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BRIEF COMMUNICATION

Bladder Cancer Mortality of Workers Exposed to Aromatic Amines: A 58-Year Follow-up

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We previously investigated bladder cancer risk in a cohort of dyestuff workers who were heavily exposed to aromatic amines from 1922 through 1972. We updated the follow-up by 14 years (through 2003) for 590 exposed workers to include more than 30 years of follow-up since last exposure to aromatic amines. Expected numbers of deaths from bladder cancer and other causes were computed by use of national mortality rates from 1951 to 1980 and regional mortality rates subsequently. There were 394 deaths, compared with 262.7 expected (standardized mortality ratio = 1.50, 95% confidence interval = 1.36 to 1.66). Overall, 56 deaths from bladder cancer were observed, compared with 3.4 expected (standardized mortality ratio = 16.5, 95% confidence interval = 12.4 to 21.4). The standardized mortality ratio for bladder cancer increased with younger age at first exposure and increasing duration of exposure. Although the standardized mortality ratio for bladder cancer steadily decreased with time since exposure stopped, the absolute risk remained approximately constant at 3.5 deaths per 1000 man-years up to 29 years after exposure stopped. Excess risk was apparent 30 years or more after last exposure.

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Aromatic amines are a group of well-known bladder carcinogens. Exposure to aromatic amines has been discontinued in most countries, but relatively little data are available on the patterns of long-term health risks many years after cessation of exposure (1,2–8). A substantial excess of mortality from bladder cancer was observed in a cohort of 664 workers who were heavily exposed to aromatic amines between 1922 and 1972 in a dyestuff factory in northern Italy (2–4). In the most recent published follow-up of this cohort through December 1989, 49 bladder cancer–specific deaths were observed overall, compared with 1.6 expected (standardized mortality ratio [SMR] = 30.4) (4). In more detailed analyses by time of exposure, risk was still elevated (SMR = 14.8; seven deaths vs 0.5 expected) 20 years or more after exposure stopped. Along with two other studies, one in the United States (5) and one in Wales (6), this cohort study is among the few providing information on bladder cancer risk after exposure specifically to *o*-toluidine.

In this analysis, we included an additional 14 years of observation of this Italian cohort through 2003 by including more than 30 years of follow-up since last exposure to aromatic amines for all workers to provide unique, long-term information on bladder cancer risk among workers after extremely heavy exposure to several aromatic amines many years in the past.

Further details on the study methods, including exposure definition, have been previously published (2–4). The original cohort definition was approved in the 1970s by the Institutional Board of the Department of Occupational Health, University of Turin, according to the regulations at the time. The study did not involve direct contact with the workers. Briefly, the original cohort was composed of 906 men who had worked at least 1 year in the dyestuff plant between 1922 and 1972 and who were alive in 1946. We did not consider 204 men who were not directly involved in jobs entailing exposure to aromatic amines because no deaths from bladder cancer were observed in this group (3) and because the expected number of deaths from bladder cancer was also low, and 112 men who had been lost to follow-up before December 31, 1989. This left 590 exposed workers; of these, 271 had died between 1946 and 1989, leaving 319 men for extended follow-up through December 31, 2003. Follow-up was truncated when a participant reached age 85 years because of the poor quality of death certification for those older than that age. We traced 305 (96%) of the 319 workers alive in 1989, yielding a total of 17 754 man-years at risk in this analysis.

Information was available on date and place of birth, dates of start and termination of employment, job history (including categories of exposure to selected amines), and the last known address. As described by Rubino et al. (2), who used knowledge of carcinogenicity of aromatic amines, workers with any of the following four categories of aromatic amine exposure were considered at highest risk and are grouped into one category for this analysis: α-naphthylamine manufacture, β-naththylamine manufacture, benzidine manufacture, and mixed manufacture of benzidine and naphthylamine (n = 133). The other three categories of workers included workers never involved in manufacture, but only in use of naphthylamine and benzidine (n = 134), workers with intermittent contact with naphthylamine and benzidine (n = 276), and workers who were involved only in manufacture of fuchsin or *o*-toluidine (n = 47). Ten workers exposed to both benzidine and/or naphthylamine and to fuchsin and/or *o*-toluidine manufacture were considered in the first category. For all time-related factors (duration and time since first or last exposure), we grouped all four categories of exposure together. Further verification of vital status was obtained from registries of current residence, and death certificates were obtained from registration offices at the municipality of death.

The expected numbers of deaths from bladder cancer and other causes were computed by use of national mortality rates (9) from 1951 to 1980 and regional mortality rates (10) when available (ie, from 1981 to 2003), stratified in 5-year age groups from

3.4 expected (SMR = 16.5, 95% CI = 12.4 to 21.4). Excess mortality was observed for all alcohol-related cancers, including cancer of the oral cavity and pharynx (SMR = 2.67, 95% CI = 1.07 to 5.50), esophagus (SMR = 2.45, 95% CI = 0.80 to 5.72), intestines (SMR = 1.99, 95% CI = 1.08 to 3.33), liver (SMR = 1.93, 95% CI = 0.71 to 4.20), and larynx (SMR = 4.12, 95% CI = 2.05 to 7.36). Similarly, excess mortality was observed for other alcohol-related causes, including cerebrovascular disease (SMR = 1.42, 95% CI = 1.01 to 1.95), cirrhosis (SMR = 3.72, 95% CI = 2.68 to 5.03), and injuries (SMR = 1.27, 95% CI = 0.79 to 1.94), but not for ischemic heart disease (SMR = 0.58, 95% CI = 0.37 to 0.87). Of the 130 excess deaths, 53 were caused by bladder cancer alone and approximately 75 were attributed to the complex of alcohol-related causes. Some excess mortality was also observed for cancer of the lung (SMR = 1.27, 95% CI = 0.84 to 1.85) and chronic obstructive pulmonary disease (SMR = 1.84, 95% CI = 1.12 to 2.84). There were two deaths from pleural cancer, both among workers who had started working in the plant after age 35 years.

We determined the numbers of observed and expected deaths from bladder cancer, all other cancers, and all causes according to time since last exposure, age at first exposure, and duration of exposure (Table 2). For time since last exposure and duration of exposure, workers contributed relevant person-time to multiple exposure categories. In this cohort, there were 16 excess bladder cancer deaths during exposure (SMR for bladder cancer = 57.8, 95% CI = 33.0 to 93.9), 15 from 1 through 9 years since stopping (SMR = 28.5, 95% CI = 16.0 to 47.1), 12 from 10 through 19 years (SMR = 14.7, 95% CI = 7.8 to 25.2), eight from 20 through 29 years (SMR = 11.0, 95% CI = 5.1 to 20.9), and two for 30 years or more after last exposure (SMR = 3.3, 95% CI = 0.7 to 9.7). The standardized mortality ratio for bladder cancer was higher in workers with exposure at younger age and decreased with increasing age at first exposure. Furthermore, the risk of bladder cancer was higher in workers with 10 years or more of exposure as compared with those with less than 10 years. For other cancers and for deaths overall, no consistent pattern of risk with time since last exposure, age at first exposure, or duration of exposure was observed.

In an analysis of bladder cancer deaths by job categories, we found 33 bladder

CONTEXT AND CAVEATS

Prior knowledge

Aromatic amines are well-known bladder carcinogens.

Study design

Cohort study of dyestuff workers with a follow-up of more than 30 years since last exposure to aromatic amines. Mortality from all causes and from bladder cancer was assessed.

Contribution

In this cohort, more deaths from all causes were observed (n = 394) than expected (n = 262.7) and more deaths from bladder cancer were observed (n = 56) than expected (n = 3.4). Although the standardized mortality ratio for bladder cancer steadily decreased with time since exposure stopped, the absolute risk for bladder cancer remained approximately constant at 3.5 deaths per 1000 man-years up to 29 years after exposure stopped.

Implications

Increased risk of bladder cancer persisted 30 years or more after last exposure.

Limitations

More than 10% of the original cohort was lost to follow-up before 1989.

From the Editors

20–24 to 80–84 years. For the period 1946–1950, we used rates of 1951–1954. Because retirement or change of job may in some cases be caused by bladder cancer, and for consistency with our previous reports (3,4), deaths that occurred within 3 years of stopping exposure were considered with those occurring during exposure.

From the numbers of observed and expected deaths, we calculated the standardized mortality ratios for selected causes of death and their corresponding 95% confidence intervals (CIs) by use of the Poisson distribution for observed deaths (11). Standardized mortality ratios were adjusted for age (in 5-year age groups) and for 5-year calendar period.

Overall, there were 394 observed deaths from all causes in the cohort for the entire period of follow-up from 1946 through 2003 vs 262.7 expected (SMR = 1.50, 95% CI = 1.36 to 1.66) (Table 1). There were 56 deaths from bladder cancer compared with

Table 1. Numbers of observed and expected deaths and standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) for selected causes of death in a cohort of dyestuff workers from northern Italy: 1946–2003*

Cause of death	No. observed	No. expected	SMR (95% CI)
Cancer type			
Oral cavity, pharynx	7	2.6	2.67 (1.07 to 5.50)
Esophagus	5	2.0	2.45 (0.80 to 5.72)
Stomach	10	9.6	1.04 (0.50 to 1.92)
Intestines	14	7.1	1.99 (1.08 to 3.33)
Liver	6	3.1	1.93 (0.71 to 4.20)
Larynx	11	2.7	4.12 (2.05 to 7.36)
Lung	27	21.3	1.27 (0.84 to 1.85)
Pleura	2	0.5	3.75 (0.45 to 13.55)
Prostate	4	4.4	0.91 (0.25 to 2.33)
Bladder	56	3.4	16.45 (12.42 to 21.36)
Lymphopoietic	3	4.8	0.62 (0.13 to 1.81)
All cancer types	163	77.3	2.11 (1.80 to 2.46)
All cancer types excluding bladder	107	73.9	1.45 (1.19 to 1.75)
Other causes of death			
Ischemic heart disease	23	39.9	0.58 (0.37 to 0.87)
Cerebrovascular disease	39	27.4	1.42 (1.01 to 1.95)
Cirrhosis	42	11.3	3.72 (2.68 to 5.03)
COPD	20	10.9	1.84 (1.12 to 2.84)
Injuries	21	16.5	1.27 (0.79 to 1.94)
All causes of death	394	262.7	1.50 (1.36 to 1.66)

* The deaths and man-years at risk from individuals aged 85 years or older were excluded. COPD = chronic obstructive pulmonary disease.

Table 2. Mortality from bladder cancer, all other cancers, and all causes by time since exposure stopped, age at first exposure, and duration of exposure in a cohort of dyestuff workers from northern Italy: 1946–2003*

Category	Bladder cancer No. Obs	Bladder cancer No. Exp	Bladder cancer SMR (95% CI)	All other cancers No. Obs	All other cancers No. Exp	All other cancers SMR (95% CI)	All causes No. Obs	All causes No. Exp	All causes SMR (95% CI)	Man-years at risk
Time since last exposure										
During exposure	16	0.3	57.8 (33.0 to 93.9)	11	9.3	1.2 (0.6 to 2.1)	56	39.0	1.4 (1.1 to 1.9)	6123
1–9 y	15	0.5	28.5 (16.0 to 47.1)	23	13.3	1.7 (1.1 to 2.6)	98	52.8	1.9 (1.5 to 2.3)	4145
10–19 y	13	0.9	14.7 (7.8 to 25.2)	28	18.4	1.5 (1.0 to 2.2)	100	68.2	1.5 (1.2 to 1.8)	3550
20–29 y	9	0.8	11.0 (5.1 to 20.9)	18	15.9	1.1 (0.7 to 1.8)	74	52.8	1.4 (1.1 to 1.8)	2335
≥30 y	3	0.9	3.3 (0.7 to 9.7)	27	17.0	1.6 (1.0 to 2.3)	66	49.8	1.3 (1.0 to 1.7)	1601
Age at first exposure										
<25 y	15	0.6	24.7 (13.8 to 40.8)	20	15.1	1.3 (0.8 to 2.1)	73	44.1	1.7 (1.3 to 2.1)	5817
25–34 y	18	1.2	15.4 (9.1 to 24.3)	38	24.7	1.5 (1.1 to 2.1)	110	80.6	1.4 (1.1 to 1.6)	6198
≥35 y	23	1.6	14.1 (9.0 to 21.2)	49	34.1	1.4 (1.1 to 1.9)	211	138.0	1.5 (1.3 to 1.8)	5739
Duration of exposure										
<10 y	15	1.6	9.3 (5.2 to 15.3)	59	37.2	1.6 (1.2 to 2.0)	191	124.7	1.5 (1.3 to 1.8)	11207
10–19 y	21	0.9	24.4 (15.1 to 37.2)	22	18.6	1.2 (0.7 to 1.8)	111	73.1	1.5 (1.3 to 1.8)	4014
≥20 y	20	0.9	21.7 (13.2 to 33.5)	26	18.1	1.4 (0.9 to 2.1)	92	64.9	1.4 (1.1 to 1.7)	2533

* CI = confidence interval; exp = expected; obs = observed; SMR = standardized mortality ratio.

cancer deaths among workers directly involved in manufacture of naphthylamine and benzidine (SMR = 48.7, 95% CI = 33.5 to 88.3), seven among utilizers (ie, workers involved in the manufacture of azo dyes as well as production of benzidine and naphthylamine salts and homologs) (2) (SMR = 8.7, 95% CI = 3.5 to 17.9), and 10 among those intermittently exposed (SMR = 6.0, 95% CI = 2.9 to 11.1) (Table 3). We also found excess bladder cancer deaths among manufacturers of fuchsin or *o*-toluidine (six observed deaths; SMR = 22.5, 95% CI = 8.3 to 49.0).

With approximately two-thirds of the members of the cohort deceased during the 58-year follow-up and with more than 30 years of follow-up since last exposure to aromatic amines, these workers provide a unique opportunity to analyze the long-term health effects of extremely heavy occupational exposure to aromatic amines. More than 96% of workers who were alive on December 31, 1989, were traced through 2003. A possible limitation of the study is losses to follow-up before 1989. In fact, 112 workers had previously been lost to follow-up. Although this may have introduced some bias, loss to follow-up cannot explain the extreme excess of bladder cancer risk observed in this cohort or the observed time–risk relation. For time-related variables (ie, duration of exposure and time since last exposure), we dynamically assigned relevant person-time for each worker to different exposure categories (11). Reliability and validity of Italian death certification since the 1950s are satisfactory (9,12).

The relative risk (RR; which was calculated as SMR) for bladder cancer declined steadily (from a high of RR = 57.8 during exposure to RR = 3.3 for ≥30 years after stopping exposure). The absolute risk, however, remained approximately constant at approximately 3.5 excess deaths from bladder cancer per 1000 man-years up to 29 years after stopping exposure and was still 1.9 per 1000 man-years 30 years or more after last exposure. This pattern parallels that of lung cancer risk observed after smoking cessation, which levels off at approximately the level reached at the time of stopping (13). Likewise, an immediate decrease in the relative risk for bladder cancer is apparent after stopping smoking, but risk does not reach the level of never-smokers even 25 years after cessation (14). In this dyestuff worker's cohort, the number of excess bladder cancer cases began to decline after 20 years or more since cessation of exposure to aromatic amines. This observation has, therefore, important implications for the long-term surveillance of workers heavily exposed to aromatic amines in the past.

Our study provides additional evidence for the carcinogenicity of *o*-toluidine on the human bladder. Workers included in this category were primarily exposed to *o*-toluidine because the 10 workers who were exposed to both *o*-toluidine and benzidine and/or naphthylamine were excluded from this group. Apart from previous reports on this cohort (2,3), cancer risk has been examined in two other occupational cohorts of workers exposed to *o*-toluidine. In one cohort of 1749 workers at a chemical plant in Western New York State (5), seven participants were diagnosed with bladder cancer cases among the 708 workers exposed to both *o*-toluidine and aniline vs 1.08 expected (standardized incidence ratio = 6.48). In the second cohort of 2160 workers in a factory manufacturing chemicals for the rubber industry in Wales (6), three bladder cancer deaths were

Table 3. Mortality from bladder cancer by job category in a cohort of dyestuff workers from northern Italy: 1946–2003*

Job category	No. Obs	No. Exp	SMR (95% CI)
Naphthylamine and benzidine manufacture	33	0.7	48.7 (33.5 to 68.3)
Naphthylamine and benzidine use	7	0.8	8.7 (3.5 to 17.9)
Intermittent contact with naphthylamine and benzidine	10	1.7	6.0 (2.9 to 11.1)
Fuchsin or *o*-toluidine manufacture	6	0.3	22.5 (8.3 to 49.0)

* CI = confidence interval; exp = expected; obs = observed; SMR = standardized mortality ratio.

observed in the toluidine department, with a trend of a borderline statistically significant increased risk with duration of employment. On the basis of those data, an International Agency for Research on Cancer (IARC) Working Group recently concluded that *o*-toluidine is a human carcinogen (1).

This is the first report from this cohort of dyestuff workers to present data on causes of death other than bladder cancer. A widespread and substantial excess was observed for all alcohol-related cancers and other major alcohol-related diseases (15) but not for lymphoid neoplasms, which have been inversely related to alcohol drinking (15). Some excess mortality was also observed for lung cancer and chronic obstructive pulmonary disease. We did not find a consistent relation with time since first or last exposure or with duration of exposure for any of these causes of death. It is therefore more likely that the excess mortality for those causes was a result of heavy alcohol drinking, smoking, and other lifestyle characteristics rather than occupational exposure. Likewise, the two observed deaths from pleural cancer were in workers who had started working in the plant after age 35 years, suggesting that exposures to asbestos in jobs held before employment in the plant under study may be relevant.

At the 1981 follow-up of this cohort (3), we assumed an additive model between exposure to aromatic amines and tobacco smoking and found a 13%–14% cumulative risk of death from bladder cancer, which is in agreement with results from the 2003 follow-up, with about two-thirds of the cohort deceased. The absolute risk of bladder cancer death among those younger than 85 years approached 10% (95% CI = 7% to 12%). This result lends support to the validity of the additive model for occupational exposure to aromatic amines and tobacco smoking on bladder carcinogenesis (16). It also confirms the excess of bladder cancer risk in this cohort of workers who were heavily exposed to aromatic amines because the number of deaths from bladder cancer was more than twice that from lung cancer or ischemic heart disease.

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