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Bladder Cancer Screening in Aluminum Smelter Workers

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Objective: To present results of a bladder cancer screening program conducted in 18 aluminum smelters in the United States from January 2000 to December 2010. **Methods:** Data were collected on a cohort of workers with a history of working in coal tar pitch volatile exposed areas including urine analysis for conventional cytology and ImmunoCyt/uCyt+ assay. **Results:** ImmunoCyt/uCyt+ and cytology in combination showed a sensitivity of 62.30%, a specificity of 92.60%, a negative predictive value of 99.90%, and a positive predictive value of 2.96%. Fourteen cases of bladder cancer were detected, and the standardized incidence ratio of bladder cancer was 1.18 (95% confidence interval, 0.65 to 1.99). Individuals who tested positive on either test who were later determined to be cancer free had undergone expensive and invasive tests. **Conclusions:** Evidence to support continued surveillance of this cohort has not been demonstrated.

Bladder cancer is the fourth and ninth most common cancer in men and women, respectively, in the United States. An estimated 74,690 people (56,205 men and 18,484 women) will be diagnosed with and 15,210 men and women will die from bladder cancer in 2014.[1] Recognized risk factors for bladder cancer include increased age, male sex, white race, smoking, family history, urinary tract infections, drugs, personal history of bladder cancer, and occupational exposures.[2] Estimates suggest that between 5% and 25% of bladder cancer incidence is attributable to occupational exposures.[3] Consequently, interest has mounted for implementation of bladder cancer screening among high-risk populations including industrial workers exposed to bladder carcinogens in the workplace.

Epidemiologic studies of aluminum smelter workers have demonstrated an association between coal tar pitch volatiles (CTPVs) generated during aluminum reduction and bladder cancer.[4–8] Coal tar pitch volatiles contain many low molecular weight polycyclic aromatic hydrocarbons (PAHs). Polycyclic aromatic hydrocarbons are lipophilic nonpolar chemicals comprising two or more benzene rings formed as a result of pyrolytic processes, in particular the incomplete combustion of organic materials.[6] Some PAHs in CTPV are recognized carcinogens.[9] Benzo(a)pyrene (BaP), a specific carcinogenic PAH, and benzene soluble materials (BSM), which include all PAHs present and other benzene soluble compounds, have consistently been found in CTPV[10,11]; therefore, BaP and BSM are often used as surrogates or indicator compounds for the presence of PAHs in the work environment.

Theriault reported on a bladder cancer screening program consisting of annual urine cytology initiated in a cohort of current aluminum smelter workers with at least a 10-year history of CTPV exposure associated with aluminum smelting and later expanded to include workers with at least 5 years of exposure.[12] Results of this screening program showed trends toward a higher proportion of early-stage bladder cancer at diagnosis (77% vs 67%) and an increased 5-year survival (rate ratio, 0.54; confidence interval [CI], 0.20 to 1.48) after the screening program was instituted; however, these differences were not statistically significant, and the authors concluded that these results did not encourage an optimistic view of screening effectiveness in the population.

Similar to the aforementioned study, most earlier screening protocols for bladder cancer primarily included testing for blood in the urine (hematuria) and/or urine cytology. Unfortunately, hematuria has a relatively low sensitivity and specificity, whereas urinary cytology, although highly specific, has poor sensitivity.[13,14] Cystoscopy, although very accurate and considered the criterion standard for the detection of bladder tumors, is an invasive and expensive procedure with complications including intense discomfort as well as bleeding, infections, and mechanical lesions.[15] Given these limitations, the focus has turned to identification of more sensitive and specific molecular markers for detection and surveillance of bladder cancer.[16–19]

One of the earlier tumor markers commercially developed and approved by the United States Food and Drug Administration for bladder cancer surveillance was the ImmunoCyt test (subsequently commercialized under two names: ImmunoCyt/uCyt+). This immunofluorescence assay uses three monoclonal antibodies directed against transitional cell carcinoma antigens in exfoliated cells for the detection of cellular markers that are relatively specific for bladder cancer.[20] In a study assessing the sensitivity and specificity of 18 bladder tumor markers including ImmunoCyt/uCyt+, the authors concluded that ImmunoCyt/uCyt+ was one of the six promising markers for surveillance of patients for recurrent bladder cancer.[21] Another report comparing ImmunoCyt/uCyt+ alone and in combination with urine cytology to five other commercially available urine tumor markers concluded that the combination of ImmunoCyt/uCyt+ with urine cytology offered a superior sensitivity to the other tests.[22]

Although the primary focus of many reports assessing various biomarkers to screen for bladder cancer has been on surveillance of bladder cancer recurrence in patients, a few studies have used different combinations of biomarkers for surveillance of high-risk occupational cohorts. In one recent study, bladder cancer screening was instituted in 76 workers exposed to 4, 4-methylenebis (2-chloroaniline) (MBOCA), a synthetic chemical used in the production of castable polyurethane parts. Ninety-two other workers who were not involved in the MBOCA manufacturing process served as controls. Urine

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occult blood tests, urine cytology, tests for tumor marker nuclear matrix protein 22 (NMP22), which uses two mononuclear antibodies, and abdominal ultrasonography were performed in all participants. This study identified one worker with confirmed bladder cancer; however, the prevalence of atypical urine cells, the NMP22 tumor marker, and positive occult blood were not significantly different between the MBOCA-exposed workers and nonexposed workers.[23]

In another study, a prospective cohort of 1323 male workers with former exposure to aromatic amines was screened for bladder cancer between 2003 and 2010. Using a combination of annual tests for hematuria, quantitative determination of NMP22, UroVysion test (a fluorescence in situ hybridization assay that assesses chromosomal instability in urothelial cells), and urine cytology, 15 bladder tumors were detected in 14 participants.[24]

Between 2006 and 2008, 171 male workers from an Italian coke plant with a median exposure duration to PAHs of 16 years were screened for bladder cancer using a medical protocol that included urine analysis, urine cytology, and urine ImmunoCyt/uCyt+. Workers with positive results on at least one of the urinary markers underwent urinary ultrasonography and cystoscopy. Overall, 12% of the workers tested positive on at least one urinary marker. Nevertheless, evidence of bladder cancer was not confirmed by cystoscopy and ultrasonography. The authors reported a specificity of urine analysis, cytology, and ImmunoCyt/uCyt+ of 98%, 96%, and 92%, respectively. Although no increased risk for bladder cancer was seen among the coke workers evaluated, the result was considered preliminary because of reported study limitations, including the small number of workers enrolled in the surveillance program, the analysis based on only one assessment with no follow-up available, and the relatively short duration of PAH exposure in these workers.[25]

We present the results of a bladder cancer surveillance program conducted between January 2000 and December 2010 in a cohort of aluminum smelter workers in the United States who were employed by a single company. Our objective in this report was to establish the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of the bladder cancer screening protocol in the context of the observed risk of bladder cancer in the cohort under surveillance.

METHODS

Alcoa Inc (and two other aluminum companies that later merged with Alcoa Inc) owned and operated 18 aluminum smelters in the United States. Currently, only five of these smelters remain in operation. Over many years, the company has worked to control exposure to CTPV in the workplace using different strategies, including engineering controls, the use of respiratory and skin protection, and administrative means such as laundering of workplace clothes, provision of shower facilities to prevent tracking of the material outside the workplace, and separate eating places to prevent contamination during breaks. In addition to these measures, a medical surveillance program to provide early detection of bladder cancer among the workers exposed to CTPV was implemented in 2000.

Coal tar pitch exposed areas in the smelters were determined by a combination of air measurements and laboratory analysis of the BaP and BSMs and a chromatographic fingerprint interpretation to confirm the presence of coal tar pitch. In areas where laboratory analysis confirmed the presence of coal tar pitch, significant exposure was defined as 5% exceedance of BSMs values (0.025 mg/m^3 or more) or 5% exceedance of BaP values (0.10 $\mu g/m^3$ or more) in the air or areas where surface contamination could provide the opportunity for visible contamination of skin or clothing. This information, in addition to all available historic exposure data, was used to establish a list of tasks and jobs with significant exposure to CTPV.

The company's bladder surveillance program includes administration of a questionnaire reviewing genitourinary symptoms, history of cancer, employment, and smoking history. In addition, a urine sample is submitted for urine cytology and ImmunoCyt/uCyt+ assay, a noninvasive method for detecting bladder tumor–associated antigen in the urine. The ImmunoCyt/uCyt+ test combines urinary cytology and fluorescence immunocytochemistry using monoclonal antibody 19A211 labeled with Texas red, which detects a high molecular weight form of the carcinoembryonic antigen, and antibodies M344 and LDQ10 labeled with fluorescein detecting cytoplasmic mucin antigens expressed in bladder cancer cells. Red fluorescence shows a cell positive for high-molecular-weight glycosylated carcinoembryonic antigen, and green fluorescence shows a cell positive for tumor mucins. Slides presenting 500 cells or more are considered suitable for evaluation. The slides are regarded as positive when there is at least one green or one red cell. The results from ImmunoCyt/uCyt+ tests are categorized by the number of cells identified and categorized as negative, positive, and suspicious for cancer cells or inadequate specimen. Slides for conventional urine cytology are stained according to the standard Papanicolaou procedure, and the results are categorized as negative, positive, or suspicious for tumor cells, atypical cells, or inadequate specimen.

The screening algorithm was as follows: all individuals testing negative for urine cytology and ImmunoCyt/uCyt+ have both tests repeated in 12 months. Individuals who test positive for either urine cytology or ImmunoCyt/uCyt+ are referred to a urologist for follow-up and cystoscopy. Individuals with a suspicious urine cytology or ImmunoCyt/uCyt+ test result undergo a repeat of the suspicious test in 1 month. If the repeat result is positive, referral to a urologist for cystoscopy is made. If the repeat test is negative, both tests are repeated in 12 months. If the repeat result is suspicious for the second time, then the individual undergoes a repeat of that test in 6 months. If this 6 month retest is still suspicious, the individual is referred to a urologist.

Individuals who are referred for cystoscopy but prove negative for bladder cancer are retested using both cytology and ImmunoCyt/uCyt+ 1 year after the initial testing. Individuals with a history of recurrent renal calculi, active urinary tract infection, or history of surgical procedure on the urinary tract within 1 month of surveillance are not tested until their infection is successfully treated or until their symptoms resolve.

This study was reviewed and approved by both the Yale and Stanford Institutional Review Boards.

Eligibility/Study Subjects

The bladder screening surveillance program was offered to all retirees, former and current employees from the 18 smelters who had a history of working in a coal tar pitch exposed area for 1 or more years at least 10 years before the start of the surveillance program. Individuals with a prior history of bladder cancer were not included as part of this workplace surveillance program because of their different risk profile. Initially, the surveillance program included workers of all ages, but after 3 years was restricted to individuals aged 45 years or older. The surveillance program was administered through the plant medical department for eligible current employees. Letters describing the surveillance program, eligibility criteria, and how to obtain the test kits through their primary physicians were sent to the last known address of former and retired employees. Toll free numbers were also provided through which questions could be answered.

The results of the surveillance program, including medical records detailing follow-up provided to participants, were maintained in a database. This database and all available medical records were reviewed by the investigators.

Statistical Analysis

Sensitivity values for urine cytology and ImmunoCyt/uCyt+ were calculated using cystoscopy as the criterion standard. Because

it was not feasible to perform cystoscopy on all or even a random sample of the individuals who were classified as "disease free" on the basis of their urine test results, these individuals were followed for a period of 1 year to determine bladder cancer status. If individuals remained cancer free, they were treated as "true negatives" for purposes of calculating specificity and standardized incidence rates of bladder cancer.

Indirect standardization, based on the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, site Rec B; Race recode W/B/AI/API data, was conducted to determine the expected number of bladder cancer cases among the study cohort. For this analysis, strata were defined by sex and age by year up to aged 84 years with those aged 85 years or older combined into the last category. The study period for each person in the surveillance cohort started on the date of their initial surveillance test and ended 1 year after their last test date. Latency was defined as the period between date of employment and the last bladder cancer screening test for each participant. Standardized incidence ratios (SIRs) were calculated and 95% CI limits were calculated using the Fisher exact test methodology.

RESULTS

A total of 7826 employees (5140 current employees and 2686 former/retired employees) from the US aluminum smelters (94.6%, male) participated in the bladder cancer surveillance program from January 2000 through December 2010 and contributed 30,976 person-years of follow-up. Table 1 depicts the demographics of participants in the surveillance program. The mean age of the participants at the time of the first test was 50 years (standard deviation [SD] = 11.9 years). The mean duration of exposure for the cohort under surveillance was 25.2 years (SD = 13.1 years). Most participants in the surveillance program (66.6%) were current employees at the time of their first test. Current employees were younger, had a shorter duration of exposure to coal tar pitch, and contributed more person-years of screening compared with individuals who were retirees or former employees at the time of their first tests.

A total of 25,531 pairs of ImmunoCyt/uCyt+ and urine cytology tests were performed with each participant receiving an average of three pairs of tests. Test results reported as inadequate were excluded from further analysis. In total, the surveillance program identified 14 cases of bladder cancer through 16 pairs of tests (two participants each underwent two tests within a few months of being diagnosed with bladder cancer). The mean age at diagnosis of bladder cancer was 63.5 years (SD = 11.8 years), with a latency of 37 years (SD = 11.7) in the cohort under surveillance.

Table 2 shows the distribution of the 22,650 paired tests on participants who were not confirmed to have bladder cancer. Table 3 shows the distribution of the 16 paired test results for the 14 cases of bladder cancer diagnosed through the surveillance program. Two individuals tested negative on both the ImmunoCyt/uCyt+ and urine cytology. Nevertheless, because hematuria was found during routine screening, these individuals were referred for cystoscopy, and bladder cancer was diagnosed despite the negative ImmunoCyt/uCyt+ and urine cytology test results. Another individual tested negative on both ImmunoCyt/uCyt+ and urine cytology but became symptomatic within 4 months of these test results and was subsequently diagnosed with bladder cancer through cystoscopy.

For 198 individuals with positive results on either test, medical records were available and reviewed; the bulk of these (95%) were current employees. Fourteen were confirmed to have bladder cancer. Medical records confirmed that 139 individuals who tested positive on either test were evaluated by a urologist and/or had additional work-up including imaging studies and were subsequently determined to be cancer free. Twenty-eight individuals who tested

TABLE 2. Surveillance Results for Participants Determined to be Free of Bladder Cancer (2000 to 2010)

	ImmunoCyt/uCyt+			
	Positive	**Negative**	**Suspicious**	**Total**
Urine cytology				
Positive	30	25	20	75
Negative	164	20,985	779	21,928
Suspicious	98	364	185	647
Total	292	21,574	984	22,650

TABLE 3. Surveillance Results for Participants Diagnosed With Bladder Cancer (2000 to 2010)

	ImmunoCyt/uCyt+			
	Positive	**Negative**	**Suspicious**	**Total**
Urine cytology				
Positive	4	0	1	5
Negative	2	4	0	6
Suspicious	3	0	2	5
Total	9	4	3	16

TABLE 1. Demographics of Participants in the Bladder Cancer Surveillance Program

			Employee Status at Time of First Test						
	All Employees, $n = 7826$		**Active, $n = 5,140$**		**Retired or Terminated, $n = 2,686$**				
Parameter	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***df***	***t* statistic**	***P***
Age at first test, yrs	50.62	11.87	48.32	8.88	55.00	15.17	3671.8	−21.03	<0.001
Years between hire and last test	25.20	13.28	23.98	12.26	33.07	16.59	932.67	−14.82	<0.001
Years between first and last tests	2.96	3.58	3.78	3.68	1.39	2.79	6836.30	32.12	<0.001
Number of tests	3.26	3.02	3.95	3.23	1.95	1.98	7633.20	33.67	<0.001

positive and therefore should have been referred to a urologist per the surveillance protocol instead had repeat testing performed at varying intervals of 1 to 6 months at the discretion of the plant physician. These subsequent tests were negative. In addition, documentation showed that 17 individuals refused further evaluation. Nevertheless, subsequent testing 1 year later for this group revealed negative test results. Medical records were unavailable for 153 individuals who tested positive on either test but did not report bladder cancer.

Among participants in this bladder cancer surveillance program, the sensitivity for conventional urine cytology was 31.3%, with a specificity of 96.8%, NPV of 99.9%, and PPV of 6.3%. The sensitivity for the ImmunoCyt/uCyt+ test was 56.3%, with a specificity of 95.2%, NPV of 99.9%, and PPV of 3%. The combination of ImmunoCyt/uCyt+ and urine cytology testing showed a sensitivity of 62.3%, specificity of 92.6%, NPV of 99.9%, and PPV of 3% (Table 4).

On the basis of the indirect standardization method using Surveillance, Epidemiology, and End Results data, the expected bladder cancer incidence in the population under surveillance was 11.82 for the 30,976 person-years of observation. The observed incidence of bladder cancer was 14 cases for this follow-up period with an SIR of 1.18 (95% CI, 0.65 to 1.99), indicating that there was no significant difference between the observed and expected number of cases of bladder cancer in the cohort participating in the surveillance program. When the analysis was repeated separately for the current employee group and for the former/retired employee group, the results showed no statistically significant excess of bladder cancer for either group. For current employees, eight cases were observed and 7.42 were expected, with an SIR of 1.08 (95% CI, 0.47 to 2.12). For former/retired employees, six cases were observed and 4.40 were expected, with an SIR of 1.36 (95% CI, 0.50 to 2.97).

DISCUSSION

By selecting populations with a historically high prevalence of disease for assessing screening tools that are sufficiently sensitive and specific to provide high predictive values, we have the ability to identify disease at an earlier stage and promote interventions, thereby decreasing the morbidity and potential mortality associated with later expression of a more advanced form of the disease.[26] The study company's bladder cancer screening program has been underway since 2000, and in this report we describe the efficacy of this screening program during the first 11 years of implementation.

In a review assessing the sensitivity and specificity of various urine markers for bladder cancer surveillance, the median sensitivity for urine cytology was reported as 48% (31% to 100%) with a median specificity of 94% (62% to 100%). The median sensitivity for ImmunoCyt/uCyt+ was reported as 83% (50% to 100%) with a median specificity of 80% (69% to 90%).[21] In another review comparing the performance of urine cytology to various other tumor markers, the sensitivity of urine cytology was reported as 20% to 90% with a specificity of more than 90% compared with a sensitivity of 67% to more than 90% and specificity of 62% to 84% for ImmunoCyt/uCyt+.[19] In our cohort of aluminum smelter workers, the sensitivities for both urine cytology and ImmunoCyt/uCyt+ were closer to the lower end of the ranges reported in the literature, and the specificities were closer to the higher end of the reported ranges.

Several studies have reported that the ImmunoCyt/uCyt+ test is highly sensitive and improves accuracy when combined with conventional urine cytology.[20,27–33] Nevertheless, other studies were unable to confirm the high sensitivity of ImmunoCyt/uCyt+.[34,35] In our analysis, the sensitivities of urine cytology (31.3%) and ImmunoCyt/uCyt+ (56.3%) improved to 62.3% when these tests were performed in combination, whereas the specificities of the paired testing remained greater than 90%, demonstrating an increase in sensitivity without significant loss of specificity in the screening protocol.

In addition to a high-sensitivity and specificity, screening tests should have high NPVs and PPVs to avoid false-negative and false-positive results, respectively. The PPV of several combinations of tests, including urine dipstick for hematuria, cytology, and different tumor markers in very high-risk populations, such as heavy smokers and men older than 60 years, have been very low, ranging from 2.4% to 8%.[36–39] The PPV of cytology, ImmunoCyt/uCyt+, and these tests in combination for our cohort was 6.3%, 2.99%, and 2.96%, respectively, whereas the NPV for all the tests was more than 99.9%. The PPV depends on the incidence of the disease of interest in the population of interest and increases as the incidence of disease increases. The very low PPV we report reflects, in part, the low incidence of bladder cancer in the population currently under surveillance by the study company. This observation is supported by the SIR of 1.18 (95% CI, 0.65 to 1.99), which suggests that the risk of bladder cancer in the population under surveillance may not differ from the general population. Separate analyses for the current employee group and the former/retired employee group showed no statistically significant excess of bladder cancer in either group. There is, therefore, no evidence that the older former/retired employees with longer periods elapsed from first exposure have a higher incidence of bladder cancer than the general population. Because of the way the program was offered, neither the proportion nor representativeness of former/retired employees who participated in the study is known, although it seems unlikely that participation in medical surveillance by former/retired employees would be systematically lower in those with higher exposures to CTPV.

There are two primary factors that determine the risk of cancer from occupational exposure to a carcinogen—the latency or time from initial exposure to diagnosis of cancer and the cumulative exposure to the carcinogen. The latency period for bladder cancer is generally very long but has been shown to vary considerably, from as short as 16 years to as long as 45 years.[3] In 2007, Gibbs et al[40] examined the latency of bladder cancer in three cohorts of aluminum smelter workers hired before 1951 and reported that there was evidence of an increased risk of bladder cancer only after 20 years of exposure. The average period of exposure to CTPVs in the cohort under surveillance was 25.2 years. Consequently, insufficient follow-up

TABLE 4. Efficacy of the Bladder Cancer Surveillance Protocol

Tests	Sensitivity, %	Specificity, %	NPV, %	PPV, %
Urine cytology	31.3	96.8	99.9	6.3
ImmunoCyt/uCyt+	56.3	95.2	99.9	2.99
Combined Cytology & ImmunoCyt/uCyt+	62.3	92.6	99.9	2.96

NPV, negative predictive value; PPV, positive predictive value.

time should not explain the low risk of bladder cancer observed in this cohort.

The other determinant of cancer risk in aluminum smelter workers, namely, cumulative exposure to CTPV, is greatly influenced by the smelting technology used. There are two main types of aluminum smelting technology—Söderberg technology and prebake technology. Söderberg technology uses anodes baked directly in the pot by the heat of the electrolytic process and CTPVs generated during the electrolytic process escape into the potroom atmosphere. Prebake technology uses anodes that are formed in a separate area called the green mill and prebaked in another area called the carbon bake furnaces, before insertion into the electrolytic cells in the potroom; therefore, lower exposure to CTPV occurs in prebake potrooms.[41] The initial epidemiologic studies of aluminum workers that reported evidence of increased risk of bladder cancer in the workforce were predominantly conducted in Söderberg smelters where exposure to CTPV was historically high.[4,5,42] Recent follow-up studies of these worker cohorts have shown a significant reduction in the risk of bladder cancer[40,43,44] likely because of the steady decline in CTPV exposure in these plants with implementation of computerized control of the smelting process, mechanization of tasks performed on the pots, and installation of alkaline scrubbing ventilation systems in the potrooms.[45] Follow-up studies of aluminum prebake smelter workers in Italy[46] and Australia[47,48] reported no excess risk of bladder cancer among these workers. Although the Australian cohort of smelter workers was relatively young and had a short follow-up period, which was a recognized limitation, the duration of follow-up for the Italian cohort was 29 years.

The participants in the study company's bladder cancer surveillance program in the United States worked predominantly in prebake smelters (95% or more). Moreover, there has been a steady decline in CTPV levels in the company's US smelters over the last 25 years[49] as shown in Figs. 1 and 2. Therefore, the risk of bladder cancer in this population is expected to be significantly lower than the risk estimated from the earlier Canadian studies.

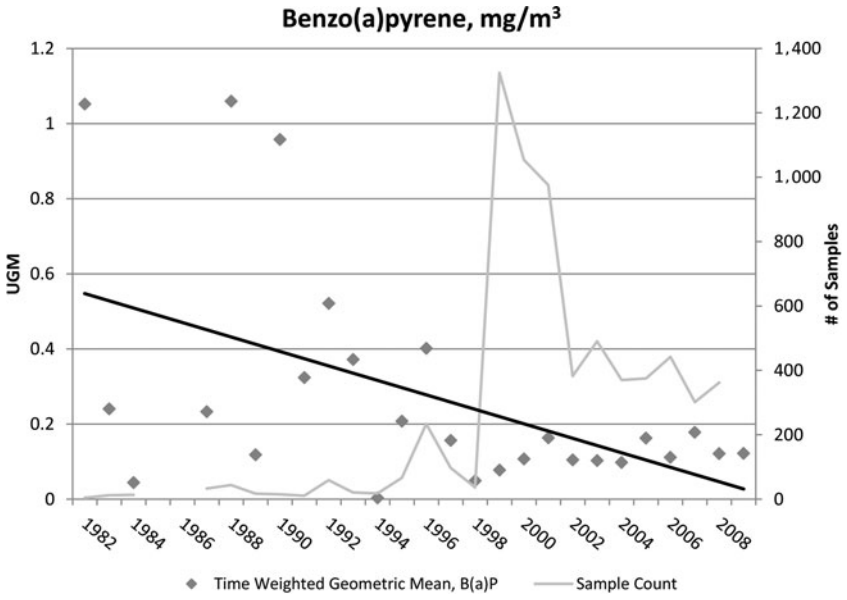

FIGURE 1. Coal tar pitch volatile exposure as benzo(a)pyrene in Alcoa 1983 to 2008.

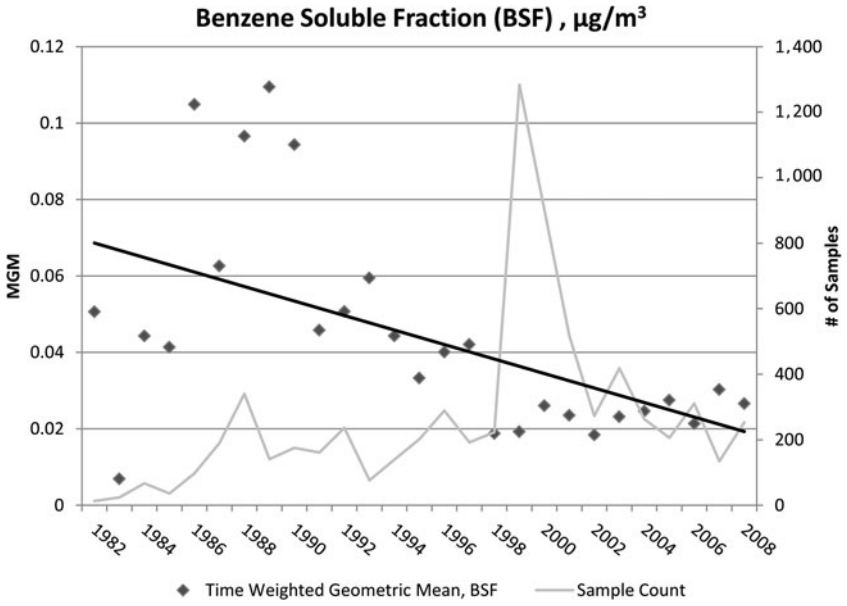

FIGURE 2. Coal tar pitch volatile exposure as benzene soluble fraction (BSF) in Alcoa 1983 to 2008.

There are several limitations to this report that must be considered. One major limitation is the potential for misclassification. As discussed above, because it was not feasible to perform cystoscopy on all the participants or even a random sample of participants who tested negative, we determined specificity of the bladder screening tests in this population by following the participants who tested negative on both ImmunoCyt/uCyt+ and cytology for 1 year to identify those diagnosed with bladder cancer. This strategy could lead to overestimation of true negative results. Because the specificities and NPVs of the screening tests reported in this analysis were 90% or more, we do not believe that our test results would have changed significantly as a result of some misclassification, although of course the SIR might.

There could also be misclassification of "false-positive" results because some individuals whose test results were classified as "false-positives" on the basis of positive ImmunoCyt/uCyt+ tests with no evidence of bladder cancer confirmed by cystoscopy, subsequently developed bladder cancer up to 5 years later. Therefore, the role of ImmunoCyt/uCyt+ in very early detection of bladder cancer needs further exploration.

Another limitation of this report is the difficulty in identifying the true "at-risk" cohort. Former and retired employees who were older and had a longer period from first exposure to CTPV were less likely to participate in the surveillance program compared with current employees. Many of these individuals worked in aluminum smelters that were closed many years ago, long before being acquired by the current company. Although the company periodically sent letters to the last known address of former and retired employees, individuals who historically worked for the parent company (Alcoa Inc) or who worked at facilities that have remained in operation were more likely to participate in the program.

The results from the initial 11 years of the bladder cancer surveillance program described in this report indicate no evidence of excess risk for bladder cancer among this cohort. We further demonstrate that a combination of ImmunoCyt/uCyt+ and urine cytology tests for screening for bladder cancer in aluminum smelter workers enhanced the sensitivity of urine cytology testing alone without a significant change in specificity. Nevertheless, because of the very low PPV of the current test regimen, the low risk of bladder cancer in this cohort, and evidence that many participants who were later determined to be cancer free underwent invasive and expensive studies, evidence for benefit from the current medical surveillance program for screening of bladder cancer in aluminum smelter workers is low. This conclusion is consistent with conclusions of a recent review completed by the United States Public Health service on bladder screening in this and other high-risk populations.[2]

DATA SHARING

As an alternative to providing a de-identified data set to the public domain, the authors allow access for the purpose of reanalyses or appropriate "follow-on" analyses by any qualified investigator willing to sign a contractual covenant with the host institution limiting use of data to a specific agreed-on purpose and observing the same restrictions as are limited in our contract with Alcoa, such as 60-day manuscript review for compliance purposes.

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