THYROID CANCER AND RADON LINK? A PREVIEW OF A HOSPITAL STUDY IN COLORADO SPRINGS, CO

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ABSTRACT

A case-control study looking at a possible correlation between indoor radon exposure and thyroid cancer is just beginning in the Colorado Springs area. The study was prompted by an observation by one of the principal investigators of the high incidence of thyroid nodules and cancers in her practice compared to the previous location at which she worked in Florida. A study has been designed which selects the cases (people with thyroid cancer) and the controls (those without thyroid cancer) from a local endocrinologist with a very large practice (hence the name, hospital study). The controls are to be matched to the cases by gender, age, smoking habits and the area of the city in which they live. It was originally envisioned that 48-hour charcoal canister results would be used to predict long-term average radon concentration. However, this plan is being reconsidered because of logistical problems and it is much more likely that long-term tests (alpha track detectors) will be employed. Exposure will be estimated from information gathered in a form filled out by the participants in which they report the time they lived in the house and the level of the house most occupied. Because no information exists concerning the exposure to radon gas and thyroid cancer, it was thought prudent to limit participants to people who have lived in their homes for at least 3 years prior to the diagnosis of thyroid cancer or, in the case of controls, people who have lived in the same house for three or more years. It is anticipated that there will be approximately 300 cases and an equal number of controls.

MOTIVATION

One of us (Dumbacher) has a medical practice as a family physician in Colorado Springs and has observed that she has seen more thyroid cancers and non-malignant nodules of the thyroid since moving her practice to Colorado Springs from Florida. This observation, along with her deep interest in radon-related health concerns, led her to an hypothesis of a possible radon-thyroid cancer link, which resulted in a collaboration with the Radon Measurements Lab housed at the University of Colorado-Colorado Springs and a graduate student[(1)] from the Biology department at that same school.

(1) *Adrien L Bickley, formerly a graduate student in the Biology Department at the University of Colorado-Colorado Springs, assisted in the original design of the survey. He is currently attending the Carver College of Medicine/Physician Assistants program in Iowa City.*

Thyroid Cancer

The National Cancer Institute estimates 33550 new cases and 1,530 deaths from thyroid cancer in the United States in 2007 (NCI, 2007). Thyroid cancer is "Cancer that forms in the thyroid gland (an organ at the base of the throat that makes hormones that help control heart rate, blood pressure, body temperature, and weight). Four main types of thyroid cancer are papillary, follicular, medullary, and anaplastic thyroid cancer. The four types are based on how the cancer cells look under a microscope" (NCI, 2007). Of the four types of thyroid cancer, by far the most common is papillary carcinoma (81%) and then follicular carcinoma (13%). The others (medullary and anaplastic) are much more rare (Hershman, 2002).

Radiation Induced Thyroid Cancer

Perhaps the best-known source of radiation that leads to thyroid cancer is the ingestion or inhalation of radioactive iodine. Iodine (chemical symbol I) is a nonmetallic solid. Its predominate isotopes are the radioactive isotopes Iodine-129 (15.7 million years half-life) and -131 (8 day half-life), especially when considering environmental-linked health effects. The fission of uranium atoms during operation of nuclear reactors and by plutonium (or uranium) in the detonation of nuclear weapons produce both isotopes. Both emit beta particles and low energy gammas upon radioactive decay. In addition, doctors may give thyroid patients radioactive iodine, usually iodine-131, to treat or help diagnose certain thyroid problems. The tendency of iodine to collect in the thyroid makes it very useful for highlighting parts of its structure in diagnostic images. Airborne I-129 and I-131 can be inhaled. In the lung, radioactive iodine is absorbed, passes into the blood stream, and collects in the thyroid. Any remaining iodine passes from the body with urine. Long-term (chronic) exposure to radioactive iodine can cause nodules, or cancer of the thyroid. In the body, iodine has a biological half-life of about 100 days for the thyroid and for the body as a whole (EPA, 2007). Short term (acute) exposures have also been strongly linked to thyroid cancers, with Chernobyl and the Marshal Island residents (who were contaminated with atomic bomb fall-out material for 48 hours and subsequently suffered a large number of nodules and cancers) being the best known examples (Mays, 1973).

Thyroid tumors can be induced by other ionizing radiation, not just radioactive iodine. "Human thyroid carcinomas have been induced following exposure…in vitro to single doses (0.14-1.57 Gy) of 3.26 MeV alpha particles from a plutonium 238 source. Tumors were detected between 50-160 days following subcutaneous transplantation of the irradiated cells in athymic mice. No tumors were observed following transplantation of unirradiated cells." (Riches, 1997)

Papillary carcinomas are induced by radiation more frequently than the other types. A history of irradiation, especially in childhood, increases the likelihood of developing papillary thyroid cancer. For example, in Chernobyl in 1986, a thyroid cancer outbreak was seen in children 5 and under from northern Ukraine and southern Belarus. This reactor explosion contaminated the air, soil, water, and food of the area. The children who were exposed *in utero* were the most vulnerable (Hershman, 2002), (Balonov, 1999).

External radiation, which was used to irradiate the thymus gland or enlarged tonsils and adenoids in the 1950's, is a risk because the thyroid was coincidentally irradiated. A study done at Michael Reese Hospital in Chicago found that 12% of the children who received radiation at age two or three developed thyroid cancer. Many more had nodules also (Ron, 1995).

Although the thyroid is not specifically discussed, several authors have calculated the dose to internal human organs caused by the inhalation of radon gas (Kendall, 2002; Kendall, 2005; Kursheed, 2000) and the subsequent transport of radon to the organs through the bloodstream. Since exposure to ionizing radiation and external beam radiation as noted above or ingesting/breathing radiation products as with Chernobyl or the Marshall Islands (Mays, 1973) is a known cause of thyroid cancer, it may be that the inhalation of radon gas will increase risk of developing thyroid cancer.

Hypothesis

Our hypothesis is, therefore, that radiation associated with radon exposure is a contributor to thyroid cancer, understanding that radiation exposure is generally believed to be responsible for only about 3 % of all cancers (Boice, 1997).

Resources

(1) The NCI Web Site

The National Cancer Institute Act (now celebrating its 70th anniversary) authorized the National Cancer Institute (NCI) to engage in activities including the dissemination of cancer incidence and cancer deaths by the type of cancer (cancer site), gender, race and other variables. Comparisons of cancer deaths are made on a state-by-state basis and are available to the public on the web. The National Cancer Institute web site places Colorado as 36th out of the 50 states for average annual thyroid cancer deaths with 0.4 deaths per 100,000 per year (NCI 2007). Thyroid cancer has a good survival rate, compared to other cancers, (there are only approximately 1300 cancer deaths in the U.S. per year), so it is possible that the low death rate in Colorado masks a relatively high incidence rate because of differences in the availability and quality of health care in Colorado compared to other states (including early detection).

(2) Colorado Department of Health and Environment Web Site

In fact, Colorado does have a higher incidence, age-adjusted[(2)], than the national average

(2) Incidence and death rate data are age-adjusted by normalizing a given population in such a way that it transforms into a standardized age distribution. This is done by dividing the per incidence or death rates into classes with a class width of 5 years and then multiplying that age group by the fraction of the population that was in that age group in the standardized age distribution, typically the most recent census.

as shown in table 1, below, where it can be seen that males of all races have a 20 % higher incidence, when compared to the national rate from 1996 to 2000, and females of all races an 8.5 % higher over the same time period. Also, it is interesting to note that in 2001, the rate increased to an unsettling 13.3 per 100,000 for females of all races, an astounding 41 % increase over the national rate for the 1996-2000 period (CDPHE, 2007).

	USA 1996-2000		**Colorado 1996-2000**		**Colorado 2001**	
	N	**Rate**	**N**	**Rate**	**N**	**Rate**
Male						
All Races	15235	3.5	396	4.2	92	4.3
White/Non-Hispanic	13606	3.6	338	4.4	75	4.4
White/Hispanic	N/A	N/A	39	3.8	15	5.1
Black	723	2.0	13	5.4	0	0.0
Female						
All Races	45361	9.4	1058	10.2	296	13.3
White/Non-Hispanic	39059	9.7	860	10.4	254	14.4
White/Hispanic	N/A	N/A	133	11.2	28	10.9
Black	2840	5.7	25	7.0	8	8.9

Table 1: Colorado thyroid cancer rate (age-adjusted) compared to the national average over the years 1996-2000 and, again, in the year 2001.

(3) Radon Measurements Laboratory

A radon laboratory, housed at the University of Colorado-Colorado Springs, has been measuring radon in the Colorado Springs since 1986. Approximately 60,000 tests, consisting of open-face charcoal canisters, diffusion-barrier charcoal canisters, alpha-track detectors and radon in water tests, have been amassed.

This data show that Colorado Springs exhibits a wide variation in radon levels, from areas (especially in the center of town) with radon levels around a few picoCuries per liter to other areas (on the perimeter of town) with radon levels near 100 pCi/L and the city has an over all average radon hovering just over 6 pCi/L. The surficial geology of Colorado Springs is highly correlated with the indoor radon levels and confirms that radon levels are associated strongly with (1) the Pikes Peak batholith and soils derived from that rock and (2) the many major and minor faults that permeate the region (Burkhart, 1993). The high average radon concentration, coupled with the large variation in radon, would seem to make Colorado Springs an ideal testing ground for any hypothesis seeking a link between radon exposure and disease.

A few years ago, Ms. Kelly C. Sparks of the Southern Colorado Geodata Laboratory housed within the Department of Geography and Environmental Science took a sample consisting of 3026 radon results from the Radon Measurements Lab data base and geocoded, using the software ArcInfo GIS version 8.3, these data onto a map of El Paso County, which includes the city of Colorado Springs.

Average radon values were then calculated for various administrative units, including (1) by zip codes, (2) census blocks, (3) census block units, (4) census tracts and, finally, by (5) interpolation techniques including geo-spatial analysis to create continuously varying surfaces (radon values) and Veroni polygons (UCCS, 2005). The resulting maps are ideal for use in small area ecological studies at various resolutions, from the very broad areal extents of zip code distributions to the more precise, albeit numerically generated, distributions generated by geo-spatial analysis or thiessen polygons(3).

(4) Colorado Springs Endocrine Clinic, PC

Susan Henley, MD, the owner of Colorado Springs Endocrine Clinic and an endocrinologist practicing in Colorado Springs more or less near the center of town, provided us with a list of about 300 patients with diagnosed thyroid cancer (malignant neoplasm of the thyroid). We are sending the patients an invitation letter, on Dr. Henley's letterhead, with consent form and HIPPA authorization form. Mountain View Medical Group, Dr. Dumbacher's clinic, gave board approval for the authorization of the use of their patient population for controls.

STEPS LEADING UP TO A CASE-CONTROL STUDY

Among the various types of epidemiology studies that are available for looking for a connection between radon and thyroid cancer, three types of studies would appear to be appropriate for our purposes and all three are being considered at this time.

(1) Descriptive Geographical Studies

The first of these so-called small area studies would be to simply map the locations of patients with thyroid cancer onto a map of the Colorado Springs area, such map having the average radon concentration for that location already displayed, say as a color-coded overlay to the map. This descriptive technique could show, for example, that thyroid cancers are clustered where the radon concentration is the highest. Although such *descriptive geographical studies* are interesting, they come with many caveats. One must be very careful at how the average radon is determined and what sized geographical area that average radon is assigned to. Further, the radon concentration acts as a rather poor surrogate to the radon exposure, which is truly the parameter of interest. Also, the medical information that is being mapped may be biased because of social, economic or clinical reasons. For example, it may be that the people who are receiving treatment at the clinic, from which the cancer data is obtained, all happen to live in a certain area of town.

(3) Thiessen polygons are constructed around each radon point. The value of that radon reading is then shown as a color shade for the entire polygon around that point. All areas within that polygon are closer to that point than to any other point. So, the number and size of polygons is determined by the number of points used to construct them.

Confounders, including sex (thyroid cancer in the U.S. has a 3:1 female to male ratio) or external or internal radiation from sources other than radon can easily mask any clustering of cases that one may be hoping to see.

In our case, the 300 or so cases were mapped on to an overlay of the radon zip code information (see figure 1, below) to look for possible clustering; that is, does it appear the thyroid cases from this one clinic are grouped in the same areas of town where the radon is highest?

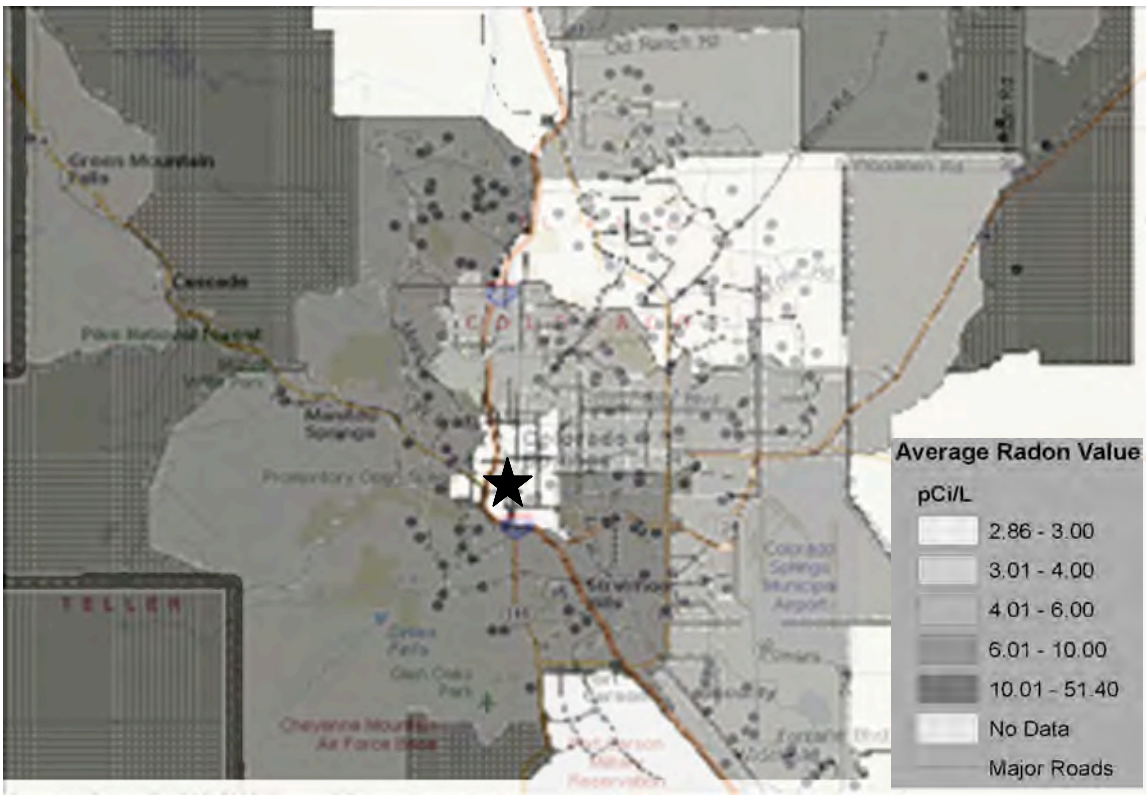

Figure 1: The small dots show the locations of the 300 thyroid cases mapped on an overlay of the average radon concentration by zip code. The location of the clinic, which diagnosed the cases, is in the center of the map, denoted with a star. The large area (in white) at the top of the map, just left of center, is the Air Force Academy, for which no data exists.

Although there is not a strong clustering, a few patterns emerge, especially to those who are familiar with the Colorado Springs area. First, the center of town, the area around the star, is almost devoid of any cases. Even though that part of town does indeed include the downtown district, which has few residences, it also includes large residential areas north and south of the star. It also corresponds to the part of the city with the lowest radon concentration. Second, there is a hint of a cluster southwest of the star, north-by-northwest of the star and south-by southeast of the star, near bottom edge of the map. These are areas of relatively high (4.01-6) and high (6.01-10) average radon concentrations. It is fair to say, however, that this map is not definitive and that, like beauty, the impact may only exist in the eye of the beholder.

(2) Ecological Study

A second type of small area study, which is probably applicable given the data we already possess, would be an *ecological study*. Here, a correlation between a variation of an environmental parameter (radon exposure) and a concomitant geographical variation in disease is looked for (Elliott, 1992). Since population data by zip code was available from the 2000 census, it was thought expedient to look for a correlation between thyroid cancer rate (number of cancers per year per 100,000 people) and average radon concentration within the same zip code. Given the number of uncertainties, no strong correlation was expected.

zip code	number of cases	population	cases per hundred thousand per year	Average Radon	
80132	11	13758	8.884	4.39	Monument
80133	1	1529	7.267	9.77	Palmer Lake
80808	4	6154	7.222	2.86	Calhan
80816	4	3555	12.502	51.4	Florissant
80817	9	16113	6.206	5.57	
80829	3	5564	5.991	9.37	Manitou
80831	6	10514	6.341	11.08	Peyton
80863	6	11367	5.865	6.33	Woodland Park
80903	7	15091	5.154	3.24	Stratton Meadows
80904	9	19652	5.089	7.54	Garden of the Gods
80906	19	49059	4.303	8.74	Broadmoor
80907	10	27421	4.052	5.13	
80908	6	9222	7.229	7.06	
80909	13	37510	3.851	4.27	
80910	9	26217	3.814	6.18	
80911	16	29618	6.002	4.88	Security
80915	11	20357	6.004	4.48	Cimmaron Hills
80916	8	33812	2.629	4.37	
80917	16	30378	5.852	3.31	
80918	24	49575	5.379	3.41	Pikeview
80919	26	28211	10.240	6.03	Rockrimmon
80920	19	32007	6.596	4.34	
80921	4	8255	5.384	5.53	
80922	10	12997	8.549	3.63	
80925	3	2602	12.811	3.91	
80926	2	1581	14.056	11.14	

Table 2: A listing of thyroid cancer incidence and average radon, by zip code. All cases came from only one clinic.

Using only the cases from the Colorado Springs Endocrine clinic, the number of cases within each zip code was divided by the population of that zip code and divided, once again, by 9 years, since the medical information indicated that the cases had been diagnosed over the previous 9 years. It can be seen that the incidence in some of the zip codes mirrors that of the national average, from two cancers per 100,000 per year to nine cases per 100,000 per year. However, some zip codes are higher, from 10 to 14 cases per 100,000 per year. Understanding that the true number of thyroid cancers must, of necessity, be higher than what we are mapping (because there are many other clinics in town) and understanding that there are many biases which are built in to this kind of study, nonetheless, a regression analysis done on this data shows a surprising correlation of $r = 0.44$ with a confidence level of 95 % ($p = 0.025$). The relative risk can be obtained from the slope of the regression line and is found to be 0.14 thyroid cancers per 100,000 people per year per picoCuries/liter.

Because of the ability of the UCCS GES lab to create surrogate radon values using various kinds of interpolation techniques, and because we are (theoretically) able to contact the cases and determine how long they lived in their house, it is possible that an in-depth ecological study may soon be instituted. Unlike the radon concentration/thyroid cancer incidence regression analysis reported above, this study would look for a correlation between thyroid cancer incidence rates and radon exposure. Radon exposure would be calculated using the surrogate radon value calculated for the actual home address multiplied by the number of years the patient lived at that address. Although this would still be an ecological study and would tend to have many of the biases of an ecological study (the so-called ecological fallacies) using an interpolated radon value and the actual residence time as a surrogate to exposure is actually an attractive feature of an ecological study because the error in measuring exposures for an individual is actually greater than the error in measuring exposure for populations (Elliott, 1992).

A CASE-CONTROL STUDY

Our hope is that a true case-control study can be done using the data we have on hand and are able, at least in theory, to obtain. With the help of Elizabeth Barrett-Connor, M.D., an epidemiologist/physician at University of California, San Diego and Dr. R. William Field, from the College of Public Health and the University of Iowa, Iowa City, Iowa, an initial plan of a case-control study has been drafted. The cases will be, of course, the 300 or so patients from the local clinic. They will each be interviewed by phone to determine several factors, including time in residence, smoking habits and area (floor) of the home in which they spend the most time. Radon concentration will be determined by either a short-term charcoal canister or a yearlong alpha track detector. The latter is appearing more likely as the study nears a start date. This is because (1) short-term tests tend to overestimate the annual concentration and (2) the logistics of getting all participants to test over the same time period, perhaps even over the same 48 hours, in order to eliminate temperature, weather and seasonal variations, seems insurmountable. We envision about 300 controls. These controls will be picked from the patient list at the Mountain View Medical group and chosen so that they mirror the cases, as much as possible, in age, gender and geographical distribution. Because no information exits concerning the exposure to radon gas and thyroid cancer, it was thought prudent to limit participants to people who have lived in their homes for at least 3 years prior to the diagnosis of thyroid cancer or, in the case of controls, people who have lived in the same house for three or more years.

Statistics will be performed on the resultant data, looking for a potential increase in thyroid cancer among those who have higher radon exposures, with the intention of looking for a means difference in the two populations (cases and controls) and, finally, formulating a relative risk if such a risk is found.

From our initial work in setting up the study, it is already clear that getting the patients to agree to participate in the study is a challenge. We are currently discussing various ways to increase the participation so that we will have a full slate of cases. Hopefully, their health concerns, which should already be heightened because of their diagnosis, and their willingness to be a part of something that may advance medical knowledge, will be sufficient to encourage them to become part of the case-control study.

SUMMARY

Working with information on thyroid cancer patients from a local endocrinologist, we have found a small, but not insignificant correlation (r = 0.44) between radon concentrations and thyroid cancer incidence, when looked at on a gross scale, that is, by zip code. The average radon concentrations were calculated using about 3000 short-term radon results provided by the University of Colorado-Colorado Springs radon lab and compiled and mapped by the university's GIS lab. Buoyed by this modest result, the authors are determined to further the study by upgrading to an ecological study in which the surrogate for radon exposure is found by determining the true time the person has lived in his or her residence and the radon concentration is found by sophisticated interpolation techniques. If this endeavor gives some reasonable results, we will then proceed to a small-area, hospital based case-control study. This study seems very feasible because we already have about 300 cases and a ready means to determine radon concentrations using short-term or, preferably, long-term tests.

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