Diagnostic x-ray exposure increases the risk of thyroid microcarcinoma: a population-based case-control study

Yawei Zhang[1], **Yingtai Chen**[2], **Huang Huang**[1], **Jason Sandler**[3], **Min Dai**[2], **Shuangge Ma**[4], and **Robert Udelsman**[5]

[1]Department of Environmental Health Sciences, Yale School of Public Health, Yale School of Medicine, New Haven, CT

[2]Cancer Institute & Hospital, Chinese Academy of Medical Sciences, Beijing, China

[3]Yale School of Medicine, New Haven, CT

[4]Department of Biostatistics, Yale School of Public Health, New Haven, CT

[5]Department of Surgery and Yale Cancer Center, Yale School of Medicine, Yale New Haven Hospital, New Haven, CT

Abstract

Objective—Thyroid cancer incidence and diagnostic x-ray exposures, particularly CT scans and nuclear medicine examinations have increased substantially in the United States. However, very few epidemiologic studies have directly investigated their associations.

Methods—A population-based case-control study was conducted in Connecticut in 2010–2011 including 462 histologically confirmed incident thyroid cancer cases and 498 population-based controls. Multivariate unconditional logistic regression models were used to estimate the associations between diagnostic x-rays and risk of thyroid cancer controlling for potential confounding factors.

Results—Exposure to any diagnostic x-rays was associated with an increased risk of well-differentiated thyroid microcarcinoma (tumor size ≤ 10 mm, OR=2.76, 95%CI: 1.31–5.81). The highest risk increase occurred with nuclear medicine examinations (excluding cardiology tests and thyroid uptake studies; OR=5.47, 95%CI: 2.10–14.23), followed by chest CT scans (OR=4.30, 95%CI: 1.66–11.14), head and neck CT scans (OR=3.88, 95%CI: 1.75–8.63), upper gastrointestinal series (OR=3.56, 95%CI: 1.54–8.21), lower gastrointestinal series (OR=3.29, 95%CI: 1.41–7.66), kidney x-rays involving dye injection into a vein or artery (OR=3.21, 95%CI: 1.20–8.54), mammograms (OR=2.95, 95%CI: 1.14–7.61), chest x-rays (OR=2.93, 95%CI: 1.37–6.29), and abdomen CT scans (OR=2.54, 95%CI: 1.02–6.30). No significant associations were found between these imaging modalities and thyroid tumors larger than 10 mm.

Conclusions—This study provides the first direct evidence that CT scans and nuclear medicine examinations are associated with an increased risk of thyroid cancer. The novel finding that an

Correspondence and Reprints: Yawei Zhang, MD, PhD, Yale School of Public Health, Yale Cancer Center, Yale School of Medicine, 60 College Street LEPH 440, New Haven, CT 06520. yawei.zhang@yale.edu; phone: 203-7856210; fax: 203-7376023.

array of diagnostic x-ray procedures are associated thyroid microcarcinomas warrants further investigation.

Keywords

diagnostic x-rays; thyroid cancer; case-control study; CT scans; nuclear medicine tests

Introduction

Thyroid cancer has shown the fastest increase in incidence rates compared to all other cancers over the past decades from 8.74/100,000 in women and 3.38/100,000 in men in 1994 to 21.82/100,000 in women and 7.37/100,000 in men in 2011(Howlader et al.). It is now the fifth-most common cancer in women in the United States (Howlader et al.). It has been suggested that the increasing incidence of thyroid cancer in the United States is predominantly due to the increased detection of subclinical disease, rather than an increase in the true occurrence of thyroid cancer, because the vast majority of cases have been small tumors and the mortality of the disease has remained stable (Davies and Welch 2006). Other investigators, however, offered different opinions (Enewold et al. 2011; Zhu et al. 2009). Recent studies have shown that approximately half of the variability in thyroid cancer incidence rates in the United States, at both the state and county level, cannot be explained by the "over-diagnosis" theory, suggesting that environmental factors might also play a role (Morris et al. 2013; Udelsman and Zhang 2014).

The thyroid gland is among the most radiosensitive organs in the body. Ionizing radiation during childhood is the only established environmental risk factor for thyroid cancer (Sinnott et al. 2010). Supportive evidence includes the dramatic outbreak of thyroid cancer, particularly in children and young adults, that occurred following atomic bomb detonations in Japan and nuclear accidents such as the Chernobyl event (Sinnott et al. 2010). Ionizing radiation has been classified by the International Agency for Research on Cancer as Group 1 human carcinogen (2012). Exposure to diagnostic x-rays has increased substantially in the United States, from an estimated mean per capita dose of 0.54 mSv in 1980 to 3.0 mSv in 2006, and this trend is likely to continue (Mettler et al. 2008). Computerized tomography (CT) scans and nuclear medicine examinations account for the majority of increased exposure (Mettler et al. 2008). Both CT and nuclear medicine studies involve much larger doses of radiation compared to conventional x-ray procedures (Mettler et al. 2008). However, very few epidemiologic studies have investigated the association between CT scans and nuclear medicine examinations and the risk of thyroid cancer. The potential risk from CT scans has been extrapolated using models from atomic bomb survivors, which estimate a thyroid cancer risk of 390 patients per million associated with neck CT scans (Mazonakis et al. 2007). One recent study based on medical records showed a 40% increased risk of thyroid cancer associated with exposure to CT scans during childhood and adolescence (Mathews et al. 2013). However, this study did not collect information on exposures to CT scans after 19 years of age. It is therefore unclear whether the results can be generalized to CT scans performed during adulthood. In light of the parallel, increasing trends of thyroid cancer incidence and diagnostic x-ray exposure coupled with the paucity of epidemiologic studies directly investigating their association, we conducted a population-

based case-control study in Connecticut to test the hypothesis that diagnostic x-ray exposure is associated with an increased risk of thyroid cancer.

Materials and Methods

Cases were histologically confirmed, incident thyroid cancer patients (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)) in Connecticut diagnosed between 2010 and 2011. Eligible subjects aged 21 to 84 years at diagnosis, had no previous diagnosis of cancer, with the exception of non-melanoma skin cancer, and were alive at the time of interview. Cases were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA). RCA acts as an agent of the Connecticut Tumor Registry. The Connecticut Public Health Code requires reporting of cancers from licensed hospitals and clinical laboratories to the Connecticut Tumor Registry. RCA field staffs are assigned geographically to survey all of the state's non-pediatric hospitals in order to identify newly diagnosed cases. Information on cases identified in the field is sent regularly to the RCA data entry staff where the case's demographic data are entered, verified and screened against the Connecticut Tumor Registry database. The Connecticut Tumor Registry has reciprocal reporting agreements with cancer registries in all adjacent states (and Florida) to identify Connecticut residents with cancer diagnosed and/or treated in these states. A total of 701 eligible incident thyroid cancer cases were identified during the study period with 462 (65.9%) completing in-person interviews. Population-based controls with Connecticut addresses were recruited using a random digit dialing method. A total of 498 subjects participated in the study, with a participation rate of 61.5%. Cases and controls were frequency-matched by age (±5 years). Distributions of age, gender, and race were similar between the participants and non-participants for both cases and controls.

All procedures were performed in accordance with a protocol approved by the Human Investigations Committee at Yale and the Connecticut Department of Public Health. After approval by the hospitals and by each subject's physician (cancer cases), or following selection through random sampling (control population), potential participants were approached by letter and then by phone. Those who agreed were interviewed by trained study interviewers, either at the subject's home or at a convenient location. After obtaining written consent, a standardized, structured questionnaire was used to obtain information on diagnostic x-ray exposures and other major known or suspected risk factors that might confound the association between diagnostic x-ray exposure and risk of thyroid cancer.

Regarding diagnostic x-ray exposure, the subjects were asked about the following diagnostic x-ray procedures: a) upper gastrointestinal series, b) lower gastrointestinal series, c) chest x-rays, d) head and neck CT scans, e) chest CT scans, f) abdomen CT scans, g) pelvic CT scans, h) nuclear cardiology tests, i) thyroid uptake studies using I-131 or another radioactive agent, j) nuclear medicine tests including bone, brain, liver scans, or other studies that utilize pre-test injection of a radioactive agent, k) kidney x-rays involving dye injection into a vein or artery, and l) mammograms. Participants were asked whether they had ever had any of the procedures. If a participant answered "yes", they were asked how

old they were during the initial procedure as well as the total number of procedures they had undergone. "Exposure" to diagnostic x-rays was defined as those who had ever been exposed, while "non-exposure" was defined as those who had never been exposed to any of these 12 procedures. For dental x-rays, participants were asked how often they had received dental x-rays, and how many of these were full mouth series and Panorex exams.

Odds ratios (OR) and 95% confidence intervals were calculated using unconditional logistic regression models to estimate the associations between diagnostic x-ray exposures and the risk of thyroid cancer by histologic subtype, tumor size and to control for potential confounders. Potential confounding variables included in the final model were age, gender, education level, family history of thyroid cancer, previous benign thyroid diseases, body mass index, alcohol consumption, and radiation treatment. Adjustment of other variables, such as family income, smoking, race, and occupational radiation exposure, did not result in material changes for the observed associations, and thus were not included in the final model. Decisions on which covariates to include in the final model were based on a greater than 10% change in the risk estimates. Because of the possibility that the diagnostic x-rays were performed as part of the diagnostic workup for thyroid cancer, we excluded participants who had their first diagnostic x-rays 5 years or less before their diagnosis (for cases) or interview (for controls). All tests of statistical significance were two-sided. All analyses were performed using SAS (version 9.3, SAS Institute Inc., Cary, NY).

Results

Of the 462 patients with thyroid cancer, the majority were diagnosed with papillary thyroid cancer (392, 84.8%) followed by follicular (56, 12.1%), medullary (12, 2.6%), anaplastic (1, 0.2%), and others (1, 0.2%). A total of 217 (47.0%) cases were microcarcinomas (≤10mm), and among them, 190 were papillary and 24 were follicular. The mean age at diagnosis of thyroid cancer was 51 years. Cases were more likely to be women, of lower education, obese, and non-drinkers than controls (Table 1). Cases were also more likely to have family histories of thyroid cancer and previous diagnosis of benign thyroid diseases, and to have previous radiation treatment. Distributions of family income, race, and smoking between cases and controls were similar.

Exposure to any diagnostic x-rays was associated with a borderline significant increased risk of thyroid cancer (OR=1.63, 95%CI: 0.98–2.72, Table 2). Several specific procedures were associated with an increased risk of thyroid cancer: upper gastrointestinal series (OR=1.82, 95%CI: 1.01–3.29), chest x-rays (OR=1.79, 95%CI: 1.06–3.02), head and neck CT scans (OR=2.13, 95%CI: 1.21–3.74), chest CT scans (OR=2.63, 95%CI: 1.30–5.29), abdomen CT scans (OR=1.97, 95%CI: 1.04–3.75), and nuclear medicine examinations (OR=2.86, 95%CI: 1.39–5.89). Several others were not significantly associated with the risk of thyroid cancer, including lower gastrointestinal series (OR=1.77, 95%CI: 0.98–3.19), pelvic CT scans (OR=1.12, 95%CI: 0.52–2.39), nuclear cardiology tests (OR=1.48, 95%CI: 0.75–2.90), kidney x-rays involving dye injection into a vein or artery (OR=1.53, 95%CI: 0.74–3.17), and mammogram (OR=1.43, 95%CI: 0.71–2.85). When we analyzed data by histologic subtypes, similar associations were observed for well-differentiated (including papillary and follicular) thyroid cancer. Slightly weakened associations were found for papillary thyroid

cancer. We did not analyze the data for follicular thyroid cancer alone and other subtypes because of small numbers.

We conducted stratified analyses by tumor size for well-differentiated thyroid cancer (Table 3). Exposure to any diagnostic x-rays was associated with an increased risk of microcarcinoma (tumor size ≤ 10mm, OR=2.76, 95%CI: 1.31–5.81). The highest risk was associated with nuclear medicine examinations (OR=5.47, 95%CI: 2.10–14.23), followed by chest CT scans (OR=4.30, 95%CI: 1.66–11.14), head and neck CT scans (OR=3.88, 95%CI: 1.75–8.63), upper gastrointestinal series (OR=3.56, 95%CI: 1.54–8.21), lower gastrointestinal series (OR=3.29, 95%CI: 1.41–7.66), kidney x-rays involving dye injection into a vein or artery (OR=3.21, 95%CI: 1.20–8.54), mammograms (OR=2.95, 95%CI: 1.14–7.61), chest x-rays (OR=2.93, 95%CI: 1.37–6.29), and abdomen CT scans (OR=2.54, 95%CI: 1.02–6.30). No significant associations were observed for well-differentiated thyroid cancer with tumor size larger than 10 mm. Similar associations by tumor size were observed for papillary thyroid cancer (data not shown).

For well-differentiated thyroid microcarcinomas, several diagnostic x-ray procedures showed an increased risk with an increasing number of procedures (Table 4). A significant dose-response was shown for exposure to ever exposure to any diagnostic x-rays ($P_{fortrend}$=0.045), chest x-rays ($P_{fortrend}$=0.0075), head and neck CT scans ($P_{fortrend}$=0.015), chest CT scans ($P_{fortrend}$=0.018), abdomen CT scans ($P_{fortrend}$=0.026), kidney x-rays ($P_{fortrend}$=0.0066), and mammogram ($P_{fortrend}$=0.037). No clear patterns were observed among patients for whom 6–10 years or more than 10 years had elapsed since their first procedure (Table 4). Similar patterns were observed for papillary thyroid microcarcinomas (data not shown).

Fewer than 10% of the study subjects reported receiving their first diagnostic x-ray procedures at age 15 years or younger. Analysis of the association for exposure/non-exposure to diagnostic x-rays demonstrated a higher increased risk of well-differentiated microcarcinoma for those who had their first diagnostic x-ray at age 15 years or younger (OR=4.07, 95%CI: 1.63–10.20) compared to those older than 15 years (OR=2.34, 95%CI: 1.10–4.98).

Compared to individuals who had dental x-rays less than once every five years, those who had dental x-rays more than once a year had a borderline significantly increased risk of thyroid cancer (OR=2.20, 95%CI: 1.03–3.72, Table 5). The increased risk associated with higher frequency of dental x-ray exposure was weakened for well-differentiated (OR=2.07, 95%CI: 0.95–4.50) and papillary thyroid cancer (OR=1.81, 95%CI: 0.81–4.04). No significant associations were observed for full mouth series and Panorex exams (data not shown). No significant associations were observed for different tumor size (data not shown).

Discussion

This study suggested a strong positive association between diagnostic x-ray exposure and the risk of thyroid cancer. It is critical to note that this increased risk was specific to microcarcinomas. Thyroid microcarcinoma has shown the fastest increase in incidence,

resulting in an apparent epidemic of thyroid cancer (Howlader et al.). Approximately half of all newly-diagnosed thyroid cancers were microcarcinomas, and the vast majority of these were micropapillary cancers in the current study, which is consistent with the data from the Surveillance Epidemiology End Results (SEER) (Howlader et al.). It is unclear why diagnostic x-ray exposures are only associated with microcarcinomas. It is possible that individuals who have had diagnostic x-ray exposures are more likely to undergo medical screening and, therefore, their thyroid cancers are more likely to be diagnosed before a microcarcinoma progresses. On the other hand, the findings that the associations remained similar for a lag period of 6–10 years or more than 10 or 20 years after the first exposure to diagnostic x-rays suggest that thyroid cancer is a very slow-growing tumor. Because of the increased detection of small thyroid nodules, newly-developed disease caused by increased diagnostic x-ray exposure is likely being identified earlier. It is also possible that diagnostic radiation-associated-thyroid microcarcinomas constitute a new disease with a different etiology profile. An observational study of papillary microcarcinoma from Japan found that the proportions of patients whose papillary microcarcinoma showed enlargement by 3 mm or more were 6.4 and 15.9% on 5-year and 10-year follow-up, respectively, and tumor enlargement was not related to patient background or clinical features (Ito et al. 2010).

A recent report suggested that the increased incidence of thyroid cancer is unlikely due to environmental or therapeutic radiation because the percentage of *RET/PTC* rearrangements decreased based on a single institute study (Jung et al. 2014). However, the higher prevalence of *RET/PTC* rearrangements in radiation-induced thyroid cancer were mainly identified from post-Chernobyl tumors which resulted from an extremely high dose-radiation exposure (Nikiforova et al. 2004). No clear evidence has shown that low-dose radiation exposure through medical practice induces *RET/PTC* rearrangements.

Several earlier epidemiological studies have investigated the association between exposure to diagnostic x-rays and thyroid cancer risk, but have provided inconsistent results (Franceschi et al. 1989; Hallquist et al. 1994; Hallquist and Nasman 2001; Inskip et al. 1995; Neta et al. 2013; Preston-Martin et al. 1987; Ron et al. 1987; Wingren et al. 1997). However, none of these examined the effect of CT scans and nuclear medicine examinations because all these studies collected information on diagnostic x-rays through the 1980s, when CT scans and nuclear medicine examinations were less common. The current study provides the first direct evidence that exposure to CT scans and nuclear medicine examinations during adulthood is associated with an increased risk of thyroid cancer, and it confirms the prior finding that exposure to CT scans in childhood is associated with an increased risk of thyroid cancer (Mathews et al. 2013). Nuclear medicine examinations deliver radiation doses comparable to CT scans. The strongest association was observed for thyroid uptake studies, which could be due to the underlying disease. Nuclear cardiology tests were not significantly associated with thyroid cancer risk in this study. Other nuclear medicine tests included bone, brain, liver scans, or other studies that utilize pre-test injection of a radioactive agent. These tests showed a significant association with thyroid cancer. The current study did not collect information on the specific organs examined by these tests, but, it is possible that the increased risk was driven by thyroid gland exposure.

This study also showed an increased risk of thyroid cancer associated with high frequency of dental x-ray exposure. Earlier studies involving dental x-rays yielded inconsistent results (Hallquist and Nasman 2001; Memon et al. 2010; Neta et al. 2013; Preston-Martin et al. 1987; Ron et al. 1987). Studies showed an increased thyroid cancer risk was mainly seen among those who had dental x-rays before the 1970s (Hallquist and Nasman 2001; Memon et al. 2010; Neta et al. 2013).

Potential limitations should be considered when interpreting this study. Information on diagnostic x-ray exposures were based on self-reporting. Therefore, potential recall bias cannot be ruled out. While medical records are generally considered an ideal tool for obtaining diagnostic x-ray exposure, data from medical records may underestimate exposure due to incomplete records (Berrington de Gonzalez et al. 2003; Inskip et al. 1995). Validation studies from the United States comparing medical records and interviews for histories of diagnostic x-rays suggested non-differential reporting error between thyroid cancer cases and controls (Berrington de Gonzalez et al. 2003; Preston-Martin et al. 1985). Since a validation study from Sweden found that differential recall bias between thyroid cancer cases and controls was found for those who were <50 years old (Hallquist and Jansson 2005), we conducted a stratified analysis by age and did not observe significant differences in associations between age groups <50 and 50 years old. In addition, our positive findings were only limited to thyroid microcarcinomas, supporting the notion that differential recall bias is less likely to play a major role. We did not collect information on age at the time of each diagnostic x-ray procedure, which limited our ability to distinguish how many procedures were administered during childhood and adolescence. We can only evaluate the association with the age of the first diagnostic x-ray exposure. Since all diagnostic x-ray procedures were based on self-reporting, information on radiation doses to the thyroid gland for each procedure were not available. Estimated doses to the thyroid gland for some of the diagnostic x-ray procedures have been published. However, many of these publications have limited information on specific procedures such as CT scans of abdomen and nuclear medicine tests. Therefore, we were unable to examine the relationship based on cumulative radiation doses from diagnostic x-ray exposures. Information on reasons for each diagnostic x-ray procedure were not available for the study, which limited our ability to examine the associations by underlying reasons. Finally, our sample size was limited for the purpose of examining rarer histologic subtypes such as follicular, medullary, and anaplastic thyroid cancers.

The possibility of reverse causation could be a potential concern, since symptoms of a precancerous condition or early symptoms of the cancer itself might prompt a diagnostic x-ray procedure. However, this phenomenon is unlikely to be the sole explanation in this study given the following observations. First, because of the possibility that the diagnostic x-rays were performed as part of the diagnostic workup for thyroid cancer, we excluded participants who had their first diagnostic x-rays 5 years or less before their diagnosis (for cases) or interview (for controls). While the associations were attenuated after excluding those who were diagnosed within 5 years of their first diagnostic x-rays, they remained statistically significant. And the associations were sustained in the "6–10 years" and "more than 10 years" ranges after the first diagnostic x-ray exposure. Second, the associations increased with increasing frequency of diagnostic x-ray procedures, and many of them

showed a significant dose-response. Third, the larger associations were found for diagnostic x-rays being given for the first time during childhood, as seen in the Life Span Study of survivors of the Japanese atomic bombings (Sinnott et al. 2010). Finally, the associations were stronger when the site of CT scans was anatomically-closer to the thyroid gland.

In conclusion, this study provides new and direct evidence showing strong associations between an array of diagnostic x-ray procedures and risk of thyroid cancer. The observed associations were mainly seen for thyroid microcarcinomas. Although we cannot rule out the possibility that increased diagnostic x-rays might have prompted the earlier diagnosis of thyroid cancer, physicians should cautiously weigh the diagnostic value of CT scans and nuclear medicine examinations against the potential risks. The estimated population attributable risk was 59% (95%CI: 37%–85%), suggesting that 37–85% of the well-differentiated thyroid microcarcinomas in the U.S. population could be explained by exposure to diagnostic x-ray. Future prospective studies are warranted to investigate the association between CT-scans and nuclear medicine tests and risk of thyroid cancer. It is also essential to identify populations that are especially-susceptible to diagnostic x-rays.

Acknowledgements

References

Berrington de Gonzalez A, Ekbom A, Glass AG, Galanti MR, Grimelius L, Allison MJ, et al. Comparison of documented and recalled histories of exposure to diagnostic x-rays in case-control studies of thyroid cancer. Am J Epidemiol. 2003; 157:652–663. [PubMed: 12672685]

Davies L, Welch HG. Increasing incidence of thyroid cancer in the united states, 1973–2002. JAMA. 2006; 295:2164–2167. [PubMed: 16684987]

Enewold LR, Zhou J, Devesa SS, Berrington de Gonzalez A, Anderson WF, Zahm SH, et al. Thyroid cancer incidence among active duty u.S. Military personnel, 1990–2004. Cancer Epidemiol Biomarkers Prev. 2011; 20:2369–2376. [PubMed: 21914838]

Franceschi S, Fassina A, Talamini R, Mazzolini A, Vianello S, Bidoli E, et al. Risk factors for thyroid cancer in northern italy. Int J Epidemiol. 1989; 18:578–584. [PubMed: 2807659]

Hallquist A, Hardell L, Degerman A, Wingren G, Boquist L. Medical diagnostic and therapeutic ionizing radiation and the risk for thyroid cancer: A case-control study. Eur J Cancer Prev. 1994; 3:259–267. [PubMed: 8061591]

Hallquist A, Nasman A. Medical diagnostic x-ray radiation--an evaluation from medical records and dentist cards in a case-control study of thyroid cancer in the northern medical region of sweden. Eur J Cancer Prev. 2001; 10:147–152. [PubMed: 11330455]

Hallquist A, Jansson P. Self-reported diagnostic x-ray investigation and data from medical records in case-control studies on thyroid cancer: Evidence of recall bias? Eur J Cancer Prev. 2005; 14:271–276. [PubMed: 15901997]

Howlader, N.; Noone, AM.; Krapcho, M.; Garshell, J.; Neyman, N.; Altekruse, SF., et al. national cancer institute; Bethesda: Seer cancer statistics review, 1975–2011. md, http://seer.Cancer.Gov/csr/1975_2011/, based on november 2013 seer data submission, posted to the seer website, april 2014.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Iarc monograph volume 100d: A review of human carcinogens—radiation. France: Lyon; 2012.

Inskip PD, Ekbom A, Galanti MR, Grimelius L, Boice JD Jr. Medical diagnostic x rays and thyroid cancer. J Natl Cancer Inst. 1995; 87:1613–1621. [PubMed: 7563204]

Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. An observational trial for papillary thyroid microcarcinoma in japanese patients. World J Surg. 2010; 34:28–35. [PubMed: 20020290]

Jung CK, Little MP, Lubin JH, Brenner AV, Wells SA Jr, Sigurdson AJ, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of braf mutations and a sharp increase in ras mutations. The Journal of clinical endocrinology and metabolism. 2014; 99:E276–E285. [PubMed: 24248188]

Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: Data linkage study of 11 million australians. BMJ. 2013; 346:f2360. [PubMed: 23694687]

Mazonakis M, Tzedakis A, Damilakis J, Gourtsoyiannis N. Thyroid dose from common head and neck ct examinations in children: Is there an excess risk for thyroid cancer induction? Eur Radiol. 2007; 17:1352–1357. [PubMed: 17021703]

Memon A, Godward S, Williams D, Siddique I, Al-Saleh K. Dental x-rays and the risk of thyroid cancer: A case-control study. Acta Oncol. 2010; 49:447–453. [PubMed: 20397774]

Mettler FA Jr, Thomadsen BR, Bhargavan M, Gilley DB, Gray JE, Lipoti JA, et al. Medical radiation exposure in the u.S. In 2006: Preliminary results. Health Phys. 2008; 95:502–507. [PubMed: 18849682]

Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: The influence of access to care. Thyroid. 2013

Neta G, Rajaraman P, Berrington de Gonzalez A, Doody MM, Alexander BH, Preston D, et al. A prospective study of medical diagnostic radiography and risk of thyroid cancer. Am J Epidemiol. 2013; 177:800–809. [PubMed: 23529772]

Nikiforova MN, Ciampi R, Salvatore G, Santoro M, Gandhi M, Knauf JA, et al. Low prevalence of braf mutations in radiation-induced thyroid tumors in contrast to sporadic papillary carcinomas. Cancer letters. 2004; 209:1–6. [PubMed: 15145515]

Preston-Martin S, Bernstein L, Maldonado AA, Henderson BE, White SC. A dental x-ray validation study. Comparison of information from patient interviews and dental charts. Am J Epidemiol. 1985; 121:430–439. [PubMed: 4014133]

Preston-Martin S, Bernstein L, Pike MC, Maldonado AA, Henderson BE. Thyroid cancer among young women related to prior thyroid disease and pregnancy history. Br J Cancer. 1987; 55:191–195. [PubMed: 3814488]

Ron E, Kleinerman RA, Boice JD Jr, LiVolsi VA, Flannery JT, Fraumeni JF Jr. A population-based case-control study of thyroid cancer. J Natl Cancer Inst. 1987; 79:1–12. [PubMed: 3474436]

Sinnott B, Ron E, Schneider AB. Exposing the thyroid to radiation: A review of its current extent, risks, and implications. Endocr Rev. 2010; 31:756–773. [PubMed: 20650861]

Udelsman R, Zhang Y. The epidemic of thyroid cancer in the united states: The role of endocrinologists and ultrasounds. Thyroid. 2014; 24:472–479. [PubMed: 23937391]

Wingren G, Hallquist A, Hardell L. Diagnostic x-ray exposure and female papillary thyroid cancer: A pooled analysis of two swedish studies. Eur J Cancer Prev. 1997; 6:550–556. [PubMed: 9496457]

Zhu C, Zheng T, Kilfoy BA, Han X, Ma S, Ba Y, et al. A birth cohort analysis of the incidence of papillary thyroid cancer in the united states, 1973–2004. Thyroid. 2009; 19:1061–1066. [PubMed: 19732011]

Table 1

Distributions of selected characteristics of the study population

	Cases (n=462)		Control (n=498)		P-value
	Number	%	Number	%	
Age (years)					
Mean (SD)	51.2 (12.3)		54.2 (13.1)		<0.01
<40	86	18.6	64	12.8	
40-	115	24.9	123	24.7	
50-	149	32.3	139	27.9	
60-	81	17.5	100	20.1	
70	31	6.7	72	14.5	0.0003
Gender					
Female	375	81.2	344	69.1	
Male	87	18.8	154	30.9	<0.01
Race					
White	415	89.8	450	90.5	
Black	18	3.9	25	5.0	
Others	29	6.3	23	4.5	0.13
Years of education					
High school or lower	160	34.6	113	22.7	
College	185	40.0	236	47.4	
Graduate school	113	24.5	143	28.7	
Missing	4	0.9	6	1.2	<0.01
Family income per capita					
Low	128	27.7	133	26.7	
Medium	113	24.5	131	26.3	
High	74	16.0	82	16.5	
Confidential or unknown	147	31.8	152	30.5	0.90
Family history of thyroid cancer among first-degree relatives					
Yes	72	15.6	48	9.6	
No	390	84.4	450	90.4	<0.01

	Cases (n=462)		Control (n=498)		
	Number	%	Number	%	P-value
Prior benign thyroid diseases[§]					
Yes	62	13.4	14	2.8	
No	400	86.6	484	97.2	<0.01
Radiation treatment[†]					
Yes	14	3.0	2	0.4	
No	448	97.0	496	99.6	<0.01
Body mass index (kg/m²)					
<25	145	31.4	203	40.8	
25–<30	146	31.6	168	33.7	
30+	166	35.9	118	23.7	
Missing	5	1.1	9	1.8	<0.01
Smoking[‡]					
Yes	141	30.5	172	34.5	
No	317	68.6	321	64.5	
Missing	4	0.9	5	1.0	0.39
Alcohol consumption[‖]					
Yes	188	40.7	267	53.6	
No	270	58.4	226	45.4	
Missing	4	0.9	5	1.0	<0.01

[§]Benign thyroid diseases included hyperthyroidism, hypothyroidism, goiter, thyroid nodules, and thyroid adenoma.

[†]Radiation treatment: a history of therapeutic external beam radiation treatment.

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

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

Table 2

Associations between diagnostic radiation exposure an risk of thyroid cancer

Diagnostic radiation exposure	Controls	Overall		Well-differentiated		Papillary	
		Cases	OR§(95%CI)	Cases	OR§(95%CI)	Cases	OR§(95%CI)
Never	56	38	1.00	38		37	
Ever	412	391	1.63(0.98–2.72)	378	1.62(0.97–2.69)	325	1.46(0.87–2.45)
Upper gastrointestinal series	78	84	1.82(1.01–3.29)	79	1.75(0.96–3.18)	67	1.60(0.86–2.94)
Lower gastrointestinal series	82	82	1.77(0.98–3.19)	77	1.69(0.93–3.08)	66	1.56(0.84–2.88)
Chest x-rays	279	284	1.79(1.06–3.02)	273	1.77(1.04–2.98)	231	1.59(0.93–2.71)
CT scans of head and neck	97	131	2.13(1.21–3.74)	127	2.10(1.19–3.71)	111	1.95(1.10–3.49)
CT scans of chest	31	49	2.63(1.30–5.29)	47	2.58(1.27–5.24)	40	2.37(1.15–4.91)
CT scans of abdomen	47	57	1.97(1.04–3.75)	55	1.95(1.02–3.73)	48	1.78(0.92–3.45)
CT scans of pelvic	31	26	1.12(0.52–2.39)	25	1.11(0.51–2.39)	24	1.14(0.52–2.48)
Nuclear cardiology test	52	45	1.48(0.75–2.90)	44	1.49(0.75–2.95)	39	1.50(0.75–3.01)
Thyroid uptake study	0	6	-	4	-	3	-
Nuclear medicine tests†	26	39	2.86(1.39–5.89)	37	2.80(1.35–5.82)	29	2.20(1.03–4.72)
Kidney x-rays‡	38	32	1.53(0.74–3.17)	32	1.60(0.77–3.33)	28	1.60(0.77–3.33)
Mamogram¶	265	268	1.43(0.71–2.85)	258	1.46(0.73–2.93)	222	1.48(0.69–3.16)

§Adjusted for age (continuous), gender (male, female), education (<college, college, >college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), BMI (<25, 25–29.9, 30kg/m², previous benign thyroid diseases (yes, no), radiation treatment (yes, no), and dental x-ray exposure (less than once every five years, once every two to five years, once a year, more than once a year).

†Excluded nuclear cardiology tests and thyroid uptake study.

‡Procedures involving use a dye injected into a vein or artery.

¶Limited to women only.

Table 3

Associations between diagnostic radiation exposure and risk of well-differentaited thyroid cancers by tumor size

Diagnostic radiation exposure	Tumor size 10mm		Tumor size >10mm	
	Cases	OR§(95%CI)	Cases	OR§(95%CI)
Never	12	1.00	25	1.00
Ever	190	2.76(1.31–5.81)	183	1.29(0.71–2.33)
Upper gastrointestinal series	43	3.56(1.54–8.21)	36	1.23(0.60–2.51)
Lower gastrointestinal series	40	3.29(1.41–7.66)	37	1.24(0.61–2.53)
Chest x-rays	133	2.93(1.37–6.29)	137	1.48(0.80–2.71)
CT scans of head and neck	69	3.88(1.75–8.63)	58	1.59(0.82–3.10)
CT scans of chest	23	4.30(1.66–11.14)	23	1.97(0.85–4.59)
CT scans of abdomen	22	2.54(1.02–6.30)	33	2.10(1.00–4.43)
CT scans of pelvic	9	1.35(0.45–4.00)	16	1.25(0.51–3.06)
Nuclear cardiology test	15	1.65(0.61–4.45)	29	1.57(0.71–3.49)
Thyroid uptake study	2	-	2	-
Nuclear medicine tests[†]	21	5.47(2.10–14.23)	15	1.76(0.71–4.39)
Kidney x-rays[‡]	18	3.21(1.20–8.54)	13	0.91(0.36–2.31)
Mamogram[¶]	141	2.95(1.14–7.61)	112	0.94(0.41–2.19)

[§]Adjusted for age (continuous), gender (male, female), education (<college, college, >college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), BMI (<25, 25–29.9, 30kg/m^2), previous benign thyroid diseases (yes, no), radiation treatment (yes, no), and dental x-ray exposure (less than once every five years, once every two to five years, once a year, more than once a year).

[†]Excluded nuclear cardiology tests and thyroid uptake study.

[‡]Procedures involving use a dye injected into a vein or artery.

[¶]Limited to women only.

Table 4

Associations between diagnostic radiation exposure and risk of well-differentiated thyroid microcarcinoma by total number of exposure and years since first exposure

Total times	Total times of exposure				Years since first exposure			
	Controls	Cases	OR§(95%CI)	P for trend	Years Since first	Controls	Cases	OR§(95%CI)
Never	56	12	1.00			56	12	1.00
Ever								
<10	175	68	2.45(1.14–5.26)		6–20	152	75	2.52(1.18–5.38)
10–19	107	49	3.16(1.37–7.26)		21–30	92	46	2.57(1.11–5.97)
20	127	70	3.78(1.54–9.31)	0.045	>30	148	57	2.51(1.05–6.05)
Upper gastrointestinal series								
1	45	26	3.37(1.37–8.26)		6–20	33	12	2.94(0.70–5.40)
>1	30	17	3.81(1.43–10.17)	0.056	>20	21	18	6.32(2.32–17.20)
Lower gastrointestinal series								
1	46	22	2.94(1.17–7.37)		6–20	64	21	2.07(0.85–5.09)
>1	32	17	3.77(1.42–10.00)	0.063	>20	27	17	4.17(1.55–11.21)
Chest x-rays								
1–2	90	39	2.58(1.13–5.88)		6–20	89	57	3.07(1.41–6.71)
3–5	107	52	2.69(1.19–6.09)		21–30	64	30	1.87(0.77–4.54)
>5	74	37	3.59(1.49–8.70)	0.0075	>30	116	38	2.26(1.05–4.84)
CT scans of head and neck								
1	62	37	3.18(1.37–7.42)		6–10	55	34	3.29(1.41–7.67)
>1	33	32	5.01(2.02–12.44)	0.015	>10	62	45	3.91(1.68–9.13)
CT scans of chest								
1	19	10	2.68(0.89–8.13)		6–10	27	14	2.92(1.07–7.95)
>1	10	12	7.16(2.12–24.19)	0.018	>10	16	13	4.76(1.54–14.71)
CT scans of abdomen								
1	26	8	1.11(0.35–3.49)		6–10	25	14	3.09(1.13–8.44)
>1	17	12	4.77(1.59–14.32)	0.026	>10	32	16	2.53(0.94–6.82)
CT scans of pelvic								
1	17	2	0.36(0.06–2.14)		6–10	14	13	5.59(1.93–16.11)

	Total times of exposure				Years since first exposure			
Total times	Controls	Cases	OR§(95%CI)	P for trend	Years Since first	Controls	Cases	OR§(95%CI)
>1	12	7	2.92(0.85–10.09)	0.22	>10	20	7	1.42(0.42–4.83)
Nuclear cardiology test								
1	27	10	2.00(0.68–5.90)		6–10	50	17	2.01(0.77–5.25)
>1	24	3	0.64(0.14–2.93)	0.60	>10	23	10	2.30(0.75–7.05)
Nuclear medicine tests†								
1	8	12	8.15(2.50–26.52)		6–10	21	21	6.35(2.39–16.92)
>1	16	9	3.47(1.06–11.29)	0.23	>10	13	10	5.60(1.73–18.07)
Kidney x-rays‡								
1	27	10	1.78(0.58–5.43)		6–10	18	9	3.86(1.21–12.32)
>1	9	7	7.72(2.06–28.89)	0.0066	>10	25	11	2.55(0.86–7.60)
Mamogram¶								
<10	90	45	2.62(1.00–6.89)		6–10	89	40	1.84(0.72–4.71)
10–15	71	39	3.26(1.14–9.32)		11–20	96	61	2.76(0.99–7.66)
>15	102	53	3.96(1.29–12.18)	0.037	>20	99	43	3.34(0.70–7.78)

§ Adjusted for age (continuous), gender (male, female), education (<college, college, >college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), BMI (<25, 25–29.9, 30kg/m^2), previous benign thyroid diseases (yes, no), radiation treatment (yes, no), and dental x-ray exposure (less than once every five years, once every two to five years, once a year, more than once a year).

† Excluded nuclear cardiology tests and thyroid uptake study.

‡ Procedures involving use a dye injected into a vein or artery.

¶ Limited to women only.

Table 5

Associations between dental x-rays and risk of thyroid cancer

Dental x-rays	Controls	Overall		Well-differentiated		Papillary	
		Cases	OR[§](95%CI)	Cases	OR[§](95%CI)	Cases	OR[§](95%CI)
<once every 5 years	96	93	1.00	90		81	
Once every 2–5 years	151	124	0.86(0.57–1.29)	121	0.88(0.59–1.32)	106	0.84(0.55–1.27)
Once a year	237	216	0.89(0.61–1.30)	210	0.89(0.61–1.31)	182	0.84(0.57–1.25)
>once a year	14	29	2.20(1.03–4.72)	27	2.07(0.95–4.50)	23	1.81(0.81–4.04)

[§]Adjusted for age (continuous), gender (male, female), education (<college, college, >college), family history of thyroid cancer (yes, no), alcohol consumption (yes, no), BMI (<25, 25–29.9, 30kg/m^2, previous benign thyroid diseases (yes, no), radiation treatment (yes, no), and diagnostic x-ray exposure (never, ever).