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Lifetime Residential Water Source And Thyroid Cancer Risk: A Connecticut Based Case-Control Study

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INTRODUCTION

The fifth most common cancer among women in the US, thyroid cancer, has had the greatest increase in incidence rates compared to all other cancers over the last three decades (Howlader et al., 2014). Debate over the true reason for increased incidence has thus ensued, with some epidemiologists pointing to the fact that the majority of cases have been small malignancies, suggesting that this increase is due to our ability to detect sub-clinical cases at a greater rate and more precisely (Davies and Welch, 2006). This hypothesis is further spurred by a lack of recorded increased mortality rates over the same time period (Davies and Welch, 2006). Conversely, some epidemiologists argue that the increase in recorded small malignancies may also be a result of environmental or occupational exposures (e.g. diagnostic radiation and broadly military service) (Zhu et al., 2009; Enewold et al., 2011). In pursuit of clarity, Morris et al. (2013), and Udelsman and Zhang (2014) both tested to what degree access to healthcare, physicians, and diagnostic technologies (at both county and state levels) effected the rate of recorded thyroid cancer cases, and found that while 'overdiagnosis' is present, it does not explain approximately half of the variability in thyroid cancer incidence rates. These analyses have opened the door for further research regarding environmental and occupational exposures' impact on thyroid cancer diagnoses.

In 2012, Aschebrook-Kilfoy et al. explored an environmental exposure theory in several Old Order Amish communities in Pennsylvania. Their theory was based on the presence of nitrate in ground water sources and its related risk to hyper/hypo-thyroidism or other clinical thyroid disease; they found a statistically significant association of subclinical hypothyroidism to high nitrate exposure, in female Old Order Amish (Aschebrook-Kilfoy et al., 2012). Nitrate in drinking water supplies, especially in agricultural areas, has become an environmental contaminant of concern due to nitrate's ability to reduce to nitrite, which gives rise to N-nitroso compounds that are highly carcinogenic (Bogovski and Bogovski, 1981). In addition to N-nitroso compounds, the thyroid itself when exposed to nitrates becomes less proficient at Iodine uptake resulting in a reduction of thyroid hormones; to counteract this, the thyroid then releases greater amounts of thyroid stimulating hormone or TSH (Ward et al., 2010). This increased stimulation by TSH has resulted in adenoma and carcinoma in animal models (Ward et al., 2010 and Hiasa et al., 1991). Several epidemiological studies have confirmed nitrate's ability to disrupt the function of the thyroid (Tajtáková et al., 2006 and van Maanen et al., 1994)

While food intake is the greatest source of nitrate exposure for most humans, type of drinking water supply can be a good indicator of lifetime nitrate exposure, especially amongst those with high nitrate water levels (Weyer et al., 2001 and Njeze et al., 2014). Agricultural use of nitrogen rich fertilizers results in high soil nitrate levels that seep into ground water and run off into rivers and streams. In North America 50% of the total population uses ground water as their primary drinking water supply, while 90% of rural communities use the same (Aschebrook-Kilfoy et al., 2012). Regulatory standards, set by the Environmental Protection Agency, are held to a 10 mg per liter nitrate-nitrogen (NO_3-N) standard (National Academy of Sciences, 1981). While we are able to regulate municipal drinking water sources, regulatory bodies are not always able to regulate the nitrate levels in private wells. Finding or measuring long-term exposure data on nitrates in drinking water would be costly and arduous to say the least. Using a history of source type for drinking water may give more precise insight regarding long-term exposure to nitrates in drinking water in thyroid cancer patients. Substantial literature on the increased load of nitrates in private wells compared to community wells or municipality water sources, provide validity for comparisons using historical data based on the types of lifetime water sources reported (Hallberg, 1996).

Beyond the most recent cross sectional analysis of nitrate measures in current water source of the Old Order Amish, The Iowa Women's Health Study produced two studies focused on all-cancer and thyroid-specific analysis respectively, of nitrate levels in drinking water sources (Weyer et al., 2001 and Ward et al., 2010). Ward et al. (2010) looked at the current water supply source and length of time using the current water source and risk of thyroid cancer. They provided results based off of total nitrate exposure, which included dietary nitrate exposure, and found little evidence for correlation of private well use and thyroid cancer, but statistically significant test for trend for increased mean nitrate concentration in public water source and increased risk of thyroid cancer (Ward et al., 2010). While Weyer et al. (2001) did not look at thyroid cancer specifically, they did not find any clear or consistent trend between risk of cancer and municipal water nitrate levels.

The aim of this study is to use not only current water source information, but lifetime residential water source information (e.g. community water, private well water, or mixed water sources, depth of well sources, and total length of time exposed to private well water sources), while controlling for various confounders (e.g. workplace water source, other dietary sources of nitrate, vitamin E/C supplementation, etc.) to assess risk to thyroid cancer in a more generalizable case-control design.

METHODS

STUDY DESIGN

Individuals from Connecticut, diagnosed between 2010 and 2011 with histologically confirmed incident thyroid cancer [papillary (ICD-O-3: 8050, 8052, 8130, 8260, 8340–8344, 8450, and 8452), follicular (ICD-O-3: 8290, 8330–8332, and 8335), medullary (ICD-O-3: 8345, 8346, and 8510), or anaplastic (ICD-O-3: 8021)] were enrolled as cases. Identification of cases occurred via the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA), part of the Connecticut Tumor Registry. All licensed hospitals and clinical laboratories have mandatory reporting requirements per The Connecticut Public Health Code to the Connecticut Tumor Registry. RCA field staff identified newly diagnosed cases in non-pediatric hospitals throughout the state. This information was then regularly updated by RCA data-entry staff via input, verification, and screening against the Connecticut Tumor Registry database. Reciprocal reporting agreements between Connecticut and adjacent states (as well as Florida) allowed us to identify residents of Connecticut treated and/or diagnosed in these surrounding states. A total of 462 (65.9%) of the 701 eligible incident thyroid cancer cases identified during the study period, completed in-person interviews. Eligible cases ranged in age from 21 to 84 years at time of diagnosis, had not been previously diagnosed with cancer (exception given to those with non-melanoma skin cancer), and were living at the time interviews were conducted. Connecticut residents recruited as population-based controls were found via the random digit dialing method. A total of 498 (61.5%) of recruited controls participated in the study. Cases and controls were frequency-matched by age (± 5 years).

An approval from both, Yale University and Connecticut Department of Public Health, Human Investigations Committees was granted for all protocols executed. Physician and hospitals approval for enrollment was granted. All potential participants were contacted via letter and then via phone call. Participants were then interviewed in their homes or at a convenient locale by trained study interviewers. Once written consent was given, a standardized, structured questionnaire was administered to obtain lifetime water source information, occupational water source information, and other major known or suspected risk factors that may have confounded the relationship between lifetime water source exposure and risk of thyroid cancer.

QUESTIONNAIRE and EXPOSURE ASSESSMENT

With regard to lifetime water source exposures, the participants were asked several questions about each home address they listed, including "What was the primary source of drinking water at this home?", "What was the depth of the private well?", and "Do/did you use any of the following to treat your water at home?" (Table 10). Participants were then categorized into several categories based on their total recorded lifetime water history (Table 2), including:

(a) Ever private well, ever community, and ever bottled/ other water sources

(b) Always private well, always community, and always bottled/ other water sources

(c) Mixed lifetime water source

(d) Long-term (>20 years) private well, long-term community, and long-term bottled/ other water sources with no alternate source for >20 years

(e) Long-term (>20 years) private well and also long-term community sources, with no (or <20 years) bottled/ other sources

(f) Long-term (>20 years) private well and long-term bottled/ other sources, with no (or <20 years) community sources

(g) Long-term (>20 years) community and long-term bottled/other sources, with no (or <20 years) private well sources

(h) No private well water source (or <1 year of private well source), 1-10 years, 11-20 years, and >20 years private well water source

(i) No private well source (or <21 years well source), 21-40 years, 41-60 years, 61-80 years private well source

(j) 1st water source private well, 1st water source community source, and 1st source bottled or other source

(k) Well depth < 50 feet, well depth 50-150 feet, well depth 151-250 feet, well depth 251-500 feet, and well depth > 500 feet

These exposure categories of time for any given source were defined using the sum of all years with those sources in an individual's lifetime water source history. A two year exposure lag time, subtracted from the date of diagnosis, was applied to all cases. Depth of private well category was defined by the deepest recorded private well in an individual's lifetime water source history. First water source was defined by the first reported source in an individual's lifetime water source history.

INCLUSION

Only those (both cases and controls) with water source histories without gaps in type of source or years lived at home were included in analyses. Of the 462 eligible incident thyroid cancer cases that completed interviews, 444 (96.1%) had complete lifetime water source histories and were included in analyses. Of the 498 controls that participated in the study, 485 (97.4%) had complete lifetime water source histories and were included in analyses. Cases had a mean residential lifetime water source history of 48 years (ranging from 14-81 years), while controls had a mean residential water source history of 52 years (ranging from 19-79 years).

STATISTICS

This analysis being the first of its kind to attempt to record lifetime water source as a surrogate to lifetime nitrate exposures from water source, explored multiple definitions of 'exposed,' focusing on length of years with private well water (compared to little or no years exposed), depth of private well (compared to most shallow depth), always, long-term, and ever use of private well water (compared to always community water source) (Table 4). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression models to estimate the associations between the various exposures and the risk of thyroid cancer, while controlling for potential confounders.

Confounding variables used in the final models included age, gender, and education level, diagnosis of prior benign thyroid disease, family history of thyroid cancer, BMI, smoking status, alcohol consumption, occupational water source type, and nitrate-rich meat consumption. Adjustment for other variables, such as family per capita income, racial identity, nitrate-rich vegetable consumption, radiation exposure, vitamin E supplementation, and vitamin C supplementation did not significantly affect the observed associations, and thus they were not included in the final models. Decisions on the covariates to be included in the final models were based on a greater than 10% change in the risk estimates. All tests of statistical significance were two-sided. All analyses were carried out using SAS (version 9.3; SAS Institute Inc., Cary, North Carolina, USA).

Some covariates not intuitively defined were designed thusly (Table 1 and 1b): Family per capita income was limited to three categories (low, medium, and high) defined by a per capita income <$25,000, ≥$25,000 - <$50,000, and ≥$50,000 respectively. Occupational water source was limited to those with at least a fulltime status of occupation (≥40 hours/ week) and was defined by the occupational source type that was reported for the greatest length of time. Vitamin C and E supplementation were defined separately as yes or no based on whether the individual reported taking

vitamin C or E supplements (not in a multi-vitamin) in the past 30 days. Radiation exposure was defined yes or no based on whether ever receiving therapeutic or diagnostic radiation. Smoking status was defined yes or no based on ever smoking a total of 100 cigarettes or more. Alcohol consumption was defined yes or no based on ever consumption of more than 12 drinks of alcoholic beverages such as beer, wine, or liquor, with 1 drink of beer = 1 can or bottle, 1 drink of wine = 14 oz glass, and 1 drink of liquor = 1 shot. Nitrate-rich meat consumption was limited to low, medium, and high, defined by tertiles of amount and frequency of consumption of various meats, such as turkey or chicken cold cuts, luncheon or deli-style ham, other cold cuts or luncheon meats, hot dogs, frankfurters, liverwurst, bacon, and sausage. Nitrate-rich vegetable consumption was limited to low, medium, high, defined by tertiles of amount and frequency of consumption of various vegetables, such as vegetable juice, spinach, turnips, collards, mustard, chard, kale, coleslaw, sauerkraut, cabbage, carrots, lettuce salads, pickled vegetables and potatoes.

RESULTS

As stated previously, 444 cases and 485 controls were included in the analyses of residential lifetime water source and incident thyroid cancer risk. The mean age at diagnosis of thyroid cancer was 51 years. Cases were much more likely to be female, obese, non-drinkers, with lower levels of education attainment (Table 1). They were more likely to have lower rates of vitamin C supplementation, and lower rates of nitrate-rich vegetable consumption (Table 1b). They were also more likely to have a prior benign thyroid disease, and a family history of thyroid cancer among first-degree relatives than controls (Table 1). Family income per capita, race, occupational fulltime water source type, vitamin E supplementation, radiation exposure, and smoking status were not significantly different between cases and controls (Tables 1 and 1b). While water filtration information was collected in the questionnaire, none of the 929 participants reported filtration usage.

All comparisons yielded associations that were not statistically significant predictors of incident thyroid cancer diagnosis (Table 3). Those individuals reporting ever living at a residence(s) with a private well water source were not statistically significantly more likely to be diagnosed with thyroid cancer when compared to individuals who reported always having a community water source (OR = 0.96, 95% CI: 0.70-1.31, Table 3). Those individuals reporting a mixed water source history of any kind were not statistically significantly more likely to be diagnosed with thyroid cancer when compared to individuals who reported always having a community water source (OR = 0.94, 95% CI: 0.69-1.29, Table 3). Those individuals reporting both living at a residence(s) with a private well water source for >20 years and living at a separate residence(s) in their lifetime with a community water source for >20 years, were not statistically significantly more likely to be diagnosed with thyroid cancer when compared to individuals who reported always having a community water source (OR = 1.44, 95% CI: 0.85-2.43, Table 3).

In comparing length of time with private well water, those reporting living at a residence(s) with a private well source >20 years were not statistically significantly at greater risk for diagnosis of thyroid cancer compared to those never having a private well or having a private well <1 year (OR = 1.05, 95% CI: 0.72-1.53, Table 3). This was also the case for those reporting a private well water source for 1-10 years and 11-20 years respectively (OR = 0.80, 0.97, 95% CI: (0.51-1.27), (0.61-1.55), Table 3). A Cochran-Armitage test for trend was applied to this category, but again no significance was yielded at the alpha = 0.05 level (p-value = 0.81, Figure 1). These intervals for length of total time with private well water source do not show a pattern of dose response based on the test for trend.

Looking at only the individuals with >20 years of private well usage, those reporting 21-40 years of private well water were not statistically significantly more or less likely to be diagnosed with thyroid cancer compared to those with 20 years or less (OR = 1.10, 95% CI: 0.75-1.60, Table 3). This was also the case for those reporting private well usage for 41-60 years and 61-80 years respectively (OR = 0.86, 0.49, 95% CI: (0.46-1.63), (0.13-1.85), Table 3). A Cochran-Armitage test for trend was also applied to this category and no significance was observed (p-value = 0.94, Figure 2). These higher intervals for length of time with private well water source do not show a pattern of dose response based on the test for trend.

All participants reported either private well or community water source as their first water source exposure. However, there was no significant relationship between private well water used as first water source compared to community water source (OR = 1.18, 95% CI: 0.79-1.78, Table 3). An analysis of depth of well (amongst those reporting ever well and providing well depth information) revealed no significant relationship between depth of well used and risk of thyroid cancer (Table 3). A Cochran-Armitage test for trend was then used to compare these depths as well, yielding no significant trend (p-value = 0.88, Figure 3).

Sub-analyses by tumor type and tumor size all yielded non-significant associations (Table 4, Table 5). The majority of cases enrolled were diagnosed with papillary tumors. Analyses of the above categories were all conducted for only those with papillary type tumors (minus 1st water source analysis, due to sample size, Table 4). Analyses of the above categories were also conducted for those with well-differentiated tumors (papillary and follicular, Table 4). Analyses by tumor size was split between those with smaller tumors (≤10 mm) and those with larger tumors (<10mm) and was only amonst those with well-differentiated tumor type (Table 5).

One relationship in sub-analyses was significant at the alpha = 0.05 level with a p-value of 0.0096. Amongst those diagnosed with a well differentiated tumor ≤10 mm, those with private well for >20 years and community sources for >20 years were statistically significantly more likely to be diagnosed with thyroid cancer compared to those with just always community water source (OR = 3.30, 95% CI: 1.49-7.31, Table 5).

DISCUSSION

Our study has not only further confirmed previous findings' measuring the lack of potency nitrates in drinking water have to effect thyroid cancer risk, but has added to the strength of the literature by analyzing lifetime water sources in this large case-control design. While using lifetime water source as a surrogate for nitrate exposures cannot provide a clear dose-response relationship like a prospective design would, it has the greatest potential to capture risk of disease from exposure with such a long latency period. Due to this advantage, our analyses provides strong insight for the base of literature continuing to investigate the spike in thyroid cancer incidence over the last twenty years. However, crude exposure assessment coupled with no quantitative nitrate exposure modeling leaves the study open to non-differential exposure misclassification.

The single statistically significant finding of increased risk of thyroid cancer amongst those with well-differentiated tumors ≤10 mm may be a predictor of how water source exposures relate to small size malignancies. However, this analyses did not adjust for multiple comparisons, the sample size of this particular group was small (n=14) and may have been due to random chance. It is unclear presently is the 0.0096 p-value would hold up under a Bonferroni correction.

Inclusion of all participants with water source histories without gaps may be a limitation. Not all participants reported water histories since birth, however a mean length of water source histories equal to 50 years and a minimum of 19 years suggests that even those unable to report since birth were able to report a large portion of their lives. Due to the questionnaire format of our study, reporting and memory bias may be of concern.

Using a Food Frequency Questionnaire to define exposures to nitrate-rich vegetables and meats presented as a challenge. Categories of low, medium, and high nitrate-rich vegetable consumption were defined based on amount and frequency of consumption of various vegetables, such as vegetable juice, spinach, turnips, collards, mustard, chard, kale, coleslaw, sauerkraut, cabbage, carrots, lettuce salads, pickled vegetables and potatoes. These vegetables outlined as highly nitrate-rich in previous literature (Meah et al., 1994 & Pennington, 1998). Categories for low, medium, and high nitrate-rich meat consumption were defined based on amount and frequency of consumption of various meats, such as turkey or chicken cold cuts, luncheon or deli-style ham, other cold cuts or luncheon meats, hot dogs, frankfurters, liverwurst, bacon, and sausage. These meats outlined as highly nitrate-rich in previous literature (Meah et al., 1994 & Pennington, 1998).

Filtration of water sources was not included in the analyses as either a confounder or as its own separate comparison due to no one individual reporting using a filtration device of any kind. This lack of reporting of filtration may be due to participant's inability to remember type or the age of the participant. Elders may not have readily had access to in-home filtration methods such as membrane filtration. Interestingly, nitrate-rich meats were a significant predictor in all models, however nitrate rich vegetables were not. Some epidemiologists postulate that nitrates' effects on our bodies are stifled by consumption of vitamin E and C. This would explain why vegetables were less of a predictor than meats (Meah et al., 1994 & Pennington, 1998). Because of this hypothesis controlling for vitamin E and C supplementation seemed to be a good idea, however neither were significant confounders in any models. Because nitrate-rich meats were such a strong predictor in every model, it would seem most logical that this exposure should be investigated more fully as a predictor of thyroid cancer risk with regard to nitrate exposure load for humans. The great majority of nitrates consumed by humans comes from our food, which makes it extremely difficult to capture how nitrates in drinking water may effect nitrate related disease.

Surprisingly, family history of thyroid cancer was not a strong predictor in any models, except for amongst those is ≤10mm. While a family history is not the strongest predictor of genetic susceptibility it is widely used for cancer studies. A personal history of thyroid disease diagnosis was a much stronger predictor of cancer diagnosis in all models.

This study was conducted amongst those serviced in the catchment area of Connecticut's tumor registry. Previous studies, such as the Iowa Women's Health study focused on a population that is much more likely to be exposed to an agricultural landscape than that found in Connecticut. Due to agricultural processes, nitrates seeping into ground water may be of a bigger concern in those communities. The generalizability of this analysis reaches to other states along the eastern seaboard with similar demographics and water resources. However, because of the lifetime water source histories collected those enrolled from Connecticut's catchment area were analyzed for exposures from sources elsewhere throughout their lives.

CONCLUSION

We fail to reject our null hypothesis that lifetime residential water source is not associated with an increased risk of thyroid cancer. This study provides new evidence showing a lack of association between residential lifetime drinking water source and the risk of thyroid cancer. While a small association was seen amongst those with long-term use of both community and private well sources, we believe this association may be due to the small number of people who had confirmed having both sources for such an extended period of time and the effect of multiple-comparisons. Further research should investigate the difference in exposure histories for small and large tumor types amongst those with papillary and follicular tumor types. Further study of measured nitrate levels in various water source environments in a prospective fashion could add to our understanding of this particular exposure. Especially when coupled with a more detailed measure of dietary nitrate consumption as a covariate.

APPENDIX

Table 1. Distributions of selected descriptive characteristics of the study population.

	Cases (n=444) [N (%)][A]	Controls (n = 485) [N (%)][A]	P-value[B]
Age (years)			<0.01
Mean (SD)	51 (12.1)	54 (13.0)	
< 40	79 (17.8)	62 (12.8)	
40-49	108 (24.3)	110 (22.7)	
50-59	145 (32.7)	133 (27.4)	
60-69	76 (17.1)	100 (20.6)	
≥ 70	30 (6.8)	70 (14.4)	
Sex			<0.01
Female	361 (81.3)	336 (69.3)	
Male	83 (18.7)	149 (30.7)	
Race			0.47
White	400 (90.1)	440 (90.7)	
Black	17 (3.8)	23 (4.7)	
Other	27 (6.1)	22 (4.5)	
Years of education			<0.01
High school or less	125 (28.2)	85 (17.5)	
College	213 (48.0)	258 (53.2)	
Graduate school	94 (21.2)	128 (26.4)	
Tobacco Smoking[C]			0.25
No	306 (68.9)	317 (65.4)	
Yes	138 (31.1)	168 (34.6)	
Alcohol Consumption[D]			<0.01
No	257 (57.9)	223 (46.0)	
Yes	187 (42.1)	262 (54.0)	
Family income *per capita*			0.83
Low	126 (28.4)	128 (26.4)	
Medium	110 (24.8)	130 (26.8)	
High	71 (16.0)	82 (16.9)	
Confidential or Unknown	137 (30.9)	145 (30.0)	
BMI (kg/m^2)			<0.01
< 25	136 (30.6)	200 (41.2)	
25-29	122 (27.5)	146 (30.0)	
≥ 30	185 (41.7)	136 (28.0)	
Family history of thyroid cancer among first degree relatives			0.03
No	390 (87.8)	447 (92.2)	
Yes	54 (12.2)	38 (7.8)	
Prior benign thyroid disease[E]			<0.01
No	386 (86.9)	472 (97.3)	
Yes	58 (13.1)	13 (2.7)	

[A]Percentages may not sum to 100 due to rounding and missing values. Totals may not sum to n due to missing values.

[B]P-values are for χ^2 test.

[C]Ever smoking was defined as ever smoked a total of 100 cigarettes or more.

[D]Ever alcohol consumption was defined as ever had more than 12 drinks of alcoholic beverages such as beer, wine, or liquor. 1 drink of beer = 1 can or bottle; 1 drink of wine = 14 oz glass; 1 drink of liquor = 1 shot.

[E]Benign thyroid disease included hyperthyroidism, hypothyroidism, goiter, thyroid nodules, and thyroid adenoma.

Table 1b. Continued distributions of selected descriptive characteristics of the study population.

	Cases (n=444) [N (%)][A]	Controls (n = 485) [N (%)][A]	P-value[B]
Occupational fulltime job water source[C]			0.22
Well source	4 (0.9)	8 (1.6)	
Community source	193 (43.5)	187 (38.6)	
Bottled or Other source	0 (0.0)	0 (0.0)	
Vitamin C supplementation[D]			0.05
No	347 (78.2)	352 (72.6)	
Yes	97 (21.8)	133 (27.4)	
Vitamin E supplementation[D]			0.44
No	398 (89.6)	427 (88.0)	
Yes	46 (10.4)	58 (12.0)	
Radiation exposure[E]			0.16
No	34 (7.7)	50 (10.3)	
Yes	410 (92.3)	435 (89.7)	
Nitrate-rich meat consumption			<0.01
Low	197 (44.4)	170 (35.1)	
Medium	143 (32.2)	217 (44.7)	
High	104 (23.4)	98 (20.2)	
Nitrate-rich vegetable consumption			0.03
Low	124 (27.9)	109 (22.5)	
Medium	245 (55.2)	271 (55.9)	
High	75 (16.9)	105 (21.6)	

[A]Percentages may not sum to 100 due to rounding and missing values. Totals may not sum to n due to missing values.

[B]P-values are for χ^2 test.

[C]Fulltime job water source defined as water source at a job worked at least 40 hours/ week longer than any other occupational source.

[D]Vitamin supplementation defined as taking vitamin C or E, besides in a multi-vitamin, in the 30 days prior to interview.

[E]Radiation exposure defined as ever receiving either therapeutic or diagnostic radiation.

Table 2. Summary of lifetime residential water sources.

	Cases (n=444) [N (%)][A]	Controls (n = 485) [N (%)][A]
Ever well source	229 (51.6)	247 (50.9)
Ever community source	432 (97.3)	470 (96.9)
Ever bottled source	7 (1.6)	12 (2.5)
Ever other source	1 (0.2)	3 (0.6)
Always well source	10 (2.3)	14 (2.9)
Always community source	197 (44.4)	215 (44.3)
Always bottled or other source	7 (1.6)	14 (2.9)
Mixed lifetime water source	230 (51.8)	242 (50.0)
Well source >20 years, no alternate source >20 years	62 (14.0)	51 (10.5)
Community source >20 years, no alternate source >20 years	325 (73.2)	352 (72.6)
Bottled or Other source >20 years, no alternate source >20 years	1 (0.2)	2 (0.4)
Well, Community, and Bottled or Other sources >20 years each	0 (0.0)	0 (0.0)
Well and Community sources >20 years, no or <20 years of Bottled or Other source	42 (9.5)	65 (13.4)
Community and Bottled or Other sources >20 years, no or <20 years of Well source	0 (0.0)	1 (0.2)
Well and Bottled or Other sources >20 years, no or <20 years of Well source	0 (0.0)	1 (0.2)
No well source or <1 year well source	221 (49.8)	243 (50.1)
Well source 1-10 years	63 (14.2)	62 (12.8)
Well source 11-20 years	56 (12.6)	63 (13.0)
Well source >20 years	104 (23.4)	117 (24.1)
No well source or <21 years well source	340 (76.6)	368 (75.9)
Well source 21-40 years	76 (17.1)	85 (17.5)
Well source 41-60 years	22 (5.0)	27 (5.6)
Well source 61-80 years	6 (1.4)	5 (1.0)
1st source private well	74 (16.7)	76 (15.7)
1st source community source	369 (83.1)	408 (84.1)
1st source bottled or other source	1 (0.2)	1 (0.2)
Well depth		
< 50 feet	11 (2.5)	13 (2.7)
50-150 feet	22 (4.5)	29 (6.0)
151-250 feet	19 (4.3)	21 (4.3)
251-500 feet	16 (3.6)	23 (4.7)
> 500 feet	7 (1.6)	9 (1.9)

[A] Percentages may not sum to 100% due to rounding and missing values. Totals may not sum to N due to missing values.

Table 3. Associations between lifetime water source and risk of thyroid cancer.

	Cases (n=444)	OR (95% CI) [A]
Ever well source	229	0.96 (0.70-1.31)
Always community source	197	1.00
Mixed water source	230	0.94 (0.69-1.29)
Always community source	197	1.00
Well and Community sources >20 years, no or <20 years of Bottled or Other source	42	1.44 (0.85-2.43)
Always community source	197	1.00
No well source or <1 year well source	221	1.00
Well source 1-10 years	63	0.80 (0.51-1.27)
Well source 11-20 years	56	0.97 (0.61-1.55)
Well source >20 years	104	1.05 (0.72-1.53)
No well source or <21 years well source	340	1.00
Well source 21-40 years	76	1.10 (0.75-1.60)
Well source 41-60 years	22	0.86 (0.46-1.63)
Well source 61-80 years	6	0.49 (0.13-1.85)
1st source private well	74	1.18 (0.79-1.78)
1st source community source	369	1.00
Well Depth		
<50 feet	11	1.00
50-150 feet	22	1.34 (0.41-4.37)
151-250 feet	19	1.82 (0.51-6.45)
251-500 feet	16	2.66 (0.73-9.71)
> 500 feet	17	2.41 (0.49-11.91)

[A] Adjusted for age (< 40, 40-49, 50-59, 60-69, ≥ 70), gender (male, female), education level (<college, college, >college), BMI (<25, 25-29, ≥30), smoking status (yes, no), previous benign thyroid disease (yes, no), and nitrogenous meat consumption (Low, Medium, High).

Table 4. Associations between lifetime water source and risk of thyroid cancer by tumor type.

	Papillary		Well differentiated	
	Cases	OR (95% CI) [A]	Cases	OR (95% CI) [B]
Ever well source	191	1.02 (0.74-1.42)	220	0.98 (0.71-1.34)
Always community source	168	1.00	193	1.00
Mixed water source	192	1.00 (0.72-1.38)	221	0.96 (0.70-1.32)
Always community source	168	1.00	193	1.00
Well and Community sources >20 years, (no or <20 years of Bottled or Other source)	34	1.54 (0.88-2.69)	39	1.48 (0.87-2.53)
Always community source	168	1.00	193	1.00
No well source or <1 year well source	190	1.00	217	1.00
Well source 1-10 years	51	0.88 (0.54-1.43)	59	0.85 (0.53-1.35)
Well source 11-20 years	46	1.08 (0.66-1.77)	55	0.98 (0.61-1.57)
Well source >20 years	88	1.12 (0.75-1.67)	100	1.06 (0.73-1.55)
No well source or <21 years well source	287	1.00	331	1.00
Well source 21-40 years	64	1.11 (0.75-1.66)	73	1.11 (0.76-1.63)
Well source 41-60 years	20	0.81 (0.42-1.56)	21	0.86 (0.45-1.65)
Well source 61-80 years	4	0.57 (0.13-2.50)	6	0.46 (0.12-1.72)

[A] Adjusted for age (< 40, 40-49, 50-59, 60-69, ≥70), gender (male, female), education level (<college, college, >college), BMI (<25, 25-29, ≥30), alcohol consumption (yes, no), previous benign thyroid disease (yes, no), and nitrogenous meat consumption (Low, Medium, High).

[B] Adjusted for age (< 40, 40-49, 50-59, 60-69, ≥70), gender (male, female), education level (<college, college, >college), BMI (<25, 25-29, ≥30), smoking status (yes, no), previous benign thyroid disease (yes, no), and nitrogenous meat consumption (Low, Medium, High).

Table 5. Associations between lifetime water source and risk of well-differentiated thyroid cancer by tumor size.

	Tumor Size ≤ 10 mm		Tumor Size > 10 mm [B]	
	Cases	OR (95% CI) [A]	Cases	OR (95% CI)
Ever well source	103	1.12 (0.75-1.66)	115	0.85 (0.59-1.23)
Always community source	94	1.00	97	1.00
Mixed water source	107	1.07 (0.72-1.60)	113	0.87 (0.60-1.25)
Always community source	94	1.00	97	1.00
Well and Community sources >20 years, (no or <20 years of Bottled or Other source)	14	3.30 (1.49-7.31)*	25	0.85 (0.47-1.54)
Always community source	94	1.00	97	1.00
No well source or <1 year well source	104	1.00	111	1.00
Well source 1-10 years	24	0.96 (0.52-1.78)	34	0.75 (0.44-1.28)
Well source 11-20 years	33	0.83 (0.48-1.44)	22	1.34 (0.74-2.45)
Well source >20 years	45	1.33 (0.81-2.18)	54	0.79 (0.51-1.24)
No well source or <21 years well source	161	1.00	167	1.00
Well source 21-40 years	30	1.57 (0.94-2.61)	43	0.84 (0.53-1.33)
Well source 41-60 years	11	0.93 (0.42-2.07)	9	0.75 (0.32-1.73)
Well source 61-80 years	4	0.41 (0.08-1.99)	2	0.29 (0.05-1.81)

* Statistically significant p-value at alpha = 0.05 level, p-value = 0.0096.

[A] Adjusted for age (< 40, 40-49, 50-59, 60-69, ≥70), gender (male, female), education level (<college, college, >college), BMI (<25, 25-29, ≥30), family history of thyroid cancer (yes, no), previous benign thyroid disease (yes, no), and nitrogenous meat consumption (Low, Medium, High).

[B] Adjusted for age (< 40, 40-49, 50-59, 60-69, ≥70), BMI (<25, 25-29, ≥30), alcohol consumption (yes, no), occupational water source (private well or community source) and previous benign thyroid disease (yes, no).

Figure 1. The distribution of thyroid cancer cases and controls by years of private well water source (lower range).

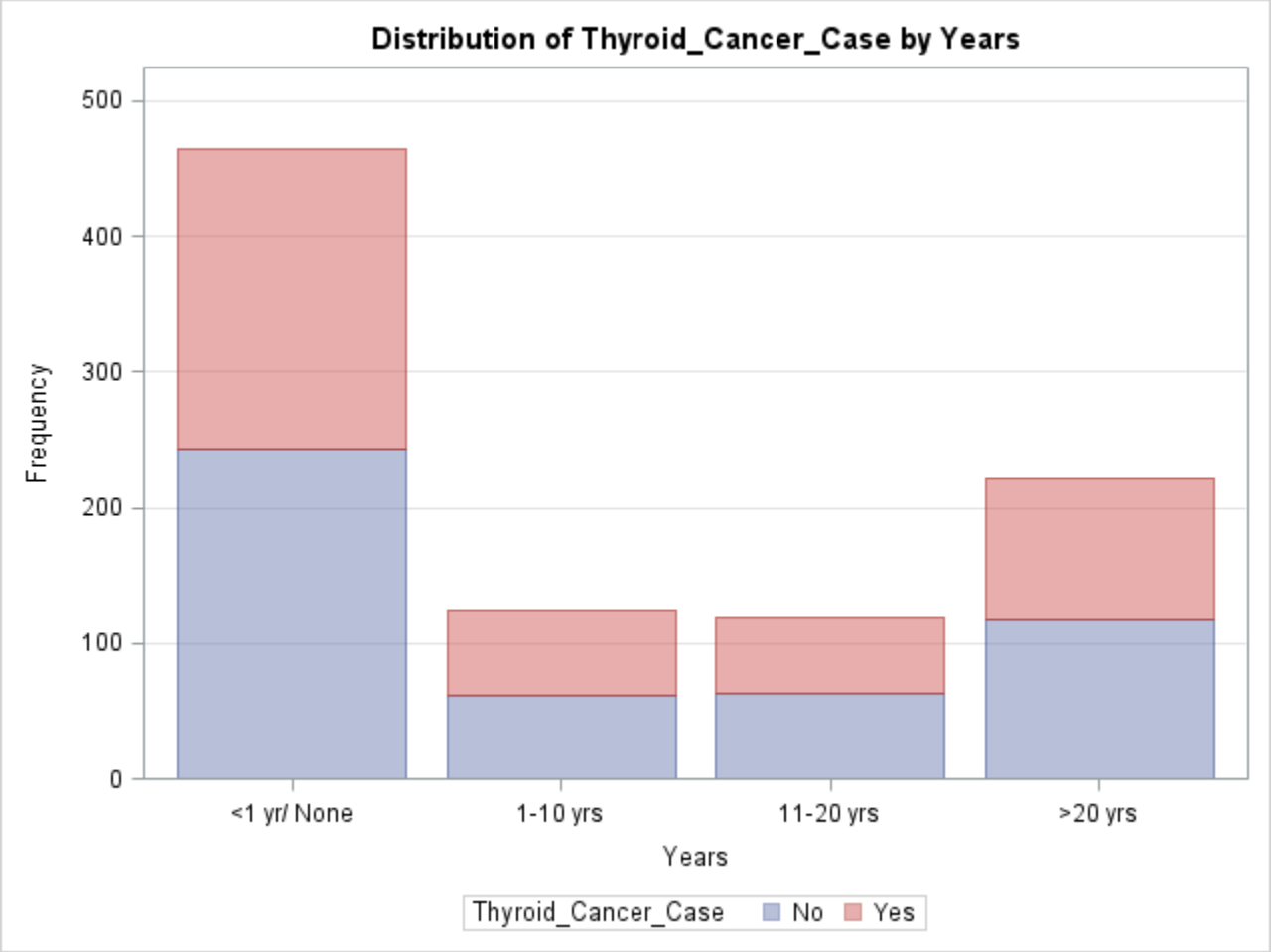

Table 6. Statistics for thyroid cancer by years of private well water source (lower range): Cochran-Armitage Trend Test

Statistic (Z)	0.2428
One-sided Pr < Z	0.4095
Two-sided Pr ≥ |Z|	0.8105

Figure 2. The distribution of thyroid cancer cases and controls by years of private well water source (upper range).

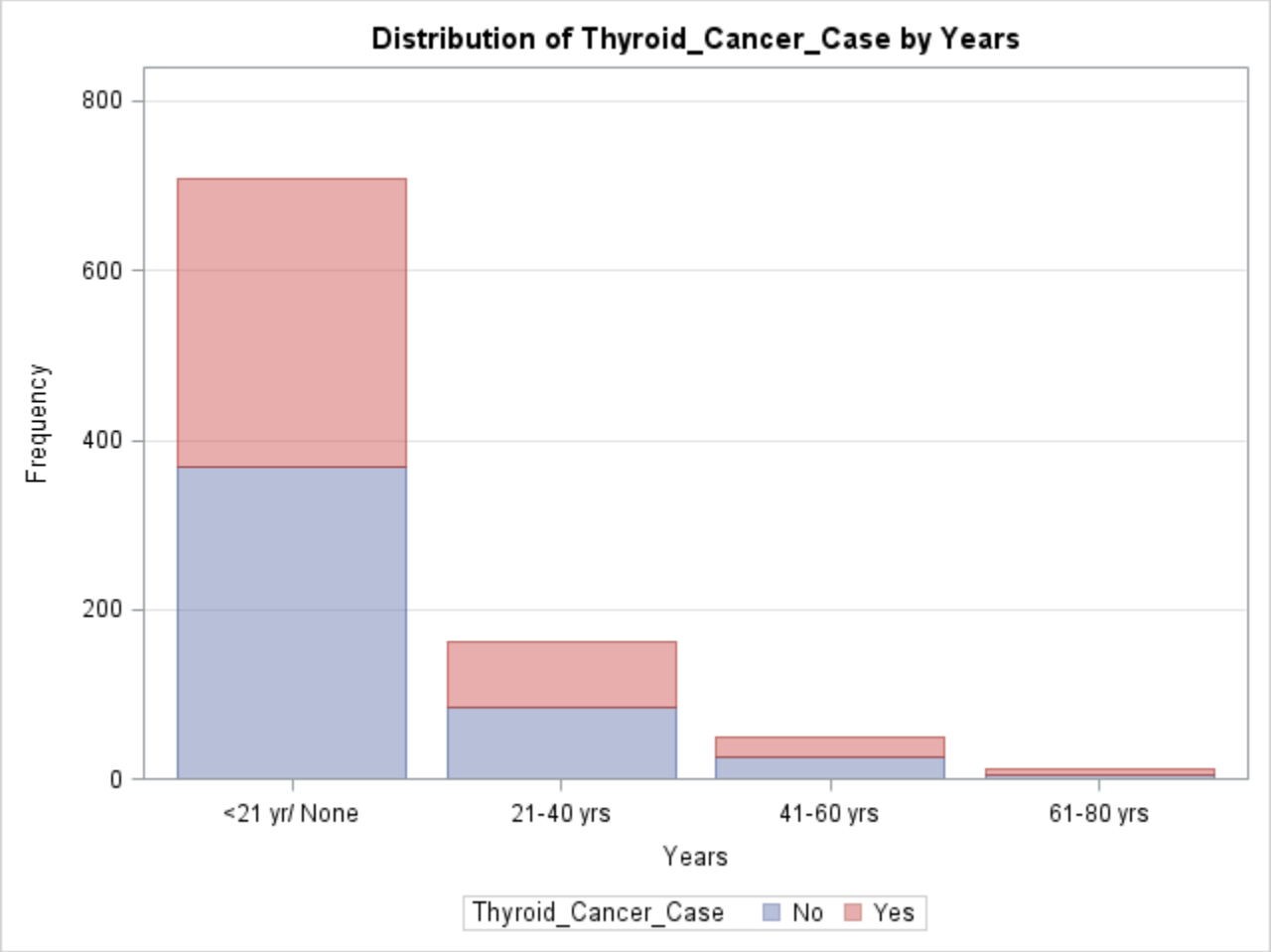

Table 7. Statistics for thyroid cancer by years of private well water source (upper range): Cochran-Armitage Trend Test

Statistic (Z)	0.1100
One-sided Pr < Z	0.4716
Two-sided Pr ≥ |Z|	0.9414

Figure 3. The distribution of thyroid cancer cases and controls by private well depth.

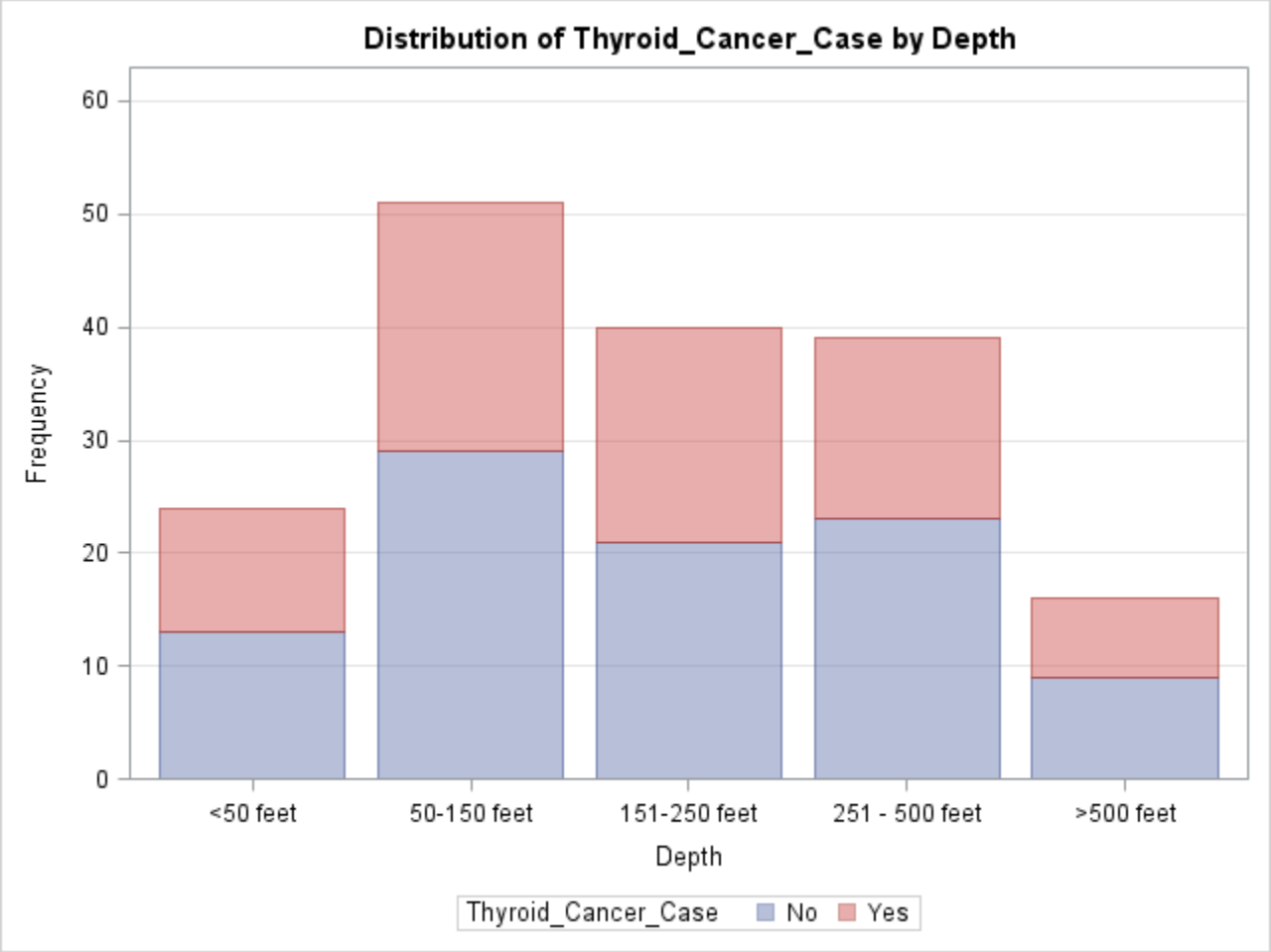

Table 8. Statistics for thyroid cancer by private well depth: Cochran-Armitage Trend Test

Statistic (Z)	0.1625
One-sided Pr < Z	0.4411
Two-sided Pr ≥ |Z|	0.8759

Table 9. Questionnaire formatting for lifetime water source information.

G1. Year

G2. Age

G3. Home Address (NUMBER,STREET, CITY, STATE, ZIP)

G4. What was the primary source of drinking water at his home? (CIRCLE ONE NUMBER.)

1.Private Well (GO TO **G5**)

2.Community Supply (GO TO **G1**)

3.Bottled Water

4.other (specify)

G5. What was the depth of the private well (CIRCLE ONE NUMBER.)

1. Less than 50 Feet
2. 50-150 Feet
3. 151-250 Feet
4. 251-500 Feet
5. 501 Feet or More
6. Don't know

G6. Do/did you use any of the following to treat your water at home? (Is/Was) it treated with:

a. Membrane cartridge or filter
b. A charcoal filter
c. Reverse osmosis
d. A water softener
e. Distillation
f. Something else (SPECIFY)
g. Unknown

G7. (Is/Was) the (TREATMENT IN H6) used to treat water used throughout the whole house, or only in the kitchen?

WHOLE HOUSE …..1

KITCHEN ONLY…….2

OTHER (SPECIFY)…6

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