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Bladder Cancer in Perfluorooctanesulfonyl Fluoride Manufacturing Workers

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PURPOSE: To determine whether bladder cancer is associated with exposure to perfluorooctane sulfonate (PFOS) in an occupational cohort.
METHODS: Incidence of bladder cancer was ascertained by postal questionnaire to all living current and former employees of the facility ($N = 1895$) and death certificates for deceased workers ($N = 188$). Exposure to PFOS was estimated with work history records and weighted with biological monitoring data. Standardized incidence ratios (SIRs) were estimated using U.S. population–based rates as a reference. Bladder cancer risk within the cohort was evaluated using Poisson regression by cumulative PFOS exposure.
RESULTS: Questionnaires were returned by 1,400 of the 1895 cohort members presumed alive. Eleven cases of primary bladder cancer were identified from the surveys ($n = 6$) and death certificates ($n = 5$). The SIRs were 1.28 (95% confidence interval [CI] = 0.64–2.29) for the entire cohort and 1.74 (95% CI = 0.64–3.79) for those ever working in a high exposed job. Compared with employees in the lowest cumulative exposure category, the relative risk of bladder cancer was 0.83 (95% CI = 0.15–4.65), 1.92 (95% CI = 0.30–12.06), and 1.52 (95% CI = 0.21–10.99).
CONCLUSIONS: The results offer little support for an association between bladder cancer and PFOS exposure, but the limited size of the population prohibits a conclusive exposure response analysis.
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KEY WORDS: Perfluorooctane Sulfonate, Bladder Cancer, Occupational Diseases, Epidemiology.

BACKGROUND

The global detection of perfluorooctane sulfonate (PFOS, $C_8F_{17}SO_3$–) in humans (1) and wildlife (2) led the primary manufacturer (3M Company) to discontinue production of materials derived from perfluorooctanesulfonyl fluoride (POSF, $C_8F_{17}SO_2F$) after more than 40years of manufacture (3). These chemicals had many commercial applications, including surface treatments (e.g., textiles, upholstery, and leather applications), paper and packaging protectants for grease and oil resistance including food contact papers, and performance chemicals such as fire-fighting foams (3). The perfluorinated chain of these materials results in extreme resistance to environmental and metabolic degradation. POSF-based products can be degraded or metabolized to PFOS, a stable and persistent end-product that has a long serum elimination half-life of several years in humans (4), which may be due to saturable renal resorption (5). The pathways leading to PFOS in human blood are not well characterized, but exposure is pervasive (3). In the United States PFOS has been measured in human serum with averages approximating 20 to 40 ng/mL from Nutrition and Health Examination Survey (NHANES) participants (6), American Red Cross blood donors (7), and children (8). Modest variations from these measurements occur in other countries (9).

Repeat-dose PFOS toxicology studies in animals have consistently demonstrated the liver to be the primary target organ with the potential to reduce body weight and weight gain, increase liver weight, and reduce serum cholesterol (10, 11). In addition, there is a steep dose-response for mortality in adult rats (10) and primates (11) as well as neonatal rats and mice exposed in utero (12, 13). Although the mechanism of toxicity in laboratory animals is not fully understood, it may be due to an effect on fatty acid transport and metabolism, membrane function, peroxisome proliferation, and/or mitochondrial bioenergetics (14–16).

Studies of health effects of PFOS in humans have focused on employees at production facilities whose average serum concentrations, depending upon job tasks, ranged between 500 and 2,000 ng/mL (17), the lowest of which are much higher than those of the general population. Variation in clinical blood and urine chemistries were unremarkable (18). Indirect measures of health-related events, as measured by frequency of health insurance claims filed by workers found more frequent claims among exposed workers for the a priori conditions of biliary tract disorders and cystitis recurrence as well as benign colon polyps, malignant colorectal tumors, and malignant melanoma (19). A cohort

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Selected Abbreviations and Acronyms

CI = confidence interval
N-EtFOSE = N-ethylperfluorooctane sulfonamide alcohol
PFOA = perfluorooctanoic acid
PFOS = perfluorooctane sulfonate
POSF = perfluorooctanesulfonyl fluoride
SIR = standardized incidence ratio
SMR = standardized mortality ratio

mortality study of employees of a POSF manufacturing plant reported null results for causes of death selected a priori as diseases of interest, but reported a large excess of death from bladder cancer in the highly exposed group (20). Although based on only 3 cases, the standardized mortality ratio (SMR) was 4.8 (95% confidence interval [CI] = 1.0–14.1) for the entire cohort and 12.8 (95% CI = 2.6–37.4) for employees with high exposure jobs.

Bladder cancer is a relatively rare malignancy that has been linked to smoking (21) and several occupational exposures (22–29). Annual age-adjusted incidence rates are 4 to 5 times the mortality rate; thus studies of mortality do not fully describe the burden of bladder cancer in a population (30). In response to the finding of excess mortality from bladder cancer, we extended the study to identify incident bladder cancers in this occupational cohort.

METHODS

Incidence of bladder cancer was assessed in this cohort study through case finding by direct contact with the study population and supplemented with mortality records. The protocol for this study was reviewed and approved by the University of Minnesota Institutional Review Board.

Study Population

The study population was the same as the previously reported mortality study (20) and included all current, retired, and former employees of a facility where POSF was produced who had at least 365 days of cumulative employment prior to 1998. The plant is divided in two major sections; the chemical plant produces specialty chemicals, including the POSF line of chemicals, and the film plant, where a variety of films are produced, but little or no occupational fluorochemical exposure occurs. A roster of all known addresses and telephone numbers were obtained from company personnel or retiree records. Address and vital status were updated through a variety of tracing resources (Lortan Data, TransUnion, National Change of Address). If a cohort member was noted to have died since the mortality study was completed, a copy of the death certificate was obtained from the state of record.

Recruitment and Case Ascertainment

Data collection was conducted in 2002. Informational meetings were held with current employees and retirees to introduce the study and allow for questions. A letter and brochure describing the study were followed with a mailed self-administered questionnaire. Addresses from returned mail were re-entered into the search process for possible alternate addresses. Nonrespondents received reminder postcards and a second mailed questionnaire. Those not responding to the second questionnaire were contacted by telephone to verify questionnaire receipt, to inquire about intent to participate, and they were offered the opportunity to complete the questionnaire by telephone. The primary purpose of the questionnaire was to identify cases of bladder cancer and the year of diagnosis. The questionnaire also recorded history of smoking; a known risk factor for bladder cancer.

Participants reporting bladder cancer were contacted by letter, with telephone follow-up, to request permission to contact their physician to verify the diagnosis. Copies of the consent and medical release forms were sent to the physician or clinic of record with a request for pathology reports, surgical notes, or any other information pertaining to the diagnosis of the reported bladder cancer. Telephone follow-up to the clinic or physician was used to assure receipt of the material and encourage appropriate response. We excluded cases if they were not primary cancers, that is, metastases from another site.

The underlying cause of death was used to identify cases of bladder cancer on death certificates obtained in the original mortality study and any death certificates obtained for decedents identified through the tracing process. The death certificates were obtained from the state of record and coded to the ICD version in effect at the time of death by a trained nosologist. Death certificates were obtained for 185 of the 188 decedents.

Exposure Assessment

The exposure assessment followed the previously described method used in the mortality study (20). This method created job-specific exposure categories based on job titles, departments, and dates of employment identified in the participant's individual work histories, and potential for PFOS exposure. Relative differences in serum PFOS by job were determined by an assessment of 186 workers in 1998, which is detailed elsewhere (17). Because production processes have remained constant over time, a simple exposure matrix was developed on the basis of work history records of the study cohort. The work histories used in the exposure analysis covered the period from when the plant opened, 1961, through 1997 when the work histories were collected for the original mortality study (20). Exposure to active employees in 1997 (N = 788) was not considered