence	10	1.06	0.82	1.36	8%
Type of industry:					
Tyre industry	16	1.09	0.91	1.31	37%
General rubber goods industry	8	1.23	0.88	1.74	52%
Employment characteristics:					
Hired after 1960	9	1.22	0.94	1.59	0%
Hired after 1970	6	1.20	0.85	1.71	0%
With the highest duration of employment	3	NA	NA	NA	NA

NA, not available.

Table 4. Results of stratified meta-analysis on occupational exposure to rubber manufacturing industry and risk of leukaemia

Analysis	Studies	SRR	95% CI		I^2
Main	39	1.29	1.11	1.52	35%
Study design:					
Cohort studies	35	1.24	1.05	1.46	32%
Case-control studies	4	2.15	0.91	5.03	11%
Gender:					
Men	33	1.29	1.08	1.53	40%
Women	8	1.15	0.52	2.54	41%
Mortality/incidence:					
Cancer mortality	31	1.21	1.01	1.44	37%
Cancer incidence	13	1.52	1.13	2.04	4%
Type of industry:					
Tyre industry	15	1.14	0.90	1.44	0%
General rubber goods industry	11	1.29	0.69	2.44	63%
Employment characteristics:					
Hired after 1960	11	0.92	0.62	1.36	6%
Hired after 1970	6	0.79	0.43	1.44	11%
With the longest duration of employment	5	1.29	0.72	2.31	0%

($P = 0.005$). None of the stratified analyses on stomach cancer showed an increased risk, with all SRR remaining close to 1 (Table 3). Risk of leukaemia remained increased for all stratified analyses except when restricted to workers employed recently, for whom risks were below 1, with low heterogeneity (Table 4).

The meta-regression comparing studies with recently employed workers (after 1960) with other studies also showed a decreasing trend, although not statistically significant ($P = 0.18$). Risk of larynx cancer appeared to be increased in rubber workers, but stratified analyses showed that the point estimate greatly varied between substrata (Supplementary Figure 5).

Discussion

As compared with past systematic reviews,[11,12] the present meta-analysis reported results from nearly twice as many

individual studies. This enabled investigation of more in-depth risks by type of study design and other study characteristics. Even if fewer studies were available on recently employed workers, it was possible to report summary relative risks from workers employed after 1960 and after 1970.

Four cancer sites were increased in risk for workers with occupational exposures in the rubber manufacturing industry: bladder cancer, lung cancer, leukaemia and larynx cancer. Although these results are not surprising for bladder, lung cancer and leukaemia, which were sites considered with sufficient evidence of causality,[1,5] results from larynx cancer were considered only as limited by previous working groups of experts. The present analysis suggests that larynx cancer could be increased among rubber workers, similarly to other sites, although risks varied in different subanalyses. Among the other cancer sites with uncertainty on the causality, risks of oesophagus and prostate cancer were not increased in rubber workers in the present meta-analysis. With SRR below 1 and low heterogeneity, a causal association between occupational exposure in the rubber manufacturing industry and prostate cancer can hardly be suspected. Similarly, the SRR for oesophagus was above but close to 1 with moderate heterogeneity: therefore unlikely to show a causal association.

Stomach cancer was considered as a cancer site with sufficient evidence of causality with occupational exposures in the rubber manufacturing industry,[5] but neither the main analysis and nor any of the stratified analyses showed increased risk. The SRR remained close to 1 with moderate heterogeneity, indicating that this evaluation is unlikely to change with further inclusion of new studies. The evidence accumulated so far could allow the conclusion that occupational exposures in the rubber manufacturing industry are unlikely to increase the risk of stomach cancer.

For all other sites, risks were not increased and SRRs remained below 2 for all but two sites. For thyroid cancer, based on only four studies, the point estimate was 2.03 with no detectable heterogeneity. It could be suggested to target this cancer site in further investigations. The SRR from four studies for pleural cancer was above 2 but with a large degree of heterogeneity between studies. An increased risk was actually only present in Vlaanderen *et al.*,[21] only in men, and in Negri *et al.*[22] These increased risks might be due to random variations, or local greater exposure to asbestos. Classification of cause of death could also be an issue, as before the introduction of a specific code for classifying mesothelioma (ICD-10), this site was showing great reporting inaccuracies within and between countries.[23]

For cancer sites showing an increased risk and included for further sub-strata evaluation, it was observed that case-control studies and studies on incidence tended to report higher risk estimates than cohort studies and studies on mortality, respectively. It could be argued that cohort studies have a better design and odds ratios bias, but results from cohort studies were in general more heterogeneous than those from case-control studies. In addition, most cohort studies and studies on mortality could not adjust for any confounding factors. It is therefore not possible to conclude on superiority of a particular design to provide appropriate assessment of risk.

The risk of cancer tended to be lower in subjects hired in the tyre industry than in the general rubber goods industry. Such patterns were already identified in previous studies.[8] However, reasons for this difference remain hypothetical and unclear. Potential explanations could be that changes in occupational hygiene were enforced more strongly and more quickly in the tyre industry than in the general rubber goods industry. Alternatively, this could also point to a stronger healthy worker effect in the tyre industry.[8] Importantly, exposures in the general rubber goods industry are very unlikely to be homogeneous, given the wide range of goods and tasks involved in this industry.

Stratified analyses showed consistently lower risks for workers hired more recently, either after 1960 or after 1970. For bladder cancer, the analysis on workers hired recently showed an SRR close to 1 and no heterogeneity between studies. A lower risk was also observed for leukaemia, for which the initial risk of 1.29 when combining all studies decreased to less than 1 with lower heterogeneity when restricted to workers hired recently. Exposure to benzene was among the first suspected carcinogens that could harm rubber manufacturing industry workers. Rubber industry workers were highly exposed to benzene in the past, and benzene is known as causally associated with risk of leukaemia. Therefore, if hygiene intervention reduced exposure to known carcinogens,[8] benzene exposure could have been particularly controlled and reduced. For lung cancer, no increased risk was observed for workers hired recently, with an SRR close to 1 whereas it was 1.08 in the main analysis. The heterogeneity remained high in these stratified analyses, and these results should be interpreted with some caution. However, the meta-regression analysis showed that studies on recently employed workers after 1960 found a lower risk of lung cancer as compared with other studies ($P = 0.005$).

The present review suggests that occupational exposures in the rubber manufacturing industry were associated with an increased risk of bladder cancer, lung cancer and leukaemia, with a suspicion for larynx cancer. Although the level of evidence was previously considered as sufficient, the present study showed no increased risk overall or in any subgroup analysis, and therefore does not support that stomach cancer is causally associated with occupational exposures in the rubber manufacturing industry. Risks of bladder cancer,

lung cancer and leukaemia were decreased in recently employed workers, suggesting that decreases in carcinogen exposure had a successful impact.

The history of hazard evaluation in rubber production is a lesson for prudence, as the initial evaluations of industries in India did not report particular risks. One of them reported that 'the occupation is productive of no definite disease, nor of lasting inconveniences',[24] whereas several risks of cancer were clearly identified in the following decades. Before ruling out a potential risk of cancer in recently employed workers, follow-up studies in more cohorts and with longer duration of exposure are required. In addition, toxicological assessments in the currently operating industries would help in drawing conclusions on cancer risk in the modern rubber industry.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author Contributions

Study concept and design: M.B. and P.B. Acquisition of data: M.B. and A.K. Analysis and interpretation of data: M.B., A.K. and P.B. Drafting of manuscript: M.B. Critical revision: M.B., A.K. and P.B.

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