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Beryllium Lymphocyte Proliferation Test Surveillance Identifies Clinically Significant Beryllium Disease

Margaret M. Mroz, MSPH^{1,*}, Lisa A. Maier, MD, MSPH^{1,2,3}, Matthew Strand, PhD^{4,5}, Lori Silveira, MS⁴, and Lee S. Newman, MD, MA^{2,3}

¹Division of Environmental and Occupational Health Sciences, Department of Medicine, National Jewish Health, Denver, Colorado

²Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, School of Medicine, University of Colorado Denver, Denver, Colorado

³Department of Environmental and Occupational Health, Colorado School of Public Health, University of Colorado Denver, Denver, Colorado

⁴Division of Biostatistics, Department of Medicine, National Jewish Health, Denver, Colorado

⁵Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Denver, Denver, Colorado

Abstract

Background—Workplace surveillance identifies chronic beryllium disease (CBD) but it remains unknown over what time frame mild CBD will progress to a more severe form.

Methods—We examined physiology and treatment in 229 beryllium sensitization (BeS) and 171 CBD surveillance-identified cases diagnosed from 1982 to 2002. Never smoking CBD cases (81) were compared to never smoking BeS patients (83) to assess disease progression. We compared CBD machinists to non-machinists to examine effects of exposure.

Results—At baseline, CBD and BeS cases did not differ significantly in exposure time or physiology. CBD patients were more likely to have machined beryllium. Of CBD cases, 19.3% went on to require oral immunosuppressive therapy. At 30 years from first exposure, measures of gas exchange were significantly worse and total lung capacity was lower for CBD subjects. Machinists had faster disease progression as measured by pulmonary function testing and gas exchange.

Conclusions—Medical surveillance for CBD identifies individuals at significant risk of disease progression and impairment with sufficient time since first exposure.

Keywords

beryllium; chronic beryllium disease; medical surveillance

INTRODUCTION

The granulomatous lung disorder chronic beryllium disease (CBD) occurs in exposed individuals who develop a cell-mediated immune response to beryllium. Cases continue to

occur in the modern beryllium industry, despite efforts to reduce exposure [Henneberger et al., 2001; Newman et al., 2001; Schuler et al., 2005; Contini et al., 2006; Stanton et al., 2006]. Workplace screening for beryllium sensitization (BeS) using the blood beryllium lymphocyte proliferation test (BeLPT) identifies workers with clinically significant, symptomatic CBD as well as workers with early evidence of granulomatous lung disease but no symptoms or physiologic abnormalities at the time of initial clinical evaluation [Kreiss et al., 1993a,b, 1997]. Some individuals with CBD may ultimately progress to require treatment with corticosteroids and supplemental oxygen [Sood et al., 2004], however, it remains unknown the rate at which this occurs and over what time frame mild CBD, detected through medical surveillance, will progress to a more severe form of disease.

Beryllium disease was first identified in the United States in the 1940s in the fluorescent light industry and soon after in beryllium processing plants [Hardy and Tabershaw, 1946; DeNardi et al., 1949a; Hardy, 1950, 1955]. The clinical picture of the disease was described by physicians first treating CBD using medical history, physical examination, chest radiograph, pulmonary function testing, and histopathology at necropsy [DeNardi et al., 1949a,b]. The establishment of the Beryllium Case Registry in 1952 [Hardy et al., 1966] allowed researchers to describe the epidemiology of both acute and chronic beryllium disease in more detail based on 888 cases reported to the registry between 1952 and 1978 [Eisenbud and Lisson, 1983]. The clinical picture of beryllium disease was described historically based on these and other cases who presented showing the signs and symptoms of the disease. Typically, these cases of CBD presented first with weight loss and shortness of breath, later followed by pulmonary function test changes and by chest X-ray abnormalities [Hardy and Tabershaw, 1946; Hardy, 1950]. In 1955, however, Hardy [1955] described a spectrum of disease from “no disability” to “completely disabling beryllium disease.” It was Hardy’s [1965] conclusion that milder disease correlated with lower intensities of exposure, yet disease still developed with low levels of beryllium exposure.

With the utilization of immunologic screening for beryllium disease in the 1980s and 1990s [Hanifin et al., 1970; Williams and Jones Williams, 1982; Rom et al., 1983; Cullen et al., 1987; Rossman et al., 1988; Kreiss et al., 1989], cases of CBD were being identified in workers before overt symptoms were present or recognized as being related to beryllium exposure. The BeLPT has been used clinically to differentiate CBD from other lung diseases [Fireman et al., 2003; Muller Quernheim et al., 2006] and is currently used in beryllium work force medical surveillance [DOE, 1999; Cummings et al., 2007]. Screening has also allowed for the identification of BeS without disease, necessitating clinical follow-up of these individuals to monitor for progression to CBD [Newman et al., 2005]. Clinical presentation of individuals diagnosed through workplace medical surveillance with the BeLPT [Kreiss et al., 1993a,b; Newman et al., 2001] ranges from identification of granulomatous disease with no symptoms to individuals who need treatment on or soon after initial evaluation [Kreiss et al., 1993a,b; Newman et al., 2005]. We know that CBD progresses and requires treatment in some cases [Sood et al., 2004], however, it remains unknown how often this occurs and over what time frame mild disease will progress to a more severe form.

We have had the opportunity to diagnose and clinically follow individuals identified with BeS through medical surveillance. Diagnostic clinical evaluation defined a cohort of individuals with BeS and identified patients with CBD in different phases of the disease process. Following these individuals longitudinally allows us to begin to study the natural history of surveillance-identified CBD from the onset of exposure. We hypothesized that early stage CBD detected through workplace medical surveillance progresses over time.

METHODS

We conducted a longitudinal cohort study of individuals who were identified as having BeS and CBD through workforce medical surveillance. All were identified by abnormal BeLPTs before reporting symptoms, physiologic abnormalities or radiographic changes. We included all individuals who were clinically evaluated at National Jewish Health between 1982 and 2002 and who were found to have CBD on baseline clinical evaluation. Patients with CBD who came to clinical attention as a result of symptoms or other physiologic abnormalities outside of a medical surveillance program were not included in this study. Our comparison group included those individuals who were identified as having BeS on medical surveillance but had no pathological evidence of CBD. Clinical re-evaluation was offered to all participants every 2 years through 2002, or sooner if a patient developed symptoms or physiologic abnormalities. The study was approved by the Center's Institutional Review Board and all participants signed informed consent.

BeS was defined as two or more abnormal BeLPTs. Blood BeLPT tests were performed within 24 hr of venipuncture using methods previously published [Mroz et al., 1991]. Results were expressed as a stimulation index (SI), which is the ratio of the counts per minute of radioactivity in cells stimulated with beryllium salts divided by the counts per minute for unstimulated cells. A test was considered abnormal if two or more of the six stimulation indices exceeded the normal range. CBD was defined as evidence of BeS plus granulomas and/or mononuclear cell infiltrates in lung tissue on biopsy.

Baseline and follow-up clinical evaluations included pulmonary function testing, exercise testing, chest radiograph with International Labor Organization (ILO) B-reading [International Labor Organization, 1980; Mroz et al., 1991], fiberoptic bronchoscopy with bronchoalveolar lavage (BAL), and transbronchial lung biopsies. Total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory volume in 1 sec (FEV₁) were measured with a pneumotachograph. The single breath method of Ogilvie and coworkers was used to evaluate the ratio of diffusing capacity of carbon monoxide (DL_{CO}). Gas exchange, maximum exercise capacity, and maximum oxygen consumption (VO₂max) were determined with a 380 B cycle ergometer with continuous cardiac rhythm and arterial oxygen content monitoring [Lundgren et al., 2001]. An indwelling arterial line measured arterial blood gases at rest and after each minute of exercise. Results are reported as the partial pressure of oxygen (PO₂) and alveolar-arterial oxygen difference ([A-a]PO₂) at rest and at maximum exercise. BAL was performed using methods previously described [Newman et al., 1989]. We reported the number of white blood cells per cubic centimeter of BAL fluid (WBC/CC) and the percent of lymphocytes in the recovered BAL fluid. We tested BAL cell response by performing the BeLPT using methods similar to the blood test. Lung tissue was fixed with 10% formalin, embedded in paraffin, cut into 2-μm thickness serial sections and were hematoxylin-eosin stained. The reviewing pathologist was unaware of clinical status.

Questionnaires gathered information on demographics, smoking history, and occupational work histories. Individuals were categorized as "never smokers" or "smokers" (current and former smokers) for the purposes of the analyses. Detailed questions regarding exposure to beryllium were completed by patients and reviewed with the evaluating physician. Industry in which the participant worked was categorized as work with ceramics, recycling, nuclear weapons facility, or nuclear/aerospace. We categorized jobs into four groups: (1) Bystanders, which included security guards and secretaries in beryllium-using areas. These individuals did not work directly with beryllium; (2) Dust disturbers which included tradespersons or janitors who would be exposed to beryllium by upsetting dusty surfaces; (3) Non-production workers which included individuals working with beryllium in a non-

production capacity such as inspectors, laboratory workers, quality control technicians, and engineers; (4) Production workers which included individuals working directly with beryllium in forming, metal production, machining, etc. Since previous studies have shown machining to be a risk factor for BeS and CBD [Kreiss et al., 1993b, 1996; Stange et al., 2001] job titles were also categorized as “machining” and “non-machining.”

Statistical Methods

We compared surveillance-identified CBD patients to those with BeS who had no pathological evidence of CBD on clinical evaluation. These groups worked in similar industries and had the same opportunity for other exposures that may affect clinical measures of physiology. Baseline clinical evaluation included demographics, smoking status, medical treatment for CBD, exposure variables, clinical evaluation results, and blood and BAL fluid markers. Wilcoxon rank sum test and the Kruskal–Wallis rank sum test were used to compare the continuous variables, while Chi-square tests or Fisher’s exact tests were used to compare the categorical variables.

Longitudinal analysis was restricted to never smokers to avoid confounding effects of changes in physiology due to smoking. Fourteen outcome variables (listed in Table II) were fit separately with mixed models (employing SAS, PROC MIXED) [SAS Institute Inc, 1988]. Each model had five core predictor variables: time since first exposure (linear term), disease type (BeS, CBD), time-by-disease type interaction, industry type (ceramics, recycling, nuclear weapons facility, other nuclear/aerospace), and decade of first exposure (pre-1970, 1970s, 1980s, post-1980s). In addition, age (at time of visit) was included in models for [A-a]PaO₂ at rest, [A-a]PaO₂ at maximal exercise, PaO₂ at rest and PaO₂ at maximal exercise; age, sex, and height were included in models for DL_{CO}, maximum workload and VO₂ at maximal exercise; age, height, sex, and race were included in models for FEV₁, FVC, FEV₁/FVC, and TLC. The inclusion of the age variable (when applicable) allowed for better estimation of the progression of the illness over time not due to aging. Decade of first exposure was included to help account for possible differences in exposure intensity and duration experienced by subjects, based on eras of production in which they worked. Longitudinal data collected on subjects were incorporated into the model. A random intercept term was added to each model to allow separate fits for individuals. This induces a compound symmetric covariance structure for within-subject repeated measures over time. An examination of more time-sensitive covariance structures did not yield improved fits.

The data were also examined to see if higher order terms (e.g., quadratic, cubic) would be necessary for time from first exposure. No consistent nonlinear trends were apparent. Three variables (peak blood BeLPT, peak BAL BeLPT, white blood cell count) were log-transformed before analysis since their distributions were highly right skewed. Results for these three variables were transformed back to original units for presentation. Consequently, estimated average changes in these variables over time from first exposure were exponential rather than linear.

Chest radiographic ILO readings were converted from a profusion score to a binary variable classifying films as normal or abnormal. We classified films as “abnormal” if the profusion rank was 1/0 or higher and “normal” if the profusion rank was 0/1 or lower. The binary variable was analyzed using a generalized linear model, logit link, and employing the generalized estimating equations (GEE), carried out with PROC GENMOD in SAS. The predictors included age, plus the core predictors as listed above, excluding decade of first exposure, which was dropped since the fit did not meet convergence criteria when this variable was included. A compound symmetric structure was used to model repeated measures within subjects over time.

Subjects were classified as either BeS or CBD. For 12 individuals (7.3% of the never smoking cohort) who had data both before and after CBD diagnosis, only the CBD portion was used. This was done for two reasons: (i) the duration of time of progression from BeS to CBD was unknown, making it unclear how subjects should be classified on certain dates, and (ii) simplification of analysis.

A second set of mixed models were fit to analyze differences between machinists and non-machinists within the never smoking CBD cohort, for each outcome variable. The same predictors as described above were used in these models, excluding industry type.

The observed data on subjects ranged from ~10 to 40 years since first exposure. Hence, slope estimates (average change in the outcome variable per year) reported in Tables III and V are meaningful for this time frame. For outcome variables analyzed on the log scale (BeLPT and WBC/CC variables), the average slope between 10 and 40 years since first exposure is reported. (The slope is not constant over time when inverted from the log scale back to the original scale).

All reported *P* values are two-sided. Since directional differences were expected for many tests (e.g., worse lung function for CBD subjects than for BeS subjects), we considered the 0.1 level of significance in addition to the 0.01 and 0.05 levels.

RESULTS

There were 171 cases of CBD and 229 cases of BeS identified through workplace medical surveillance with the blood BeLPT. At baseline clinical evaluation, CBD cases did not differ from BeS significantly in age, gender, or duration of beryllium exposure. Of BeS patients, 36.2% were never smokers compared to 47.4% of CBD cases. BeS patients were more likely than those with CBD to be current smokers (19.7% vs. 10.1%, $P = 0.01$) and CBD patients were more likely to work in the ceramics industry (12.9%) compared to those with BeS (1.8%), $P = 0.0013$. Patients with BeS were more likely to have bystander exposure (21.4%) compared to those with CBD (8.2%), $P < 0.001$, while CBD patients were more likely to be machinists (21.1%) compared to those with BeS (12.7%), $P = 0.03$. Table I shows differences between BeS and CBD demographics at baseline clinical evaluation based on smoking status.

We observed no significant differences at baseline evaluation between CBD cases and beryllium-sensitized individuals in pulmonary function parameters, DL_{CO}, measures of exercise physiology and gas exchange (Table II). Median values for all pulmonary function measures were within the normal range reflecting a healthy worker population. We found 18.9% of CBD cases to have an abnormal profusion score (1/0 or greater) on initial clinical evaluation compared to 5.5% of BeS patients, $P = 0.003$. Of CBD cases, 19.3% developed clinical abnormalities requiring oral immunosuppressive therapy an average of 1.4 years after initial diagnosis or an average of 22.8 years after first exposure.

All individuals were identified with BeS or CBD through workplace screening, as such, the time of actual sensitization and development of disease was unknown. Since time of first beryllium exposure was identifiable for all individuals, we examined progression of disease from first beryllium exposure. Among 164 known never smokers within the cohort, 83 (51%) were classified as BeS, and 81 (49%) were identified as having CBD. The baseline demographic comparisons for never smokers were similar to those reported above for the entire group as demonstrated in Tables I and II. Pulmonary function measures for never smokers reflected a healthy worker population. On baseline clinical evaluation, among the never smokers, 80% of CBD patients and 83% of BeS patients had a FVC percent predicted of >80%; 85% of both CBD and BeS had an FEV₁ percent predicted >80%; and 85% of

CBD and 90% of BeS had a DL_{CO} percent predicted $>80\%$. Among the 81 never smoking CBD subjects, 17 (21.0%) were machinists compared to 4 of 83 BeS cases (4.9%), $P = 0.002$. BeS cases were more likely to have bystander exposure (28.7%) compared to CBD cases (8.6%), $P = 0.0004$.

Clinical course of surveillance-identified CBD in this study was modeled using baseline and follow-up data from participants. Among CBD never-smoking subjects, 54 (67%) had two or more visits with an average of 6.2 visits (range 2.0–19.0) and an average span between first and last visits of 5.7 years (range: 0.5–14.0 years). For the BeS never-smoking subjects, 36 (43%) had two or more visits, with an average of 3.0 visits (range 2.0–8.0) and the average span between first and last visits was 3.4 years (range: 1.1–11.0 years). CBD subjects tended to have more follow-up visits, spanning a longer time period. Since study subjects were diagnosed at different stages of BeS and CBD, modeling was conducted based on “time since first exposure” which could be estimated for all participants. Table III shows average change per year by disease group (BeS, CBD) for several health indicators, based on mixed model results. Also included are average values of the health indicators for groups at 10 and 30 years after first exposure. Estimates for subjects with characteristics not represented in Table III can be obtained by employing the estimates presented in Table IV. CBD subjects had higher levels of BAL fluid markers (WBC/CC;%lymphocytes; BAL BeLPT SI) than did BeS subjects, regardless of time since first exposure ($P < 0.01$ at 10 and 30 years), indicating that changes in these variables occurred rapidly and remained that way over time. Differences were not apparent for any other variables at 10 years from time of first exposure. At 30 years from first exposure, $[A-a]PaO_2$ at rest was higher ($P < 0.05$), and PaO_2 at rest lower ($P < 0.1$) for CBD subjects; DL_{CO} ($P < 0.05$) and TLC ($P < 0.1$) were also lower for CBD subjects at this time. Average FEV_1/FVC dropped over time for BeS subjects, but not for CBD subjects ($P < 0.05$ for difference between groups). Changes over time also indicated that CBD subjects had a greater decline than BeS subjects in maximum workload, ($[A-a]PaO_2$) at maximal exercise and PaO_2 at maximal exercise, although this did not reach statistical significance. For abnormal chest X-ray (profusion score 1/0 or greater), no significant differences between BeS and CBD groups were observed (data not shown). For CBD subjects, abnormal X-ray declined from 11% to 6% between 10 and 30 years from first exposure, whereas the rates for the BeS group were 3% and 1% at these same time points. However, differences between groups and changes over time were not significant. Figure 1 shows graphs of key outcome variables versus time from first exposure, by diagnosis group, and demonstrates a greater decline in DL_{CO} , PaO_2 at rest, maximum workload, and a widening of $[A-a]PaO_2$ at rest in CBD compared with BeS.

To examine the effect of exposure on disease progression, we compared machinists to non-machinists from the never smoking CBD patients. At baseline, workload at maximum exercise was higher for machinists compared to non-machinists. Machinists also had higher VO_2 at maximum exercise, lower PaO_2 at rest and a narrower $[A-a]PaO_2$ at rest. Peak blood BeLPT results were also higher for the machinists at baseline. The longitudinal mixed model analyses showed significant declines in FEV_1 and FVC over time from first exposure for machinists, relative to non-machinists ($P < 0.01$). These changes were evident at 30 years from first exposure, but not at 10 (Table V). Significant differences between groups also indicated faster progression into illness for machinists, with respect to PaO_2 at rest ($P < 0.05$) and $[A-a]PaO_2$ at rest ($P < 0.1$). Machinists also had lower TLC at 30 years ($P < 0.1$). Blood and BAL fluid markers did not differ between machinists and non-machinists over time. Figure 2 shows graphs of four outcome variables versus time from first exposure, for machinists and non-machinists, demonstrating the faster decline in PaO_2 at rest for machinists, widening of $[A-a]PaO_2$ at rest for machinists and more significant decreases in FEV_1 and FVC over time for machinists compared to non-machinists.

Over the course of the study 22 individuals with BeS developed CBD. They were classified as CBD and only their data since time of CBD diagnosis were used in analysis. However, if we included the 22 among the 229 individuals initially classified as BeS, we estimated that 8.8% (22/251) of individuals with BeS developed CBD. Among the never smokers, 12.6% (12/95) progressed from BeS to CBD and 6.4% (10/156) of the ever smokers with BeS developed CBD ($P = 0.10$).

DISCUSSION

This longitudinal study demonstrated that workforce medical surveillance with the blood BeLPT identifies individuals at significant risk of disease progression and future impairment with sufficient time since first exposure. Of those with CBD identified through workforce medical surveillance, 19.3% required treatment with corticosteroids within an average of 2 years of initial diagnosis. Fifteen years after initial beryllium exposure, physiologic measures in never smoking CBD subjects began to diverge from those of never smoking BeS subjects. Significant differences were seen 30 years after first beryllium exposure for TLC, DL_{CO} , (A-a)PaO₂ at rest, and PaO₂ at rest. CBD in machinists was significantly worse than in other CBD patients at baseline and upon follow-up in measures of gas exchange, FVC, FEV₁, and TLC. Machining has been associated with a higher exposures and a higher risk of CBD [Kreiss et al., 1996, 1997; Stange et al., 2001], suggesting a relationship between dose and both disease severity and progression. Similarly, workers from the beryllium ceramics industry and in the copper recycling industry showed steeper declines in FEV₁/FVC and in PaO₂ at maximal exercise, respectively. Taken in aggregate, these data suggest that the clinical course of CBD may vary by industry and job task.

This study benefited from the ability to study the effects of beryllium exposure and the progression of disease in never smokers without the confounding of smoking-related health effects. The prevalence of CBD among ever smokers was significantly lower than among never smokers (38.1% vs. 49.4%, $P = 0.025$). In addition, never smokers with CBD were more likely to develop CBD over the course of the study compared to smokers (12.6% vs. 6.4%, $P = 0.10$), suggesting that smoking may have a protective effect against the development of granulomatous lung disease as has been seen in hypersensitivity pneumonitis. However, those who have pulmonary complications from smoking may be at risk for faster declines in lung function and gas exchange. Smokers with CBD compared to never smokers had significant differences in gas exchange evidenced at baseline clinical evaluation (Table II). (A-a)PaO₂ at rest was significantly worse and PaO₂ at rest was significantly lower in smoking versus never smoking CBD case at baseline. Smokers were also more likely to be treated with corticosteroids than were never smokers, suggesting that they may have worse disease. Future studies can be aimed at looking at changes over time for all CBD patients, now that patterns of physiologic change have been identified in a never smoking cohort.

It is important to note that while this article describes the natural history of CBD in patients discovered through workforce medical surveillance programs, it does not describe the full spectrum of CBD cases being seen today. Our clinical cohort includes more than 70 individuals with CBD who came to clinical attention due to symptoms, changes in physiology or misdiagnosed disease, none of whom are included in this analysis. By design, our study did not include any of these patients, as our goal was to assess progression of surveillance identified CBD. Thus, the full picture would include patients whose clinical presentation may be even more severe than that seen in our medical surveillance-identified cohort.

We chose to examine progression of disease from time since first beryllium exposure, since it is unknown when BeS and CBD develop in workers who are first discovered at the time of a workplace medical surveillance program. Studies have shown that BeS and CBD can be diagnosed within months of first exposure in some individuals [Henneberger et al., 2001; Newman et al., 2001; Stanton et al., 2006] and after many years of exposure in others [Henneberger et al., 2001; Newman et al., 2005]. Among the 22 individuals who were initially identified with BeS and developed CBD over the course of this study, we estimated their time from first beryllium exposure to CBD diagnosis to be an average of 24 years, ranging from 4 to 45 years. Between 20% and 100% of individuals have CBD on initial clinical evaluation depending on the workforce studied [Kreiss et al., 1993a,b; Henneberger et al., 2001; Welch et al., 2004; Rosenman et al., 2005]. It is speculated that both exposure and genetics may affect the differences in development of CBD after first exposure. Thus, looking at time from first exposure allows us to define progression in a known time frame for most individuals, since onset of sensitization and disease in some is unknown. We found that 15 years after first exposure, CBD patients started to diverge from those with BeS, with significant changes in physiology observed 30 years from first exposure. Yet for some individuals physiologic changes associated with disease may first develop past 30 years, as evidenced by the patients noted above who had an average time from first beryllium exposure to CBD diagnosis of 24 years. This time frame demonstrates the need to provide ongoing medical surveillance and clinical follow-up for individuals. For many, physiologic changes may occur after they leave the beryllium workforce, emphasizing the need for ongoing medical surveillance and clinical follow-up. CBD has been described as a slowly progressing disease and our study demonstrates that for most patients this is true. However, it is important that health practitioners not ignore the pulmonary changes seen in older patients who may have worked in the beryllium industry in the past. Conversely, it is also important to note that we have identified individuals who have remained beryllium sensitized up to 30 years after first exposure, without developing CBD. It is unknown what proportion of individuals will eventually go on to develop CBD. Rosenman et al. [2005] studied 577 workers of a beryllium processing plant whose first exposure on average began in the 1960s. They identified 7% to have CBD and another 7.6% with BeS at the time of their cross sectional study. Those with BeS had a shorter duration of exposure, began work later, last worked with beryllium longer ago, had lower measures of cumulative and peak exposure and had lower non-soluble exposures than those with CBD suggesting that exposure may impact progression from BeS to CBD. We were unable to calculate exposures on individuals in our study, since they came from a variety of different work forces. We did find that those with BeS showed no differences in time since first or last exposure but were less likely to have been exposed in the ceramics industry and more likely to have bystander exposures compared to those with CBD suggesting that, as shown in the Rosenman study, form and dose of beryllium may contribute to development of CBD.

It should be noted that the average participant was 52 years old at time of first evaluation. As participants age and as follow-up periods extend, we may see a different picture of progression. We also know that individuals within the cohort progressed at different rates, noting that a sizable proportion required immunosuppressive therapy. However, examining the progression of the group as a whole does not allow us to examine whether different presentations of CBD have different outcomes or rates of progression. Those individuals with lung granulomas and abnormal blood BeLPTs, but with normal BAL cell counts and BeLPTs may have a different clinical course than those who present with granulomas in the presence of an elevated lung lymphocyte count and a response of lung cells to beryllium in vitro. In addition, this study also does not address risk factors related to the more severe disease seen in a subset of individuals. Progression may also be influenced by genetics and the identification of disease severity markers currently known and those not yet identified [Jonth et al., 2007].

Few studies to date have examined the natural history of CBD identified through medical surveillance. Early studies of the natural history of CBD by Hardy and Tabershaw [1946], Hardy [1955, 1965], DeNardi et al. [1949b], and Hardy et al. [1966] described different patterns of progression ranging from no disability, similar to some of our surveillance-identified cases, to severe disabling beryllium disease, with the more severe cases related to the high beryllium exposures of early workplaces. Gaensler et al. [1959] studied respiratory changes in a case series of 30 patients with early CBD. All patients studied demonstrated abnormalities in gas exchange as measured by rudimentary exercise testing. They exhibited low arterial oxygen tensions and incomplete saturation of arterial blood at rest, as we found in this study. With the advent of the BeLPT in the 1980s, cases of BeS and early CBD were being diagnosed as the result of workforce screening and surveillance [Rom et al., 1983; Cullen et al., 1986; Kreiss et al., 1989] at earlier stages than those who presented to the physicians in the 1940s and 1950s. A cross-sectional study by Pappas and Newman [1993] examined early physiologic abnormalities in surveillance-identified cases. The most common abnormality identified was a rise in dead space to tidal volume ratio during exercise, suggesting pulmonary vascular abnormalities. Similarly, we found abnormalities in gas exchange which differentiated BeS and CBD over time. A study by our group in 2005 [Newman et al., 2005] examined the progression of BeS to CBD and longitudinal follow-up was available on 11 of the 17 individuals who progressed to CBD. We observed statistically significant interval declines in DL_{CO} and declines in VO_2 at maximal exercise in 9 of the 11 CBD patients an average of 4.2 years after diagnosis. This study demonstrated that soon after development of disease changes in physiology were apparent. Sood et al. [2004] reported response to corticosteroid therapy in CBD. The six subjects in this study had a mean follow-up time of 10.1 years and showed a variable response to steroids with the most common pattern being a short-lived improvement in pulmonary function. Stopping beryllium exposure was associated with improvements in lung function. Possibly those with ongoing exposure may have a different rate of decline than among those patients who are no longer beryllium exposed. Future investigations of our cohort should explore these possible differences.

Some researchers have proposed in the literature that the BeLPT should not be used in medical surveillance in asymptomatic individuals with beryllium exposure [Borak et al., 2006]. The authors argue that screening identifies “latent lesions that might go otherwise undetected over the life of the patient” and that the large proportion of persons identified with BeS and CBD will live their entire lives without perceptible adverse health effects [Borak et al., 2006]. However, our study shows that CBD does progress over time from first exposure and that decrements in breathing tests and gas exchange are evident. Many of these changes in physiology have required individuals to be treated with corticosteroids, many immediately after initial diagnosis. Our study also suggests that exposure may affect progression, as demonstrated by differences observed between machinists and non-machinists. Other studies have suggested that additional factors such as cytokine production may influence the progression of CBD over time [Maier et al., 2001; Pott et al., 2005]. As more studies examine the interaction between exposure and the genetic basis of CBD and BeS we may begin to understand why some individuals manifest changes in physiology early after exposure in comparison to those with later changes. However, our study has shown that it is important to follow individuals over time and that what may initially be viewed as asymptomatic disease may go on to cause decrements in breathing and gas exchange many years after exposure to beryllium has ceased. Future studies focusing on disease phenotypes and prognosis based on baseline diagnostic features will help us to better understand CBD and provide more information to physicians who are following these patients. Ongoing studies using this cohort should focus on identifying risk factors for treatment and other physiologic measures of outcome.

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FIGURE 1.

Estimated average response in outcome (PaO₂ at rest, (A-a)PaO₂ at rest, DL_{CO}, maximum work load) as a function of years from first exposure for non-smokers within the cohort: CBD (solid) and BeS (dashed). Estimates are based on mixed model fits. Vertical bars extend ± 1 SE from the average.

FIGURE 2.

Estimated average response in outcome (PaO₂ at rest, (A-a)PaO₂ at rest, FEV₁, FVC) as a function of years from first exposure for CBD non-smokers within the cohort: machinists (solid) and non-machinists (dashed). Estimates are based on mixed model fits. Vertical bars extend ± 1 SE from the average.

TABLE I
Baseline Clinical Evaluation Characteristics of BeS and CBD Cases Stratified by Smoking Status

	Never smokers			Ever smokers		
	BeS (n = 83)	CBD (n = 81)	P-value	BeS (n = 146)	CBD (n = 90)	P-value
Age at diagnosis (years)	50 (34.5–83)	50.3 (27–74)	1	53 (26–79)	54.8 (32–80)	0.37
Gender (M/F)	56 (67.5%)/27 (34.2%)	63 (77.8%)/18 (22.2%)	0.14	121 (82.9%)/25 (17.1%)	81 (90.0%)/9 (10.0%)	0.12
Race (%)			0.01			0.43
White	64 (84.2%)	77 (96.2%)		124 (93.2%)	85 (96.6%)	
African American	8 (10.5%)	3 (3.8%)		4 (3.0%)	2 (2.3%)	
Other	4 (5.3%)	0 (0.0%)		5 (3.8%)	1 (1.1%)	
Industry (%)			0.002			<0.0001
Ceramics	1 (1.3%)	10 (12.5%)		3 (2.1%)	12 (13.3%)	
Nuclear/aerospace	51 (63.7%)	32 (40.0%)		73 (51.0%)	23 (25.6%)	
Recycling	8 (10.0%)	7 (8.7%)		12 (8.4%)	12 (13.3%)	
Nuclear weapons	20 (25.0%)	55 (38.5%)		55 (38.5%)	43 (47.8%)	
Treatment ^a /N	0 (0.0%)	10 (12.3%)	— ^b	0 (0.0%)	23 (25.5%)	— ^b
Years from first Be exposure to last exposure	18 (2–50)	20 (0–43)	0.68	21 (0–55)	22 (0–44)	0.37
Years from first Be exposure to diagnosis	11.5 (0–40)	13 (0–36)	0.45	14 (0–39)	16.5 (1–36)	0.23
Years from last exposure to diagnosis	1.7 (0–44)	1.7 (0–35)	0.69	3.7 (0–50)	1.5 (0–43)	0.32
Job			0.002			0.45
Machinist	4 (4.9%)	17 (21.0%)		25 (17.1%)	19 (21.1%)	
Non-machinist	78 (95.1%)	64 (79.0%)		121 (82.9%)	71 (78.9%)	
Job type			0.0004			0.01
Bystander	23 (28.7%)	7 (8.6%)		26 (17.8%)	7 (7.8%)	
Dust disturber	17 (21.3%)	13 (16.1%)		40 (27.4%)	17 (18.9%)	
Non-production	25 (31.3%)	25 (30.9%)		33 (22.6%)	19 (21.1%)	
Production	15 (18.7%)	36 (44.4%)		47 (32.2%)	47 (52.2%)	

Data presented are medians (ranges) or frequencies (percentages).

^aOral prednisone, methotrexate, pentoxifylline.

^bZero values; no statistical analysis.

Baseline Pulmonary Physiology, Exercise Physiology, and Bronchoalveolar Lavage in BeS and CBD Subjects Stratified by Smoking Status

TABLE II

	Never smokers			Ever smokers		
	BeS (n = 83)	CBD (n = 81)	P-value	BeS (n = 146)	CBD (n = 90)	P-value
Pulmonary function						
FVC ^a	89.5 (59–121)	92 (43–129)	0.46	90 (31–126)	91 (45–129)	0.87
FEV ₁ ^a	94.5 (62–127)	96.5 (47–126)	0.65	92 (34–137)	94.5 (56–127)	0.49
FEV ₁ /FVC ^a	107 (71–135)	108 (64–128)	0.75	105 (67–136)	106 (77–140)	0.30
TLC ^a	103 (77–169)	106 (66–139)	0.34	109 (59–137)	105 (70–154)	0.03
DL _{CO} ^a	96 (69–146)	94 (44–146)	0.80	90.5 (26–143)	88 (55–144)	0.93
Exercise physiology						
Maximum workload (W)	175 (12–300)	177.5 (90–270)	0.32	160 (20–300)	166 (60–320)	0.72
VO ₂ at maximal exercise (L/min)	1.92 (.66–3.5)	2.0 (1.2–3.2)	0.22	1.9 (.61–3.3)	2.0 (.96–3.1)	0.54
PaO ₂ at rest (mm Hg)	74 (34–88)	74 (56–89)	0.99	70 (52–94)	70 (48–83)	0.94
PaO ₂ at maximal exercise (mm Hg)	78.8 (59–97)	80 (57–99)	0.69	77 (40–83)	76 (48–93)	0.58
(A-a)PaO ₂ at rest (mm Hg)	6 (0–21)	7 (0–23)	0.47	10 (0–27)	12 (0–32)	0.11
(A-a)PaO ₂ at max exercise (mm Hg)	12 (0–32)	13 (0–36)	0.45	13.6 (0–35)	17 (0–45)	0.12
Bronchoalveolar lavage						
Peak blood BeLPT (SI)	3.6 (.6–306.1)	5.0 (.5–162.5)	0.05	2.3 (.5–174.1)	4.4 (.3–83.1)	0.01
Peak lavage BeLPT (SI)	1.5 (.8–18.5)	7.6 (.5–362.4)	<0.0001	1.5 (0–18.2)	8.1 (.9–503.6)	<0.0001
Percentage lymphocytes	9.8 (1.5–48)	26 (1.9–74)	<0.0001	9 (.5–42.5)	22.9 (1.2–95.7)	<0.0001

Data are medians (ranges) or frequencies (percentages). Kruskal–Wallis rank sum tests were used to compare the continuous variables, while Chi-square tests or Fisher's exact tests were used to compare the categorical variables.

^aPercent predicted.

TABLE III

Progression of Illness for BeS Versus CBD Subjects, Never Smokers Only

	Average change per year			Average measure 10 years after first exposure			Average measure 30 years after first exposure		
	BeS	CBD	P-value ^a	BeS	CBD	P-value ^a	BeS	CBD	P-value ^a
Pulmonary function									
FVC (L)	-0.02	-0.03		4.82	4.80		4.37	4.20	
FEV ₁ (L)	-0.02	-0.02		3.77	3.65		3.35	3.29	
FEV ₁ /FVC	-0.16	0.04	<0.05	79.4	77.1		76.3	78.0	
TLC (L)	0.03	0.01	<0.1	6.42	6.53		6.98	6.67	<0.1
DL _{CO} (ml/min/mm Hg)	-0.69	-0.74		44.8	43.3		30.9	28.5	<0.05
Exercise physiology									
Maximum workload (W)	0.13	-0.73		197.9	202.6		200.6	188.1	
VO ₂ at maximal exercise (L/min)	-0.01	-0.01		2.44	2.35		2.15	2.08	
PaO ₂ at rest (mm Hg)	-0.03	-0.18		77.9	78.0		77.2	74.5	<0.1
PaO ₂ at maximal exercise (mm Hg)	-0.19	-0.37		83.6	85.0		79.9	77.5	
(A-a)PaO ₂ at rest (mm Hg)	-0.07	0.05		6.96	6.90		5.48	7.80	<0.05
(A-a)PaO ₂ at maximal exercise (mm Hg)	-0.01	0.05		11.3	11.8		11.1	12.7	
Blood and bronchoalveolar lavage fluid markers									
Peak blood BeLPT (SI)	-0.24 ^b	-0.36 ^b		9.29	12.77		3.50	3.84	
Peak BAL BeLPT (SI)	-0.03 ^b	-0.10 ^b		2.15	8.02	<0.01	1.58	5.96	<0.01
BAL lymphocyte (%)	-0.44	-0.81	<0.1	18.8	38.7	<0.01	10.1	22.4	<0.01
WBC/CC	-0.35 ^b	-0.60 ^b		20.2	30.3	<0.01	12.5	16.6	<0.05

Tabled values are estimates obtained from mixed model analyses.

Results apply to white males aged 52, height of 68 inches, 1970s start of employment, in the nuclear weapons industry.

Estimates for individuals with other characteristics can be obtained by using covariate information in Table IV.

^aP-value for BeS versus CBD comparison.

^bAverage slope between 10 and 40 years from first exposure.

TABLE IV

Additional Effects of Covariates Relative to Estimates Presented in Table III

	Decade of first exposure			Industry type		Age ^b	Height ^c	Sex		Race	
	Pre-1970	1980s	1990-current	Ceramics	Aerospace			Female	Male	Black	Other
Pulmonary function											
FVC (L)	0.28*	-0.275*	-0.38*	0.06	-0.10	-0.03*	0.12*	-0.75*		-0.61*	-0.35*
FEV ₁ (L)	0.19	-0.13	-0.25	-0.13	-0.03	-0.02*	0.08*	-0.58*		-0.44*	-0.25*
FEV ₁ /FVC (%)	-0.44	0.88	-0.11	-4.88**	1.43**	-0.02	-0.17	0.64		0.97	0.98
TLC (L)	0.15	0.13	0.28	0.23	-0.09	-0.01	0.14*	-0.97*		-0.88*	-0.52*
DL _{CO} (ml/min/mm Hg)	10.4*	-4.4*	-13.3*	0.25	-1.45	-0.24*	0.48*	-7.29*			
Exercise physiology											
Max workload (W)	-6.1	-4.2	-8.0	-5.92	-11.01	-1.66*	3.50*	-57.9*			
VO ₂ at maximal exercise (L/min)	0.16	-0.04	-0.27	0.04	-0.11	-0.02*	0.04*	-0.63*			
PaO ₂ at rest (mm Hg)	-4.1*	-3.5*	-1.4*	-1.9	-2.9	-0.09**					
PaO ₂ at maximal exercise (mm Hg)	2.9	-3.4	-1.1	-3.6**	-2.1**	0.06					
(A-a)PaO ₂ at rest (mm Hg)	2.4	0.8	-1.7	3.1	0.6	0.09					
(A-a)PaO ₂ at maximal exercise (mm Hg)	-1.1	0.1	-3.2	1.7	1.7	-0.06					
Blood and BAL fluid markers											
Peak blood BeLPT ^a	7.8*	-2.0*	-3.6*	-1.3	0.01						
Peak BAL BeLPT ^a	2.7	2.1	-2.3	11.0*	0.3*						
BAL lymphocyte (%)	7.6	-3.0	-10.9	15.7*	-1.5*						
WBC/CC ^a	3.0	-2.9	-7.2	10.3**	0.05**						

These effects are not time dependent (except for BeLPT and WBC/CC variables, which were analyzed on the natural log scale) and can be added to 10 and 30-year estimates in Table III.

* $P < 0.05$ for effect of variable (relative to effect for subjects with characteristics in Table III).

** $P < 0.1$ for effect of variable (relative to effect for subjects with characteristics in Table III).

^a Estimates were calculated at 25 years after first exposure.

^b Add/subtract tabled amount for each year above/below 52 years of age.

^c Add/subtract tabled amount for each inch above/below 68 inches of height.

TABLE V

Progression of Illness for CBD Never Smokers: Non-Machinist Versus Machinist

	Average change per year			Average measure 10 years after first exposure			Average measure 30 years after first exposure		
	Non-machinist	Machinist	P-value ^a	Non-machinist	Machinist	P-value ^a	Non-machinist	Machinist	P-value ^a
Pulmonary function									
FVC (L)	-0.02	-0.05	<0.01	4.80	4.94		4.47	3.88	<0.01
FEV ₁ (L)	-0.01	-0.03	<0.01	3.58	3.69		3.47	3.00	<0.05
FEV ₁ /FVC (%)	0.17	0.02		74.7	75.8		78.2	76.2	
TLC (L)	0.001	-0.02		6.85	6.68		6.88	6.37	<0.1
DL _{CO} (L)	-0.79	-0.84		45.1	44.6		29.3	27.9	
Exercise physiology									
Max workload (W)	-0.31	-1.08		199.6	203.0		193.5	181.4	
VO ₂ at maximal exercise (L/min)	-0.01	-0.01		2.29	2.28		2.10	2.07	
PaO ₂ at rest (mm Hg)	-0.26	-0.63	<0.05	78.5	82.2		73.2	69.5	
PaO ₂ at maximal exercise (mm Hg)	-0.63	-0.71		87.7	90.1		75.1	76.0	
(A-a)PaO ₂ at rest (mm Hg)	-0.01	0.22	<0.1	8.24	5.19		8.05	9.64	
(A-a)PaO ₂ at maximal exercise (mm Hg)	0.20	0.29		10.1	9.9		14.1	15.7	
Blood and BAL fluid markers									
Peak blood BeLPT (SI)	-0.39 ^b	-0.48 ^b		13.6	16.4		3.7	4.2	
Peak BAL BeLPT (SI)	0.07 ^b	-0.32 ^b		6.0	13.2		7.3	5.6	
BAL lymphocyte (%)	-0.86	-1.24		38.2	50.5	<0.1	21.0	25.7	
WBC/CC	-0.69 ^b	-0.75 ^b		32.3	35.2		16.4	17.8	

Tabled values are average estimates, obtained from mixed model analysis. Results apply to white males aged 52, height of 68 inches, 1970s start of employment, in the nuclear weapons industry.

^a P-value for non-machinist versus machinist comparison.

^b Average slope between 10 and 40 years from first exposure.