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RESEARCH ARTICLE

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The effect of age on the relative risk of lung cancer mortality in a cohort of chromium production workers

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Abstract

Background: Hexavalent chromium has been found to increase the risk of lung cancer in occupational studies. It has been suggested that the relative risk of lung cancer may vary by age.

Methods: The cohort examined is the Baltimore cohort of chromium production workers. The effect of age on the lung cancer risk from hexavalent chromium exposure was examined using a conditional Poisson regression modeling approach of Richardson and Langholz (R&L) and Cox models with interaction terms of age and cumulative hexavalent chromium exposure.

Results: The inclusion of multiple age groups in the R&L approach suggests the existence of an age effect that is also supported by a Cox proportional hazard analysis. The hazard ratio in Cox models with age-cumulative exposure interaction terms was significantly elevated for the youngest age group and significantly decreased for the oldest age group.

Conclusions: Our analyses are consistent with the observation that younger chromium production workers have a greater lung cancer risk than older workers.

KEYWORDS

chromium (VI), conditional Poisson regression, lung cancer, proportional hazard, Richardson Langholz

1 | INTRODUCTION

The lung cancer risk from exposure to hexavalent chromium (Cr(VI)) in the occupational setting is well-established, particularly for the chromate-producing industry.[1-5] The current study is based on a cohort mortality study of workers at a chromium production plant in Baltimore, MD.[2] The study has previously been described.[1,2] Results of the study[1] were used to derive the Occupational Safety and Health Administration's permissible exposure level for Cr(VI).[6] The study[1] was also used to derive a quantitative risk estimate for hexavalent lung cancer,[7] which became the basis of the National Institute of Occupational Safety and Health recommended exposure limit for Cr(VI).[5]

Poisson regression and proportional hazards modeling have previously been used for risk estimates of Cr(VI) for both the Baltimore and the Painesville, Ohio cohorts of chromium production workers.[7-9] These studies do not consider the effect of age on chromium exposures. In addition to proportional hazards modeling,[10] the current study employs the conditional Poisson regression approach proposed by Richardson

Abbreviations: CI, confidence interval; IRB, Institutional Review Board; R&L, Richardson and Langholz; RR, relative risk; SE, standard error.

and Langholz (R&L)[11] to estimate the relative risk (RR) per unit of cumulative exposure. An advantage of the R&L modeling procedure is that it does not require the merging of strata to reduce the number of stratum-associated parameters to be estimated. In the current study, the R&L method allowed us to examine the effect of age on the RR. The effect of interaction between age and cumulative exposure on the risk was further explored using the Cox proportional hazards model.[10]

2 | MATERIALS AND METHODS

Since the current study involves only certain additional statistical analyses to the data reported in Gibb et al,[2] no new Institutional Review Board (IRB) approval is required.

2.1 | Study population

On 1 August 1950, a new mill and roast plant was completed at the chromium production facility in Baltimore, and extensive exposure information on Cr(VI) began being collected from that date forward. Male workers who began work at the chromium production facility on or after 1 August 1950 were included in the study.[1,2] Estimates of exposure to Cr(VI) (CrO_3) were assigned by job title and based on ~70 000 exposure measurements of airborne Cr(VI) concentration spanning the period of 1 August 1950 through July 1985, the date that operations at the plant ceased. Vital status follow-up was through 31 December 2011.[2] Smoking status (yes/no) at the time of employment was available for 93% of the cohort.

The cohort included 2354 workers (1243 White, 879 non-White, and 232 individuals of unknown race).[2] There were 91 186 person-years of observation, 1613 deaths from all causes, and 217 lung cancer deaths.[2] There was a high proportion of cigarette smokers and any smoking (includes cigarettes, cigars, and pipes) in the cohort. About 80%, 79%, and 65% of Whites, non-Whites, and race unknown were smokers, respectively. The vast majority of lung cancer deaths occurred among cigarette smokers (93%, n = 202); 2% (n = 4) of lung cancer cases occurred among nonsmokers; 5% (n = 11) of lung cancer cases occurred among individuals whose smoking status was unknown.[2]

Expected deaths for those with race unknown assumed a race distribution similar to the rest of the cohort. The standardized mortality ratio (SMR) for cancer of the trachea, lung, and bronchus was 1.63 (95% confidence interval [CI], 1.42-1.86); the SMR was derived using United States national rates.[2] A trend test for lung cancer mortality by cumulative Cr(VI) quartile was significant although the response across quartiles was not monotonic. When the mortality analysis was limited to smokers, the observed/expected lung cancer mortality became more pronounced within each exposure quartile, and the exposure response across quartiles became monotonic.[2] Only four lung cancer cases did not smoke which restricted the ability to test for smoking × Cr(VI) interaction.[2] The odds of lung cancer by number of nasal irritations (eg, irritated nasal septum, ulcerated nasal septum, etc) demonstrated an increased risk of lung cancer by number of irritations.[2]

2.2 | Statistical methods

The age effect on the risk of lung cancer associated with exposure to Cr(VI) was evaluated using two statistical methods: (a) the conditional Poisson regression modeling approach of Richardson and Langholz (R&L) and (b) Cox proportional hazard models with interaction terms of age and cumulative Cr(VI) exposure.

2.2.1 | R&L approach

Rather than using the standard Poisson likelihood, the R&L approach maximizes an "alternative" expression for the likelihood that avoids estimation of the stratum-specific parameters by treating them as nuisance terms. This property is made possible by separating and then canceling the nuisance terms in the likelihood function. All individual workers in the cohort contributed to follow-up time and events in a stratum defined by age and smoking status, which results in a broad range of cumulative exposures (exposure, hereafter).

In general, a general relative rate model with binary indicator variables for the k levels of strata, $S_1, \ldots, S_k$, and an exposure variable Z can be expressed as $h(\alpha_s, \beta) = \exp(\alpha_1 S_1 + \ldots + \alpha_k S_k + \gamma x) g(\beta, Z)$, where α_s are the strata-specific parameters, and $g(\beta, Z)$ is the relative hazard rate due to the exposure Z. This model encompasses log-linear model forms, the Cox proportional hazards model, and a linear excess relative rate. The exponential form of this model is the following.

$$g(\beta, Z) = \exp(\beta Z).$$

Under this model structure, the contribution of the sth stratum of the data to the log-likelihood is given by:

$$l_s(\beta) = \ln[\prod_{z \varepsilon R_s} g(z; \beta)^{c_{sz}}] - c_s[\ln(\sum_{z \varepsilon R_s} P_{sz} g(z; \beta))],$$

where R_s is the set of individuals with unique exposure z in the stratum s, and c_s is the number of cases in the stratum s. This log-likelihood is a function only of parameter β. The optimization of the likelihood function was done using the R statistical package, using R optimization routines, nonlinear minimization, and/or optimize (stat.ethz.ch/R-manual/R-devel/library/stats/html/nlm.html).[12]

The effect of age was explored with different numbers of age groups and 0, 5, 10, and 15 year lag times. At least 20 lung cancer cases were included in each group to stabilize the model fitting.

2.2.2 | Cox modeling

Proportional hazards modeling of the age·exposure interaction with different polynomial degrees was done as follows:

Model 1. (Time, Event) ~ Exposure + Age × Exposure + Smoking

Model 2. (Time, Event) ~ Exposure + Age × Exposure + Age^2 × Exposure + Smoking

TABLE 1 Results of proportional hazards modeling of cumulative chromium exposure (per mg CrO_3/m^3-y) by different lag periods, adjusted for smoking (Wald-based CIs)

Lag period (y)	β	SE	Hazard ratio	95% CI	−2 Log(L)
0	.4712	0.1133	1.60	1.28-2.00	2830.23
1	.4739	0.1135	1.61	1.29-2.01	2830.14
2	.4768	0.1137	1.61	1.29-2.01	2830.05
5	.4868	0.1145	1.63	1.30-2.04	2829.80
10	.4939	0.1197	1.64	1.30-2.07	2830.52
15	.4812	0.1333	1.62	1.25-2.10	2833.03
20	.4764	0.1497	1.61	1.20-2.16	2834.99

Abbreviations: CI, confidence interval; SE, standard error.

Model 3. (Time, Event) ~ Exposure + Age × Exposure + Age^2 × Exposure + Age^3 × Exposure + Smoking

The proportional hazards models with interaction terms were conducted with 0, 1, 2, 5, 10, 15, and 20 year lag periods; the R& L models were fitted with lag periods of 0, 5, 10, and 15 years. The proportional hazards models and the R&L models were fitted using cumulative Cr(VI) exposure in mg CrO_3/m^3-years. All proportional hazards models were run using SAS Version 9.4.[13]

3 | RESULTS

The fit of the Cox proportional hazards models of the lung cancer risk adjusted for smoking were similar for all lag periods (0, 1, 2, 5, 10, 15, and 20 years); the best fit was for the 5-year lag (Table 1).

Results using the R&L approach with smoking in the model are provided for 1, 2, 3, 4, 5, and 6 age groups (Table 2). The age groups are shown below the table. The RR is highest for the

TABLE 2 Results for relative exponential exposure-response (R&L) model $g(\beta z) = \exp(\beta z)$, adjusted for smoking (Wald-based CIs)

No. of age groups[a]	Lag (y)	β	SD	$RR = \exp(\beta z)$	95% CI	−2Log(L)
1	0	.454	0.098	1.57	1.30-1.91	9283.51
	5	.454	0.098	1.57	1.30-1.91	9283.62
	10	.451	0.101	1.55	1.29-1.91	9286.50
	15	.414	0.108	1.51	1.22-1.87	9291.89
2	0	.454	0.098	1.57	1.30-1.91	9283.50
	5	.461	0.098	1.59	1.31-1.92	9282.79
	10	.463	0.100	1.59	1.31-1.93	9284.08
	15	.474	0.107	1.60	1.30-1.98	9286.46
3	0	.915	0.047	2.50	2.28-2.74	8854.75
	5	.933	0.048	2.59	2.31-2.79	8846.57
	10	.982	0.050	2.67	2.42-2.94	8845.78
	15	1.088	0.056	2.97	2.66-3.31	8848.71
4	0	.506	0.133	1.66	1.28-2.15	4327.08
	5	.522	0.133	1.69	1.30-2.19	4326.07
	10	.548	0.139	1.73	1.32-2.27	4325.97
	15	.599	0.152	1.82	1.35-2.45	4325.95
5	0	1.179	0.036	3.25	3.03-3.49	8153.85
	5	1.246	0.036	3.48	3.24-3.73	8091.17
	10	1.387	0.040	4.00	3.70-4.33	8035.39
	15	1.559	0.044	4.75	4.36-5.18	8030.41
6	0	1.142	0.036	3.13	2.92-3.36	8253.33
	5	1.164	0.036	3.20	2.98-3.44	8235.51
	10	1.200	0.038	3.39	3.08-3.58	8238.56
	15	1.375	0.043	3.95	3.64-4.30	8223.38

Abbreviations: CI, confidence interval; R&L, Richardson and Langholz; RR, relative risk; SD, standard deviation.

[a]One age group (all ages, 15-96); two age groups (≥15 to 65 and ≥65); three age groups (ages ≥15 to 60, ≥60 to ≥70); four age groups (≥15 to 60, ≥60 to 65, ≥65 to 75, and ≥75); five age groups (ages ≥15 to 60, ≥60 to 65, ≥65 to 70, ≥70 to 75, and ≥75); six age groups (ages ≥15 to 55, ≥55 to 60, ≥60 to 65, ≥65 to 70, ≥70 to 75, and ≥75).

TABLE 3 Maximum likelihood estimates for three models examining interaction of cumulative hexavalent chromium exposure and age (in years) with smoking in the models

Parameter	Parameter estimate	Standard error	χ^2	*P*-value
Model 1: (Time, Event) ~ Exposure + Age × Exposure + Smoking				
Exposure	8.78775	1.16328	57.0667	<.0001
Age × Exposure	−0.12800	0.01891	45.8390	<.0001
Smoking (1/0)	−0.00359	0.03141	0.0130	.9091
Model 2: (Time, Event) ~ Exposure + Age × Exposure + Age^2 × Exposure + Smoking				
Exposure	12.51452	4.13667	9.1522	.0025
Age × Exposure	−0.24855	0.12795	3.7737	.0521
Age^2 × Exposure	0.0009701	0.00100	0.9391	.3325
Smoking (1/0)	−0.00225	0.03142	0.0051	.9430
Model 3: (Time, Event) ~ Exposure + Age × Exposure + Age^2 × Exposure + Age^3 × Exposure + Smoking				
Exposure	50.87213	25.10762	4.1053	.0427
Age × Exposure	−2.19117	1.23486	3.1486	.0760
Age^2 × Exposure	0.03289	0.02000	2.7032	.1001
Age^3 × Exposure	−0.0001703	0.0001064	2.5621	.1095
Smoking (1/0)	−00.0183	0.03146	0.0034	.9537

groupings with five and six age groups. The fit of the model is considerably improved when there are four age groups but the standard deviation is much larger. Similar results (better fit but larger standard deviation) were found when the cutpoints for the four age groups were more than or equal to 15 to less than 60, more than or equal to 60 to less than 65, more than or equal to 65 to less than 70, and more than or equal to 70 as opposed to those described in Table 2.

In the Cox model, the interaction of age and Cr(VI) exposure was significant only for the simple polynomial (model 1): (Time, Event) ~ Exposure + Age × Exposure + Smoking (Table 3). Hazard ratios for 1 mg CrO_3/m^3-years for ages 61 (25th percentile), 69 (the median), and 79 (75th percentile) are found in Table 4. The hazard ratio was significantly elevated for age 61 and significantly decreased for age 79 in all three models. In model 1, the only model with significant age × exposure interaction, the hazard ratios for ages 61, 69, and 79 in model 1 are 2.674 (95% CI, 2.237-3.196); 0.938 (95% CI, 0.668-1.317); and 0.277 (95% CI, 0.142-0.540), respectively.

TABLE 4 Hazard ratios for 1 unit increase of exposure (1 mg CrO_3/m^3-y) fixed for age and adjusted for smoking at 1st, 2nd, and 3rd quartiles of age (ages 61, 69, and 79) by three different models, 5 y lag

Model	Age (y)	Hazard ratios (95% CI)
1	61	2.67 (2.24-3.20)
	69	0.94 (0.67-1.32)
	79	0.28 (0.14-0.54)
2	61	2.63 (2.18-3.17)
	69	0.97 (0.69-1.34)
	79	0.36 (0.17-0.76)
3	61	2.53 (2.07-3.09)
	69	1.34 (0.84-2.15)
	79	0.41 (0.17-0.98)

Abbreviation: CI, confidence interval.

4 | DISCUSSION

It should be noted that the “age effect” calculated by the Cox procedure is not the same as that calculated from an extended Cox model with time varying covariate (often called a counting process) in which the exposure at any age can be defined. The extended Cox proportional model is similar to the R&L procedure in which exposure at any age can be explicitly defined. On the other hand, the age of the basic Cox model is restricted to the age an event (death or censored) occurred. In this sense, the age effects have different implications.

With regard to the R&L approach, it is reassuring to note that when age was not categorized (one age category), the estimations of the coefficient are very similar to the hazard ratio estimation from the Cox proportional hazards model as expected by theoretical consideration alone (Table 2). The small numerical difference is likely due to the difference in how age is treated in the modeling process.

It is clear from the R&L modeling that age has an effect on the risk estimation, but we cannot determine from the R&L model alone what the effect is. When the effect of age is explored by interaction terms in a proportional hazard model, the only age group where the hazard ratio is significantly elevated is the youngest age; the hazard ratio is significantly decreased in the oldest age group. Again, the cause of the age effect is unknown. It may be that other causes of lung cancer (eg, smoking) become relatively more important at older ages, that there are Cr(VI) and smoking interactions that cannot be accounted for in the current study, or there are other occupational or lifestyle factors.

Another explanation may be the extremely irritating nature of Cr (VI). In 1974, a review of epidemiologic studies of workers engaged in the refining of chromite ore noted that the lung cancer risk was greatest among younger chromium production workers.[14] The author noted that the data suggest "a short latent period probably as a result of exposure to a very potent carcinogen."[14] Although the irritating nature of Cr(VI) could increase the risk of lung cancer at any age, it is assumed that the group of workers described by Enterline began work in their 20s, thus resulting in lung cancer mortality being manifested at a younger age. The mean age of hire in the Baltimore cohort was 29.6 (median = 28, range, 16-62).

Clinical signs of respiratory irritation in chromium production workers have been reported to be associated with an increased lung cancer risk,[2] and irritation is recognized as having a role with respect to lung cancer.[15-17] Further exploration will be useful in evaluating the effect of age and the potential effect of irritation on the carcinogenic risk (eg, using a proportional hazards model with time-dependent covariates, such as a counting procedure).

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AUTHOR CONTRIBUTIONS

HG, CC, JW, and KO'L participated in the conception design, analysis, and interpretation of the work. All authors participated in the drafting or critical revision of the manuscript and provided final approval for the manuscript to be published. All authors accept responsibility for the contents of the manuscript.

ETHICS APPROVAL AND INFORMED CONSENT

The Institutional Review Board (IRB) approval for Gibb et al (2015) was granted by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (FWA#0000287). The current study provides different statistical approaches to the data reported in Gibb et al (2015) and therefore does not require new IRB approval.

DISCLAIMER

The views expressed in this article are those of the authors and do not necessarily represent the views or policies of the US Environmental Protection Agency.

DISCLOSURE

Dr. Gibb has provided testimony regarding hexavalent chromium.

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REFERENCES

1. Gibb HJ, Lees PSJ, Pinsky PF, Rooney BC. Lung cancer among workers in chromium chemical production. *Am J Ind Med*. 2000;38(2):115-126. https://doi.org/10.1002/1097-0274(200008)38:23.3.CO;2-P
2. Gibb HJ, Lees PSJ, Wang J, O'Leary KG. Extended followup of a cohort of chromium production workers. *Am J Ind Med*. 2015;58: 905-913. https://doi.org/10.1002/ajim.22479
3. Mancuso TF Consideration of chromium as an industrial carcinogen. International Conference on Heavy Metals in the Environment. Toronto, Canada October 27-31; 1975. pp 343-356.
4. Luippold RS, Mundt KA, Austin RP, et al. Lung cancer mortality among chromate production workers. *Occup Environ Med*. 2003;60: 451-457.
5. NIOSH. Criteria for a Recommended Standard. Occupational Exposure to Hexavalent Chromium. DHHS (NIOSH) Publication No. 2013-128. https://www.cdc.gov/niosh/docs/2013-128/pdfs/2013_128.pdf. Accessed January 24, 2020.
6. OSHA. Part II. Department of Labor, Occupational Safety and Health Administration. 29 CFR Parts 1910, 1915, et al. Occupational Exposure to Hexavalent Chromium; Final Rule. February 28, 2006. https://www.govinfo.gov/content/pkg/FR-2006-02-28/pdf/06-1589.pdf. Accessed January 24, 2020.
7. Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, Lees PSJ. Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment. *Risk Anal*. 2004;24(5):1099-1108. https://doi.org/10.1111/j.0272-4332.2004.00512.x
8. Crump C, Crump K, Hack E, et al. Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. *Risk Anal*. 2003;23(6):1147-1163.
9. Proctor DM, Suh M, Mittal L, et al. Inhalation cancer risk of hexavalent chromium base on updated mortality for Painesville chromate production workers. *J Expo Sci Environ Epidemiol*. 2016;26(2), https://doi.org/10.1038/jes.2015.77
10. Cox DR. Regression models and life tables (with discussion). *J R Statist Soc B*. 1972;34:187-220.
11. Richardson DB, Langholz B. Background stratified Poisson regression analysis of cohort data. *Radiat Environ Biphys*. 2012;51:15-22. https://doi.org/10.1007/s00411-011-0394-5
12. R Core Team. *R: A Language and Environment for Statistical Computing*. 2017. Vienna, Austria: R Foundation for Statistical Computing; 2017.
13. SAS Institute Inc. *SAS Statistical Software, Version 9.4*. 2013. Cary, NC: SAS Institute Inc; 2013.
14. Enterline PE. Respiratory cancer among chromate workers. *J Occup Med*. 1974;16(8):523-526.
15. Azad N, Rojanasakul Y, Vallyathan V. Inflammation and lung cancer: roles of reactive oxygen/nitrogen species. *J Toxicol and Env Heal B*. 2008;11(1):1-15.
16. Engels EA. Inflammation in the development of lung cancer: epidemiological evidence. *Expert Rev Anticancer Ther*. 2008;8(4):605-615.
17. Lee JM, Yanagawa J, Peebles KA, Sharma S, Mao JT, Dubinett SM. Inflammation in lung carcinogenesis: new targets for lung cancer chemoprevention and treatment. *Cr Rev Oncol-Hem*. 2008;66(3): 208-217.

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