Exposing the Thyroid to Radiation: A Review of Its Current Extent, Risks, and Implications

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Radiation exposure of the thyroid at a young age is a recognized risk factor for the development of differentiated thyroid cancer lasting for four decades and probably for a lifetime after exposure. Medical radiation exposure, however, occurs frequently, including among the pediatric population, which is especially sensitive to the effects of radiation. In the past, the treatment of benign medical conditions with external radiation represented the most significant thyroid radiation exposures. Today, diagnostic medical radiation represents the largest source of man-made radiation exposure. Radiation exposure related to the use of computerized tomography is rising exponentially, particularly in the pediatric population. There is direct epidemiological evidence of a small but significant increased risk of cancer at radiation doses equivalent to computerized tomography doses used today.

Paralleling the increasing use of medical radiation is an increase in the incidence of papillary thyroid cancer. At present, it is unclear how much of this increase is related to increased detection of subclinical disease from the increased utilization of ultrasonography and fine-needle aspiration, how much is due to a true increase in thyroid cancer, and how much, if any, can be ascribed to medical radiation exposure. Fortunately, the amount of radiation exposure from medical sources can be reduced. In this article we review the sources of thyroid radiation exposure, radiation risks to the thyroid gland, strategies for reducing radiation exposure to the thyroid, and ways that endocrinologists can participate in this effort. Finally, we provide some suggestions for future research directions. (*Endocrine Reviews* 31: 756–773, 2010)

I. Introduction

In this review we discuss trends in radiation exposures to the thyroid from diagnostic imaging and treatment and the potential risks to the thyroid from them. We limit ourselves largely to medical, as opposed to occupational, radiation because medical exposure is increasing rapidly and is more controllable than other sources. The main focus of the

Abbreviations: CI, Confidence interval; CT, computerized tomography (scan); ERR, excess RR; FNA, fine-needle aspiration; RR, relative risk.

review is on childhood exposure because the sensitivity of the thyroid gland to radiation is significantly greater at young ages (1).

The main concern is radiation-induced thyroid cancer because radiation is the most important modifiable cause. Although it is not entirely clear how much radiation is contributing to the increasing incidence of thyroid cancer, it makes sense to reduce radiation exposure, especially of children. To better understand the relationship between radiation and thyroid cancer incidence, in the first sections of this review we describe the trends in thyroid cancer incidence, review the basic nomenclature used to explain radiation dosing, and discuss current medical radiation exposures, with special attention to the pediatric population. The last sections summarize some of the public health guidelines and initiatives that deal with radiation protection and the directions of future research in this area.

A. Trends in thyroid cancer

Thyroid cancer rates come from many sources, and therefore the time periods covered vary, but the upward trend in incidence has been observed in many developed countries. Data from developing countries are limited.

The worldwide age-standardized incidence of thyroid cancer during the 2–5 yr before 2002 was estimated to be 3.3 and 1.3 per 100,000 for women and men, respectively (International Agency for Research on Cancer, http://www-dep.iarc.fr). In more developed regions, the incidence is much higher; in the United States during 2002–2006, it was 14.2 and 4.9 per 100,000 for women and men, respectively (International Agency for Research on Cancer, http://www-dep.iarc.fr) (3). Thyroid cancer comprises about 2.0% of all malignancies in women and 0.62% in men, and it is one of a small number of cancers for which the incidence is increasing (International Agency for Research on Cancer, http://www-dep.iarc.fr). In the United States between 1980 and 1997, it increased by 2.4% per year, and between 1997 and 2006 it increased by 6.4% per year (3). Among women, thyroid cancer is the cancer that is rising the most rapidly. Projections for 2009 in the United States are that about 37,200 people (10,000 men and 27,200 women) will be diagnosed, and 1,630 will die of thyroid cancer (3). For a person born in the United States today, the lifetime risk of developing thyroid cancer is 1 in 119 based on 2004–2006 data (3). It is estimated that about 410,000 people currently living in the United States have been diagnosed with thyroid cancer at some time (3).

It is probable that much of the increased incidence of thyroid cancer is due to a greater rate of detection of "subclinical" disease fostered by the popularity and improvements in thyroid ultrasonography and fine-needle aspiration (FNA) of the thyroid, leading to the detection of small

papillary cancers that otherwise would not become clinically evident. This hypothesis is supported by evidence that papillary thyroid cancer accounts for essentially all of the increase and that the average size of papillary thyroid cancers at detection is becoming smaller, with up to 87% of the increase attributable to cancers <2 cm in size (4, 5). However, large papillary cancers have also increased, with those larger than 5.0 cm more than doubling among white women along with increases in tumors that had spread within the neck and to distant sites (6, 7).

Radiation-related cases may be contributing to the increasing incidence because it is the papillary form of thyroid cancer that is most closely associated with radiation exposure. The extreme radiosensitivity of the thyroid is evident from the fact that the slope of the dose-response curve for thyroid cancer is as great, or greater, than many other radiation-related malignancies (8). Although external radiation therapy for benign conditions largely ended in the early 1960s, people can be exposed to radiation from nuclear accidents (as at Chernobyl), selected occupations (*e.g.*, radiologists), diagnostic examinations [especially computerized tomography (CT)], and radiation therapy for malignant conditions. CT involves much larger radiation doses compared with conventional x-ray imaging procedures. Although direct epidemiological data are not yet available, statistical risk models based on data from survivors of atomic bomb radiation exposure have estimated a small but significant increase in the overall risk of cancer associated with the radiation exposure from CT scans (9, 10). Even a small increased risk, when applied to a large number of individuals, could have significant public health implications.

B. Units of radiation measurement

An understanding of the basic terminology pertaining to radiation dose measurement is imperative. The absorbed dose is the radiation dose absorbed by a specific organ or tissue per unit of mass. It is expressed in the Système International (SI) units of Gray (Gy) and is often measured or calculated using anthropomorphic or mathematical phantoms. The "equivalent" dose is derived from the absorbed dose using factors that take into account the different types of radiation and the rates with which they are delivered. For x-rays, the absorbed dose and equivalent dose are the same. The equivalent dose is measured in rem or sieverts (Sv).

"Effective" doses are calculated from organ doses and are a method of representing whole body doses. They are also measured in sieverts. Effective doses are calculated using the International Commission on Radiological Protection (ICRP) guidelines and are used to compare radiation effects, such as the risk of cancer from different sources of exposure (11).

TABLE 1. Units related to radiation safety used by the National Council on Radiation Protection and Measurements

Absorbed dose
  SI units: 1 gray (Gy) = 1000 mGy
  Old units: 1 rad = 10 mGy
Effective dose
  SI units: 1 sievert (Sv) = 100 rem; 1 rem = 10 mSv
  Old units: 1 rad = 1 rem (for x-rays)
Amounts of radioactivity
  1 megabequerel (MBq; 10^6Bq) = 0.027 mCi
  1 mCi = 37 MBq
  30 mCi = 1111 MBq

Radiation effects are divided into deterministic effects and stochastic effects. The frequency and severity of deterministic effects rise with increasing dose after a threshold dose is reached. Deterministic effects include skin reddening and infertility at estimated thresholds of about 2.5 and 6 Gy, respectively (11). Typically, diagnostic radiological procedures do not reach the doses at which these effects occur. In contrast, stochastic effects do not have a threshold at which they begin to occur (11). Rather, the chance of occurrence, but not severity, increases with increasing lifetime accumulation of radiation exposure. Carcinogenesis is a stochastic effect. Major national and international organizations responsible for evaluating radiation risks agree that there is probably no safe lower dose radiation "threshold" for inducing cancer. For the purpose of public health decisions, they generally use a "linear nonthreshold" model that assumes the probability of incurring radiation-related cancer increases proportionately to any given increment in dose.

The expression of radiation-related measurements has changed over time, but currently most organizations and publications use SI units, *i.e.*, gray, sievert, and becquerel for absorbed dose, effective dose, and activity, respectively. Table 1 shows the relationships between commonly used units.

Radiation epidemiologists relate risk to dose. In addition to relative risk (RR), they often express risks in terms of excess RR (ERR), which is RR − 1. In other words, when the risk is doubled, RR = 2 and ERR = 1. ERR is usually considered statistically significant when the 95% confidence interval (CI) does not include zero.

C. Sources of radiation exposure

The average exposure from background radiation in the United States is about 3.0 mSv/yr. Most of the background radiation comes from radon and thoron (12). In the 1980s in the United States, the average total exposure, including background radiation, was 3.6 mSv/yr, with only about 15% (0.54 Sv) coming from man-made sources (13, 14). By 2006, the average total exposure had in-

creased nearly 2-fold to 6.2 mSv/yr, with the fraction from man-made sources increasing to about 50% (3 mSv/yr) (12, 14). A breakdown of radiation sources, comparing 1980 to 2006, is given in Fig. 1 (12). Between 1980 and 2006, the average exposure to medical x-rays increased more than 5-fold, from an estimated 0.4 to 2.2 mSv. The fraction of man-made sources in 2006 (3 mSv) due to CT imaging increased dramatically to 48% (1.5 mSv), whereas the fraction from nuclear medicine, mostly for cardiac imaging, rose to 24% (0.74 mSv) (12, 14).

D. Effect of age on radiation sensitivity

Epidemiological studies of radiation-exposed populations have demonstrated a much greater sensitivity to radiation in children compared with adults. Even doses as small as 50–100 mGy have been associated with an increased risk of thyroid malignancy in children, with a linear dose-response up to about 10–20 Gy when the risk begins to level off (1, 15, 16). Of note, the excess risk persists for at least four decades after exposure (1, 17).

Children develop radiation-related cancer more often than adults for a number of reasons. Their tissues are growing and cells are dividing more rapidly, making them more prone to the mutagenic effects of ionizing radiation. Effective doses from CT scans that are not modified for pediatric patients are higher in children because of their smaller organs and masses compared with adults (18, 19). The carcinogenic potential of radiation appears to continue throughout life, and children have a long life expectancy during which time radiation-induced cancers may be expressed. As a result, the adverse effects of radiation are much greater in children than in adults. For all solid tumors, the RR decreases by 17% for each 10-yr increase in age at exposure, and for thyroid cancer the corresponding decrease is 56% (11).

A pooled analysis of studies evaluating thyroid cancer risk after radiation exposure to the head and neck of children showed a strong inverse relationship between age at
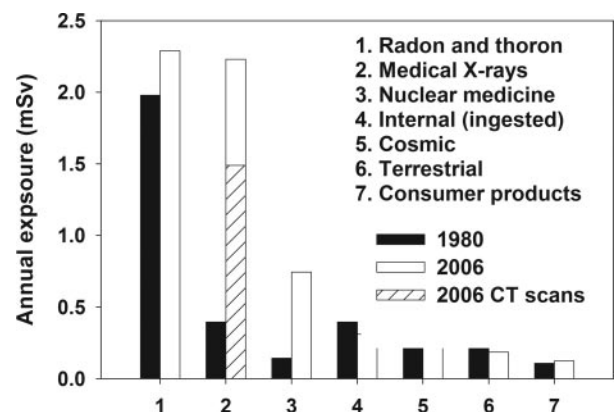
FIG. 1. Sources of radiation exposure in the United States, comparing 1980 and 2006.

exposure and the risk of thyroid cancer. By age 15, the risk of thyroid cancer diminished to the point where it was not statistically significant (1). In the Childhood Cancer Survivors Study of over 14,000 patients, patients treated with radiation before age 10 had a higher risk of developing thyroid cancer compared with those older than age 10 (16). A small, significant risk for thyroid cancer has been detected among female, but not male, survivors of the atomic bomb who were older than 20 yr at the time of the explosion (20).

II. Exposure of the Thyroid Gland from Medical X-Rays

As mentioned in *Section I, subsection C,* medical radiation is currently the largest source of man-made radiation exposure. It has been estimated that the cancer risk attributable to diagnostic radiation ranges from 0.6 and 0.9% in the United Kingdom and the United States, respectively, to 3.8% in Japan (21, 22). Figure 2 shows typical doses from common radiological procedures.

A. Conventional x-rays

In general, conventional x-rays result in relatively low levels of thyroid radiation exposure (Fig. 1). However, due to the small size of newborns, conventional radiographs performed in the neonatal intensive care unit are associ-

FIG. 2. Magnitude of radiation exposure from various sources. [Adapted from N. F. Metting: http://lowdose.energy.gov/imagegallery.aspx (32).] For cranial CT, the dose takes into account the multiple scans performed for the typical patient. GI, Gastrointestinal; PET, positron emission tomography.

ated with high radiation exposure of nonrelevant body regions. In one study, 95% of chest x-rays and 45% of abdominal x-rays included the neck, thus exposing the thyroid to potentially unnecessary radiation (23). In addition, up to 20% of all radiographs needed to be repeated because the radiographs did not include the intended body tissues, further increasing radiation exposure of infants. However, even during prolonged and complicated neonatal intensive care unit stays, the cumulative effective dose from conventional diagnostic x-rays is relatively low, between 0.04 and 0.54 mSv in one study (24).

B. CT scans

This is the area that is currently receiving the most attention. First we review issues related to CT in general and then focus on the thyroid gland.

1. General cancer risks associated with diagnostic CT

Much of the concern about thyroid radiation exposure results from the escalating use of CT scans in children (9, 26). Since its introduction in 1970, CT has become the gold standard imaging study for the diagnosis of many disease entities (27, 28). In 2006 in the United States, 67 million CTs were performed, including 4–7 million on children (14, 29). The use of pediatric CTs has risen 8-fold since 1980, *i.e.*, an increase of about 10% per year, even faster than in adults (30). In the United Kingdom and elsewhere, there has been a similar trend (31).

Radiation doses from CT scanning are considerably larger than those from conventional radiological studies. A CT scan of the abdomen and chest obtained in 15 sec can impart up to 100 mSv of radiation, which is about 1000 times the dose from a conventional chest x-ray (about 0.1 mSv) (32). In the United States, CT scans account for only about 15% of all radiological diagnostic procedures performed, yet they result in more than half of the radiation dose to patients from these procedures (14, 33). Data from the United Kingdom also demonstrate the disproportionate contribution of CT scans to exposure; they account for only 7% of all radiological procedures but contribute 47% to the collective diagnostic radiation dose (31). Advances in CT technology have permitted faster imaging and potentially lower doses, but the imaging of more body regions per scan and the selection of a greater number of slices per scan have counterbalanced this.

The typical organ dose from a CT is 10–20 mGy; for example, the stomach receives 10 mGy from an adult abdominal CT (9). As a result, increased attention has been focused on the potential for radiation exposure from CT leading to the development of cancers, including thyroid cancer. A study evaluating CT use in a cohort of 31,462 adults seen at a tertiary referral center found very high rates of re-
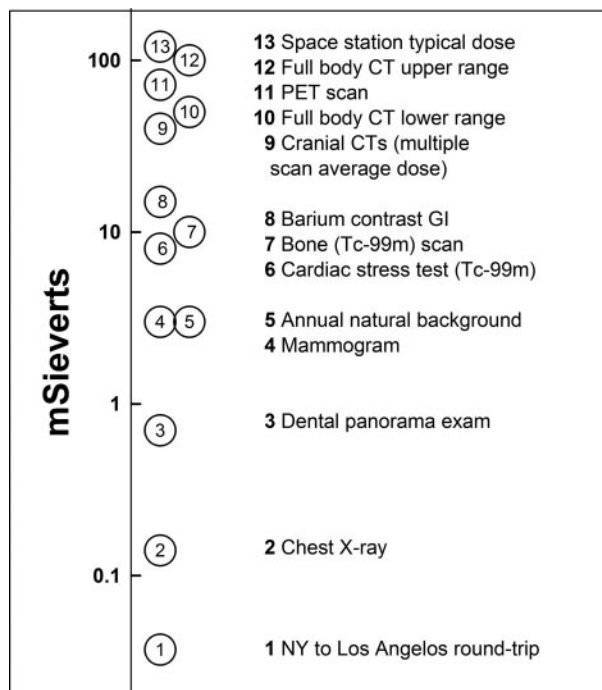
current CT imaging, with 33% of patients having undergone more than five CT examinations and 5% of patients having undergone at least 22 CT examinations over a 22-yr period (35). Alarmingly, 15% of the cohort had accrued cumulative effective doses in excess of 100 mSv. There is epidemiological evidence, particularly from atomic bomb survivors, of a small yet significant increase in the risk of cancer mortality at about 35 mSv (36, 37). This is in the range of the typical organ doses from two to three CT scans. Based on CT use in the United States from 1991 to 1996, it has been estimated that the attributable risk for cancer through age 75 yr due to exposure from CT scans is 0.9% (22). Given the current use of CT technology, this estimate will be getting higher.

Brenner *et al.* (38) estimated that for a 1 yr old, the estimated lifetime cancer mortality risk attributable to radiation exposure was 0.18 and 0.07% for a single abdominal or head CT scan, respectively. On a population basis, they estimated that in the United States there would be an increase of 0.35% over the background rate in lifetime cancer mortality related to the radiation exposure from 1 yr of CT scans in children less than 15 yr old (38). This estimate is equivalent to a lifetime cancer mortality risk attributable to radiation from an abdominal CT in a 1 yr old of about 1 in 550 and about 1 in 1500 for a head CT (38). They went on to estimate that 500 future excess cancer deaths would result from 600,000 pediatric CT studies. A similar analysis from Israel based on the current annual pediatric CT use projected an increase in the lifetime risk of cancer mortality of 0.29% (39).

In summary, CT is a powerful tool in the practice of pediatric medicine, and the benefits to an individual generally outweigh the risks. Currently, there are no empirical data quantifying cancer risks associated with CT; however, risk models based on extrapolation from the atomic bomb survivors cohort predict small but meaningful risks. Thus, the use of CT should be based on a proper understanding of its risks and benefits and when used correctly, the benefits of CT outweigh the potential risks. The primary public health issue is the increasingly large pediatric population exposed to these small risks (29).

2. Thyroid-specific risks related to diagnostic CT

Over one third of all CT scans are performed in the region of the head and neck (30). A survey of physicians of the American Society of Emergency Radiology revealed that 61% of respondents included the thyroid gland as part of the coincident CT studies of the cervical spine and the chest in trauma protocols (40). There is increasing concern regarding radiation exposure to the thyroid gland from pediatric CT scans. Over a 10-yr span, from 1996 to 2005, at one large academic institution the fraction of multiregion CT scans in children increased from 4.9% to 7.8%, likely increasing the radiation dose to the thyroid

(41). If multiphase CT examinations are performed, the dose is increased even more (29, 42). Additionally, the use of iodinated contrast with CT increases the radiation absorbed by the thyroid by up to 35% (43).

A study evaluating patient and organ doses in pediatric and adult chest examinations demonstrated that for each CT scan the thyroid doses depended on the scanner and protocol used and for children and adults were up to 21 and 20 mGy, respectively (44). For CT torso protocols in children, the thyroid doses were from about 10 to 21 mGy, corresponding to ages from newborn to 10 yr (45). Notably, the dose could be decreased by about 60% in a 10 yr old by using automatic exposure control. In a cohort of 80 cystic fibrosis patients managed in a French regional referral center with a total follow-up of 1231 patient years, each CT scan resulted in a mean dose of 3.5 mGy (range, 0.3–19.5) to the thyroid (46). Because the mean lifetime number of CT scans per patient was 3.2 (range, 0–13) scans, the average lifetime thyroid dose was about 10 mGy per patient, but in some cases it was substantially higher.

Common indications in children often result in the performance of cervical spine and chest CTs at the same time. A recent survey has disclosed that in many instances there is an overlap of the radiation fields, including the thyroid in the overlapped area (40). Avoiding or reducing this overlap and the use of contrast when it is not necessary are ways to reduce thyroid exposure.

Baker and Bhatti (47) present arguments, predominantly based on temporal patterns, that the dose burden to the thyroid from CT exams of the thorax, head, and neck and the increasing number of CT scans has contributed to the increasing incidence of thyroid cancer. Mazonakis *et al.* (48) studied radiation doses and their associated risk for thyroid cancer induction associated with common head and neck CT examinations performed during childhood. They found that during CT of the neck, the thyroid gland is exposed to 15.2–52 mGy, and they projected that this would increase the cases of thyroid malignancies by up to 390 per million exposed people. Scattered radiation during CTs of the head would be associated with an increase of 4 to 65 thyroid cancer cases per million people. Berrington de González *et al.* (49) estimated that there would be 1200 excess future cases of thyroid cancer resulting from the CT scans performed in the United States in 2007.

C. Fluoroscopy

Interventional fluoroscopy is an increasingly valuable tool for diagnosis and guiding treatment; however, radiation doses to the patient can be substantial. CT fluoroscopy used as imaging guidance generates a radiation dose of about 10 times the dose of conventional CT (50). Interventional fluoroscopy is widely used in pediatric cardiology, urology, and neurointerventional procedures,

and as it has become more complex, patient doses have risen. Pediatric procedures requiring fluoroscopy are typically more time consuming than adult procedures, thus exposing a child to higher cumulative radiation doses.

The number and extent of neurointerventional procedures being performed in clinical practice is growing rapidly, including among children (51, 52). Fluoroscopy is also used with mounting frequency in pediatric cardiology for both diagnostic and therapeutic purposes. The Spanish Society of Cardiology reported a 13% increase in pediatric procedures from 2000 to 2004 (53, 54). The radiation exposure associated with fluoroscopically guided cardiac resynchronization device procedures in adults is considerable, especially in complicated and prolonged procedures (55, 56). Based on an analysis of doses received by 137 pediatric patients who underwent diagnostic catheterizations or therapeutic procedures, it was estimated that the probability of a fatal cancer attributable to each fluoroscopically-guided cardiac procedure would be 0.07% (54). During pediatric cardiac catheterization, in one study, the dose measured at the surface of the skin above the thyroid was between 0.2 and 0.6 R (roentgen, in this setting about equivalent to a rad), depending on fluoroscopy settings (57). The thyroid dose would depend on age and length of the procedure (58).

Micturating cystourethrography (MCU) accounts for 30–50% of all fluoroscopic examinations in children (59, 60). MCU is regarded as the best test detecting and grading vesicoureteric reflux and evaluating urethral or bladder abnormalities (59). Because the mean dose to the thyroid during MCU is very low (0.006 mGy), the calculated risk of developing radiation-related thyroid cancer from MCU was less than 1 per million exposed patients (59).

Methods of reducing thyroid exposure from fluoroscopic examinations are available. Shortt *et al.* (61) reported that the high thyroid dose exposure received during neurointerventional procedures requiring fluoroscopy could be reduced by half by simply shielding of the thyroid (unshielded, 8.29 mSv; shielded, 4.09 mSv).

D. Nuclear medicine procedures

The number of diagnostic nuclear medicine procedures being performed in the United States has increased from 3.5 million in 1973 to 7.5 million in 1982 and 17.2 million in 2005 (62). The estimated average radiation dose per person from diagnostic nuclear medicine examinations increased by 550% between 1982 and 2005 (62). By far the largest contributor to this trend is cardiac imaging, which, fortunately, is rarely performed in children (62).

Despite the large increase in diagnostic nuclear medicine procedures, thyroid radiation exposure from them has gone down. There has been a dramatic decrease in thyroid imaging, from 13.1% of all nuclear medicine di-

agnostic examinations in 1973 to less than 1% in 2005, and there has been a shift away from ^{131}I to other isotopes (62, 63). For a 40-pound, 5-yr-old child, assuming a 15% uptake, a thyroid scan with 0.1–0.3 MBq/kg ^{123}I-iodide exposes the thyroid to 18–55 mGy, compared with 500-2000 mGy using 0.025–0.1 MBq/kg ^{131}I-iodide (64). Using 1–5 MBq/kg ^{99m}Tc-pertechnetate, the upper large intestine is exposed to 3.8–19 mGy, a dose larger than the thyroid receives (64). No significant increase in the risk of thyroid cancer has been found after the use of ^{131}I for diagnostic purposes in children (65–67); however, because the number of children studied has been very limited, the statistical power was not adequate to detect small risks.

E. Dental x-rays

Radiation exposure to children via routine intraoral dental x-rays is of potential concern given the anatomic position of the thyroid. For the U.S. population in general, dental x-rays account for 2.5% of the effective dose received from conventional radiographs and fluoroscopies (12). Orthodontic therapy is highly prevalent in children and adolescents, and in the United States it has increased from 1 million patients treated in 1992 to 1.6 million in 2006 (68).

At the University of Washington in Seattle, the thyroid dose received during orthodontic care decreased from 7 mGy before 1992 to 2.8 mGy afterward (69). A study evaluating orthodontic treatment and radiation exposure demonstrated that the use of a smaller field of irradiation combined with specified collimator dimensions compared with what is normally used led to a statistically significant reduction in the absorbed radiation dose to the thyroid gland of around 30% (70).

There has been an increasing use of preoperative CT imaging of the lower third molars and, according to Ohman *et al.* (71), in an adult, this exposes the thyroid to 1.5 mGy, about 15–60 times more than other imaging modalities. They do not provide data for children. In adults, a single jaw or panoramic radiograph results in very low exposure to the thyroid, 0.06 and 0.07 mGy, respectively (72). The American Dental Association recommends the use of shielding to reduce thyroid radiation exposure, and these recommendations appear to be partly successful (73). Results of surveys indicate that rates of thyroid collar use to reduce thyroid radiation exposure exceeds 48% in dental practice (74).

F. Radiation treatment

Because survival from the majority of childhood cancers is relatively high and is continuing to improve, with a 5-yr survival of about 79% in the United States during 1995–2000, treatment-related second cancers are becoming a disturbing problem (75). In many studies, the use of

radiotherapy for the treatment of malignancies involving the head and neck and for Hodgkin's disease, especially among children, has been associated with an increase in the development of secondary malignancies, including those of the thyroid (16, 76–83). One indication of the magnitude of the risk is that 7.5% of all secondary malignancies identified in a cohort of childhood cancer survivors in 58 hospitals in Germany, Austria, and Switzerland were thyroid cancers (84). Most persuasively, observations from the Late Effects Study Group and the Childhood Cancer Survivor Study established dose-response relationships and large estimated odds ratio for the development of thyroid cancer after high-dose therapy in childhood (for the Childhood Cancer Survivor Study, odds ratio, 9.8; 95% confidence interval, 3.2–34.8) (16). Although exposure to high-dose external radiation leads to an increased risk of secondary thyroid cancer, it is uncertain whether the risk decreases at the highest doses. The Childhood Cancer Survivor Study suggested a fall-off of risk at doses greater than 30 Gy (16). It is also unclear how long the risk persists, but it appears to continue for decades (1, 67, 76, 85, 86).

Childhood leukemia patients often received prophylactic cranial irradiation because it significantly reduces the occurrence of leukemic relapses in the central nervous system. However, an increased risk of thyroid cancer has been recognized in survivors receiving this therapy. In one case series of 142 survivors of childhood malignancy, cranial radiation therapy for hematological malignancies was found to be a significant risk factor for the development of thyroid cancer (80). Thyroid doses from prophylactic cranial irradiation vary according to whether gamma rays of ^{60}Co or 6 MV photon beams are used and the angle of administration. In adults and children, the ranges are 0.12 to 0.22 Gy and 0.23 to 0.32 Gy, respectively (87).

In recent decades, there has been an increase in the use of several types of radiation treatment, such as high-dose gamma-knife and stereotactic therapy for the treatment of benign central nervous system tumors such as acoustic neuromas, meningiomas, pituitary adenomas, and hemangioblastomas. To date, no data have been published linking them to thyroid cancer (88).

Cancer is not the only thyroid-related disease caused by high-dose radiation (89). There is a substantial risk of developing hypothyroidism, where the underlying mechanism is felt to be cellular death. This is now usually detected by TSH screening. Benign thyroid nodules also develop as a result of radiation exposure, the risk increasing with increasing dose (90). As discussed in *Section V, subsection A*, these benign nodules complicate the decision about whether to use ultrasound for routine follow-up.

The sequelae of the external radiation treatments once used for benign conditions such as "enlarged thymus" or "enlarged tonsils" are well known and have been reviewed elsewhere (67). Although these have been abandoned, there remain a few benign conditions for which external radiation is still employed (Table 2) (91). One of the conditions on the list that is not rare in children is craniopharyngioma. Also, based on the paucity of reports of cancer after its use, it has been suggested that radiation can be used as an adjunct to surgery in the treatment of keloids, including in children (92).

The results regarding cancer incidence or cancer-related death are somewhat inconsistent after the therapeutic use of ^{131}I for adults with hyperthyroidism (93–99). Small increases in thyroid cancer (96, 97), total cancer incidence, or mortality have been observed in some studies, but no clear dose-response was demonstrated (93, 94, 98, 99).

III. *In Utero* Exposure of the Thyroid Gland

The Oxford Survey of Childhood Cancer was one of the first epidemiological studies to look at the effect of low-dose radiation in humans (100). The study found that *in utero* exposure to one or two x-rays, the equivalent of 10–20 mSv, in a pregnant woman increased the incidence of cancer in the offspring by age 10 by about 50%. This was the first definitive human evidence linking x-ray to the development of cancer. The *in utero* effects of radiation have been confirmed—such exposure among atomic bomb survivors resulted in a dose-response associated increase in solid cancers (101).

TABLE 2. Benign conditions for which external radiotherapy may be used, according to Jha *et al.* (91)[a]

I. Tumors
  Ameloblastomas
  Craniopharyngiomas
  Desmoid tumors
  Meningiomas
  Keratoacanthomas
  Pituitary adenomas
II. Dermatological conditions
  Keloids
  Plantar warts
  Skin hemangiomas
III. Other benign conditions
  Aneurysmal bone cysts
  Arteriovenous malformations
  Exophthalmos
  Gynecomastia
  Hepatic cavernous hemangiomas
  Ocular pseudotumors
  Ovarian castration
  Peyronie's disease
  Pterygiums
  Vertebral hemangiomas

[a] It should be noted that radiotherapy is rarely the primary mode of therapy.

Accidental fetal exposure occurred as a result of the Chernobyl nuclear accident. A screening study of thyroid cancer prevalence among individuals exposed *in utero* to iodine isotopes, principally ^{131}I, from the Chernobyl fallout suggested that *in utero* exposure to radioiodines may have increased the risk of thyroid carcinoma approximately 20 yr later (102). The mean thyroid dose was 72 mGy, with a range of 0–3230 mGy. Although the excess odds ratio in this study was quite large, the number of cases was small and the estimate was not statistically significant.

Accidental medical exposure is possible when ^{131}I is given to a woman with an unrecognized pregnancy. The whole body dose to the fetus from maternal ^{131}I is greatest when ^{131}I is given at 2 months fetal age, is dependent on how much is taken up by the mother's thyroid, and has been estimated to be 1.8–3.1 mGy/mCi (103). The dose specifically to the fetal thyroid is much larger and is greatest when the ^{131}I is given at 6 month gestation, estimated to be between 4.8 and 44 Gy/mCi (104). The carcinogenic potential of such exposure has not been established (105).

Currently, it is only in extreme situations that a fetus is exposed to medical radiation. At the earliest time of gestation, maternal CT scanning for renal stones, appendicitis, and pulmonary embolism results in doses of approximately 10, 16, and 0.3 mGy, respectively (106). For a fetus at 3 month gestation, the corresponding doses would be 5.5, 30, and 0.6 mGy (106).

IV. Thyroid Cancer Risk Associated with Low-Dose Radiation Exposure

Although the shape of the dose-response relationship below the level of epidemiological observation is unknown, most scientific and regulatory organizations consider it unlikely that there is a threshold for radiation-induced cancer (11, 13, 107, 108).

It is still relevant to ask what is the lowest level at which effects have been demonstrated. Much of the quantitative information on radiation-related cancer risk comes from studies of atomic bomb survivors, and these data are often used to project radiation-related risks for other populations (13). Specifically, there is a significant increase in the incidence of cancer among atomic bomb survivors exposed to doses between 5 and 150 mSv (mean dose, 40 mSv) (37, 109, 110). Although the atomic bomb survivors received acute radiation exposure, a recent study of 400,000 radiation workers in the nuclear industry who were chronically exposed to an average dose of 19.4 mSv showed a significant association between radiation dose and all cancer (5233 cases) mortality (111, 112). There were only 17 thyroid cancer cases, and only lung cancer (1447 cases) showed a dose-response relationship.

From the 1930s to the 1960s, radiation therapy was used for the treatment of a variety of benign conditions The most complete description of the relationship between radiation dose and thyroid cancer is a study pooling data from seven studies, five of which were cohort studies. An elevated risk of thyroid cancer was observed at doses as small as 100 mGy (1). More recently, an updated analysis of thyroid cancer after irradiation for tinea capitis in Israel showed a significantly elevated risk at levels near 50 mGy (113). As seen in Fig. 3 of the review by Brenner and Hall (26), similar thyroid doses can be reached when an infant receives multiple head CT scans.

The pooled analysis also demonstrated a strong inverse relationship between age at exposure and the risk of thyroid cancer development; however, above age 15 the risk was no longer statistically significant. The ERR of thyroid cancer was 7.7/Gy for irradiation before age 15 (1). For a patient who received 1 Gy to the thyroid, the estimated attributable risk of developing thyroid cancer (the proportion of thyroid cancer that occurred due to radiation exposure) was 88% (1). The radiation effect was somewhat greater in women, but not significantly so.

Whether radiation-related thyroid cancer has the same clinical behavior as sporadic thyroid cancers is not known with certainty. Radiation-related thyroid cancers are frequently multifocal and have a different spectrum of somatic molecular mutations. Although most studies find that these features do not affect their behavior, other studies suggest a more aggressive course (67, 114–117). The Chernobyl-related thyroid cancer cases in children are of interest because they presented at a particularly early age, had short latency periods, and had features associated with aggressive behaviors, namely extrathyroidal extension and frequent lymph node metastases (118). Possible explanations for the apparent aggressive behavior of the Chernobyl-related thyroid cancers include their younger age at diagnosis and the presence of iodine deficiency in some areas near Chernobyl, which may have promoted more rapid progression of cancers.

V. Practice and Public Health

A. Screening for thyroid cancer

For asymptomatic people, the only way to adequately screen for thyroid nodules and thyroid cancer is by imaging, usually with ultrasound. Palpation, even by an experienced examiner, has low sensitivity. Imaging by other modalities is neither more sensitive nor more specific and is more costly. The question of when the benefits of screening outweigh the risks is a difficult one, in part because it has not been tested in a prospective trial.

The presence of thyroid nodules in cancer survivors and other patients exposed to moderate to high dose ionizing radiation are of particular concern because of the risk of malignancy, leading some to propose periodic ultrasound surveillance (119). The rationale for screening is stronger as radiation dose increases and age at exposure decreases (89). The goal of early detection of thyroid nodules is to decrease the morbidity and mortality of radiation-related thyroid cancers. Although ultrasound increases the detection of thyroid cancer, it also results in surgery for some cancers that may never progress and for some benign nodules that cannot be adequately evaluated by FNA (120).

A review in 1989 suggested that after an exposure of 2–5 Gy, new nodules developed at a rate of about 2% annually, reaching a peak at 15–25 yr (121). Similarly, in a retrospective case series of 142 survivors of childhood malignancy, there was a statistically significant increase (odds ratio, 1.2; 95% CI, 1.1–1.3) in the risk of an abnormal ultrasound result with each year after original diagnosis (80). The prevalence of thyroid nodules approached 70% during follow-up. Although a palpable thyroid nodule was the only significant predictor of malignancy, the authors recommended following radiation-treated patients with annual evaluation of the thyroid by physical examination, ultrasound, thyroid function tests, and thyroglobulin levels (80). Crom *et al.* (119) recommended a baseline ultrasound evaluation within 1 yr of completion of radiotherapy for childhood cancer and screening every 2–3 yr for this high-risk population.

Schneider *et al.* (67, 89, 122) recommended that patients who have received external irradiation to the head and neck region as children be evaluated for thyroid nodule and cancer development, hyperparathyroidism, salivary gland tumors, and neural tumors. For those where the risk is thought to be high, they recommend thyroid ultrasound. Because thyroid cancers typically grow slowly, they recommended repeating an ultrasound examination every 12–24 months in patients with small nodules that otherwise are not suspicious, more often in those with larger or suspicious nodules, and every 3–5 yr in patients with no evident nodules.

The Children's Oncology Group, in its guidelines for survivors of childhood cancer, recommends annual evaluations of the thyroid gland (123). To evaluate function, they suggest TSH and free T_4 annually, more often during rapid growth. With respect to neoplasia, they recommend annual palpation, followed by ultrasound and other tests if a palpable nodule is present. As mentioned earlier in this section, others advocate routine imaging.

The American Thyroid Association, in their guidelines for the management of thyroid nodules, suggests that FNA should be performed for smaller nodules than usual when there is a history of radiation exposure (124). A study by Hatipoglu *et al.* (125) demonstrated that for a given nodule, the sensitivity and specificity of FNA in irradiated patients is similar to that reported for the general population. This was borne out by a similar study in a prospectively followed cohort exposed by the Chernobyl accident (126). However, malignancy in smaller nodules in other areas of the thyroid cannot be excluded (125, 127).

B. Regulations and guidelines

Several organizations issue periodic scholarly reports on the medical effects of radiation (Table 3). The most current expert opinions regarding radiation exposure derive from the BEIR (Biological Effects of Ionizing Radiation) VII, phase 2 report of the National Academy of Sciences and ICRP reports 103 and 105 (11, 13, 128). BEIR VII evaluates and employs data from atomic bomb survivor studies and from medical and occupational radiation studies (13). It provides risk estimates for the general U.S. population. It supports the linear no-threshold risk model for low-dose x-ray exposures (13). According to the report, a single effective dose of 10 mSv to an adult population results in a 1 in 1000 lifetime risk of developing an associated solid cancer or leukemia. From the same dose of radiation, the risk is 10–15 times greater in a 1-yr-old child than a 50-yr-old adult (13).

In the 1970s, the ALARA (As Low As Reasonably Achievable) principle regarding radiation exposure was enunciated. It is based on the nonthreshold linear model which, as described in *Section I, subsection B*, presumes that any amount of radiation exposure can increase the chance of negative biological effects such as cancer, and that the probability of the occurrence of such a negative effect increases with cumulative lifetime doses (128). The risks related to pediatric CT scans led the Society for Pediatric Radiology in 2001 to convene an ALARA conference, and at about the same time the U.S. Food and Drug Administration issued a Public Health Notification including the warning that "children less than 10 yr of age are several times more sensitive to radiation than middle-aged adults" (33, 129, 130). The amount of radiation exposure to the pediatric population can be reduced by performing CT scans only when necessary, adjusting exposure parameters for pediatric CTs, setting scan resolution to the lowest level necessary, and minimizing the use of multiple scans obtained during different phases of contrast enhancement (multiphase exams) (129, 131, 132). Without loss of quality, age- and/or weight-related adjustments to the tube current of CT scanners or using automatic current modulation techniques can reduce exposure in pediatric CT examinations (133–135). Additionally, innocent bystander tissues such as the thyroid gland should be protected with appropriate lead shielding dur-

TABLE 3. Organizations (listed alphabetically) that issue scholarly reports on the effects of ionizing radiation

Organization	Mission statement[a]	Latest thyroid cancer-related publication(s)
The International Commission on Radiological Protection (ICRP)	"The ICRP is an Independent Registered Charity, established to advance for the public benefit the science of radiological protection, in particular by providing recommendations and guidance on all aspects of protection against ionising radiation." "[The ICRP] is an Independent Registered Charity (a "not-for-profit organisation') in the United Kingdom; and currently has its small Scientific Secretariat in Canada."	2007 Recommendations of the ICRP. Publication no. 103 (11) 2007 Radiological protection in medicine. ICRP Publication no. 105 (128)
The National Council on Radiation Protection and Measurements (NCRP)	"The NCRP seeks to formulate and widely disseminate information, guidance and recommendations on radiation protection and measurements which represent the consensus of leading scientific thinking. The Council is always on the alert for areas in which the development and publication of NCRP materials can make an important contribution to the public interest." "The Council's mission also encompasses the responsibility to facilitate and stimulate cooperation among organizations concerned with the scientific and related aspects of radiation protection and measurements." "It should be noted that while the [Congressional] Charter recognizes the importance and the national character of the NCRP, it does not make the Council a governmental body; it is a private corporation."	2009 Risks to the thyroid from ionizing radiation. Report no. 159. Bethesda, MD; NCRP (17)
The National Research Council: Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation	"The National Research Council was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine."	2006 Health risks from exposure to low levels of ionizing radiation. BEIR VII Phase 2. Washington, DC: National Academy Press (13)
The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)	"UNSCEAR was established by the General Assembly of the United Nations in 1955. Its mandate in the United Nations system is to assess and report levels and effects of exposure to ionizing radiation. Governments and organizations throughout the world rely on the Committee's estimates as the scientific basis for evaluating radiation risk and for establishing protective measures."	2006 UNSCEAR Report: effects of ionizing radiation. Vol 1. New York: United Nations (108)

[a] From the organization's web site as of November, 2009.

ing all CT examinations. The risk to selected organs can be lowered by a factor of two with appropriate shielding (136).

A policy document issued jointly by the National Cancer Institute and the Society for Pediatric Radiology concluded that a small radiation exposure dose from CT to the pediatric population represents "a public health concern" (29). Besides endorsing the concept that there is no low-dose threshold for inducing cancer, they call for strategies to "minimize CT dose, disseminate relevant information, and clarify the relationship between CT radiation and cancer risk." Recently, 13 organizations comprising the Alliance for Radiation Safety in Pediatric Imaging are attempting to minimize pediatric exposure to radiation with an "Image Gently Campaign" (137).

Although there was a doubling of the number of CT scans from 1998 to 2003, a study found that referring physicians don't appreciate and do not explain to patients the radiation exposure involved (138). Of concern is the inappropriate use of CT scans. In a retrospective study in one hospital in Finland, based on the guidelines of the European Commission, 3–77% of diagnostic CTs, depending on anatomic site, were found to be unjustified (139). Many physicians appear to be ill-informed about the risks of diagnostic examinations utilizing radiation (138, 140, 141). A study of physician awareness of radiation risks demonstrated that only 47% of radiologists and less than 10% of the other physicians surveyed believed CT examinations might increase a patient's cancer risk (138). There is a clear need to educate the medical profession and the general public about the risks regarding CT imaging.

An anonymous survey of members of the American Pediatric Surgical Association (APSA) revealed that only

half of them believed that one abdominal/pelvic CT increased the lifetime risk of cancer, and more than 75% of them underestimated CT scan's radiation dose compared with a conventional x-ray (142). To increase awareness of radiation exposure and risks associated with CT scans, the National Cancer Institute and the Society of Pediatric Radiology published guidelines and recommendations for clinicians and the general public (29), and the APSA published a review of the medical literature.

The European Union and the United Kingdom each regulate safety precautions for medical radiation (143, 144). There are no corresponding regulations in the United States, but the American College of Radiology has published a "white paper" on the subject (145). These are general statements of radiation safety principles and have no specific measures related to protecting the thyroid gland.

VI. Research Directions

A. Determination of risks at lower doses and with longer follow-up times

There is a need for follow-up studies of large cohorts to determine the risks at lower doses and over longer times spans (36). The question of risks at lower doses pertains particularly to CT scans, especially for children, and to other forms of low-dose radiation exposure. A status report of several ongoing large studies, including the follow-up of some cohorts cited in this review, was recently published (146). Large studies of cancer incidence and mortality associated with CT scans in young patients are planned or are under way in the United States, the United Kingdom, Canada, Australia, Europe, and Israel. Despite their planned size, they will be limited in their ability to quantify site-specific risks, especially of sites such as the thyroid where mortality is rare and ascertainment is highly dependent on diagnostic methods.

B. Methods to ameliorate the risks

The efforts at minimizing the risk of ionizing medical radiation, particularly associated with CT, are summarized in *Section V, subsection B,* but new innovative methods need to be developed and evaluated. For example, a tertiary referral hospital in Boston is modifying its electronic medical record system to track how often a patient receives radiation (35). This should enable doctors to calculate the cumulative dose a patient has been exposed to in the past.

C. Identification of radiation-related thyroid cancers, *i.e.,* radiation "signatures"

Perhaps the greatest barrier to studying radiation-induced thyroid cancer at low levels of exposure is the fact that it is not possible to distinguish a case caused by radiation from one that is not. By studying somatic mutations in thyroid cancers, attempts are ongoing to overcome this problem. However, it is not yet clear that radiation and nonradiation cases can be distinguished by this approach.

A distinctive feature of radiation-related cases is the high frequency of RET proto-oncogene rearrangements. Two studies using model systems, one normal human thyroid tissue transplanted to severe combined immunodeficient mice and the other fetal human thyroid cells transfected with SV40 (simian virus 40), have been used to demonstrate the sensitivity of the RET gene to radiation (148, 149). The preferred recombination with the H4 gene to form PTC1 is likely a result of the fact that the two genes are in proximity to each other within the nucleus of the thyroid cell (150). In Japanese survivors of the atomic bombs, RET rearrangements have been correlated to the dose of radiation exposure, strongly supporting the idea that RET activation is not only age related, but also radiation related (151). A similar correlation was not found in Russians exposed to radiation from the Chernobyl accident, perhaps due to limited sample size (152).

Because RET rearrangements are, by themselves, insufficient to identify radiation-induced cases of thyroid cancer, efforts were made to see whether identifying the specific breakpoints would be informative (153–155). The most extensive of these studies, involving 26 cases of RET rearranged, post-Chernobyl cases, found evidence for topoisomerase I sites near each breakpoint and the use of nonhomologous DNA end joining to repair radiation-induced DNA damage (155). However, this has not as yet been replicated and would probably not be sufficiently specific to identify radiation-induced cases.

Most recently, efforts have been made to apply genome-wide expression studies using microarray analysis (156–159). Two promising studies report expression patterns that might distinguish radiation and sporadic cases, but the findings do not appear to overlap (157, 159). These studies are complicated by the fact that patterns may arise from factors other than radiation exposure. For one, iodine deficiency and ethnic patterns related to Chernobyl cases could affect expression patterns (160). Also, as discussed in a recent review of the subject, radiation susceptibility factors may also show up in expression array patterns (157).

In summary, at the present time it is not possible to identify radiation-induced cases unequivocally. It is not clear whether this goal will be achieved with advancing technologies. However, even presumptive identifications, making it more or less likely that a case is related to radiation, might augment epidemiological studies. Specifi-

cally, if the increased incidence of thyroid cancer is related to low-dose exposure from diagnostic radiation, one might expect an accompanying proportionate increase in cases with somatic recombination events.

D. Increased susceptibility to the effects of radiation

That there are a few, uncommon syndromes associated with markedly increased radiation susceptibility is well known (161). It is less clear whether there are more subtle variations in susceptibility in the general population. With respect to thyroid cancer, one cohort study that included a large number of sibling groups was unable to detect patterns that would indicate a genetic basis for susceptibility (162). Recently, there have been intriguing findings suggesting that there are germ-line factors associated with an increased risk of developing thyroid cancer (163, 164). So far, these have not been linked to susceptibility radiation-induced thyroid cancer. However, one study in people exposed to radioactive fallout from nuclear tests in Kazakhstan has found evidence of genetic factors associated with thyroid nodules, and one of them, *XRCC1*, appears to interact with radiation exposure as a risk factor (165).

Understanding these factors might lead to enhanced protection, or at least enhanced subsequent screening, for susceptible people. In the longer term, it may also lead to ways of reducing the risks of radiation exposure.

VII. Conclusions

Radiation therapy for the treatment of benign conditions of the head and neck area carries a checkered history, having resulted in a substantial increased risk for thyroid, parotid, parathyroid, and central nervous system tumors (67, 166). This legacy emphasizes the need for continued research on radiation risks and for strategies to minimize radiation exposures. The literature on potential cancer risks related to radiation exposure from diagnostic CT scanning, currently the largest man-made radiation exposure, continues to evolve. The implications for public health may be substantial because even a small increased cancer risk associated with CT use, if applied to a large population, can result in many, potentially avoidable cases.

Although there is an increasing awareness for the potential cancer risks from radiation exposure, especially from CT, a strong need for educating the physicians who order the tests remains. Knowing the potential risks of radiation exposure is important for promoting the proper use of CT imaging for children. Radiation exposures related to imaging need to be optimized to reduce exposure. The risks need to be weighed against the anticipated pa-

TABLE 4. Methods of reducing thyroid radiation exposure in children

Use fields and instrument adjustments specific for children.
Avoid contrast when it is not necessary, especially when the thyroid will be exposed.
Avoid overlapping fields, if possible, especially when cervical spine and chest CTs are performed together.
Protect the thyroid from exposure with shielding, when possible.
Institute policies, both procedural and educational, among radiologists and Radiology Departments to institute the above.
Increase the awareness of practicing pediatricians about the risks and benefits of radiological procedures and how to reduce the former without compromising the latter.
Institute methods to explain the risk and benefits in an accurate and understandable way.

tient benefit from the diagnostic information obtainable from the scan, even while there are uncertainties regarding the risks at the low doses encountered in diagnostic CT examinations (36, 107, 167). It is prudent to act on the assumption that such risks are real and assume, as do most national and international radiation protection and regulatory agencies, that they are proportional to dose (147).

As exemplified by the ALARA principle, it is recognized that the population should not be exposed to more radiation than is necessary, and diagnostic modalities that do not involve ionizing radiation should always be considered (25, 34). Attention should be paid to the total number of CTs performed on an individual because the cumulative doses of radiation over time may reach meaningful doses (2). The realization that the estimated lifetime radiation risks for children undergoing CT are not negligible may stimulate more careful calibration of the CT exposure settings for pediatric patients.

Physicians and health authorities should work together to minimize the medical radiation exposure of pediatric patients by encouraging responsible use of CT and other radiological procedures (Table 4) (39). Endocrinologists have a special role in pointing out radiation risks related to the thyroid. They should be aware of the current sources of radiation exposure so they can be active participants in encouraging policies and procedures that implement strategies to reduce radiation doses to the thyroid.

Acknowledgments

Disclosure Summary: A.B.S. has served as an expert witness in cases related to radiation and thyroid cancer. B.S. and E.R. have nothing to declare.

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