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Non-Malignant Thyroid Diseases Following a Wide Range of Radiation Exposures

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Abstract

Background—The thyroid gland is one of the most radiosensitive human organs. While it is well known that radiation exposure increases the risk of thyroid cancer, less is known about its effects in relation to non-malignant thyroid diseases.

Objectives—The aim of this review is to evaluate the effects of high and low dose radiation on benign structural and functional diseases of the thyroid.

Methods—We examined the results of major studies from cancer patients treated with high-dose radiotherapy or thyrotoxicosis patients treated with high doses of iodine-131, patients treated with moderate to high dose radiotherapy for benign diseases, persons exposed to low doses from environmental radiation and survivors of the atomic bombings who were exposed to a range of doses. We evaluated radiation effects on structural (tumors, nodules), functional (hyper- and hypothyroidism), and autoimmune thyroid diseases.

Results—Following a wide range of doses of ionizing radiation, an increased risk of thyroid adenomas and nodules was observed in a variety of populations and settings. The dose response appeared to be linear at low to moderate doses, but in one study there was some suggestion of a reduction in risk above 5 Gy. The elevated risk for benign tumors continues for decades following exposure. Considerably less consistent findings are available regarding functional thyroid diseases including autoimmune diseases. In general, associations for these outcomes were fairly weak and significant radiation effects were most often observed following high doses, particularly for hypothyroidism.

Conclusions—A significant radiation dose-response relation was demonstrated for benign nodules and follicular adenomas. The effects of radiation on functional thyroid diseases are less clear, partly due to the greater difficulties studying these diseases.

INTRODUCTION

The thyroid gland is a butterfly shaped organ with two lobes connected by an isthmus which is located in the lower part of the neck. It is among the larger endocrine glands typically weighing 10–30 grams in individuals with sufficient iodine intake. The thyroid gland produces and stores thyroxine (T4) and triiodothyronine (T3), hormones that are instrumental in regulating growth, metabolism, reproduction and other physiological processes including heart rate, blood pressure, body temperature and energy expenditure (1). Because the thyroid affects so many organs in the body, maintaining normal function is necessary for good health.

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Radiation effects on the thyroid were first reported in the 1920s. In 1950, Duffy and Fitzgerald (2) noted that 9 out of 28 children with thyroid cancer had a history of external head and neck irradiation. Later in the 1950's, the first observations of thyroid cancer occurring in atomic bomb survivors were published (3). Since then we have learned a great deal about radiation-related thyroid cancer, but much less is known about radiation effects in relation to non-malignant thyroid diseases.

In this paper, we summarize the current evidence concerning the effects of various types of radiation on the development of benign structural and functional diseases of the thyroid. We review the results of major epidemiologic studies of cancer patients treated with high-dose external radiotherapy, patients with thyrotoxicosis treated with high doses of iodine-131 (I-131), patients treated with moderate to high-dose radiotherapy for benign diseases, persons exposed to low doses from environmental radiation and survivors of the atomic bombings who were exposed to a range of doses. Environmental exposures occurred as a result of fallout from the Chornobyl (Chernobyl) nuclear power plant accident in Ukraine, nuclear weapons testing in Nevada, Kazakhstan and the Pacific Ocean, and emissions from the Hanford or Mayak nuclear weapons facilities. We evaluated radiation effects on follicular adenomas, benign nodules, overt and subclinical hyperthyroidism, hypothyroidism and autoimmune thyroiditis and related outcomes. For a more detailed summary of all aspects of radiation and thyroid diseases see the recently published report by the National Council on Radiation Protection (4).

THYROID DISEASES

There are two main types of thyroid disease: structural and functional. Malignant and benign tumors and nodules, as well as diffuse goiter (enlargement of the thyroid gland) are considered structural diseases and hypothyroidism, hyperthyroidism and thyroiditis are the main functional diseases. Thyroid cancer is relatively rare, but benign thyroid nodules are common, especially among women and in iodine deficient areas, and their incidence increases with age (5). With palpation performed during a physical examination, thyroid nodules are detected in up to about 7% of healthy adults (6), but using ultrasound the detection rate is many times greater and in one study reached 67% (5,7,8). In the U.S., approximately 300,000 nodules are diagnosed annually (9). In general, thyroid nodules occur at later age than thyroid cancer (4).

The term benign thyroid nodule is extremely general and includes both neoplasms (adenomas) and non-neoplastic nodules. Follicular adenoma is the most common benign thyroid neoplasm, comprising about 80% of these tumors, whereas papillary adenomas are infrequent. Non-neoplastic nodules generally include colloid nodules and hyperplastic nodules. It is difficult to distinguish between benign tumors and nodules, so often radiation studies group them together as a single endpoint. New molecular techniques are showing that many nodules actually are clonal in origin and thus are true benign tumors (10). These new methods should result in improved diagnoses in the future.

Because the probability of detecting a benign nodule is highly dependent on the diagnostic method used, as well as the age and gender distribution of the population, it is not straightforward to compare results from different studies. If all types of nodules are equally radiation related, then the excess relative risk should reflect the true risk, however, the magnitude of the excess absolute risk would be related to the quality of the diagnostic method. Therefore, the focus of this review is on the excess relative risk.

Functional thyroid diseases involve an excess or deficit of blood levels of T4, T3 and/or thyroid stimulating hormone (TSH), which is produced by the pituitary gland. Abnormal levels of these hormones can occur alone or in various combinations (1). The main types of

functional thyroid disease are hyperthyroidism and hypothyroidism and the most common cause of both of these diseases is autoimmunity, but the underlying autoimmune mechanisms differ. Overt hypothyroidism is defined as a low serum fT4 and elevated TSH level, whereas overt hyperthyroidism is defined as a high serum fT4 or fT3 or both and suppressed TSH level. More subtle degrees of altered thyroid status include subclinical hypothyroidism (elevated TSH, normal fT4 levels) and subclinical hyperthyroidism (suppressed TSH, normal fT4 and fT3 levels)., The exact values for the lower and, particularly, the upper limit of the TSH reference range, however, remain controversial (11–13). While subclinical hypothyroidism and hyperthyroidism were previously considered to be biochemical abnormalities, recent studies have suggested that they may have clinical relevance including effects on lipid and bone metabolism as well as cardiac disorders (14). The most convincing is the link between subclinical hyperthyroidism and atrial fibrillation (11,13). The prevalence of subclinical thyroid dysfunction changes depending on the definition used, but in general thyroid dysfunction is relatively common especially among older women. Prevalence of subclinical hypothyroidism tends to increase with age and is approximately 15% in 80 year old individuals (12). Subclinical hyperthyroidism is less common and, while it also tends to increase with age, the increase is more moderate reaching 3% in 80 year old individuals (12).

Clinical manifestations of hypothyroidism are broad. These may include fatigue, depression, weight gain, bradycardia, cold intolerance, and mental impairment. The most common cause of hypothyroidism in areas of adequate iodine intake is chronic autoimmune thyroiditis or Hashimoto thyroiditis, a progressive autoimmune thyroid disease that ultimately leads to thyroid failure and is characterized by lymphocytic infiltration of the thyroid gland, elevated serum levels of antithyroid antibodies (particularly antibodies to thyroid peroxidase, ATPO), and sometimes by an enlarged thyroid with diffusely hypoechoic pattern on ultrasound. Hyperthyroidism has a different spectrum of clinical manifestations including increased body metabolism, weight loss, rapid or irregular heart beat, nervousness, heat intolerance and increased perspiration. It is most often caused by Graves' disease, which also is an autoimmune disease. In addition to Hashimoto thyroiditis and Graves' disease, another autoimmune thyroid disease is radiation-induced acute thyroiditis. To diagnose functional thyroid diseases, serum tests with or without clinical examinations are required on all study participants and thus only a few epidemiologic studies have collected data on these disease endpoints.

Structural Thyroid Diseases Following Radiation

Follicular adenoma—The data on follicular adenoma are relatively sparse, largely due to the difficulty in distinguishing them from follicular thyroid cancers or other benign nodules, but there are a few cohort studies that have quantified the radiation risk for adenomas. Patients receiving low to moderate dose radiotherapy for benign conditions of the head and neck have been evaluated in both the Israel (15) and New York tinea capitis studies (16), the study of infants irradiated in Rochester, NY for an enlarged thymus gland (17) and the study of French infants treated for a hemangioma (18), whereas radioactive I-131 was assessed in the Ukraine-NCI Chornobyl thyroid screening study (19) and in a revised analysis of people living near the Nevada weapons test site when they were children (20). The study populations range from about 2,500 to 27,000 subjects of both genders, all of whom were irradiated before the age of 18 years. The mean thyroid doses ranged from 0.06 Gy for the New York tinea capitis study to 1.4 Gy for the enlarged thymus study. In the Israel tinea capitis study (15) and the Ukraine-NCI Chornobyl screening study (19), pathology slides of tumor tissue were obtained and the final diagnosis was made by pathologists after a slide review, whereas the diagnosis was made by reviewing the records from the earlier screening exams performed in the Nevada test site study (20), and the diagnoses for tumors reported

on questionnaires were verified through review of medical records in the NY tinea capitis (16), Rochester thymus (17) and French hemangioma studies (18). As can be seen in Table 1, the excess relative risk at 1 Gy (ERR_{Gy}) ranged from two to eight in four of the studies and could not be estimated in the Nevada study. The ERR_{Gy} was 93 in the NY tinea study, but the confidence interval was extremely large and included the point estimates from the other studies. A linear dose response fit the data in the Israel tinea capitis and the Chornobyl study; however, there was downward curvature at the high doses in the thymus study. In that study, when patients receiving 6 Gy or more were excluded from the analysis, the ERR_{Gy} increased from 6.3 to 7.8 and the dose response became linear. It should be noted that the risks generally were somewhat higher for malignant tumors than for follicular adenomas (Table 1). Women had a higher risk of radiation-related adenomas than men in the Chornobyl study, but significant gender effects were not observed in the other studies. Risk appeared to decrease with increasing age at exposure in the Israel tinea study; however age at exposure was not a clear modifying factor in the other studies and all studies had a very limited age at exposure range.

From the data reviewed, exposure to external x-ray or internal radioactive iodine at low to moderate doses was associated with a significant excess of follicular adenomas. Risk was elevated throughout follow-up, but detailed evaluation of time since exposure was not possible. To our knowledge, there are no quantitative risk estimates for follicular thyroid adenomas following high doses, i.e. above 10 Gy, or following adult exposure.

Thyroid nodules—Data on the role of radiation in the development of thyroid nodules come from cohorts of medically irradiated patients, persons exposed to radiation from the atomic bombings in Hiroshima and Nagasaki, fallout from nuclear testing or emissions due to nuclear weapons production. The definition of nodules is not uniform across studies, and in some studies they are based on palpation and in others on ultrasound examination. Size criteria also differ from study to study. With the beginning of thyroid cancer screening, the detection of thyroid nodules increased dramatically in members of the Chicago tonsil study (21).

At the high dose range, studies of childhood cancer survivors treated with radiotherapy have been informative. Hodgkins lymphoma patients treated with Mantle field radiation (neck, the mid-chest and the armpits) receive thyroid doses of ten's of Gy up to about 55–60 Gy. Years after radiotherapy, approximately 30–40% of patients examined with ultrasound are diagnosed with thyroid nodules (6,22,23). In a study of 1,791 Hodgkins lymphoma patients participating in the Childhood Cancer Survivor Study, 135 survivors reported that they were diagnosed with a benign thyroid nodule following a median thyroid dose of 35 Gy (24). Compared to a cohort of 2,808 sibling controls, the incidence of thyroid nodules was significantly elevated among the Hodgkins patients ($P < 0.0001$). In addition to dose, gender and time since exposure influenced risk with female patients and patients who had survived Hodgkins lymphoma for more than 10 years found to be at higher risk.

Among patients treated with low to moderate doses of x-radiation for benign conditions of the head and neck, significantly elevated risks of developing a thyroid nodule have been reported. Table 2 summarizes the data from studies with over 1,000 informative subjects. Information on the occurrence of nodules was obtained by conducting ultrasound examinations on the participants in the Hanford (25,26), Kazakhstan (27), and atomic bomb survivor studies (28), by clinical exams not including ultrasound in participants of the Nevada test site study (20) and the diagnostic I-131 Swedish study (29), by reviewing pathology records for members of the Israel tinea study (15) and through self reports on questionnaires in the other studies (21,30). In all but the population of persons exposed to emissions from Hanford nuclear facility (25), there was a dose response, with the ERR_{Gy}

ranging from 0.74 for persons exposed to fallout from nuclear weapons testing in Kazakhstan (27) to 64 for patients treated with external radiation to the head and neck for lymphoid hyperplasia (4,30). In the Hanford study, several criteria for defining nodules were used (25,26), yet the risks were not significantly elevated based on any of the seven definitions and the point estimate of the risk was only positive in using three definitions (any ultrasound detected abnormality, non-palpable ultrasound detected nodule and diffuse ultrasound detected abnormality).

Data from the Marshall Islanders exposed to fallout from nuclear weapons testing in the Pacific Ocean are complicated by the fact that people were exposed to a variety of external radiation and short-lived and long-lived radionuclides. There was a clear increase in nodules among persons exposed to tens of Gy on the islands of Rongelap, Allinginae and Utrik (31), but the results were inconsistent and not well quantified among individuals living on islands receiving low-doses. An inverse relationship between thyroid nodules and distance from the test site was found in one study (32), but these results were not confirmed in a later study (33).

Both internal and external radiation appears to significantly increase the risk of thyroid nodules; however the non-uniformity in diagnosing nodules makes it difficult to adequately compare results from various studies.

Functional Thyroid Diseases Following Radiation

Hyperthyroidism—There have been several reports concerning risk of hyperthyroidism following high dose external irradiation to the thyroid (24,28,34). In a study of Hodgkins lymphoma survivors, the overall incidence of hyperthyroidism (5% based on 82 cases) was eight-fold greater ($P < 0.0001$) than that reported in sibling controls (24). In addition, the relative risk (RR) of hyperthyroidism in those receiving a thyroid dose of ≥ 35 Gy was 2.2 (95% CI: 1.2–4.7) compared to those who received < 35 Gy. In a recent study of thyroid outcomes among survivors of acute lymphoblastic leukemia (ALL), the incidence of hyperthyroidism was low (0.6% based on 23 cases) (35). Nonetheless, the results suggested that thyroid doses of ≥ 15 Gy were associated with an increased risk of hyperthyroidism.

The data concerning risk of hyperthyroidism following external or internal thyroid irradiation at lower doses are limited. In a study of thyroid diseases in Hiroshima and Nagasaki atomic bomb survivors in which 69% of the participants received doses < 0.5 Sievert (Sv), there were 38 cases of Graves' disease diagnosed up to 55–58 years after radiation exposure (28). Based on a linear model, at age ten years at exposure to the bombings, the estimated excess odds ratio per Sv (EOR_{Sv}) for survivors was elevated ($EOR_{Sv} = 0.49$, 95% CI: −0.06–1.69), although not significantly so ($P = 0.10$). To the best of our knowledge, only two studies have reported results concerning the relationship between environmental I-131 exposure and subsequent risk of hyperthyroidism. Based on different outcome definitions for hyperthyroidism, the results were null in the Hanford thyroid disease study (mean I-131 thyroid dose = 0.17 Gy) five decades after exposure (36); similarly, in preliminary analyses of the Ukraine-NCI Chornobyl thyroid screening study 12–14 years following the Chornobyl accident (mean I-131 thyroid dose = 0.77 Gy) no association was observed for subclinical hyperthyroidism overall, although a suggestive non-significant association was observed in females (37).

In summary, there is some evidence that thyroid irradiation at high doses could be associated with increased risk of hyperthyroidism, however the magnitude and shape of the dose-response remain uncertain. The data concerning risk of hyperthyroidism following medium to low thyroid doses of external or internal I-131 irradiation are particularly sparse and more research in this field is needed.

Hypothyroidism—The data that hypothyroidism might be induced by radiation derives from many sources (38,39). Primary hypothyroidism is the most common clinical consequence of irradiation of the thyroid in patients who have received high therapeutic doses of radiation to the head and neck area (24,34,35,40). For subjects with a history of Hodgkins lymphoma treated with radiotherapy, the incidence of hypothyroidism was significantly increased (RR = 17.1, $P < 0.0001$) compared to that in sibling controls (24). The greatest risk of hypothyroidism occurred during the first 5 years after treatment, but new cases continued to emerge more then 20 years after radiotherapy for Hodgkins lymphoma. In another study of Hodgkins lymphoma survivors, the actuarial risk of both overt and subclinical hypothyroidism at 20 years was 44% for patients who received ≥ 30 Gy to the thyroid, 27% for those who had received 7.5–30 Gy, and 2% for those who had not undergone irradiation of the thyroid region ($P < 0.009$) (34). Among the ALL survivors, the highest risk of subsequent hypothyroidism was among those who received ≥ 20 Gy of cranial radiotherapy plus any spinal radiotherapy compared to those treated with chemotherapy alone (hazard ratio, HR = 8.3, 95% CI: 3.3–20.5) (35).

Hypothyroidism is also a major side effect of radioactive iodine treatment (I-131) for hyperthyroidism with cumulative incidence between 42–72% 20–25 years after the treatment (41). Thyroid doses of I-131 used in conventional treatment for hyperthyroidism are comparable or even higher (typically ranging from 30 to 80 Gy) than those used in irradiating tumors of the head and neck, with the lower doses usually given for Graves' disease and the higher doses for toxic nodular goiter (38). However, there is no consensus about what schedule of radioactive iodine administration is preferred (fixed empirical activity for all patients or individualized administration based on size of thyroid gland and uptake of radioiodine) (42). There have been conflicting reports on whether a larger amount of administered activity of I-131 is associated with higher risk of hypothyroidism (41,43). One recent study reported that those who were administered 370 MBq and 600 MBq of I-131 compared to those who were administered 185 MBq of I-131 had 1.75-fold ($P = 0.001$) and 3.79-fold ($P < 0.001$) increase in risk of hypothyroidism one year later (43). In contrast, another study that compared the effects of 259 MBq and 370 MBq relative to 185 MBq of administered I-131 activity did not find a difference in risk of hypothyroidism (41). Because the same administered activity of I-131 can result in substantially different absorbed thyroid doses, and thyroid doses typically are not estimated, these results should be interpreted cautiously.

In contrast to high dose thyroid irradiation, data concerning risk of hypothyroidism after medium to low doses of external or internal irradiation have been inconsistent (20,25,33,44). Although there was an increased prevalence of subclinical hypothyroidism following high-dose exposure to short-lived radioiodines (I-132, I-133, I-135) and external irradiation as a consequence of nuclear weapons testing in Marshall Islanders from Rongelap atoll (44), this was not confirmed in a later larger study that primarily included individuals exposed to substantially lower radiation doses in Ebeye or Majuro atolls (33). The latter negative finding for the Marshallese is in agreement with the results from the Hanford thyroid disease study in which no association was shown between I-131 dose estimates and hypothyroidism, based on various outcome definitions (25). Similarly, no association with hypothyroidism was found in a small screening study of people exposed to I-131 emitted from the Mayak nuclear weapons facility (45). As part of the Adult Health Study (AHS), 4,091 atomic bomb survivors had a clinical thyroid assessment (28). While the dose-response relationship for hypothyroidism as an independent outcome was not presented, the risks for antibody-positive and antibody-negative hypothyroidism were evaluated. The $EORs_{Sv}$ for antibody-positive and antibody-negative hypothyroidism were 0.01 and 0.17 respectively, and neither was significantly different from zero ($P = 0.92$ and $P = 0.31$, respectively). In the most recent analysis of persons exposed to radiation from the Nevada nuclear test site (mean

thyroid dose = 0.12 Gy), there was a suggestive dose-response relationship (P = 0.18) for thyroiditis with hypothyroidism (20) that seemed to be driven by individuals whose thyroid doses were 0.41 Gy or higher, but no data on hypothyroidism alone were presented. The results of post-Chornobyl studies have been mixed. While some studies reported a significant upward shift in TSH levels and increased rates of juvenile hypothyroidism in children living in radionuclide contaminated areas (46–48), the remaining ecological studies were negative (49–52). In a recent cohort study of 11,853 individuals under the age of 18 years at the time of the Chornobyl accident living in an area of mild-to-moderate iodine deficiency (53), the overall prevalence of subclinical hypothyroidism was about 6% (54), an estimate that is somewhat higher than that reported for the U.S. population of comparable age (12). A significant, but small, association between I-131 thyroid dose estimates and prevalent subclinical hypothyroidism, with the EOR_{Gy} of 0.10 (95% CI: 0.03–0.21) based on a linear model was observed in this cohort (Figure 1) (54). The results of this study are noteworthy as the I-131 dose estimates were based on individual thyroid radioactivity measurements taken within eight weeks following the accident and all cohort members underwent in-depth thyroid examination according to a standardized protocol.

Taken together, there is little doubt that risk of hypothyroidism is strongly related to high-dose external or internal I-131 irradiation. While some epidemiologic evidence of such an association at moderate to low doses exists, it is less compelling and requires additional well-designed studies with individual dose estimates to characterize the shape of the dose-response. Much less is known about factors that could potentially modify the dose-response relationship for hypothyroidism (gender, age at exposure, etc.) with the exception of perhaps time since exposure. Although it is not based on formal interaction analyses between individual thyroid doses and time since exposure, there is a suggestion that risk of radiation-related hypothyroidism might be highest within the first 5 years following exposure (24) or that higher doses might be associated with shorter time to onset of hypothyroidism (34). A more exact pattern of radiation risk remains to be clarified.

Autoimmune thyroiditis and related outcomes—Radiation-related thyroiditis includes acute thyroiditis and chronic autoimmune thyroiditis (Hashimoto thyroiditis), while related outcomes would include antibody-positive hypothyroidism and elevated levels of antithyroid antibodies. Because there is no internationally accepted classification or criteria for diagnosis of autoimmune thyroid diseases (55), it is challenging to systematically review studies. In this paper, we used the terms from the original publications although antibody-positive hypothyroidism in the absence of histologically confirmed lymphocytic infiltration of the thyroid is not accepted as Hashimoto thyroiditis by everyone. There is more agreement that elevated levels of antithyroid antibodies in the absence of other clinical or laboratory findings should be considered as evidence of thyroid autoimmunity rather than clinically important autoimmune disease.

The data concerning acute radiation-induced thyroiditis largely come from case reports. Typically, the illness is self-limited. Early onset (within days) of radiation-induced thyroiditis with hyperthyroidism has been reported and is known to occur following I-131 treatment of Graves' disease (56). It is more likely to occur in patients who are thyrotoxic at the time of treatment. Acute radiation-induced thyroiditis following high-dose external beam radiotherapy for cancer has also been reported, but it tends to occur later, starting from two months on (57). It has been speculated that early occurring radiation-induced thyroiditis may often be missed because its symptoms may mimic those attributable to the malignancy or its treatment and thyroid tests may not be performed in such patients on completion of treatment (57). In general, it could be surmised that acute radiation-induced thyroiditis tends to be a high dose phenomenon, but whether it occurs in a dose-dependent fashion remains unclear.

Unlike acute radiation-induced thyroiditis, chronic thyroiditis can be regarded as a long-term consequence of thyroid gland irradiation at low to moderate doses. There have been numerous conflicting analytical and ecological studies concerning autoimmune related outcomes in populations exposed to radiation from atomic bombs in Hiroshima or Nagasaki (58–61), populations exposed at the Nevada nuclear test site (62), Marshall Islands (33,44), and in the vicinity of Chornobyl (47–52). These studies were thoroughly reviewed by Eheman et al. (63) but only five of these studies had reconstructed individual radiation doses and adequate sample size for conducting dose-response analyses (four atomic bomb survivor studies (58–61) and one Nevada test site study (62)). Only the study of Nagasaki atomic bomb survivors found a significant association between thyroid dose and prevalence of antibody-positive hypothyroidism (58). In that study, a linear-quadratic model predicted the maximum prevalence of antibody-positive hypothyroidism at a dose of 0.7 Sv. The Nagasaki study, together with post-Chornobyl ecologic studies that used location at the time of the accident as a surrogate of dose served as the basis for Eheman's conclusion that there is suggestive evidence of a higher than expected increase in prevalence of antithyroid antibodies due to environmental radiation exposure, but more long-term studies with adequate dosimetry and standardized outcome definitions are necessary to validate these findings. Since this review, only a few additional studies have been published adding both negative and positive data (Table 3). Specifically, no association between thyroid dose and risk of antibody-positive hypothyroidism was found in the Hanford thyroid disease study (25) and the updated study of atomic bomb survivors in Hiroshima and Nagasaki (28). In the most recent analysis of the Nevada cohort, Lyon et al. presented an updated analysis that included modifications to dosimetry model and thyroid disease diagnoses (20). The authors found an increasing risk of autoimmune thyroiditis with increasing thyroid dose ($P < 0.001$). By contrast, no association for clinically important autoimmune thyroiditis or antibody-positive hypothyroidism with I-131 thyroid doses was found in a cohort study of 12,240 residents of northern Ukraine who were less than age 18 at the time of the Chornobyl accident and were examined 12–14 years after exposure (64). Interestingly, in this study prevalence of elevated levels of ATPO alone was associated with I-131 thyroid dose (Figure 1). The association was modest and best described by several concave models. In a similar study of Russian children exposed to Chornobyl fallout who had measurement-based individual thyroid doses, there was no evidence of a dose-response relationship for autoimmune thyroiditis that was diagnosed by ultrasound and confirmed by TSH and ATPO measurements 11–13 years after the accident (65). The authors did not evaluate the dose-response relationship for ATPO prevalence separately because ATPO measurements were not available for all study participants. Finally, Agate et al. (66) recently confirmed an earlier finding (51) of a higher prevalence of ATPO in children living in contaminated relative to non-contaminated Belarusian settlements, but the prevalence of ATPO 13–15 years after the Chornobyl accident was lower than that reported six to eight years after the accident. No changes in levels of TSH or fT4 were observed during either time period. The authors concluded that the autoimmune reaction may have been transient, without triggering clinical autoimmune thyroid disease, although the study populations and antibody assays in the original and follow-up report were different and therefore may have provided the reason for the observed changes in ATPO prevalence.

In summary, studies of autoimmune-related thyroid outcomes are difficult to interpret due to the multi-symptom nature of these complex diseases and lack of standard definitions. Very high thyroid doses may result in acute radiation-induced thyroiditis, however the data are limited and whether there is a dose-response is unknown. Data concerning chronic autoimmune thyroiditis and antibody-positive hypothyroidism from environmental radiation of the thyroid gland are abundant, yet inconsistent. The current evidence is more supportive of radiation effects on prevalence of antithyroid antibodies rather than clinically relevant disease. When trying to reconcile all pieces of evidence, one needs to consider the unique

circumstances of population exposure including different types of radiation or mix of radionuclides, dose rates, ages at exposure, or time since exposure and how little is known about whether radiation-related risk of autoimmune thyroid outcomes varies according to these factors.

Mechanisms for radiation-induced thyroid diseases—Precise physiological events that lead to benign thyroid diseases following radiation remain largely unknown (39,67). RET/PTC chromosomal rearrangements commonly are involved in the molecular pathogenesis of radiation-associated papillary thyroid carcinomas and ionizing radiation has been reported to induce these rearrangements in many studies (68–70), but the frequency of RET/PTC activation was not related to radiation dose in one study (71). The role of RET/PTC rearrangements in relation to thyroid nodules is much less obvious. Elisei et al. reported that the frequency of RET/PTC rearrangements was higher in post-Chornobyl thyroid nodules and those occurring after external radiation than in spontaneous occurring nodules (72); however, Tuttle et al. did not find a radiation dose-response relation with frequency of RET/PTC activation (71). Recently, 23 polymorphisms in 13 genes were examined in 1,821 persons (907 with thyroid nodules and 914 controls) exposed to radiation from nuclear testing in Kazkhstan (73). Polymorphisms in RET signaling, DNA repair and growth stimulation genes were associated with nodule occurrence and there was a suggestion of a gene-radiation interaction for a variant in a DNA repair gene.

It is likely that acute functional changes in the thyroid gland following very high doses of radiation may result from direct killing of follicular thyroid cells, reduced number of functional follicles, and damage to thyroid vessels or vascular permeability. It has been suggested that functional thyroid changes occurring at a later point in time or changes at lower doses, could be due primarily to indirect vascular damage, inflammation contributing to thyroid ischemia, and various degrees of lymphocytic infiltration and/or immunologic reactions (39,67). Exactly how thyroid irradiation triggers an immune response is unknown, but possibly could result from the immune system being exposed to existing or transformed antigens on already radiation-damaged thyroid cells. Given that biological mechanisms underlying structural and functional changes in the irradiated thyroid might differ, one may anticipate that the shape of the dose response and the pattern of radiation risk with age at exposure, time or other characteristics may also differ for structural and functional thyroid outcomes. However, more human data are needed to establish if this is likely to be true.

CONCLUSIONS

While a great deal of information on radiation-related risks is available regarding thyroid cancer, only limited data exist on benign nodules and functional thyroid diseases. Partly this is due to the difficulties in defining the endpoints and partly it is due to the expense in obtaining information on diseases that are not routinely collected by national or regional registries. Thus, the data presented in this review are complicated by the various methods used for case ascertainment and the diagnostic criteria which were not uniform across studies. As with all studies of thyroid disease, there is also a potential bias from differing levels and frequency of medical surveillance and the types of diagnostic examinations performed. However, when the same clinical protocol was used in a specific study, e.g. the Hanford thyroid disease study or Ukraine-NCI Chornobyl studies, such bias is unlikely.

A review of the studies that provided quantified risk estimates demonstrates a significant dose response for follicular adenomas and benign nodules. In those studies that evaluated the shape of the dose response, a linear dose response appeared to fit the data up to at least 5 Gy. Few studies had the statistical power to evaluate effect modification by sex, age or time. Considerably less consistent findings are available regarding functional thyroid diseases,

partly due to the greater difficulties studying these diseases. In general, associations for functional thyroid diseases were fairly weak with some suggestion that they may be transitory. Significant effects of radiation were most often observed following high radiation doses. Significantly increased risks of hyperthyroidism were only demonstrated following radiotherapy doses of >15 Gy although there was some suggestion of an elevated risk among atomic bomb survivors receiving substantially lower doses. Hypothyroidism is a well known effect of high dose radiotherapy for cancer and of I-131 treatment for hyperthyroidism, but effects at low to moderate doses are not clear. High dose radiation exposure appears to enhance the risk of acute thyroiditis, but the role of lower doses in the etiology of chronic autoimmune thyroiditis and related outcomes is unresolved. To improve our understanding of the relation between radiation and functional thyroid disease, large studies with clearly defined endpoints and individual dose estimates will need to be conducted.

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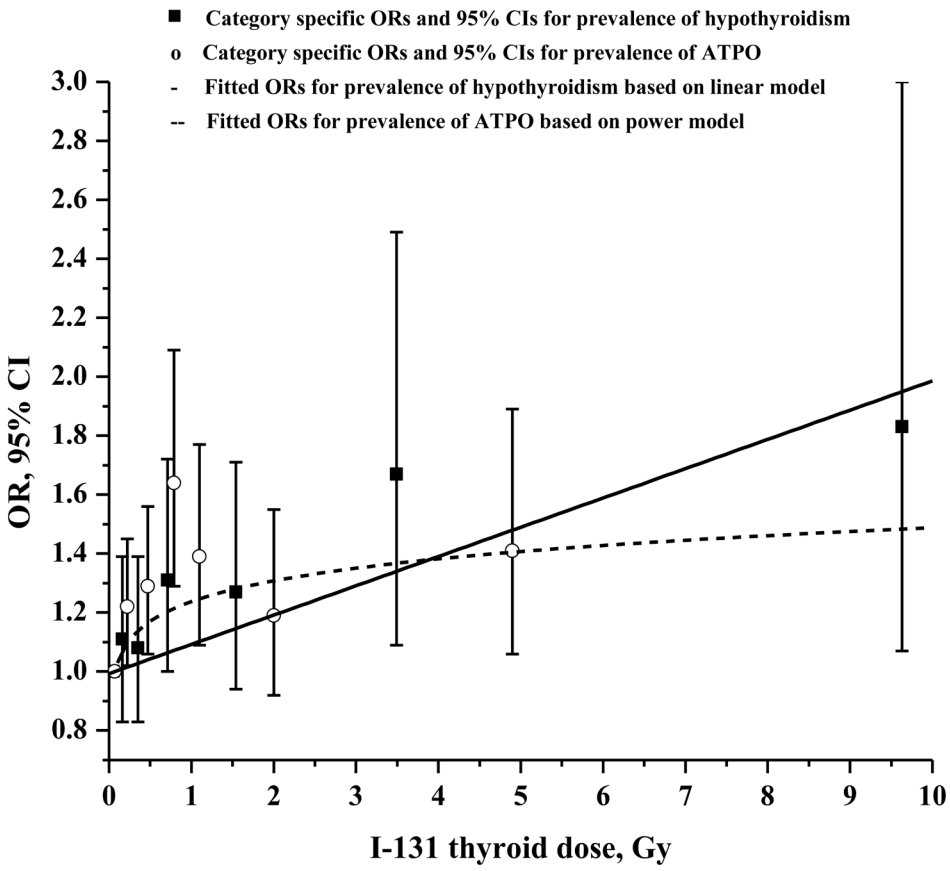

Figure 1.

Dose-response relationships for prevalence of antibodies to thyroid peroxidase (ATPO) and hypothyroidism with I-131 thyroid dose estimates: Ukrainian-American cohort study of thyroid cancer and other thyroid diseases following the Chornobyl accident, 1998–2000. Power dose-response model for prevalence of ATPO was plotted as OR = dose $^{0.08}$ and linear dose-response model for prevalence of hypothyroidism was plotted as OR = 1 + 0.10*dose; both lines were adjusted to pass through the lowest I-131 category.

TABLE 1

Radiation-Related Risks for Follicular Adenoma Compared With Cancer

Study (Reference)	Exposed/Non-exposed	Mean thyroid dose (range), Gy	Type of radiation	Age at exposure, yr	Follicular adenoma		Cancer	
					Cases[a]	ERR_{Gy} (95% CI)	Cases[a]	ERR_{Gy} (95% CI)
Israel Tinea Capitis (15,74)	10,834/26,226	0.09 (0.04–0.5)	Medical X-ray	0–15 Mean=7.4	43	8 (7–10)	159	20.2 (11.8–32.3)
New York Tinea Capitis (4,16)	2,224/1,389	0.06	Medical X-ray	1–15 Mean=7.8	12	93 (1.7–647)	2	∞[b]
Rochester Thymus[c] (17)	2,475/4,991	1.36 (0.03–11)	Medical X-ray	0–1 Median=5 (weeks)	97	6.3 (3.7–11.2)[d]	42	9.0 (4.2–21.7)
French Hemangioma (18)	3,795/972	0.039 (0–5.4)	Medical X-ray, ^{90}Sr, ^{32}P, ^{90}Yr	0–68 Mean=1.5	44	5.7 (0.7–19)	11	14.7 (1.6–63)
Ukraine-NCI Chornobyl Screening (19,75)	12,504	0.77	Atmospheric emissions I-131	0–18 Mean=7.8	23	2.07 (0.28–10.3)	45	5.25 (1.7–27)
Nevada Test Site (20)	2,492	0.12	Fallout I-131	<7	13	NE[f], P < 0.001	8	0.8 (0–15)

[a] Includes irradiated and non-irradiated cases

[b] There were 2 cancers among the exposed and 0 among the non-exposed subjects

[c] Includes subjects with 5+ years of follow-up

[d] When individuals with doses over 6 Gy were excluded, the ERR_{Gy} was 7.8 (90% CI: 4.6–14.1)

[e] Follicular adenoma cases defined as any benign adenoma ≥1.0 cm

[f] Not estimable

TABLE 2

Radiation-Related Risks for Thyroid Nodules

Study (Reference)	Exposed/Non-exposed	Mean thyroid dose (range), Gy	Type of radiation	Age at exposure, yr	Method of detection	Cases[a]	ERR_{Gy} (95% CI)
Israel Tinea Capitis (15,74)	10,834/26,226	0.09 (0.04–0.5)	Medical X-ray	0–15 Mean=7.4	Thyroid pathology search in all pathology departments in country, slides or records reviewed by study pathologist	53	8 (7–9)
Chicago Tonsils (21)	2,634/0	0.59 (0.46–0.72)	Medical X-ray	0–15 Mean=4.3	Thyroid palpation, surgically confirmed nodules	549	8.2 (3–37)
Boston Lymphoid Hyperplasia (4,30)	1,195/1,063	0.24 (0.03–0.55)	Medical X-ray	0–18 Mean=6.5	Self reported on questionnaire, medical verification		64 (18–225)
Swedish Diagnostic I-131 (29)	1,005	0.54	Medical I-131	Adult	Thyroid palpation by two thyroid specialists		0.9 (0.3–2.3)
Atomic Bomb Survivors[b] (28)	1,815/1,370	0.50	Bomb explosions Gamma radiation	All ages Mean=15.4	Thyroid exam including palpation and ultrasound, nodules >1 cm histologically or cytologically confirmed	156	1.5 (0.76–2.7)
Nevada Test Site (20)	2,492	0.12	Fallout I-131	<7	Thyroid exam, method changed from palpation only to palpation and ultrasound, some nodules were cytologically confirmed	49[c]	4.6 (1.1–12)
Hanford Thyroid Diseases[d] (25,26)	2,823/368	0.17 (0–2.8)	Atmospheric emissions I-131	0–17	Thyroid exam including palpation and ultrasound, nodules >1.5 cm histologically or cytologically confirmed	235	−0.008 (<−0.02–0.04)
Kazakhstan Test Site (27)	2,994	External: 0.04 (0–0.65) Internal: 0.31 (0–9.6)	Fallout I-131	0–21	Ultrasound exam, nodules cytologically confirmed	916[e]	0.74 (0.22–1.2)

[a] Includes irradiated and non-irradiated cases

[b] Non-exposed defined as persons exposed to less than 0.005 Sv. Follicular adenomas were included in the nodule category, and they were not analyzed separately. ERR is for 10 years of age at exposure

[c] Includes 8 cancers

[d] The 249 persons (14 with benign nodules) living outside of the study area are not included in the dose response analyses. Non-exposed defined as persons exposed to 0 to 0.009 Sv

[e] Include 26 thyroid cancers

TABLE 3

Radiation Risks for Autoimmune-Related Outcomes

Study (Reference)	Mean thyroid dose, Gy	Type of radiation	Age at exposure, yr	Time since exposure, yr	Outcome definitions	EOR_{Gy} (95% CI)
Hanford Thyroid Diseases (25)	0.17	Atmospheric emissions I-131	0–17	35–53	Elevated levels of antibodies ATPO[a]/ATG[b]/AMA[c] Antibody-positive hypothyroidism Antibody-positive hypothyroidism with very high levels of ATPO	−0.039 (<−0.071–0.036) 0.000 (<−0.010–>0.015) 0.000 (<−0.001–>0.001)
Nevada Nuclear Weapons Test Site (20)	0.12	Fallout I-131	≤ 7	24–35	Autoimmune thyroiditis [d]	4.9 (2.0–10.0)
Atomic Bomb Survivors (28)	< 0.5 (69%)	Bomb explosions Gamma radiation	All ages Mean=15.4	55–58	Elevated levels of antibodies: ATPO ATG Antibody-positive hypothyroidisim	0.01 (−0.12–0.19) −0.04 (−0.13–0.09) 0.01 (−0.20–0.40)
Ukrainian-NCI Chornobyl Thyroid Screening (64)	0.79	Atmospheric emissions I-131	0–18 Mean=7.8	12–14	Autoimmune thyroiditis[e] Antibody-positive hypothyroidism Elevated levels of ATPO	−0.05 (−0.11–0.11) 0.03 (−0.10–0.38) OR_{1Gy} = 1.2–1.4[g] (P < 0.01)
Children from Kaluga and Bryansk regions of Russian Federation exposed to Chornobyl fallout (65)	0.13	Atmospheric emissions I-131	0–10	11–13	Autoimmune thyroiditis [f]	NA [h] (P > 0.05)
Populations exposed to Chornobyl fallout during childhood (66)	NA [g]	Atmospheric emissions I-131	Mean=1	13–15	Elevated levels of ATPO/ATG	Prevalence of ATPO > in residents of contaminated Belarussian villages compared to non-contaminated villages (6.4 vs. 2.4%; P = 0.02)

[a] Antibodies to thyroid peroxidase

[b] Antibodies to thyroglobulin

[c] Antimicrosomal antibodies

[d] Defined as ATG/AMA above normal limit with or without other thyroid abnormalities or based on pathology reports when available

[e] Defined as a combination of laboratory (ATPO/TSH), ultrasonographic, and palpable findings indicative thyroid gland abnormality

[f] Defined based on ultrasonographic findings and confirmed by ATPO/TSH measurements

[g] For a dose of 1 Gy, the OR was between 1.2–1.4 based on several curvilinear models

[h] Not available