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The Association of Living in a County in Wisconsin Containing High Radium Levels with Rates of Lymphoma and Melanoma

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Abstract:

Objective:

The objective of this research is to explore the association of living in a high-risk county for radium contamination in Wisconsin and rates of lymphoma and melanoma.

Design and Methods:

This study used an ecological study design of the 72 counties of Wisconsin. Information on the incidence rate of melanoma and lymphoma from 1995-2018 was from the Wisconsin Cancer Reporting System (WCRS). All incidence rates were standardized using the United States 2000 standard population. Data for the risk of radium, nitrate, and arsenic was obtained from the Wisconsin Department of Natural Resources and the University of Wisconsin Stevens Point Well Viewer. The radium belt is an arc shaped region in Wisconsin that stretches from the northeast to the southeast region. There are 22 counties included within Wisconsin's radium belt. Information on the level of urbanization was obtained from the Wisconsin Department of Health Services. The outcome was defined as a county having an incidence rate of lymphoma and melanoma above the United States National average from the years 1995-2018. To determine the association between the rate of melanoma and lymphoma with the covariates, univariate and multivariate logistic regression models were used.

Results:

The odds of a Wisconsin county having rates of melanoma that are higher than the United States national average was elevated (OR 7.371 95% CI 2.314-23.481, P-value: .0007) when being located within the radium belt. Counties within the radium belt also had a similar impact on the odds of a county having rates of lymphoma being higher than the United States national average (OR 7.857 95% CI 1.656-37.283 P-value: .0095). For the melanoma multivariate model, it was determined that the interaction between the county being within the radium belt and the percentage of households not on municipal water had a P-value of .0129. The parameter value for the interaction term was .1307. The Concordance Statistic for the multivariate model of melanoma is .900. The Concordance Statistic for the multivariate model of lymphoma was .704.

Conclusion:

From the analyses from this study, it was determined that there is statistically significant association between counties within the radium belt having elevated rates of melanoma and lymphoma between the years of 1995-2018. The association was statistically significant both at the univariate and multivariate level. Additionally, it was determined that a counties classification as rural or urban was also a statistically significant predictor of elevated melanoma and lymphoma rates. A county's percentage of households not on municipal water systems modified the association between the radium belt status and the rates of melanoma. Information from the study contributes to the understanding of the health effects of living in a high-risk area of radium contamination.

Introduction:

Approximately 1 in 3 households in Wisconsin rely on well-water and 1 in 7 households in the United States rely on well-water. The State of Wisconsin has a heavier reliance on well water than most of the United States. A private well is defined as a well that has fewer than 15 connections and serves less than 25 people (12). Testing and maintenance of a private well is the responsibility of the owner. The Environmental Protection Agency (EPA) states that individuals should test a private well annually for total coliform bacteria, nitrates, total dissolved solids, pH and in some locations for arsenic. The EPA also acknowledges that the recommendation for testing varies depending on the most common contaminants found in the location of the private well. The local health departments are responsible for answering questions about the contaminants in each area. Analytical laboratories are certified by federal and state agencies. The only exception is some towns require testing occasionally. A majority of those on well-water are individuals residing in rural areas (8).

Approximately 1 in 5 private wells contain contaminants. Well water can be contaminated with biological, organic, and inorganic contaminants. The most common contaminants that affect well-water are listed in Figure 1 below (10). The contaminants that this paper focuses on are radium, nitrate/nitrites, and arsenic. Radium is formed in the ground when naturally occurring elements such as uranium and thorium undergo radioactive decay. Once the radium is formed in the ground it can be present in three common forms Ra-228, Ra-226, and Ra-334. Radium forms in groundwater through water passing through underground pores and dissolving uranium and thorium isotopes (6). Radium tends to be found in quantities that are approximately 1 picocurie/liter (pCi/L) but can occur at a higher level depending on locations. 1 pCi/L is safe and levels at this concentration have not been implicated in elevated rates of chronic or acute health conditions (1). Levels within regions containing elevated combined radium can have levels that commonly exceed 5 pCi/L. A pCi/L is defined as the breakdown of 1 picogram per second (7,11). Exposure to radium can occur by multiple methods including both consumption and inhalation. Consumption of radium is primarily through drinking water. Radium can also be inhaled when it is in dust form. Radium can also cause harm when it undergoes nuclear decay to form radon gas (1,7).

Figure 1: Most common groundwater contaminants

Contaminant:	Health Effects:
Arsenic	Acute Toxicity, Cancer, Heart Disease, and Neurological Disorder
Coliform Bacteria	Gastrointestinal Infections and Diseases
Dissolved Solids	None Identified
Heavy Metals	Acute Toxicity, Neurological Disorders, Cancer
Nitrate/Nitrite	Kidney Disease, Cancers, Methemoglobinemia, Gastrointestinal Disorders
Organic Compounds	Cancer, Kidney Damage, Liver Damage, Central Nervous System Damage
Radium/Radon	Anemia, Vision Problems, Cancer, Infertility, Osteoporosis
Volatile Organic Compounds	Kidney Damage, Liver Damage, Central Nervous System Damage

Figure 1 shows the most the contaminants that are most frequently found in groundwater and the health effects that the contaminants can cause. The contaminants can be biological, organic, and inorganic.

Nitrates/Nitrites can enter groundwater through a variety of methods that include both natural and anthropogenic methods. Nitrates can enter well-water through excessive fertilizer use, wastewater, and septic tanks. Nitrates can also enter the groundwater through animal waste and from decomposing organic matter (4). Arsenic can be found in the bedrock naturally. Arsenic can also enter the groundwater through mining and manufacturing (9,11).

The risk of having contaminated groundwater varies depending on the location and geology of the given area. An area of elevated concern in Wisconsin is called the radium belt which is an area in Eastern Wisconsin where radium can be detected in underground aquifers. Figure 2 below shows the counties found within the radium belt. Levels within this area have been increasing over the past 30 years with 80 municipalities during that time having high levels of radium detected (10, 11).

Figure 2: The Wisconsin Radium Belt

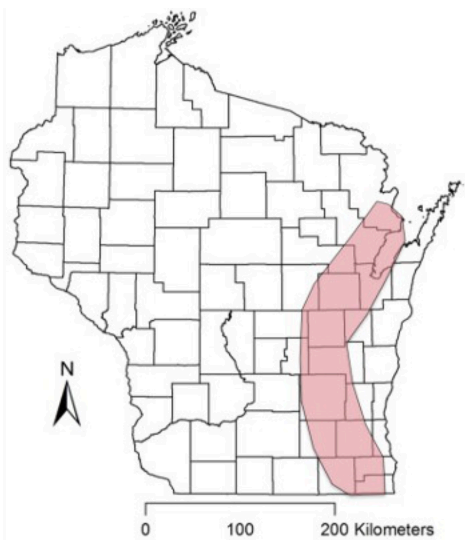

Table 2 shows the geological feature of Wisconsin that is commonly referred to as the radium belt. The radium belt in as area of Wisconsin's geology has elevated levels of uranium, thorium, and radium within the bedrock and groundwater. The radium belt of Wisconsin accounts for 22 counties within the state of Wisconsin.

The risk of exposure to contaminants in drinking water is most likely to occur to individuals living in rural environments. Exposure is more likely to occur in rural communities because of the high level of private drinking water wells that do not require testing (10). The risk of exposure is also higher due to lower access to testing in rural communities. Additionally, we are assuming that rural communities are more unaware of contamination issues due to the lower access of testing and public health facilities. Once individuals are exposed to radium, multiple health effects can arise. The effects depend on a variety of factors. These factors include the level of exposure whether it is chronic or an acute exposure, the pathway of exposure, and the other chemicals exposed to. The individuals' characteristics can also influence the health effects of exposure. For Individuals exposed to radium acutely little is known about the health effects. However, chronic exposure to radium can lead to anemia, cataracts, teeth fracturing, numerous cancers, and death (1,3).

When radium is consumed either through drinking water or through food most of the radium will be eliminated through feces. Approximately 80 % of the consumed radium will be eliminated and the other 20 % will enter the bloodstream. The radium within the bloodstream will be deposited throughout the body and can accumulate within bone tissue. Deposited radium in the body will begin to undergo atomic decay and will release ionizing radiation. Additionally external exposure to ionizing radiation from radium can increase the risk of cancer of all tissues and organs (11).

There is limited information available on the effects of radium on lymphoma and melanoma. The objective of this research is to explore the association of living in a high-risk county for radium contamination in Wisconsin and rates of lymphoma and melanoma. This research also explored the relationship between well water consumption, the number of superfund sites, county classification, arsenic levels, and nitrate levels with lymphoma and melanoma rates. It was hypothesized that rates of lymphoma and melanoma would be higher in counties that were classified as high radium counties because of the increased exposure to ionizing radiation. Prior research has demonstrated a link between radiation exposure and the development of lymphoma and melanoma. This analysis used an ecological study design.

Methods:

Sampling and Data Collection

Data for the rates of lymphoma and melanoma from 1995-2018 were acquired from the Wisconsin Cancer Reporting System (WCRS). Rates of lymphoma and melanoma were standardized using the United States 2000 standard population with 19 age groups. The values for defining the outcome of melanoma and lymphoma were obtained from National Institute of Health's National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER). The outcome was based on lymphoma and melanoma data from 1995-2018 that was standardized to the 2000 United States Standard population. The data for radium risk level of Wisconsin counties were acquired from the Wisconsin Department of Natural Resources Groundwater Coordinating Council Report to the Legislature in 2022. Data for the number of not-municipal water systems was acquired through the Wisconsin Department of Natural Resources Drinking Water Systems Portal. Data for the number of households in Wisconsin counties was acquired from the United States Census Bureau. Data on Wisconsin County Classifications was acquired from the Wisconsin Department of Health Services. Data for the number of superfund sites in Wisconsin counties was acquired from the United States Environmental Protection Agency (USEPA). Finally, data for assigning nitrate and arsenic risk groups to Wisconsin counties was acquired from the University of Wisconsin Stevens Point Center for Watershed Science and Education Well Water Quality Viewer. All data collected was based on the age-adjusted rates.

Variables

Equation 1:

$$\textit{Dane County}:$$

$$\frac{204{,}760\ \textit{Total Households} - 46{,}890\ \textit{Households Not on Municipal}}{204{,}760\ \textit{Total Households}} * 100\% = 22.9\%\ \textbf{Not on Municipal Water}$$

All data for the rates of lymphoma and melanoma were based on the age-adjusted rates per 100,00 individuals from the years of 1995-2018. The percentage of households on private well water in Wisconsin counties was calculated from subtracting the number of households on municipal water from the total number of households divided by the total number of households (%Not Municipal). An example calculation is shown in equation 1. above. The radium risk group for Wisconsin counties was assigned in a binary manner with "High-Risk" =1 and "Low-Risk" =0 (RadiumRiskGroup). Counties found entirely or partially within the radium belt were classified as "High-Risk". Rates of lymphoma and melanoma were converted to binary to serve as the outcome in logistic regression analysis. Non-Hodgkin's and Hodgkins's lymphoma were grouped together and defined as lymphoma. The outcome for the rates of lymphoma and melanoma was defined as being greater than the United States National average rates and not having the outcome as being less than the United States national average. The United States National Averages were averaged based on data from the National Institute of Health's National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER).

Additionally, Wisconsin county classifications were assigned as rural counties being equal to 0 and urban counties being equal to 1. The information for the counties level of urbanization in Wisconsin was acquired from the Wisconsin Department of Health Services. Urban was classified as areas with 50,000 inhabitants or centers exceeding 2,500 inhabitants outside the city center. Arsenic risk group was assigned as 0 being less than or equal to 5 parts per billion (very low risk), 1 being equal to 6-10 parts per billion (low risk), 2 being equal to 11-15 parts per billion (medium risk), 3 being equal to 16-20 parts per billion (high-medium risk), and 4 being greater than or equal to 21 parts per billion (high risk). Exposed was defined as a county being above the Nitrate risk group is assigned with 0 being assigned as less than or equal to 2 parts per million as nitrogen (very low risk), 1 being assigned as equal to 2.1-5.0 parts per million as nitrogen (low risk), 2 being equal to 5.1-10.0 parts per million as nitrogen (medium risk), 3 being equal to 10.1-20.0 parts per million as nitrogen (high-medium risk), and 4 being greater than or equal to 20.1 parts per million as nitrogen (high risk). Exposed was defined as a county having a risk classification greater than 1. County risk classification for nitrate and arsenic contamination were determined using the University of Wisconsin Stevens Point Well-Water Quality Viewer. The Well-Water Quality Viewer graphically showed the number of wells with varying contaminant levels.

Geographical Information Service Mapping

Data collected on the rates of lymphoma and melanoma in Wisconsin from 1995-2018 was mapped using ESRI ArcGIS. The rates of melanoma and lymphoma were displayed using heat mapping with rates of melanoma and lymphoma being color coded from low rates being dark blue, middle rates being red, and high rates being white. In addition to the rates of lymphoma and melanoma, the risk groups for radium, arsenic, and nitrates were assigned to Wisconsin counties. Counties with enhanced risk of radium exposure were color coded as red and the baseline risk was color coded as yellow. Arsenic risk levels were assigned with baseline risk being color coded as white, medium risk being coded as yellow, high-medium risk being coded as orange, and high risk being coded as red. Nitrate risk levels were assigned in the same manner as arsenic risk levels. The risk groups were mapped with the rates of lymphoma and melanoma for the counties of Wisconsin.

Statistical Analysis

All analyses were conducted using the SAS Institute's SAS On-Demand ®. Descriptive statistics of the variables of interest were calculated at the individual county level. The descriptive statistics were calculated using the proc univariate and proc frequency statement in SAS On-Demand ® with variables being divided using the counties of Wisconsin. The mean age, mean % of households not on municipal water systems, counts of county classification, and counts of radium, arsenic, and nitrate/nitrite risk groups. The statistics are displayed in Table 1 below. The summary statistics for the entire state of Wisconsin are displayed at the bottom of Table 1. All analyses were done investigating the exposure at the county level of Wisconsin. In both our univariate and multivariate model's logistic regressions were utilized. Separate models for both lymphoma and melanoma were created. The outcome of interest for each model was defined as being greater than the average United States rate of melanoma and lymphoma from 1995-2018. The primary exposure of interest for the given statistical analyses was defined as the county being within the Radium Belt in Wisconsin. The variables included within the multivariate models were variables that were first assessed for effect measure modification and confounding. Effect measure modification was assessed using an interaction term with the logistic regression models. Variables that affected the outcome by more than 10% were considered confounders. Variables that were not confounder or effect measure modifiers were assessed to determine if the variables were statistically significant independent predictors of the rates of lymphoma and melanoma. The final multivariate logistic regression models had concordance statistics calculated (C-Statistic).

Table 1: Wisconsin County Characteristics

County:	County Classification	Population	# of Households	% Not Municipal	Median Age	# of Super Fund Sites	Radium Risk Group	Arsenic Risk Group	Nitrate/Nitrite Risk Group
Adams	Rural	20654	8341.5	79.0	54.2	0	Low Risk	Very Low Risk	Low Risk
Ashland	Rural	16027	6671	32.1	41.6	1	Low Risk	Very Low Risk	Very Low Risk
Barron	Rural	46711	18410	56.9	44.4	0	Low Risk	Very Low Risk	Low Risk
Bayfield	Rural	16220	6782.5	75.2	52.6	0	Low Risk	Very Low Risk	Very Low Risk
Brown	Urban	268740	97533.5	15.3	37.2	3	High Risk	Medium Risk	Very Low Risk
Buffalo	Rural	13125	5530.5	64.2	46.6	0	Low Risk	Very Low Risk	Low Risk
Burnett	Rural	16526	6801.5	79.8	53.1	1	Low Risk	Very Low Risk	Very Low Risk
Calumet	Urban	52442	17688.5	58.9	40.1	1	High Risk	Very Low Risk	Medium Risk
Chippewa	Urban	66297	23706	53.3	41.3	1	Low Risk	Very Low Risk	Low Risk
Clark	Rural	34659	12319	70.4	37.6	0	Low Risk	Very Low Risk	Low Risk
Columbia	Urban	58490	22227.5	39.3	42.7	0	Low Risk	Very Low Risk	Medium Risk
Crawford	Rural	16113	6592.5	44.4	47	0	Low Risk	Very Low Risk	Low Risk
Dane	Urban	561504	204760	22.9	35.2	5	Low Risk	Very Low Risk	Medium Risk
Dodge	Rural	89396	33354	47.8	43	2	High Risk	Low Risk	Low Risk
Door	Rural	30066	12720	64.7	53.3	0	High Risk	Very Low Risk	Very Low Risk
Douglas	Urban	44295	18336.5	40.9	42.3	0	Low Risk	Very Low Risk	Very Low Risk
Dunn	Rural	45440	15807	56.0	35.1	0	Low Risk	Very Low Risk	Medium Risk
Eau Claire	Urban	105710	38899	27.2	34.9	2	Low Risk	Very Low Risk	Low Risk
Florence	Rural	4558	2104.5	72.6	54.3	0	Low Risk	Medium Risk	Very Low Risk
Fond du Lac	Urban	104154	39541	39.4	41.7	1	High Risk	Low Risk	Low Risk
Forest	Rural	9179	3851.5	58.1	47.2	0	Low Risk	Very Low Risk	Very Low Risk
Grant	Rural	51938	19120	34.7	36.1	0	Low Risk	Very Low Risk	Low Risk
Green	Urban	37093	14302	44.9	43.4	0	Low Risk	Very Low Risk	Medium Risk
Green Lake	Rural	19018	7845	51.7	45.6	0	High Risk	Very Low Risk	Medium Risk
Iowa	Urban	23709	9256.5	44.9	42.9	0	Low Risk	Very Low Risk	Low Risk
Iron	Rural	6137	2942	41.9	55.6	0	Low Risk	Very Low Risk	Very Low Risk
Jackson	Rural	21145	7510	58.2	42	0	Low Risk	Very Low Risk	Low Risk
Jefferson	Rural	84900	31033	31.1	41.3	0	High Risk	Low Risk	Low Risk
Juneau	Rural	26718	10029.5	55.8	45.6	0	Low Risk	Very Low Risk	Low Risk
Kenosha	Urban	169151	60967	32.9	38.7	0	High Risk	Very Low Risk	Very Low Risk
Kewaunee	Urban	20563	7863.5	58.3	44.2	1	High Risk	Very Low Risk	Low Risk
La Crosse	Urban	120784	45601	25.0	36.3	1	Low Risk	Very Low Risk	Low Risk
Lafayette	Rural	16611	6439	52.7	41.7	0	Low Risk	Low Risk	Medium Risk
Langlade	Rural	19491	8428	53.9	48.8	0	Low Risk	Very Low Risk	Low Risk
Lincoln	Rural	28415	11888	53.7	47.9	0	Low Risk	Very Low Risk	Very Low Risk
Manitowoc	Rural	81359	33777.5	29.9	44.9	4	Low Risk	Very Low Risk	Low Risk
Marathon	Urban	138013	51960	35.1	40.8	4	Low Risk	Very Low Risk	Low Risk
Marinette	Rural	41872	17964.5	54.5	48.9	1	High Risk	Low Risk	Very Low Risk
Marquette	Rural	15792	6337	91.6	50.2	0	Low Risk	Very Low Risk	Low Risk
Menominee	Rural	4289	1298	100.0	31	0	Low Risk	Very Low Risk	Very Low Risk
Milwaukee	Urban	928059	382560.5	1.6	34.7	4	High Risk	Very Low Risk	Very Low Risk
Monroe	Rural	46193	16566	51.1	39.8	4	Low Risk	Very Low Risk	Low Risk
Oconto	Urban	39356	15165.5	74.5	47.2	0	High Risk	Low Risk	Very Low Risk
Oneida	Urban	38259	15528.5	71.8	51.4	0	Low Risk	Very Low Risk	Very Low Risk
Outagamie	Urban	191545	68188.5	14.1	38.4	1	High Risk	High Risk	Very Low Risk
Ozaukee	Urban	92497	33873	39.7	43.9	2	Low Risk	Low Risk	Very Low Risk
Pepin	Rural	7364	2908.5	63.6	46.8	0	Low Risk	Very Low Risk	Medium Risk
Pierce	Urban	42587	14437.5	39.9	37.3	0	Low Risk	Very Low Risk	Medium Risk
Polk	Rural	45431	17258.5	65.3	45.9	0	Low Risk	Very Low Risk	Low Risk
Portage	Rural	70468	27040.5	38.3	36.7	1	Low Risk	Very Low Risk	Medium Risk
Price	Rural	14050	6570	59.9	51.9	0	Low Risk	Very Low Risk	Very Low Risk
Racine	Urban	196896	74929.5	23.9	40.1	1	High Risk	Very Low Risk	Very Low Risk
Richland	Rural	17212	7137.5	59.0	45.8	0	Low Risk	Very Low Risk	Low Risk
Rock	Urban	164381	62323.5	25.6	39.8	3	High Risk	Very Low Risk	Medium Risk
Rusk	Rural	14123	6079	65.7	48.9	0	Low Risk	Very Low Risk	Very Low Risk
St. Croix	Urban	95044	29398.5	57.6	39.2	0	Low Risk	Very Low Risk	Low Risk
Sauk	Rural	65697	24247	39.7	41	1	Low Risk	Very Low Risk	Medium Risk
Sawyer	Rural	18295	7286	82.0	50.7	0	Low Risk	Very Low Risk	Very Low Risk
Shawano	Rural	40859	16273.5	51.8	45.5	0	High Risk	Medium Risk	Low Risk
Sheboygan	Urban	117747	46148	28.8	41.3	3	Low Risk	Very Low Risk	Very Low Risk
Taylor	Rural	19923	7610	68.1	43.9	1	Low Risk	Low Risk	Very Low Risk
Trempealeau	Rural	30724	11474	46.6	40.7	0	Low Risk	Very Low Risk	Medium Risk
Vernon	Rural	30915	11329	59.8	42	0	Low Risk	Very Low Risk	Low Risk
Vilas	Rural	23520	9808	89.2	55.1	0	Low Risk	Very Low Risk	Very Low Risk
Walworth	Rural	106799	38270	39.3	40.4	1	High Risk	Very Low Risk	Low Risk
Washburn	Rural	16752	6844	71.3	51.7	0	Low Risk	Very Low Risk	Very Low Risk
Washington	Urban	137175	49824.5	36.7	42.9	1	High Risk	Very Low Risk	Very Low Risk
Waukesha	Urban	408756	149685	87.3	43.1	4	High Risk	Very Low Risk	Very Low Risk
Waupaca	Rural	51570	21018	51.0	45.5	0	High Risk	Very Low Risk	Low Risk
Waushara	Rural	24828	9611	75.7	49.6	0	High Risk	Very Low Risk	Low Risk
Winnebago	Urban	171623	66286.5	19.6	38.3	1	High Risk	High Risk	Very Low Risk
Wood	Rural	74070	30962.5	38.3	43.9	0	Low Risk	Low Risk	Low Risk
Wisconsin	Rural: 45 Urban: 27			51.19575848	43.81527778	0.777777778	High Risk: 22 Low Risk: 50	High Risk: 2 High Medium Risk: 0 Medium Risk: 3 Low Risk: 8 Very Low Risk: 59	High Risk:0 High Medium Risk:0 Medium Risk:13 Low Risk:30 Very Low Risk:29

Results:

There was a total of 72 counties in the state of Wisconsin. Within the 72 counties the average age was 43.82 years old. Of the 72 counties in the state there are 27 counties (37.5%) that are classified as urban and 45 counties (62.5%) that are classified as rural. Additionally, 22 counties were classified as being at an enhanced risk of radium exposure and 50 counties were classified as being in the baseline risk of radium contamination. Two (2) counties were at high risk for arsenic contamination, 3 were at medium risk of arsenic contamination, 8 were at low risk of arsenic contamination, and 59 were at a very low risk of arsenic contamination. Of the 72 counties 13 were considered at medium risk of nitrate contamination, 30 were at low risk of nitrate contamination, and 29 were at very low risk of nitrate contamination.

The univariate logistic regression analysis of melanoma displayed 5 variables that were statistically significantly associated with the age adjusted rates of melanoma. County radium risk level, arsenic risk group, county classification, percent not municipal, and the number of superfund sites were all statistically significantly associated with the age-adjusted melanoma rates. For the univariate analysis of the age-adjusted rates of lymphoma revealed 1 variable that was statistically significantly associated with the age-adjusted rates of lymphoma. County radium risk level was the single variable that was statistically significantly associated with the age-adjusted lymphoma rates.

The odds of a county having rates of melanoma that are higher than the United States national average was elevated (OR 7.371 95% CI 2.314-23.481, P-value: .0007) for counties that were found to be within the radium belt of Wisconsin. Counties within the radium belt also had a similar impact on the odds of a county having rates of lymphoma being higher than the United States national average (OR 7.857 95% CI 1.656-37.283 P-value: .0095). Additionally, it was determined that the odds of the rate of melanoma being above the United States national average was increased when a county was at enhanced risk of arsenic contamination (OR 4.569 95% CI 1.294-16.130 P-value: .0182). Counties were also more likely to have higher rates of melanoma than the national average when counties were classified as being urbanized (OR 8.613 95% CI 2.601-28.527 P-value: .0004). The number of superfund sites in a county had a statistically significant impact on the odds of melanoma rates being above the United States national average with every additional super fund site increasing the odds (OR 1.559 95% CI 1.053-2.309 P-value: .0267). A county's % of households not being on municipal water impacted the odds of a county being above the United States national average by decreasing the odds by 3.12% for every percentage of households not being on municipal water systems (OR .9693 95% CI .941-.998 P-value: .0383). Additional results from the univariate analyses of lymphoma are displayed in table 2a and univariate analysis of melanoma in table 2b below.

Table 2: Univariate Analysis

a.

Variables	Unadjusted Analysis Parameter	Effect Size	95% CI	p-value	C-Statistic
% Not Municipal	-0.0106	0.989	.965-1.015	0.4065	0.575
Radium Risk Group (Baseline Risk)					
Enhanced Risk	2.0614	7.857	1.656-37.283	0.0095	0.667
Arsenic Risk Group (Baseline Risk)					
Enhanced Risk	0.1431	1.154	.316-4.214	0.8286	0.51
Nitrate/Nitrite Risk Group (Baseline Risk)					
Enhanced Risk	-0.4418	0.643	.231-1.787	0.3971	0.552
County Classification (Rural)					
Urban	0.8473	2.333	.788-6.911	0.1261	0.594
Number of Superfund Sites	0.3613	1.435	.880-2.341	0.1477	0.628

95% CI=95% Confidence Interval

b.

Variables	Unadjusted Analysis Parameter	Effect Size	95% CI	p-value	C-Statistic
% Not Municipal	-0.0312	0.9693	.941-.998	0.0383	0.667
Radium Risk Group (Baseline Risk)					
Enhanced Risk	1.9976	7.371	2.314-23.481	0.0007	0.721
Arsenic Risk Group (Baseline Risk)					
Enhanced Risk	1.5194	4.569	1.294-16.130	0.0182	0.628
Nitrate/Nitrite Risk Group (Baseline Risk)					
Enhanced Risk	-0.1028	0.902	.311-2.615	0.8499	0.512
County Classification (Rural)					
Urban	2.1533	8.613	2.601-28.527	0.0004	0.746
Number of Superfund Sites	0.4442	1.559	1.053-2.309	0.0267	0.697

95% CI=95% Confidence Interval

Upon completion of the univariate analysis, a multivariate analysis of the given variables was completed. It was determined that the number of superfund sites in a county was not a confounder, effect measure modifier, or an independent predictor of the association between the age-adjusted rate of melanoma and the counties radium risk group. The multivariate analysis of melanoma revealed that the association between the counties radium risk group and age-adjusted rate of melanoma was modified by the percentage of households not on municipal water systems. Additionally, the association between the age-adjusted rate of melanoma and the counties radium risk group was confounded by the counties arsenic contamination risk. It was also determined that the counties classification was also independently associated with the age-adjusted rate of melanoma. The multivariate analysis of the age-adjusted rate of lymphoma and the counties radium risk group revealed that the percentage of households not on municipal water systems and the number of superfund sites were not confounders, an effect measure modifier, or independent predictors. However, it was determined that the counties risk of arsenic contamination and the county classification were confounders to the association between the radium risk group and the age-adjusted rate of lymphoma.

For the melanoma multivariate model, it was determined that the interaction between the county being within the radium belt and the percentage of households not on municipal water had a P-value of .0129. The parameter value for the interaction term was .1307. When comparing a county that is in the radium belt and 75 % of the community is not on municipal water to a county that is not in the radium belt and 50 % of the community is not on municipal water. The odds of the county being higher than the United States national average rate of melanoma was 3.018 when holding all other variables constant. The Concordance Statistic for the multivariate model of melanoma is .900. When considering the multivariate model of lymphoma there was no statistically significant interaction term between variables. The P-value of a county being within the radium belt is .0121. When comparing a county in the radium belt to a county that is not in the radium belt while holding all other variables constant the odds of being above the United States national average was 11.06. The Concordance Statistic for the multivariate model of lymphoma was .704. The variables included in the multivariate analysis of lymphoma are included in table 3a. and the variables of the multivariate analysis of melanoma are included in table 3b.

Table 3: Multivariate Analysis

a.

Variables	Multivariate Analysis Parameter	p-value	C-Statistic
Radium Risk Group (Baseline Risk)			
Enhanced Risk	2.4031	0.0121	
Arsenic Risk Group (Baseline Risk)			0.704
Enhanced Risk	-1.0554	0.2438	
County Classification (Rural)			
Urban	0.4534	0.4505	

b.

Variables	Multivariate Analysis Parameter	p-value	C-Statistic
% Not Municipal	-0.0863	0.0633	
Radium Risk Group (Baseline Risk)			
Enhanced Risk	-4.3829	0.0553	
Arsenic Risk Group (Baseline Risk)			
Enhanced Risk	1.5732	0.0834	0.900
County Classification (Rural)			
Urban	1.9065	0.0223	
Interactions			
RadiumRiskGroup*PercentOtherthan Muncipal	0.1307	0.0129	

Discussion:

This ecological study was conducted to investigate the impact that the radium belt has on the rates of melanoma and lymphoma at the county level of Wisconsin. It was determined that individually a county being in the radium belt statistically significantly elevated the rates of both melanoma and lymphoma. This association between the rate of melanoma and the county being in the radium belt was confounded by a county having a risk of arsenic contamination. Additionally, the number of households not on municipal water was determined to be an effect measure modifier between the association of melanoma rates and the radium belt of Wisconsin. It was also determined that a counties arsenic risk and the level of urbanization were confounders to the association between a counties rate of lymphoma and if the counties in the radium belt.

There was a concern with the co-occurrence of arsenic and radium exposure in groundwater. The co-occurrence of radium and arsenic can lead to collinearity between the variables. The presence of collinearity can affect the coefficient estimates of the independent variables. Collinearity can also reduce the precision of the coefficient estimates and can weaken the statistical power of the logistic regression model. The reduction in precision can affect the validity of the p-values within the model. Any concerns with collinearity were addressed by accessing the variance inflation factor in SAS and it was determined that radium risk and arsenic risk were not highly collinear with each other. The lack of collinearity fits with scientific findings that radium and arsenic do not co-occur on a consistent basis (11). There was also a concern with the precision of incidence rate for melanoma and lymphoma as the occurrence of disease is rare. The Wisconsin Cancer Reporting System acknowledges that the incidence rates can be unstable when the occurrence of disease is rare.

The findings from this study add depth to the understanding of the association between exposure to radium through contaminated water and developing numerous cancers. Exposure to radium has been linked to developing lymphomas, leukemia, and bone cancers. The exposure to radium has also been implicated in individuals having an enhanced risk of developing lung cancer through the radioactive decay of radium into radon gas. While the association between radium exposure and lymphomas is well established, the link between exposure to radium and the development of melanoma is not well documented. Even though there has not been a well-established link between radium exposure and melanoma there is information that demonstrates a link between exposure to high levels of radiation and the development of melanoma. Prior association of melanoma and radiation may explain how exposure to radium is associated with higher risk levels of developing melanoma in individuals.

Exposure to radium can lead to the development of lymphoma and melanoma through a few different pathways. If an individual consumes water that is contaminated with radium and the majority of the radium is eliminated in an individual’s feces and urine. However, approximately 20% of the consumed radium will make its way into the individual's blood stream and bodily fluids where it will begin to undergo radioactive decay. Individuals can also become exposed to radium if they live in an environment that contains high levels of radium in the soil. When radium undergoes radioactive decay, it will lead to the formation of radon gas and release both gamma and alpha radiation. Alpha radiation is unable to penetrate deep into the body but is still considered to be the most ionizing form of radiation. However, if formed within the body many internal organs and tissues can be exposed to dangerous levels of ionizing radiation. The exposure to gamma radiation can lead to tissue damage throughout the body.

Individuals who have been exposed to alpha radiation will experience irreparable and irreversible damage to the DNA of cells from alpha particles causing a high linear energy transfer. The damage to DNA usually is manifested in a complete break of the DNA strand and this event typically only requires the energy transfer of one alpha particle. The complete destruction of DNA can lead to an individuals' cells undergoing apoptosis (2). Exposure to gamma radiation can penetrate deeper into tissues with the potential of causing damage to chromosomal DNA. Cellular DNA damage that does not cause death from ionizing radiation can lead to cells repairing DNA which has the potential to cause mutations that will ultimately lead to the formation of malignant cells. The depth of the damage depends on what form of ionizing radiation an individual has been exposed to with alpha particles failing to penetrate deep into tissues (3).

The data obtained from this study is not free of limitations. This study is an ecologic study and thus is limited on generalizing to the individuals living within the counties in Wisconsin. It is difficult to ascertain if the exposure to the radium belt is associated with higher rates of lymphoma and melanoma at an individual level. Additionally, there may be variations in the rates of lymphoma and melanoma within the given counties of Wisconsin. This study fails to account for there being variations in the collection and recording of disease information. Systematic differences in the collection of disease data are a common theme with all ecologic study designs. For this analysis data on the ambient air pollution levels for the given counties was not obtained. A lack of air pollution data can result in there being some confounding with respect to an elevation in cancer rates due to air pollution. Additional area where there is unmeasured confounding is with the amount of sun exposure and the use of tanning beds in the counties. A lack of measuring sun exposure may have resulted in confounding of the rates of melanoma. There were also relatively large 95% confidence intervals for the effect sizes both at the univariate and multivariate level. The presence of large confidence intervals potentially may be due to the sample of this study being relatively small with only 72 counties within Wisconsin. The large confidence intervals may also be due to there being a high level of variability within the state of Wisconsin. Finally, this study was not able to determine if the individuals who developed lymphoma and melanoma are the individuals who are being exposed to radium or other contaminants.

The use of an ecological study design did result in there being strengths to the analysis. Our analysis was successful in demonstrating a potential association between radium exposure and elevated rates of melanoma and lymphoma. The results from this study were highly significant and can be useful in further investigations into the association of radium and rates of lymphoma and melanoma. Additionally, this study was able to obtain data on rates of cancer for an extended period from 1995-2018 that were age-adjusted. This analysis was also successful in being able to compare the rates of melanoma and lymphoma between the counties of Wisconsin. Another strength of this analysis was it was able to collect data on numerous variables in a relatively short period of time. Finally, this analysis was able to be accomplished in a relatively short period of time.

In the future there are some additional methods of analysis that could be used to obtain more precise results. An alternative method to explore the association between the radium belt and the incidence rate of melanoma and lymphoma would be to calculate a standard incidence ratio. The use of a Standard Incidence Ratio (SIR) would allow for a comparison of the incidence that would be expected and observed. Using SIR to compare incidence rates would also allow for comparisons to larger populations. Additionally, an alternative method of analysis would be to classify the outcome of disease when the 95% confidence intervals do not overlap. Another variable that would be included in future studies would be a classification of regions for the counties and obtain additional variables for potential confounding factors.

Conclusions:

From the analyses from this study, it was determined that there is statistically significant association between counties within the radium belt having elevated rates of melanoma and lymphoma between the years of 1995-2018. The association was statistically significant both at the univariate and multivariate level. Additionally, it was determined that a counties classification as rural or urban was also a statistically significant predictor of elevated melanoma rates. A county's percentage of households not on municipal water systems modified the association between the radium belt status and the rates of melanoma. The results of this study and the result from prior research suggest that further work needs to be done to explore the association between environmental radium exposure and the rates of both melanoma and lymphoma. Future research should focus on individualized data to determine if the association remains significant at the individual level. Additionally, future work should be done to explore the association between well water consumption in high radium areas and rates of lymphoma and melanoma. More work should be done to determine potential mechanisms for how radium could lead to melanoma.

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