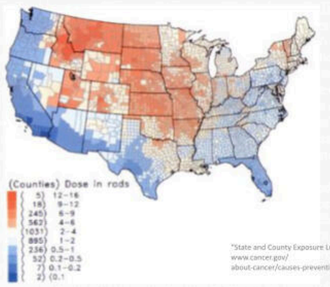
An Epidemiological Study Quantifying Differences in Thyroid Cancer Risk across Birth Cohorts and I-131 Exposure Levels

BACKGROUND

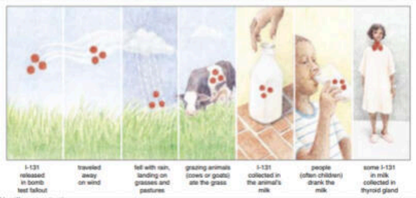
With a dramatic 2.4-fold increase over the past several decades (1973-2002), thyroid cancer is the fastest growing cancer in the United States. Researchers speculate this increase is due to improvements in screening technology, allowing detection of smaller papillary cancers that would have otherwise gone unnoticed throughout a patient's lifetime (Davies & Welch). Thyroid cancer is the most common cancer of the endocrine system, and the rising levels have incited researchers to consider what may contribute to heightened risk in addition to screening improvements. Risk factors that have been found to influence variations of incidence rates include geographical location, race, age, female sex, hereditary conditions, a low iodine diet, and exposure to radioactive iodine or I-131. If the rise in thyroid cancer cases could be attributed to improvements in screening then we would expect to see an even increase of cases across the nation, however, if results show that this is untrue then environmental factors must be in play. Because the thyroid is specifically connected to iodine levels, I-131 exposure and its relation to thyroid cancer has been a topic of interest. This study seeks to more clearly describe the association between age, exposure levels of I-131, and thyroid cancer rates.

From 1951 to 1992, the United States Atomic Energy Commission conducted a series of nuclear weapon tests at the Nevada Test Site. The highest levels of radioactive substances were released during the tests that occurred from 1952 to 1958, the most relevant being I-131.



"State and County Exposure Levels to I-131." *National Cancer Institute*, www.cancer.gov/about-cancer/causes-prevention/risk/radiation/stateandcountyexposure#27.

In 1958 President Eisenhower instituted a testing moratorium, followed by the Test Ban Treaty of 1963, neutralizing the threat of I-131 exposure from nuclear testing. Unfortunately, the fallout from this testing had already affected the nearby or 'downwinders' communities. With a half-life of eight days, I-131 lingers long enough to disperse onto vegetation eaten by cattle and contaminate milk prepared for human consumption.



I-131 milk contamination
"I-131 Radiation Exposure from Fallout." *National Cancer Institute*, www.cancer.gov/about-cancer/causes-prevention/risk/radiation/i-131.

Research on the Nevada Test Site and the similar Chernobyl disaster indicates that exposure to I-131 could lead to an increased risk of thyroid cancer . Research specific to the Nevada Test Site has been done; however, most of this research evaluates time periods very close to the actual testing, therefore assuming a short latency period. An analysis conducted by Kikuchi et al reveals that the median latency period after radiation exposure for benign tumors was 38.0 years for men and 30.0 years for women while the latency period for follicular adenomas had a median of 36.5 years. While the latency period for each variation of thyroid cancer was different, nearly all had similar medians; this data indicated to us that while some repercussions of the I-131 exposure were investigated, there may have been further consequences that can only be identified when analyzing subjects with a longer latency period. Additional research on the association between exposure to I-131 and long-term effects on thyroid cancer risks is needed.

Multiple analyses of the Chernobyl disaster suggest an association between exposure to radiation and greater rates of thyroid disease, especially in younger age groups . Studies on the fallout of the explosions of the Nevada Test Site, such as Kerber et al 1993 and fallout from testing in Russia support the theory that I-131 exposure contributes to a heightened risk of thyroid cancer 12-18 years after exposure. However, this research was conducted very soon after exposure, leaving long term effects of exposure uninvestigated. In-utero exposure to I-131 and exposure during childhood have been linked to an increased risk of thyroid cancer . Children's thyroids are developing during this period of growth and are therefore more susceptible to changes in iodine levels and radioactive iodine. In addition to increased sensitivity, children are also suspected to have higher levels of exposure through milk consumption . However, the correlation between exposure to I-131 and thyroid cancer is debated; studies such as Davis et al 2004 have found no association between exposure to radioactive iodine and the incidence of thyroid cancer. However, Davis et al studied populations exposed to relatively low amounts of I-131 and did not compare to a control group not exposed. Theories describing I-131 as a causal risk factor of thyroid cancer incidence have been difficult to support largely due to problems of limited available data, bias, government suppression, and the ecological nature of this topic.

This study utilizes data collected by the Surveillance, Epidemiology, and End Results Program (SEER), which provides a comprehensive report of cancer incidence for one-third of the nation's population. This database gives us the ability to compare rates across geographical locations; a varying risk over the geographical site can indicate environmental factors such as the association with radioactive exposure.

METHODS

DESCRIPTIVE ANALYSIS
Create a descriptive plot of thyroid cancer rates by exposure level, sex, and birth cohort

STATISTICAL ANALYSIS
Created Poisson regression models for years for which state and sex specific smoking and migration data were available.

Poisson Regression Models:

1. We created a model by exposure level where the dependent variable was the rate of thyroid cancer incidence:
   a) By age group, period of diagnosis, and birth cohort (with low exposure, age 25, period 2, and birth cohort 1968 as reference);
   Example Code:
   glm(formula = Analysis2m$Count ~ Analysis2m$agegr + Analysis2m$birthcohort + Analysis2m$period3 + Analysis2m$period4 + Analysis2m$period5 + Analysis2m$highexposure + Analysis2m$medexposure, family = poisson(link = log), offset = Analysis2m$logdenom)

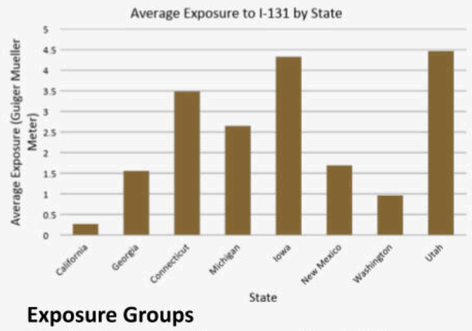
2. We created a model by exposure level where the dependent variable was the rate of thyroid cancer incidence and all models controlled for sex-specific smoking levels and state migration rates:
   a) By age group (with low exposure and age 25 as reference),
   b) By period of diagnosis (with low exposure and period 2 as reference),
   c) By birth cohort (with low exposure and birth cohort 1968 as reference),
   d) By age and period of diagnosis,
   e) By period of diagnosis and birth cohort,
   f) By age and cohort,
   g) By age, period, and birth cohort (with low exposure, age 25, period 2, and birth cohort 1968 as reference);
   Example Code:
   glm(formula = Analysis2m$Count ~ Analysis2m$agegr + Analysis2m$birthcohort + Analysis2m$period3 + Analysis2m$period4 + Analysis2m$period5 + Analysis2m$highexposure + Analysis2m$medexposure + Analysis2m$current.state.percent +Analysis2m$smokingpercent, family = poisson(link = log), offset = Analysis2m$logdenom)

3. We reran the model of step 2 using medium exposure rather than low exposure as the reference variable in order to test for significance between medium and high exposure;

4. We completed a model to test for trend in order to test for a dose response where exposure was set as a continuous variable and the model controlled for sex-specific smoking levels and state migration rates
   Example Code:
   glm(formula = Analysis2m$Count ~ Analysis2m$agegr + Analysis2m$birthcohort + Analysis2m$period3 + Analysis2m$period4 + Analysis2m$period5 + Analysis2m$expcont + Analysis2m$current.state.percent +Analysis2m$smokingpercent + Analysis2m$highexposure * Analysis2m$birthcohort, family = poisson(link = log), offset = Analysis2m$logdenom)

5. We created a model with an interaction term between exposure level and birth cohort to find if the effect of exposure differed between birth cohorts;
   Example Code:
   glm(formula = Analysis2m$Count ~ Analysis2m$agegr + Analysis2m$birthcohort + Analysis2m$period3 + Analysis2m$period4 + Analysis2m$period5 + Analysis2m$highexposure + Analysis2m$medexposure + Analysis2m$current.state.percent +Analysis2m$smokingpercent + Analysis2m$highexposure * Analysis2m$birthcohort, family = poisson(link = log), offset = Analysis2m$logdenom)

6. Using the model which controlled for sex-specific smoking levels and state migration rates, we calculated and graphed predicted probabilities by sex, exposure level, age, and birth cohort;
   Please see printed lab notebook for code.



Exposure Groups

In order to examine by exposure level, states were grouped: Connecticut, Utah, and Iowa for high exposure, Georgia, Michigan, and New Mexico for medium exposure, and California and Washington for low exposure. We used Poisson regression to construct models of incidence by state and sex as models of birth cohort, period, and age.

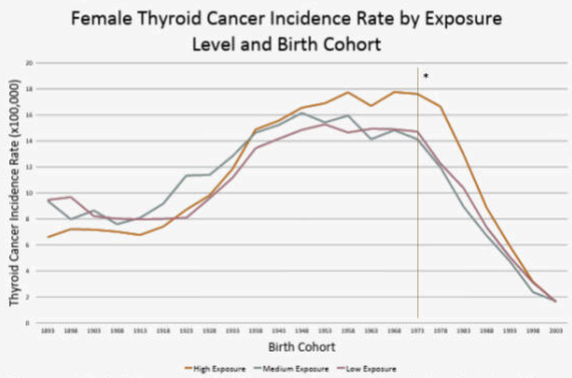
Birth Cohorts and Periods

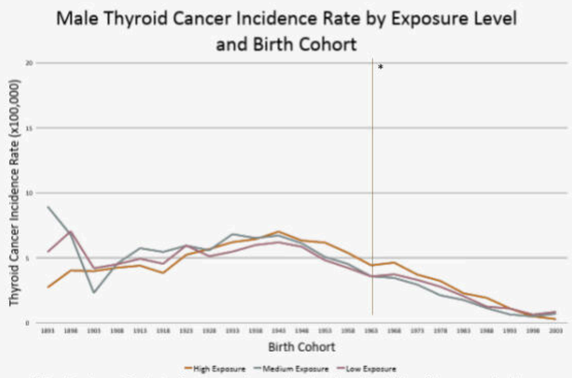
This table provides information regarding how birth cohorts and periods were defined. The data provided an age range and diagnosis year so birth cohorts were defined according to the maximum birth year. Periods were defined by advancements in screening processes in order to control for these improvements.

Innovations & Testings	Year	Birthcohorts	Periods
SEER registry begins	1972		
	1973	1973-1977	period 1
	1974		
	1975		
	1976		
	1977		
	1978	1978-1982	
	1979		
	1980		
	1981		
	1982		
	1983	1983-1987	period 2
	1984		
Intro. of Neck Ultrasonography	1985		
	1986		
	1987		
	1988	1988-1992	
	1989		
Fine Needle Aspiration use increases	1990		period 3
	1991		
	1992		
	1993	1993-1997	
	1994		
Intro. of Guided Biopsy's Increased detection & biopsy of smaller (2mm) nodules	1995		period 4
	1996		
	1997		
PET Scans	1998	1998-2002	
	1999		
CT scans in US nearly tripled	2000		
	2001		
	2002		
	2003	2003-2007	period5
	2004		
	2005		
	2006		
	2007		
	2008		

RESULTS

Descriptive Plots





*Because of the limited years available for analysis due to a data collection limitation, later years on this plot do not include diagnoses of people who developed thyroid cancer at old ages. These lines are the last year for which the data includes populations that reach the median latency period after radiation exposure for benign tumors. (38 years for men and 30 years for women) as determined by Kikuchi et al.

Interaction Term (Exposure and Birth Cohort)

We found that the effect of exposure significantly differed between birth cohorts for females, but not for males. The effect for medium exposure was significantly higher for females born in 1923, 1928, and 1933. The effect of high exposure was slightly lower for females born in 1913, 1928, 1953, and 1978.

Test for Trend

We also found that there was a significant trend when exposure was treated as a continuous variable. The slopes of incidence increases as exposure increased was 0.15 (p-value: <2e-16) for both females and males. As dose (exposure to I-131) increased, as did incidence.

OBJECTIVE

In this project, we aim to quantify differences in cohort trends in thyroid cancer by I-131 exposure region and sex in the United States. We incorporate historical information about x-ray exposure, I-131 exposure, smoking, and migration and screening practices to elucidate factors that may precipitate observed differences.

HYPOTHESIS

We hypothesize that thyroid cancer rates will incrementally increase with increases in exposure to I-131. Geographic regions exposed to higher levels of I-131 will have a higher incidence of thyroid cancer. We also hypothesize that people exposed under the age of 15 (birth cohorts 1943 – 1963) will have higher risk than those exposed as adults. Lastly, we expect to see higher rates of thyroid cancer in women.

METHODS

OVERVIEW

Variables

Independent Variable: I-131 Exposure Level
Dependent Variable: Thyroid Cancer Incidence
Control: Low Exposure Incidence
Variables Controlled For: State Migration Rates, Sex-Specific Smoking, Screening Advancements, Age, and Sex

Data Collection

We incorporate historical information about I-131 exposure in order to perform an analysis of the relationship between exposure and thyroid cancer risk. We include migration data, smoking data, and screening practices in order to create a model that adjusts for these variables. We include data from states California, Connecticut, Georgia, Iowa, Michigan, New Mexico, Utah, and Washington, for which SEER data are available.

We collected data from several different sources: thyroid cancer data (1984-2010) from SEER (Surveillance, Epidemiology, and End Results Program) which provides a comprehensive report of cancer incidence for one-third of the nation's population, exposure data (1984-2010) from the NCI (National Cancer Institute), smoking data (1984-2015) from BRFSS (Behavioral Risk Factor Surveillance System), and migration data (1980, 1990, 2000, 2010) from The US Census Data. We used the program R Studio to examine cohort differences by state, and by exposure level (please see our code in the binder provided).

Analysis

We first conducted a descriptive analysis. Next we conducted a statistical analysis. In order to check for trend and for statistical significance we used Poisson regression. An interaction term was used to test for significant differences by exposed birth cohorts.

General Equation:

$$g(\mu) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$$

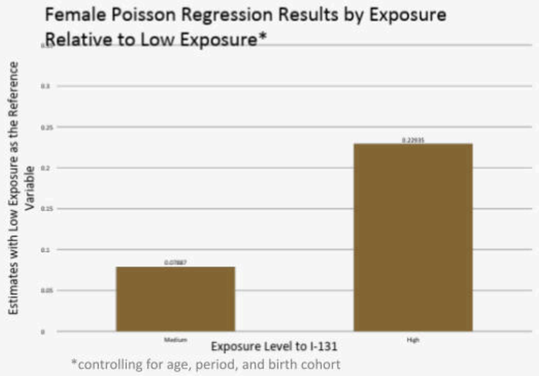
Full Model:

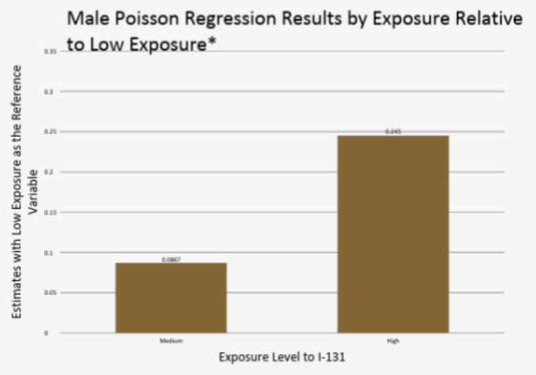
$$g(\mu) = \beta_0 + \beta_1 Exposure + \beta_2 Age + \beta_3 BirthCohort + \beta_4 Period + \beta_5 Migration + \beta_6 Smoking$$

Interaction Term:

$$log(Thyroid\ Cancer\ Incidence\ Rate) = \alpha + \beta_1 Exposure + \beta_2 Age + \beta_3 BirthCohort + \beta_4 Period + \beta_5 Migration + \beta_6 Smoking + \beta_7 BirthCohort * Exposure$$

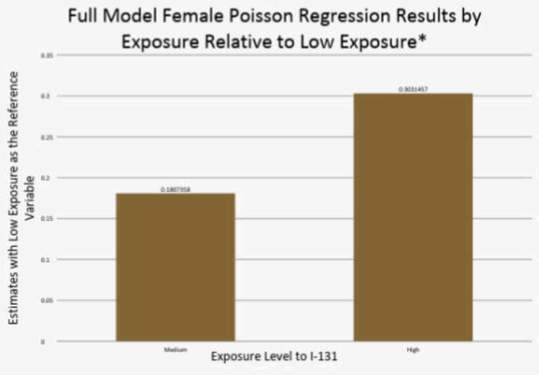
Poisson Regression Results

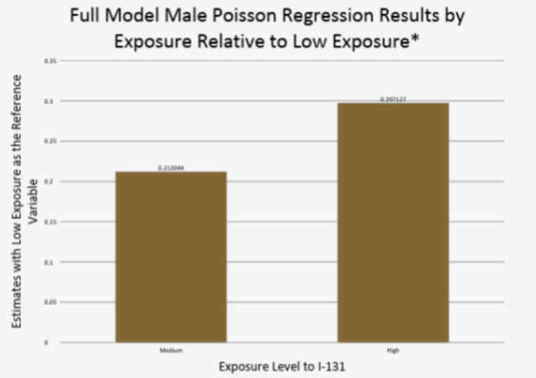




*controlling for age, period, and birth cohort

Without controlling for smoking and migration, we found that the difference between medium and low exposure (p-value female: 1.72E-12 , p-value male: 1.75E-05), and high and low exposure (p-value female: <2e-16, p-value male: <2e-16) were significant. In the test using medium exposure as the reference variable the differences between high and medium exposure (p-value female: < 2e-16, p-value male: < 2e-16) were significant.

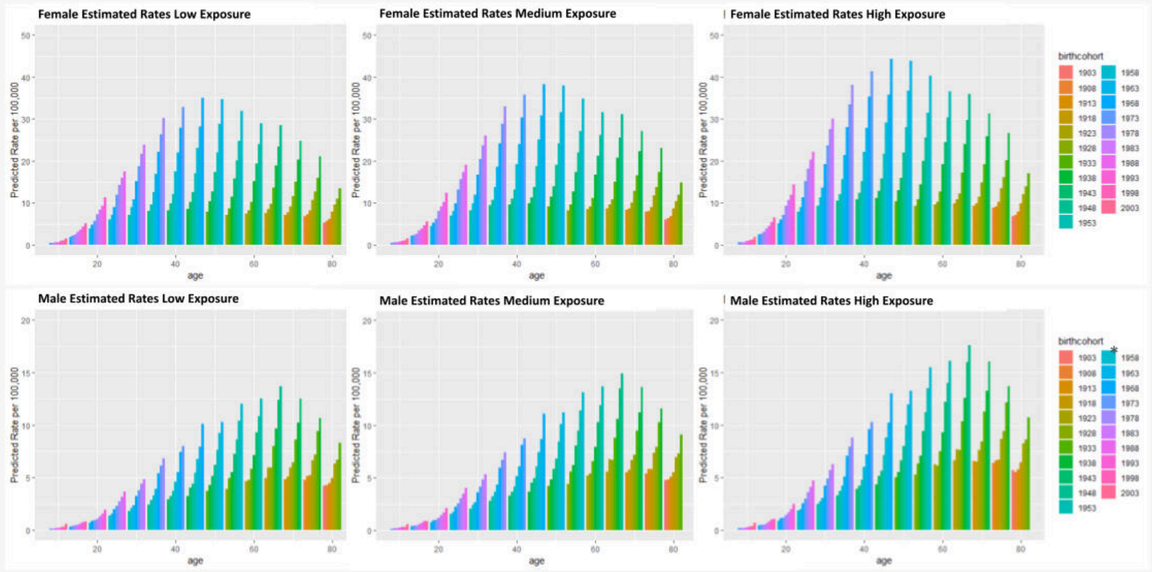




*controlling for age, period (changes in screening practices), birth cohort, smoking, and migration

When controlling for smoking and migration, we found that the difference between medium and low exposure (p-value female: <2e-16, p-value male: 3.24e-11), high and low exposure (p-value female: <2e-16, p-value male: <2e-16) were significant. In the test using medium exposure as the reference variable the differences between high and medium exposure (p-value female: < 2e-16, p-value male: 0.000732) were significant.

Predicted Probabilities



*note that the male graphs have different scale for the y-axis (Predicted Rate per 100,000); this is because the rates for males are significantly lower than those for females, and so different scales were more appropriate.
*controlling for age, period (changes in screening practices), birth cohort, smoking, and migration; mean values for sex-specific smoking levels and state migration rates were used for the predictions

The predicted probabilities of the model controlling for each variable showed that the probabilities increased with exposure. These values were calculated by the model which approximated the effect of each variable based on the counts in a given population.

DISCUSSION

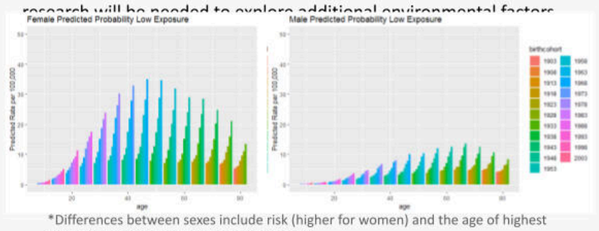
The results of this project support our hypothesis that I-131 exposure is a factor of increased thyroid cancer incidence; however they do not support our hypothesis that individuals exposed under the age of 15 would have an increased risk. Given the high variation in rates by location, we deduced that additional environmental factors which are not assessed in this study may be at play. There are several variables that affect the variation across time and location; we considered birth cohort, sex, I-131 exposure, and the relationship to thyroid cancer risk. In order to isolate the variable of exposure to I-131 as much as possible, we controlled for variation in sex-specific smoking levels and state migration rates and created periods defined by developments in screening practices.

Descriptive plots show a higher rate of thyroid cancer in populations that experienced high levels of exposure. The full model Poisson regressions, which included migration, smoking, thyroid screening over time, birth cohort, and age, yielded a significant difference in thyroid cancer incidence in regions exposed to high, medium, and low levels of I-131. All of the differences were evaluated for significance. The corresponding estimated rates, which control for the confounding factors included in the model, give meaning to the Poisson estimates, demonstrating that there is a real difference in rates by exposure level. Additionally, a trend analysis showed a significant dose-response, meaning that the effect of exposure increased with exposure level. The calculated slopes for incidence between each level of exposure were 0.15 for females and for males. This indicates that the level of exposure to I-131 is associated with risk. The results of both our descriptive and statistical analyses indicate that increased levels of thyroid cancer risk may be associated with an increase in exposure to I-131 and that increasing levels of thyroid cancer are due to more than solely improved screening practices.

While the results of this project did support a correlation between I-131 and thyroid cancer incidence, there were outcomes which we did not predict. Initially, our descriptive plots seemed to support the theory that people exposed under the age of 15 would have a higher risk of developing thyroid cancer than adults. However, the full model Poisson regression, which controlled for all variables, showed otherwise; an interaction term between exposure and birth cohort revealed no significant trend to support our hypothesis, and the significant differences were not for the birth cohorts we expected. This not only detracts from the link between exposure to I-131 and thyroid cancer but further indicates that there are other environmental factors in addition to nuclear fallout that influences thyroid cancer incidence for future research to explore.

This project had several limitations. First, we were limited by the years of data collection available for use. The full model Poisson regression required data for smoking, migration, and thyroid cancer, which limited our analysis to years for which all three datasets were available. Additionally, the exposure data was unspecific; the data provided levels of I-131 exposure, but there were no defining years, and the fallout was not specified to explosions and testing. This limited our ability to analyze the full relationship between fallout exposure and thyroid cancer.

Considering these limitations, there are many ways this project can be expanded upon to further illuminate causal factors of the increase in thyroid cancer incidence and overall risk. While I-131 has been a topic of interest, many other radioactive materials were released during nuclear testing. The effects of these materials, such as Strontium 90 and Cesium 137, have yet to be fully researched, partly due to the lack of available exposure data. For research purposes, I-131 cannot be used as an accurate indication of levels of other radioactive materials including Strontium 90 and Cesium 137 because each disperses differently, varying amounts were released during each test, and each has a distinct half-life. An analysis of the effects of fallout on women and men could be done to find rate differences in sex after exposure. Lastly, it is clear that further research will be needed to explore additional environmental factors



*Differences between sexes include risk (higher for women) and the age of highest risk (which seems to be younger for women).