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Cohort Study of Carbon Black Exposure and Risk of Malignant and Nonmalignant Respiratory Disease Mortality in the US Carbon Black Industry

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Objective: To evaluate lung cancer and respiratory disease mortality associations with cumulative inhalable carbon black exposure among 6634 US carbon black workers. **Methods:** This analysis was performed using standardized mortality ratio (SMRs) and Cox regression analyses. **Results:** Lung cancer mortality was decreased overall (SMR = 0.77; 95% confidence interval [CI], 0.67 to 0.89) but less so among hourly male workers (SMR = 0.87; 95% CI, 0.71 to 1.05). No exposure–response association was observed with time-dependent cumulative inhalable carbon black: hazard ratio [HR] = 1.0 (95% CI, 0.6 to 1.6) for 20 to less than 50 mg/m^3·yr); HR = 1.3 (95% CI, 0.8 to 2.1) for 50 to less than 100 mg/m^3·yr; and HR = 1.4 (95% CI, 0.9 to 2.1) for 100 mg/m^3·yr or more compared with referent (<20 mg/m^3·yr). No consistent associations were observed between cumulative inhalable carbon black exposure and respiratory disease mortality. **Conclusion:** Quantitative carbon black exposure estimates were not related to lung cancer or nonmalignant respiratory disease mortality.

Carbon black is used in automobile tires as a reinforcing agent and in printing inks, cables, coatings, and films.[1,2] Carbon black is manufactured by the incomplete combustion of a heavy aromatic feedstock introduced into a hot gas stream in a closed reactor. Within the reactor, spherical-like particles (nodules) of carbon black collide and fuse together to form aggregates, the primary indivisible unit of carbon black. Carbon black is frequently described as a nanostructured material when the size of the primary particles is less than 100 nm; nevertheless, manufactured carbon black products are aggregate or agglomerate particulates and are not nanoscale materials. The size of aggregates ranges from about 85 nm to more than 500 nm, whereas agglomerates—aggregates held together by weak electrical forces—range in size from about 1 to 100 μm.[2,3]

Inhalation is the primary exposure route to carbon black and, similar to other particles, the lung is considered the target organ of concern. There is no evidence, however, that inhaled carbon black as encountered in the workplace can deagglomerate or disaggregate in the presence of lung fluids into smaller, and potentially more hazardous, particles that could translocate to tissues or organs beyond the lung.[3]

Previously, we reported mortality results for a cohort of 5011 employees who worked for 1 year or more in the US carbon black industry.[4] Through 2003, mortality from all causes was significantly lower than expected (standardized mortality ratio [SMR] = 0.72; 95% confidence interval [CI], 0.68 to 0.76). Mortality from lung cancer was similarly low, but approached expectation after conservatively assuming 15% of 76 decedents with unknown cause of death had died of lung cancer (SMR = 0.97; 95% CI, 0.82 to 1.15).

In addition to the US study,[4] mortality has been studied in two other large cohorts of carbon black producers in Germany [5–8] and the UK.[9] The International Agency for Research on Cancer (IARC) considered these studies when it last evaluated the possible carcinogenicity of carbon black in 2006. The IARC working group noted inconsistencies across the three large cohort studies, notably the deficit of lung cancer mortality in the US cohort versus the excess lung cancer mortality noted in the German and UK cohorts.[10] In addition, the working group identified the following limitations: (1) lack of quantitative exposure measures in the US cohort; (2) limitations of the carbon black exposure assessment, possibly leading to exposure misclassification in the UK cohort, as well as potential bias from confounding in the UK cohort by unmeasured factors such as smoking and previous occupational exposure; and (3) unusual patterns of results in studies of the German cohort[5,6,8] that in combination, suggested selection factors of uncertain origin and confounding by previous occupational exposures and smoking in the German cohort. (The uncertainties in the analyses of the German cohort were later described and the impact of potential biases quantified [7,12]). The IARC subsequently classified carbon black as ''possibly carcinogenic to humans'' (Group 2B) primarily on the basis of positive lung cancer findings in chronic bioassays in the rat.[10] In the UK, Sorahan and others reported a lung cancer SMR of 173 (95% CI, 132 to 222) among 1147 carbon black workers employed 1 year or more at five facilities, but no evidence of excess lung cancer mortality in relation to cumulative exposure to carbon black.[9] Mortality was later updated through 2004 (lung cancer SMR = 146; 95% CI, 113 to 185).[11] The authors applied a novel method (a ''lugged analysis'') to evaluate carbon black exposures received in the most recent 15 years before the end of follow-up. The authors reported a positive exposure–response relationship at two of the five carbon black facilities, and suggested that carbon black exposure received in recent years potentially might act on late stages of lung cancer development. Nevertheless, because smoking data were unavailable, it is not known what influence smoking had on these observations.

In Germany, Wellman and others reported a two-fold excess of lung cancer mortality (SMR = 2.18; 95% CI, 1.61 to 2.87 using national referent rates, and SMR = 1.83; 95% CI, 1.36 to 2.41 using state referent rates) among a cohort of 1535 men who had worked for at least 1 year and were employed between 1960 and 1998 at a single carbon black factory.[5] Similar to the UK study, there was no pattern of increasing risk of lung cancer mortality with a semi-quantitative indicator of cumulative carbon black exposure[5] or other

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indices of carbon black exposure.[7] Additional analyses to evaluate and quantify the effects of potential biases and confounding identified by the IARC were performed.[6,7,12] Morfeld and McCunney [13,14] also evaluated whether carbon black exposure received in recent years might act on late stages of lung cancer development by performing "lugged analyses" on the German cohort. The investigators found that SMRs for lung cancer were elevated for all categories of time since end of employment and increased with time since employment.[13] In addition, hazard ratios in multimodel Cox regressions were not increased with more recent carbon black exposure,[14] contradicting the lugging hypothesis proposed by Sorahan and Harrington.[11]

Several studies have reported that carbon black exposure was associated with other observable effects on the respiratory system.[15–17] These studies have reported statistically significant decrements in pulmonary function parameters in carbon black workers when compared with unexposed controls, including decreased forced expiratory volume in 1 second (FEV_1)[15–17] and an increased prevalence of chest radiographic abnormalities.[18] Reductions in percent predicted peak expiratory flow, forced expiratory flow at 25% to 75% vital capacity, and FEV_1 to forced vital capacity (FVC) ratio (FEV_1/FVC) were also reported.[15,17] No associations between carbon black exposure and decrements in FVC have been observed.[15–17] van Tongeren and others[18] reported chest radiographic abnormalities in carbon black workers; nevertheless, a large percentage reverted to normal chest x-rays after reduction in or cessation of exposure. Zhang and others[17] reported a possible link between human exposure to carbon black and proinflammatory cytokines, on the basis of elevated median levels of five of the six proinflammatory cytokines measured in workers' serum compared with a control group not exposed to carbon black. Sorahan et al[9] reported an SMR of 1.69 (95% CI, 1.03 to 2.61) from nonmalignant respiratory disease (NMRD) among male workers employed for at least 1 year who were 30 years or more from the first employment. These results suggest that NMRD mortality is also an outcome of interest.

To address some of the questions raised by the IARC working group and subsequent studies that used novel methods (lugging analysis), we updated the US carbon black industry cohort for mortality through 2011. Our specific objectives were to (1) derive quantitative estimates of cumulative inhalable carbon black for each employee using a job-exposure matrix (JEM); (2) conduct exposure–response analyses for lung cancer and NMRD mortality; and (3) replicate methods used in the UK and German studies—a lagged analysis to allow for latency associated with lung cancer and a separate "lugged" analysis to evaluate whether carbon black exposures in the 15 years preceding lung cancer death were predictive of risk—to allow for direct comparisons of results between the cohorts.

METHODS

Cohort Definition and Follow-Up

Cohort enumeration was described previously.[4] In brief, we comprehensively identified employees at 18 carbon black facilities (of a total of 20 that were actively manufacturing carbon black as of January 1, 2000), primarily using company personnel records supplemented by data from the archive of an earlier study of carbon black employees.[19–21] When the cohort was initially constructed, date of hire, first available job title, and department assignment had been captured, but not detailed work histories. We conducted additional site visits to obtain detailed work histories: job assignments, departments, and dates of each assignment.

From a total of 8063 employees identified during site visits, we excluded duplicate records and ineligible individuals (Fig. 1). Cohort enumeration dates for each facility were identified by reviewing the number of employee hires and separations for each year and selecting the year when separations from employment began to be consistently reported. Thus, the full study cohort was composed of 6634 individuals actively employed on or hired after facility-specific enumeration dates. We also defined an inception (entry) cohort of 4882 workers by removing study subjects hired before the facility enumeration date (Fig. 1). These study subjects are subject to selective survival, because employees who died or left employment before the cohort enumeration date are not included in the study cohort. We further excluded female workers because their numbers were few, and employees who began their employment in administrative jobs because they were considered not likely exposed to carbon black. After these exclusions, an inception subcohort of 3890 male hourly workers (about 59% of the total cohort) considered to have the greatest potential for exposure to carbon black—and not subject to selective survival—remained for analysis (Fig. 1).

Carbon Black Exposure Assessment

We created a JEM on the basis of more than 8000 time-weighted average measurements collected during several industry-wide sampling campaigns conducted in the following years: 1979 to 1980, 1982 to 1983, 1987 to 1988, 1993 to 1995, 2000 to 2001, 2003 to 2004, and 2007.[22–24] These measurements represented primarily total dust and some respirable dust measurements; additionally, inhalable dust measurements were sampled in 2000 to 2001, 2003, and 2007. Total dust measurements were converted to inhalable dust measurements using an empirical factor of 2.97:1 (inhalable to total) derived by Kerr and Muranko during side-by-side sampling of the inhalable aerosol and total dust aerosol during 1998 to 2000.[24]

For each facility, the arithmetic means were calculated and summarized by calendar year of sampling campaign for each of the five similar exposure groups (SEGs): administration, production, laboratory, maintenance, or material handling (warehouse operations) (Fig. 2). From the 1987 to 1988 and earlier sampling campaigns, only summary data (arithmetic mean and/or geometric mean, range of values, and sometimes geometric standard deviation or 95% CI, for the geometric mean) were available. (The 1979, 1982 to 1983, and 1987 to 1988 sampling campaigns were conducted by researchers at the University of Michigan; however, the individual data were lost when computer systems were updated in the 1990 s [personal communication, H. Muranko, CIH, August 2007]. Nevertheless, the sampling methods were documented in company reports: total dust samples were collected from closed-face filter cassettes worn in the breathing zone for full-shift samples, as were inhalable samples.) Arithmetic means, if not reported, were derived at each facility or company from the geometric mean, geometric standard deviation, range of values, or CI for the geometric mean using formulas reported by LaVoue et al.[25] When only company-wide data were available (during 1982 to 1983 for some companies, and 1987 to 1988 for all companies), we applied them to each of their facilities.

To create the JEM, values for the years between the sampling campaign years were interpolated. Summary estimates for the years between 1960 and 1979 were extrapolated backward on the basis of the slope derived by linear regression of the existing data, typically using the three sampling campaigns (collected during 1979, 1982 to 1983, and 1995) proximal to the years for which industrial hygiene (IH) data were not available. We assumed that exposures decreased over time for the years before 1979 because of improvements in housekeeping practices and dust control. Therefore, if the slope of the linear regression of the existing data predicted lower concentrations in earlier years, the most proximal data value was applied to all earlier years. This primarily affected SEGs for which IH data were relatively sparse at certain facilities: laboratory at two facilities; administration at one facility; maintenance at one facility; and materials handling/warehouse at one facility.

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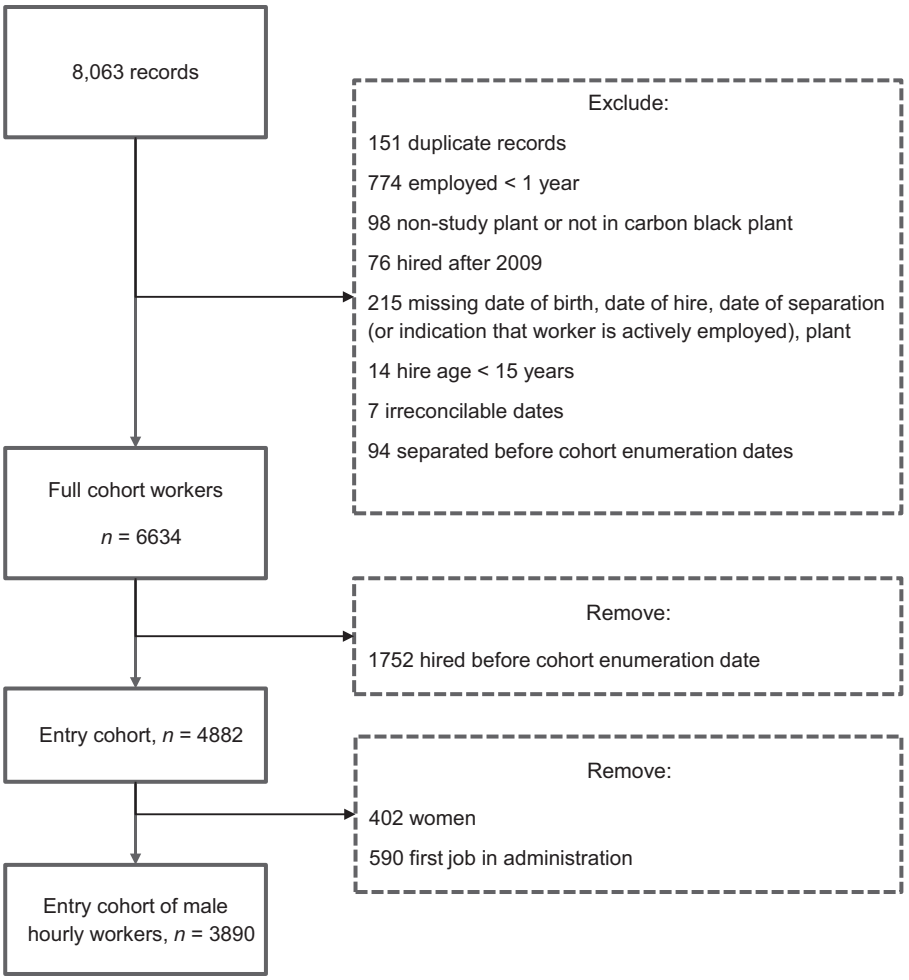

FIGURE 1. Cohort enumeration.

To calculate individual estimates of cumulative carbon black exposure, the work history data for each cohort member were linked to the JEM through the SEG for each job title and job assignment dates. Cumulative exposure was calculated as the sum of the duration in an SEG multiplied by the summary value for the SEG calendar period over the course of an individual's work history. Four of the 18 carbon black facilities had ceased operations before the site visits in 2010, and comprehensive work history records were reported by company personnel as missing. For individuals with a single job title, we assigned that job over the duration of employment at that facility.

A total of 1183 (17.8%) study subjects without job titles but identified as carbon black workers were assigned the average exposure for their facility for each year worked. Approximately 87% of these employees without job titles were identified from the rosters of one company. These study subjects had been included in earlier carbon black studies.[19,21] The employee rosters had identified carbon black production employees by the state in which the facility was located (Louisiana or Texas), without identifying the specific facility. For analysis, we treated the employees on these rosters as if they had worked at a single facility in each state and assigned them the average exposure for the company's facilities in their respective states.

Vital Status Ascertainment

Vital status was determined by searching databases maintained by the US Social Security Administration (SSA) and the National Death Index (NDI) of the US National Center for Health Statistics. The SSA's Death Master File before the start of the NDI in 1979 is known to be incomplete and may identify only half of all deaths, especially in its earliest years.[26,27] To address potential underascertainment of deaths from using the SSA databases, and to reduce the possibility of a survivor bias, we conducted extensive searches of web-based genealogical services (eg, ancestry.com and archives.com) to search for evidence of death, including state death indexes, obituaries, or cemetery and burial information. We focused these searches on workers hired in the earliest years who had discontinued employment before 1979 (start of the NDI) and were not identified as "alive" in SSA searches or "dead" in SSA and NDI searches.

For deaths occurring since 1979, the coded underlying cause of death was provided by the NDI. For study subjects who died before 1979, and for uncertain NDI matches, we obtained death certificates from state vital statistics offices to verify the fact of death and to identify the underlying cause of death code (according to the revision in effect at the time of death). When not coded on the death certificate, the underlying cause of death was coded by a nosologist according to the ninth revision of the International Classification of Diseases (ICD-9).

Person-Time at Risk and Reference Rates

Person-time at risk was accrued starting 1 year after the first employment at any study facility or its cohort enumeration date, whichever was later, but no earlier than January 1, 1940 (see Supplemental Table 1, http://links.lww.com/JOM/A209, for cohort enumeration dates for each plant). Person-years continued accruing

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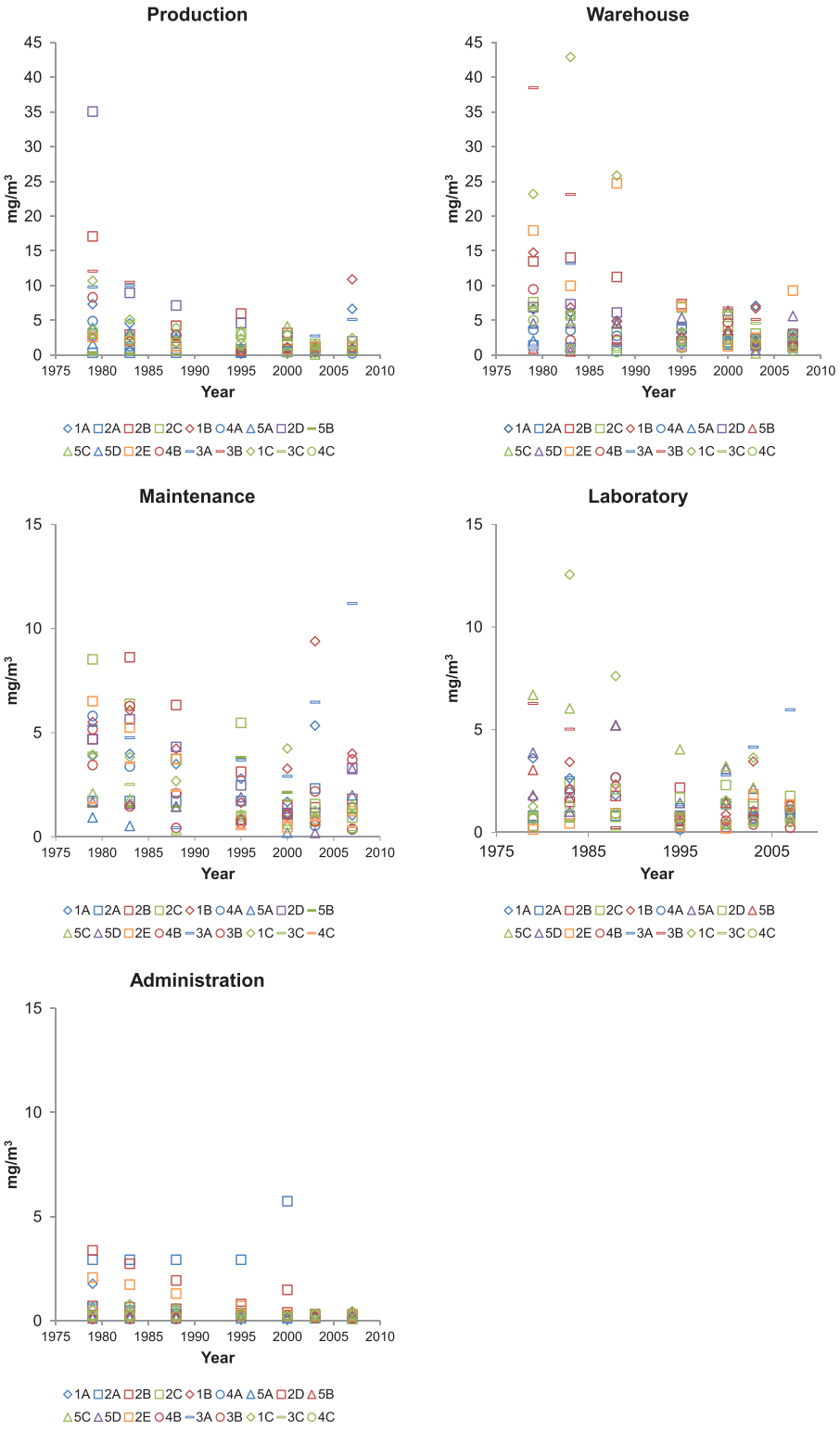

FIGURE 2. Average inhalable carbon black exposure by facility and year of sampling campaign for each similar exposure group.

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TABLE 1. Demographic and Employment Characteristics for Full Cohort (6634 Carbon Black Workers) and Entry Cohort of Male Hourly Workers and Followed Up for Mortality Through 2011

Characteristic	Full Cohort: 6634 Carbon Black Workers *n* (%)	Entry Cohort of Male Hourly Workers: 3890 Men *n* (%)
Vital status*		
Alive	4588 (69.2)	2732 (70.2)
Dead†	1947 (29.3)	1098 (28.2)
Unknown	99 (1.5)	60 (1.5)
Sex		
Males	5887 (88.7)	3616 (93.0)
Females	448 (6.8)	–
Unknown	299 (4.5)	274 (7.0)
Race		
White	2655 (40.0)	1464 (37.6)
Nonwhite	443 (6.7)	292 (7.5)
Unknown	3536 (53.3)	2134 (54.9)
Employment status as of December 31, 2009		
Active	864 (13.0)	614 (15.8)
Former employee	5770 (87.0)	3276 (84.2)
Birth year		
1884–1919	977 (14.7)	467 (12.0)
1920–1939	1767 (26.6)	953 (24.5)
1940–1959	2519 (38.0)	1491 (38.3)
1960–1989	1371 (20.7)	979 (25.2)
Age at hire, yrs		
<25	2428 (36.6)	1500 (38.6)
25–34	2753 (41.5)	1571 (40.4)
≥35	1453 (21.9)	819 (21.1)
Decade of hire		
1920s	19 (0.3)	–
1930s	169 (2.6)	–
1940s	894 (13.5)	564 (14.5)
1950s	956 (14.4)	519 (13.3)
1960s	1069 (16.1)	635 (16.3)
1970s	1045 (15.8)	544 (14.0)
1980s	1057 (15.9)	620 (15.9)
1990s	808 (12.2)	570 (14.7)
2000s	617 (9.3)	438 (11.3)
Plant		
A	1324 (20.0)	945 (24.3)
B and C	1532 (23.1)	773 (19.9)
D	882 (13.3)	595 (15.3)
Other	2896 (43.7)	1577 (40.5)
Length of follow-up		
Mean (SD)	29.6 (14.9)	29.7 (15.7)
Median (range)	29.6 (>0.0–67.6)	29.9 (>0.0–66.8)
25th percentile	18.5	16.5
75th percentile	41.3	42.2
95th percentile	54.2	55.2
Age at start of follow-up		
Mean (SD)	32.3 (9.3)	29.9 (8.0)
Median (range)	30.3 (16.3–69.1)	28.1 (16.9–65.2)
25th percentile	25.1	23.9
75th percentile	37.8	34.6
95th percentile	50.5	45.2
Age at end of follow-up		
Mean (SD)	61.9 (14.5)	59.7 (14.7)
Median (range)	62.5 (18.8–85.0)	59.9 (19.4–85.0)
25th percentile	51.8	49.7
75th percentile	73.2	70.8
95th percentile	85.0	83.8
Length of employment		
Mean (SD)	13.2 (11.7)	10.1 (9.9)
Median (range)	8.6 (1.0–49.0)	5.9 (1.0–49.0)
25th percentile	3.1	2.4
75th percentile	22.0	15.3
95th percentile	35.8	31.3
Time since first exposure		
Mean (SD)	32.5 (15.6)	30.7 (15.7)
Median (range)	33.2 (1.0–68.6)	30.9 (1.0–67.8)
25th percentile	20.7	17.5
75th percentile	44.9	43.2
95th percentile	57.2	56.2
Time since cessation of exposure		
Mean (SD)	19.4 (15.9)	20.6 (17.3)
Median (range)	15.4 (0–67.3)	15.7 (0–66.8)
25th percentile	5.4	4.5
75th percentile	31.2	35.5
95th percentile	49.9	51.6
Inhalable carbon black exposure		
Cumulative exposure, mg/m^3·yr		
Mean (SD)	76.0 (137.4)	69.8 (131.0)
Median (range)	33.1 (<1 to 2122)	33.5 (<1 to 1745)
25th percentile	8.6	12.1
75th percentile	84.6	71.8
95th percentile	289.3	268.6
Average exposure, mg/m^3		
Mean (SD)	8.0 (10.7)	10.0 (11.6)
Median (range)	3.7 (0.03–68.4)	4.7 (0.1–68.3)
25th percentile	1.4	2.1
75th percentile	8.4	11.9
95th percentile	34.3	34.3
Cumulative exposure, low cut points, mg/m^3·yr		
<5	1140 (17.2)	369 (9.5)
5 to <10	662 (10.0)	453 (11.7)
10 to <20	763 (11.5)	557 (14.3)
≥20	4069 (61.3)	2511 (64.5)
Cumulative exposure, high cut points, mg/m^3·yr		
<20	2565 (38.7)	1379 (35.5)
20 to <50	1519 (22.9)	1115 (28.7)
50 to <99	1127 (17.0)	733 (18.8)
≥100	1423 (21.4)	663 (17.0)
Cumulative exposure, quartile cut points‡, mg/m^3·yr		
<12	1996 (30.1)	968 (24.9)
12 to <34	1353 (20.4)	990 (25.5)
34 to <72	1387 (20.9)	966 (24.8)
≥72	1898 (28.6)	966 (24.8)
Duration of exposure, yrs		
Mean (SD)	12.6 (11.2)	9.9 (9.7)
Median (range)	8.1 (<1 to 49.0)	5.8 (<1 to 49.0)
25th percentile	3.0	2.4
75th percentile	20.8	15.2
95th percentile	34.7	31.0

*As of December 31, 2011.
†Person-time censored at age 85 years.
‡Quartiles of exposure on the basis of entry cohort of 3890 workers after women and white-collar workers were excluded.
SD, standard deviation.

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until date of death, attaining age 85 years, or December 31, 2011. For individuals whose vital status could not be determined as of the end of follow-up, person-time was censored as of the date of separation from employment. We censored study subjects at age 85 years for several reasons: (1) causes of death reported on death certificates for the very old are less reliable in general; (2) causes of death at very old ages may be less likely to reflect causes associated with occupational exposures; and (3) the comparison rates for ages over 85 years are open ended (ie, no upper bound). We obtained race- and sex-specific mortality rates by age and calendar interval for 119 cause-specific categories of death from the National Institute for Occupational Safety and Health (NIOSH) for each state where a study carbon black facility was located.[28] Male mortality rates were used for the small percentage of workers with unknown sex. For workers of unknown race, we generated a rate set using race-specific mortality rates weighted according to the proportion of person-time for workers with known race by state. State-referent rates may better represent the experience of the source population for the cohort than overall US rates. Lung cancer mortality rates vary considerably by geographic areas.[29,30]

Statistical Analysis

We computed SMRs for all categories of death combined and for cause-specific categories of death using SAS software, Version 9.3 (SAS Institute Inc, Cary, NC). Exact 95% CIs for a Poisson mean were calculated.[31] In addition, we evaluated the time-dependent relationship between individual inhalable carbon black exposure estimates and lung cancer mortality using Cox proportional hazards models. Cox analyses were performed using Stata v. 12.1 (StataCorp, College Station, TX). Attained age in years was used as the time-scale variable in all Cox models. Cumulative inhalable carbon black exposure was modeled both as a continuous variable and a categorical variable. Continuous cumulative inhalable carbon black exposure was modeled in increments of 100 mg/m^3·yr. Categorical cumulative exposure was modeled using three sets of cut points: ''low cut points'' (<5, 5 to <10, 10 to <20, and ≥20 mg/m^3·yr) consistent with cut points reported for the carbon black exposure score reported in the German cohort[2]; ''high cut points'' (<20, 20 to <50, 50 to <99, and ≥100 mg/m^3·yr), consistent with categories of cumulative carbon black inhalable concentrations reported in the UK study[9]; and categories on the basis of quartiles of cumulative exposure in the entry cohort of 3890 US male hourly workers (<12, 12 to <34, 34 to <72, and ≥72 mg/m^3·yr).

All Cox models controlled for age at hire, year of birth, and facility, to be comparable to the UK and German cohort studies; nevertheless, none of these factors were associated with lung cancer mortality and therefore could not be true confounding factors. In models of continuous cumulative inhalable carbon black exposure, both age at hire and year of birth were included as continuous variables. In models of categorized cumulative inhalable carbon black exposure, age at hire was included in the model categorically as earlier than 20 years, 20 to less than 30 years, 30 to less than 40 years, and 40 or more years at hire; year of birth was included in the model categorically as earlier than 1940, 1940 to 1949, 1950 to 1959, 1960 to 1969, and 1970 or later. Facilities were grouped and included in all models categorically as ''A'' (a single facility that began operations in the early 1930 s and included employees identified on Employee Roster 1—see Supplemental Table S1, http://links.lww.com/JOM/A209), ''BC'' (two facilities located in a single state and operated by the same company, one that started operations in the early 1940 s and the second that started operations in the early 1950 s, and included employees identified on Employee Roster 2), ''D'' (a single facility that began operations in mid-1930 s), or ''other'' (remaining 14 facilities, most of which began operations since 1950 and had employment records available in the years since 1960).

Cumulative exposure was lagged by 10, 15, and 20 years and ''lugged'' by 10, 15, and 20 years to evaluate time windows of exposure. The ''lugged'' cumulative exposure for each year was obtained by subtracting the lagged cumulative exposure from the cumulative exposure.[11] In a time-dependent Cox analysis, lagged cumulative exposure weights earlier exposure more heavily, while lugged exposure weights recent exposure more heavily and therefore allows evaluation of the association between more recent carbon black exposure and mortality.[11,14]

RESULTS

A total of 6634 study subjects comprising the full cohort were followed up for mortality through December 31, 2011, and contributed a total of 196,088 person-years (Fig. 1). The entry (ie, inception) cohort of 4882 contributed 138,564 person-years. The entry subcohort of 3890 male workers who began their employment in hourly jobs contributed 115,575 person-years. The SMR results from the entry cohort of 4882 consistently fell between those for the full cohort and the entry cohort of male hourly workers and therefore are not presented (available upon request). Demographic and employment characteristics for the full cohort and the entry cohort of male hourly workers broken down by plant are presented in Supplemental Tables S1 and S2 (http://links.lww.com/JOM/A209).

Vital status was traced successfully for 6535 members (98.5%) of the full cohort (Table 1). Vital status was not known for 99 study subjects in the full cohort and 60 study subjects in the entry cohort of male hourly workers. These individuals were censored as of their date of last employment (Table 1). After censoring, a total of 1947 deaths in the full cohort and 1098 deaths in the entry cohort of hourly male employees were analyzed by cause of death, including 92 and 51 deaths without an identifiable cause (ie, death certificate was not found for 4.7% and 4.6% of the deaths, respectively). These deaths were included in all-causes combined mortality only.

Mortality from all causes combined was significantly decreased (SMR = 0.78; 95% CI, 0.75 to 0.82) in the full cohort, as was mortality from all cancers combined (SMR = 0.79; 95% CI, 0.72 to 0.86) and mortality from all heart diseases combined (SMR = 0.78; 95% CI, 0.72 to 0.84) (Table 2). Mortality was decreased for these outcomes, but less pronounced in the entry cohort of male hourly workers (all causes: 0.86; 95% CI, 0.81 to 0.92; all cancers: SMR = 0.87; 95% CI, 0.77 to 0.98; all heart diseases: SMR = 0.84; 95% CI, 0.75 to 0.94). Although not among the current study hypotheses, excess mortality was observed for 2 of the 119 NIOSH categories of cause of death. For diseases of the blood-forming organs (ICD-10 codes D46.7–D46.9, D70–D75, D77, D89.2, I88, R72; ICD-9 codes 288 to 289), SMR = 2.81 (95% CI, 1.40 to 5.03 on the basis of 11 deaths) in the full cohort and SMR = 3.09 (95% CI, 1.13 to 6.73 on the basis of 6 deaths) in the entry cohort of male hourly workers (results not shown in Table 2). For peritoneal and unspecified digestive organ cancers (ICD-10 codes C26, C48; ICD-9 codes 158 to 159), SMR = 3.35 (95% CI, 1.22 to 7.29 on the basis of 6 deaths) in the full cohort and SMR = 4.39 (95% CI, 1.19 to 11.23 on the basis of 4 deaths) in the entry cohort of male hourly workers (results not shown in Table 2).

Lung Cancer Mortality

Significant deficits of lung cancer mortality were observed in the full cohort (SMR = 0.77; 95% CI, 0.67 to 0.89 on the basis of 184 deaths) but not in the entry cohort of male hourly workers (SMR = 0.87; 95% CI, 0.71 to 1.05 on the basis of 103 deaths) (Table 2). Results were similar when US national referent rates were used (Supplemental Table 3, http://links.lww.com/JOM/A209). Because approximately 10% of the observed deaths from known causes for this cohort were lung cancer deaths, we estimate that the

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TABLE 2. Observed and Expected Deaths, Standardized Mortality Ratios, and 95% Confidence Intervals Using State-Specific Referent Rates* for All Causes Combined, All Cancers Combined, and Selected Causes for Full Cohort of 6634 Carbon Black Employees and for Entry Cohort of 3890 Male Hourly Carbon Black Employees

	Full Cohort of 6634 Carbon Black Workers			Entry Cohort of 3890 Male Hourly Workers		
Cause of Death	**Observed**	**Expected**	**SMR (95% CI)**	**Observed**	**Expected**	**SMR (95% CI)**
All causes	1947	2481.4	0.78 (0.75–0.82)	1098	1272.0	0.86 (0.81–0.92)
All cancers	512	646.2	0.79 (0.72–0.86)	283	324.1	0.87 (0.77–0.98)
Cancer of the digestive organs	127	154.2	0.82 (0.69–0.98)	67	79.0	0.85 (0.66–1.08)
Esophagus	20	18.2	1.10 (0.67–1.69)	11	9.6	1.15 (0.57–2.05)
Cancer of the respiratory system	189	248.0	0.76 (0.66–0.88)	105	123.8	0.85 (0.69–1.03)
Larynx	4	8.2	0.49 (0.13–1.25)	2	4.22	0.47 (0.06–1.71)
Trachea, bronchus, and lung	184	237.9	0.77 (0.67–0.89)	103	118.6	0.87 (0.71–1.05)
Pleura	1	0.5	2.17 (0.05–12.09)	0	0.24	– (–)
Other respiratory sites	0	1.4	– (–)	0	0.75	– (–)
Cancer of the urinary organs	22	30.6	0.72 (0.45–1.09)	14	15.6	0.90 (0.49–1.51)
Bladder	15	13.3	1.13 (0.63–1.86)	8	6.5	1.23 (0.53–2.42)
Diseases of the heart	616	790.7	0.78 (0.72–0.84)	332	394.2	0.84 (0.75–0.94)
Ischemic heart disease	511	622.5	0.82 (0.75–0.90)	272	309.6	0.88 (0.78–0.99)
Diseases of the respiratory system	163	185.8	0.88 (0.75–1.02)	99	90.7	1.09 (0.89–1.33)
Pneumonia	35	45.6	0.77 (0.53–1.07)	23	22.4	1.03 (0.65–1.54)
Chronic obstructive pulmonary disease	96	104.2	0.92 (0.75–1.12)	60	50.4	1.19 (0.91–1.53)
Other respiratory system diseases	26	29.3	0.89 (0.58–1.30)	14	14.6	0.96 (0.52–1.61)

*State-specific referent rates: 196,088.1 person-years for full cohort of 6634 workers; 115,575.9 person-years for entry cohort of 3890 male hourly workers.
SMR, standardized mortality ratio.

number of lung cancer deaths reported in the analyses below may be underestimated by a total of 10 deaths in the full cohort, and about 5 in the entry cohort of male hourly workers.

In stratified analyses, no clear associations between duration of employment and lung cancer mortality were observed in the full cohort or entry cohort of male hourly workers employed for less than 20 years. In workers employed for 20 or more years, lung cancer mortality was similarly decreased in both the full cohort (SMR = 0.70; 95% CI, 0.54 to 0.90) and the entry cohort of male hourly workers (SMR = 0.74; 95% CI, 0.40 to 1.23) (Table 3). Further SMR analyses stratified by time since the first exposure or time since cessation of exposure did not identify any clear excess of lung cancers or any patterns suggesting an association with employment for either the full cohort or the entry cohort of male hourly

TABLE 3. Observed and Expected Deaths, Standardized Mortality Ratios, and 95% Confidence Intervals Using State-specific Referent Rates* for Lung Cancer According to Length of Employment, Time Since First Exposure, and Time Since Cessation of Exposure

	Full Cohort: 6634 Carbon Black Workers			Entry Cohort of 3890 Male Hourly Workers		
Exposure Surrogate	**Observed**	**Expected**	**SMR (95% CI)**	**Observed**	**Expected**	**SMR (95% CI)**
Length of employment, yrs						
1–4	63	74.9	0.84 (0.65–1.08)	53	59.9	0.88 (0.66–1.16)
5–9	28	35.3	0.79 (0.53–1.15)	22	22.2	0.99 (0.62–1.50)
10–19	32	40.6	0.79 (0.54–1.11)	14	17.5	0.80 (0.44–1.34)
≥20	61	87.0	0.70 (0.54–0.90)	14	19.0	0.74 (0.40–1.23)
Time since first exposure, yrs						
<10	4	6.3	0.63 (0.17–1.62)	3	3.9	0.76 (0.16–2.22)
10–19	6	20.1	0.30 (0.11–0.65)	3	11.4	0.26 (0.05–0.77)
20–29	34	45.5	0.75 (0.52–1.04)	22	23.3	0.95 (0.59–1.43)
≥30	140	165.9	0.84 (0.71–1.00)	75	80.0	0.94 (0.74–1.18)
Time since cessation of exposure, yrs						
0 to <1	10	33.8	0.30 (0.14–0.54)	3	11.4	0.26 (0.05–0.77)
1–4	21	18.1	1.16 (0.72–1.78)	7	6.0	1.17 (0.47–2.41)
5–14	37	50.4	0.73 (0.52–1.01)	14	16.5	0.85 (0.46–1.42)
≥15	116	135.7	0.85 (0.71–1.02)	79	84.6	0.93 (0.74–1.16)
Plant						
A	56	65.9	0.85 (0.64–1.10)	44	46.1	0.96 (0.69–1.28)
B and C	56	75.3	0.74 (0.56–0.97)	29	30.9	0.94 (0.63–1.35)
D	27	35.0	0.77 (0.51–1.12)	16	23.1	0.69 (0.40–1.12)
Other	45	61.7	0.73 (0.53–0.98)	14	18.6	0.75 (0.41–1.27)

*State-specific referent rates: 196,088.1 person-years for full cohort of 6634 workers; 115,575.9 person-years for entry cohort of 3890 male hourly workers.
SMR, standardized mortality ratio.

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workers. Additional stratified analyses for all-cause mortality are presented in Supplemental Table S4 (http://links.lww.com/JOM/A209).

Lung cancer mortality was closest to expectation at facility A in both the full cohort (SMR = 0.85; 95% CI, 0.64 to 1.10, on the basis of 56 deaths) and in the entry cohort of male hourly workers (SMR = 0.96; 95% CI, 0.69 to 1.28, on the basis of 44 deaths) (Table 3). Lung cancer mortality remained lower than expected but the magnitude varied by facility, in part reflecting considerable variability in lung cancer rates by state. Part of the remaining deficit likely is due to underascertainment of lung cancer deaths because of missing cause of death for 56 decedents at these facilities.

In Cox regression models of the full cohort, the adjusted HRs for lung cancer without lagging were not statistically significant (HR = 1.0; 95% CI, 0.6 to 1.6 for 20 to <50 mg/m^3·yr; HR = 1.3; 95% CI, 0.8 to 2.1 for 50 to <99 mg/m^3·yr; and HR = 1.4; 95% CI, 0.9 to 2.1 for ≥100 mg/m^3·yr) (Table 4) (referent group was exposed to <20 mg/m^3·yr, cut points equivalent to those reported by Sorahan et al[6]). Similarly, in analyses of cumulative exposure lagged by 10, 15, or 20 years, adjusted HRs were slightly elevated in the highest cumulative exposure categories but were of only borderline significance (Table 4). Patterns were similar when cumulative exposure category cut points were used on the basis of quartiles from the entry cohort of male hourly workers (referent group exposed to <12 mg/m^3·yr) (Table 4).

In the full cohort, using cumulative exposure categories approximate to the low cut points (in unit-years) reported by Wellman et al[2] (referent group exposed to <5 mg/m^3·yr), there were no clear or consistent patterns of exposure relative to lung cancer mortality. Although some exposure strata were above the null, hazard ratios did not consistently rise with higher categories of exposure. Statistically significant associations were seen in the 15- and 20-year lagged analyses (Table 4), but these also did not indicate an exposure–response relationship and possibly reflect variability because of small numbers of lung cancer deaths in the referent categories.

For the entry cohort of male hourly workers, no consistent association with lung cancer was observed (Table 5). Similar to the results in the full cohort, an association with lung cancer in the 15- and 20-year lagged analysis was suggested, but only when using the low cumulative exposure cut points (Table 5). Among the entry cohort of male hourly workers, the adjusted hazard ratios in lagged analyses using higher or quartile cut points were unremarkable (Table 5).

Analyses of lugged cumulative exposure were also unremarkable in both the full cohort and the male hourly cohort (Supplemental Tables 5 and 6, http://links.lww.com/JOM/A209).

When duration of employment was used as a surrogate of cumulative carbon black exposure, Cox regression analysis of lung cancer mortality in the entry cohort of male hourly workers showed no significant or consistent association with duration of employment category after adjusting for facility, age at hire, and decade of birth: compared with the referent group (1 to 4 years of employment), HR = 1.18 (95% CI, 0.72 to 1.95) for 5 to 9 years; HR = 1.03 (95% CI, 0.55 to 1.92) for 10 to 19 years; and HR = 0.83 (95% CI, 0.44 to 1.54) for 20 or more years' duration of employment.

NMRD Mortality

Mortality was similar to expected for NMRD in both cohorts (full cohort: SMR = 0.88; 95% CI, 0.75 to 1.02; entry cohort of male hourly workers: SMR = 1.09; 95% CI, 0.89 to 1.33). Mortality was slightly but nonsignificantly elevated for chronic obstructive pulmonary disease (COPD) in the entry cohort of male hourly workers (SMR = 1.19; 95% CI, 0.91 to 1.53) but not in the full cohort (SMR = 0.92; 95% CI, 0.75 to 1.12) (Table 2).

TABLE 4. Hazard Ratios and 95% Confidence Intervals for Lung Cancer by Inhalable Carbon Black Exposure for Full Cohort of 6634 Workers*

	No Lugging or Lagging		Exposure Lagged 10 yrs		Exposure Lagged 15 yrs		Exposure Lagged 20 yrs	
	n	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)
Cumulative exposure, per 100 mg/m^3·yr per 100	184	1.1 (1.0–1.1)	184	1.1 (1.0–1.2)	184	1.1 (1.0–1.2)	184	1.1 (1.0–1.2)
Cumulative exposure, mg/m^3·yr (low cut points)								
<5	7	Reference	10	Reference	10	Reference	14	Reference
5 to <10	14	2.1 (0.8–5.3)	14	2.0 (0.9–4.6)	14	2.8 (1.2–6.6)	18	4.0 (1.9–8.4)
10 to <20	13	1.7 (0.7–4.2)	12	1.4 (0.6–3.4)	16	2.7 (1.2–6.0)	18	3.2 (1.5–6.7)
≥20	150	2.0 (0.9–4.3)	148	1.9 (1.0–3.7)	144	2.7 (1.4–5.5)	134	2.9 (1.5–5.4)
Cumulative exposure, mg/m^3·yr (high cut points)								
<20	34	Reference	36	Reference	40	Reference	50	Reference
20 to <50	28	1.0 (0.6–1.6)	29	1.0 (0.6–1.7)	28	1.0 (0.6–1.7)	28	1.0 (0.6–1.5)
50 to <99	40	1.3 (0.8–2.1)	40	1.4 (0.9–2.3)	42	1.5 (1.0–2.4)	38	1.3 (0.8–2.1)
≥100	82	1.4 (0.9–2.1)	79	1.5 (1.0–2.3)	74	1.5 (1.0–2.3)	68	1.4 (0.9–2.2)
Cumulative exposure, mg/m^3·yr (cut points on the basis of quartiles of cumulative exposure after women and white-collar workers excluded)								
<12	24	Reference	27	Reference	27	Reference	39	Reference
12 to <34	21	1.1 (0.6–1.9)	24	1.2 (0.7–2.1)	26	1.5 (0.9–2.6)	22	1.0 (0.6–1.8)
34 to <72	41	1.3 (0.8–2.1)	39	1.2 (0.8–2.1)	41	1.6 (0.9–2.6)	42	1.4 (0.8–2.2)
≥72	98	1.4 (0.9–2.3)	94	1.5 (0.9–2.3)	90	1.7 (1.1–2.8)	81	1.4 (0.9–2.2)

*Models adjusted for age at hire, decade of birth, and plant (A, BC, D, OTHER).
CI, confidence interval; HR, hazard ratio.

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TABLE 5. Inhalable Carbon Black Hazard Ratios and 95% Confidence Intervals for Lung Cancer by Carbon Black Exposure for Entry Cohort of 3890 Male Hourly Workers*

	No Lugging or Lagging		Exposure Lagged 10 yrs		Exposure Lagged 15 yrs		Exposure Lagged 20 yrs	
	n	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)
Cumulative exposure, per 100 mg/m^3·yr	103	1.1 (1.0–1.2)	103	1.1 (1.0–1.2)	103	1.0 (1.0–1.2)	103	1.0 (1.0–1.2)
Cumulative exposure, mg/m^3·yr (low cut points)								
<5	3	Reference	5	Reference	5	Reference	7	Reference
5 to <10	12	1.5 (0.4–5.7)	12	1.8 (0.6–5.4)	12	3.4 (1.1–10.9)	13	5.1 (1.8–14.6)
10 to <20	8	0.9 (0.2–3.5)	7	0.9 (0.3–3.0)	8	2.0 (0.6–6.5)	10	3.3 (1.1–9.8)
≥20	80	1.1 (0.3–3.6)	79	1.3 (0.5–3.6)	78	2.6 (0.9–7.4)	73	3.3 (1.3–8.4)
Cumulative exposure, mg/m^3·yr (high cut points)								
<20	23	Reference	24	Reference	25	Reference	30	Reference
20 to <50	20	0.8 (0.4–1.4)	20	0.9 (0.5–1.6)	20	1.0 (0.5–1.8)	22	1.0 (0.6–1.9)
50 to <99	26	1.1 (0.6–2.1)	26	1.3 (0.7–2.4)	28	1.6 (0.8–2.9)	27	1.5 (0.8–2.7)
≥100	34	1.2 (0.6–2.1)	33	1.4 (0.7–2.5)	30	1.5 (0.8–2.8)	24	1.2 (0.6–2.3)
Cumulative exposure, mg/m^3·yr (cut points on the basis of quartiles of cumulative exposure after women and white-collar workers excluded)								
<12	17	Reference	19	Reference	19	Reference	23	Reference
12 to <34	14	0.7 (0.4–1.5)	14	0.8 (0.4–1.6)	14	1.0 (0.5–2.0)	16	1.2 (0.6–2.3)
34 to <72	29	0.9 (0.4–1.7)	29	0.9 (0.5–1.8)	30	1.3 (0.7–2.4)	32	1.4 (0.7–2.5)
≥72	43	1.0 (0.5–1.9)	41	1.1 (0.6–2.0)	40	1.4 (0.7–2.7)	32	1.2 (0.6–2.3)

*Models adjusted for age at hire, year of birth, and plant (A, BC, D, other).
CI, confidence interval; HR, hazard ratio.

As with lung cancer, SMR analyses stratified by length of employment, time since the first exposure, or time since cessation of exposure did not identify any clear excess of NMRD or COPD or any patterns suggesting an association with employment for either the full cohort or the entry cohort of male hourly workers (Supplemental Tables S7–S8, http://links.lww.com/JOM/A209). Differences in NMRD and COPD mortality were observed by facility and tended to be nonsignificantly elevated for plants A and D and decreased for plants B and C.

Cox regression analyses of the full cohort and the entry cohort of male hourly workers also produced no clear or consistent patterns of exposure–response for NMRD mortality or COPD mortality (Supplemental Tables S9 to S12, http://links.lww.com/JOM/A209).

DISCUSSION

This study updates mortality through 2011 and evaluates lung cancer mortality risks in relation to individual exposure estimates in the industry-wide cohort of US carbon black employees, the largest epidemiological cohort of workers engaged in carbon black manufacturing. This study also identified an inception subcohort of nonadministrative male hourly employees to allow a greater focus on those most likely exposed to carbon black, and to eliminate survivor bias present in cross-sectional cohorts. We also used aggressive and redundant mortality follow-up procedures to maximize the ascertainment of fact and causes of death. Vital status was ascertained for 98.5% of the cohort and cause of death determined for 95% of decedents.

As seen in the previous update, mortality for this cohort overall remains low, with some significant deficits noted that cannot be explained by incomplete ascertainment of deaths common in studies examining mortality in periods before the advent of the NDI in 1979. Among the 119 specific causes of death examined, excess mortality was observed for the NIOSH categories ''diseases of the blood forming organs'' and ''cancers of the peritoneum and other digestive organs.'' We reviewed the specific causes of death reported for decedents in these broad categories, and confirmed heterogeneity of specific causes of death within these categories (see Supplemental Appendix, http://links.lww.com/JOM/A209).

Lung cancer mortality was consistently lower than expected among both the full cohort of 6634 employees and the entry cohort of 3890 male hourly workers, providing no support for the hypothesis that employment in carbon black production increases lung cancer mortality. We found no consistent relationship between the risk of lung cancer mortality with carbon black exposure lagged or lugged in the full cohort or in the entry cohort of male hourly workers. The few associations seen when exposures were lagged did not differ across lagging periods for the high cut-point categories. These findings possibly reflect differing lung cancer risks among those hired earlier in the employment period for the study, but could also be due to confounding by smoking, small numbers of lung cancer deaths among those in the referent exposure categories (when low cut points were used), an actual relationship reflecting long latencies, or a combination of these. The deficit in lung cancer mortality observed in the 10 to 19 years since the first exposure in both cohorts suggests that workers hired into the study plants were less likely to have been smokers (full cohort: SMR = 0.30; 95% CI, 0.11 to 0.65; entry cohort of male hourly workers: SMR = 0.26; 95% CI, 0.05 to 0.77). The absence of a clear relationship between estimated carbon black exposure and lung cancer is consistent with the findings from the UK and German carbon black studies, although the lack of an excess of lung cancer mortality in this cohort is a striking difference.

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TABLE 6. Comparison of the Characteristics and Results From the Three Carbon Black Manufacturing Cohort Studies

Characteristics/Description	UK Cohort (8, 11)	German Cohort (5–8)	US Cohort
Cohort description			
Size of cohort			
Full cohort	1,147	1,535	6,634
Inception subcohort	NA	1,276	3,890
Follow-up period	1951–2004	1976–1998	1940–2011
Person-years at risk			
Full cohort	NR (11) 27,550 (9)	25,759	196,088
Inception subcohort	NA	21,214	115,576
Inclusion criteria			
Full cohort	Male manual workers at five facilities; all employed ≥1 yr and all employed before 1975	Male manual workers at one facility; all employed ≥1 yr between 1920s and 1997, survived until 1975	Men and women employed at any of 18 carbon black facilities; all employed ≥1 yr
Inception subcohort	NA	Hired on or after January 1, 1960	Male hourly workers hired on or after facility cohort enumeration date, no earlier than 1940
Vital status ascertainment			
Full cohort			
Alive	600 (52.3%)	1,184 (77.1%)	4,588 (69.2%)
Dead	514 (44.8%)	332 (21.6%)*	1,947 (29.3%)†
Lost to follow-up	33 (2.9%)‡	19 (1.2%)§	99 (1.5%)
Inception subcohort			
Alive	NA	1,053 (82.5%)	2,732 (70.2%)
Dead	NA	218 (17.1%)	1,098 (28.2%)
Lost to follow-up	NA	5 (0.4%)	60 (1.5%)
Cohort characteristics			
Average age at end of follow-up, yrs			
Full cohort	NR	54.6 (median = 56.5)	61.9 (median = 62.5)
Inception subcohort	NA		59.7 (median = 59.9)
Average duration of employment, yrs			
Full cohort	NR	14.5	13.2 (median = 8.6)
Inception subcohort		NR	10.1 (median = 5.9)
Average length of follow-up, yrs			
Full cohort	NR	16.8	29.6 (median = 29.6)
Inception cohort	NA	16.7§	29.7 (median = 29.9)
Exposure			
Exposure assessment	JEM, inhalable dust on the basis of existing exposure monitoring data (collected during 1987–1995) at two facilities still operating in the late 1990s: 12 job categories over six 5- or 10-yr calendar periods; data for factory 4 was used to estimate exposures for factories 2, 3, and 5	JEM, existing exposure monitoring data not available, semiquantitative score (0–20) on the basis of expert judgment; score reflects intensity of exposure: 0 = no contact with carbon black; 20 = carbon black shoveled into bags	JEM, inhalable dust on the basis of existing exposure monitoring data (primarily total dust, collected 1979–2007 during industry-wide sampling campaigns); linear regression models to interpolate summary values for years between sampling data; summary values extrapolated to 1960 on the basis of slope of regression for the years when IH data were available
Average cumulative exposure			
Full cohort	NR	25 carbon black unit-years	76.0 mg/m^3·yr (median = 33.1 mg/m^3·yr)
Inception cohort	NA	18 carbon black unit-years	69.8 mg/m^3·yr (median = 33.5 mg/m^3·yr)
Data analysis			
Lung cancer deaths, *n*			
Full cohort	67	50	184
Inception cohort	NA	40	103
Lung cancer results—external comparison			
Full cohort	SMR = 1.46 (95% CI, 1.13–1.85)‖	SMR = 2.18 (95% CI, 1.61–2.87)¶ SMR = 1.81 (95% CI, 1.34–2.39)**	SMR = 0.77 (95% CI, 0.67–0.89)††

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TABLE 6. (*Continued*)

Characteristics/Description	UK Cohort (8, 11)	German Cohort (5–8)	US Cohort
Inception cohort		SMR = 2.92 (95% CI, 2.09–3.98)[¶] SMR = 2.42 (95% CI, 1.73–3.30)[**]	SMR = 0.87 (95% CI, 0.71–1.05)[††]
Lung cancer results—internal comparison			
Full cohort[‡‡]			
<20 mg/m^3·yr	RR = 1.0 (reference)		HR = 1.0 (reference)
20–49 mg/m^3·yr	RR = 0.89 (95% CI, 0.46–1.72)		HR = 1.0 (95% CI, 0.6–1.6)
50–99 mg/m^3·yr	RR = 0.61 (95% CI, 0.25–1.48)		HR = 1.3 (95% CI, 0.8–2.1)
≥100 mg/m^3·yr	RR = 0.70 (95% CI, 0.30–1.63)		HR = 1.4 (95% CI, 0.9–2.1)
Per 100 unit-years (continuous)	NA	HR = 0.52 (P = 0.22)[§§]	NA
Inception cohort			
<20 mg/m^3·yr	NA		HR = 1.0 (reference)
20–49 mg/m^3·yr	NA		HR = 0.8 (95% CI, 0.4–1.4)
50–99 mg/m^3·yr	NA		HR = 1.1 (95% CI, 0.6–2.1)
≥100 mg/m^3·yr	NA		HR = 1.2 (95% CI, 0.6–2.1)
Per 100 unit-years (continuous)	NA	HR = 0.36 (P = 0.24)[§§]	NA
Adjustments for internal analysis	Attained age[‖‖]	Attained age, date of birth, age at hire	Attained age, decade of birth, age at hire, plant (A, BC, D, other)

[*]Number of decedents with unknown cause of death (% of decedents): 7 (2.1%).
[†]Number of decedents with unknown cause of death (% of decedents): 92 (4.8%) in full cohort, 51 (4.6%) in inception subcohort.
[‡]A total of 30 emigrated, three with unknown vital status.
[§]Dr Peter Morfeld, personal communication, July 21, 2014.
[‖]On the basis of national mortality rates for England and Wales, excess mortality restricted to two facilities: factory 1 (SMR = 2.19; 95% CI, 1.40 to 3.26 on the basis of 24 deaths) and factory 5 (SMR = 2.59; 95% CI, 1.29 to 4.64 on the basis of 11 deaths).
[¶]On the basis of national mortality rates for Germany.
[**]On the basis of rates for North Rhine-Westphalia.
[††]On the basis of state rates.
[‡‡]UK results are from Sorahan et al.[9]
[§§]95% confidence interval not reported.
[‖‖]Additional internal analyses adjusted for period from first employment, employment status, year of commencing employment, and factory; mortality patterns remained similar to analyses adjusted for attained age only.
CI, confidence interval; HR, hazards ratio calculated using Cox proportional hazards models; IH, industrial hygiene; JEM, job-exposure matrix; NA, not applicable; NR, not reported; RR, relative risk calculated using Poisson regression; SMR, standardized mortality ratio.

Excess mortality from NMRD was not observed in the full cohort or the entry cohort of male hourly workers when compared with state referent rates; nevertheless, the entry cohort of male hourly workers showed a 19% relative excess in COPD deaths. Cox proportional hazards models did not show an association between increasing cumulative inhalable carbon black exposure and COPD mortality, although models consistently showed estimates of relative risk above the null. Nevertheless, numbers of COPD in the referent group were few, and could have contributed both to the slightly increased point estimates and to their imprecision.

This analysis allowed us to compare cohort characteristics, methods, and lung cancer results according to exposure estimates from studies of the three cohorts (Table 6) to address limitations identify by the IARC.[10] Previously, the IARC[10] noted an ''unusually low'' SMR from lung cancer for the category 20 to 29 years since hire (SMR = 0.79; 95% CI, 0.53 to 1.18) on the basis of 24 deaths in the US cohort followed up through 2003.[4] For mortality through 2011, low SMRs for lung cancer were again observed among workers with 20 to 29 years since hire (SMR = 0.75; 95% CI, 0.52 to 1.04 on the basis of 34 deaths) and 30 years or more since hire (SMR = 0.84; 95% CI, 0.71 to 1.0 on the basis of 140 deaths) in the full cohort. These ''low'' SMRs were attenuated in the entry cohort of male hourly workers through 2011: SMR = 0.95 (95% CI, 0.59 to 1.43) on the basis of 22 lung cancer deaths and SMR = 0.94 (95% CI, 0.74 to 1.18) on the basis of 75 deaths for 20 to 29 and ≥30 years since hire, respectively. The combined deficit lung cancer deaths for these categories were only 6, about the number expected among decedents in this subcohort with unknown cause of death. Although the lung cancer deficit was noticeable for the category 10 to 19 years since hire on the basis of few reported lung cancer deaths, this result possibly represents random variation because of small numbers of observed and expected deaths. The role of smoking and the impact of the clear rise and fall of lung cancer rates among men in the United States over the duration of the study also cannot be overlooked as a possible contributing factor.

Assuming that lung cancer deaths accounted for 10% of the 92 deaths of unknown cause in this study (on the basis of the proportion of known lung cancer deaths among those with known causes of death), we have underestimated lung cancer deaths by 9 deaths. Increasing the observed by 9, however, only modestly increases the SMR for lung cancer: SMR = 0.81 (95% CI, 0.70 to 0.94). Thus, the deficit of lung cancer mortality is more likely due to the lower prevalence of smoking among cohort members documented by Harber et al.[16]

Several differences are seen at first inspection, in SMR results especially, across studies (Table 6). First, the US cohort showed a healthy worker effect that diminished with increasing time since hire, as expected. Mortality from all causes increased from an SMR of 0.49 (95% CI, 0.39 to 0.62) for less than 10 years since the first exposure to an SMR of 0.87 (95% CI, 0.83 to 0.92) for 30 years or more since the first exposure, which also reflects an expected diminishing of the healthy worker effect over time. Similar patterns

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of increasing SMRs with time since hire have been reported in other studies[32] and the resulting bias described by others.[33,34] This pattern was also seen with time since cessation of exposure (Table 3).

In contrast to the US study, both the UK study[11] and the German study[5] showed excess mortality overall: all-cause SMR = 1.10 (95% CI, 1.01 to 1.21) on the basis of 493 observed deaths through 2004 and all-cause SMR = 1.20 (95% CI, 1.08 to 1.34) on the basis of 332 observed deaths through 1998, respectively. Time-related factors affecting the structure of the US, UK, and German cohorts reflect different types of selection forces and likely explain the differences in the cohorts. Differences in the underlying distributions of age across the three different cohorts may also have contributed to residual confounding by age that is inherent when comparing SMRs from populations with different age profiles.

Some important methodological differences in the ways the cohorts were defined may also contribute to the seemingly inconsistent results for mortality from all causes combined and lung cancer. In the German study, a ''fixed'' cohort began follow-up in 1976, although 52% of the cohort was hired before 1970 and 36% of the cohort had left employment before 1980. In contrast, follow-up began as early as 1951 for the UK study, a fixed census cohort comprised entirely of workers hired before 1975. At least 24% of the 1147 male manual workers employed 1 year or more had left employment by the late 1970 s, and only 44 (4%) were still employed at some time during the 1990 s.[11]

By starting follow-up in 1976 for the German cohort, the accrual of ''active employment'' person-time was limited (and eliminated for some study subjects). ''Active employment'' person-time represents person-time accrued when study subjects were working and most subject to healthy selection forces, coupled with little to no actual risk of mortality. By definition, some cohort members left employment between 1960 (when the inception cohort was enumerated) and 1976 when follow-up began. These ''inactive'' person-years at risk after study subjects left employment at the facility are accompanied by the greatest risk of mortality.[35] Nearly one third of the cohort members were former workers when follow-up began, thus excluding their contribution of person-years during active employment from the analysis. As a result, older, formerly employed study subjects contributed deaths to the numerator of the SMR, while contributing relatively few person-years to the denominator. This likely resulted in underestimation of expected deaths and artificial inflation of the SMRs. Furthermore, by restricting the analysis to include sizeable proportions of workers (whether actively employed or not) who were first employed many years before follow-up began, a healthy worker effect may be mitigated.[34] For workers hired before 1976, a minimum of 1 year to a maximum of 16 years elapsed before follow-up began, whereas deaths and person-years for study subjects who died before 1976 were not included in the analysis. An association with exposure indicators would not be expected if the apparent increase in mortality resulted from these methodological problems.

Therefore, we performed several sensitivity analyses by restricting the entry cohort of male hourly employees to resemble the German and UK cohorts. We further evaluated the findings in the US cohort by restricting the entry cohort of male hourly workers for additional sensitivity analyses. For comparison to the German cohort, we restricted the entry cohort of male hourly workers to 3610 traced alive as of 1979, when states were required by statute to report all deaths that occurred to the NDI. The lung cancer SMR increased to an SMR of 0.93 (95% CI, 0.75 to 1.14) from an SMR of 0.87 (95% CI, 0.71 to 1.05). Lung cancer hazard ratios in the restricted entry cohort of male hourly workers were largely unchanged when carbon black exposure was included as a continuous variable in the Cox regression model, regardless of lagging or lugging interval (results available upon request). Lung cancer hazard ratios were consistently lower when carbon black was included as a categorical variable in the Cox regression models (results available upon request).

To evaluate bias from including workers from three facilities for which follow-up began in 1989 or more recently, and thus likely had inadequate disease induction/latency time, we performed an analysis in which we excluded these 268 study subjects from the entry cohort of male hourly workers (all-causes combined SMR = 0.87; 95% CI, 0.82 to 0.92; and lung cancer SMR = 0.87; 95% CI, 0.71 to 1.06).

For comparison to the UK cohort, we performed an analysis of the entry cohort of male hourly workers restricted to 2008 study subjects (52%) who had left employment before 1990 (lung cancer SMR = 0.93; 95% CI, 0.75 to 1.14 on the basis of 92 deaths). This restriction effectively eliminated the observed healthy worker effect in the US cohort (all-causes combined SMR = 0.95; 95% CI, 0.89 to 1.01 on the basis of 983 deaths).

Potential confounding has been evaluated by the German investigators in sensitivity analyses and bias analyses. Additional analyses conducted on the German cohort identified previous exposures to quartz and cigarette smoking as risk factors for lung cancer.[6] Morfeld et al[8] reported that the lung cancer SMR estimates might be biased upward by 30% to 50% as a result and conducted sensitivity analyses. The lung cancer SMR for the inception cohort was 1.57 (95% CI, 1.11 to 2.17, local rates), 1.67 (95% CI, 1.17 to 2.30, state rates), or 1.73 (95% CI, 1.23 to 2.40, national rates) after adjusting for previous exposure to quartz and smoking.[8] Morfeld and McCunney also conducted a Bayesian analysis to adjust SMRs for bias from smoking and previous occupational exposures and calculated the range of the adjusted lung cancer SMR as 1.32 (central 95% region 0.7 to 2.1) to 1.0 (central 95% region 0.2 to 3.3).[12]

Information on individual smoking habits was not available in the US cohort, and there was no excess lung cancer or excess of tobacco-related diseases. Harber et al[16] surveyed 1755 carbon black workers—employed at facilities included in this study—who participated in a medical surveillance program during the year 2000. Harber et al[16] reported that 22% of respondents were current smokers, 25% were former smokers, and 53% had never smoked. The percentage of self-reported nonsmokers varied from 42% to 69% across carbon black facilities, suggesting considerable variation by location. On the basis of a national survey of smoking habits in the United States in 2000, 25.7% of men were active smokers, 28.7% were former smokers, and 45.6% had never smoked.[36] Albeit a crude comparison, it seems that carbon black workers in 2000 had smoking prevalence no higher than that of the United States, and possibly lower. A lower smoking prevalence among carbon black workers is supported by a deficit of both cardiovascular and lung cancer mortality.

There was no information on smoking in the UK cohort; nevertheless, mortality from other tobacco-related diseases was slightly increased, albeit based on small numbers (6 observed cancers of the esophagus compared with 3.7 expected and 6 observed cancers of the bladder compared with 3.5 expected).[9] NMRD mortality was similar to expected (SMR = 1.07; 95% CI, 0.75 to 1.49).[9]

Overall, there is evidence from industrial hygiene surveys in the United States and UK that average intensities of carbon black exposure decreased over time. Therefore, the overall estimates of lung cancer mortality observed in the UK and German cohorts may be biased away from the null because of possible confounding by time since hire, which is related to both cumulative exposure and lung cancer induction and latency. Workers first employed in the earliest years and who survived until follow-up began were more likely to be exposed to higher average intensities, and therefore higher cumulative inhalable carbon black. These workers also contributed person-time to the oldest age groups where lung cancer mortality rates, overwhelmingly because of tobacco smoking, are

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higher. In contrast, workers employed on or after the date follow-up began are more likely to be exposed to lower average intensities of carbon black and experience lower cumulative exposures to carbon black because they had not worked as long, and to contribute person-time to younger age groups for which lung cancer mortality rates are low.

CONCLUSIONS

Aggressive tracking of an established cohort to reduce under-ascertainment of lung cancer mortality, and defining an inception subcohort to reduce potential survivor bias, confirmed the lack of any excess of lung cancer mortality in the US carbon black industry cohort. Quantitative exposure–response analyses were performed to elucidate possible underlying relationships between cumulative carbon black exposure and lung cancer risk among US carbon black workers, the largest cohort of carbon black workers to date. Our exposure–response results are compatible with results of the UK and German carbon black cohort studies that showed no consistent patterns of increased lung cancer risk in relation to estimates of carbon black exposure, duration of employment, or semiquantitative estimates of exposure. This study further suggests that carbon black exposure levels prevalent in the US carbon black production industry (ie, 10 to 50 mg/m^3) from the 1970 s into the 1990 s are not associated with the risk of lung cancer. Regardless of whether exposure was based on lagged, lugged, or total cumulative estimates, no consistent association was seen with lung cancer or NMRD mortality.

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