

Understanding Lung Cancer Risk Among Navajo Former Uranium Miners

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**Abstract**

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**Problem statement:** Historically, uranium mining caused many Navajo to develop lung cancer, but little is known about the contribution of uranium mining to lung cancer cases diagnosed in years following the demise of that industry.

**Background:** Results from two previous case-control studies demonstrated that a high proportion (67%-72%) of Navajo lung cancers diagnosed between 1969-1993 were attributable to employment in the uranium industry. In one study, approximately 72% of Navajo lung cancers occurred in uranium miners with little to no exposure to tobacco. The smoking prevalence among American Indians living in the Southwest has been observed to be lower than American Indians living in the Northern Plains and the general U.S. population. More recent studies have observed that younger age tribal members and males living in the Southwest have higher rates of smoking. Such changes in smoking prevalence may affect lung cancer rates despite a moratorium on uranium mining in the Southwest.

**Methods:** We conducted a population based case-control study to characterize the association between employment in the uranium industry and lung cancer during the period 1994-2006. Eligible subjects were all Navajo residents of New Mexico and Arizona. Cases were diagnosed

with lung cancer and controls had a confirmed cancer diagnosis other than lung or kidney during the study period. Multivariate logistic regression was used to assess the association between employment in the uranium industry and lung cancer, adjusted for age and smoking.

**Results:** Navajo lung cancer cases had greater odds than controls to have a history of employment in the uranium industry (Odds Ratio=3.9; 95% CI: 2.08, 7.36). Approximately 31 percent of lung cancer cases were employed in the uranium industry. The mean age of cases and controls was 70.1 years (SD=13.1). Males made up approximately 68% of both cases and controls. A higher proportion of cases compared to controls were deceased during the study period 1994-2006, 53.1% and 32.8%, respectively.

**Conclusions:** Employment in the uranium industry continued to influence lung cancer incidence among the Navajo well into the 21st century. However, the proportion of lung cancers attributable to uranium mining has diminished over time.

**Benefits of research:** This study will help the Navajo Nation better understand the risks associated with uranium mining.

## **INTRODUCTION**

### ***Background***

#### ***Summary of uranium mining and the source of exposure***

Uranium mining in the U.S. is centered in the Southwest, particularly in the Colorado Plateau region.<sup>1</sup> In this region is the Navajo Indian Reservation which spans approximately 27,000 square miles and contains many former and prospective future uranium mine sites. One of the elements formed through the uranium decay process is radon which produces other radioactive daughter or progeny products, which includes polonium 218, lead 214, bismuth 214, and polonium 214.<sup>2,3</sup> It is these decay progeny that attach to dust particles.<sup>4</sup>

At the beginning of the mining era in the 1940s in the U.S., underground uranium mines were poorly ventilated which increased both the availability of dust particles that bound radionuclides and increased the likelihood of a miner inhaling these particles as reported in a thesis by Harley and Bale in 1951.<sup>5</sup> Although most of the breathed-in radon is exhaled, it is the radioactive dust particles that settle and deposit in the tracheobronchial epithelium delivering a radiation dose 20 times greater than from inhaled radon.<sup>6</sup> These particles subsequently deposited in miner's lungs, delivering direct radiation to the tissue as they decayed. In the U.S., as early as 1951, researchers reported that uranium decay products in mines attached to dust particles.<sup>2,3</sup>

#### ***Previous studies that indicate high rates of lung cancer in uranium miners***

Uranium miners are at particularly high risk for developing lung cancer, particularly if they have worked in poorly-ventilated mines. According to the Committee on the Biological Effects of Ionizing Radiation 6<sup>th</sup> meeting (BEIR VI), it has been known for nearly a century that higher rates of lung cancer affected some underground miners compared to the general population.<sup>4</sup> In the early 1940's, greater lung cancer incidence was recorded in German miners

by Hueper et al. and Lorenz et al.<sup>7, 8</sup> Subsequent reports document the spread of uranium mining activities, as well as the associated increased incidence of lung cancer in uranium miners, throughout Europe and then the United States.<sup>5</sup>

Previous health studies in European countries examining the association between radon and lung cancer prompted similar U.S. health studies.<sup>1</sup> The registry of Colorado Plateau uranium miners assembled by Dr. Archer and colleagues for the US Public Health Service (PHS) starting in 1950 has been the focus of many US-based uranium miner studies.<sup>1, 9</sup> A study conducted by Archer et al. followed up on 3,366 white and 780 non-white workers who had been employed in an underground uranium mine for one or more months prior to January 1, 1964; the cut-off date was January 1, 1974 for Indians, and September 30, 1974 for whites.<sup>6</sup> Among Indians, they observed a higher number of deaths than was expected for respiratory cancer within this group who reported minimal tobacco use. Similarly, among white miners a higher number of deaths than expected was observed for respiratory cancer. Among non-smokers, there was a linear relationship between cumulative radon exposure and respiratory cancer suggesting a dose-response relationship. This dose response relationship was also recently described by the BEIR Committee who agreed with earlier experts that the risk of lung cancer increases linearly with higher levels of radon exposure.<sup>4</sup>

A series of reports on increased likelihood of lung cancer in Navajo uranium miners who did not smoke (utilizing the PHS registry, New Mexico Tumor Registry, and a separate registry of uranium miners obtained in Grants, NM) obtained between 1957–1976 by Samet and Gilliland helped clarify the large role occupational exposure played as a risk factor for lung cancer.<sup>10-12</sup>

Gilliland et al. conducted a nested case-control study on non-smoking uranium miners in the

western US.<sup>11</sup> In this study, a significant association was observed between higher levels of cumulative radon progeny exposure and lung cancer risk compared to lower levels of cumulative radon progeny exposure (Odds Ratio 29.2: 95% CI: 5.1, 167.2).<sup>11</sup>

Samet et al. reported in a follow-up case-control study data on 32 cases of lung cancer in Navajo men (71% of whom were former uranium miners) from 1969 to 1981.<sup>10</sup> Later, Gilliland et al. extended the study and expanded the follow-up period from 1969–1993, again finding similar, yet lower, increased odds of lung cancer cases having been a uranium miner versus age and diagnosis date-matched non-lung cancer controls.<sup>12</sup>

Employment in the uranium industry remained an important factor in the development of lung cancer among Navajo men in this region. In the U.S., Archer et al. clearly demonstrated an excess of lung cancer in Navajo men in the early 1970's.<sup>6</sup> A more recent study by Gilliland et al. reported a 67 % history of employment in the uranium industry among 94 incident lung cancer cases among Navajo men between 1969 and 1993.<sup>12</sup> Additional research is needed to further characterize the constellation of risk factors responsible for lung cancer in the Navajo Nation.

### ***Smoking***

Chief among the concerns raised in some of these studies has been the lack of information about tobacco smoking in this population, by far the largest risk factor for lung cancer known to date. Epidemiologic evidence since the 1950s using cohort and case-control studies have shown associations between smoking and lung cancer.<sup>13</sup> Smoking prevalence among Navajo men and women have been historically lower than the general population. As reported by the 1991 Navajo Health and Nutrition Survey, 16% of Navajo males and 5% of

Navajo females over 12 years of age reported being current smokers.<sup>14</sup> These rates were much lower than the U.S. general population rates as reported by the Centers for Disease Control and Prevention in 1991, 28% for males and 24% for females, over 18 years of age.<sup>15</sup>

More recent data on the smoking prevalence among American Indians (AIs) living in the Southwest U.S. show a lower prevalence of commercial tobacco use compared to the national prevalence use of commercial tobacco. Between 1995-1997, a telephone survey was conducted by Gilliland, Mahler, and Davis on AIs aged 18 years and older living in rural New Mexico.<sup>16</sup> They observed that of 1,266 respondents, 38.5% (95% CI: 34.5%, 42.1%) reported ever smoking with a lower prevalence of current smokers, 16.3% (95% CI: 13.5%, 19.0%). They concluded that among AIs living in rural New Mexico, the prevalence of current smoking was lower than AIs in other regions of the US, lower than all New Mexicans, and lower than the national population.

Another recent cross-sectional study, conducted between 1997-1999, ascertained smoking status among 15-54 year old AIs living in the Northern Plains and Southwest.<sup>17</sup> They observed a lower prevalence of current smokers living in the Southwest compared to the Northern Plains, 14% and 50%, respectively. In addition, they reported a higher proportion of never smokers among AI men and women living in the Southwest compared to the Northern Plains, 56% and 75% versus 19% and 10%, respectively.

### ***Updating Information***

Uranium exposure continues to be a topic of concern on the Navajo reservation. Demand for uranium for nuclear power has driven an increased interest in new uranium mines that would



be located on or near the reservation. As reported in The Daily Times, a local newspaper near Shiprock, NM, uranium mining companies are renewing their interest in uranium ore located on the Navajo Nation.<sup>18</sup> In addition, a recent collaborative effort by multiple U.S. Government entities is working to increase efforts to identify and address former uranium mining sites and nearby homes.<sup>19</sup> As one component of the government collaborative efforts a final follow-up of the Navajo uranium miners' registry cohort was requested to determine long-term lung cancer outcomes resulting from uranium exposure. Thus, this case-control study is designed as a follow-up to previous uranium epidemiologic studies examining the relationship between uranium mining exposure and lung cancer incidence among former Navajo uranium miners.

### ***Research Hypothesis***

This study will further examine the exposure-response relation between uranium mining and lung cancer incidence among former Navajo uranium miners.

### ***Specific Aims***

Aim 1: To examine the relationship between lung cancer incidence and underground uranium mining in Navajos.

Aim 2: To better understand why lung cancer rates are not decreasing despite the lack of occupational exposure to uranium mining and reportedly low smoking rates.

## **Methods**

### ***Sample Size***

This study is a population-based cancer case-control study that attempted to replicate as closely as possible the methodological approach used by Gilliland et al.<sup>12</sup> Using this approach, we selected every lung cancer incident case diagnosed in New Mexico and Arizona during the study period 1994-2006. Two controls were then selected from the same base population for each case and frequency matched with sex, age (+/- 5 years) and diagnosis date (+/- 5 years). Using this method, we selected 96 cases and 192 controls. Matching selected cases to controls on each factor, such as age, provided an optimal distribution of each factor across each stratum. This is routinely done to improve the efficiency of a case-control study, and additional stratification is often done to control for residual confounding effects, even after matching.<sup>20</sup>

### ***Study Design***

A population based case-control study design was used to examine the association between uranium exposure and lung cancer incidence among former Navajo male and female uranium miners. This design compared to other epidemiologic study designs, such as a prospective cohort or cross-sectional study, offer several advantages. First, case-control study designs are used to study rare outcomes.<sup>21</sup> In this study, incident cases of lung cancer as a health outcome are considered rare and thus choosing a case-control study design is appropriate. Second, this design will provide efficiency to avoid any lengthy follow-up of the study population as would be done in a prospective cohort study. Thus, by selecting reported incident

cases of lung cancer, a case-control method is more time efficient and cost-saving compared to lengthier study designs such as a prospective cohort study.

The methodological approach for control selection in this study attempted to replicate, as closely as possible, that used by Gilliland et al.<sup>12</sup> While cases were persons with lung cancer, controls in this study design were individuals who had a cancer other than lung or kidney cancer randomly selected from frequency-matched age groups (described below) from the same study population from which the cases arose. Controls were identified as having a cancer diagnosis not shown to be associated with uranium exposure (all other cancers excepting kidney cancer). Although kidney cancer has not consistently been shown to be associated with uranium exposure there are a few studies that indicate the possibility.<sup>22</sup> Eliminating these cancers as possible controls is a conservative measure but one likely to enhance the validity of the study.

### ***Study setting***

As in previous studies conducted by Samet and Gilliland, cases and controls were selected from the New Mexico Tumor Registry (NMTR) located in Albuquerque, New Mexico.<sup>10, 12</sup> The NMTR is a population based-cancer registry for the state of New Mexico established in 1966 which is part of the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program.<sup>23</sup> Population-based cancer surveillance for Native American populations- including members of the Navajo and Hopi tribes whose reservations cover portions of Arizona, New Mexico, Utah - is conducted by the NMTR in collaboration with the tribes, Utah and Arizona Cancer Registries, and the Indian Health Service.

### *Study Subjects*

This study was designed to replicate as closely as possible previous methods used by both the Samet and Gilliland.<sup>10, 12</sup> The focus of this study was on members of the Navajo tribe as there were readily-available resources with which to verify occupational and some exposure history. Cases were identified from existing records in the NMTR whose race/ethnicity is described as “Navajo” (as abstracted by tumor registrars from hospital records) based on the following criteria: 1.) Diagnosed with malignant cancer of the lung or bronchus (International Classification of Diseases for Oncology – Third Edition (ICDO-3) topography codes C34.0-C34.9); 2.) Diagnosed during the time period 1994-2006; 3.) American Indians known to be members of the Navajo Nation; and 4.) Residents of New Mexico or Arizona at the time of diagnosis. The NMTR has conducted population cancer surveillance since 1969. Two Navajo controls were selected for each case and frequency matched with sex, age (+/- 5 years) and diagnosis date (+/- 5 years) to account for age and diagnosis-associated differences that may confound the relationship.

Cases and controls selected from the NMTR were also cross-referenced with two databases, the Uranium Epidemiologic Studies (UES) Miners Registry and the Office of Navajo Uranium Workers (ONUW) as described below. This was done to assess what proportion of cases and control were identified between the NMTR and UES and also between the NMTR and ONUW.

## *Exposure*

The primary exposure to be evaluated in this study is occupational exposure to uranium mining which was documented using occupational history collected from multiple sources. The first source is the NMTR, which contains occupational history abstracted from patient medical records as part of routine cancer surveillance. The second source is the occupational history from the UES Miners Registry, previously organized by Samet et al. and maintained within the New Mexico Tumor Registry.<sup>10, 24</sup> The third source of data used to collect occupational history was from the ONUW located in Shiprock, New Mexico.<sup>25</sup> This office was established by the Navajo Tribal Council in 1990 to register former Navajo uranium miners. Individuals who register at the ONUW are filing compensation documentation as part of the Radiation Exposure Screening and Education Program (RESEP).<sup>26</sup> This program was created by the Radiation Exposure Compensation Act of 2000 to assist those who may have been diagnosed with diseases, such as cancer, caused by exposure to radiation. The fourth dataset source from which occupational history was abstracted was death certificates. Death certificates housed at the NMTR and at the ONUW were used to cross reference occupational history. In addition, we compared the proportion of occupational history observed on death certificates for both cases and controls. In previous epidemiologic studies, occupational exposure to uranium mining was categorized by Working Level Months (WLM).<sup>6, 11, 12, 27</sup> In this study occupational history to uranium mining was categorized as “yes” or “no” due to limited occupational history at the individual participant level.

## ***Covariates***

### ***Age***

It is well known lung cancer risk increases as people age according to the Centers for Disease Control & Prevention.<sup>28</sup> The proportion of US men currently age 60 in 10 years who will develop lung cancer is 2.27%.<sup>28</sup> Similarly, the proportion of US women currently age 60 in 10 years who will develop lung cancer is 1.72%. Age as a potential confounder was categorized as 20-64, 65-74, and 75+ and included in the logistic regression model.

### ***Smoking***

A potential limitation to this study was the collection of smoking exposure information. Smoking history was first abstracted from the NMTR and then cross-referenced with smoking information from the ONUW. The NMTR database categorizes smoking as follows: never smoked, current cigarette smoker, current cigar/pipe smoker, current snuff/chew/smokeless, and current combination of use, former smoker/user, non-smoker/user, non-smoker/unknown previous smoking, and unknown. These smoking categories were collapsed as follows: ever smoked, never smoked, and unknown, as was done in the Gilliland et al. study.<sup>12</sup> As stated in the above logistic regression model, adjustment for smoking was assessed by including this variable as a categorical variable.

### ***Vital Status***

Vital status was obtained from both the NMTR and the ONUW. The NMTR routinely documents vital status based on information obtained from death certificates issued by the New

Mexico Office of Vital and Health Records and from the National Death Index. NMTR also documents vital status based on information contained in medical records and through linkages with records from the Social Security Administration. Follow-up for NMTR records utilized in the present study was complete through December 31, 2008. A second source of vital status was the ONUW database in which a status of deceased was also noted if a death certificate was in the individual's record.

### *Data Analysis*

Univariate and bivariate analyses were conducted in addition to multivariate logistic regression, which was used to examine the exposure-response relationship between uranium mining exposure and lung cancer incidence among former Navajo uranium miners. A logistic regression model was used to test the association between occupational exposure to uranium and lung cancer adjusting for smoking and age. Adjusting for these covariates was assessed to reduce any potential confounding between occupational exposure to uranium mining and lung cancer incidence.

Categorization of variables utilized in the logistic regression model was as follows. Disease was classified as 1 for lung cancer and 0 for other cancers not associated with uranium mining. Smoking was categorized as 1 if ever smoked and 0 for never smoked. Age was categorized as such: 1= 20-64, 2=65-74, and 3=75+. The age group between 20-64 was stratified as such because the number of individuals, when stratified by finer age categories, was too few (Table 1). For example, stratifying by age categories of ten we observed the following number of lung cancer cases and controls in each strata: 20-29, 2 cases and 2 controls; 30-39, 0 cases and

2 controls; 40-49, 4 cases and 8 controls; 50-59, 10 cases and 20 controls; 60-69, 28 cases and 104 controls; and 70+, 52 cases and 104 controls.

### ***Period of Diagnosis***

Gilliland et al. previously conducted a case-control study examining lung cancer risk among former Navajo uranium miners from 1969-1993.<sup>12</sup> In this study, researchers assessed temporal trends in risk by stratifying their data into two time periods. Using conditional logistic regression, this group of researchers observed a higher relative risk of lung cancer (RR=32.5; 95% CI=9.4-112.7) in the 1969-1983 time period compared to a lower relative risk in the time period 1984-1993 (RR=23.3; 95% CI: 8.7-62.3).<sup>12</sup> As a follow up, this case-control study assessed lung cancer risk from 1994-2006. As with the Gilliland et al. study, the time period studied between 1994-2006 was divided into two time periods, 1994-2000 and 2001-2006. By categorizing the most recent time period as such, a lower lung cancer risk would be expected in 2001-2006 compared to 1994-2000. This rationale is based on two assumptions. First, recent incident lung cancer cases would be less likely to be associated with uranium mining given that uranium mining on the Navajo Reservation was ceased in the mid- 1980s.<sup>29</sup> Moreover, miners exposed to uranium in the mid-1980s assuming an induction latency period of approximately 25 years, if diagnosed with lung cancer, may or may not have been reported to the NMTR at the time of this study.<sup>29</sup> Second, this group of individuals in the 2001-2006 time-period would be comprised of younger aged individuals who are at lower risk of lung cancer due to their age. According to the National Cancer Institute, during the time period 2006-2010 the median age at diagnosis for lung cancer was 70 years of age.<sup>30</sup>



## RESULTS

### *Cases and Controls*

In this study, we identified 96 cases and 192 controls (Table 1). Because this was a record-based study, we did not exclude any cases or controls once they were selected. All cases and controls were included in the data analysis. During the time period between 1994-2006, 53.1% of lung cancer cases were observed to be deceased, while only 32.8% of controls were found to be dead (Table 1). Among cases and controls, 39% had a death certificate on file. Of this group, an occupation was listed on the death certificate less often for cases than controls, 45% and 55%, respectively. The gender distribution was such that males made up approximately 68% of both cases and controls. The mean age of cases and controls was 70.1 years (SD=13.1).

Among cases, the majority of individuals were aged 65-74 (40.6%), while those aged 75+ made up the next largest group (35.4%), and the smallest aged group was made up of those aged 20-64 (24.0%). Among controls, the largest age group was made up of those 75+ (38.0%), while those aged 65-74 made up the next largest group (31.8%), and the smallest group was made up of those age 20-64 (30.2%). Among cases, the proportion of miners exposed to uranium during the time period 1994-2006 was 31.3% while only 10.4% of controls were exposed to uranium during this same time period (Table 1).

238 participants had information related to smoking. The majority of cases were never-smokers (80.2%), with only 8.3% having some record indicating ever smoking, and 11.5% unknown. Controls reported similar percentages of smoking status (never 75.5%, ever 4.2%, and unknown 20.3%).

***Exposed and Unexposed:*** Among exposed during the period 1994-2006, 58.0% were deceased in comparison to 35.7% of unexposed participants (Table 2). We also observed that age categories between exposed and unexposed were approximately equivalent in distribution (Table 2). Smoking status among exposed consisted of 82.0% never smokers (Table 2). Similarly, 76.1% of unexposed were never smokers.

In Table 3, we examined the proportion of cases and controls identified from the NMTR against the UES and ONUW databases. In the NMTR-UES comparison, no cases identified from the NMTR were found in the UES database and only one control from the NMTR was found in the UES database. In comparison, 25.0% of cases and 9.4% of controls from the NMTR were also found in the ONUW database.

In Table 4, the odds ratio of lung cancer was estimated as follows. Cases had a 3.9 odds (95% CI: 2.1, 7.4) of being a uranium miner in comparison to controls. This odds ratio remained significant when adjusting for age and smoking. Adjusting for smoking status, cases had a 3.8 odds (95% CI: 2.0, 7.1) of being exposed to uranium compared to controls. Adjusting for smoking status and age, cases had a 3.8 odds (95% CI: 2.0, 7.2) of being exposed to uranium compared to controls.

Temporal trends were also assessed as in previous studies by estimating an odds ratio for the association between uranium exposure and lung cancer for two different time periods, 1994-1999 and 2000-2006 (Table 5). A strong association between uranium exposure and lung cancer was observed during the time period 1994-1999 (OR=17.2; 95% CI: 4.3, 96.5). In the latter time period, this odds ratio diminished (OR=1.8; 95% CI: 0.73, 4.3). Adjusting for time period, the

odds ratio remained elevated at 3.8 (95% CI: 2.0, 7.1) indicating strong evidence for an association between uranium exposure and lung cancer ( $p < 0.001$ ).

To assess whether participants in the Uranium Epidemiologic Studies (UES) also appeared in the NMTR we cross-referenced each database to the other. No lung cancer cases from the NMTR were identified in the UES database and only one control was listed in both the NMTR and UES database (Table 3).

The occupational history ascertained from the Office of Navajo Uranium Workers in Shiprock, NM had one main limitation. This limitation was that participant files located at the ONUW only included individuals who actively filed paperwork to receive compensation as part of RESEP.<sup>26</sup> A second limitation was that only a fraction of cases and controls identified in the NMTR were also matched with the ONUW database, 9.4% for controls and 25.0% lung cancer cases (Table 3). Cross-referencing cases from NMTR with the UES databases found no matches, while only one control was matched.

Death certificates often have no accurate sources of occupational history.<sup>31, 32</sup> One limitation is the lack of standardization on how occupation is reported on death certificates. In this study, approximately 39% of the study population had death certificates with an occupation listed. Of this group, more controls than cases had an occupation listed on their death certificate, 55% and 45%, respectively.

Occupation and industry documented by the central cancer registry is often based on information from death certificates and medical records. Results from previous studies show that these sources may not provide a complete picture of an individual's employment history.<sup>33-35</sup>

## DISCUSSION

### *Cases and Controls*

Comparing cases and controls, we observed the following characteristics. A higher proportion of cases than controls were deceased, 53.1% and 32.8%, respectively. In both cases and controls, the majority of individuals were 65 years and older, 76.0% and 69.8%, respectively. Exposure to uranium mining was approximately three times as high among cases compared to controls, 31.3% and 10.4%, respectively. The proportion of lung cancer cases exposed to uranium in this study was much lower than that previously reported by Gilliland et al., 31.3% and 67.0%.<sup>12</sup> In addition, the proportion of never smokers for cases and controls was similar, 80.2% and 75.5%, respectively. However, the proportion of persons with an unknown smoking status among cases was lower compared to controls, 11.5% and 20.3%, respectively.

In this study, we observed that cases had a 3.9 odds (95% CI: 2.1, 7.4) of having been exposed to uranium in the occupational industry compared to controls. We also observed an elevated odds ratio even after adjusting for age and smoking. Further examination of the odds ratios by two time periods showed a higher odds ratio in the earlier time period 1994-1999 (OR=17.2; 95% CI: 4.3, 96.5) compared to the latter time period 1999-2006 (OR=1.8; 95% CI: 0.73, 4.3). A higher odds ratio in the earlier time period 1994-1999 provides evidence that uranium exposure most likely contributed to the elevated odds ratio during this time period. In contrast, when a moratorium was placed on uranium mining during the latter time period, leading to decreased exposure to uranium ore products, a lower odds ratio would be expected as was observed in this study.

There are several strengths to this study. First, this study examined an association between uranium exposure and lung cancer among a group known to have a low smoking prevalence. Due to this low smoking prevalence among AIs living in the Southwest, it is likely lung cancer cases were attributable to having been exposed to uranium in the occupational industry.

Second, the results of this study show similar positive associations as in previous epidemiologic studies. This study attempted to duplicate Gilliland et al. in methodology as closely as possible as a follow-up. In this regard, a decrease in the proportion of cases reported to have been exposed to uranium was 31.3% (Table 1) for the time period 1994-2006, compared to a higher proportion of cases associated with uranium mining in the Gilliland et al. study, 67% for the time period 1969-1993.<sup>12</sup> This decrease in the proportion of cases exposed to uranium in the occupational industry was expected considering a moratorium was placed on uranium mining in the mid 80's.

A third strength is that the results observed in this study are consistent with those of Gilliland et al., but that the odds ratio is considerably lower. In the Gilliland et al. study, comparing miners unexposed to uranium, there was a 28.6-fold (95% CI: 13.2, 61.7) increased risk of lung cancer among miners exposed to uranium.<sup>12</sup> In this study, an elevated odds ratio was also observed in that lung cancer cases had a 3.9 odds (95% CI: 2.1, 7.4) of being exposed to uranium mining in comparison to controls.

A fourth strength is in regards to similar temporal trends observed in both the Gilliland et al. study and this study. In the Gilliland et al. study, a higher relative risk of lung cancer comparing miners exposed to uranium to those unexposed was 32.5 (95% CI: 9.4, 112.7) for the

time period 1969-1983, but decreased in the later time period 1984-1993 to 23.3 (95% CI: 8.7, 62.3). This same trend was observed in this study. A higher odds ratio of lung cancer of 17.2 (95% CI: 4.3, 96.5) was observed for the earlier time period 1994-1999 with a lower odds ratio of lung cancer of 1.8 (95% CI: 0.73, 4.3) observed in the later time period 2000-2006. Because this study was intended to follow that of Gilliland et al., a lower odds ratio of lung cancer was expected because the length since first exposure to uranium mines, which closed in the 80s, has lengthened over time most likely decreasing the potential for occupational exposure to uranium mining.

### *Limitations*

Limitations to each source regarding occupational data are briefly described as follows. The NMTR is a population based-cancer registry intended to capture new cancer cases from existing records such as medical records and death certificates.<sup>36</sup> However, such records may not accurately capture occupational history. In this study, occupational information abstracted from the NMTR was first recorded as verbatim and then categorized in the following manner. Exposure to uranium in the occupational industry included the following two groups: 1) individuals with an occupation related to the uranium industry, such as mining and milling and 2) individuals who had mining and miller listed with industry other than uranium listed, e.g., coal mining. Unexposed individuals included the following two groups: 1) individuals who had no occupation or industry available and 2) individuals with an occupation listed and assumed not to be associated with the uranium industry, such as “camper sales or retired engineer”. Three individuals in the study had occupations listed as “mining, miner, and miller”, but with an unspecified industry. We used this last group of individuals with unspecified industries to

estimate two sets of odds ratios. In the first estimate, we assumed these three persons were unexposed to uranium and calculated an odds ratio of 3.90 (95% CI: 2.1, 7.4). In the second estimate we categorized these individuals as exposed and calculated a higher odds ratio of 4.5 (95% CI: 2.4, 8.4). Based on these estimates, we chose to report the more conservative estimate in which we assumed three individuals with unspecified industries were unexposed. Additionally, we pinpointed the approximate residence at the time of diagnosis for these three individuals. Based on the place of residence, exposure to uranium in the occupational industry most likely occurred; however, we took a more conservative approach.

Selection bias was reduced in this study by selecting cases and controls from the same source registry, the NMTR. This population-based cancer registry routinely collects information on diagnosed cancer cases among Navajo people living in New Mexico and Arizona. Ascertaining cases and controls from the NMTR most likely reduced any potential for selection bias. The selection of cases and controls in this study were aimed at replicating methods previously used by Gilliland et al.<sup>12</sup> The controls in this study were identified as having a cancer diagnosis not shown to be associated with uranium exposure (all other cancers except kidney cancer). Eliminating cancers potentially associated with uranium exposure, such as kidney, was done to increase the validity of the study.<sup>37-39</sup> While steps were taken to select the most appropriate controls, it is also worthwhile to mention tobacco has been reported to increase the risk of at least 14 different types of cancers.<sup>40</sup> In retrospect, these controls most likely may not have impacted the observed results in this study due to the low prevalence of never smokers in both cases and controls.

Information bias must be considered regarding ascertainment of occupational and smoking status. Occupational status was documented from multiple sources, the NMTR, former uranium epidemiologic databases housed at the NMTR, the ONUW, and death certificates. First, even after inspecting these multiple data sources for occupational history, 45.5% of cases and controls were found not to have any occupation or industry information available from any of the sources. Within this group occupational history was unavailable for 32.2% of cases compared to 52.1% of controls. Second, 36.1% of cases and controls were documented to have no evidence of occupation in the uranium industry. Among this group the proportion of unexposed to the uranium industry was roughly equal between cases and controls, 33.3% and 37.5%, respectively. To estimate the odds ratio for this study, individuals who had no occupational information available along with persons found to not have any uranium industry were classified as unexposed, while the remaining persons from these groups were classified as exposed to uranium. This method of classifying exposed and unexposed most likely would result in an underestimation of the estimated odds ratio for this study.

Like occupational history, smoking information was ascertained from multiple data sources, the NMTR, death certificates, previous uranium epidemiologic study databases, and the ONUW. Based on these data sources, 77.1% of cases and controls were categorized as never smokers. Among this group, roughly equal proportions of cases and controls were observed to be never smokers, 80.2% and 75.5%, respectively. In addition, 11.5% of cases and 20.3% of controls had no information on smoking and were classified as unknown. Given this information, the high percentage of documented never smokers accounted for over 75% of this sample reflecting previously reported statistics stating a low smoking prevalence among Navajos.



As with previous uranium epidemiologic studies, this study estimated positive associations between uranium exposure and lung cancer. As a follow-up to the Gilliland et al. study conducted from 1969-1993, this study aimed to examine the time period 1994-2006. During this latter time period, this study also found strong associations between occupational exposure to uranium and lung cancer among the Navajo people. The findings in this study are consistent with those of Gilliland et al., but that the odds ratio is much smaller. A lower odds ratio is rational because the length since first exposure to uranium mines has augmented over time most likely decreasing the potential for occupational exposure to uranium mining. This demonstrates that historical exposure to uranium continues to impact the health of the Navajo people. Further, these results also demonstrate a need to continue monitoring a group of people impacted by such exposures. By monitoring health effects associated with uranium exposure, it is also imperative additional research be conducted to assess why lung cancer rates are not dropping despite a moratorium on uranium mining.

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## TABLES

**Table 1 Cases and Control Characteristics, 1994-2006**

	<b>Cases (%)</b> (n=96)	<b>Control Group (%)</b> (n=192)
Vital status (dead)	53.1	32.8
Age (years)		
20-64	24.0	30.2
65-74	40.6	31.8
75+	35.4	38.0
Gender		
Male	67.7	67.7
Female	32.3	32.3
Uranium Miner		
Yes	31.3	10.4
No	68.8	89.6
Smoking status		
Ever	8.3	4.2
Never	80.2	75.5
Unknown	11.5	20.3

**Table 2 Lung Cancer Case Characteristics for Navajo Miners and Non-Miners, 1994-2006**

	<b>Uranium Miner (%)</b>			<b>Non-uranium miner (%)</b>		
	1994-2006 (n=50)	1994-1999 (n=20)	2000-2006 (n=30)	1994-2006 (n=238)	1994-1999 (n=101)	2000-2006 (n=137)
Vital status (dead)	58.0	70.0	50.0	35.7	32.7	38.0
Age (years)						
20-64	14.0	10.0	16.7	31.1	25.7	35.0
65-74	52.0	60.0	46.7	31.1	34.7	28.5
75+	34.0	30.0	36.7	37.8	39.6	36.5
Smoking status						
Ever	8.0	10.0	6.7	5.0	4.9	5.1
Never	82.0	80.0	83.3	76.1	73.3	78.1
Unknown	10.0	10.0	10.0	18.9	21.8	16.8

**Table 3 Database Comparisons for Cases and Controls**

		<b>Cases (%)</b> (n=96)	<b>Control Group (%)</b> (n=192)
NMTR-UES	Match	0.0	0.5
	No Match	100.0	99.5
NMTR-ONUW	Match	25.0	9.4
	No Match	75.0	90.6

**Table 4 Odds Ratio of Lung Cancer**

Factor	OR	95% CI
Uranium miner <sup>*</sup>	3.9	(2.1, 7.4)
Ever smoked <sup>**</sup>	3.8	(2.0, 7.1)
Ever smoked and age <sup>***</sup>	3.8	(2.0, 7.2)

\*Reference group is non-uranium worker

\*\*Reference group is never smoked

\*\*\*Adjusted for smoking and age

**Table 5 Odds Ratio of Lung Cancer Adjusted by Diagnosis Date**

Factor	OR	95% CI
1994-1999 (uranium miner)	17.2	(4.3, 96.5)
2000-2006 (uranium miner)	1.8	(0.73, 4.3)
Period Adjusted OR	3.8	(2.0, 7.1)

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