

Environmental Exposures and Autoimmune Thyroid Disease

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Background: Environmental exposures, ranging from perchlorate in rocket fuel to polychlorinated biphenols, have been shown to influence thyroid function. Although most of these agents are associated with reduced thyroid hormone levels or impaired thyroid hormone action, a number of environmental exposures confer an increased risk of autoimmune thyroid disease.

Summary: Factors that increase autoimmune thyroid disease risk include radiation exposure, both from nuclear fallout and medical radiation, increased iodine intake, as well as several contaminants in the environment that influence the thyroid. Although ~70% of the risk for developing autoimmune thyroid disease is attributable to genetic background, environmental triggers are thought to play a role in the development of autoimmune thyroid disease in susceptible individuals.

Conclusions: Understanding the association of environmental agents with thyroid dysfunction can be utilized to reduce the risk to populations. Knowledge of the specific factors that trigger autoimmune thyroid disease and their mode of action, however, may also inform risk reduction in the individual patient. These factors are especially relevant for those at increased risk of autoimmune thyroid disease based on family history.

Assessing the Impact of Environmental Agents on the Thyroid

ENVIRONMENTAL AGENTS interfere with thyroid function at multiple sites, including thyroid hormone synthesis, thyroid hormone metabolism and excretion, and thyroid hormone action (1–4). Most of these agents reduce circulating thyroid hormone levels or impair thyroid hormone action, although some may influence the pituitary and thyrotropin (TSH) secretion, or even be partial thyroid hormone receptor agonists. A number of environmental agents interfere with iodine uptake. For these agents, low iodine intake increases susceptibility and adequate iodine intake is recommended to reduce their effect (3,5).

The thyroid is able to compensate, continue to produce a normal amount of thyroid hormone despite disruption, in response to some of these agents by increasing serum TSH (3,5). The success of this compensation can be assessed in the adult based on markers of thyroid hormone action, but is much more difficult to determine during fetal development and in infants and children. Brain development is the best-characterized pathway that is thyroid hormone dependent and vulnerable to thyroid hormone disruption (6). Local thyroid hormone activation and timing of availability of tri-

iodothyronine (T3) is critical in brain and sensory development. Agents that interfere with thyroid hormone signaling during this period are the most difficult to detect and quantify. A significant focus in clinical thyroid disease is to detect and evaluate thyroid disease at the earliest stages (7). Recent efforts in assessing the impact of environmental agents that disrupt thyroid function have focused on identifying the earliest and subtle effects (8).

A less often recognized impact of environmental agents that influence the thyroid is triggering autoimmune thyroid disease. The etiology of most functional disorders of the thyroid is autoimmunity. Abnormal thyroid function detected in association with an environmental exposure is usually thought to be a direct effect of the agent. The dysfunction, however, could be due to the agent triggering autoimmune thyroid disease.

The ideal study of the impact of a thyroid toxicant matches a direct measure of exposure in an individual to their thyroid function. These findings are best interpreted with knowledge of the factors that can influence thyroid function, including thyroid autoantibody status, iodine intake, smoking history, family history of autoimmune thyroid disease, pregnancy, and use of medication. In most studies, these data are not all available. Thyroid autoimmunity should be considered as a

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contributing factor to thyroid changes seen with environmental agents. These studies are also relevant to understanding the pathogenesis of autoimmune thyroid disease and the potential role of environmental agents in this process.

Autoimmune Thyroid Disease

The common model of the onset of autoimmune thyroid disease involves an underlying genetic predisposition and a trigger(s) that initiate the cascade of events and sustain the process, culminating in thyroid hypofunction or hyperfunction. This process has been extensively studied and described (9). It has been estimated, based on twin studies (10), that 70%–80% of susceptibility to autoimmune thyroid disease is on a genetic basis. The specific genes involved include human leukocyte antigen-DR3, cytotoxic T lymphocyte-associated factor 4, CD40, protein tyrosine phosphatase-22 gene, thyroglobulin (Tg), and TSH receptor (9). The identified genetic association with autoimmune thyroid diseases confers susceptibility to Graves' disease, Hashimoto's disease, or both.

The remaining 20%–30% contribution to the onset of autoimmune thyroid disease is thought to be due to environmental exposures or triggers. There are a number of exposures that have been identified and proposed, both from human and animal studies (11–14). These include infections, life stress, iodine intake, smoking, medications such as amiodarone and interferon, radiation, and environmental toxicants (Table 1). A prospective study of 790 women with first- or second-degree relatives with proven autoimmune thyroid disease determined the strongest predictors of a thyroid event, overt hypothyroidism or hyperthyroidism (11). Those who developed a thyroid event had, at baseline, a higher TSH, higher thyroid peroxidase (TPO) antibody levels, and more relatives with Hashimoto's disease (11). None of the triggers of autoimmune thyroid disease that were studied directly contributed to the development of a thyroid event. Geographic susceptibility has also been shown for some autoimmune diseases, but thyroid autoimmunity occurs throughout the world and does not have a distinct geographic distribution

(15). This study did not look at iodine intake in specific regions, however, which would be expected to impact the incidence of autoimmune thyroid disease in a specific area as described below.

The relative importance of these environmental factors in the development of autoimmune thyroid disease is not established. Only a few prospective studies have followed at-risk individuals to determine the relative importance of these exposures. A recent prospective study followed a cohort of 521 individuals, with a family history of autoimmune thyroid disease, but negative thyroid autoantibodies (16). Stressful life events, pregnancy, drug exposure, iodine intake, and other factors were assessed. All of these events were equal in the group that developed autoimmune thyroid disease and the group of those that did not, except smoking. There was a significant association with cessation of smoking and an increase in the incidence of hypothyroidism. Smoking has been associated with reduced thyroid hormone action (17) and exacerbating Graves' disease, especially Graves' ophthalmopathy (18). The increase in the onset of autoimmune thyroid disease with cessation of smoking fits with an overall lower incidence of hypothyroidism and TPO antibody positivity in smokers compared to nonsmokers (19).

The relative high prevalence of thyroid autoantibodies in the population, especially in women, the wide range of known triggers, and slow onset of autoimmune thyroid disease make this process difficult to associate with environmental agents. Environmental exposures are, for the most part, subtle and occur over a long period, and exposure is difficult to determine in an individual. These factors make it a challenge to confidently link a specific exposure to thyroid autoimmune disease. Additionally, most individuals are exposed to multiple environmental toxicants, and the combination of factors may also be significant for effects on the thyroid. The presence of thyroid autoantibodies is clearly a risk for autoimmune thyroid disease, but the magnitude of thyroid autoantibody titer may also be important (11).

The environmental factors most closely associated with susceptibility to autoimmune thyroid disease include

TABLE 1. PARTIAL LIST OF ENVIRONMENTAL AGENTS THAT INTERFERE WITH THYROID FUNCTION

<i>Agent</i>	<i>Example of sources</i>	<i>Mode of action</i>	<i>Associated as a trigger or accelerating autoimmune thyroid disease</i>
PCBs	Found in coolants and lubricants, multiple congeners, lipophilic	TR agonist/antagonist, can alter levels of T4 and TSH	Possible increase in TSH, thyroid autoantibodies, thyroid volume
Organochlorine pesticides	Used as pesticide on crops	Induce hepatic UDPGTs and glucuronidate T4, accelerating metabolism	No human studies establishing association
PBDEs	Found in flame retardants	Bind to TRs, displaces T4 from binding proteins	Increase in HT in some studies
BPA	Used in plastic bottles	Antagonize TR	No human studies establishing association
Perchlorate, thiocyanate	Rocket fuel, fertilizer, smoking	Inhibits iodine uptake	No human studies establishing association
Triclosan	Antibacterial in soaps	Reduce serum T4, disrupt amphibian development	No human studies establishing association
Isoflavones	Soy products	Inhibits TPO activity	Possible increase in HT

PCBs, polychlorinated biphenyls; TR, thyroid hormone receptor; T4, thyroxine; TSH, thyrotropin; UDPGTs, uridine diphosphate glucuronyltransferase; PBDE, polybrominated diphenylethers; HT, Hashimoto's thyroiditis; BPA, Bisphenol-A; TPO, thyroid peroxidase.

radiation, iodine intake, and environmental toxicants. The mechanism of action for most thyroid toxicants is not established, but this information is not required to make an association of exposure with thyroid dysfunction. Although there are limited data in this area to translate to the management of individual patients, there are findings that can contribute to a strategy of risk reduction.

Radiation

Radiation is perhaps the best characterized environmental exposure linked to effects on the thyroid. The most common thyroid manifestation of radiation is hypofunction, as well as thyroid nodules and thyroid cancer. Autoimmune thyroid disease has been linked to therapeutic medical radiation (20–22), as well as environmental radiation exposure (23–28). Both the atomic bomb detonations in Japan (24) and nuclear contamination from the Chernobyl nuclear power plant accident (27) have been associated with an increased risk of autoimmune thyroid disease. This association, however, has not been a consistent finding in all studies, with several showing no effect (24,28). Radiation exposure from a nuclear incident generally occurs at a known time, and an approximation of the exposure can be obtained from the location of the exposed individual and content and patterns of radioactive release and fallout. Significant variation in individual effects of radiation on the thyroid is likely, however, due to factors such as age, gender, the presence of thyroid autoantibodies, dietary iodine intake, use of dairy products where iodine isotopes are concentrated, and variations in weather patterns and food and water intake.

Medical radiation

Stimulation of antithyroid antibodies and autoimmune thyroid disease has been associated with external radiation for Hodgkin's disease (20,21). Thyroid hypofunction is the most common manifestation, due to direct destruction of the radiation, but stimulation of thyroid autoantibodies may be another mechanism for both hypothyroidism and hyperthyroidism due to Graves' disease. Several studies have shown that patients receiving ^{131}I for toxic goiter later develop Graves' disease and, in some cases, Graves' ophthalmopathy (21). In patients treated with radioiodine for thyroid autonomy, a sensitive TSH receptor antibody measurement showed that low level thyroid autoantibody positivity was associated with the development of Graves' disease after radioiodine (21). Awareness of the spectrum of thyroid functional disorders reported after medical radiation exposure, both hypothyroidism and hyperthyroidism, should lead to earlier recognition in those who are at risk.

Radiation release from nuclear bomb and accidents

An association of autoimmune thyroid diseases with radiation exposure from nuclear fallout, from the atomic bomb detonated in Japan and the Chernobyl disaster, have been reported. Radiation is clearly associated with thyroid hypofunction, thyroid nodules, and thyroid cancer (23,24). These effects are generally associated with greater radiation exposure and can be tracked with position of the exposed individual at time of the accident, or, in the case of the Chernobyl

exposure, the pattern of the wind currents dispersing radiation. Other exposures, such as Hanford in Washington State, the site of radioisotope production for the atomic bomb, have not been associated with measurable thyroid effects in those exposed compared to controls (29). The initial study of atomic bomb survivors in Japan showed an increase in the incidence of thyroid autoimmunity (23), but a more recent study, with longer follow-up, did not (24). A study of children exposed to radiation from Chernobyl showed an increase in thyroid size, higher serum TSH levels, and a greater incidence of thyroid autoantibody positivity, although iodine intake in the area was low (27). A more recent study of those exposed to radiation from the Chernobyl accident showed an increase in thyroid autoantibodies, but not an increase in the incidence of hypothyroidism (28). It is possible that there is not an increase in autoimmune thyroid disease in response to radiation exposure (26). Another possibility is that the increase in autoimmune thyroid disease occurs during a specific window of time after exposure, in contrast to the increase incidence of thyroid hypofunction, nodules, and cancer that persists after exposure for as long as it has been studied. This is consistent with studies in Japan and Chernobyl showing an increase in autoimmune thyroid disease in the initial follow-up studies after exposure, but not in later studies with longer follow-up. Workers at nuclear power plants did not have an increase in thyroid cancer or autoimmune thyroid disease, but did have a higher serum TSH than controls (30). A long-term follow-up of children exposed to nuclear testing in Nevada, from 1951–1962, showed an increased risk of autoimmune thyroid disease for those in the highest dose exposure group (31).

The thyroid manifestations of radiation exposure vary, likely due to underlying genetic susceptibility, iodine intake, and pattern of radiation exposure. Some individuals have thyroid destruction, others develop nodules and cancer, and others activate thyroid autoantibodies, some of whom, in a specific time frame, develop autoimmune thyroid disease.

Iodine

Iodine is essential for thyroid hormone production, although a number of regulatory factors allow a normal amount of thyroid hormone to be produced across a fairly wide range of iodine intake (32). Iodine intake in the United States has been declining (33), although more recent studies shows that it has stabilized at a sufficient level (34). Concerns remain, though, in the United States and other areas for iodine sufficiency during pregnancy, a time of increased iodine requirements (3). Deficient iodine intake is well known to be associated with reduced thyroid hormone production. Excess iodine, however, can also have adverse effects depending on underlying thyroid function, as well as the extent and duration of iodine excess (32). The acute response to increased iodine intake with a normal underlying thyroid is reduced thyroid hormone production and release, the Wolff–Chaikoff effect. In most individuals with normal thyroids, there is an escape from this effect after 5–7 days. Those with underlying thyroid dysfunction, however, may be unable to escape from this effect and have persistent hypothyroidism. Patients with multinodular goiter and associated areas of autonomous, TSH-independent, thyroid hormone production can have excess thyroid hormone production in response to iodine, the Jod–Basedow effect.

In response to iodine supplementation in areas of iodine deficiency, there is an increase in thyroid autoantibodies and in some cases autoimmune thyroid disease (13,14,35,36). A similar finding of response to iodine has been reported in animal studies of rats with a genetic predisposition to thyroid autoimmunity (37). The interaction between the existing iodine intake in a community and the magnitude of iodine supplementation, with resulting thyroid disease, is complex and has been reviewed in detail (35). Most, but not all, reports of an increase in thyroid autoimmunity are in communities with iodine deficiency after repletion with relatively high dose iodine.

The mechanism of stimulation of autoimmune thyroid disease in response to iodine supplementation is not established. Excess iodine intake is associated with highly iodinated Tg, which is thought to be more immunogenic than poorly iodinated Tg (13,35). Other mechanisms include a direct toxic effect of iodine on thyroid cells via free oxygen radical generation, and immune stimulation by iodine (35). Dietary goitrogens, such as forms of the root cassava, may also increase thyroid immunogenicity and promote thyroid autoantibodies.

Regular and adequate iodine intake is optimal for the thyroid and reduces susceptibility to agents that influence the thyroid by interfering with iodine uptake, such as perchlorate (3). Excess iodine, however, is associated with adverse effects, especially in those with underlying multinodular goiter or with thyroid autoantibodies. Recognition of these effects of iodine supplementation are important, but should be kept in perspective (32,35). The benefits of iodine repletion far outweigh any increase in thyroid autoimmunity and should not deter continued progress in efforts to ensure global iodine sufficiency. Adequate and consistent iodine intake is recommended.

Environmental Toxicants

A wide range of environmental toxicants have been identified that interfere with thyroid hormone production, metabolism, and action (1–3). Most of these agents, at sufficient doses, interfere with thyroid function and their effect can be detected by an elevation in serum TSH or a reduction in serum thyroxine (T4) or T3. It is now recognized, however, that a number of these agents may also interfere with the hypothalamic–pituitary–thyroid regulatory axis and be associated with a reduced serum T4 or T3 concentration, but a normal range TSH (8). Animal and human studies, especially those examining brain development, indicate the potential for a more subtle disruption of local thyroid hormone production or action that may be difficult to detect based on circulating thyroid hormone levels (4,8). There are also some agents, such as polychlorinated biphenyls (PCBs), that may have intrinsic thyroid hormone agonist actions (8). The challenge with any toxicant is to link exposure in an individual to specific actions on thyroid function.

An increased incidence of autoimmune thyroid disease has been associated with exposure to a number of environmental agents, and a few examples will be discussed. Mechanistic studies for how these environmental agents might trigger autoimmune thyroid disease have not, for most agents, been done. The association, however, may be similar to thyroid hypofunction associated with some medications in the back-

ground of autoimmune thyroid disease. An individual with thyroid autoantibodies or susceptibility is exposed to an agent that interferes with thyroid hormone production or metabolism, and is not able to compensate with an increase in thyroid hormone production.

Soy protein and soybean isoflavones have been associated with reduced T4 absorption (important for hypothyroid infants on soy formula), interference with thyroid hormone action (38), and, in a few studies, increased thyroid autoimmune disease. In clinical studies, the usual intake of dietary soy in those with normal thyroid function has no consistent adverse effects (39). Most studies of isoflavone interference with thyroid hormone action have been *in vitro* (39). A case-control study of children with autoimmune thyroid disease showed that cases received significantly more soy formula as infants compared to their nonaffected sibling controls (40).

Chemical exposure is ubiquitous and many have been shown to affect thyroid function (Table 1). Perchlorate, an oxidizer in rocket fuel that inhibits iodine uptake, is found in water, food, and even breast milk (3,41). A large study of pregnant women in Chile with high perchlorate exposure showed no increase in autoimmune thyroid disease or antibodies in pregnancy or the postpartum period, although iodine intake was quite high (42). PCBs were used in electrical equipment manufacturing and include over 200 congeners (2). A large long-term study of adults in Slovakia measured PCB exposure in individuals and found an association of greater exposure with an increase in thyroid volume, serum TSH, and thyroid autoantibodies, especially in women (43). Exposure to polyhalogenated biphenyls and polyhalogenated biphenyl oxides in male factory workers was associated with an increased incidence of antimicrosomal thyroid antibodies and hypothyroidism (44). Organic pollutants, such as polycyclic aromatic hydrocarbons, have also been associated with goiter and thyroid disease (13). A study of people living in proximity to a petrochemical complex in Brazil, however, found no increase in thyroid abnormalities by ultrasonography, thyroid function, and thyroid antibody testing (45).

It is likely that environmental chemicals are increasing susceptibility to autoimmune thyroid disease, but it is difficult to confirm and study. Further mechanistic studies on the environmental toxicants most associated with the induction of autoimmunity should provide a better view of the spectrum of the impact of these agents.

Managing Autoimmune Thyroid Disease Risk in the Individual Patient

Most studies of the thyroid effects of environmental toxicants assess the impact on the population, and it is challenging to apply these findings to an individual patient (Table 2). A further problem in extrapolating findings to the individual is the wide range of cumulative exposures that a single patient can have, most of which are very difficult to assess or monitor. For most of the agents discussed, the individual should obviously avoid exposure. For others, though, knowledge of the increased risk could potentially lead to earlier diagnosis and treatment of autoimmune thyroid disease.

Genetic background

Given that 70%–80% of susceptibility to autoimmune thyroid disease is based on genetics, individuals with a personal

TABLE 2. RISK REDUCTION OF THYROID AUTOIMMUNITY IN THE INDIVIDUAL PATIENT

<i>Susceptibility factor</i>	<i>Mechanism</i>	<i>Reduce or monitor risk</i>
Genetic background: family history of thyroid disease	Increases genetic susceptibility to environmental triggers	Awareness/avoidance of triggers; low clinical threshold for thyroid function testing
Dietary iodine	Increased immunogenicity of thyroglobulin, thyroid cell destruction	Maintain regular and sufficient intake, especially during pregnancy
Dietary selenium	Interaction with immune response	Avoid deficiency, benefit of supplements not established, but may reduce antibody production in specific settings
Cigarette smoking	May increase cytokines in orbit and thyroid, complex interactions with the immune system	Increased risk of Graves' disease and Graves' ophthalmopathy; reduced risk of Hashimoto's disease
Medical radiation	Increases thyroid antigens, inflammation	Awareness of increased incidence of Hashimoto's and Graves' disease, thyroid function test monitoring
Nuclear incident	Direct thyroid destruction, increased thyroid antigens	Potassium iodine ingestion at time of incident
Medications	Stimulation of immune response at multiple sites	Thyroid function tests and thyroid autoantibodies in susceptible individuals, thyroid function test monitoring
Environmental toxicants/chemicals	Promote autoimmune thyroiditis in susceptible animal models	Monitoring thyroid function tests and thyroid autoantibodies, test well water for contaminants

history of autoimmune disease or family history of autoimmune thyroid disease are the most susceptible. Those with a sibling that has autoimmune thyroid disease are at increased risk, especially strong for Hashimoto's thyroiditis (46). Well-established risk factors for autoimmune thyroid disease include being female and older age. In a prospective study, the higher the serum TSH and antithyroid antibody levels, and the more relatives with thyroid disease, the greater risk of progression of thyroid disease (11). Elevated antithyroid antibodies were associated with increased risk of autoimmune thyroid disease in long-term follow-up in the Whickham survey (47). Although reducing exposure risk for autoimmune thyroid disease can be applied to any individual, those in the high-risk categories based on family history are especially susceptible.

Dietary iodine and selenium

The transition from low to high iodine intake is a risk for autoimmune thyroid disease, so maintaining a regular and sufficient iodine intake is prudent. It is recommended that pregnant women take an iodine supplement of 150 μg per day (48), which should also be considered by women of reproductive age planning pregnancy. Dietary goitrogens, such as cassava, grown and eaten primarily in tropical and subtropical regions, may also increase risk and should be avoided. Low selenium intake has been associated with an increase in thyroid autoantibodies, and selenium supplementation with a reduction in antibodies (12). Areas associated with low selenium include China and Western Africa.

Cigarettes

Cigarette smoking, as well as cessation of smoking, have been linked to the onset of autoimmune thyroid disease. The

increase in risk of the onset of autoimmune thyroid disease with cessation of smoking may be useful in monitoring susceptible patients who stop smoking for the myriad health benefits. For example, cessation of smoking may be associated with weight gain, and hypothyroidism should be considered as a cause. Cigarette smoke contains cyanide, which is metabolized to thiocyanate, and can interfere with iodine concentration in the thyroid and in the lactating breast (2).

Pregnancy and the postpartum period

The transition from immune suppression to release from suppression is associated with the onset of a number of autoimmune diseases; postpartum thyroiditis is the most common. The impact of fetal cells on maternal immune response, fetal microchimerism, is increasingly recognized as a trigger for thyroid autoimmunity (12).

Radiation exposure

Those with positive thyroid autoantibodies should be especially vigilant after medical radiation for the onset of autoimmune thyroid disease. Although there are no specific guidelines, follow-up thyroid function tests at 3 and 6 months after therapy should identify most patients with this response to radiation. Those living in the vicinity of a nuclear power plant can keep potassium iodide to use in the event of radiation release. The dose recommendation in adults is an initial dose of 100 mg iodide (130 mg KI) and then a daily dose of 15 mg if the exposure persists (49,50). The dose is adjusted down for children and infants, and there should be caution of use in the elderly as the benefit is less and the potential for iodine-induced hyperthyroidism is higher (49,50). Prompt ingestion of iodine as described should block uptake of at least 95% of radioactive iodine.

Medications

Medications associated with the onset of autoimmune thyroid disease include lithium, amiodarone, interferon α , interleukin 2, campath-1h, and highly active anti-retroviral therapy (2,13). For most of these medications, patients at greatest risk for developing autoimmune thyroid disease are those with previous thyroid autoantibody positivity. Some medications, such as lithium, may not trigger autoimmunity, but accelerate the autoimmune process by interfering with thyroid function. Thyroid function testing and measurement of TPO antibodies should be considered in patients before beginning these medications. Medications differ in their mechanisms of stimulating thyroid autoimmunity, as well as the relative effect on promoting hypothyroidism or Graves' disease (12).

Toxicants

Most municipal water sources are now closely monitored for a range of toxicants, including those that affect the thyroid. Individuals using well water should ensure that it is tested regularly for contaminants. Reduction of exposure to toxicants in the environment and occupational settings, including agents that affect the thyroid, is an ongoing effort involving many groups and agencies (1–6).

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References

- Brucker-Davis F 1998 Effects of environmental synthetic chemicals on thyroid function. *Thyroid* **8**:827–856.
- Pearce EN, Braverman LE 2009 Environmental pollutants and the thyroid. *Best Pract Res Clin Endocrinol Metab* **23**:801–813.
- Brent GA, Braverman LE, Zoeller RT 2007 Thyroid health and the environment. *Thyroid* **17**:807–809.
- Zoeller RT, Dowling ALS, Herzig CTA, Iannacone EA, Gauger KJ, Bansal R 2002 Thyroid hormone, brain development, and the environment. *Environ Health Perspect* **110** (Suppl 3):355–361.
- National Academy of Sciences 2005 Health Implications of Perchlorate Ingestion. National Research Council, National Academy Press, Washington, DC.
- Howdeshell KL 2002 A model of development of the brain as a construct of the thyroid system. *Environ Health Perspect* **110** (Suppl 3):337–348.
- Biondi B, Cooper DS 2008 The clinical significance of sub-clinical thyroid dysfunction. *Endocr Rev* **29**:76–131.
- Miller MD, Crofton KM, Rice DC, Zoeller RT 2009 Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcome. *Environ Health Perspect* **117**:1033–1041.
- Tomer Y, Huber A 2009 The etiology of autoimmune thyroid disease: a story of genes and environment. *J Autoimmun* **32**:231–239.
- Hansen PS, Brix TH, Iachine I, Kyvik KO, Hegedus L 2006 The relative importance of genetic and environmental effects for the early stages of thyroid autoimmunity: a study of healthy Danish twins. *Eur J Endocrinol* **154**:29–38.
- Strieder TGA, Tijssen JGP, Wenzel BE, Endert E, Wiersinga WM 2008 Prediction of progression to overt hypothyroidism or hyperthyroidism in female relatives of patients with autoimmune thyroid disease using the thyroid events Amsterdam (THEA) score. *Arch Intern Med* **168**:1657–1663.
- Prummel MF, Streider T, Wiersinga WM 2004 The environment and autoimmune thyroid diseases. *Eur J Endocrinol* **150**:605–618.
- Burek CL, Talor MV 2009 Environmental triggers of autoimmune thyroiditis. *J Autoimmun* **33**:183–189.
- Tanda ML, Piantanida E, Lai A, Lombardi V, Dalle Mule I, Liparulo L, Pariani N, Bartalena L 2009 Thyroid autoimmunity and environment. *Horm Metab Res* **41**:436–442.
- Shapira Y, Agmon-Levin N, Shoenfeld Y 2010 Defining and analyzing geoepidemiology and human autoimmunity. *J Autoimmun* **34**:J168–J177.
- Effraimidis G, Tijssen JGP, Wiersinga WM 2009 Discontinuation of smoking increases the risk for developing thyroid peroxidase antibodies and/or thyroglobulin antibodies: a prospective study. *J Clin Endocrinol Metab* **94**:1324–1328.
- Muller B, Zulewski H, Huber P, Ratcliffe JG, Staub JJ 1995 Impaired action of thyroid hormone associated with smoking in women with hypothyroidism. *N Engl J Med* **333**:964–969.
- Bahn RS 2010 Mechanisms of disease: Graves' ophthalmopathy. *N Engl J Med* **362**:726–738.
- Belin RM, Astor BG, Powe NR, Ladenson PW 2004 Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the third National Health and Nutrition Examination Survey (NHANESIII). *J Clin Endocrinol Metab* **89**:6077–6086.
- Skla C, Whitton J, Mertens A, Stovall M, Green D, Marina N, Greffe B, Wolden S, Robison L 2000 Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the childhood cancer survivor study. *J Clin Endocrinol Metab* **85**:3227–3232.
- Dunkelmann S, Wolf R, Koch A, Kittner C, Groth P, Schuemichen C 2004 Incidence of radiation-induced Graves' disease in patients treated with radioiodine for thyroid autonomy before and after introduction of a high-sensitivity TSH receptor antibody assay. *Eur J Nucl Med Mol Imaging* **31**:1428–1434.
- Simon Z, Ress Z, Toldi J, Trauninger A, Miltenyi Z, Illes A 2009 Rare association of Hodgkins lymphoma, Graves' disease and myasthenia gravis complicated by post-radiation neurofibrosarcoma: coincidence or genetic susceptibility? *Int J Hematol* **89**:523–528.
- Nagataki S, Shibata Y, Inoue N, Yokoyama N, Izumi M, Shimaoka K 1994 Thyroid diseases among atomic bomb survivors in Nagasaki. *JAMA* **272**:364–370.
- Imaizumi M, Usa T, Tominaga T, Neriishi K, Akahoshi M, Nakashima E, Ashizawa K, Hida A, Soda M, Fujiwara S, Yamada M, Ejima E, Yokoyama N, Okubo M, Sugino K, Suzuki G, Maeda R, Nagataki S, Eguchi K 2006 Radiation dose-response relationships for thyroid nodules and autoimmune thyroid diseases in Hiroshima and Nagasaki atomic bomb survivors 55–58 years after radiation exposure. *JAMA* **295**:1011–1022.

25. Imaizumi M, Ashizawa K, Neriishi K, Akahoshi M, Nakashima E, Usa T, Tominaga T, Neriishi K, Hida A, Sera N, Soda M, Fujiwara S, Yamada M, Maeda R, Nagataki S, Eguchi K 2008 Thyroid diseases in atomic bomb survivors exposed *in utero*. *J Clin Endocrinol Metab* **93**:1641–1648.
26. Boice JD 2006 Thyroid disease 60 years after Hiroshima and 20 years after Chernobyl. *JAMA* **295**:1060–1062.
27. Vermiglio F, Castagna MG, Volnova E, Lo Presti VP, Moleti M, Violi MA, Artemisia A, Trimarchi F 1999 Post-Chernobyl increased prevalence of humoral thyroid autoimmunity in children and adolescents from a moderately iodine-deficient area in Russia. *Thyroid* **9**:781–786.
28. Agate L, Mariotti S, Elisei R, Mossa P, Pacini F, Molinaro E, Grasso L, Masserini L, Mokhort T, Vorontsova T, Arynchyn A, Tronko MD, Tsyb A, Feldt-Rasmussen U, Juul A, Pinchera A 2008 Thyroid autoantibodies and thyroid function in subjects exposed to Chernobyl fallout during childhood: evidence for a transient radiation-induced elevation of serum thyroid antibodies without an increase in thyroid autoimmune disease. *J Clin Endocrinol Metab* **93**:2729–2736.
29. Davis S, Kopecky KJ, Hamilton TE, Onstad L; Hanford Thyroid Disease Study Team 2004 Thyroid neoplasia, autoimmune thyroiditis, and hypothyroidism in persons exposed to iodine 131 from the Hanford nuclear site. *JAMA* **292**:2600–2613.
30. Kindler S, Roser M, Below H, Hoffmann W, Kohlmann T, Kramer A, Kirsch G, Volzke H 2006 Thyroid disorders in employees of a nuclear power plant. *Thyroid* **16**:1009–1017.
31. Lyon JL, Alder SC, Stone MB, Scholl A, Reading JC, Holubkov R, Sheng X, White GL, Hegmann KT, Anspaugh L, Hoffman FO, Simon SL, Thomas B, Carroll R, Meikle AW 2006 Thyroid disease associated with exposure to the Nevada nuclear weapons test site radiation: a reevaluation based on corrected dosimetry and examination data. *Epidemiology* **17**:604–614.
32. Zimmerman MB 2009 Iodine deficiency. *Endocr Rev* **30**:376–408.
33. Hollowell JG, Staehling NW, Hannon WH, Flanders DW, Gunter EW, Maberly GF, Braverman LE, Pino S, Miller DT, Garbe PL, DeLozier DM, Jackson RJ 1998 Iodine nutrition in the United States—trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971–1974 and 1988–1994). *J Clin Endocrinol Metab* **83**:3401–3408.
34. Caldwell KL, Jones R, Hollowell JG 2005 Urinary iodine concentration: United States National Health and Nutrition Examination Survey 2001–2002. *Thyroid* **15**:692–699.
35. Papanastasiou L, Vatalas I-A, Koutras DA, Mastorakos G 2007 Thyroid autoimmunity in the current iodine environment. *Thyroid* **17**:729–739.
36. Laurberg P, Jorgensen T, Perrild H, Ovesen L, Knudsen N, Pedersen IB, Rasmussen LB, Carle A, Vejbjerg P 2006 The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol* **155**:219–228.
37. Allen EM, Appel MC, Braverman LE 1987 Iodine-induced thyroiditis and hypothyroidism in the hemithyroidectomized BB/W rat. *Endocrinology* **121**:481–485.
38. Messina M, Redmond G 2006 Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. *Thyroid* **16**:249–258.
39. Doerge DR, Sheehan DM 2002 Goitrogenic and estrogenic activity of soy isoflavones. *Environ Health Perspect* **110 (Suppl 3)**:349–353.
40. Fort P, Moses N, Fasano M, Goldberg T, Lifshitz F 1990 Breast and soy-formula feedings in early infancy and the prevalence of autoimmune thyroid disease in children. *J Am Coll Nutr* **9**:164–167.
41. Kirk AB, Martinelango PK, Tian K, Dutta A, Smith EE, Dasgupta PK 2005 Perchlorate and iodide in dairy and breast milk. *Environ Sci Technol* **39**:2011–2017.
42. Téllez R, Michaud Chacón P, Reyes Abarca C, Blount BC, Van Landingham CB, Crump KS, Gibbs JP 2005 Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. *Thyroid* **15**:963–975.
43. Langer P, Tajtáková M, Kóčan A, Petrik J, Koska J, Kšinantová L, Radiková Z, Ukropec J, Imrich R, Hucková M, Chovancová J, Drobná B, Jursa S, Váček M, Bergman A, Athanasiadou M, Hovander L, Shishiba Y, Trnovec T, Sebková E, Klimes I 2007 Thyroid ultrasound volume, structure and function after long-term exposure of large population to polychlorinated biphenyls. *Chemosphere* **69**:118–127.
44. Bahn AK, Mills JL, Synder PJ, Gann PH, Houten L, Bialik O, Hollmann L, Utiger RD 1980 Hypothyroidism in workers exposed to polybrominated biphenyls. *N Engl J Med* **302**:31–33.
45. Camargo RYA, Tomimori EK, Neves SC, Knobel M, Medeiros-Neto G 2006 Prevalence of chronic autoimmune thyroiditis in the urban area neighboring a petrochemical complex and a control area in Sao Paulo, Brazil. *Clinics* **61**:307–312.
46. Villanueva R, Greenberg DA, Davies TF, Tomer Y 2003 Sibling recurrence risk in autoimmune thyroid disease. *Thyroid* **13**:761–764.
47. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F, *et al.* 1995 The incidence of thyroid disorders in the community: a twenty-year follow-up of the Wickham survey. *Clin Endocrinol* **43**:55–68.
48. Becker DV, Braverman LE, Delange F, Dunn JT, Franklyn JA, Hollowell JG, Lamm SH, Mitchell ML, Pearce E, Robbins J, Rovet JF 2006 Iodine supplementation for pregnancy and lactation—United States and Canada: recommendations of the American Thyroid Association. *Thyroid* **16**:949–951.
49. Verger P, Aurengo A, Geoffroy B, Le Guen B 2001 Iodine kinetics and effectiveness of stable iodine prophylaxis after intake of radioactive iodine: a review. *Thyroid* **11**:353–360.
50. Schneider AB, Becker DV, Robbins J 2002 Protecting the thyroid from accidental or terrorist-instigated 131I releases. *Thyroid* **12**:271–272.

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