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Occupational risk factors for mortality from stomach and lung cancer among rubber workers: an analysis using internal controls and refined exposure assessment

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Objectives To determine occupational risk factors for stomach and lung cancer among workers in the German rubber industry.

Methods A cohort of all male German rubber workers (n = 11 633) who had been employed for at least one year in one of five study plants and who were alive and actively employed or retired on 1 January 1981 was followed for mortality from 1 January 1981 through December 1991. A subcohort of n = 8933 workers who were hired after 1 January 1950 was defined to focus on working conditions in the more recent rubber industry. Work histories were reconstructed using routinely documented 'cost centre codes' and classified into six work areas as well as subgroups of some work areas. The work areas are: 1. preparation of materials, 2. production of technical rubber goods, 3. production of tyres, 4. storage and dispatch, 5. maintenance, 6. others. Standardized mortality ratios (SMR) and Cox proportional hazards models were calculated for each of the work areas (>1 year of employment in the respective work area). Hazard rate ratios were adjusted for age (time marker) and stratified for year of hire (1950–1959, ⩾1960) and years of employment in the respective work area (1–9 years, ⩾10 years); years of employment were lagged 10 years to account for latency.

Results Compared to the national reference population mortality from cancer of stomach (observed 44, SMR = 117; 95% CI : 85–157) and lung (observed 154, SMR = 123; 95% CI : 104–144) was slightly increased. Using internal controls we observed excess deaths from stomach cancer in work area 1 (relative risk [RR] = 2.3; 95% CI : 1.2–4.2) and from lung cancer in work areas 1 (RR = 1.7; 95% CI : 1.2–2.3), 2 (RR = 1.5; 95% CI : 1.1–2.1), and 3 (RR = 1.3; 95% CI : 0.9–1.8). On the basis of cumulative years of employment an exposure response relationship was observed for mortality from both cancer sites among a subcategory of work area I: weighing and mixing. Increased risks were also seen for lung cancer among workers employed in production of technical rubber goods.

Conclusion Our results support an association between an excess mortality from stomach and lung cancer and employment in early production stages of rubber manufacturing, especially weighing and mixing. This may point to an aetiologic role of asbestos or carbon black. For stomach cancer additional risk factors, e.g. exposure to dust and talc, deserve further investigation. The results of the present study do not support a causal role of nitrosamines for stomach or lung cancer.

Keywords Rubber industry, stomach cancer, lung cancer, exposure assessment, standardized mortality ratios, hazard rate ratios

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Epidemiological studies among workers employed in the rubber industry have indicated an excess occurrence of cancer in a variety of sites. In 1982 a working group of the International

Agency for Research on Cancer[1] reviewed the evidence for carcinogenic risks in the rubber industry and concluded that there was sufficient evidence for excess occurrence of cancers of the stomach, lung and bladder as well as leukaemia.[1] The evidence for an association of occupational exposures or specific work areas with excess occurrence of stomach and lung cancer, however, remained limited.

Higher than expected mortality rates from cancer of these sites have been found in a historical cohort of German rubber workers.[2–4] Although the standardized mortality ratios (SMR) for stomach and lung cancer were only moderately increased in our study many of the excess cancer deaths were attributable to these two cancer sites.

Most of these cohort studies, including our previous reports, compared the mortality of the cohort with national or regional reference populations to calculate SMR. These are the effect estimate of choice of the majority of reported occupational cohort studies.[5] However, besides potential estimation errors due to the 'healthy worker effect', the SMR may be biased if social status and personal risk factors of the cohort differed from the external reference population.

Furthermore, the comparison of SMR between different exposure categories may be invalid, if age is an effect modifier and age distribution varies between the categories.[6,7] Therefore, evaluation of an exposure response relationship, which is often used as an argument to support causality,[8] may be misleading, if interpreted on the basis of two SMR. The use of an internal control group and the calculation of hazard rate ratios (HRR) allows a valid assessment of exposure response relationships and may reduce potential biases due to unmeasured confounders. This paper reports analyses of stomach and lung cancer mortalities among a cohort of German rubber workers using internal controls and a refined exposure assessment.

Methods

Cohort definition and follow-up

The cohort definition and follow-up, including the assessment of vital status and cause of death, have previously been described in detail[2] and are only briefly summarized here. The original cohort included all male German blue-collar workers of five study plants who were alive and actively employed or retired on 1 January 1981 (n = 11 633; 2719 deaths). To focus on potential risks of working conditions in the more recent rubber industry and to reduce the potential for a healthy worker survivor effect, this cohort was then restricted to all workers hired after 1 January 1950 (n = 8933; 1521 deaths).

Follow-up of individual cohort members started on 1 January 1981 but not before completion of one year of employment, and ended at the age of 85 years, at death, date of loss to follow-up or the end of the follow-up period, 31 December 1991. Health insurance data and personnel files of the participating plants as well as German population registries were used to determine the vital status at the end of the observation period. For all cohort members reported to have died, death certificates were requested from the respective community health departments. Death certificates were coded by professional nosologists from the State Institute of Statistics of North-Rhine-Westphalia according to the 9th revision of the International Classification of Diseases, Injuries and Deaths.[9] Assessment of vital status and cause of death was successful for 99.7% of the cohort members and 96.8% of the deceased.

Exposure classification

Complete individual work histories within the rubber companies were reconstructed using routinely documented and archived cost centre codes ('Kostenstellen'). These were originally generated for accounting purposes, but allow identification of employment in specific working areas and the respective time periods. For active employees information on cost centre codes was obtained from employer personnel files. For retirees and employees with missing information in these electronic files, individual work histories were abstracted from paper records. For a small proportion of individuals with missing information on the exact time of change between work areas, the midpoint between start of work in the previous and end of work in the latter work area was used.

All cost centre codes were classified into six work areas according to type and stage of the manufacturing process to allow for analyses of the entire cohort across the five study plants: 1. preparation of materials, 2. production of technical rubber goods, 3. production of tyres, 4. storage and dispatch, 5. maintenance, 6. others. In addition, we present results for subgroups of work areas 1 and 3: 1a. weighing and mixing (i.e. mainly exposure to dusts) and 1b. milling and calendering (i.e. mainly exposure to low temperature fumes); 3a. vulcanization of tyres and 3b. manufacturing of tubes. For production of technical rubber goods no further consistent subgrouping across factories is suitable. This categorization of work areas is also comparable with previously published studies, including those that were restricted to either the tyre or the technical rubber goods sector.

Data analysis

The mortality experience of the cohort was compared with the mortality of the general population using mortality ratios standardized on calendar year and 5-year age group. The male population of German nationality of former West Germany was used as the reference.[2] Time dependent Cox proportional hazards models were calculated for $\geqslant$1 year of employment in a specific work area compared to all other workers as the reference population.[10] Age-adjusted (time marker) HRR were calculated for categories of year of hire (1950–1959, $\geqslant$1960), and current (time dependent) years of employment in the respective work area (1–9 years, $\geqslant$10 years). Years of employment in work areas were lagged for 10 years based on empirical knowledge of minimal latency periods. SAS PROC PHREG 6.12 was used for the proportional hazards models.

Results

Compared to the national reference population mortality from stomach (44 deaths, SMR 117; 95% CI : 85–157) and lung cancer (154 deaths, SMR 123; 95% CI : 104–144) was slightly increased among this cohort (Table 1). Stratified analyses by date of hire and years of employment show no higher SMR among those hired earlier, i.e. between 1950–1959, or among those with longer cumulative employment. Table 2 shows the number of workers, person-years of follow-up and means of date of hire, and years of employment by years of employment in work area.

Table 1 Person-years of follow-up, deaths from all causes, cancer of stomach (ICD-9 151) and lung (ICD-9 162) and standardized mortality ratios (SMR) with 95% confidence intervals (CI), overall, by years of employment, and by date of hire in the rubber industry

		All cause mortality			Stomach cancer			Lung cancer		
	Person-years	Deaths	SMR	95% CI	Deaths	SMR	95% CI	Deaths	SMR	95% CI
Years of employment										
1–9 years	10 691	171	121.5	104.0–141.2	4	117.3	31.9–300.2	16	185.2	105.8–300.7
⩾10 years	78 914	1349	101.4	96.0–106.9	40	116.5	83.3–158.7	138	118.4	99.5–139.9
Date of hire										
1950–1959	43 669	943	100.4	94.1–107.0	25	101.8	65.9–150.3	94	115.9	93.7–141.9
⩾1960	45 953	577	108.3	99.7–117.6	19	144.2	86.8–225.1	60	136.1	103.8–175.1
Overall	89 622	1520	103.3	98.2–108.6	44	116.6	84.7–156.5	154	123.0	104.3–144.0

Table 2 Number of workers, person-years of follow-up, and means of date of hire, and years of employment, by years of employment in work area

Work area	No. of workers[a]	Person-years[b]	Mean date of hire[c]	Mean years of employment
1. Preparation of materials				
<1 Year	7069	71 448	1962.1	23.6
⩾1 Year	1864	18 174	1960.2	24.4
2. Technical rubber goods				
<1 Year	5534	55 283	1962.6	22.8
⩾1 Year	3399	34 339	1960.3	25.4
3. Production of tyres				
<1 Year	6683	66 745	1962.4	22.9
⩾1 Year	2250	22 877	1959.8	26.4
4. Storage and dispatch				
<1 Year	8338	83 871	1961.9	23.7
⩾1 Year	595	5751	1959.1	24.3
5. Maintenance				
<1 Year	6724	67 283	1961.9	23.4
⩾1 Year	2209	22 339	1961.1	25.0
6. Others				
<1 Year	8014	81 102	1962.0	23.9
⩾1 Year	919	8520	1959.3	23.1
Total cohort	8933	89 622	1961.7	23.8

[a] Classification for time in work area as of date of end of follow-up.

[b] Each worker-day classified by cumulative work experience prior to that day.

[c] Refers to original hiring into the factory, not into work area.

Stomach cancer

The only statistically significant risk increase for mortality from stomach cancer was observed in work area 1, preparation of materials (Table 3). Each HRR suggested a similar strength of association between exposure in work area and mortality as the corresponding SMR. Among workers employed in work area 1 the risk increased with longer cumulative employment in that work area (Table 4). A more detailed analysis of risks by subcategories of work area 1 (Table 4) shows the highest HRR for stomach cancer among workers with more than 10 years of employment in weighing and mixing (10 deaths, HRR 4.0, 95% CI : 1.9–8.3). In weighing and mixing a statistically significant HRR was also observed among workers hired before 1960 (7 deaths, HRR 2.5, 95% CI : 1.1–5.8).

Lung cancer

Statistically significant SMR and HRR for lung cancer were observed among workers employed in work areas 1 and 2 and a non-significantly increased risk was observed in work area 3 (Table 3). There was no substantial difference between risks calculated on the basis of national (SMR) and internal (HRR) reference populations. In work area 1 HRR by years of employment were consistent with an exposure response relationship (Table 5). Results for subcategories of work area 1 show statistically significantly increased risks for all strata in weighing and mixing and for workers with more than 10 years of employment in milling and calendering. The risk in work area 2, production of technical rubber goods, was borderline significant in both categories of years of employment. In work area 3, production

Table 3 Deaths from cancer of stomach (ICD-9 151) and lung (ICD-9 162), standardized mortality ratios (SMR) and hazard rate ratios (HRR) with 95% confidence intervals (CI) by years of employment in work area (lagged 10 years)

	Stomach cancer					Lung cancer[a]				
Work area	Deaths	SMR	95% CI	HRR	95% CI	Deaths	SMR	95% CI	HRR	95% CI
1. Preparation of materials										
<1 Year	27	94	62–137	1.0	–	105	110	90–133	1.0	–
⩾1 Year	17	194	113–311	2.3	1.2–4.2	48	166	122–220	1.7	1.2–2.3
2. Technical rubber goods										
<1 Year	31	128	87–182	1.0	–	90	115	92–141	1.0	–
⩾1 Year	13	98	52–167	0.9	0.5–1.8	63	138	106–176	1.5	1.1–2.1
3. Production of tyres										
<1 Year	35	121	84–168	1.0	–	116	123	102–148	1.0	–
⩾1 Year	9	106	48–200	1.0	0.5–2.2	37	122	86–168	1.3	0.9–1.8
4. Storage and dispatch										
<1 Year	43	125	91–169	1.0	–	141	124	104–146	1.0	–
⩾1 Year	1	32	–	0.3	0.0–2.0	12	118	61–206	1.0	0.6–1.8
5. Maintenance										
<1 Year	36	124	87–172	1.0	–	121	126	105–151	1.0	–
⩾1 Year	8	93	40–184	0.9	0.4–1.9	32	112	77–158	1.0	0.7–1.5
6. Others										
<1 Year	40	124	89–169	1.0	–	138	127	107–150	1.0	–
⩾1 Year	4	76	20–193	0.6	0.2–1.7	15	96	54–158	0.7	0.4–1.2

[a] Results are based on n = 153 cases, for one case occupational history within the rubber industry is not available.

Table 4 Deaths from stomach cancer, hazard rate ratios (HRR) and 95% confidence intervals (CI), by years of employment (lagged 10 years) and by date of hire in work area 1

		Years of employment		Date of hire	
Work area	**Internal reference group**	1–9	⩾10	1950–1959	⩾1960
1. Preparation of materials					
Deaths	27	4	13	9	8
HRR	1.0	1.2	3.2	2.0	2.8
95% CI	–	0.4–3.5	1.6–6.2	0.9–4.2	1.3–6.2
1a. Weighing and mixing					
Deaths	27	1	10	7	4
HRR	1.0	0.5	4.0	2.5	2.4
95% CI	–	0.1–3.8	1.9–8.3	1.1–5.8	0.8–6.8
1b. Milling and calendering					
Deaths	27	3	2	2	3
HRR	1.0	2.2	1.7	1.5	2.5
95% CI	–	0.7–7.2	0.4–7.1	0.4–6.3	0.8–8.1

of tyres, we observed a slight inverse trend with years of employment. In tyre vulcanization and manufacturing of tubes the only increased mortality from lung cancer was seen among vulcanization workers with short employment in work area. In general, the risks seem to be higher among workers hired after 1960.

Discussion

The focus on stomach and lung cancer allows, due to the larger number of observed deaths, meaningful analyses using refined exposure categories corresponding to the nine categories used in the IARC monograph.[1] In particular, it allows a further discrimination of work areas where increased SMR for stomach and lung cancer were observed previously among this cohort.[3,4] Work area 1, 'Preparation of materials', was divided into 1a. 'weighing and mixing', where heaviest exposure to dusts including carbon black, talc and asbestos occurred, and 1b. 'milling and calendering' with exposure to rubber fumes but only limited formation of nitrosamines.[1] Both subcategories of work area 3, 'vulcanization of tyres' and manufacturing of 'tubes', entail exposure to hot rubber fumes and high exposure to nitrosamines, while only the manufacturing of tubes additionally involves a substantial exposure to detackifiers.

Table 5 Deaths from lung cancer, hazard rate ratios (HRR) and 95% confidence intervals (CI), by years of employment (lagged 10 years) and by date of hire in work areas 1, 2 and 3

		Years of employment		Date of hire	
Work area	**Internal reference group**	1–9	⩾10	1950–1959	⩾1960
1. Preparation of materials					
Deaths	105	20	28	25	23
HRR	1.0	1.5	1.8	1.4	2.1
95% CI	–	0.9–2.5	1.2–2.7	0.9–2.2	1.3–3.2
1a. Weighing and mixing					
Deaths	105	15	19	18	16
HRR	1.0	1.8	1.9	1.7	2.4
95% CI	–	1.0–3.1	1.2–3.1	1.0–2.7	1.4–4.0
1b. Milling and calendering					
Deaths	105	3	9	7	5
HRR	1.0	0.5	1.9	1.3	1.0
95% CI	–	0.2–1.7	1.0–3.7	0.6–2.8	0.4–2.5
2. Technical rubber goods					
Deaths	105	29	34	33	30
HRR	1.0	1.5	1.5	1.2	2.0
95% CI	–	1.0–2.3	1.0–2.2	0.8–1.8	1.3–3.0
3. Production of tyres					
Deaths	116	15	22	22	15
HRR	1.0	1.4	1.2	1.1	1.6
95% CI	–	0.8–2.4	0.7–1.9	0.7–1.8	0.9–2.7
3a. Vulcanization					
Deaths	116	8	7	8	7
HRR	1.0	1.3	1.0	0.9	1.4
95% CI	–	0.6–2.6	0.5–2.1	0.5–1.9	0.7–3.1
3b. Tubes					
Deaths	116	2	1	2	1
HRR	1.0	0.9	0.7	0.8	0.9
95% CI	–	0.2–3.7	0.1–5.3	0.2–3.3	0.1–6.6

A consistent subcategorization of the production stages of 'technical rubber goods' across plants is not possible, because work processes are structured according to a very large variety of manufactured goods, and usually no distinction between component building and vulcanization is feasible.

Due to the use of an internal reference population it is unlikely that a lower socioeconomic status of rubber workers or the anecdotally noted high prevalence of smoking among rubber workers resulted in a serious overestimation of effect estimates in our study. Most of the observed HRR on the basis of internal controls were similar to the SMR and this finding indicates that no major confounding by use of an external reference population occurred in this study. The restriction of the cohort to workers who were first hired after 1950 results in a more homogenous cohort and reduces the potential for a healthy worker survivor effect. In addition to our study there is only one other study among rubber workers[11] since the last IARC evaluation which presented results using internal controls, a similarly fine categorization of work areas and exposure response assessments, while no results on the basis of agent-specific exposure assessments were published.

Two recent reviews of occupational risk factors for gastric cancer and cancer risks among rubber workers came to different conclusions. One concluded that there was little evidence of an excess risk of stomach cancer among rubber workers[12] while the other suggested that exposure to nitrosamines may be responsible for excess gastric cancer risk among rubber workers.[13] Our results support an association between employment in 'preparation of materials' and an increased mortality from stomach cancer among rubber workers. The relationship between cumulative time of employment and mortality from stomach cancer was most pronounced in 'weighing and mixing.' These results are consistent with the IARC evaluation in 1982[1] and the recent literature[11,14–27] that indicates no substantially increased risk of stomach cancer among rubber workers in general, but shows consistently an increased risk in early production stages, especially in weighing and mixing.[11,26,27] This includes the only other study that presented analyses using internal controls.[11] This study also found a positive trend for duration of employment in work areas with dust exposure and mortality from stomach cancer. One study investigated the role of polycyclic aromatic amines,

nitrosamines, carbon black and detackifiers.[28] Detackifiers were associated with stomach cancer mortality, and it was speculated that contamination of detackifiers by asbestos may be the underlying cause. No increased risk of stomach cancer was found in any of the other work areas,[14–17,27] especially not among vulcanization workers with presumably high exposure to nitrosamines.[14,16,27]

For lung cancer mortality our results suggest an association with employment in work area 1, especially in 'weighing and mixing'. To a lesser degree our data also indicate an association between employment in production of technical rubber goods and mortality from lung cancer. The observed pattern of risks does not support a causal association with employment in 'production of tyres'.

Four previous studies that reported results for weighers and mixers observed an association between employment in weighing and mixing and mortality from lung cancer,[21,22,26,27] while no positive associations between 'compounding and mixing' and lung cancer were found in two other studies.[11,28] However, the mean duration of employment in these jobs in one of these studies was only 0.7 years.[11]

A small cohort study[27] and a nested case control study in the American rubber industry found no association of lung cancer with employment in vulcanization or curing,[28] while five other studies reported an increased risk of lung cancer in these work areas.[11,14,16,21,22] Studies which presented data by product group suggest an increased risk of lung cancer among vulcanization workers in the tyre industry[16,22,27] and specifically in the 'inner tyre' department.[22,27] Results for the industrial product or footwear sector are inconsistent.[11,15,19] Our results, however, only point to an increased lung cancer mortality in the industrial product sector and do not support an association with employment in 'tubes' or 'vulcanization' in the tyre sector.

Potential confounding by smoking was assessed only in one small subcohort of workers in 'curing and inner tyre' (seven cases)[22] and for three rarely used occupational title groups.[28] Based on a comparison of crude and adjusted point estimates there was no indication of confounding by differential smoking habits in these studies.

Conclusions

The IARC working group in 1982 concluded that there was limited evidence for a causal association of an excess occurrence of stomach cancer with employment in compounding, mixing and milling.[1] Our study results and the literature published since this evaluation support an association between employment in weighing and mixing and an increased risk of stomach cancer. This may point to an aetiologic role of dust, possibly talc, asbestos or carbon black. A causal role of nitrosamines is not corroborated.

With regard to lung cancer our results and the literature support an association with exposures in early production stages of rubber manufacturing and possibly in vulcanization. On the basis of knowledge on exposure distributions by work areas it may be speculated that asbestos, asbestos contaminated talc and carbon black may be risk factors for the excess lung cancer mortality among rubber workers. The role of nitrosamines, where highest exposure probably occurred among vulcanization workers, remains equivocal. Future studies need to incorporate exposure information for specific carcinogens.

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