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Title: Cancer incidence in cohorts of workers in the rubber manufacturing industry first employed since 1975 in United Kingdom and Sweden.

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Abstract (249 words)

Objectives: Increased cancer risks have been reported among workers in the rubber manufacturing industry employed before the 1960s but it is unclear for workers hired subsequently. The present study focused on cancer incidence among rubber workers first employed after 1975 in Sweden and the United Kingdom.

Methods: Two cohorts of rubber workers employed for at least one year were analysed. Standardised incidence ratios (SIRs), based on country- and period-specific incidence rates, were analyzed for all cancers combined (except non-melanoma skin), bladder cancer, lung cancer, stomach cancer, leukaemia, non-Hodgkin's lymphoma and multiple myeloma. Exploratory analyses were conducted for other cancers with a minimum of ten cases in both genders combined.

Results: 16,026 individuals (12,441 men; 3,585 women) contributed to 397,975 person-years of observation, with 846 cases of cancer observed overall, 437 in United Kingdom and 409 in Sweden. No statistically significant increased risk was observed for any site of cancer. A reduced risk was evident for all cancers combined (SIR=0.83, 95%CI (0.74; 0.92)), lung cancer (SIR=0.74, 95%CI (0.59; 0.93)), non-Hodgkin's lymphoma (SIR=0.67, 95%CI (0.45; 1.00)), and prostate cancer (SIR=0.77, 95%CI (0.64; 0.92)). For stomach cancer and multiple myeloma, SIRs were 0.93 (95%CI (0.61; 1.43)) and 0.92 (95%CI 0.44; 1.91), respectively. No increased risk of bladder cancer was observed (SIR=0.88, 95%CI (0.61; 1.28)).

Conclusions: No significantly increased risk of cancer incidence was observed in the combined cohort of rubber workers first employed since 1975. Continued surveillance of the present cohorts is required to confirm absence of long-term risk and confirmatory findings from other cohorts would be important.

Keywords: rubber, occupational exposure, cohort study, cancer, incidence

What this paper adds:

- Occupational exposure in the rubber manufacturing industry is an IARC group 1 human carcinogen. But recent studies suggested that, following improvement in occupational hygiene, cancer risks were no longer observable among recently employed workers.
- In a prospective cohort of 16,026 workers employed since 1975 in the rubber manufacturing industry in United Kingdom and Sweden, and followed for 23 years on average, no consistent increased cancer incidence 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

Occupational exposure in the rubber manufacturing industry, i.e. production of tyres and general rubber goods and process of re-treading, is an IARC group 1 human carcinogen ¹. The IARC evaluation, based mainly on observational studies on workers mostly employed before the 1960s, concluded there was sufficient evidence of an increased risk of bladder cancer, leukaemia, stomach, lung cancer and lymphoma. The carcinogens involved in these excesses are as yet unknown but exposure to aromatic amines, and solvents have been suspected to play a role ².

The rubber manufacturing industry has undergone radical technological changes since the 1950s, entailing major reductions in rubber dust ³ and fume exposure and the decrease of known carcinogenic agents like benzene and beta naphthylamine, although others, such as nitrosamines, are still present. A recent study from five European countries on 38,457 workers employed since 1975, with nearly a million person-years, showed no increased of cancer mortality for bladder cancer, leukaemia, lung cancer and lymphoma ⁴. However, this study suggested an increased risk of stomach cancer and multiple myeloma in the general rubber goods (GRG) sector, but not in the tyre sector. These findings were driven by an increased risk in one of the five contributing cohorts.

Incidence data were also collected in the United Kingdom and Sweden, part of the European cohorts, and provide a helpful complementary evaluation of the association between occupational exposure in the rubber manufacturing industry and cancer. While easier to collect and widely available in several countries, mortality data is a heterogeneous mix of cancers diagnosed in the preceding years with various latencies between exposure and outcome. In addition, incidence data are less affected by misclassification problems as compared to mortality data and are not affected by trends in curability of some forms of cancers ⁵.

The present study reports data on incidence of cancer in the United Kingdom and Sweden with two objectives: first, to confirm whether no increased risk of cancer was also observed for cancer incidence; second, to evaluate whether the suspected increased risk of stomach cancer and of multiple myeloma were also present in cancer incidence.

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. Details on the methods and mortality data have been published elsewhere ⁴. The initial cohort consisted of rubber workers employed since 1975 for at least one year in rubber manufacturing industries in Germany, Italy, Poland, Sweden and the United Kingdom, but incidence data were available only in Sweden

and the United Kingdom. In Sweden, data from a cohort of workers **first** employed in 1975 or later were extracted from an initial cohort using personnel records from Swedish rubber manufacturing plants, situated in 11 different places all over the country. Vital statistics were obtained from Statistics Sweden and with linkage to the Swedish cancer registry, information on up to two tumours per worker were extracted. In the United Kingdom, an initial cohort of workers employed for the first time in the rubber manufacturing industry within the period 1982-1991 was established from 41 rubber factories in England, Wales and Scotland. Incidence of cancer was obtained from the UK Health and Social Care Information Centre. For both Sweden and United Kingdom, the follow-up with vital statistics and cancer incidence was conducted up to 31st December 2011.

Primary, secondary and exploratory outcomes were defined in the study protocol, prior to study conduct, based on the IARC's evaluation and on the strength of association as reported in the systematic review of Kogevinas et al 1998 ⁶. The primary outcomes of interest were therefore incidence of bladder cancer and lung cancer. Secondary outcomes were incidence of all cancers combined (excluding non-melanoma skin cancer), stomach cancer, leukaemia, multiple myeloma and non-Hodgkin's lymphoma (NHL). Data from other cancer sites, not previously defined, were also included in exploratory analysis but only if more than ten cases were observed in men or women combined. Non-melanoma skin cancers and benign neoplasms were excluded from the analysis. The list of international classification of diseases (ICD) codes used in the present article is reported in supplementary table 1 (S-Table 1). ICD-7 and ICD-8 codes were used in Sweden, whereas ICD-9 and ICD-10 codes were used in the United Kingdom.

The observed numbers of cases for each cancer site were compared with the expected numbers calculated on the basis of national gender-, age- and period-specific incidence rates. Five-year age groups were used for age and time period. Reference rates were obtained from the CI5+ Database (Revision of February 2014). In Sweden, national reference rates were obtained. In the UK, reference rates were obtained separately for Scotland and England/Wales. Rates of Scotland and England/Wales were pooled as all UK factories were located in these three areas of United Kingdom. Patients were followed from one year after date of hire until the earliest of the following: date of death, date of loss to follow-up/emigration or right censored at 31st of December 2011. For each country, standardized incidence ratios (SIRs, i.e., the ratio of observed to expected cases) were calculated together with their confidence intervals based on the Poisson distribution of observed cases ^{7 8}. Country-specific SIRs were combined using random-effects models ⁹, which take into account potential heterogeneity among cohorts.

Measures of heterogeneity were reported using I^2 statistics¹⁰ as well as tests for heterogeneity based on Cochran's Q statistic although this test is known for having poor statistical power¹¹. In a sensitivity analysis, an induction-latency period of ten years was applied.

The role of the duration of employment on the risk of all cancers combined was investigated in a Poisson model with a smooth function of duration of employment as an explanatory variable, and the logarithm of the expected number of cancers as 'offset'. Duration of employment was modelled with cubic natural splines and three degrees of freedom. Cutpoints (*knots*) of duration of employment were built from duration of employment of subjects diagnosed with cancer, such that at least eight cases occurred between two points. This enables a stable estimation of SIR while keeping enough points for modelling the splines for the parameter of duration. Because duration could not be estimated for several workers still employed at the last job history update, this analysis was restricted to the subset of 8,100 workers (51% of the cohort) with complete job history.

All data were anonymised prior to statistical analysis. This study did not require a specific IRB approval as performed on fully anonymised secondary data. P-values below 5% were considered as statistically significant.

Results

A total of 16,026 workers (12,441 men and 3,585 women) were included in the present study (Table 1). The median follow-up was 23 years, contributing to a total of 397,975 person-years of observation. The majority of workers (77.6%) were men; more women were recruited in Sweden. Overall, 846 malignant cancer cases (excluding non melanoma skin cancers) were observed during the follow-up, 437 in United Kingdom and 409 in Sweden.

Table 2 shows observed cases and SIRs for different cancer sites for Sweden, the United Kingdom and both countries combined. Based on 45 cases observed during the follow-up, the risk of bladder cancer was SIR=0.88 (95% CI (0.61; 1.28)) with no evidence of heterogeneity between countries. This absence of increased risk for bladder cancer remained when stratified by gender (S-Table 2 and S-Table 3), although the analysis restricted to women is based on less than ten cases from most outcomes. The risk of lung cancer was based on 82 cases and was significantly decreased in rubber workers as compared to the general population with a SIR of 0.74 (95% CI (0.59; 0.93)) with no heterogeneity between countries.

Concerning secondary outcomes, a statistically significant decrease was observed for all cancer combined (SIR= 0.83, 95% CI (0.74; 0.92)) and for non-Hodgkin's lymphoma (SIR = 0.67, 95% CI (0.45; 1.00)). Risks of other secondary outcomes were neither significantly increased nor

significantly decreased. At country level, the risk of all cancer combined was significantly decreased in both Sweden and the United Kingdom. In addition the risk of leukaemia was significantly decreased in Sweden.

Analysis of exploratory outcomes revealed no significantly increased risk for any cancer site when both countries were combined. A significantly decreased risk of prostate cancer was found: SIR = 0.77 (95% CI (0.64; 0.92)) based on 123 cases.

Results for cancers appearing after an induction-latency period of ten years are shown in S-table 4. This analysis covered 15,466 subjects (7,131 in Sweden and 8,335 in the UK) representing overall 240,561 person-years of observation. Results remained close to those of the main analysis.

Results of analyses stratified by gender are given in S-table 2 (men) and S-table 3 (women). In men, there were significantly reduced SIRs for lung cancer and prostate cancer. In women, there was a significantly reduced SIR for all cancers combined, and SIRs below unity for most cancers. The only significantly increased SIR was for melanoma, SIR 1.65 (95% CI (1.04; 2.60)). It was based on 21 cases, of which 20 occurred in Sweden (table S-3). This association was not found in men, neither in UK nor in Sweden; the SIR was 0.74 (95% CI (0.44; 1.24)) and was based on 30 cases (19 in Sweden and 11 in the United Kingdom).

The risk of all cancers combined (except non-melanoma skin cancer) was further investigated in a Poisson regression with a spline function applied to the duration of employment (Figure 1). This analysis was restricted to the 8,100 workers (4,005 in the UK and 4,095 in Sweden) with complete information on job history, i.e. representing 51% of the cohort. When compared to the rest of the cohort, these workers only slightly differed with more men (81.2% vs 73.5% for complete vs incomplete job history) and older on average (mean age at recruitment 29.7 vs 26.0 for complete vs incomplete job history). For employment durations under 20 years the risk of cancer remained close to 0.8, and then the trend went up until about 1.

Discussion

In this cohort of workers employed for at least one year in the rubber manufacturing industry first employed since 1975 in two European countries, there was no consistent indication of an increased risk of cancer incidence among the cancer sites pre-identified as primary or secondary outcomes of interest, i.e. all cancers combined, and site-specific incidence for bladder, lung, stomach, leukaemia, myeloma and non-Hodgkin's lymphoma. In addition, none of the exploratory outcomes had their risk significantly increased when both genders were combined. From the Poisson regression, the risk of all cancers combined remained relatively stable with duration of employment

with a slight increase after 20 years; confident interpretation of these regression findings is not possible.

A statistically significant increased risk of melanoma was identified, but it was limited to Swedish women. With such an increased only observed in one country and one gender, and because rubber manufacture is not an outdoor employment, a difference in job exposure is unlikely to offer a good explanation for the increase. Non-melanoma skin cancer incidence is a tentative marker of solar exposure, but is markedly affected by access to screening and by registration bias. Hence, there is no solid data to help interpret the increase in melanoma incidence in Swedish women by either a role of non-occupational or occupational solar exposure, an overdiagnosis in women within the health care system in the rubber factory areas, or a chance finding.

Analysis of cancer mortality data in five European countries also did not report an increased risk of cancer⁴. Results on incidence for Sweden and United Kingdom were in the same order of magnitude as results based on mortality for all sites except multiple myeloma in United Kingdom. The SMR for multiple myeloma deaths in the UK cohort was 2.26 (95% CI (0.97; 4.44)) for both genders, whereas in the present report on incidence the corresponding SIR was 1.04 (95% CI (0.45; 2.05)). In addition, the observed increased risk in the mortality study was observed only in men in the general rubber goods sector, which represents only 36% of workers in the UK cohort. This suggests that the initially observed high multiple myeloma mortality observed in United Kingdom could be a chance finding, but specific exposure –related explanations cannot be fully excluded. Risk of stomach cancer mortality was high in Poland in the mortality study. Similarly to previously reported mortality findings, in United Kingdom and Sweden the incidence of stomach cancer remained not increased.

The absence of increased risk of cancer in the present study, in contrast to findings in the “old” rubber industry, could be the result of changes in the rubber manufacturing industry. Data collected within the European project ExAsRub (improved EXposure ASsessment for prospective cohort studies and exposure control in the RUBber manufacturing industry), which combined comparable exposure information in rubber industry across Europe in a database, are in line with this hypothesis by showing a continuous decreasing time trends of inhalable dust from 1975 to 2005³.

The study has a number of limitations. First, there was a lack of accurate data on duration of employment in the rubber industry, due to no recent update of job histories which limited the analysis of long-term exposures. Secondly, the cohort of workers employed since 1975 in these two

countries is young with an average age at the end of follow-up of 50 years, hence the magnitude of impact of cancer in these populations could only be partially evaluated and longer follow-up would be needed to evaluate the potential impact of these occupational exposures on entire life. Thirdly, as for most studies which evaluated the impact of occupational exposure in the rubber manufacturing industry and risk of cancer ¹, no behavior data were available and it was therefore not possible to adjust for tobacco smoking and other potential confounders.

The findings of no observed increased risk of cancer **in these cohorts** from the rubber manufacturing industry are reassuring. However, it is recommended that these cohorts continue to be monitored regularly to investigate if absence of increased cancer risk is present after longer follow-up, and long-term positive effects of industrial hygiene improvements are maintained. Confirmatory findings from other cohorts would also be important.

Contributorship

The study Working Group comprised iPRI staff (M. Boniol, A. Koechlin and P. Boyle) and national Principal Investigators, T. Sorahan (United Kingdom) and K. Jakobsson (Sweden). M. Boniol, P Boyle and T. Sorahan were involved in the planning of the study. T. Sorahan supervised data gathering for UK cohort. K. Jakobsson supervised data gathering for Swedish. M. Boniol and A. Koechlin conducted data analysis. M. Boniol prepared the first draft of manuscript. All authors contributed during the revision phase of the manuscript. All authors approved the final version submitted.

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Competing interests

The authors have declared no conflicts of interest.

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

	Sweden	UK
Number of workers	7424	8602
Number of factories	11	41
Follow-up (Median, years)	21.7	24.1
Number of deaths	376	546
Number of cancer cases	409	437
Gender (% men)	66.3%	87.4%
Type of industry (%Tyre/%GRG/%Other*)	5.5/32.2/62.4	51.0/36.2/12.8
Age at hiring (Median, IQR)	25 (20; 35)	25 (21; 33)
Duration of employment (Median, IQR)	4.6 (2.2; 10.3**)	4.9 (2.6; 12.7)
Date of first recruitment	01/01/1975	01/01/1982
Date of last follow-up	31/12/2011	31/12/2011
Date of last job history update	01/07/2002	- 31/12/2011 (4005 subjects/47%) - Variable between 1988 and 1995 (4597 subjects/53%) - Last job history update 2011: 14.5% among 4005 subjects
% Still employed at last job history update	44.8%	
Person-years by induction-latency: <20 vs. ≥ 20 years	133,629 vs. 41,138	166,688 vs. 56,520
Person-years by duration of employment: < 5 vs. ≥ 5 years	102,837 vs. 71,930	131,592 vs. 91,616

GRG: factories producing general rubber goods; Tyre: factories producing tyres; IQR: inter-quartile range; UK: United Kingdom

*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 cases and standardised incidence ratios (SIRs) among 16,026 workers first employed in the European rubber manufacturing industry since 1975, by country.

Cancer sites	Sweden (N=7,424; PY=174,767)		United Kingdom (N=8,602; PY=223,208)		Combined (N=16,026; PY=397,975)	
	Observed	SIR (95% CI)	Observed	SIR (95% CI)	Observed	SIR (95% CI)
Primary outcomes						
Bladder	23	1.15 (0.73, 1.72)	22	0.68 (0.42, 1.02)	45	0.88 (0.61, 1.28)
Lung	30	0.78 (0.63, 1.34)	52	0.72 (0.53, 0.94)	82	0.74 (0.59, 0.93)
Secondary outcomes						
All cancers combined (except skin)	409	0.90 (0.81, 0.99)	437	0.76 (0.69, 0.85)	846	0.83 (0.74, 0.92)*
Stomach	8	0.87 (0.37, 1.71)	16	0.97 (0.55, 1.57)	24	0.93 (0.61, 1.43)
Leukaemia	4	0.34 (0.09, 0.88)	15	0.96 (0.54, 1.58)	19	0.79 (0.48, 1.28)
Non-Hodgkin's lymphoma	10	0.64 (0.31, 1.18)	18	0.69 (0.41, 1.08)	28	0.67 (0.45, 1.00)
Multiple myeloma	1	0.19 (<0.01, 1.04)	8	1.04 (0.45, 2.05)	9	0.92 (0.44, 1.91)
Exploratory outcomes**						
Brain and central nervous system	15	0.90 (0.50, 1.49)	10	0.65 (0.31, 1.20)	25	0.79 (0.52, 1.21)
Colon, rectum and anus	48	1.06 (0.78, 1.41)	37	0.55 (0.39, 0.75)	85	0.77 (0.49, 1.22)*
Kidney	11	0.87 (0.43, 1.55)	16	0.85 (0.49, 1.39)	27	0.86 (0.57, 1.29)
Larynx	3	-	7	0.91 (0.37, 1.87)	10	0.98 (0.49, 1.96)
Melanoma	39	1.30 (0.92, 1.78)	12	0.43 (0.22, 0.75)	51	0.79 (0.37, 1.70)*
Oesophagus	4	-	14	0.82 (0.45, 1.37)	18	0.84 (0.51, 1.39)
Oral cavity and pharynx	13	1.18 (0.63, 2.02)	19	0.93 (0.56, 1.44)	32	1.02 (0.71, 1.48)
Pancreas	8	0.88 (0.38, 1.74)	9	0.72 (0.33, 1.37)	17	0.80 (0.47, 1.34)
Prostate	70	0.80 (0.63, 1.02)	53	0.72 (0.54, 0.94)	123	0.77 (0.64, 0.92)
Testis	13	1.26 (0.67, 2.16)	11	0.61 (0.32, 1.04)	26	0.87 (0.53, 1.45)
Breast	51	0.82 (0.60, 1.08)	38	1.04 (0.67, 1.29)	89	0.91 (0.73, 1.13)
Endometrial	6	0.69 (0.25, 1.50)	5	1.00 (0.32, 2.33)	11	0.82 (0.42, 1.58)
Ovary	9	1.14 (0.52, 2.16)	7	1.23 (0.50, 2.54)	16	1.18 (0.69, 2.02)

Statistically significant associations are in bold

N: number of workers; PY: Person-years; SIR: Standardized Incidence Ratio; 95%CI: 95 % confidence interval

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

** Results of exploratory analyses with less than 5 cases observed were not reported

Legend of Figure

Figure 1. Analysis of risk of cancer from two cohorts of European rubber-manufacturing workers by duration of employment among 8,100 workers with complete follow-up information. The horizontal dotted line corresponds to the global SIR for all cancers except skin. The plain black lines represent the spline curve of SIR by duration of employment (bold line) with its 95% confidence interval (plain lines).