Exhibit 246

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Gender Differences in Risk of Renal Cell Carcinoma and Occupational Exposures to Chlorinated Aliphatic Hydrocarbons

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Background: *Organic solvents have been associated with renal cell cancer; however, the risk by gender and type of solvents is unclear.*

Methods: *We evaluated the risk of renal cell carcinoma among men and women exposed to all organic solvents-combined, all chlorinated aliphatic hydrocarbons (CAHC)-combined, and nine individual CAHC using a priori job exposure matrices developed by NCI in a population-based case-control study in Minnesota, U.S. We interviewed 438 renal cell cancer cases (273 men and 165 women) and 687 controls (462 men and 225 women).*

Results: *Overall, 34% of male cases and 21% of female cases were exposed to organic solvents in general. The risk of renal cell carcinoma was significantly elevated among women exposed to all organic solvents combined (OR = 2.3; 95% CI = 1.3–4.2), to CAHC combined (OR = 2.1; 95% CI = 1.1–3.9), and to trichloroethylene (TCE) (OR = 2.0; 95% CI = 1.0–4.0). Among men, no significant excess risk was observed among men exposed to any of these nine individual CAHCs, all CAHCs-combined, or all organic solvents-combined.*

Discussion: *These observed gender differences in risk of renal cell carcinoma in relation to exposure to organic solvents may be explained by chance based on small numbers, or by the differences in body fat content, metabolic activity, the rate of elimination of xenobiotics from the body, or by differences in the level of exposure between men and women, even though they have the same job title.* Am. J. Ind. Med. 36:54–59, 1999. *Published 1999 Wiley-Liss, Inc.*†

KEY WORDS: renal cell cancer; solvents; chlorinated hydrocarbons; trichloroethylene

INTRODUCTION

The role of occupational risk factors in the etiology of renal cell carcinoma (RCC) is poorly understood [McLaughlin et al., 1996]. Although RCC is not commonly considered an occupational cancer, a number of occupational risk factors have been suggested [Mandel et al., 1995; McLaughlin et al., 1996]. For example, excess risks of RCC have been reported among workers exposed to asbestos [Selikoff et al., 1979; Enterline et al., 1987; McCredie and Stewart, 1993], arsenic [Tsuda et al., 1990; Enterline et al., 1995], polycyclic aromatic hydrocarbons (PAH) [Sharpe et al., 1989; Poole et al., 1993; Mellemgaard et al., 1994; Boffetta et al., 1997], gasoline [Siemiatycki et al., 1988; Partanen et al., 1991; Mellemgaard et al., 1994; Lynge et al., 1997], benzidine [Morikawa et al., 1997], solvents [Lynge et al., 1995], formaldehyde [Hansen and Olsen, 1995], and lead [Steenland et al., 1992, Cocco et al., 1997]. Workers employed in certain industries also have been found to have elevated risks, including dry cleaning and laundry workers [Katz and Jowett, 1981; Duh and Asal, 1984; McCredie and Stewart, 1993; Lynge et al., 1995], steel workers [Urbaneja Arrue et al., 1995], textile workers and tailors [Auperin et al., 1994],

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TABLE I. Prevalence of Exposure to Solvents and Chlorinated Aliphatic Hydrocarbons (CAHCs): NCI JEM Applied to Minnesota Cancer Registry Data (1988–1990)

	Men		Women		Total	
Solvents type	**Case**	**Control**	**Case**	**Control**	**Case**	**Control**
All organic solvents combined	0.34	0.34	0.21	0.11	0.29	0.27
CAHCs combined	0.26	0.26	0.18	0 09	0.23	0.21
1,1,2 Trichloroethane	0 07	0.08	0 02	0.02	0.05	0.06
1,2 Dichloroethane	0.10	0.08	0 09	0.04	0.09	0.07
Carbon tetrachloride	0.16	0 19	0.07	0.04	0.12	0.14
Chloroform	0.03	0.02	0.04	0.02	0.03	0.02
Methyl chloride	0 08	0.09	0.04	0.05	0.06	0.07
Methyl chloroform	0.19	0.21	0.08	0.07	0 15	0.17
Methylene chloride	0.21	0.24	0.06	0.07	0.16	0.18
Perchloroethylene [PCE]	0.15	0.13	0.05	0.06	0.11	0 11
Trichloroethylene [TCE]	0.12	0.11	0.13	0.07	0.13	0.10

oil refinery workers [Bertazzi et al., 1989; Shallenberger et al., 1992; Poole et al., 1993; Rushton, 1993], gasoline station attendants [McLaughlin et al., 1985], farmers [Forastiere et al., 1993], printers [Paganini-Hill et al., 1980; Sinks et al., 1992], and coke-oven operators [Redmond et al., 1972; McCredie and Stewart, 1993; Mellemgaard et al., 1994]. Most of these occupations suggest that organic solvents, particularly chlorinated aliphatic hydrocarbons (CAHCs), may be associated with risk of RCC. To evaluate the effects of organic solvents on RCC risk, we analyzed data from a population-based case-control study of RCC in Minnesota, using job exposure matrices (JEMs) for ten CAHCs and organic solvents developed at the National Cancer Institute.

METHODS

Details concerning the design of this population-based case-control study of RCC are presented elsewhere [Chow et al., 1994]. Briefly, a total of 796 white patients newly diagnosed with histologically confirmed RCC were identified through the Minnesota Cancer Surveillance System, a statewide cancer registry from July 1, 1988, to December June 31, 1990. Interviews were obtained for 690 (87%) cases, including 241 interviews with next of kin of patients. For subjects age 20–64 years, an age- and gender-stratified random sample of white controls was obtained with random digit dialing. For subjects age 65–85 years, an age- and gender-stratified systematic sample of white controls was obtained from the listing of the Health Care Financing Administration. A total of 707 population-based controls were interviewed, representing an overall response rate of 86% from these two sampling frames. In the occupational analysis, 438 cases (273 men and 165 women) and 687 controls (462 men and 225 women) with complete personal interviews were included. A questionnaire, which covered demographic and ethnic variables, occupational and residential history, diet, smoking habits, medical history, and drug use, was administered in the homes of the respondents by trained interviewers unaware of the case or control status of the study subject. Occupational history included the most recent and usual occupation and industry, job activities, year started and year ended, and part-time/full-time status. In addition, duration of employment in 13 specific occupations/industries and seven jobs with specific exposures was ascertained.

Occupations and industries were coded according to the standard occupational classification (SOC) [US DOC, 1980] and standard industrial classification (SIC) [US OMB, 1987] schemes. The National Cancer Institute has developed JEMs for nine individual CAHCs (i.e., 1,1,2 trichloroethane, 1,2 dichloroethane, carbon tetrachloride, chloroform, methyl chloride, methyl chloroform, methylene chloride, perchloroethylene (PCE), and trichloroethylene (TCE)), all CAHCs-combined, and all organic solvents-combined for use in various case-control studies. These JEMs were merged with assigned SOC and SIC to determine the exposure status to these chemicals for each study subject. Details of the application of the job exposure matrices are presented elsewhere [Dosemeci et al., 1994; Gomez et al., 1994].

The logistic regression model was used to estimate relative risks and the 95% confidence limits [Breslow and Day, 1980]. The relative risk was estimated in terms of odds ratio (OR) and adjusted for age, smoking, hypertension status and/or use of diuretics and/or anti-hypertension drugs, and body mass index for men and women separately.

RESULTS

The prevalences of exposure to all solvents and individual and combined CAHCs are presented in Table I.

TABLE II. Risk of Renal Cell Cancer by Exposure to Solvents and Chlorinated Aliphatic Hydrocarbons Adjusted for Age, Gender (for total), Smoking, Hypertension and/or Use of Diuretics and/or Anti-hypertension Drugs and Body Mass Index, Minnesota Registry Data (1988–1990)

Solvents type	Men OR [n] (95% CI)	Women OR [n] (95% CI)	Total OR [n] (95% CI)
Solvents in general	0.93 [91]	2.29 [35]	1.16 [126]
	(0.7–1.3)	(1.3–4.2)	(0.9–1.5)
CHC combined	0.94 [70]	2.08 [29]	1.15 [99]
	(0.7–1.3)	(1.1–3.9)	(0.9–1.6)
1,1,2 Trichloroethane	0.90 [20]	0.95 [3]	0.91 [23]
	(0.5–1.6)	(0.2–4.4)	(0.5–1.6)
1,2 Dichloroethane	1.13 [26]	2.34 [14]	1.37 [40]
	(0.7–1.9)	(0.9–5.9)	(0.9–2.2)
Carbon tetrachloride	0.79 [43]	1.88 [11]	0.90 [54]
	(0.5–1.2)	(0.7–5.0)	(0.6–1.3)
Chloroform	1.27 [9]	1.89 [6]	1.48 [15]
	(0.5–3.2)	(0.5–6.7)	(0.7–3.1)
Methyl chloride	0.85 [21]	0.88 [7]	0.87 [28]
	(0.5–1.5)	(0.3–2.4)	(0.5–1.4)
Methyl chloroform	0.88 [53]	1.26 [13]	0.94 [66]
	(0.6–1.3)	(0.6–2.8)	(0.7–1.3)
Methylene chloride	0.85 [58]	0.95 [10]	0.87 [68]
	(0.6–1.2)	(0.4–2.2)	(0.6–1.2)
Perchloroethylene [PCE]	1.12 [42]	0.82 [8]	1.07 [50]
	(0.7–1.7)	(0.3–2.1)	(0.7–1.6)
Trichloroethylene [TCE]	1.04 [33]	1.96 [22]	1.30 [55]
	(0.6–1.7)	(1.0–4.0)	(0.9–1.9)

The prevalence of exposure to all organic solvents-combined was 34% among male controls, and 11% among female. For individual CAHC, estimated exposure prevalence ranged from 2% for chloroform to 24% for methylene chloride among male controls, and from 2% for chloroform and 1,1,2-trichloroethane to 7% for methylene chloride, methyl chloroform and TCE among female controls.

Relative risks of RCC by exposure to all solvents-combined and individual and combined CAHC are presented in Table II. Among women, significantly elevated relative risks of RCC were observed exposed to all organic solvents-combined (OR = 2.3; 95% CI: 1.3–4.2), all CAHCs combined (OR = 2.1; 95% CI: 1.1–3.9) and TCE (OR = 2.0; 95% CI: 1.0–4.0). Nonsignificant excess risks were observed for 1,2 dichloroethane (OR = 2.3; 95% CI: 0.9–5.9), chloroform (OR = 1.9; 95% CI: 0.5–6.7), carbon tetrachloride (OR = 1.9; 95% CI: 0.7–5.0), and methyl chloroform (OR = 1.3; 95% CI: 0.6–2.8). Among men, little or no excess risk of RCC was associated with all solvents-combined, all CAHC-combined or any individual CHAC.

TABLE III. Gender-Specific Risks of Renal Cell Cancer for Various Exposures in Other Studies

Investigators/citation	Exposure/ industry	Men OR (95% CI)	Women OR (95% CI)
Asal et al., [1988]	Dry-cleaning	0.7	2.8
		(0.2–2.3)	(0.8–9.8)
Mellemgaard et al., [1994]	Dry-cleaning	2.3	2.9
		(0.2–27)	(0.3–33)
	Solvents	1.5	*6.4*
		(0.9–2.4)	(1.8–2.7)
	Herbicides	1.7	5.7
		(0.7–4.3)	(0.6–58)
Ward et al., [1994]	Cable mfg.	1.2	1.5
	Cohort	(0.7–1.9)	(0.5–3.6)
Ruder et al., [1994]	Dry-cleaning cohort	0.7	2.4
		(0.02–3.7)	(0.5–7.0)
Mandel et al., [1995]	Dry-cleaning	*1.4*	*1.6*
		(1.1–1.7)	(1.0–2.7)

DISCUSSION

Our findings suggest that there may be gender differences in RCC risk associated with occupational exposure to organic solvents. Previous studies of RCC in relation to organic solvent exposure have primarily focused on men. Table III presents studies that have reported gender-specific risk estimates for various exposures and industries. Although in some studies, risks were not significant due to the small number of women in the study population, women consistently showed higher RCC risk than men for the same exposures. Asal et al. [1988] and Ruder et al. [1994] reported almost 3-fold risk differences between men and women who worked in the dry-cleaning industry, in which various chlorinated aliphatic hydrocarbons (e.g., carbon tetrachloride, TCE, PCE, and 1,1,1 trichloroethane) have been used since the 1930s [IARC, 1995]. Mellemgaard et al. [1994] reported more than 4-fold significant risk differences between men and women exposed to solvents in general.

Recently, a critical review of epidemiologic studies of TCE and PCE and risk of renal-cell cancer [McLaughlin and Blot, 1997] concluded that "the totality of epidemiologic evidence clearly does not support a causal association with TCE and PCE." In some of the articles reported in this review, women employed in the dry-cleaning industry showed excess risk of RCC [Katz and Jowett, 1981; Asal et al., 1988; McCredie and Stewart, 1993; Mandel et al., 1995]. In general, associations between solvents and renal-cell cancer are more consistent among women than men. Studies without a gender-specific evaluation are less likely to observe these associations due to the small proportion of women exposed to solvents in most study populations.

Gender differences in cancer have been suggested in other epidemiologic and laboratory studies. For example, the linear increase in risk of oral cancer was significantly higher for women than men for every category of smoking [Moscat et al., 1996]. Similar gender differences have been reported for the association between lung cancer and smoking [Brownson et al., 1992; Risch et al., 1993; Zang and Wynder, 1996]. Higher levels of p53 mutations and hydrophobic DNA adduct level have also been found in female lung cancer patients than in male, even though the level of exposure to carcinogens from cigarette smoking was lower among the females than among the males [Kure et al., 1996; Guince et al., 1995]. Experimental studies showed a higher level of hepatic tumor promotion activity in female mice compared to male mice [Siglin et al., 1995].

There is no clear evidence to explain these gender differences in risk of renal-cell cancer associated with exposure to solvents. Our observation may be explained by chance based on small number; however, previous studies evaluating gender differences in cancer development have pointed to some hints that might support our findings. For example, anatomical and physiological parameters, such as body composition (fat and water content), surface area, metabolism, and cardiovascular, pulmonary, gastrointestinal, and renal function are generally different in men and women [Silvaggio and Mattison, 1994]. On average, total body water is 40% greater in men than women, and women have almost 100% more fat tissue than men [Headapohl, 1993]. As most solvents are stored in fat tissue, this difference in body fat content suggests that women may have longer internal exposure to solvents than men. Other studies suggest that there may be gender differences in genetic susceptibility enzymes, such as GSTM1, which may play a role in the detoxification process of various environmental xenobiotics [Ryberg et al., 1994; Rodilla et al., 1996; Kihara et al., 1995; Alexandrie et al., 1994]. Indeed, the GSTM1 null genotype was markedly more prevalent among women than men, suggesting a poorer detoxifying capability against environmental xenobiotics [Kihara et al., 1995]. In another study, gender differences in the elimination rate of xenobiotics from the body have been reported [Silvaggio and Mattison, 1994]. In general, after adjustment for body surface area, it has been shown that renal blood flow, glomerular filtration, tubular secretion, and tubular reabsorption are greater in men than women, suggesting that men have a higher elimination rate of xenobiotics than women [Hytten and Chamberlain, 1980]. Finally, it is possible that there may be differences in the level of exposure between men and women even though they have the same job title. Several studies have reported gender differences in exposure both qualitatively and quantitatively, even when men and women worked in the same industry or in the same job title [Hernberg et al., 1988; Messing et al., 1994; Greenberg and Dement, 1994; Stewart and Blair, 1994; Roxburgh, 1996].

Limitations in this study include potential survival bias, as all cases who died (35%) were excluded from the analysis to avoid using next-of-kin interviews, and limited occupational history, since we had only current and usual jobs, rather than a lifetime work history. However, a priori assessment of exposure to solvents using JEMs was a crucial component in this study because this approach avoids recall bias between men and women or between cases and controls. Without a detailed work history, the ability of an a priori JEM to capture potential exposures is limited [Dosemeci et al., 1994]. We were unable to evaluate the risk by level of exposures to individual solvents in this report, due to the small number of exposed subjects in our study population. Larger interdisciplinary studies with sufficient numbers of men and women are needed to confirm and to provide new evidence to explain the gender differences observed in this study.

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