Trichloroethylene Is Associated with Kidney Cancer Mortality: A Population-based Analysis

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Abstract. *Aim: To examine the association between the distribution of trichloroethylene (TCE) exposure and mortality from kidney cancer (Kca) across United States counties. Materials and Methods: Multiple linear regression was used to assess the association of TCE discharges from industrial sites and age-adjusted incidence and mortality rates for Kca during 2005 through 2010, controlling for confounders. A total of 163 counties were included in analysis. Results: We observed an excess risk of Kca mortality associated with higher amounts of environmental TCE releases. A significant dose-response relationship was observed between TCE releases and Kca mortality in females. Smoking, education, income, hypertension, and obesity were significant predictors of incidence and mortality, consistent with previous research on the epidemiology of Kca. Conclusion: TCE exposure may increase the risk of mortality from Kca, an association not highlighted before. There is a need for policy measures to limit TCE discharge to the environment if these results are validated.*

There are 63,930 cases of kidney cancer diagnosed in the United States each year, and about 13,860 patients die because of this disease. Smoking is the only lifestyle risk factor found to be associated with kidney cancer; however, only 7% of all kidney cancer is attributable to this exposure. Other described causes for kidney cancer are obesity, hypertension, and utilization of anti-hypertensive medications (1). A large proportion of the United States population continues to be exposed to environmental pollutants (2) despite the effort to reduce the discharge of these pollutants into the environment (3). Multiple authors have reported a significant association between exposure to trichloroethylene (TCE) and kidney cancer risk (4). However, to our knowledge, there exist no large-scale studies that evaluated the association between distribution of TCE in relationship to population kidney cancer risk at the national level, and how these associations are distributed across United States counties related to race and gender.

The Toxic Release Inventory (TRI) dataset provides standardized national-level data on environmental release of different chemical pollutants for the entire United States (3). In this study, we used the TRI database to conduct a study to assess the association of TCE release from TRI sites and kidney cancer incidence and mortality rates in the United States during the years 2005 through 2010, stratified by race and gender.

Materials and Methods

TRI database. The TRI database, originally established under the Emergency Planning and Community Right-to-Know Act (EPCRA) in 1986 (5), EPCRA requires manufacturing facilities that have 10 or more full-time employees and manufacture or process over 11,340 kilograms annually, or otherwise use more than 4,536 kilograms annually of any chemical specified on the TRI list, to report their estimated releases and transfers of toxic chemicals to the US Environmental Protection Agency (EPA). The TRI database is available online with data on chemical releases beginning in 1987 (6). In this study, we used the TRI database to extract information on releases of TCE from 1988 through 1997. We excluded data for 1987 because the reporting system was incomplete during the first year of its development. To estimate exposure, we calculated the cumulative release in pounds for 1988-1997. These amounts were not normally distributed; however, the logarithmic transformation of the volumes did not produce significant changes in our results. For the purpose of the final results, we decided to classify the exposure (TCE release volume) as a categorical variable (low, intermediate, and high release) ensuring that there was an equal number of counties in each category using the cut point of 11,279 and 33,417 kilograms of TCE release (Figure 1).

Mortality from kidney cancer. Age-adjusted kidney cancer incidence and mortality rates between 2005 and 2010 by gender and race were extracted from the Surveillance, Epidemiology, and End Results

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Table I. *Characteristics for the 163 US counties grouped by level of total release of Trichloroethylene 1988-1997.*

	Low		Intermediate		High	
Variable	Mean	SD	Mean	SD	Mean	SD
Volume of TCE release in kg	5,455.27	3,053.37	20,677.15	5,977.05	81,782.82	47,911.77
Incidence rate						
Male	29.86	8.95	30.78	6.51	30.49	9.66
Female	14.91	5.01	15.75	3.57	13.83	4.57
White	22.28	4.28	17.74	32.15	17.31	37.17
Black	6.44	14.04	7.68	11.32	12.83	15.57
Mortality rate						
Male	65.91	36.25	55.32	35.5	79.1	39.93
Female	19.48	20.73	25.64	22.28	33.84	21.88
White	44.76	22.95	50.26	20.65	55.09	22.01
Black	*	*	*	*	*	*
Proportion of population below poverty line	12.61%	4.82	12.83%	6.52	11.49%	6.41
Proportion of population with less than high school education	16.17%	6.25	17.38%	7.61	16.69%	7.64
County surface area in square miles	897.48	1244.7	708.68	628.56	808.93	597.52
Number of primary care providers	151.96	305.86	174.88	419.5	334.11	101.3
Prevalence of obesity	33.06%	3.29	32.99%	4.96	33.74%	5.13
Prevalence of hypertension	39.00%	3	39.00%	5	40.00%	5
Prevalence of smoking	28.55%	4.5	25.98%	4.57	25.89%	4.2
Number of counties	53		54		56	

*Small numbers suppressed by SEER to protect patient confidentiality. Incidence rates are per 100,000. Mortality rates are per 1000,000.

(SEER) cancer registries website using the SEER Stat Software developed by the SEER Program of the National Cancer Institute (7). In addition, county attributes data for 2000 were extracted with the same SEER Stat software as potential confounders, including the proportion of the population with less than a high school education, and the proportion of families below the federal poverty rate (7). Rural-urban continuum codes correlated strongly with other variables and were not used for this analysis. The number of active, non-federal primary-care doctors in the year 2011, and the surface area in square miles, of each county was obtained from the Area Resource File. The adult smoking, obesity, and hypertension rates for each county were obtained from Behavioral Risk Factor Surveillance System data between 2003 and 2006(8). The county area in square miles was measured from the Area Resource File(9). We limited data on TCE releases up to 1997 and examined their effects on kidney cancer incidence and mortality between 2005 and 2010 to allow enough time for the biological effect of the exposure on the disease.

Statistical analysis. Overlap of the 3,141 US counties included in the TRI database and the 616 counties included the SEER database produced 163 counties with data available for analysis. Counties were excluded when there were no available disease rates or TCE exposure data. Multivariate linear regression analyses were used to determine the association of age-adjusted kidney cancer incidence and mortality with different levels of TCE release, controlling for covariates. Prior to the regression analyses, we performed Pearson correlations among the covariates for co-linearity, and we excluded rurality as it correlated strongly with proportion of the population with less than high school education, proportion of families below the poverty line, and number of primary care providers in US counties. Thus, in the multivariate models, we adjusted for the prevalence of smoking, prevalence of obesity, prevalence of hypertension, number of active nonfederal primary-care doctors, surface area of the county in square miles, proportion with less than high school education, and proportion of families below poverty line. Most of these variables did not contribute to the predictability of the model, but they were left in based on their association with cancer incidence and mortality shown on literature research. Furthermore, we assessed the association of covariate-adjusted kidney cancer incidence and mortality stratified by gender and race. Analyses by race were limited to whites and blacks due to the small counts of patients included in other racial groups. Statistical Analysis Software (SAS) version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Table I presents the 2000 characteristics for the 163 US counties grouped by levels of total release of the carcinogen. Compared to counties with low release, counties with intermediate and high TCE release had higher average mortality rates for kidney cancer, and more primary-care doctors (ANOVA $p<0.05$). No noteworthy differences were observed for the rest of the variables (Table I).

The association of TCE exposure with age-adjusted kidney cancer incidence. The association of age-adjusted kidney cancer incidence with TCE release is presented in Table II. After adjusting for potential confounders in the multivariate

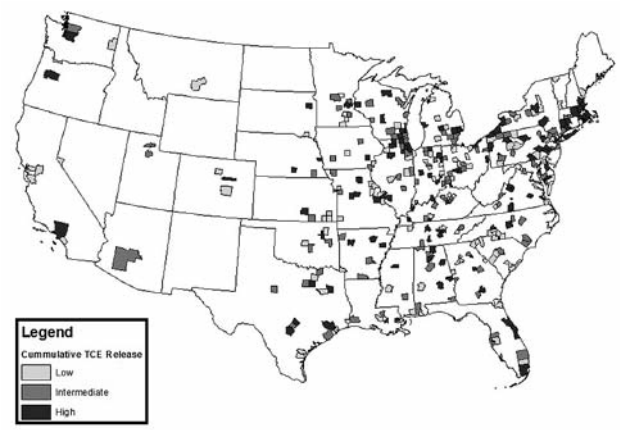

Figure 1. *Trichloroethylene (TCE) discharge volumes by county.*

analyses, overall, we observed that kidney cancer incidence was not significantly associated with TCE release when controlling for confounders. Smoking was associated with increasing risk of kidney cancer in males and blacks (p=0.03), while income and education marginally affected the risk of kidney cancer in females (Table II).

The association of TCE exposure with age-adjusted kidney cancer mortality. The association of age-adjusted kidney cancer mortality with TCE release is presented in Table III. After adjusting for potential confounders in the multivariate analyses, overall, we observed the risk of kidney cancer mortality to be significantly associated with intermediate and high TCE release in males, and with high TCE release in females. In addition, we observed a significant dose–response relationship in females and Whites of kidney cancer mortality with the amount of TCE release. Smoking was significantly associated with kidney cancer mortality in males, females, and Whites. Obesity was significantly associated (negative association) with kidney cancer mortality in males and Blacks. For Blacks, specifically, there was a positive significant association between kidney cancer mortality and hypertension, and a much weaker association between kidney cancer mortality and number of primary-care providers.

Discussion

TCE is an industrial solvent that has been used for a long period of time in degreasing metal parts. This same material has also been used in many other industries including healthcare itself (10, 11). The utilization of TCE has been declining due to public health concerns (11), but it continues to be a common environmental pollutant at multiple sites (12, 13). In a recent assessment from the US EPA, TCE classification was increased to 'carcinogenic to humans' (14). In previous literature, TCE associations with cancer risk were strongest for kidney cancer (15). TCE is lipophillic in nature, and thus it can rapidly accumulate in the kidney and is then activated into cysteine-S-conjugates, the metabolites suspected of being responsible for nephrotoxic and nephrocarcinogenic effects of TCE (16).

In this analysis, we found TCE to be significantly associated with mortality from kidney cancer. Due to lack of extensive research, and the difficulty of measuring environmental exposure, it is still hard to conclude that TCE exposure is definitely associated with kidney cancer (13). Karami *et al*. conducted a recent PubMed MEDLINE research for studies published from 1950 to 2011 assessing occupational exposure to chlorinated solvents, degreasers, or TCE. The authors examined 15 studies in their analysis and found significantly elevated summary estimates (risk ratio=1.26-1.32 and odds ratio=1.35) for studies that examined TCE exposure supporting an association between TCE exposure and increased renal cancer risk, particularly among individuals with genetic variants directly involved in the reductive metabolism and formation of nephrotoxic and carcinogenic TCE metabolites (4). Our study incorporates data from three large national databases to examine the association between kidney cancer incidence and mortality. Our results show absence of any association between TCE exposure and kidney cancer incidence. This finding is plausible considering previous data showing the risk of kidney cancer to be higher in individuals with direct occupational exposure to TCE (4), and the fact that a large proportion of kidney cancer incidence in recent years is attributed to incidental findings associated with rising utilization of imaging studies. The present analysis, however, shows high TCE releases to be associated with increased kidney cancer mortality at the county level. This result is important because it indicates that TCE exposure may be predisposing patients to a more aggressive form of kidney cancer that has higher rates of mortality. This hypothesis could not be tested in the current study because of the ecological nature of the analysis, and the lack of individual data on TCE exposure. Still, this study directs attention to a new aspect of the association of TCE with kidney cancer that requires further investigation.

Furthermore, we showed a dose–response relationship between TCE exposure and mortality from kidney cancer. Low levels of exposure did not contribute to the predictability of the regression models, and only high exposure was significantly associated with mortality from kidney cancer in females. We offer two possible explanations for gender differences in TCE relationship with mortality. Excess mortality in our study could be attributed to occupational exposure, which is more likely in males, and would explain why females were only affected by higher levels of TCE release where environmental exposure

Table II. *The association of age-adjusted incidence rate of kidney cancer with Trichloroethylene (TCE) release.*

	Males	*p*-Value	Females	*p*-Value	Whites	*p*-Value	Blacks	*p*-Value
Variable	Parameter estimate		Parameter estimate		Parameter estimate		Parameter estimate	
TCE release:								
Low (reference)								
Intermediate	0.841	*	–0.0014	*	–5.1181	*	–0.1392	*
High	2.1794	*	–0.4195	*	–4.7742	*	7.3128	*
Smoking	2.334	0.03	0.3111	*	–0.0785	*	1.2135	0.03
Obesity	–0.0728	*	–0.4952	*	–1.3194	*	–0.2551	*
Hypertension	32.1721	*	13.63	*	28.6524	*	140.9823	*
Number of providers	–0.0028	*	–0.0027	*	–0.0029	*	–0.0027	*
Area in square miles	–0.0008	*	–0.0007	*	–0.0003	*	0.0007	*
Education	0.0026	*	0.0062	<0.0001	0.0083	*	–0.0004	*
Income	*	*	*	*	*	*	*	*

*$p>0.05$.

Table III. *The association of age-adjusted mortality rate of kidney cancer with Trichloroethylene (TCE) release.*

	Males	*p*-Value	Females	*p*-Value	Whites	*p*-Value	Blacks	*p*-Value
Variable	Parameter estimate		Parameter estimate		Parameter estimate		Parameter estimate	
TCE release:								
Low (reference)								
Intermediate	33.2813	0.03	14.5725	*	6.0138	*	0.4338	*
High	29.8936	0.01	20.9716	0.01	13.8471	0.03	0.5567	*
Smoking	3.0771	0.04	3.023	0.01	2.8907	0.01	0.055	*
Obesity	–5.7979	0.02	–1.9074	*	–2.3093	*	–0.222	0.04
Hypertension	184.1464	*	–16.5396	*	7.9847	*	26.7548	0.01
Number of providers	0.0039	*	0.0092	*	0.0047	*	0.0032	<.0001
Area in square miles	0.0023	*	0.0013	*	0.0011	*	–0.0002	*
Education	0.0229	*	0.0086	*	0.0135	0.04	–0.0001	*
Income	–0.0344	*	–0.0159	*	–0.021	0.01	0.0001	*

*$p>0.05$.

becomes more likely (4). Another possible explanation is the difference in the metabolism of TCE by gender. Lash *et al.* investigated the metabolism and tissue distribution of orally administered TCE in male and female rats. In that study, male and female Fischer 344 rats were administered TCE (2, 5, or 15 mmol/kg body weight) in corn oil by oral gavage and TCE and its metabolites were measured at times up to 48 h in liver, kidney, blood, and urine. Lash *et al.* then tested the hypothesis that sex-dependent differences in the distribution and metabolism of TCE could help explain differences in toxicity. They found higher levels of TCE were generally observed in tissues of males (17).

Finding an association between smoking, obesity, and hypertension and different aspects of kidney cancer is reassuring to the validity of this analysis. In our study, smoking was associated with kidney cancer risk, while obesity and hypertension were associated with mortality. This is in line with previous literature solidifying smoking as the most profound risk factor for kidney cancer incidence (1). In addition, we show a negative association between obesity and mortality from kidney cancer, which corroborates recent data on the protective effect of obesity against aggressive kidney cancer from Hakimi *et al.* at the Memorial Sloan Kettering Cancer Center. In their study, obese and overweight patients were less likely to present with advanced-stage disease compared with normal-weight patients (odds ratio=0.61, 95% confidence interval=0.48 to 0.79 *vs.* odds ratio=0.65, 95% confidence intervall=0.51 to 0.83, respectively). Higher BMI was also associated with reduced cancer specific mortality. The authors concluded that tumors developing in an obesogenic environment may be more indolent (18).

Limitations of this study are those of any ecological study in that county-level associations may not translate into individual level data. In addition, we were unable to adjust

for individual occupation exposure, smoking status, obesity and hypertension. We were also unable to adjust for the changes in risk factors over time due to migration and changing demographics. The proximity of the population to the facilities emitting the TCE was also not captured given our use of county-level data. TCE could also be a surrogate for other exposures that were not measured in this study, and therefore individual level data are essential in order to make final conclusions. Other limitations are associated with the use of TRI data. TRI data apply only to facilities that emit large volumes of specific contaminants, and they only include emissions from facilities with at least 10 employees that manufacture or process in excess of 11,340 kilograms of a listed chemical annually, or use an excess of 4,536 kilograms annually. Despite these limitations, the TRI is currently the most consistent and comprehensive source of information on environmental contaminant releases.

This study is unique in that it is a population-based study using a national sample that indicates a possible association between TCE and kidney cancer that may go beyond mere occupational exposure. It also examines a new aspect of TCE–kidney cancer association (*i.e.* mortality) that did not receive much attention in previous literature. Although the causal nature of the relationship between TCE release and mortality from kidney cancer is uncertain, our findings from a nationwide ecological study suggest a possible association that deserves further investigation with individual level data.

Conclusion

We present a large population study examining the association of TCE exposure with kidney cancer incidence and mortality. Our results suggest that exposure to higher TCE releases may increase the risk of mortality from kidney cancer, an aspect of TCE–cancer association not highlighted before. These results need validation on an individual patient level to allow for policy measures that limit TCE discharge to the environment.

Conflicts of Interest

The Authors declare no conflict of interest.

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References

1 Park S, Jee SH, Shin HR, Park EH, Shin A, Jung KW, Hwang SS, Cha ES, Yun YH, Park SK, Boniol M and Boffetta P: Attributable fraction of tobacco smoking on cancer using population-based nationwide cancer incidence and mortality data in Korea. BMC Cancer *14*: 406, 2014.

2 Centers for Disease Control and Prevention. FourthNational Report on Human Exposure to EnvironmentalChemicals. Atlanta, GA: CDC; 2009.

3 Chakraborty J: The geographic distribution of potential risks posed by industrial toxic emissions in the U.S. J Environ Sci Health A Tox Hazard Subst Environ Eng *39*: 559-575, 2004.

4 Karami S, Lan Q, Rothman N, Stewart PA, Lee KM, Vermeulen R and Moore LE: Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. Occup Environ Med *69*: 858-867, 2012.

5 Sharpe CR, Rochon JE, Adam JM and Suissa S: Case-control study of hydrocarbon exposures in patients with renal cell carcinoma. CMAJ *140*: 1309-1318, 1989.

6 Spirtas R, Stewart PA, Lee JS, Marano DE, Forbes CD, Grauman DJ, Pettigrew HM, Blair A, Hoover RN and Cohen JL: Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br J Ind Med *48*: 515-530, 1991.

7 Surveillance, Epidemiology, and End Results (SEER) Program of the NCI.

8 http://www.cdc.gov/brfss/.

9 http://ahrf.hrsa.gov/.

10 Kelsh MA, Alexander DD, Mink PJ and Mandel JH: Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology *21*: 95-102, 2010.

11 Bakke B, Stewart PA and Waters MA: Uses of and exposure to trichloroethylene in U.S. industry: a systematic literature review. J Occup Environ Hyg *4*: 375-390, 2007.

12 International Agency for Research on Cancer. Trichloroethylene. IARC Monogr Eval Carcinog Risks Hum 1995;63:75–158. http://monographs.iarc.fr/ENG/ Publications/techrep42/TR42-14.pdf (accessed Dec 15th 2014). .

13 National Toxicology Program. Reports on Carcinogens. Trichloroethylene,2000. http://ntp.niehs.nih.gov/ntp/newhomeroc/roc10/TCE.pdf (accessed Dec 10th 2014). .

14 Integrated Risk Information System. Trichloroethylene (CASRN 79–01-6). http://www.epa.gov/IRIS/subst/0199.htm (accessed December 12th 2014).

15 U.S. Environmental Protection Agency. Trichloroethylene health risk assessment: synthesis and characterization, external review draft. Washington DC: US. Environmental Protection Agency, Risk Assessment Forum, 2001. (EPA/630/P-03/001F). .

16 Brüning T and Bolt HM: Renal toxicity and carcinogenicity of trichloroethylene: key results, mechanisms, and controversies. Crit Rev Toxicol *30*: 253-285, 2000.

17 Lash LH, Putt DA and Parker JC: Metabolism and tissue distribution of orally administered trichloroethylene in male and female rats: identification of glutathione- and cytochrome P-450-derived metabolites in liver, kidney, blood, and urine. J Toxicol Environ Health A *69*: 1285-1309, 2006.

18 Hakimi AA, Furberg H, Zabor EC, Jacobsen A, Schultz N, Ciriello G, Mikklineni N, Fiegoli B, Kim PH, Voss MH, Shen H, Laird PW, Sander C, Reuter VE, Motzer RJ, Hsieh JJ and Russo P: An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. J Natl Cancer Inst *105*: 1862-1870, 2013.

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