
ARTICLE

Lung Cancer Incidence Among Patients With Beryllium Disease: A Cohort Mortality Study

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We have conducted a cohort mortality study on 689 patients with beryllium disease who were included in a case registry. An earlier mortality study on 421 of these patients was limited to males and resulted in a determination of a nonsignificant twofold lung cancer excess based on only seven lung cancer deaths. We have extended this earlier study by including females and by adding 13 years of follow-up. Comparison of the 689 beryllium disease patients with the U.S. population resulted in a lung cancer standardized mortality ratio (SMR) of 2.00 (95% confidence interval = 1.33-2.89) based on 28 observed lung cancer deaths. Adjustment for smoking did not change these results. All causes of mortality were also significantly elevated (SMR = 2.19), largely because of the very high rate of deaths due to pneumoconioses (primarily beryllium disease) (SMR = 34.23; 158 deaths). No other causes of death were significantly elevated. The excess of lung cancer was consistent for both sexes and did not appear to increase with duration of exposure to beryllium or with time elapsed since first exposure to this element. The case registry included those with acute beryllium disease, which resembles a chemical pneumonitis, and those with chronic beryllium disease, which resembles other pneumoconioses. The lung cancer excess was more pronounced among those with acute disease (SMR = 2.32) than among those with chronic disease (SMR = 1.57). [J Natl Cancer Inst 83:1380-1385, 1991]

The present study is a cohort mortality study on 689 beryllium disease patients (males and females) listed by the Beryllium Case Registry, which was begun in 1952 at the Massachusetts General Hospital (1). This registry is the only such U.S. registry and is thought to include most of the recognized cases of beryllium disease in the United States. A prior mortality study on 421 male case subjects listed by the registry was based on follow-up through 1975 (2). This study found a nonsignificant twofold lung cancer excess (standardized mortality ratio [SMR] = 2.11) based on a small number of lung cancer deaths (seven observed).

Beryllium is a suspected carcinogen, although epidemiologic data are sparse. In two prior studies (3,4), researchers have noted significant elevations of lung cancer incidence among beryllium-exposed workers (SMRs of 1.97 and 1.37 at two different plants), but these studies have been criticized methodologically. Combining the observed and expected lung cancer cases from these two plants leads to an estimated lung cancer risk of approximately 1.5. The International Agency for Research on Cancer has concluded that there is limited evidence of beryllium carcinogenicity in the lungs in humans and sufficient evidence in animals (5). Data from the National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health (NIOSH) in the early 1980s indicate that approximately 44 000 people have had potential dermal or airborne exposure to beryllium alloys or compounds (6). The use of beryllium may be increasing, especially in high-technology industries such as the aircraft, telecommunications, computer, and ceramic industries (7).

Beryllium disease, sometimes called berylliosis, occurs in two forms (8): the acute form and the chronic form. The acute form has a short induction period, frequently occurs during exposure, is of brief duration, and can be thought of as a type of chemical pneumonitis. Acute cases are thought to have been the product of early high exposures, and few acute cases have been reported since the 1940s. The chronic form has a much longer induction period, sometimes developing decades after exposure has ended, and is a progressive granulomatous disease which may lead to reduced lung volumes, dyspnea, and diffuse irregular opacities on radiographs. Chronic beryllium disease involves a cell-mediated immune response, and recent studies suggest that

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those who are sensitized may in turn be those at risk of developing clinical disease (7). Susceptibility to sensitization is likely to have a genetic basis, as reflected in beryllium disease occurring in identical twins (9) and, as shown by animal studies, in one strain of guinea pigs but not in another (10). Good evidence for evaluating a dose-response pattern in humans for beryllium disease is lacking (i.e., there are few data on dose). However, there have been suggestions that chronic beryllium disease does not show a dose response, and chronic beryllium disease has often been noted to occur in people with minimal exposure (1). Individual susceptibility might be a partial explanation for this phenomenon.

There are epidemiologic grounds to believe that people with either acute or chronic beryllium disease might have a high risk of lung cancer. First, those with beryllium disease, particularly the acute form, may have received higher doses of beryllium, a suspected lung carcinogen. Second, the chronic disease resembles other pneumoconioses such as asbestosis and silicosis, and there have been multiple epidemiologic studies providing good evidence of an increased lung cancer risk for asbestotics and silicotics of a greater magnitude than for cohorts simply exposed to asbestos or silica (11-30).

The present study was undertaken to determine whether the lung cancer excess previously observed among beryllium disease patients by Infante et al. (2) persisted after further follow-up and the inclusion of data for women.

Subjects and Methods

In the late 1970s, the Beryllium Case Registry data were copied by NIOSH, and these records provide the basis for the present study ($n = 888$). A description of these records has been published previously (1). Only a handful of cases have been added to the NIOSH registry data since 1980.

The criteria for entry in the registry included either documented past exposure to beryllium or the presence of beryllium in lung tissue as well as clinical evidence of beryllium disease (8). Seven individuals had been admitted tentatively to the registry subject to further evidence of either exposure or disease, which was not forthcoming. Seven other individuals lacked virtually any data at all, including last names or dates of birth, and follow-up was consequently impossible. These 14 individuals were excluded from the study.

Those who had died prior to being entered in the registry ($n = 169$) were also excluded from the study for two reasons. The first was the concern that decedents with lung cancer may have been preferentially referred to the registry. The second reason was the fact that the date of diagnosis of beryllium disease was often missing for decedents in the registry data, and therefore it could not be determined when to begin person-years at risk for these people. Sixteen additional individuals who were not known to have died were excluded from the study because their last known date alive preceded their date of entry into the registry.

Of those remaining ($n = 689$), all of whom were known to have been alive at the time of entry into the registry, person-years at risk of death were begun on the date they were entered in the registry. Follow-up for this cohort was complicated by the

fact that Social Security numbers had not been routinely gathered by the registry. Our follow-up of this cohort included the use of Social Security Administration data on death, the National Death Index through 1988, records from the Internal Revenue Service and the U.S. Postal Service, and personal letters and phone calls. Follow-up (enumerated as person-years at risk) extended either to the date of death or to the date last observed alive (1988 for most live individuals).

Analyses of these data used life-table techniques to compare mortality rates in the cohort of beryllium disease cases with mortality rates in the U.S. population as a whole after stratification by age, race, sex, and calendar time. The analysis was conducted with a computer program developed by NIOSH (31). Observed and expected deaths were summed over strata, and a summary SMR was calculated. Confidence intervals (CIs) for SMRs were calculated assuming a Poisson distribution by an approximation suggested by Byar when seven or more deaths were observed or by the exact methods when six or fewer deaths were observed (32).

Registry data included minimal information on dates of first and last exposure to beryllium, and these dates were used to conduct analyses by duration of exposure and time since first exposure. The cutoff point for the two duration-of-exposure groups (4 years) was chosen a priori to create approximately equal expected numbers of lung cancers in each group. Based on registry data on disease type, separate analyses were conducted for the acute and the chronic forms of beryllium disease.

Information about smoking habits as of 1965 was available for 223 (32%) of the cohort members from direct interviews or interviews with next-of-kin or from registry records. These smoking data were compared with the known smoking habits of the U.S. population of similar age and sex, as of 1965 (33). The year 1965 was chosen as a time point because U.S. survey data were available at that time and because smoking habits in the 1960s are considered to have been most relevant for lung cancer mortality in the 1980s. Cohort and U.S. data were compared to determine the effect that smoking differences might have had on the lung cancer SMRs using a technique described by Axelson and Steenland (34).

Results

Table 1 provides a description of the cohort. We were able to successfully trace 95% of the cohort until date of death or, in the case of live individuals, through 1988. The cohort was primarily male (66%), and chronic beryllium disease was more common (64%) than acute disease. Virtually all of the women had chronic disease (93%), whereas only half of the men did (50%). Most of the women (61%) had worked in the fluorescent tube industry, whereas half of the men (50%) had worked in basic manufacturing.

Table 2 provides the results of the mortality analysis for causes with 10 or more observed deaths; no category with fewer than 10 deaths showed a significant excess. It is clear that overall mortality in this cohort was extremely high, largely the result of the excess in the category "Pneumoconiosis, other respiratory disease," virtually all of which was due to beryllium disease. The cohort failed to show a typical healthy worker effect, in that

Table 1. Cohort description

No. in cohort	689
Male, %	66
White, %	90
No. of deaths	428
No. of death certificates obtained	418
No. of subjects traced alive through at least 1988	224
No. of individuals not known dead but not traced past 1978	37
Person-years at risk	13 899
Subjects with acute disease, %	34
Subjects with chronic disease, %	64
Subjects with unknown disease type, %	2
Subjects entering registry during 1952–1959, %	70
Subjects entering registry during 1960–1969, %	19
Subjects entering registry after 1969, %	11
Cases arising from fluorescent tube industry, %	34
Cases arising from basic manufacturing, %	36
Cases arising from community, %	6
Cases missing information on industry, %	10
Average y of diagnosis	1953
Acute disease	1947
Chronic disease	1956
Average y of first exposure	1944
Average y of last exposure	1950
Average No. of y of follow-up for total cohort	20

Table 2. Mortality results by causes with 10 or more deaths for individuals in the Beryllium Case Registry

Cause of death (ICD*)	Observed No. of deaths	SMR (95% CI)
All cancers including lung cancer (140–208)	70	1.51 (1.17–1.91)
Lung cancer (162)	28	2.00 (1.33–2.89)
Males	22	1.76 (1.02–2.67)
Females	6	4.04 (1.47–8.81)
Exposure ≤4 y	17	2.01 (1.11–3.23)
Exposure >4 y	11	1.98 (0.99–3.55)
Time since first exposure		
≤20 y	10	1.95 (0.94–3.59)
>20 y	18	2.03 (1.20–3.21)
Basic manufacturing	19	2.69 (1.61–4.20)
Fluorescent light industry	3	0.85 (0.18–2.49)
Digestive system cancer (150–154)	15	1.23 (0.69–2.03)
Ischemic heart disease (410–414)	76	1.17 (0.92–1.47)
Cerebral vascular disease (430–438)	15	1.12 (0.63–1.86)
Pneumoconioses, other respiratory disease (470–478, 494–519†)	158	34.23 (29.1–40.0)
Exposure ≤4 y	72	26.30 (20.6–33.1)
Exposure >4 y‡	86	45.78 (36.6–56.5)
Nonmalignant digestive disease (520–579)	15	1.61 (0.90–2.67)
Beryllium poisonings (E850–869, E929.2)	13	35.93 (19.1–61.4)
Total deaths	428	2.19 (1.17–1.91)

*Ninth revision International Classification of Disease code.

†Includes pneumoconiosis and chronic obstructive pulmonary disease not elsewhere classified, as well as miscellaneous upper respiratory infections. Asthma, influenza/pneumonia, emphysema, and chronic bronchitis are not included in this category.

‡Significantly ($P<.001$) higher than the SMR for exposure ≤4 y via the test described by Breslow et al. (35).

ischemic heart disease was elevated. Lung cancer was elevated in both men and women, but especially in women. Dividing the cohort by duration of exposure (greater or less than 4 years) and time since first exposure (greater or less than 20 years) showed no significant trends in lung cancer rates. However, it is worth keeping in mind that the data in the registry for duration of ex-

posure are likely to contain numerous inaccuracies and that duration of exposure to beryllium may be a very poor surrogate for actual cumulative dose.

Table 3 reports analyses for acute beryllium disease, and Table 4 reports analyses for chronic beryllium disease. Acute cases had a higher lung cancer SMR than chronic cases. Deaths from pneumoconioses and other respiratory diseases, virtually all of which were due to beryllium disease, were markedly elevated in the chronic disease group. The incidence of pneumoconioses and other respiratory diseases was less elevated in the acute disease group, where the elevation was the result of patients who had acute cases but who later developed chronic disease. Data on patients with acute disease who died at the time of disease were entered in the registry only after death and hence were not included in this study.

Smoking data as of 1965 indicated that the cohort smoked less than the U.S. population (Table 5). There were more former smokers and fewer current smokers (as of 1965) among the cohort, possibly due to the fact that the presence of respiratory disease may have discouraged smoking. Current smokers in the

Table 3. Mortality for selected causes for those with acute beryllium disease (n = 237)

Cause of death	No. of observed deaths*	SMR (95% CI)
All cancers including lung cancer	37	1.64 (1.16–2.27)
Lung cancer	17	2.32 (1.35–3.72)
Exposure ≤4 y	13	2.41 (1.29–4.13)
Exposure >4 y	4	2.05 (0.55–5.27)
Time since first exposure		
≤20 y	3	3.05 (0.62–8.94)
>20 y	14	2.21 (1.12–3.43)
Ischemic heart disease	43	1.18 (0.85–1.60)
Pneumoconioses, other respiratory disease	16	6.55 (3.74–10.60)
Beryllium poisonings	0	0.00 (0.00–0.00)
Total deaths	140	1.35 (1.14–1.60)

*Sums across acute and chronic disease types may not add up to the number of cause-specific deaths for the total cohort because disease type was unknown for 2% of the cohort. ICD codes are the same as in Table 2.

Table 4. Mortality for selected causes for those with chronic beryllium disease (n = 439)

Cause of death	No. of observed deaths*	SMR (95% CI)
All cancers including lung cancer	32	1.40 (0.96–1.98)
Lung cancer	10	1.57 (0.75–2.89)
Exposure ≤4 y	4	1.35 (0.37–3.48)
Exposure >4 y	6	1.75 (0.64–3.84)
Time since first exposure		
≤20 y	1	1.80 (0.02–10.12)
>20 y	9	1.52 (0.70–2.89)
Ischemic heart disease	33	1.20 (0.83–1.69)
Pneumoconioses, other respiratory disease	141	68.64 (57.8–81.0)
Beryllium poisoning	13	71.66 (38.1–122.6)
Total deaths	428	3.21 (2.84–3.61)

*Sums across acute and chronic disease types may not add up to the number of cause-specific deaths for the total cohort because disease type was unknown for 2% of the cohort. ICD codes are the same as in Table 2.

Table 5. Cigarette smoking habits of cohort and U.S. population as of 1965*

Subjects	% of cohort	% of U.S. population— age adjusted
Males		
Current smokers, 1 pack or less	26	39
Current smokers, more than 1 pack	15	15
Former smokers	33	22
Never smokers	26	24
Females		
Current smokers, 1 pack or less	17	32
Current smokers, more than 1 pack	5	6
Former smokers	16	9
Never smokers	62	53

*There were data on smoking status of cohort members as of 1965 (current, former, or never smokers) for 141 males and 82 females. Data on amount smoked, for current smokers in 1965, were available for 51 males and 16 females out of a total of 58 and 18 current smokers, respectively. These data were used to estimate lung cancer SMRs based on differences in smoking habits using the technique described by Axelson and Steenland (34). For males, the calculation was as below, where I_0 is the rate for never smokers, I_{cohort} is the lung cancer mortality rate for the cohort (which is partitioned among categories of never smokers, former smokers, and current smokers), I_{US} is the lung cancer mortality rate for the U.S. population (also partitioned), and the ratio $I_{\text{cohort}}/I_{\text{US}}$ provides an estimate of the lung cancer SMR based on smoking differences alone. Rate ratios for former smokers (6.2), light smokers (6.5), and heavy smokers (13.8) were taken from (22). $I_{\text{cohort}} = 0.255I_0 + 0.333(6.2)I_0 + 0.258(6.5)I_0 + 0.153(13.8)I_0 = 6.11I_0$; $I_{\text{US}} = 0.239I_0 + 0.216(6.2)I_0 + 0.397(6.5)I_0 + 0.150(13.8)I_0 = 6.24I_0$; $I_{\text{cohort}}/I_{\text{US}} = 0.98$. A similar calculation was conducted for females.

cohort in 1965 smoked fewer cigarettes than current smokers in the U.S. population in 1965. If one takes into account known relative risks for smoking (36), the SMR for lung cancer among the cohort would be expected to have been less than 1.0 (0.98 for men, 0.86 for women) because of differences in smoking habits (see footnote to Table 5).

Discussion

Our data showed significant excesses of mortality from lung cancer and from nonmalignant beryllium disease and a nonsignificant elevation of mortality from ischemic heart disease. The marked elevation for death from beryllium disease was expected in this cohort of individuals known to have contracted the disease. The apparent elevation of mortality because of heart disease may be due to a tendency by the physician to overlook underlying beryllium disease when filling out the death certificate; beryllium disease can lead to cor pulmonale, which might in turn be misclassified as ischemic heart disease (8). On the other hand, beryllium-exposed cohorts have been found to have excess heart disease (4), and the possibility that heart disease is indeed associated with exposure cannot be excluded.

The twofold increase in lung cancer in the cohort was based on 28 lung cancer deaths. Our findings confirm the twofold risk previously observed among males in this cohort in 1980 (2), a finding which had been based on only seven cases of lung cancer. The lung cancer excess occurred predominantly among those who had acute beryllium disease (SMR = 2.32), although there was also a nonsignificant excess among those with chronic disease (SMR = 1.57). The observed difference in lung cancer risk between persons with the acute disease and those with the

chronic form was not that dramatic (i.e., CIs overlap) and may have occurred by chance. Another possibility is that the lower lung cancer SMR for those with chronic beryllium disease may be an artificial result of the extremely high death rate from beryllium disease itself (i.e., a competing cause).

Possible explanations for the lung cancer excess observed in this cohort include excess smoking by the cohort, selection bias, beryllium carcinogenicity, and carcinogenicity secondary to the beryllium disease process itself.

We were able to obtain data on history of smoking for only 32% of the cohort. On the basis of this sample, it was concluded that the cohort smoked less than the U.S. referent population as of 1965. If the 32% sample were representative of the entire cohort, it would be unlikely that smoking was a cause of the observed lung cancer excess.

Selection bias, in which beryllium disease cases with accompanying lung cancer were preferentially referred to the registry, is also an unlikely explanation for our results. Such selection bias might be hypothesized because physicians diagnosing lung cancer might have also discovered present (chronic) or past (acute) beryllium disease and may have then reported the case to the registry. Three observations can be made in support of the contrary view. First, we excluded from the study individuals who had died before they were included in the registry. (If selection bias did occur, it was more likely to have occurred among decedents, given the short survival time of lung cancer patients.) Second, among the cohort actually studied, a review of the registry records indicated that only five individuals were known to have had cancer when they entered the registry, and none of these had lung cancer. Third, if patients with lung cancer had entered the registry preferentially, one might expect that their follow-up period would be short. However, only three of the 28 observed lung cancer deaths occurred within 5 years of entering the registry, and the lung cancer patients had similar length of follow-up (date entered registry through date last observed) as compared with the total cohort (21 years for those with lung cancer versus 20 years for the cohort).

A more probable explanation for the observed lung cancer excess in this cohort is that these beryllium disease patients had received high doses of beryllium, a suspected lung carcinogen. The fact that the excess lung cancer observed here was concentrated among those with acute disease (an SMR of 2.32 for acute cases versus an SMR of 1.57 for chronic cases) supports the argument that an increased dose of beryllium is likely to explain, at least partially, the lung cancer excess, because patients with the acute disease are presumed to have received higher doses than those with the chronic disease.

An alternative explanation to the hypothesis that an increased dose of beryllium had caused the lung cancer excess among the beryllium disease patients is that some factor (or factors) in the disease process may have increased the risk of lung cancer. Patients with acute disease had a pneumonitis which for one reason or another may have made them more susceptible to the later development of lung cancer (15). The nonsignificant excess of lung cancer seen in the chronic beryllium disease group duplicates the excess of lung cancers seen for asbestotics and silicotics and conceivably could have been due to some aspect of either the immune response or fibrosis. However, the lung

cancer excess observed here (SMR = 1.57) for those with chronic beryllium disease is of a smaller magnitude than the lung cancer excess typically observed among silicotics and asbestotics, for whom SMRs ranged from approximately 2.0 to 9.0 [see (11-30)]. Furthermore, this excess is not different from the lung cancer excess observed for beryllium-exposed cohorts in general [approximately 50%; see (3,4)], most of whose members did not have beryllium disease. Hence, the data for the chronic cases do not strongly suggest that fibrosis and granulomatous disease independently increase lung cancer risk, as might be inferred from the data on asbestosis and silicosis.

One question which can be partly addressed by our data is whether the lung cancer excess observed in previous studies (3,4) of cohorts exposed to beryllium (approximately 50%) might be solely due to the lung cancer excess among the minority of those workers who did develop beryllium disease. An upper limit on the number of beryllium workers who developed beryllium disease is likely to be about 5% (1,7). If we assume 1) that the incidence of beryllium disease in worker cohorts is 5%, 2) that those with beryllium disease have a twofold risk of lung cancer, and 3) that the lung cancer risk was confined to those with beryllium disease, then we can construct the following equation for lung cancer incidence (where I = incidence): $I_{\text{Be-exposed}} = I_{\text{background}}(0.95) + I_{\text{background}}(2)(0.05)$. Solving the equation, we find that $I_{\text{Be-exposed}}$ is 5% above $I_{\text{background}}$. Consequently, only about a 5% excess of lung cancer among beryllium workers might be expected if the lung cancer risk were confined to those with beryllium disease. An additional lung cancer risk on the order of 10%-20% might have occurred because of increased smoking among workers as compared with the general population (23). Using actual smoking data from a survey of beryllium workers, Wagoner et al (4) have estimated that the additional lung cancer risk due to smoking among beryllium workers when compared with the lung cancer risk in the U.S. population would be about 14%. Adding this smoking risk to the 5% excess risk calculated above, one might expect a lung cancer excess among beryllium-exposed workers on the order of 20%, which is less than the approximately 50% excess risk observed in prior studies (3,4). On the basis of these calculations, it would appear that the lung cancer risk which previously has been observed among cohorts exposed to beryllium exceeds what might be expected if the excess risk was confined to those with beryllium disease. On the other hand, these calculations are quite crude. If the incidence of berylliosis were underestimated, if smoking differences between beryllium-exposed workers and the U.S. population were greater than have been estimated, or if the lung cancer rate ratio for beryllium-exposed workers were less than the estimated 50%, it remains possible that those with berylliosis are important contributors to any excess lung cancer risk observed among beryllium-exposed workers.

In conclusion, we have observed a twofold excess of lung cancer incidence among men and women with beryllium disease. The most likely explanation for this excess is exposure to beryllium, a suspected lung carcinogen. It is also possible that the beryllium disease process itself might contribute at least partially to the lung cancer excess.

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