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Occupational Trichloroethylene Exposure and Renal Carcinoma Risk: Evidence of Genetic Susceptibility by Reductive Metabolism Gene Variants

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Abstract

Trichloroethylene (TCE) is a suspected renal carcinogen. TCE-associated renal genotoxicity occurs predominantly through glutathione *S*-transferase (*GST*) conjugation and bioactivation by renal cysteine β-lyase (*CCBL1*). We conducted a case-control study in Central Europe (1,097 cases and 1,476 controls) specifically designed to assess risk associated with occupational exposure to TCE through analysis of detailed job histories. All jobs were coded for organic/chlorinated solvent and TCE exposure (ever/never) as well as the frequency and intensity of exposure based on detailed occupational questionnaires, specialized questionnaires, and expert assessments. Increased risk was observed among subjects ever TCE exposed [odds ratio (OR) = 1.63; 95% confidence interval (95% CI), 1.04–2.54]. Exposure-response trends were observed among subjects above and below the median exposure [average intensity (OR = 1.38; 95% CI, 0.81–2.35; OR = 2.34; 95% CI, 1.05–5.21; P_{trend} = 0.02)]. A significant association was found among TCE-exposed subjects with at least one intact *GSTT1* allele (active genotype; OR = 1.88; 95% CI, 1.06–3.33) but not among subjects with two deleted alleles (null genotype; OR = 0.93; 95% CI, 0.35–2.44; $P_{interaction}$ = 0.18). Similar associations for all exposure metrics including average intensity were observed among *GSTT1*-active subjects (OR = 1.56; 95% CI, 0.79–3.10; OR = 2.77; 95% CI, 1.01–7.58; P_{trend} = 0.02) but not among *GSTT1* nulls (OR = 0.81; 95% CI, 0.24-2.72; OR = 1.16; 95% CI, 0.27–5.04; P_{trend} = 1.00; $P_{interaction}$ = 0.34). Further evidence of heterogeneity was seen among TCE-exposed subjects with ≥1 minor allele of several *CCBL1*-tagging single nucleotide polymorphisms: rs2293968, rs2280841, rs2259043, and rs941960. These findings provide the strongest evidence to date that TCE exposure is associated with increased renal cancer risk, particularly among individuals carrying polymorphisms in genes that are important in the reductive metabolism of this chemical, and provides biological plausibility of the association in humans. *Cancer Res; 70(16); 6527–36. ©2010 AACR.*

Introduction

Recent studies have implicated the solvent trichloroethylene (TCE) as a risk factor for cancer, with the strongest evidence observed for renal cell cancer (RCC), liver cancer, and lymphoma (1–4). Because of public health concerns, most industrial use of TCE has been phased out and workplace levels were reduced in most high-resource countries. However, TCE remains a major contaminant at toxic waste disposal sites and is found at low concentrations in public drinking water supplies in the United States and worldwide (4). In the third National Health and Nutrition Examination Survey, it was found that ~10% of the U.S. population had detectable levels of TCE in their blood (3). Both the IARC (4) and the National Toxicology Program (5) consider TCE "a probable" human carcinogen. The uncertainty surrounding the carcinogenic

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potential of TCE stems from debate over the inconsistent findings in epidemiologic studies. Final determination of the carcinogenicity of TCE in humans will rely on additional scientific evidence from studies that use improved epidemiologic methods, refined solvent exposure assessment approaches, and that minimize uncertainty in disease classification compared with the past (6).

Here, a sophisticated questionnaire-based exposure assessment method that incorporated job-specific evaluations and a molecular epidemiologic approach were used to evaluate the association between occupational TCE exposure and RCC risk in a case-control study conducted in Central and Eastern Europe. This region is of interest for the study of occupational exposures because the prevalence and intensity of exposures have been greater than in other industrialized regions (7). This study specifically assessed exposure to chlorinated solvents and TCE through a detailed occupational exposure assessment conducted by trained industrial hygienists, chemists, and occupational health professionals, with knowledge pertaining to their use in each study region (8, 9).

TCE can be metabolized through both an oxidative and reductive pathway. Toxicologic studies in animal models suggest that TCE-associated kidney damage occurs only after bioactivation through the reductive metabolic pathway that requires prior hepatic and renal glutathione *S*-transferase (GST) conjugation and subsequent cleavage by renal cysteine conjugate β-lyase (CCBL1) to form cysteine S-conjugates; S-(1,2,dichlorovinyl-L-cytseine) and S-(1,2,2-trichlorovinyl-L-cysteine) (9–12). These metabolites are highly reactive and have been shown experimentally to form DNA adducts, strand breaks, bacterial mutagenicity, and renal cell genotoxicity and cytotoxicity (11–13). Therefore, the second aim of this study was to evaluate the significance of the reductive pathway in human carcinogenicity and whether common variation in genes involved in reductive metabolism would modify TCE-associated RCC risk. Because the enzyme GSTT1 is known to conjugate small, halogenated compounds such as TCE, and because it is highly active in the kidney, we hypothesized that RCC risk would be elevated among TCE-exposed subjects with at least one intact *GSTT1* allele and would not be elevated among TCE-exposed subjects with deleted alleles. In addition, the renal *CCBL1* gene was selected for analysis. Because there are currently no known functional polymorphisms identified that directly affect isoform formation, enzyme activity, or expression, a comprehensive tagging single nucleotide polymorphism (SNP) approach was used to capture common variation across the *CCBL1* gene region, to explore whether common variants modified associations between RCC and TCE exposure.

Materials and Methods

Study population

A hospital-based case-control study of RCC was conducted between 1999 and 2003 in seven centers in four countries of Central and Eastern Europe (Moscow, Russia; Bucharest, Romania; Lodz, Poland; and Prague, Olomouc, Ceske-Budejovice and Brno, Czech Republic) as previously described (14, 15). All newly diagnosed and histologically confirmed cases of kidney cancer (ICD-O2 code C.64) were identified at participating hospitals in each area between 1999 and 2003. Cases had to reside in the study area for at least 1 year before diagnosis. Histologic slides of renal tumor tissue from cases were reviewed by an international renal cancer pathology expert at the U.S. National Cancer Institute (NCI; MM) for standardized confirmation and disease classification. Only confirmed cases of RCC were retained in this analysis. Controls in each center were chosen among subjects admitted as in-patients or out-patients in the same hospital as the cases, with nontobacco-related conditions and were frequency matched with cases by sex and age (±3 y), and by study center. Patients with cancer or genitourinary disorders, except for benign prostatic hyperplasia, were also excluded from the controls. Although controls had to be cancer free at time of enrollment, previous history of cancer was not an exclusion criterion in either cases or controls. No single disease made up >20% of the diseases among selected controls from each center. Diagnoses of controls included digestive (20.3%), central nervous system (14.3%), eye and ear (16.9%), and musculoskeletal/connective tissue diseases (12.1%). The study protocol was approved by relevant ethics committees, and all study subjects provided informed consent. This study was approved by the Institutional Review Boards of all participating study centers, the IARC (Lyon, France), and the U.S. NCI at the U.S. NIH (NIH). Written informed consent for participation was obtained from all subjects. The final study population included 1,097 cases and 1,476 controls.

Interviewers were trained at each center to perform face-to-face interviews using standard questionnaires. Cases and controls were asked about their life-style habits, in particular tobacco consumption, anthropometric measures 1 year before diagnosis, and their personal and familial medical history. A general questionnaire was given for each job held for at least 1 year and included a description of the tasks performed, machines used, working environment, location of tasks performed, and time spent on each task. To improve precision of the exposure assessment, specialized occupational questionnaires were also used in cases of employment in specific jobs or industries likely to entail exposure to known or suspected occupational carcinogens of interest. Details on the questionnaires have been reported previously (8).

Exposure assessment teams from each center with extensive knowledge of industries in each region received additional training by the NCI industrial hygienist (PS) for the evaluation of chlorinated solvents and TCE, in addition to that received for an earlier study of lung/head and neck cancers conducted in each center (16). For every job in each subject's work history, the team from each center evaluated the frequency and intensity of exposure to agents and groups of agents, based on the general occupational questionnaire, the specialized questionnaires, and their own experience in industrial hygiene and knowledge about historical working conditions at specific plants in their study area while blinded to case-control status. Job-specific questionnaires covered the following: (*a*) possible organic and chlorinated solvent exposures, (*b*) hours per week of exposure, (*c*) source of solvent

exposure, and (*d*) a description of solvent use. Every job of each participant was coded for exposure to the agents previously evaluated in a case-control study of lung/head and neck cancer (16). Organic solvents included any organic chemical used as a dry cleaner, degreaser, thinner, resin solvent, or liquid extraction agent; and petroleum solvents (e.g., white spirits); aliphatic chlorinated solvents; oxygenated solvents (e.g., alcohol and glycol ethers); and others, such as gasoline, kerosene, and mineral spirits. The general category of aliphatic chlorinated organic solvents included perchloroethylene, methylene chloride, carbon tetrachloride, and trichloroethane, and specifically TCE. In attempt to reduce exposure misclassification, after completion of coding for all agents, all subjects originally coded as exposed to organic solvents in the original assessment were reevaluated at a later date by the same group of experts at each center. All coding in the reassessment was performed while blinded with respect to the previous assessment and to disease status.

Experts assessed the frequency, intensity, and confidence of exposure to each of the two solvent categories and TCE in particular for each exposed job held by each subject. Frequency of exposure was coded into three categories, representing the average percentage of a working day during which occupational exposure was likely as follows: 1% to 4.9% of a day (i.e., 5–20 min/d), 5% to 30% of a day (0.5–2.4 h/d), and >30% of a day (>2.5 h/d). For estimation of subjects' cumulative exposure (ppm-year), the midpoint of the frequency categories used was as follows: 0.025, 0.175, and 0.50, respectively. A midpoint of 0.50 was used for the highest category because we assumed a log-normal exposure distribution. The intensity of exposure to organic and chlorinated solvent groups was coded on a three-point scale (low, medium, and high). For cumulative organic and chlorinated solvent exposure, respective weights equal to 2.5, 25, and 100 were assigned to the three intensity categories, each corresponding to the midpoint of the estimated range of the solvent exposure levels (ppm). TCE intensity was coded to one of three categories: 0 to <5 ppm (<27 $\mu g/m^3$), 5 to 50 ppm (27–270 $\mu g/m^3$), and >50 ppm (>270 $\mu g/m^3$), with midpoint weights for cumulative exposure of 2.5, 25, and 75, respectively. For each solvent considered to be present, the industrial hygienists also noted the degree of confidence that a job would entail exposure to an agent. Confidence of exposure that represented the expected percentage of workers that would be exposed in that job was categorized as possible (i.e., <40% workers at a job were expected to be exposed), probable (40–89% of workers were expected to be exposed), or definite (at least 90% of workers were expected to be exposed). After reassessment of TCE exposure, agreement was 100% in Romania (13 subjects) and Poland (3 subjects), and 83% in the Czech Republic (90 subjects). Reassessment of TCE exposure was not conducted in Moscow because Moscow subjects who were exposed to organic solvents were very unlikely to be exposed to TCE.

Laboratory analysis

Blood samples were aliquoted shortly after collection, and buffy coat samples were stored in nitrogen vapor and shipped to the NCI biorepository on dry ice. DNA was extracted using a standard phenol-chloroform extraction. Genotyping was conducted at the IARC and at the NCI's Core Genotyping Facility. DNA was blinded and randomized on PCR plates to avoid any potential bias; duplicate genotyping was performed for a randomly selected 5% of the total series for quality control. In total, 925 (84.3%) cases and 1,192 (80.8%) controls were genotyped for the *GSTT1* deletion as previously described (17, 18). To capture common genetic variation across the renal *CCBL1* gene, SNPs with minor allele frequencies of at least 5% in Caucasians using a tag SNP method with an estimated $r^2 > 0.80$ (19) were selected that would provide with high genomic coverage (80–90%) to capture common genetic variation across the renal *CCBL1* gene region. Seven SNPs spanning from chromosomal regions 130627061 (rs2293968) through 130700708 (rs941959) were selected to tag the *CCBL1* region. In this exercise, boundaries for SNP selection were 20 kb 5′ to the start of the *CCBL1* transcription site and 10 kb 3′ to the last exon. SNPs were selected from publicly available sequencing information (19) and analyzed on an Illumina GoldenGate Oligo Pool All assay as previously described (20). Genotyping of the *CCBL1* gene region was performed on 777 cases and 1,035 controls that provided a sufficient quantity and suitable quality of genomic DNA for genotyping on the Illumina GoldenGate platform because this method had more stringent requirements than the *GSTT1* analysis that used quantitative PCR. Tagging SNPs included rs2293968 (*c9orf114*; IVS8+16A>G), rs2280841 (*CCBL1*; IVS5-19C>T), rs2259043 (*CCBL1*; IVS1-231G>A), rs12554930 (*CCBL1*; IVS1+17336C>G), rs941960 (*CCBL1*; IVS1+3144G>C), rs10988141 (*LRRC8A*; IVS1-1865G>T), and rs941959 (*LRRC8A*; IVS2-8549T>C). The genotype frequencies among controls showed no deviation from the expected Hardy-Weinberg equilibrium proportions ($P > 0.05$). Genotyping concordance was 100% for all SNPs except *rs941959* (99%) and *rs2259043* (92%). Completion rates for all SNPs ranged between 99.5% and 100%.

Statistical analysis

Categorical exposure metrics rather than continuous measures were used to evaluate exposure-response relationships because categorical methods were used to estimate exposure levels for each job. Unconditional logistic regression modeling was initially used to estimate associations between exposures and RCC risk, expressed as odds ratios (OR) and 95% confidence intervals (CI). Estimates of risk among exposed subjects were calculated in reference to unexposed. All regression models were adjusted for sex, age, and study center. Other potential RCC risk factors such as place of residence (rural/urban), tobacco smoking (never, former, current), body mass index (BMI; calculated as weight/height^2: < 25, 25–27.4, 27.5–29.9, 30–34.5, and ≥35 or more kg/m^2), and self-reported history of hypertension did not alter ORs by >10%; therefore, these characteristics were not included in the final models. Analyses were also modeled to account for a 20-year lag, in which jobs held in the last 20 years before diagnosis (cases) or interview (controls) were excluded. ORs for the two solvent exposure groups (organic, chlorinated)

Table 1. Renal cancer risk and occupational organic, chlorinated solvent, and TCE exposure in central and eastern Europe, 1999 to 2003

Solvent exposure*	All subjects				High-confidence assessments only†			
	Cases	Controls			Cases	Controls		
	n (%)	*n* (%)	OR‡ (95% CI)	*P*§	*n* (%)	*n* (%)	OR‡ (95% CI)	*P*
Organic solvents								
Any								
No	590 (71.4)	874 (73.7)	**1.00 Reference**		590 (72.2)	874 (75.0)	**1.00 Reference**	
Yes	236 (28.6)	312 (26.3)	1.12 (0.92–1.38)	0.26	227 (27.8)	291 (25.0)	1.17 (0.95–1.44)	0.15
Years								
<15.5	107 (45.3)	156 (50.0)	1.03 (0.78–1.36)		102 (44.9)	145 (49.8)	1.07 (0.80–1.41)	
≥15.5	129 (54.7)	156 (50.0)	1.22 (0.94–1.58)	0.17	125 (55.1)	146 (50.2)	1.27 (0.97–1.65)	0.09
Hours								
<2,160	119 (50.4)	154 (49.4)	1.12 (0.86–1.47)		112 (49.3)	138 (47.4)	1.19 (0.90–1.57)	
≥2,160	117 (49.6)	158 (50.6)	1.13 (0.86–1.47)	0.29	115 (50.7)	153 (52.6)	1.15 (0.88–1.50)	0.20
Cumulative (ppm-years)								
<5.26	117 (49.6)	156 (50.0)	1.04 (0.79–1.36)		109 (48.0)	136 (46.7)	1.11 (0.84–1.48)	
≥5.26	119 (50.4)	156 (50.0)	1.22 (0.93–1.59)	0.17	118 (52.0)	155 (53.3)	1.22 (0.93–1.59)	0.12
Average intensity (ppm)								
<0.44	104 (44.1)	122 (39.1)	1.14 (0.85–1.53)		97 (42.7)	105 (36.1)	1.25 (0.92–1.69)	
≥0.44	132 (55.9)	190 (60.9)	1.11 (0.87–1.43)	0.31	130 (57.3)	186 (63.9)	1.12 (0.87–1.44)	0.24
Chlorinated solvents								
Any								
No	749 (90.8)	1,108 (93.6)	**1.00 Reference**		749 (93.5)	1,108 (94.8)	**1.00 Reference**	
Yes	76 (9.2)	76 (6.4)	1.33 (0.95–1.88)	0.10	52 (6.5)	61 (5.2)	1.12 (0.76–1.66)	0.56
Years								
>14.5	32 (3.9)	38 (3.2)	1.12 (0.68–1.81)		25 (3.1)	31 (2.7)	1.06 (0.62–1.83)	
≥14.5	44 (5.3)	38 (3.2)	1.56 (0.99–2.46)	0.06	27 (3.4)	30 (2.6)	1.19 (0.69–2.03)	0.52
Hours								
<1,290	31 (3.8)	39 (3.3)	1.03 (0.63–1.67)		21 (2.6)	31 (2.7)	0.88 (0.50–1.55)	
≥1,290	45 (5.5)	37 (3.1)	1.68 (1.06–2.64)	**0.04**	31 (3.9)	30 (2.6)	1.39 (0.82–2.33)	0.35
Cumulative (ppm-years)								
<1.86	34 (4.1)	39 (3.3)	1.15 (0.71–1.86)		19 (2.4)	30 (2.6)	0.84 (0.46–1.51)	
≥1.86	42 (5.1)	37 (3.1)	1.53 (0.96–2.42)	0.07	33 (4.1)	31 (2.7)	1.4 (0.84–2.34)	0.33
Average intensity (ppm)								
<0.076	33 (4.0)	43 (3.6)	1.01 (0.62–1.63)		16 (2.0)	30 (2.6)	0.71 (0.38–1.33)	
≥0.076	43 (5.2)	33 (2.8)	1.75 (1.09–2.81)	**0.04**	36 (4.5)	31 (2.7)	1.52 (0.92–2.50)	0.26
TCE								
Any								
No	777 (94.2)	1,144 (96.6)	**1.00 Reference**		777 (96.4)	1,144 (98.4)	**1.00 Reference**	
Yes	48 (5.8)	40 (3.4)	1.63 (1.04–2.54)	**0.03**	29 (3.6)	19 (1.6)	2.05 (1.13–3.73)	**0.02**
Years‖								
<13.5	22 (2.7)	20 (1.7)	1.44 (0.77–2.69)		15 (1.9)	10 (0.9)	1.89 (0.84–4.28)	
≥13.5	26 (3.2)	20 (1.7)	1.82 (0.99–3.34)	**0.03**	14 (1.7)	9 (0.8)	2.25 (0.95–5.29)	**0.02**
Hours¶								
<1,080	17 (2.1)	20 (1.7)	1.07 (0.55–2.09)		9 (1.1)	9 (0.8)	1.22 (0.48–3.12)	
≥1,080	31 (3.8)	20 (1.7)	2.22 (1.24–3.99)	**0.01**	20 (2.5)	10 (0.9)	2.86 (1.31–6.23)	**0.01**
Cumulative (ppm-years)**								
<1.58	17 (2.1)	19 (1.6)	1.19 (0.61–2.35)		9 (1.1)	7 (0.6)	1.77 (0.64–4.80)	

(*Continued on the following page*)

Table 1. Renal cancer risk and occupational organic, chlorinated solvent, and TCE exposure in central and eastern Europe, 1999 to 2003 (Cont'd)

Solvent exposure*	All subjects				High-confidence assessments only†			
	Cases	Controls			Cases	Controls		
	n (%)	*n* (%)	OR‡ (95% CI)	*P*§	*n* (%)	*n* (%)	OR‡ (95% CI)	*P*
≥1.58	31 (3.8)	21 (1.8)	2.02 (1.14–3.59)	**0.02**	20 (2.5)	12 (1.0)	2.23 (1.07–4.64)	**0.02**
Average Intensity-(ppm)††								
<0.076	31 (3.8)	30 (2.5)	1.38 (0.81–2.35)		13 (1.6)	10 (0.9)	1.73 (0.75–4.02)	
≥0.076	17 (2.1)	10 (0.8)	2.34 (1.05–5.21)	**0.02**	16 (2.0)	9 (0.8)	2.41 (1.05–5.56)	**0.02**

*Exposure metric cut points equal to the 50th percentile among exposed controls for years, hours, cumulative, and average intensity exposure metrics.

†Analyses conducted for jobs classified as having probable or certain exposure (i.e., at least 40% of workers expected to be exposed).

‡OR and 95% CI adjusted for age, sex, and center.

§*P* value for trend given for years, hours, cumulative and average intensity of exposure.

‖The interquartile range (IQR) among controls (25th, 75th percentile) was 6.3 to 26.3 y. Among cases, the median exposure and IQR were 19.5 (5.8–31.0) y.

¶The IQR among controls (25th, 75th percentile) was 420 to 1920 h. Among cases, the median exposure and IQR were 1470 (660–3700) h.

**The IQR among controls (25th, 75th percentile) was 0.77 to 2.87 ppm-years. Among cases, the median exposure and IQR were 1.95 and (0.83–7.25) ppm-years.

††The IQR among controls (25th, 75th percentile) was 0.08 to 0.16 ppm. Among cases, the median and IQR were 0.08, (0.08 to 0.44) ppm.

and TCE were calculated for any occupational exposure, as well as duration (in years and hours of exposure), cumulative exposure (ppm-years), and average intensity (ppm). Duration in hours was calculated for each subject using the following formula, and summing over all jobs: duration (years) × 50 (wk/y) × 40 (h/wk) × frequency weight. Cumulative exposure (ppm-years) was calculated for each subject using the following formula, summing over all jobs: intensity weight (ppm) × frequency weight × duration (y). The average exposure intensity (ppm) estimate derived by dividing the cumulative exposure as assessed above [intensity weight (ppm) × frequency weight × duration (years)], by the total number of years exposed. Correlation analyses (Spearman) were conducted to identify agents or groups of agents that were associated with solvent exposures in this study. No significant coexposures were identified that were associated with TCE exposure except for chlorinated and organic solvents groups, as would be expected because TCE is both a chlorinated and an organic solvent (r^2 >0.30). Because organic solvent and chlorinated solvent exposures were evaluated as grouped exposures, it was not possible to control for other individual solvents in our analysis of TCE.

Subgroup analyses among subjects with the highest confidence of each solvent exposure category were conducted by restricting analyses to jobs with a confidence rating of certain or probable. To determine if variation in genes important in the reductive pathway of TCE metabolism would modify exposure-disease relationships, analyses stratified by the *GSTT1* genotype were evaluated. Genotypes were considered "active" if subjects had at least one intact *GSTT1* allele present and "inactive" (or null) if they had none. The association between *CCBL1* tagging SNPs and RCC risk was estimated using unconditional logistic regression models, adjusted for age, sex, country, and *GSTT1* genotype. Unlike the other characteristics evaluated, inclusion of the *GSTT1* genotype altered ORs by at least 10% and therefore was included in final regression models. Linear tests for trend were conducted by including a variable coded 0 (reference), 1, and 2, corresponding to the number of minor alleles. Interaction between TCE exposure (ever/never) and SNPs using additive and dominant models were evaluated using the likelihood ratio test to compare models with and without interaction terms. Multiplicative interactions evaluated using the likelihood ratio test were considered statistically significant at an $\alpha \leq 0.05$. All analyses were conducted in STATA 9.0 unless otherwise specified (STATA Corp.).

Results

Among the 1,097 RCC cases and 1,476 controls included in this study, there was a higher proportion of female cases than controls. A higher proportion of cases had a high BMI (BMI ≥ 30) and self-reported hypertension than controls (Supplementary Table S1). As previously described, the prevalence of smoking among cases and controls did not differ after adjustment for age, BMI, hypertension, center, and sex (14), and a larger proportion of cases than controls reported having a first-degree relative with cancer than did controls (15). ORs

Table 2. Renal cancer risk associated with occupational TCE exposure, by GST θ (*GSTT1*) genotype in central and eastern Europe, 1999 to 2003

***GSTT1* null**	**Cases**	**Controls**			
TCE exposure*	***n* (%)**	***n* (%)**	**OR† (95% CI)**	***P*‡**	**P_{int}§**
Any					
No	**119 (92.2)**	**149 (93.1)**	**1.00 Reference**		
Yes	10 (7.8)	11 (6.9)	0.93 (0.35–2.44)	0.89	
Years					
<13.5	7 (70.0)	6 (54.5)	1.30 (0.40–4.23)		
≥13.5	3 (30.0)	5 (45.5)	0.52 (0.11–2.45)	0.41	
Hours					
<1,080	4 (40.0)	6 (54.5)	0.70 (0.18–2.70)		
≥1,080	6 (60.0)	5 (45.5)	1.22 (0.33–4.54)	0.95	
Cumulative (ppm-years)					
<1.58	4 (40.0)	3 (27.3)	1.40 (0.28–7.03)		
≥1.58	6 (60.0)	8 (72.7)	0.76 (0.24–2.42)	0.75	
Average intensity (ppm)					
<0.076	6 (60.0)	7 (63.6)	0.81 (0.24–2.72)		
≥0.076	4 (40.0)	4 (36.4)	1.16 (0.27–5.04)	1.00	
GSTT1 active					
Any					
No	**466 (93.6)**	**729 (96.9)**	**1.00 Reference**		
Yes	32 (6.4)	23 (3.1)	1.88 (1.06–3.33)	**0.03**	0.18
Years					
<13.5	11 (34.4)	10 (43.5)	1.54 (0.63–3.74)		
≥13.5	21 (65.5)	13 (56.5)	2.13 (1.04–4.39)	**0.03**	0.31
Hours					
<1,080	9 (28.1)	9 (39.1)	1.27 (0.49–3.30)		
≥1,080	23 (71.9)	14 (60.9)	2.28 (1.14–4.58)	**0.02**	0.51
Cumulative (ppm-years)					
<1.58	9 (28.1)	11 (47.8)	1.10 (0.44–2.74)		
≥1.58	23 (71.9)	12 (52.2)	2.59 (1.25–5.35)	**0.01**	0.17
Average intensity (ppm)					
<0.076	20 (62.5)	17 (73.9)	1.56 (0.79–3.10)		
≥0.076	12 (37.5)	6 (26.1)	2.77 (1.01–7.58)	**0.02**	0.34

*Cut points at the 50th percentile among exposed controls for years, hours, and cumulative and average intensity exposure metrics.
†OR, 95% CI calculated using logistic regression models adjusted for age, sex, and center.
‡*P* values for trend are given for years, hours, and cumulative and average exposure analyses.
§*P* value calculated from the likelihood ratio test comparing logistic regression models with and without an interaction term for TCE exposure category and *GSTT1* genotype.

associated with occupational exposure to organic solvents, chlorinated solvents, and TCE are presented in Table 1. Association with occupational exposure to organic solvents and RCC was not observed before or after analyses were restricted to high-confidence assessments. An association with duration and average intensity of exposure to chlorinated solvents was observed but was no longer elevated after the analysis was restricted to high-confidence assessments. For TCE exposure, ORs were significantly elevated for all exposure indices (OR = 1.63–2.34) and were strengthened after analyses were restricted to high confidence assessments (OR = 2.05–2.86). Almost all TCE exposure occurred at least 20 years before the onset of disease among cases; therefore, similar relationships between exposure indices and RCC risk were observed in analyses restricted to exposures that occurred at least 20 years before disease diagnosis (data not shown).

Table 2 presents associations between TCE exposure and RCC risk after stratification by *GSTT1* genotype. The percentage of cases and controls genotyped did not significantly differ among TCE-exposed and unexposed subjects (data not shown). Overall, the active *GSTT1* genotype was not

associated with RCC risk when compared with the null genotype (OR = 0.94; 95% CI, 0.75–1.19; ref. 18). After stratification by *GSTT1* genotype, significant associations were only observed among subjects ever exposed to TCE with an active genotype (OR = 1.88; 95% CI, 1.06–3.33) but not among *GSTT1* nulls (OR = 0.93; 95% CI, 0.35–2.44). Similarly, associations with other exposure metrics were observed only among subjects with at least one active *GSTT1* genotype (ORs from 2.13–2.77 in the top 50th percentile) but not among *GSTT1* null subjects (ORs from 0.53–1.22 in the top 50th percentile), compared with unexposed subjects. The interaction between TCE exposure and *GSTT1* genotype did not reach statistical significance.

Further evidence of heterogeneity was observed for particular tagging SNPs of the renal *CCBL1* gene, which encodes the enzyme known to bioactivate TCE in the kidney. Supplementary Fig. S1 shows the correlation (r^2) values between renal *CCBL1*–tagging SNP minor alleles. Elevated ORs were observed among TCE-exposed individuals with at least one minor allele for SNPs rs2293968, rs2280841, rs2259043, and rs941960, when compared with unexposed subjects, among persons with the different tag SNP genotypes in the *CCBL1*

Table 3. Renal cancer risk and TCE exposure among renal cysteine conjugate β-lyase (*CCBL1*) tagging SNP variants

Tagging SNP		TCE exposed		TCE unexposed		OR* (95% CI)		
rs2293968	**Genotype**	**Cases (%)**	**Controls (%)**	**Cases (%)**	**Controls (%)**	**TCE exposure**	***P***	$P_{interaction}$†
IVS8+16A>G	AA	19 (48.7)	17 (65.4)	285 (54.0)	409 (51.8)	1.17 (0.57–2.39)	0.67	
	AG	14 (35.9)	8 (30.8)	204 (38.6)	296 (37.5)	2.25 (0.86–5.83)	0.10	
	GG	6 (15.4)	1 (3.9)	39 (7.4)	84 (10.7)	12.8 (1.40–117.2)	0.03	**0.03**
	AG+GG	20 (51.3)	9 (34.7)	243 (46.0)	380 (48.2)	3.04 (1.29–7.14)	**0.01**	**0.05**
rs2280841								
IVS5-19C>T	CC	21 (53.9)	21 (77.8)	319 (60.1)	461 (58.4)	1.10 (0.56–2.15)	0.78	
	CT	14 (35.9)	5 (18.5)	183 (34.5)	265 (33.6)	2.99 (1.02–8.73)	0.05	
	TT	4 (10.3)	1 (3.7)	29 (5.5)	63 (8.0)	7.15 (0.67–76.1)	0.10	**0.03**
	CT+TT	18 (46.2)	6 (22.2)	212 (40.0)	328 (41.6)	3.57 (1.37–9.34)	**0.01**	**0.03**
rs2259043								
IVS1-231G>A	GG	19(48.7)	18 (66.7)	290 (54.6)	410 (51.8)	1.09 (0.54–2.22)	0.81	
	GA	14 (35.9)	8 (29.6)	203 (38.2)	299 (37.8)	2.28 (0.88–5.94)	0.09	
	AA	6 (15.4)	1 (3.7)	38 (7.2)	82 (10.4)	11.33 (1.24–103.4)	0.03	**0.02**
	G+A	20 (51.3)	9 (33.6)	241 (42.4)	381 (48.2)	3.05 (1.30–7.16)	**0.01**	**0.04**
rs125545930								
IVS1+17336C>G	CC	28 (71.8)	19 (70.4)	392 (73.7)	594 (75.1)	1.67 (0.88–3.16)	0.12	
	CG	9 (23.1)	7 (25.9)	132 (24.8)	174 (22.0)	1.24 (0.44–3.53)	0.68	
	GG	2 (5.1)	1 (3.7)	8 (1.5)	23 (2.9)	6.59 (0.46–94.1)	0.16	**0.81**
	C+G	11 (28.2)	8 (29.6)	140 (26.3)	197 (24.9)	1.53 (0.58–4.01)	0.39	**0.88**
rs941960								
IVS1+3144G>C	GG	16 (41.0)	17 (63.0)	277 (52.1)	399 (50.4)	1.01 (0.47–2.17)	0.97	
	GC	18 (46.2)	7 (25.9)	209 (39.3)	306 (38.7)	2.89 (1.16–7.23)	0.02	
	CC	5 (12.8)	3 (11.1)	46 (8.7)	86 (10.9)	2.92 (0.60–14.3)	1.19	**0.11**
	G+C	23 (59.0)	10 (37.0)	255 (48.0)	392 (49.6)	2.72 (1.25–5.90)	**0.01**	**0.06**
rs10988141								
IVS1-1865G>T	GG	31 (79.5)	21 (77.8)	443 (83.3)	664 (84.1)	1.77 (0.97–3.23)	0.06	
	GT	8 (20.5)	6 (22.2)	86 (16.2)	122 (15.4)	1.45 (0.46–4.48)	0.52	
	TT	0	0	3 (0.6)	4 (0.5)	NA	NA	**0.70**
	G+T	8 (20.5)	6 (22.2)	89 (16.8)	126 (15.9)	1.42 (0.46–4.40)	0.54	**0.69**
rs941959								
IVS2-8549T>C	TT	34 (87.2)	25 (92.6)	487 (91.5)	731 (92.7)	1.56 (0.89–2.73)	0.12	
	TC	5 (12.8)	2 (7.4)	44 (8.3)	56 (7.1)	2.32 (0.40–13.4)	0.35	
	CC	0	0	1 (0.2)	2 (0.3)	NA	NA	**0.52**
	T+C	5 (12.8)	2 (7.4)	45 (8.5)	58 (7.4)	2.39 (0.42–13.7)	0.32	**0.50**

*ORs, 95% CIs, and *P* values calculated from logistic regression models adjusted for age, sex, country, and *GSTT1* genotype.
†*P* value from likelihood ratio test comparing regression models with/without an interaction term for TCE exposure and *CCBL1* genotype, adjusted for age, sex, country, and *GSTT1* genotype.

gene region (Table 3). Significant interactions were observed between TCE exposure (ever/never) and *CCBL1* gene minor alleles using both additive and dominant models for rs2293968 [P_{int} (additive) = 0.03 and *P*-int (dominant) = 0.05), rs2280841 (*P*-int (additive) = 0.03 and *P*-int (dominant) = 0.03), and rs2259043 (*P*-int (additive) = 0.02 and *P*-int (dominant) = 0.04]. After examination of correlation (r^2) values between renal *CCBL1* gene tag SNPs in Haploview in this population, we observed that rs2293968 (IVS8 + 16A > G), rs2280841 (IVS5-19C > T), and rs2259043 (IVS1-231G > A) were highly correlated (r^2 = 0.98), and r^2 values were greater than those observed between tagging SNPs in HapMap at the time of SNP selection, which ranged from 83% to 92% (Supplementary Fig. S1).

Discussion

This study provides notable epidemiologic evidence to support an association between occupational TCE exposure and RCC risk. Specifically, risk associated with TCE exposure was increased among individuals with a functionally active *GSTT1* genotype and particularly among those with minor alleles in SNPs spanning the *CCBL1* gene region. Several epidemiologic studies of occupational TCE exposure and kidney cancer have been conducted but only one study had analyzed (and reanalyzed) the modification of TCE-associated risk and common variation in GST genes (21, 22). No studies to date have examined modification in risk associated specifically with both *GSTT1* and renal-*CCBL1*, key enzymes involved in the conjugation, reduction, and subsequent bioactivation of TCE in the kidney. The findings from this study were consistent with several case-control studies that specifically assessed TCE exposure and kidney cancer (23–30) and a meta-analysis of cohort studies assessing occupational TCE exposure in which studies were grouped by the quality of exposure assessments used, in attempt to reduce exposure misclassification (6). Other case-control studies have not reported positive associations between RCC risk and TCE exposure (31–34). Each of these case-control studies used less detailed exposure assessment methods than the current study, which may have lead to exposure misclassification and insufficient variability in exposure levels among subjects. Other factors such as disease misclassification (inclusion of all kidney cancers versus exclusively RCC) and low power to detect the ORs observed may also have played a role, as very few exposed cases were identified in each study. In the current study, we observed a positive, exposure-dependent association for all TCE exposure metrics, which were strengthened when analyses were restricted to high-confidence assessments. In contrast, the positive associations that were observed with chlorinated solvents among all subjects were no longer observed after exclusion of low-confidence assessments from the analysis.

The results of this study agree with a wealth of experimental evidence supporting involvement of reductive metabolism in the nephrocarcinogenicity of TCE; however, the evidence is still unclear at which exposure levels the oxidative pathway becomes saturated and reductive metabolism begins to occur, and also whether common genetic variation in the enzymes involved could modify metabolism, bioactivation, and cancer susceptibility in humans (9, 35, 36). As hypothesized, risk was elevated only among individuals with at least one intact *GSTT1* allele, supporting experimental evidence that glutathione conjugation is necessary to form substrate for the renal-CCBL1 enzyme. Further evidence of heterogeneity was observed among subgroups defined by their renal *CCBL1* genotypes. Because the specific functional SNPs that modify CCBL1 splicing and activity are currently unknown, we used a comprehensive tagging SNP approach with high genomic coverage to capture common genetic variation across the entire gene region. Elevated ORs were observed among TCE-exposed subjects that had at least one minor *CCBL1* allele for SNPs: rs2293968, rs2280841, rs2259043, or rs941960. Although these SNPs are intronic and not known to be functional, each is a marker of regional genomic variation across an area to which it is highly correlated, and can be used to further define a region of interest. Although not genotyped in this study, one potentially functional SNP to which the high-risk region is highly correlated includes rs10988134 (r^2 = 0.95), a C > T transition in the 3′ untranslated region of the *CCBL1* gene, which could affect *CCBL1* transcript stability. Several *CCBL1* gene transcript variants have been identified that are known to influence substrate specificity (37). The significant interactions observed between TCE exposure and several highly correlated *CCBL1* gene minor alleles might indicate that particular isoforms of this enzyme exist that may have different affinities to the glutathione conjugate or that could modify the rate at which TCE metabolites are bioactivated in the kidney. Fine mapping and functional studies will be required to elucidate these hypotheses.

It has been contended that TCE is a weak, indirect mutagen in the kidney, and the relevance of the reductive pathway in humans could be exposure dependent (38, 39). Our results support experimental evidence that this pathway does modify renal carcinogenesis in humans exposed to TCE at the doses estimated in this study, and that genetically susceptible subpopulations exist. This mechanism is biologically plausible in humans as follows: (*a*) *GSTT1* is the most active, highly expressed GST in the kidney (40, 41); (*b*) GST θ enzyme expression is directly related to *GSTT1* genotype (42); (*c*) the GST θ enzyme metabolizes small halogenated compounds such as TCE (40); (*d*) the renal CCBL1 enzyme is expressed primarily in the kidney; and (*e*) GST conjugation is required before formation of mutagenic isomers in the kidney. The major isomer, S-(1,2,-dichlorovinyl)-L-cysteine is significantly more toxic than S-(2,2,-dichlorovinyl)-L-cysteine (12, 13). The importance of these genetic polymorphisms in the general public with regard to activation of small halogenated compounds such as TCE could have public health importance because both alleles associated with increased risk in the presence of TCE exposure are not uncommon. Approximately 80% of Caucasians harbor a least one intact *GSTT1* allele, and the minor allele prevalence of the renal *CCBL1* SNPs associated with elevated ORs associated with increased renal cancer risk among exposed subjects ranged from 14% to 30% in this particular population.

Our findings are similar to one genetic susceptibility study of the *GSTT1* genotype and RCC risk among workers with

long-term high-level occupational exposure to TCE (29), but dissimilar to a more recent reassessment of the same TCE-exposed cases (20 exposed and 78 nonexposed) and 324 controls, after the addition of 445 controls from various sources (22). Although the reassessment study was sufficiently powered to detect an OR of at least 2.0, the results of this analysis were not adjusted for possible confounders, as they were in our study.

Strengths of this study include a large sample size of cases and controls that were well characterized with respect to RCC risk factors, a high participation rate, histologic confirmation of all cases, availability of genomic DNA from a high proportion of subjects, and use of high-quality laboratory methods for genotyping, which resulted in very high completion and concordance rates for all genotypes of interest. Moreover, use of job-specific questionnaire modules to collect individual, detailed exposure information, and local expert-based exposure assessments to evaluate and independently reassess solvent exposure histories of study subjects are considered a superior approach for retrospective assessment of occupational exposures in community-based studies (43). Moreover, this study determined that exposure misclassification (observed as low interteam agreement) consistently attenuated risk estimates observed, and attenuation was greatest for agents with low-exposure prevalence in the study population. At the same time, data on jobs and exposures obtained through interview and subsequent expert assessment should be critically evaluated as the likelihood of exposure misclassification is higher than for studies with actual exposure measurements. For this reason, we included a measure of exposure confidence for each job to reflect the likelihood of exposure, conducted analyses restricted to high-confidence assessments, and reassessed all subjects exposed to organic solvents, whereas assessors were blinded to the original assessment and disease status. Although exposure misclassification is always of concern, the result of misclassification would likely diminish the elevated risks and significant trends observed toward the null if they were nondifferential. This result has been shown previously in an analysis conducted in these centers, with the same exposure assessment teams (16). Recall bias is also a concern when occupational exposures are assessed retrospectively; however in this study, controls were also hospitalized patients, and systematic bias introduced from recall would likely be nondifferential with respect to exposure.

Potential limitations of the study include the use of hospital-based controls that may not represent the general population in each study region. To avoid selection bias from control selection, those recruited had diseases unrelated to RCC and the prevalence of individual diagnoses did not exceed 20% of the group as a whole. Nonetheless, that selection bias may have occurred is suggested by the lack of association observed between tobacco smoking and RCC risk as previously reported (14). In a comparative study across different types of epidemiologic study designs and associations between tobacco and kidney cancer, the strength of association has generally been weaker in hospital-based case-control studies, compared with population-based case-control and cohort studies (44). Another limitation of this study is that environmental exposure to solvents in drinking water or air pollution was not assessed. Although environmental solvent exposure could have resulted in some exposure misclassification, it would tend to be nondifferential. Adjustment for primary place of residence (urban/rural) was not found to alter the risks observed. Due to limited resources, with the exception of TCE, we were unable to assess exposure to each specific organic or chlorinated solvent used occupationally, and many chlorinated solvents were used in combination or use had overlapped while being phased into or out of the workplace. Because other solvents with the exception of TCE were not evaluated, we were unable to assess and adjust for other individual solvent exposures.

In conclusion, the current study provides evidence to support an association between occupational TCE exposure and RCC risk that was limited to individuals with an active *GSTT1* genotype and certain variants within the renal *CCBL1* gene. Although use of TCE has declined in the United States and other high-resource countries (45), it remains a common occupational exposure elsewhere. TCE exposures also occur at lower levels through environmental sources such as contamination of public water supplies and releases from toxic waste sites. Therefore, studies of potential health effects associated with low-dose exposures and consideration of factors that influence metabolism and cancer susceptibility in humans are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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