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MORTALITY FROM CANCER AND OTHER CAUSES IN AN ITALIAN COHORT OF MALE RUBBER TIRE WORKERS

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Objective: To investigate mortality among workers of an Italian rubber tire factory employed between 1954 and 2008.
Methods: This cohort study included 6246 men, totaling 190,512 man-years of observation. Employment data were obtained from personnel records, whereas vital status and causes of death were ascertained from local authorities. We computed standardized mortality ratios (SMRs) using national and regional death certification rates.
Results: Mortality was significantly lower than expected for all cancers (SMR = 79) and all causes (SMR = 85). The SMRs were 99 for cancer of stomach, 78 for lung, 121 for urinary bladder, 116 for lymphoma, and 89 for leukemia, none being significant. Decreased mortality emerged for cancers of the oral cavity and pharynx (SMR = 45), esophagus (SMR = 29), colorectum (SMR = 71), liver (SMR = 57), and kidney (SMR = 33).
Conclusions: This study shows no excess cancer risk among male rubber tire workers employed after 1954.

Studies of workers of the rubber industry before the 1950s showed excess risk of bladder cancer.[1] This was related to exposures to ß-naphthylamine in the rubber industry up to the early 1950s.[2] A potential role of other aromatic amines, asbestos, benzene, and other solvents has also been suggested with reference to potential cancer risk in the rubber industry,[3–6] in particular for lung, stomach, and lymphoid neoplasms.[6–9]
Types and levels of exposure varied widely according to industry setting (eg, manufacture of tires, general rubber goods), rubber chemicals used, work process, tasks, and specific circumstances (e.g., methods of ventilation and production, control and safety measures).[10,11] Furthermore, exposures changed over time and differed across countries.[12]
A review of the epidemiological evidence to 1997 from the rubber industry concluded that bladder, laryngeal, lung cancers and leukemia were the cancers for which some apparent excess of risk was found, in the presence of substantial heterogeneity of results.[7] Nevertheless, a meta-analysis based on cohort studies published through 2003 showed no excess risk for any of the cancer sites.[13]
An International Agency for Research on Cancer Working Group recently reviewed the literature on several occupational exposures, including the rubber manufacturing industry, and cancer risk.[14] The working group concluded that there was sufficient evidence for an increased risk of cancers of the stomach, lung, urinary bladder, lymphoma, and leukemia among rubber manufacturing workers, whereas there was limited evidence for an increased risk of cancers of the esophagus, larynx, and prostate.
Recent studies based on workers who entered the rubber industry in Germany[15] and Britain[16] after 1980 showed no excess risk of total cancer mortality as well as of bladder, stomach, and lung cancer.
With the aim to provide further information on mortality from cancer and other causes in rubber workers employed over recent decades, we examined data from a cohort study of more than 6200 male employees of a rubber tire factory in the greater Turin area, northwestern Italy.

METHODS

The cohort included 6251 men who worked in the factory between March 1, 1954, when production started, and December 31, 2008. Workers employed for fewer than 180 days, as well as a few subjects with first employment dated before March 1, 1954 (ie, likely builders/set up workers), were excluded from the cohort. Five subjects (0.1%) lacked or had contradictory information about dates of birth, first employment, or death and were thus excluded from the analysis, leaving 6246 subjects who were followed-up from the date of first employment to December 31, 2008, or until reaching 85 years of age, if this occurred earlier. A total of 190,512 man-years of observation were covered. Overall, 4841 subjects (77.5%) were alive at the end of the follow-up period, 1131 (18.1%) died, and 274 (4.4%) emigrated or were lost to follow-up. The latter were included in the study, considering the date for which last information was available as the end of follow-up. Information about cause of death was available for 1068 out of 1131 deceased subjects (94.4%).

Employment data were obtained from personnel records at the factory, whereas vital status and causes of death were ascertained through population registers and death certificates from local authorities (ie, municipal registration offices and local health units). Information was available for date and place of birth, migration(s) and death, cause of death and contributory causes, and period(s) of employment.

We computed the expected number of deaths from several cancers and other major causes using Piedmont Region death rates[17] whenever available (ie, between 1981 and 2001), and national death rates before 1981, for each 5-year calendar period and age group. National death rates were taken from the Italian National Institute of Statistics[18] and the World Health Organization.[19] Piedmont death rates were not available after 2001. National death rates for 2004 and 2005 were still unavailable following the introduction of the ICD-10 (International Classification of Diseases, 10th Revision) coding system in 2003. Therefore, we used Piedmont death rates of 2000 to 2001 for the periods 2000 to 2004 and 2005 to 2008. We then calculated the standardized mortality ratios (SMRs) of selected cancers and other causes of death overall, as well as according to period at first employment and several time-dependent factors related to exposure. The Poisson distribution was used to test statistical significance.[20] The Poisson trend statistic was used to detect trends in the SMRs.

Most subjects (n = 5899, 94.4% of the cohort) had only one period of employment in the factory, and many of those that had more than one period had missing information for date of second or subsequent hiring. Therefore, we calculated duration of exposure for all subjects using only date of first hiring and last termination of employment. We conducted a sensitivity analysis on duration of exposure by excluding the 347 subjects with more than one period of employment.

RESULTS

Table 1 reports the observed and expected number of deaths from selected cancers and major non-neoplastic causes, and the corresponding SMRs and 95% confidence intervals (CIs), in the whole cohort of male workers from the tire factory. Mortality from several cancer sites was significantly lower than expected, including the oral cavity and pharynx (SMR = 45; based on 9 observed deaths), esophagus (SMR = 29; 4 deaths), colorectum (SMR = 71; 39 deaths), liver (SMR = 57; 17 deaths), lung (SMR = 78; 132 deaths), and kidney (SMR = 33; 4 deaths). A total of 413 cancer deaths were reported, as compared with 526 expected (SMR = 79). The SMRs for other cancer sites suspected to be increased after employment in the rubber industry were 99 for stomach, 49 for larynx, 118 for pleural, 94 for prostate, 121 for urinary bladder, 116 for lymphoma, and 89 for leukemia. All of the latter estimates were not significant. With reference to non-neoplastic causes, there were 104 deaths from ischemic heart diseases (vs 178 expected; SMR = 58), 69 from cerebrovascular diseases (vs 94 expected; SMR = 74), 22 from chronic obstructive pulmonary disease (vs 35 expected; SMR = 63), and 80 from accidents and violence (vs 126 expected; SMR = 64). All-cause mortality was significantly lower than expected (1131 observed vs 1338 expected deaths; SMR = 85).

Table 2 shows the number of deaths from selected cancers (possibly related according to the International Agency for Research on Cancer Monograph 10014 plus pleural cancer) and the corresponding SMRs and 95% CIs, according to various time-related characteristics of employment. No significant trend in risk was found with increasing duration of employment nor with time since first and last employment for any cancer considered. The SMRs were generally lower for men first employed before 25 years of age than for those employed at ages 25 to 34 and 35 years or older, but no clear pattern of risk emerged, except for lymphomas (SMRs = 19, 130, and 226, respectively; P value for trend = 0.004). No clear trend in risk emerged with period at first employment, but limited data was available for subjects first employed since 1975. In a sensitivity analysis, results of duration of exposure were materially unchanged after excluding subjects with more than one period of employment.

Table 3 gives the number of deaths from all cancers and all causes and the corresponding SMRs and 95% CIs, according to time-related characteristics of employment. Observed deaths were lower than expected in almost all subgroups examined. There was no clear trend in cancer mortality with duration of employment and time since first and last employment. Standardized mortality ratios for both all cancers and all causes were lowest for age at first employment less than 25 years (64 and 67, respectively) and highest for 35 years or older (86 and 102, respectively), with significant trends in risk ($P < 0.05$).

DISCUSSION

This cohort study of male workers of a rubber tire factory reported no significant excess mortality from any cancer site considered. We found decreased mortality from several cancers, including lung, as well as from all cancers combined. Total mortality and most non-neoplastic causes of death examined also showed lower risks in this cohort of workers compared with the background population.

The healthy worker effect could, partly or largely, explain the findings for cardiovascular deaths. This is supported by the reduced mortality for cardiovascular diseases, as well as the strong reduction in all-cause mortality in the strata of shorter time since first employment.[21,22] Other possible explanations include confounding from socioeconomic status and/or tobacco smoking. Of notice, decreased mortality was observed for major tobacco-related causes of death (ie, neoplasm of the lung and chronic obstructive pulmonary disease) but mostly for upper aerodigestive and respiratory tract cancers, related to both tobacco and alcohol.[23] This suggests different patterns of tobacco and alcohol consumption between subjects in the cohort and the reference population. With reference to confounding from socioeconomic status, internal migration from southern Italy to richer regions of northwestern Italy, including the Turin area, was common during the 1950s and 1960s, and, in fact, several workers in the cohort were born in southern Italy, and tobacco-related mortality was lower in the South in the 1970s and 1980s.[24] In any case, we calculated expected deaths using national death rates until 1979.

No trend in risk with increasing duration of employment was found for several neoplasms considered, including bladder. This provides convincing evidence of a lack of meaningful associations between occupational exposure and cancer mortality in this cohort. Also, no trend in risk of pleural cancer was found with latency period, that is, the main determinant for this neoplasm.[25,26]

Thus, our findings indicate a lack of excess cancer risk in this cohort. Results from epidemiological studies of the rubber industry were heterogeneous, with excess (bladder cancer) risk for exposures up to the mid 1950s.[2,7] This is likely explained by the fact that individual exposure levels to a variety of chemicals in the rubber industry varied widely over time, as well as within and between plants, being determined by personal tasks and other specific circumstances.[10] Furthermore, mutagenic activity of rubber dust and fumes was shown to vary even between companies with similar production processes because of differences in chemicals used and control measures.11

The absence of increased cancer risk in this cohort is consistent with multiple studies of recent entrants, that is, those exposed after control of β-naphthylamine exposure.[1,27,28] In particular, an Italian investigation found no significant excess risk of any cancer, except of pleura, in workers employed after 1940, reporting a similar number of observed and expected deaths from all cancers.[27] There was no excess cancer death in a cohort of recent entrant German rubber workers over the period 1981 to 2000.[15] Similarly, in a British study of rubber workers, bladder cancer risk was increased for workers exposed before 1950 (standardized registration rate = 171), whereas no association emerged in subjects exposed from 1950 on-ward (standardized registration rate = 102).1 A Polish cohort study of rubber tire workers reported significantly lower cancer mortality (SMR = 67 in men) and total mortality (SMR = 72 in men) compared with the background population.[28] A meta-analysis of cohort studies of tire workers gave an overall relative risk of 0.88 (95% CI, 0.75 to 1.04) for all cancers and of 0.97 (95% CI, 0.58 to 1.63) for bladder cancer.[13]

Still, information on subjects first employed since the 1970s or 1980s is scanty.[15,16] Our study, including 1676 subjects (27%) first employed from 1975 onward, provides some information about this issue. However, the follow-up period of these workers is still short and their age at end of follow-up, on average, still young. Thus, the number of expected deaths was relatively small. In any case, there was no evidence of increased cancer mortality (SMR = 82) or total mortality (SMR = 86) in the subgroup of recent entrants. An investigation of UK rubber workers first employed in the period 1982 to 1991 reported a significant increase in mortality from multiple myeloma in both men (5 deaths, SMR = 385) and women (2 deaths, SMR = 952).[16] All seven subjects who died from multiple myeloma were employed in the general rubber goods sector, whereas no deaths occurred among tire workers. In this study, we observed one death from multiple myeloma, compared with 0.2 expected, among subjects first employed from 1975 onward. Likewise, only one death from bladder cancer was observed among workers employed after 1975. That worker was first employed in this factory in 1983, at the age of 50 years, and died in 1998. A causal relation between his employment in this factory and his bladder cancer is thus unlikely.

Limitations of this study are the lack of information about specific job categories and exposure measurements. Information about cause of death was missing only for a small proportion (n = 63, 5.6%) of deceased subjects. The latter was mainly due to untraceable death certificates by competent authorities and a few deaths occurring outside Italy. Other strengths of this investigation, besides the large size of the cohort, are the low proportion of subjects lost to follow-up, limiting potential selection bias, and the long follow-up period, covering more than 50 years of observation.

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TABLE 1
Observed and Expected Deaths From Selected Causes, and Corresponding Standardized Mortality Ratios (SMR) and 95% Confidence Intervals (CI), in a Cohort of Male Employees of a Tire Factory, Italy, 1954–2008

Cause of Death	Observed Deaths	Expected Deaths	SMR (95% CI)
Neoplasms			
Oral cavity/pharynx	9	20.1	**45 (20–85)**
Esophagus	4	13.8	**29 (8–74)**
Stomach	34	34.3	99 (69–138)
Colorectum	39	54.6	**71 (51–98)**
Liver	17	29.9	**57 (33–91)**
Pancreas	22	22.0	100 (62–151)
Peritoneum	3	3.8	80 (16–233)
Larynx	7	14.2	49 (20–101)
Lung	132	170.4	**78 (65–92)**
Pleura	7	5.9	118 (47–244)
Pleura + peritoneum	10	9.7	103 (49–190)
Prostate	19	20.2	94 (57–147)
Bladder	22	18.1	121 (76–184)
Kidney	4	12.0	**33 (9–85)**
Brain	17	14.2	120 (70–192)
Lymphoma	19	16.4	116 (70–181)
Myeloma	6	6.2	97 (35–211)
Leukemia	13	14.5	89 (48–153)
All lymphatic and hematopoietic	38	37.1	102 (72–141)
All cancers	413	526.2	**79 (71–86)**
Major non-neoplastic causes			
Ischemic heart disease	104	178.1	**58 (48–71)**
Cerebrovascular disease	69	93.6	**74 (57–93)**
Chronic obstructive pulmonary disease	22	35.2	**63 (39–95)**
Hepatic cirrhosis	54	64.1	84 (63–110)
Accidents and violence	80	125.6	**64 (50–79)**
Other causes	326	—	—
Unknown	63	—	—
All causes	1131	1337.7	**85 (80–90)**

In bold, statistically significant results (95% CI).
Analyses are based on 6246 men, for a total of 190,512 man-years of observation. Deaths and man-years occurring at age ≥85 years are excluded.

TABLE 2
Observed Deaths (O) From Selected Cancers, and Corresponding Standardized Mortality Ratios (SMR) and 95% Confidence Intervals (CI), According to Various Characteristics of Exposure in a Cohort of Male Employees Of A Tire Factory , Italy, 1954–2008

	Stomach Cancer		Lung Cancer		Pleural Cancer		Bladder Cancer		Lymphoma		Leukemia	
Characteristic (yrs)	O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)
Duration of employment												
<10	14	89 (49–150)	56	78 (59–102)	2	81 (10–293)	6	81 (29–176)	8	101 (43–199)	6	87 (32–189)
10–19	9	108 (49–206)	32	85 (58–120)	3	243 (50–710)	8	183 (79–360)	4	116 (31–297)	4	124 (34–317)
≥20	11	107 (53–191)	**44**	**72 (52–97)**	2	90 (11–326)	8	127 (55–251)	7	140 (56–288)	3	69 (14–201)
P for trend		0.64		0.69		0.88		0.40		0.53		0.81
Age at first employment												
<25	6	81 (30–177)	**28**	**66 (44–95)**	0	0	2	59 (7–213)	1	19 (1–108)	5	120 (39–280)
25–34	15	97 (54–161)	69	82 (64–104)	5	176 (57–411)	12	138 (71–242)	10	130 (62–239)	3	44 (9–130)
≥35	13	113 (60–193)	35	79 (55–110)	2	152 (18–550)	8	132 (57–261)	8	226 (98–446)	5	138 (45–322)
P for trend		0.49		0.48		0.17		0.39		**0.004**		0.84
Time since first employment												
<20	4	50 (13–127)	**12**	**53 (27–93)**	1	165 (4–921)	4	203 (55–520)	4	91 (25–233)	5	134 (43–311)
20–29	14	162 (89–273)	37	84 (59–116)	1	67 (2–374)	5	118 (38–275)	1	26 (1–146)	3	98 (20–285)
30–39	13	106 (56–182)	58	80 (60–103)	3	110 (23–320)	11	142 (71–255)	**13**	**226 (120–387)**	4	77 (21–197)
≥40	3	55 (11–161)	25	81 (52–120)	2	185 (22–669)	2	48 (6–173)	1	41 (1–228)	1	40 (1–222)
P for trend		0.99		0.39		0.70		0.16		0.39		0.20
Time since last employment												
0	0	0	**15**	**58 (32–95)**	0	0	2	101 (12–366)	4	97 (26–247)	5	152 (49–355)
1–9	13	175 (93–299)	**21**	**57 (35–88)**	1	81 (2–451)	7	198 (80–409)	1	30 (1–169)	4	139 (38–357)
10–29	15	107 (60–176)	65	92 (71–117)	5	202 (65–470)	11	130 (65–233)	10	164 (79–302)	2	35 (4–127)
≥30	6	98 (36–213)	31	85 (57–120)	1	75 (2–415)	2	48 (6–173)	4	140 (38–358)	2	74 (9–267)
P for trend		0.19		0.07		0.43		0.24		0.28		0.11
Period at first employment												
Before 1965	13	72 (38–123)	**58**	**72 (55–93)**	3	117 (24–342)	9	94 (43–179)	5	70 (23–163)	9	134 (61–254)
1965–1974	19	123 (74–192)	72	85 (66–106)	4	127 (34–324)	12	148 (76–258)	14	166 (91–279)	3	42 (8–121)
1975 or after	2	232 (28–838)	2	43 (5–154)	0	0	1	236 (6–1316)	0	0	1	176 (4–981)
P for trend		0.06		0.67		0.89		0.21		0.34		0.22

In bold, statistically significant results (95% CI). Deaths and man-years occurring at age ≥85 years are excluded.

TABLE 3.
Observed Deaths (O) From Cancer and All Causes, and Corresponding Standardized Mortality Ratios (SMR) and 95% Confidence Intervals (CI), According to Various Characteristics of Exposure in a Cohort of Male Employees of a Tire Factory, Italy, 1954–2008

	All Cancers		All Causes	
Characteristic (yrs)	**O**	**SMR (95% CI)**	**O**	**SMR (95% CI)**
Duration of employment				
<10	**166**	**73 (62–85)**	**538**	**88 (80–95)**
10–19	108	91 (75–110)	285	91 (81–102)
≥20	**139**	**77 (65–91)**	**308**	**75 (67–84)**
P for trend		0.61		0.05
Age at first employment				
<25	**84**	**64 (51–79)**	**224**	**67 (59–77)**
25–34	**207**	**82 (71–94)**	**510**	**83 (76–91)**
≥35	122	86 (72–103)	397	102 (92–112)
P for trend		**0.04**		**<0.01**
Time since first employment				
<20	**57**	**68 (52–88)**	**233**	**77 (68–88)**
20–29	**107**	**82 (67–99)**	294	92 (82–103)
30–39	**168**	**78 (67–91)**	**417**	**86 (78–95)**
≥40	81	84 (67–105)	**187**	**80 (69–93)**
P for trend		0.33		0.77
Time since last employment				
0	**49**	**56 (41–74)**	**162**	**60 (51–70)**
1–9	91	83 (67–103)	239	91 (79–103)
10–29	**190**	**86 (74–99)**	516	93 (85–102)
≥30	**83**	**76 (60–94)**	**214**	**86 (75–98)**
P for trend		0.12		**<0.01**
Period at first employment				
Before 1965	**193**	**77 (66–88)**	**527**	**80 (73–87)**
1965–1974	**207**	**80 (69–92)**	**561**	**89 (82–97)**
1975 or after	13	82 (44–140)	43	86 (62–116)
P for trend		0.66		0.13

In bold, statistically significant results (95% CI). Deaths and man-years occurring at age ≥85 are excluded