Original Study

# Lung Cancer Hormesis in High Impact States Where Nuclear Testing Occurred

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## Abstract

**Hormesis is a favorable biological response to low toxin exposure. In the case of radiation, large doses are carcinogenic, but low doses might be protective. Lung cancer incidence is significantly lower in states affected by nuclear testing. Our analysis adds to the body of evidence suggesting that the linear no threshold model of radiation carcinogenicity in lung cancer might not be correct. Low-level radiation exposure might protect against lung cancer rather than cause it.**

**Background:** Hormesis is a favorable biological response to low toxin exposure. In the case of radiation, large doses are carcinogenic, but low doses might be protective. In the current study, we analyzed lung cancer incidence in high-impact radiation states where nuclear testing occurred and compared it with lung cancer incidence in the remaining normal-impact radiation states and the District of Columbia. **Materials and Methods:** Lung cancer incidence data were from the American Cancer Society. Tobacco use 2012 data were from the Centers for Disease Control and Prevention. The distribution of states grouped according to lung cancer incidence interval was from the Centers for Disease Control and Prevention. Total background radiation measurements (terrestrial + cosmic + radon) were from Assessment of Variations in Radiation Exposure in the United States (2005). Data on high- and normal-impact states were from the National Radiation Exposure Screening & Education Program (RESEP). Congress passed the Radiation Exposure Compensation Act Amendments of 2000, creating RESEP, to help thousands of people diagnosed with cancer and other diseases caused by exposure to nuclear fallout or radioactive materials such as uranium. These people live in 12 high-impact states where nuclear testing had occurred. High-impact states were not designated according to measurements of background radiation. **Results:** Lung cancer incidence is significantly lower in high-impact states in men ($t = 5.4$ for unequal variance; $P < .001$) and women ($t = 3.0$; $P < .001$). The clustering of the 12 high-impact states in the 2 lowest lung cancer incidence intervals (26.8-56.9 and 57.0-63.2) is statistically significant ($P < .001$, Fisher exact test, 2-tailed). Because cigarette smoking is ordinarily the most powerful risk factor for lung cancer, multivariate linear regression analysis of the effect of U.S. state group (normal-impact, high-impact, or extra high-impact for Nevada, Utah, and Arizona) on lung cancer incidence in men and women was performed. (In Nevada, Utah, and Arizona, men and women would have been downwind.) The U.S. state group impact was significant ($P < .001$ for men; $P = .015$ for women). The effect of percentage of smokers in the population was significant ($P < .001$ for men; $P < .001$ for women). The effect of total background radiation was significant ($P = .029$ for men; $P < .029$ for women); like the state group impact, more background radiation exposure was associated with less lung cancer. **Conclusion:** Hormesis is still mired in controversy. Yet, it is of vital medical importance because of the continuing debate over whether the low-level radiation doses from diagnostic x-ray procedures, such as computed tomography scans, are harmful. Our analysis adds to the body of evidence suggesting that the linear no threshold model of radiation carcinogenicity in lung cancer might not be correct. Low-level radiation exposure might protect against lung cancer rather than cause it.


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## Introduction

Hormesis is a favorable biological response to low toxin exposure. A pollutant or toxin demonstrating hormesis has the opposite effect in small doses as in large doses.[1] In the case of radiation, large doses are carcinogenic. However, Frigerio et al found lower overall cancer rates in U.S. states with high-impact radiation.[2]

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Large doses of radiation from radon in houses, exceeding 10 pCi per liter (2000 mrem/y), are associated with increased lung cancer incidence.[3,4] However, low-dose radon home exposure is associated with reduced rates of lung cancer. Bogen compared Environmental Protection Agency radon data, county by county, with lung cancer mortality records for women. He confirmed the inverse correlation between lung cancer and radon.[5]

Cohen examined the linear no threshold (LNT) model of radiation carcinogenicity in lung cancer.[6] This model is used in radiation protection to quantify radiation exposure and set regulatory limits. LNT assumes that the long-term, biological damage caused by ionizing radiation (in other words, the cancer risk) is directly proportional to the dose. LNT presumes that radiation is always harmful with no safety threshold, and the sum of multiple small exposures has the same effect as 1 large exposure (ie, response linearity).[7]

Cohen found that the LNT model overstated the effects of radiation. For example, lung cancer incidence in the high-radon area of Cumberland County, Pennsylvania was lower than the Pennsylvania average.[6] Thompson found that the maximum hormesis for lung cancer occurred at 70 Bq $m^3$ or 350 mrem/y.[8] Nevertheless, hormesis in lung cancer is still controversial.

People who live in 12 U.S. states where nuclear weapons testing occurred are classified as living in high-impact states. These states are Arizona, Colorado, Idaho, Nevada, New Mexico, North Dakota, Oregon, South Dakota, Texas, Utah, Washington, and Wyoming.[9] In the current study, we analyzed lung cancer incidence in high-impact states and compared it with lung cancer incidence in the remaining normal-impact states and the District of Columbia.

## Materials and Methods

Lung cancer incidence data were from the American Cancer Society.[10] Tobacco use 2012 data were from the Centers for Disease Control and Prevention.[11] The distribution of states grouped according to lung cancer incidence interval (used in Table 1) data were from the Centers for Disease Control and Prevention.[12] Total background radiation measurements (terrestrial + cosmic + radon) were from the Assessment of Variations in Radiation Exposure in the United States.[13]

Data on high- and normal-impact states were from the National Radiation Exposure Screening & Education Program (RESEP).[9] Congress passed the Radiation Exposure Compensation Act Amendments of 2000, creating RESEP, to help thousands of people diagnosed with cancer and other diseases caused by exposure to nuclear fallout or nuclear materials such as uranium. RESEP set the following criteria to identify affected individuals in high-impact states:

- Uranium Mine Worker: a person who operated or otherwise worked for at least 1 year, or could establish radon exposure equivalent to 40 working level months, in above-ground or underground uranium mines in specified states (AZ, CO, ID, OR, ND, NM, SD, TX, UT, WA, WY) during the period beginning January 1, 1942 and ending December 31, 1971.
- Uranium Mill Worker: a person who was employed for at least 1 year as a uranium mill worker in specified states (AZ, CO, ID, OR, ND, NM, SD, TX, UT, WA, WY) during the period beginning January 1, 1942 and ending December 31, 1971.
- Uranium Ore Transporter: a person who was employed for at least 1 year as a transporter of uranium ore or vanadium-uranium ore from a uranium mine or uranium mill located in a specified state (AZ, CO, ID, OR, ND, NM, SD, TX, UT, WA, WY) during the period beginning January 1, 1942 and ending December 31, 1971.
- Downwinder: a person who was exposed to fallout from the atmospheric detonation of nuclear devices at the Nevada Test Site because of their physical presence in Arizona counties: Apache, Coconino, Gila, a portion of Mohave County (north of the Grand Canyon), Navajo, or Yavapai; Nevada counties: Eureka, Lander, Lincoln, Nye, White Pine, and a portion of Clark; Utah counties: Beaver, Garfield, Iron, Kane, Millard, Piute, San Juan, Sevier, Washington, or Wayne. Downwind counties were determined based on wind patterns around the dates of atmospheric nuclear tests at the Nevada Test Site. Under the current law, only portions of Nevada, Utah, and Arizona are considered downwind. The other 9 high-impact states have significant concentrations of uranium miners, millers, or ore transporters. Nevada also has a significant number of "onsite participants." Some lawmakers have introduced bills to expand the high-impact area, most recently the Radiation Exposure Compensation Act Amendments of 2013, but the amendments have not been passed by Congress.

High-impact states and normal-impact states were not designated according to measurements of background radiation.

## Results

Lung cancer incidence was significantly lower in high-impact states in men ($t = 5.4$ for unequal variance; $P < .001$) and women ($t = 3.0$; $P < .001$; Figure 1).

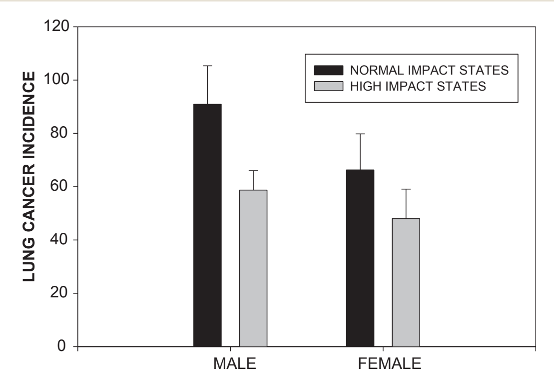
High- and normal-impact states grouped according to lung cancer incidence interval (cases per 100,000) are shown in Table 1. The clustering of the 12 high-impact states in the 2 lowest incidence

**Table 1 High- and Normal-Impact Radiation States Grouped According to Lung Cancer Incidence Interval (Cases Per 100,000)**

| Incidence Interval | States |
|---|---|
| 26.8 to 56.9 | **ARIZONA**, California, **COLORADO**, Hawaii, **IDAHO**, Montana, New Jersey, **NEW MEXICO**, **NORTH DAKOTA**, **OREGON**, **TEXAS**, **UTAH**, and **WYOMING** |
| 57.0 to 63.2 | Connecticut, District of Columbia, Florida, Kansas, Maryland, Nebraska, **NEVADA**, New York, **SOUTH DAKOTA**, Virginia, **WASHINGTON**, and Wisconsin |
| 63.3 to 68.4 | Alaska, Delaware, Georgia, Illinois, Iowa, Massachusetts, New Hampshire, Ohio, Oklahoma, Pennsylvania, Rhode Island, and South Carolina |
| 68.5 to 97.3 | Alabama, Indiana, Kentucky, Louisiana, Maine, Michigan, Mississippi, Missouri, North Carolina, Tennessee, Vermont, and West Virginia |

The 12 high-impact states are in all capital letters and bold. The clustering of the 12 high-impact states in the 2 lowest incidence intervals (26.8-56.9 and 57.0-63.2) is statistically significant ($P < .001$; Fisher exact test, 2-tailed). No data were available for Arkansas and Minnesota.

**Figure 1** Lung Cancer Incidence (Mean + SD) Per 100,000 in Normal and High Impact Radiation States. Lung Cancer Incidence Is Significantly Lower in High Impact States in Men ($t$ = 5.4 for Unequal Variance; $P$ < .001) and Women ($t$ = 3.0; $P$ < .001)




intervals (26.8-56.9 and 57.0-63.2) was statistically significant ($P < .001$, Fisher exact test, 2-tailed).

Because cigarette smoking is ordinarily the most powerful risk factor for lung cancer,[14] multivariate linear regression analysis of the effect of U.S. state group (normal-impact or high-impact) on lung cancer incidence in men and women was performed (Table 2). The U.S. state group impact (high or normal) was significant ($P < .001$ for men; $P = .015$ for women). The effect of percentage of smokers in the population was also significant ($P < .001$ for men, $P < .001$ for women). The effect of total background radiation approached statistical significance ($P = .079$ for men; $P < .055$ for women); like the state group impact, more background radiation exposure was associated with less lung cancer.

In 3 states—Nevada, Utah, and Arizona—men and women would have been downwind. A separate multivariate analysis for these 3 extra high-impact states and for the 9 other high-impact states, compared with the normal states, is presented in Table 3. The U.S. state group impact was significant ($P < .001$ for men; $P = .020$ for women). The effect of percentage of smokers in the population was also significant ($P < .001$ for men; $P < .001$ for women). The effect of total background radiation was significant ($P = .029$ for men; $P < .029$ for women); like the state group impact, more background radiation exposure was associated with less lung cancer.

**Table 2** Multivariate Linear Regression Analysis of the Effect of U.S. State Group (Normal-Impact or High-Impact) on Lung Cancer Incidence in Men and Women; 50 U.S. States and the District of Columbia

| Variable | β | *P* |
|---|---|---|
| **Men** | | |
| Total background | −0.123 | .079 |
| Percent smokers | 0.738 | <.001 |
| State impact | −0.344 | <.001 |
| **Women** | | |
| Total background | −0.229 | .055 |
| Percent smokers | 0.527 | <.001 |
| State impact | −0.310 | .015 |

The U.S. state group impact (high or normal) was significant ($P < .001$ for men; $P = .015$ for women). The effect of percentage of smokers in the population was also significant ($P < .001$ for men; $P < .001$ for women). The effect of total background radiation approached statistical significance ($P = .079$ for men; $P < .055$ for women); like the state group impact, more exposure was associated with less lung cancer.

**Table 3** Multivariate Linear Regression Analysis of the Effect of U.S. State Group (Normal Impact, High Impact, or Extra-High Impact for Nevada, Utah, and Arizona) on Lung Cancer Incidence in Men and Women, 50 U.S. States and the District of Columbia, Controlling for the Fact That in 3 States, Nevada, Utah, and Arizona, a Large Proportion of Men and Women Would Have Been Downwind

| Variable | β | *P* |
|---|---|---|
| **Men** | | |
| Total background | −0.159 | .029 |
| Percent smokers | 0.734 | <.001 |
| State impact | −0.321 | <.001 |
| **Women** | | |
| Total background | −0.260 | .029 |
| Percent smokers | 0.519 | <.001 |
| State impact | −0.298 | .020 |

The U.S. state group impact was significant ($P < .001$ for men; $P = .020$ for women). The effect of percentage of smokers in the population was also significant ($P < .001$ for men; $P < .001$ for women). The effect of total background radiation was significant ($P = .029$ for men; $P < .029$ for women); like the state group impact, more exposure was associated with less lung cancer.

## Discussion

Hormesis is still hotly disputed, yet it is of vital medical importance because of the continuing debate over whether the low-level radiation doses from diagnostic x-ray procedures, such as computed tomography scans, are harmful.[15]

Radiation-induced cell repair or regeneration is a contested phenomenon. Yet, many natural mechanisms exist for DNA repair in a cell, which radiation might facilitate. Redpath et al demonstrated that exposure of human fibroblast skin cells in vitro to gamma radiation doses of up to 10 cGy induced resistance of these cells to neoplastic transformation.[16] Day et al used a 2-dose in vivo experiment and showed that a low follow-on x-ray dose (0.01-1 mGy) to mice can protect against a larger, initial whole-body x-ray dose (1000 mGy) given several hours earlier.[17]

A weakness in our analysis as presented herein, is possible confounding by the ecological fallacy (or ecological inference fallacy), a logical fallacy in the interpretation of statistical data where inferences about the nature of individuals are derived from inference for the group to which those individuals belong.[18] In this case, inferences about individuals are being drawn from the characteristics of U.S. states where they reside, rather than from the individuals themselves. Another intrinsic difficulty with correlational studies is that 2 variables might be associated, even if there is no causal link between them, if each is associated with some other variable.

The results of our analysis indicate that the state group effect differs between men and women. A plausible explanation is that more men than women had radiation-related occupations (including onsite participants), which would have affected all 12 high-impact states.

Three of the 12 high-impact states—Nevada, Utah, and Arizona—are downwind and had a radiation exposure to a substantial proportion of the general population from fallout after the testing of nuclear devices. In the other 9 high-impact states, the exposure that defined high-impact pertained only to the small percentage of the population with radiation-related employment.Thus, the hypothesis representing the LNT model in these 9 states is that the greater incidence of lung cancer in persons with such radiation-related employment would make the overall incidence high, after taking into account rates of smoking.

## Conclusion

Our analysis adds to the body of evidence suggesting that the LNT model of radiation carcinogenicity in lung cancer might not be correct. Low-level radiation exposure might protect against lung cancer rather than cause it.

### *Clinical Practice Points*

- Our analysis adds to the body of evidence suggesting that the LNT model of radiation carcinogenicity in lung cancer might not be correct.
- Low-level radiation exposure might protect against lung cancer rather than cause it.

## Disclosure

The authors have stated that they have no conflicts of interest.

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