Cancer mortality in cohorts of workers in the European rubber manufacturing industry first employed since 1975

Sorahan, Thomas; Boniol, M; Koechlin, Alice; Swiatkowska, Beate; Wellmann, Jurgen; Taeger, Dirk; Jakobsson, Kristina; Pira, Enrico; Boffetta, Paolo ; La Vecchia, Carlo; Pizot, C; Boyle, Peter

DOI:
10.1093/annonc/mdw061

Document Version
Peer reviewed version

Citation for published version (Harvard):
Sorahan, T, Boniol, M, Koechlin, A, Swiatkowska, B, Wellmann, J, Taeger, D, Jakobsson, K, Pira, E, Boffetta, P, La Vecchia, C, Pizot, C & Boyle, P 2016, 'Cancer mortality in cohorts of workers in the European rubber manufacturing industry first employed since 1975', *Annals of Oncology*, vol. 27, pp. 933-941. https://doi.org/10.1093/annonc/mdw061

Cancer mortality in cohorts of workers in the European rubber manufacturing industry first employed since 1975

Journal:	*Annals of Oncology*
Manuscript ID	ANNONC-2015-2052.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Boniol, Mathieu; University of Strathclyde Institute of Global Public Health, Biostatistics; International Prevention Research Institute, Biostatistics Koechlin, Alice; University of Strathclyde Institute of Global Public Health, Biostatistics; International Prevention Research Institute, Biostatistics Świątkowska, Beata; Nofer Institute of Occupational Medicine, Environmental Epidemiology Sorahan, Tom; Institute of Occupational and Environmental Medicine, University of Birmingham Wellmann, Jürgen; University of Muenster, Institute of Epidemiology and Social Medicine Taeger, Dirk; Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA) Jakobsson, Kristina; Lund University, Occupational and Environmental Medicine Pira, Enrico; University of Turin, Public health and Paediatrics Boffetta, Paolo; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai La Vecchia, Carlo; Università degli Studi di Milano, Clinical Sciences and Community Health Pizot, Cecile; International Prevention Research Institute, Biostatistics Boyle, Peter; International Prevention Research Institute, President; International Prevention Research Institute, Biostatistics
Keywords:	rubber, occupational exposure, cohort study, cancer, mortality
Abstract:	Background: Increased cancer risk has been reported among workers in the rubber manufacturing industry employed before the 1960s. It is unclear whether risk remains increased among workers hired subsequently. The present study focused on risk of cancer mortality for rubber workers first employed since 1975 in 64 factories. Patients and methods: Anonymised data from cohorts of rubber workers

	employed for at least one year from Germany, Italy, Poland, Sweden and the United Kingdom were pooled. Standardised mortality ratios (SMRs), based on country-specific death rates, were reported for bladder and lung cancer (primary outcomes of interest), for other selected cancer sites, and for cancer sites with a minimum of 10 deaths in men or women. Analyses stratified by type of industry, period and duration of employment were performed. Results: 38,457 individuals (29,768 men; 8,689 women) contributed to 949,370 person-years. No increased risk of bladder cancer was observed (SMR=0.80, 95%CI (0.46; 1.38)). The risk of lung cancer death was reduced (SMR=0.81, 95%CI (0.70; 0.94)). No statistically significant increased risk was observed for any other cause of death. A reduced risk was evident for total cancer mortality (SMR=0.81, 95%CI (0.76; 0.87)). Risks were lower for workers in the tyre industry compared to workers in the general rubber goods sector. Analysis by employment duration showed a negative trend with SMRs decreasing with increasing duration of employment. In an analysis of secondary endpoints, when stratified by type of industry and period of first employment, excess risks of myeloma and gastric cancer were observed each due, essentially, to results from one centre. Conclusion: No consistent increased risk of cancer death was observed among rubber workers first employed since 1975, no overall analysis of the pooled cohort produced significantly increased risk. Continued surveillance of the present cohorts is required to confirm absence of long-term risk.

Article type: Original article

Word count: 3705 (3207 text+ 498 refs)+1050 (figures and tables 150 each) = 4755 words (software: word 2013)

Title: Cancer mortality in cohorts of workers in the European rubber manufacturing industry first employed since 1975

M. Boniol[1,2,*], A. Koechlin[1,2], B. Świątkowska[3], T. Sorahan[4], J. Wellmann[5], D. Taeger[6], K. Jakobsson[7], E. Pira[8], P. Boffetta[9], C. La Vecchia[10], C. Pizot[2], P. Boyle[1,2]

1. University of Strathclyde Institute of Global Public Health, Lyon ouest Ecully, France

2. International Prevention Research Institute, iPRI, Lyon, France

3. Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland

4. Institute of Occupational and Environmental Medicine, University of Birmingham, United Kingdom

5. Institute of Epidemiology and Social Medicine, University of Muenster, Germany

6. Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA), Germany

7. Division of Occupational and Environmental Medicine, Lund University, Sweden

8. Department of Public Health Sciences and Pediatrics, University of Turin, Italy

9. Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, USA

10. Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Italy

** Corresponding author:*

Prof. Mathieu Boniol, International Prevention Research Institute, 95 cours Lafayette, 69006 Lyon, France (mathieu.boniol@i-pri.org)

Abstract (298 words)

Background: Increased cancer risk has been reported among workers in the rubber manufacturing industry employed before the 1960s. It is unclear whether risk remains increased among workers hired subsequently. The present study focused on risk of cancer mortality for rubber workers first employed since 1975 in 64 factories.

Patients and methods: Anonymised data from cohorts of rubber workers employed for at least one year from Germany, Italy, Poland, Sweden and the United Kingdom were pooled. Standardised mortality ratios (SMRs), based on country-specific death rates, were reported for bladder and lung cancer (primary outcomes of interest), for other selected cancer sites, and for cancer sites with a minimum of 10 deaths in men or women. Analyses stratified by type of industry, period and duration of employment were performed.

Results: 38,457 individuals (29,768 men; 8,689 women) contributed to 949,370 person-years. No increased risk of bladder cancer was observed (SMR=0.80, 95%CI (0.46; 1.38)). The risk of lung cancer death was reduced (SMR=0.81, 95%CI (0.70; 0.94)). No statistically significant increased risk was observed for any other cause of death. A reduced risk was evident for total cancer mortality (SMR=0.81, 95%CI (0.76; 0.87)). Risks were lower for workers in the tyre industry compared to workers in the general rubber goods sector. Analysis by employment duration showed a negative trend with SMRs decreasing with increasing duration of employment. In an analysis of secondary endpoints, when stratified by type of industry and period of first employment, excess risks of myeloma and gastric cancer were observed each due, essentially, to results from one centre.

Conclusion: No consistent increased risk of cancer death was observed among rubber workers first employed since 1975, no overall analysis of the pooled cohort produced significantly increased risk. Continued surveillance of the present cohorts is required to confirm absence of long-term risk.

Keywords:

rubber, occupational exposure, cohort study, cancer, mortality

Key message:

In a prospective cohort of 38,457 workers employed since 1975 in the European rubber manufacturing industry and followed on average for 26 years, no consistent increased risk of cancer death was observed. Although the findings from this study are reassuring, continued surveillance of the present cohorts is required to confirm absence of long-term risk.

Introduction

Epidemiological studies have reported increased risk of bladder cancer and leukaemia among workers in the rubber manufacturing industry mainly among those employed before the 1960s: these excess risks have been associated with exposure to aromatic amines, and solvents, respectively [1]. A narrative (qualitative) review of epidemiological studies published up to 1997 concluded that bladder, laryngeal, lung cancer and leukaemia were the cancers with an increased risk among rubber workers, with however evidence of substantial heterogeneity of results [2]. However, a meta-analysis based on cohort studies published through 2003 showed no excess risk for any of the cancer sites although there was not differentiation made between natural rubber and synthetic rubber (styrene butadiene) [3]. Recently, the IARC has re-evaluated the rubber industry, and has classified rubber production as a group 1 carcinogen for cancers of the stomach, the lung and lymphoma in addition to bladder cancer and leukaemia [4], employing all data available irrespective of the period of exposure.

The rubber manufacturing industry, which employed approximately 380,000 workers in EU-15 in 1990-1993 [5], has undergone radical technological changes since the 1950s, entailing major reductions in rubber dust and fume exposure or the removal of known carcinogenic agents, although the changes in technology were gradual and took place at variable pace in different countries. Data collected by the EU-ExAsRub consortium in the rubber manufacturing industry showed a general reduction in the exposure of workers to inhalable dust from the 1970s to 2003 however with marked differences between countries [6]. These results are of interest but are of an ecological nature and such data are not available on a personal level.

Two studies of workers first employed after 1980 in the rubber manufacturing industry in Germany [7] and United Kingdom [8] showed no excess risk of overall cancer mortality, as well as bladder, stomach and lung cancers. The present study reports data on risk of death from cancer and

major causes of death from a large-scale epidemiologic study of workers first employed since 1975 in the rubber manufacturing industry from five European countries. This study provides therefore a direct evaluation of risk of cancer in the modern rubber manufacturing industry.

Material and methods

A protocol specifying inclusion criteria and a detailed statistical analysis plan was prepared between local principal investigators of the present study prior to data analysis (available upon request from corresponding author). The cohort consisted of rubber workers employed in Germany, Italy, Poland, Sweden and the United Kingdom. Workers were included if they (i) were employed for at least one year in one of the cohorts, and (ii) had a first employment in the rubber manufacturing industry at 1st of January 1975 or later. This first employment period varied from country to country, being 1981 for the German cohort, 1982 for United Kingdom and 1975 for all other countries. Factories were distributed throughout all regions in Poland, Sweden and the United Kingdom. For Italy, workers were employed in factories of the north of Italy: in the region of Piemonte (Italy). For Germany, workers were employed in factories located in western Germany in the Federal States of Lower Saxony and North Rhine–Westphalia.

For all countries but Germany, follow-up data were complete until a right censoring date (Table 1). For Germany, the follow-up data and vital status was complete until 2000, and from 2001 to 2003, cause of death and migration status was missing for the majority of workers. The period 2001-2003 was therefore excluded from the analysis for Germany. From 2004 to 2012 vital status became partially available and enabled evaluating vital status and causes of death. In order to avoid underestimation of mortality rates, correction factors, depending on migration and risk of deaths from all causes, were applied to person-years from 2001 onward. These correction factors were estimated from the 2,042 workers in Hannover city for which complete information on vital status and migration was available. Sensitivity analyses were conducted to evaluate the influence of these correction factors.

The primary outcomes of interest were mortality from bladder cancer and lung cancer. Secondary outcomes were mortality from all cancers combined, stomach cancer, leukaemia, multiple myeloma and non-Hodgkin lymphoma (NHL). Exploratory outcomes included all other neoplasms with more than ten observed deaths in men or women in the combined analysis and mortality from cardiovascular diseases, respiratory diseases (without pneumonia) and all-causes. If an exploratory outcome was considered for a particular site, the SMR for the other gender group

was reported only if the number of deaths was greater than five. The list of ICD-9 codes used in the present article is reported in supplementary table 1 (S-Table 1).

The observed numbers of deaths for each cause of death considered was compared with the expected number calculated on the basis of national or regional (Italy) gender, age- and period-specific mortality rates. Five-year age groups were used for age and time period. National reference rates were obtained from the WHO Mortality Database (Revision of November 2014). For Italy, reference rates could be obtained from the region of Piedmont. Data from the Central Statistical Office of Poland were used when data from the WHO mortality database were not available (earlier years for a few cancer sites). For each country, standardized mortality ratios (SMRs, i.e., the ratio of observed to expected deaths) were calculated together with their confidence intervals based on the Poisson distribution of observed deaths [9, 10]. Country-specific SMRs were combined using random-effects models [11], which take into account potential heterogeneity among cohorts. Forest plots were reported for bladder and lung cancer mortality (primary outcomes) to evaluate the relative contribution of each country in the overall risk estimate.

Measures of heterogeneity was reported using I^2 statistics [12] as well as test for heterogeneity based on Cochran's Q statistic although this test is known for having poor statistical power [13].

As a sensitivity analysis, several stratified analyses were conducted. To evaluate whether the risk differed by type of industry, workers were separated between tyre production, general rubber goods, and a mixed category for factories that manufactured both tyres and general rubber goods. The role of the period of first employment on the risk of death was also investigated separating workers employed before 1985 to those employed from 1985 onwards.

The role of the duration of employment on the risk of death was investigated in a Poisson model with gender and a gender specific smooth function of duration of employment as explanatory variables, and the logarithm of the expected number of deaths as 'offset'. Duration of employment was modelled with cubic natural splines and three degrees of freedom. Cut-points (*knots*) of duration of employment were built from duration of employment of deceased subjects, such as at least eight deaths occurred between two points. The knots for the spline were built in a way that the knots divide duration of employment in intervals that contain the duration of employment of eight deceased workers each. This enables a stable estimation of SMR while keeping enough points for modelling the splines for the parameter of duration.

All data were anonymised prior to statistical analysis. P-values below 5% were considered as statistically significant.

Results

In the five European countries, a total 38,457 workers (29,768 men and 8,689 women) were included in the present study. Each country contributed rather homogeneously to the number of workers with Poland and the United Kingdom providing the greatest number of workers (Table 1). The average follow-up was 26 years and ranged from 18.7 years in Germany to 29.4 years in Poland, contributing to a total of 949,370 person-years of observation. The majority of workers (77.4%) were men. More women were recruited in Poland and Sweden. No major difference was observed between the cohorts assembled by each country. Overall, 2,725 deaths were observed during the follow-up.

Table 2 shows observed deaths and SMRs for primary, secondary and exploratory outcomes for men, women and both genders combined. In men, there were significantly reduced SMRs for lung cancer, colorectal cancer, all cancers combined, all causes combined, and cardiovascular diseases. In women, there were significantly reduced SMRs for all cancers combined, all causes combined, and cardiovascular diseases. In the total study population (both genders combined), there were significantly reduced SMRs for lung cancer, colorectal cancer, all cancers combined, all causes combined, and cardiovascular diseases.

Table 3 shows observed deaths and SMRs for primary and secondary outcomes for men, women and both genders combined, by industry sector. In the tyre sector, there were significantly reduced SMRs for lung cancer in men and in both genders combined, and for all cancers combined in men, women and both genders combined. There were no significant excesses. In the general rubber goods sector there were significantly elevated SMRs for stomach cancer in men and in both genders combined, and for multiple myeloma in men and both genders combined. There were no significant deficits. In the mixed sector, there were significantly reduced SMRs for all cancers combined in men and both genders combined. There were no significant excesses.

Based on 17 deaths observed during the follow-up, the risk of death from bladder cancer was SMR=0.80 (95%CI 0.46 to 1.38) with no evidence of heterogeneity between countries (Figure 1). This absence of increased risk for bladder cancer remained when stratified by gender (Table 2),

employment period (S-Table 2) and type of industry (Table 3). The risk of death from lung cancer was significantly decreased in rubber workers as compared to the general population with an SMR of 0.81 (95%CI 0.70 to 0.94) with no heterogeneity between countries (Figure 2).

For all other cancer sites as well as all-cause mortality, cardiovascular and respiratory mortality, the risk of death was not significantly increased for neither men nor women (Table 2). On the contrary, a statistically significant decrease was observed for mortality from all causes of cancer ~~total cancer mortality~~ (SMR=0.81, 95%CI 0.76 to 0.87), all causes of death ~~total mortality~~ (SMR=0.81, 95%CI 0.73 to 0.89), cardiovascular diseases (SMR=0.79, 95%CI 0.70 to 0.89), and for risk of death from colorectal cancer (SMR=0.72, 95%CI 0.55 to 0.94). Even if only eight deaths in men were observed for mesothelioma, the SMR was estimated for this cancer site and was 1.32 (95%CI 0.72 to 2.43). The overall results were not affected by the correction factors applied to person-years in Germany to account for migration and risk of death in the 2001-2003 period with no follow-up information.

Workers in the tyre industry were hired at around the same age as workers in the general rubber goods industry (median age of hire being 23 and 25 years respectively), and they were followed for about the same duration (25 and 23.5 years respectively). However, workers in the tyre industry were more frequently men (80% men) than in the general rubber goods industry (74% men). The greatest difference was the duration of employment which was a median of 10.5 years in the tyre industry while it was 4.2 years in the general rubber good industry. When stratifying workers by type of industry, a clear difference could be observed between these two populations with lower SMR in the tyre industry as compared to general rubber goods (Table 3). For total cancer mortality the risk of death was SMR=0.68 (95%CI 0.60 to 0.76) among workers in the tyre industry while it was close to 1 in workers in the general rubber goods industry with an SMR of 1.03 (95%CI 0.91 to 1.18) (Figure 3). In this stratified analysis, workers in the general rubber goods industries had a significant increased risk of stomach cancer (SMR=1.83, 95% CI 1.23 to 2.72) and multiple myeloma (SMR=3.18, 95% CI 1.61 to 6.27). Elevated SMRs were observed only among workers employed before 1985 (S-Table 2). These results were not consistent between countries and primarily driven by a majority of deaths in Poland for stomach cancer and a majority of deaths in the United Kingdom for multiple myeloma.

Workers employed from 1985 onwards had an apparently, though not significantly lower risk of total cancer mortality with a SMR of 0.74 (95%CI 0.65 to 0.84) as compared to workers employed before 1985 for which the SMR was 0.86 (95%CI 0.79 to 0.94). Such a decreased risk in

more recently employed workers was also observed for other primary and secondary outcomes (S-Table 2).

The risk of death from any cause was further investigated in a Poisson regression with a spline function applied to the duration of employment. With a risk initially above the general population, especially among men and women in general rubber goods production, a marked decline of the risk of death was observed with increasing years of employment (Figure 4, S-Figure 2). This trend seemed slightly stronger in men but went in the same direction for women. A similar trend was observed when limiting the analysis to total cancer mortality (S-Figure 1). Although difficult to interpret because of small numbers, a similar trend was observed for lung cancer mortality.

Discussion

In this cohort of workers in the rubber manufacturing industry first employed since 1975 in five European countries, there was no consistent indication of an increased risk of cancer mortality among the cancer sites pre-identified as primary or secondary outcomes of interest, i.e. total cancer mortality, and site-specific mortality for bladder, lung, stomach, leukaemia, myeloma and non-Hodgkin's lymphoma. In addition, none of the exploratory outcomes had their risk significantly increased.

There are a number of noticeable issues among a number of stratified analyses showing inconsistencies in the outcomes. In an analysis of secondary endpoints, when stratified by type of industry and period of first employment, excess risks of myeloma and gastric cancer were observed due, essentially, to results from the United Kingdom and Poland, respectively. Increases in risk of multiple myeloma and stomach cancer were observed mainly for the workers first employed before 1985, but not workers employed more recently. It is ~~likely~~ possible that these increased risks, which are further decreasing in more recently exposed workers, are the result of decrease of exposure to carcinogens. However, these results should be interpreted with caution as they were not consistent across countries, gender and type of industry, and mainly driven by a few excess deaths observed in the United Kingdom for multiple myeloma and a few excess deaths observed in Poland for stomach cancer.

Lung cancer, one of the primary hypotheses of the study, showed decreased risks in most countries. Secondary outcomes such as colorectal cancer, total cancer mortality, all-cause mortality and cardiovascular diseases also showed decreased risks. The reduction of risks for causes of death

were lower for workers in the tyre industries than for the general rubber goods industries. Several factors could be responsible for such a reduced risk. Such a pattern of decreased risk could be the sign of a "healthy worker effect" [14] in particular because the observed numbers of deaths from any cause and for total cancer mortality were systematically lower than expected. The healthy worker effect is a classical bias in epidemiology of occupational mortality and results in biased estimation of SMR when mortality of workers is compared to mortality of the general population. Its impact could play at the inception of cohort of workers with a "healthy population selection effect" and during follow-up with a "survivor population effect" [15].

In the cohorts of European rubber workers, a decreased risk of all-cause mortality is consistent with a healthy population selection effect, in particular because the follow-up started at recruitment in each cohort [16]. It has been suggested that the initial health advantage conferred by selection is expected to progressively dissipate with prolonged follow-up [16]. This would be in contradiction with the decreasing trend in SMR for longer duration of employment in rubber workers. However, staying active in the industry could be a secondary effect of selection with less healthy workers being more likely to be removed from hazardous exposure than healthier workers [17]. Longer duration in employment could be interpreted as a marker of improved economic status, better access to medical care and changes in life-style [18]. The healthy worker effect has been reported in previous studies on SMRs for cancer mortality [15, 17] but this bias usually affected less the SMRs for cancer than the SMRs for total mortality [15, 16]. In the present study, SMRs were significantly decreased for several cancer sites with values even lower than the total mortality.

The difference between tyre industry and general rubber goods could be an artefact with workers in the general rubber goods industry were employed for a shorter duration. However, the effect of type of industry and duration of employment seemed independent when conducting the spline regression separately by type on industry (S-Figure 2). This indicates that both working in the tyre industry and for a long duration were actually associated with a decreased risk of overall mortality. In contrast, in the general rubber goods industry a similar healthy worker effect was not evident for total mortality: elevated SMRs were evident up to 15 years duration of employment.

Rubber production is an occupation classified as group 1 carcinogen by IARC, without clear indication of what the responsible agent might be [4]. A particular focus has been made on tyre production, in particular the tyre curing process during which high temperatures are reached to stimulate reaction between different chemical compounds of the tyre. Measurements conducted with the European project ExAsRub [19] where the results can be consulted online (http://exasrub.iras.uu.nl/) revealed higher exposure to several agents in workers working in the

general rubber goods as compared to workers in the tyre industry. For example, in the period 1989-1993 in the UK, personnal representative measurement of rubber dust was 2.82 mg/m^3 (geometric mean) in the general rubber goods and 1.18 mg/m^3 in the tyre industry. ~~It could be hypothesised that the greater efforts in the tyre industry to decrease exposure to chemical agents was potentially strengthened with additional health measures such as anti-smoking policies in the workplace.~~ The differences in the overall SMRs between tyre and general rubber goods sectors might also be due to differences in smoking habits, however no clear data was identified to confirm this hypothesis.

Major industries in Europe have experienced major changes in occupational hygiene through increased surveillance and actions to protect workers. In the rubber manufacturing industry, these changes seemed to have started earlier as the analysis of the data collected within the EU-ExAsRub consortium showed a continuous decreasing time trends of inhalable dust from 1975 to 2005 although there was national variation [6]. The results stratified by period of employment showed that decreased risks of lung cancer and total cancer mortality were even stronger after 1985 than before 1985 which is in line with data showing a progressive decline in exposure to inhalable dust measured in rubber industries in Europe. Caution must be expressed in interpreting these findings. Comparison with mortality data in the prospective cohort, whether overall or by subgroup (such as type of manufacturing), and the dust levels are on an ecological basis, a weak type of study design compared to the prospective cohort study reported here.

The findings from this study are reassuring. However, it is recommended that these cohorts continue to be monitored regularly to ensure that the absence of increased risk is maintained for longer follow-up, and the long-term positive effects of the continual implementation of technology innovations to reduce exposures to workers can be maintained. Longer follow-up will also allow examination of cohorts employed in more recent years (after 1985). In addition, it will allow more detailed evaluation of the healthy worker effect.

Acknowledgements and funding

The study was partially funded by an unrestricted research grant from the European Tyre and Rubber Manufacturers' Association (ETRMA) and was conducted and reported in full independence from the sponsor. The study Working Group comprised iPRI staff (Mathieu Boniol and Peter Boyle) and each national Principal Investigator (Beata Świątkowska (Poland), Tom Sorahan (United Kingdom), Jürgen Wellmann (Germany), Kristina Jakobsson (Sweden), Enrico Pira (Italy)). Alice Koechlin and Cecile Pizot were iPRI staff working on the project. Dirk Taeger was the co-principal investigator with Jürgen Wellmann working on the German cohort. Carlo La Vecchia and Paolo Boffetta were co-principal investigators with Enrico Pira working on the Italian cohorts. The authors would like to thank Faustine Valentini and Kim Coppens (iPRI) for the editorial support during the preparation of this manuscript, and Maria Bota (iPRI) for help in literature scoping. Prof. Neonila Szeszenia-Dąbrowska and Urszula Wilczyńska, PhD, provided background information on the rubber industry workers and allowed the follow-up of the already existing rubber manufacturing cohorts in Poland. The German study was partially funded and supported by the BG RCI (formerly Berufsgenossenschaft der Chemischen Industrie, Heidelberg) and the Wirtschaftsverband der deutschen Kautschukindustrie e V, Frankfurt/M. Zoli Mikoczy and Ulf Bergendorf were responsible for the assembly of the Swedish database.

Disclosure

The authors have declared no conflicts of interest.

References

1. IARC. The rubber industry. In: IARC, editor. Monographs on the Evaluation of the Carcinogenic Risks to Humans, Suppl 7 Overall Evaluations of Carcinogenicity: an Updating of IARC Monographs Volumes 1 to 42. Lyon, France: IARC; 1987. p. 332-334.
2. Kogevinas M, Sala M, Boffetta P et al. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. Occup Environ Med. 1998; 55(1):1-12.
3. Alder N, Fenty J, Warren F et al. Meta-analysis of mortality and cancer incidence among workers in the synthetic rubber-producing industry. Am J Epidemiol. 2006; 164(5):405-420.
4. IARC A review of human carcinogens. Volume 100 Part F: Chemical agents and related occupations / IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: IARC; 2012.
5. Kauppinen T, Toikkanen J, Pedersen D et al. Occupational exposure to carcinogens in the European Union. Occup Environ Med. 2000;57(1):10-8.
6. de Vocht F, Vermeulen R, Burstyn I et al. Exposure to inhalable dust and its cyclohexane soluble fraction since the 1970s in the rubber manufacturing industry in the European Union. Occup Environ Med. 2008;65(6):384-91.
7. Taeger D, Weiland SK, Sun Y et al. Cancer and non-cancer mortality in a cohort of recent entrants (1981-2000) to the German rubber industry. Occup Environ Med. 2007; 64(8):560-561.
8. Dost A, Straughan J, Sorahan T. A cohort mortality and cancer incidence survey of recent entrants (1982-91) to the UK rubber industry: findings for 1983-2004. Occupational Medicine (Oxford, England). 2007; 57(3):186-190.
9. Breslow NE, Day NE. Statistical Methods in Cancer Research, Vol. 2. The Design and Analysis of Cohort Studies. IARC, editor. Lyon, France: IARC; 1987.
10. Owen DB. Handbook of statistical tables. . Reading, editor. MA: Addison-Wesley Publishing Co.; 1962.
11. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med. 2002; 21(4):589-624.

12. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21(11):1539-1558.
13. Gavaghan DJ, Moore RA, McQuay HJ. An evaluation of homogeneity tests in meta-analyses in pain using simulations of individual patient data. Pain. 2000; 85(3):415-424.
14. Checkoway H, Pearce N, Kriebel D. Cohort studies. Research methods in occupational epidemiology. 2nd ed. New York, USA: Oxford University Press; 2004. p. 123-178.
15. Fox AJ, Collier PF. Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. Br J Prev Soc Med. 1976;30(4):225-30.
16. Goldblatt P, Fox J, Leon D. Mortality of employed men and women. Am J Ind Med. 1991;20(3):285-306.
17. Applebaum KM, Malloy EJ, Eisen EA. Reducing healthy worker survivor bias by restricting date of hire in a cohort study of Vermont granite workers. Occup Environ Med. 2007;64(10):681-7.
18. Wen CP, Tsai SP. Anatomy of the health worker effect - a critique of summary statistics employed in occupational epidemiology. Scand J Work Environ Health. 1982;8 Suppl 1:48-52.
19. De Vocht F, Straif K, Szeszenia-Dabrowska N et al. A database of exposures in the rubber manufacturing industry: design and quality control. Ann Occup Hyg. 2005;49(8):691-701

Legends to Figures

Figure 1. Forest plot of the risk of bladder cancer mortality (men and women combined) from five cohorts of European rubber workers. Numbers of deaths are reported in brackets. The red line corresponds to a standardised mortality ratio (SMR) of 1, i.e., no difference in mortality between the cohort and the general population. The blue line corresponds to the SMR for all-cause mortality.

Figure 2. Forest plot of the risk of lung cancer mortality (men and women combined) from five cohorts of European rubber workers. Numbers of deaths are reported in brackets. The red line corresponds to a standardised mortality ratio (SMR) of 1, i.e., no difference in mortality between the cohort and the general population. The blue line corresponds to the SMR for all-cause mortality.

Figure 3. Forest plot of the risk of all cancers mortality (men and women combined) from five cohorts of European rubber workers in the tyre industry (red), in the general rubber goods (GRG) industry (blue) and in mixed industry (purple). Numbers of deaths are reported in brackets. The black line corresponds to a standardised mortality ratio (SMR) of 1, i.e., no difference in mortality between the cohort and the general population

Figure 4. Analysis of risk of death from any cause from five cohorts of European rubber workers by duration of employment in the rubber manufacturing industry. The horizontal red line corresponds to the global SMR for all causes of death. The plain black lines represent the spline curve of SMR by duration of employment (bold line) with its 95% confidence interval (normal lines).

Table 1. Characteristics of the five European cohorts of workers first employed in the rubber manufacturing industry since 1975

	Germany	Italy	Poland	Sweden	UK
Number of workers	7616	5115	9700	7424	8602
Number of factories	8	2	2	11	41
Follow-up (years)	18.7	19.1	29.4	21.7	24.1
Number of deaths	136	216	1451	376	546
Gender (% Men)	85.9%	91.1%	63.2%	66.3%	87.4%
Type of industry (%Tyre/%GRG/%Other*)	0/34.1/65.9	100/0/0	77.1/22.9/0	5.5/32.2/62.4	51.0/36.2/12.8
Age of hire (Median, IQR)	24 (21; 29)	25 (22; 31)	21 (19; 26)	25 (20; 35)	25 (21; 33)
Duration of Employment (Median, IQR)	5.3 (2.5; 10.5**)	10.7 (4.9; 16.3**)	7.4 (3.0; 17.2)	4.6 (2.2; 10.3**)	4.9 (2.6; 12.7)
Date of first recruitment	05/01/1981	01/01/1975	01/01/1975	01/01/1975	01/01/1982
Date of Last Follow-up	31/12/2012 (LS) or 31/12/2013 (NRW)	31/03/2013	30/06/2012	31/12/2011	31/12/2011
Date of last job history update	31/12/2000	31/03/2013	31/10/2011	01/07/2002	- 31/12/2011 (4005 subjects/47%) - variable between 1988 and 1995 (4597 subjects/53%)
% Still employed at last job history update	51.2%	46.4%	0.5%	44.8%	- Last job history update 2011: 14.5% among 4005 subjects

LS: Lower Saxony; NRW: North Rhine-Westphalia; GRG: general rubber goods

*Other includes mixed factories (both tyre and GRG)

**: not estimable as more than 25% of workers were still employed at the last job history update

Table 2. Observed deaths and standardised mortality ratios (SMRs) among 38,457 workers first employed in the European rubber manufacturing industry since 1975, by gender.

	Men (N=29,768; PY=714,612)		Women (N=8,689; PY=234,758)		Combined (N=38,457; PY=949,370)	
Cause of deaths	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
Primary outcomes						
Bladder cancer	16	0.87 (0.49; 1.52)	1	0.36 (0.06; 2.29)	17	0.80 (0.46; 1.38)
Lung cancer	157	***0.80 (0.68; 0.94)***	29	0.91 (0.61; 1.35)	186	***0.81 (0.70; 0.94)***
Secondary outcomes						
All cancers	582	***0.81 (0.74; 0.88)***	187	***0.83 (0.72; 0.97)***	769	***0.81 (0.76; 0.87)***
Stomach cancer	47	1.15 (0.84; 1.56)	10	1.23 (0.61; 2.46)	57	1.16 (0.88; 1.53)
Leukaemia	18	0.97 (0.58; 1.63)	4	0.76 (0.14; 4.02)	22	0.84 (0.53; 1.35)
Non-Hodgkin's lymphoma	14	0.74 (0.40; 1.37)	4	0.85 (0.28; 2.57)	18	0.79 (0.47; 1.34)
Multiple myeloma	12	1.55 (0.81; 2.98)	4	1.68 (0.56; 5.11)	16	1.54 (0.89; 2.68)
Exploratory outcomes**						
All causes of death	2259	***0.80 (0.71; 0.89)****	466	***0.86 (0.78; 0.94)***	2725	***0.81 (0.73; 0.89)****
Cardiovascular diseases	655	***0.80 (0.71; 0.90)***	110	***0.75 (0.61; 0.90)***	765	***0.79 (0.70; 0.89)***
Respiratory diseases excluding pneumonia	68	0.93 (0.72; 1.19)	12	0.74 (0.38; 1.42)	80	0.90 (0.71; 1.13)
Brain and central nervous system cancer	33	0.95 (0.66; 1.39)	9	0.99 (0.46; 2.14)	42	0.96 (0.69; 1.34)
Colorectal cancer	39	***0.61 (0.44; 0.86)***	20	1.16 (0.71; 1.91)	59	***0.72 (0.55; 0.94)***
Kidney cancer	18	0.83 (0.49; 1.38)	3	-	21	0.82 (0.51; 1.32)
Larynx cancer	17	1.18 (0.69; 2.04)	0	-	17	1.12 (0.65; 1.93)
Liver cancer	15	0.73 (0.40; 1.31)	2	-	17	0.69 (0.40; 1.20)
Melanoma	11	0.88 (0.45; 1.71)	1	-	12	0.68 (0.36; 1.28)
Oesophagus	23	0.90 (0.57; 1.41)	1	-	24	0.84 (0.54; 1.30)
Oral cavity and pharynx	23	0.97 (0.62; 1.53)	1	-	24	0.92 (0.59; 1.43)
Pancreas cancer	33	0.93 (0.64; 1.36)	13	1.31 (0.70; 2.44)	46	0.98 (0.72; 1.35)
Prostate cancer	26	0.79 (0.52; 1.21)	-	-	-	-
Breast cancer	1	-	36	0.86 (0.60; 1.23)	-	-
Cervical cancer	-	-	17	1.25 (0.74; 2.10)	-	-
Ovarian cancer	-	-	12	0.73 (0.38; 1.40)	-	-

Statistically significant associations are in bold

* Significant heterogeneity between the five countries ($p<0.05$)

** Results of exploratory analysis with less than 5 deaths observed were not reported

Table 3. Observed deaths and standardised mortality ratios by type of industry among 38,457 workers first employed in the European rubber manufacturing industry since 1975, by industry sector

	Tyre		General rubber goods		Mixed	
Cause of deaths	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
Men	N=13,962; PY=359,318		N=7,684; PY=185,206		N=8,122; PY=170,021	
Bladder cancer ¤	9	1.03 (0.48; 2.20)	6	0.84 (0.32; 2.18)	1	0.23 (0.03; 1.90)
Lung cancer¤	72	***0.72 (0.57; 0.92)***	67	0.95 (0.74; 1.23)	18	0.78 (0.47; 1.31)
All cancers	235	***0.67 (0.59; 0.77)***	263	1.05 (0.92; 1.19)	84	***0.70 (0.56; 0.88)***
Stomach cancer	20	0.97 (0.60; 1.57)	24	***1.75 (1.12; 2.71)***	3	0.58 (0.12; 2.75)
Leukaemia	11	1.15 (0.60; 2.19)	6	0.84 (0.34; 2.08)	1	0.14 (0.02; 1.15)
Non-Hodgkin's lymphoma	6	1.12 (0.21; 5.93)	6	0.95 (0.35; 2.64)	2	0.44 (0.08; 2.57)
Multiple myeloma	3	0.94 (0.25; 3.55)	8	***3.02 (1.40; 6.51)***	1	0.32 (0.04; 2.68)
Women	N=3,437; PY=107,540		N=2,628; PY=68,544		N=2,624; PY=58,672	
Bladder cancer ¤	0	0.00 (0.01; 2.98)	0	0.00 (0.01; 1.62)	1	1.30 (0.14; 11.92)
Lung cancer¤	8	0.61 (0.29; 1.26)	16	1.68 (0.96; 2.92)	5	0.63 (0.23; 1.73)
All cancers	66	***0.68 (0.53; 0.88)***	80	1.01 (0.74; 1.38)	41	0.85 (0.61; 1.17)
Stomach cancer	3	0.64 (0.19; 2.19)	5	2.07 (0.77; 5.59)	2	1.37 (0.23; 8.14)
Leukaemia	1	0.29 (0.04; 2.29)	1	0.36 (0.05; 2.51)	2	0.84 (0.04; 16.90)
Non-Hodgkin's lymphoma	1	0.45 (0.06; 3.56)	2	1.08 (0.20; 5.81)	1	0.54 (0.06; 4.73)
Multiple myeloma	2	1.69 (0.37; 7.73)	2	1.08 (0.12; 9.56)	0	0.00 (0.01; 2.56)
Men and Women combined	N=17,399; PY=466,858		N=10,312; PY=253,750		N=10,746; PY=228,693	
Bladder cancer ¤	9	0.97 (0.46; 2.08)	6	0.76 (0.29; 1.98)	2	0.50 (0.11; 2.30)
Lung cancer¤	80	***0.71 (0.56; 0.90)***	83	1.02 (0.81; 1.29)	23	0.73 (0.47; 1.14)
All cancers	301	***0.68 (0.60; 0.76)***	343	1.03 (0.91; 1.18)	125	***0.74 (0.61; 0.88)***
Stomach cancer	23	0.92 (0.59; 1.44)	29	***1.83 (1.23; 2.72)***	5	0.71 (0.24; 2.13)
Leukaemia	12	0.96 (0.52; 1.78)	7	0.80 (0.35; 1.84)	3	0.60 (0.15; 2.37)
Non-Hodgkin's lymphoma	7	1.08 (0.24; 4.90)	8	1.08 (0.46; 2.50)	3	0.50 (0.13; 1.99)
Multiple myeloma	5	1.12 (0.41; 3.04)	10	***3.18 (1.61; 6.27)***	1	0.25 (0.03; 2.06)

Statistically significant associations are in bold

¤: Primary outcomes; *: significant heterogeneity between studies

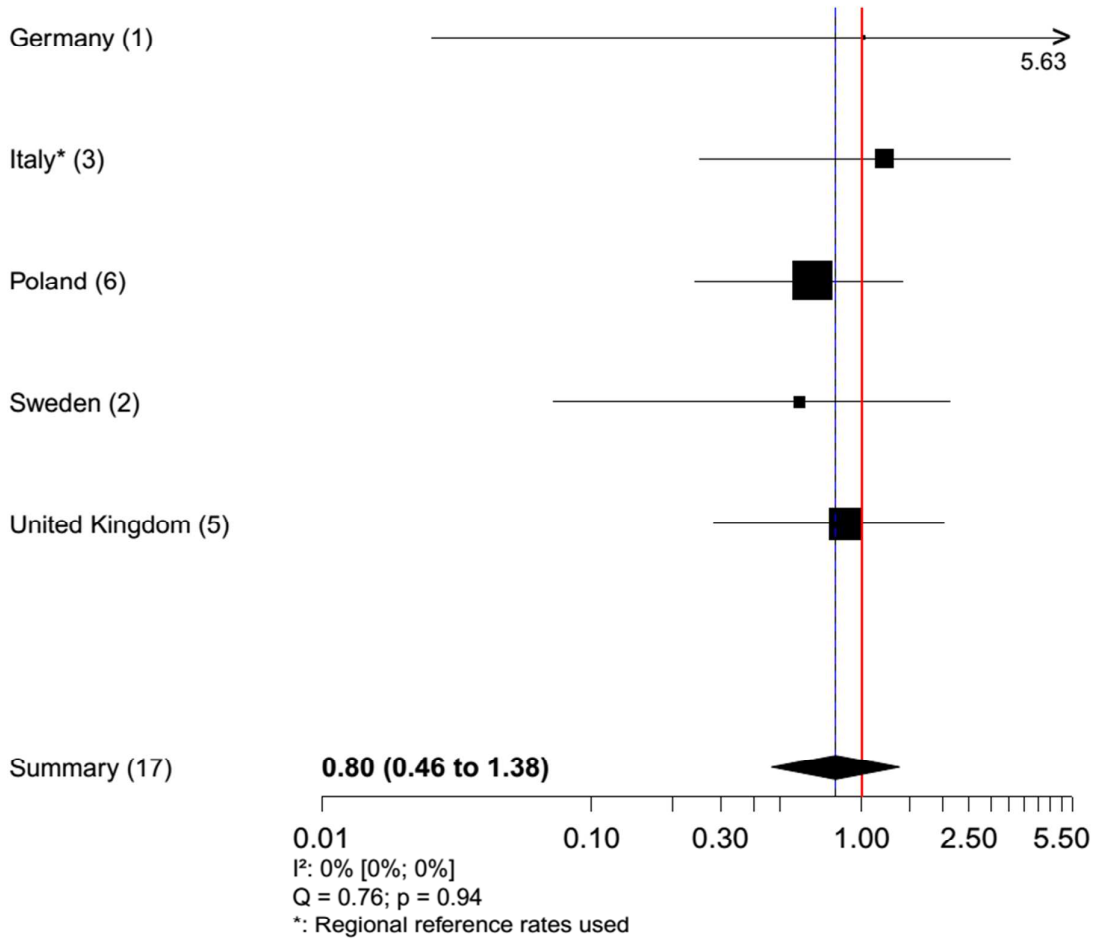


Figure 1. Forest plot of the risk of bladder cancer mortality (men and women combined) from five cohorts of European rubber workers. Numbers of deaths are reported in brackets. The red line corresponds to a standardised mortality ratio (SMR) of 1, i.e., no difference in mortality between the cohort and the general population. The blue line corresponds to the SMR for all-cause mortality.

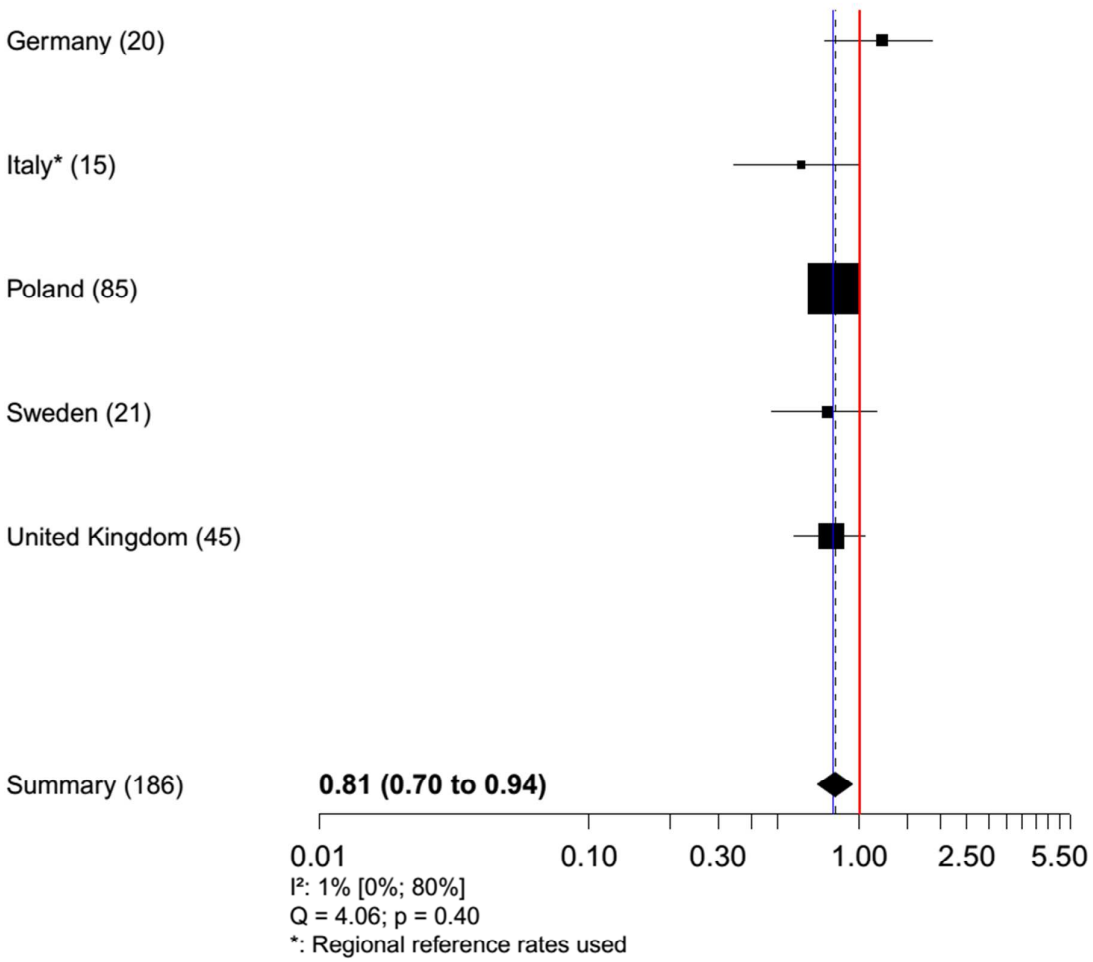


Figure 2. Forest plot of the risk of lung cancer mortality (men and women combined) from five cohorts of European rubber workers. Numbers of deaths are reported in brackets. The red line corresponds to a standardised mortality ratio (SMR) of 1, i.e., no difference in mortality between the cohort and the general population. The blue line corresponds to the SMR for all-cause mortality.

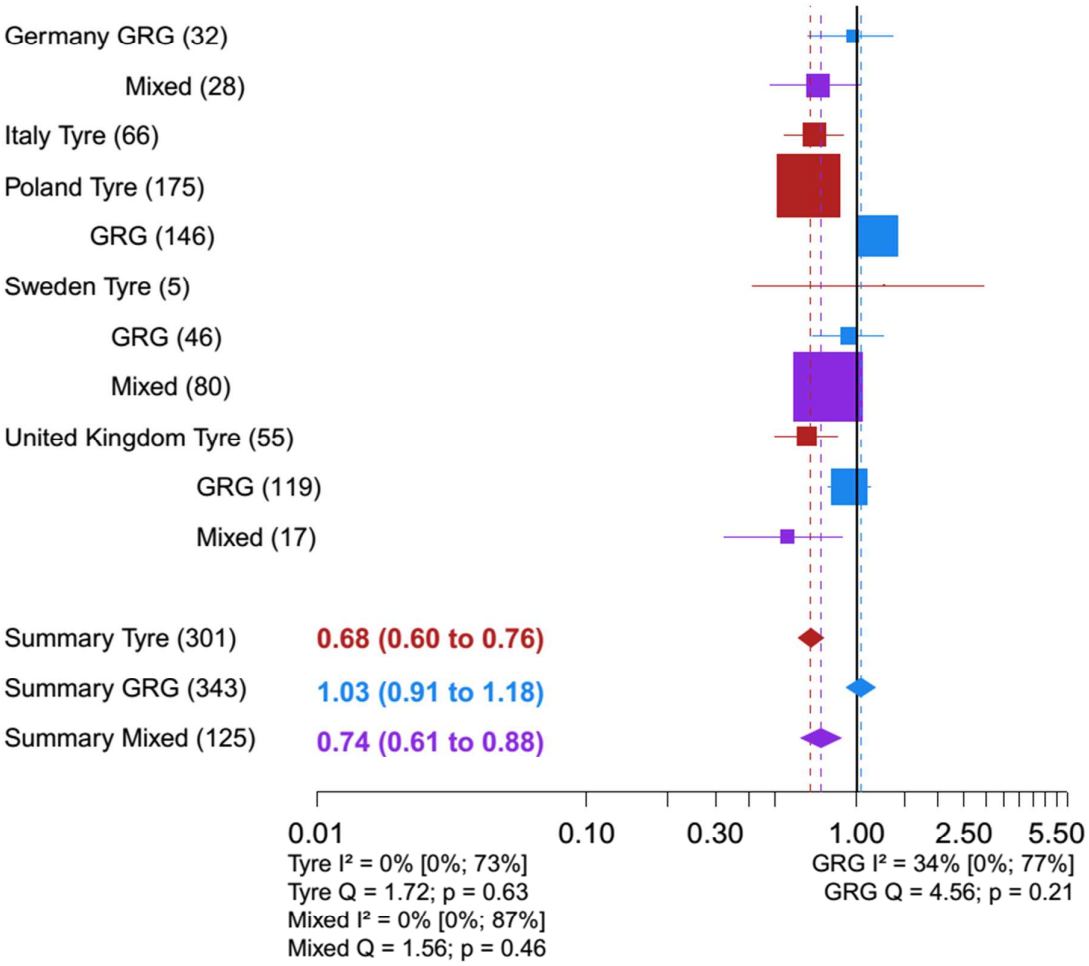


Figure 3. Forest plot of the risk of all cancers mortality (men and women combined) from five cohorts of European rubber workers in the tyre industry (red), in the general rubber goods (GRG) industry (blue) and in mixed industry (purple). Numbers of deaths are reported in brackets. The black line corresponds to a standardised mortality ratio (SMR) of 1, i.e., no difference in mortality between the cohort and the general population

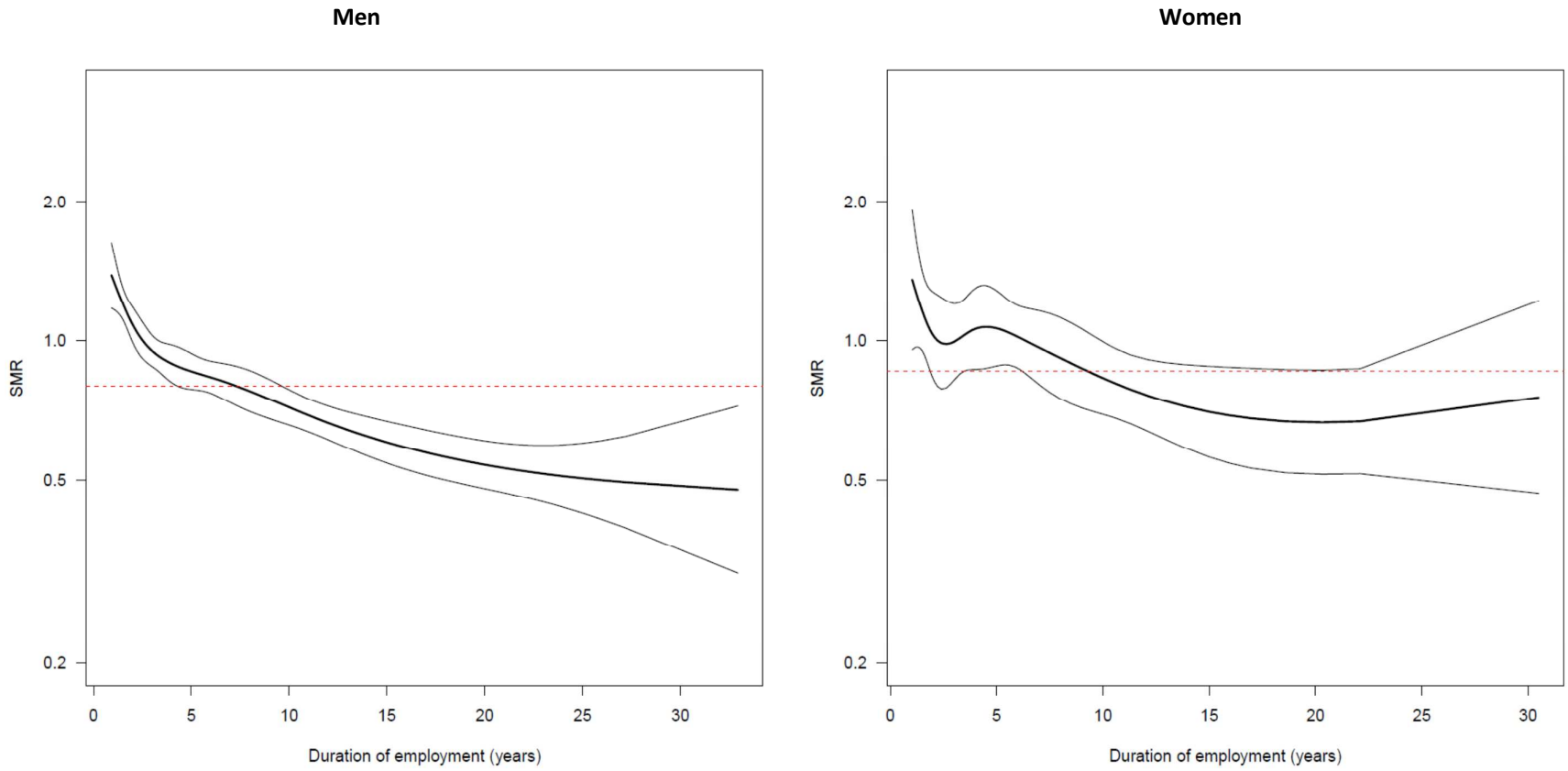


Figure 4. Analysis of risk of death from any cause from five cohorts of European rubber workers by duration of employment in the rubber manufacturing industry. The horizontal red line corresponds to the global SMR for all causes of death. The plain black lines represent the spline curve of SMR by duration of employment (bold line) with its 95% confidence interval (normal lines).

Appendix

S-Table 1. List of ICD codes used for classifying deaths in the five countries

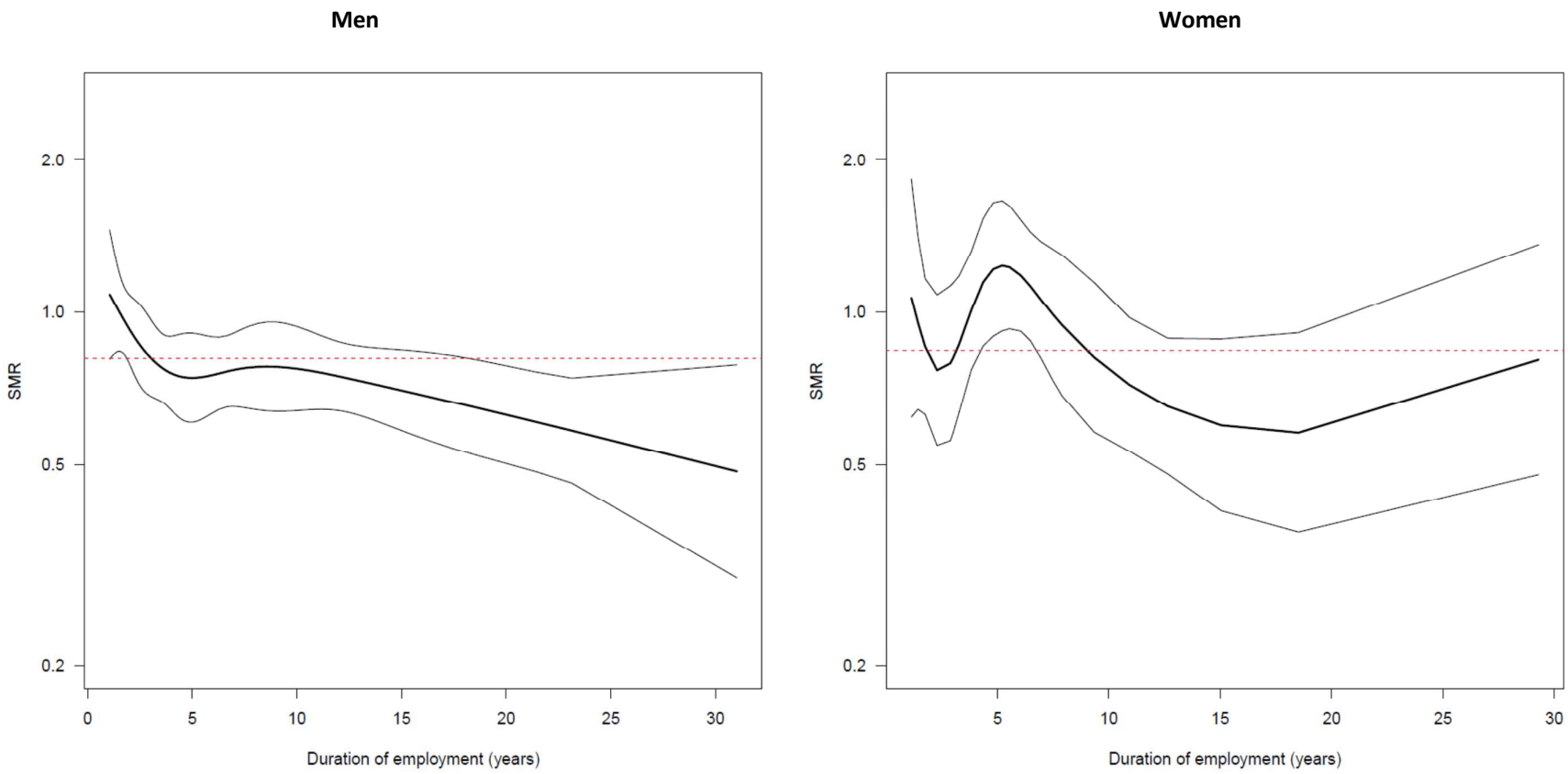
Cause of death	ICD8	ICD9	ICD10
Primary outcomes			
Bladder cancer	188	188	C67
Lung cancer	162	162	C33-C34
Secondary outcomes			
All cancers	140-209	140-208	C00-C97
Stomach cancer	151	151	C16
Leukaemia	204-207	204-208	C91-C95
Non-Hodgkin's lymphoma	200, 202	200, 202	C82-C86
Multiple myeloma	203	203	C90
Exploratory analyses			
Other diseases			
All causes	000-796	001-799	A00-R99
Cardiovascular diseases	390-458	390-455	I00-I99
Respiratory diseases without pneumonia	460-474, 490-519	460-478, 487-519	J00-J11, J19-J99
Cancers			
Brain and central nervous system	191-192	191-192	C47, C70-C72
Colorectal cancer	153-154	153-154	C18-C21
Kidney	189	189	C64-C66, C68
Larynx	161	161	C32
Liver with unspecified liver cancers	155, 197.8	155	C22
Melanoma	172	172	C43
Oesophagus	150	150	C15
Oral cavity and pharynx	140-149	140-149	C00-C14
Pancreas	157	157	C25
Prostate	185	185	C61
Breast	174	174	C50
Cervix	180	180	C53
Ovary	183	183	C56-C57

S-Table 2. Standardised mortality ratios by year of hire for 38,457 workers first employed in the European rubber manufacturing industry since 1975

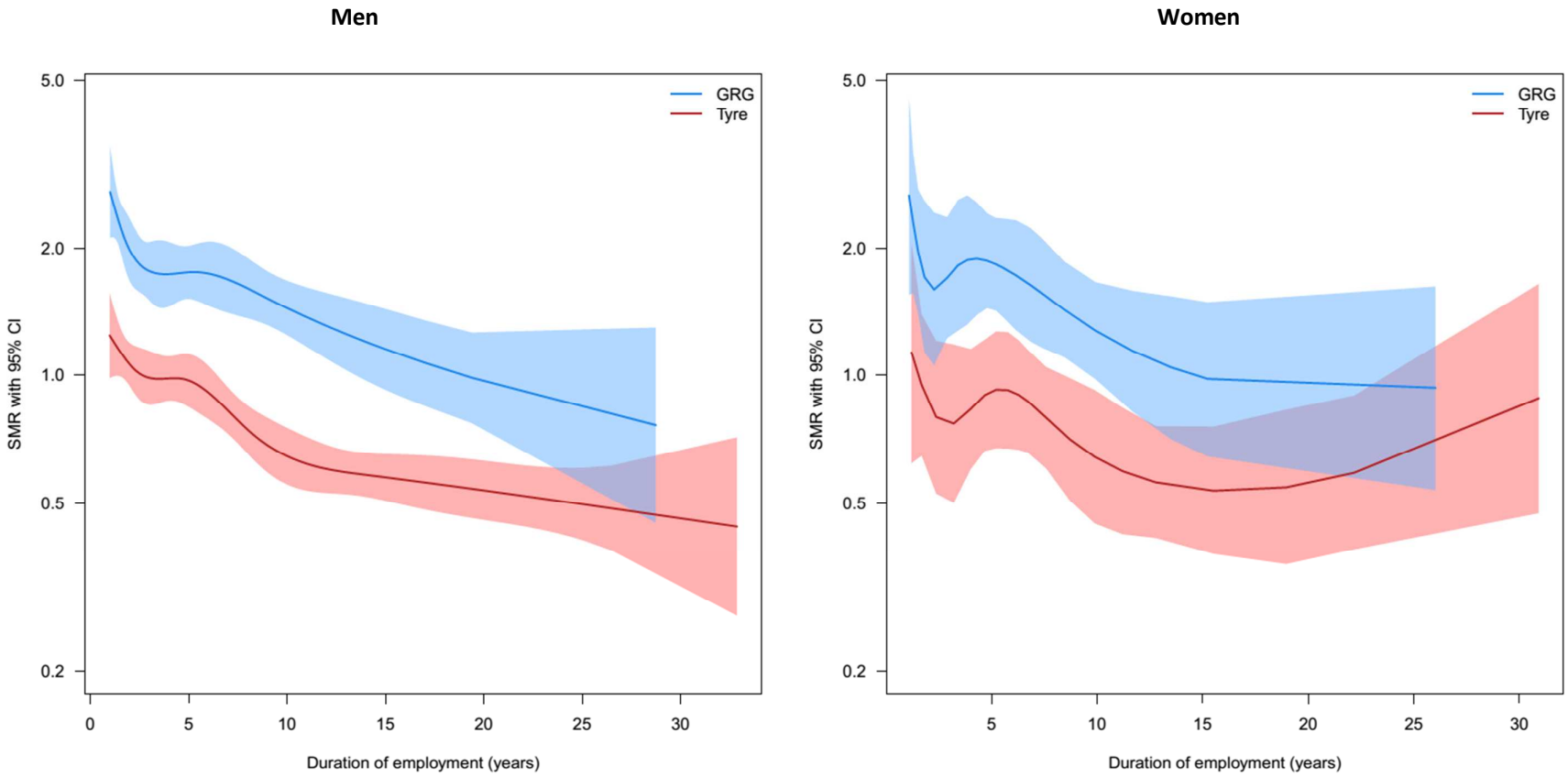
	Employed before 1985		Employed from 1985 onwards	
Cause of deaths	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
Men	N= 10,086; PY=307,721		N= 19,682; PY=406,891	
Bladder cancer¤	10	0.81 (0.38; 1.71)	6	1.05 (0.42; 2.66)
Lung cancer¤	112	0.84 (0.69; 1.02)	45	0.78 (0.56; 1.08)
All cancers	380	***0.85 (0.76; 0.94)***	202	***0.75 (0.65; 0.86)***
Stomach cancer	36	1.35 (0.95; 1.92)	11	0.98 (0.50; 1.95)
Leukaemia	13	1.26 (0.70; 2.26)	5	0.48 (0.17; 1.35)
Non-Hodgkin's lymphoma	8	0.87 (0.36; 2.07)	6	0.61 (0.25; 1.48)
Multiple myeloma	7	1.61 (0.65; 3.96)	5	1.29 (0.46; 3.65)
Women	N= 4,462; PY=145,661		N= 4,227; PY=89,097	
Bladder cancer¤	0	0.00 (0.01; 1.07)	1	1.06 (0.15; 7.37)
Lung cancer¤	21	0.98 (0.61; 1.57)	8	0.74 (0.32; 1.70)
All cancers	143	0.90 (0.76; 1.06)	44	***0.71 (0.51; 0.97)***
Stomach cancer	9	1.46 (0.70; 3.03)	1	0.33 (0.05; 2.07)
Leukaemia	2	0.47 (0.06; 3.83)	2	0.97 (0.20; 4.79)
Non-Hodgkin's lymphoma	3	0.82 (0.22; 2.97)	1	0.43 (0.07; 2.78)
Multiple myeloma	4	2.29 (0.60; 8.76)	0	0.00 (0.01; 1.80)
Both genders	N= 14,548; PY=453,382		N= 23,909; PY=495,988	
Bladder cancer¤	10	0.73 (0.35; 1.54)	7	1.08 (0.44; 2.63)
Lung cancer¤	133	0.85 (0.71; 1.02)	53	0.76 (0.57; 1.02)
All cancers	523	***0.86 (0.79; 0.94)***	246	***0.74 (0.65; 0.84)***
Stomach cancer	45	***1.37 (1.00; 1.88)***	12	0.93 (0.47; 1.81)
Leukaemia	15	1.06 (0.61; 1.84)	7	0.61 (0.25; 1.49)
Non-Hodgkin's lymphoma	11	0.91 (0.45; 1.84)	7	0.65 (0.29; 1.48)
Multiple myeloma	11	1.81 (0.88; 3.71)	5	1.11 (0.39; 3.13)

Statistically significant associations are in bold

¤: primary outcomes



S-Figure 1. Analysis of risk of death from cancer from five cohorts of European rubber workers by duration of employment in the rubber manufacturing industry. The horizontal red line corresponds to the global SMR for cancer death. The black lines represent the spline curve of SMR by duration of employment (bold line) with its 95% confidence interval (normal lines).



S-Figure 2. Analysis of risk of death from any cause from five cohorts of European rubber workers by duration of employment in the rubber manufacturing industry. The plain blue line represents the spline curve of SMR for workers in the general rubber goods industry by duration of employment with its 95% confidence interval (blue area). The plain red line represents the spline curve of SMR for workers in the tyre industry by duration of employment with its 95% confidence interval (red area).