

CARCINOMA OF FOLLICULAR EPITHELIUM

PATHOGENESIS

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The thyroid gland is an uncommon site of cancer, accounting for only 0.74% and 2.3% of cancers among men and women, respectively, in the United States. Because of its favorable prognosis, thyroid carcinoma causes an even lower percentage of cancer deaths, 0.17% and 0.26% for men and women, respectively (1). During the past several decades, the incidence of thyroid carcinoma has been increasing (Fig. 77.1), particularly among women, whereas the mortality rate for thyroid carcinoma has significantly decreased among both men and women (2). In part, the increased incidence is due to improved diagnosis, whereas the reduced mortality is due to earlier detection, improved treatment, and a decline in anaplastic thyroid carcinoma. In Connecticut, where the incidence of thyroid carcinoma increased from 1935 to 1975, the results of a birth cohort analysis fit the hypothesis that the increase was due to radiation treatment to the head and neck area of children, which is the only proven carcinogen (3). However, studies from Sweden (4), Switzerland (5), and Norway (6), where childhood radiation treatment was not used widely, suggest that other factors may be important as well. In some countries the incidence of thyroid carcinoma is no longer increasing (7,8), but U.S. and Austrian data from 1973 to 1994 and 1957 to 1994, respectively, still show increases (2,9).

Although external radiation is the clearest pathogenetic factor associated with thyroid carcinoma, other risk factors undoubtedly exist. Because thyroid carcinoma is two to three times more common in women than in men, especially during the reproductive ages (2,10), hormonal factors probably are involved (Fig. 77.1). However, after years of study, epidemiologic data are still inconclusive. In addition to radiation, other environmental factors, diet for example, have been implicated in the etiology of thyroid carcinoma. Many of these factors are thought to operate through the action of thyrotropin (thyroid-stimulating hormone, TSH). There is considerable evidence from animal experiments that prolonged TSH stimulation can cause thyroid carcinoma,

but in humans the evidence is not as clear (11,12). Inherited genetic factors are related to thyroid carcinoma in familial adenomatous polyposis syndrome, Cowden's disease, and, possibly, other familial occurrences of thyroid carcinoma.

RADIATION

Although radiation can damage cells in several ways, it is generally accepted that it causes carcinoma by its effects on DNA. The site of this initial DNA damage and the path leading to the eventual carcinoma involve multiple, as yet not completely understood, steps (13). And although radiation can induce thyroid carcinoma, additional factors probably are required before clinically evident carcinoma occurs. Factors that increase TSH secretion may not be sufficient to cause thyroid carcinoma, but may stimulate tumorigenic growth. Thus, even after radiation damage has occurred, giving thyroid hormone treatment may prevent the development of clinically important thyroid tumors.

External Radiation and Thyroid Carcinoma

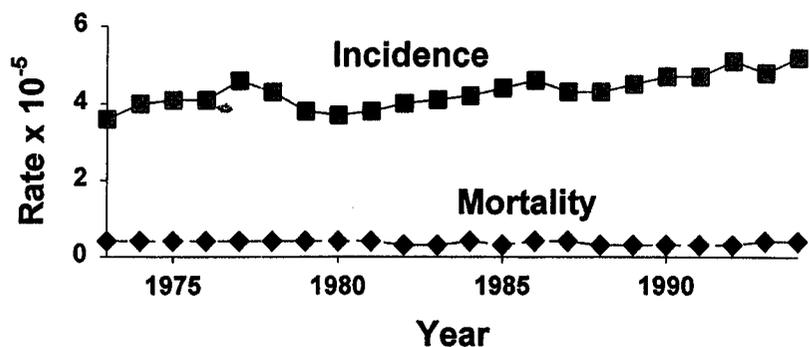
The relationship between radiation and thyroid carcinoma was first recognized by Duffy and Fitzgerald in 1950 (14). They found that an unusually large fraction of their childhood thyroid carcinoma patients had a history of radiation therapy. This relationship was subsequently confirmed by many epidemiologic studies (15,16).

Several difficulties arise in studying the relationship between radiation exposure and thyroid carcinoma. Because thyroid carcinoma is a rare disease, few studies have the statistical power to adequately quantify risk; the very good survival rate of thyroid carcinoma patients requires that thyroid carcinoma incidence rather than mortality be assessed; because radiation exposure frequently occurred at a young age, people often are unaware of, or uncertain about, their exposure; and finally, the diagnosis of thyroid tumors is highly dependent on the extent of the procedures used to look for them (diagnostic bias). The evidence in Table 77.1 is especially strong because multiple studies conducted in various locations using different methodologies have similar findings. In the case-control studies, cases of thyroid carcinoma were identified by their entry into a tumor registry or by their admission to a hospital. The control subjects were comparable subjects without thyroid carcinoma. Information on risk factors,

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Thyroid Cancer Time Trends 1973-1994



Age-specific Thyroid Cancer Incidence 1988-1992

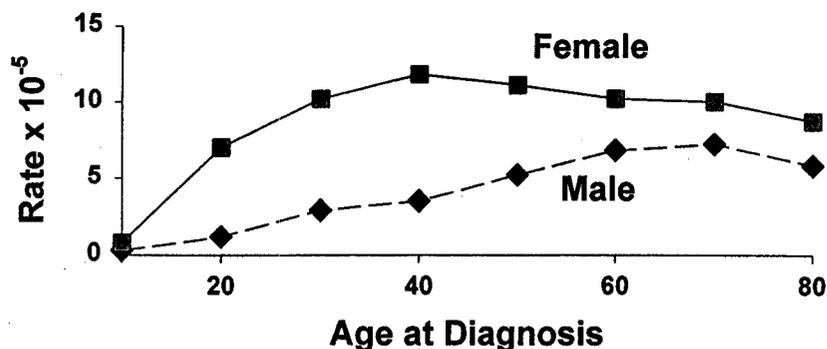


FIG. 77.1. Time trend in the United States for thyroid carcinoma incidence and mortality (upper) and thyroid carcinoma incidence in the U.S. by age and sex (lower). (Data from Ries LAG, Kosary CL, Hankey BF, et al. *SEER Cancer Statistics Review, 1973-1994*. Bethesda, MD: National Cancer Institute. NIH Publication No. 97-2789;1997.)

TABLE 77.1. SELECTED EPIDEMIOLOGIC STUDIES OF THE RELATIONSHIP BETWEEN EXTERNAL RADIATION AND THYROID CARCINOMA

Location (reference)	Study Population			Comments
	Age at Exposure	Exposed (n)	Nonexposed (n)	
Cohort studies^a				
Boston, tonsils (18)	Children	1,192	1,063	Elevated risk for nodules
Chicago, tonsils (19)	Children	2,643	0	ERR/Gy = 2.5
China, background radiation (20)	All ages	1,001	1,005	No effect
China, radiology workers (21)	Adults	27,000	26,000	Doses unknown, Rel. risk = 2.1
Israel, tinea capitis (22)	Children	10,834	16,226	ERR/Gy = 32.5
Japan, atomic bomb (23)	All ages	41,234	38,738	ERR/Gy = 4.7 (children), 0.4 (adults)
Marshall Islands, fallout (24)	All ages	250	600	ERR/Gy = 0.3 (children), 0.5 (adults)
New York City, tinea capitis (15)	Children	2,200	1,400	ERR/Gy = 7.7 (not significant)
Rochester, NY, thymus (25)	Children	2,475	4,991	ERR/Gy = 9.1
Utah-Nevada-Arizona, fallout (26)	Children	1,055	1,418	ERR/Gy = 7 for benign and malignant neoplasms combined, carcinoma not significant
		Cases (n)	Controls (n)	
Nested Case-control studies^a				
International, cervical cancer (27)	Adults	43	81	ERR/Gy = 34.9
International, childhood cancer (28)	Children	22	82	ERR/Gy = 1.1

^aIn the cohort studies, dose response was evaluated. In the nested case-control studies, cases had thyroid carcinoma and controls did not. In the two case-control studies, the cases were derived from 150,000 patients treated for carcinoma of the uterine cervix and 9,170 children treated for carcinoma, respectively. Controls in the Japan atomic bomb study were exposed to less than 0.01 Sievert and in the Utah-Nevada-Arizona fallout study to <0.05 Gy. ERR, excess relative risk. All of the estimates of ERR are taken from Shore (15), except for the Marshall Island study taken from Robbins and Adams (24) and for the Utah-Nevada-Arizona study taken from Kerber et al. (26).

such as radiation exposure, was obtained, and the distribution in the two groups was compared. In case-control studies, cases may report exposure to risk factors more completely than controls (recall bias). In the cohort studies, exposure to radiation generally was documented, and the characteristics and amount of exposure was known. The frequency of thyroid carcinoma in the radiation-exposed group was compared with a group of similar subjects who had little or no exposure. Therefore, in cohort studies, recall bias was minimized, but diagnostic bias could have been important.

Ron et al. (17) recently conducted an analysis of radiation exposure and thyroid carcinoma, combining the data from seven large studies that had individual thyroid dose estimates. Their analysis of childhood exposure, which included nearly 500 patients with thyroid carcinomas, demonstrated a strong positive association between radiation dose and thyroid carcinoma. Based on an excess relative risk model (i.e., risk increases multiplicatively with dose) a linear dose-response relationship fit the data well. A consistent and strong relationship between radiation exposure, possibly at doses as low as 0.1 Gy (10 rad), and thyroid carcinoma was found (15-17). At doses below 0.1 Gy, results have been equivocal, but a no-threshold dose response fits the data well.

Several additional observations, with important clinical implications, follow from the analysis of the pooled data. First, there is a strong, inverse relationship between age at exposure and risk. In fact, there was little evidence for a radiation effect among persons exposed after age 15 years (Fig. 77.2). Second, overall women tended to be more sensitive to the effects of radiation, although the difference between men and women is not statistically significant and is not consistent across studies. Third, the risk remains elevated several decades after the initial exposure. Between 5 and 30 years after exposure the risk is

essentially constant. After 30 years, it appears to decline, but still remains elevated.

Internal Radiation and Thyroid Carcinoma

Although it was previously a matter of controversy, it is now clear from the Chernobyl accident experience that exposure to radioactive iodine during childhood is associated with an increased risk of thyroid carcinoma. However, in the past few years, additional evidence has been obtained that adds strong support to the safety of using ^{131}I in the clinical setting. The following two sections summarize the evidence for both of these observations and discuss the likely explanations for this apparent paradox.

^{131}I RELEASES INTO THE ENVIRONMENT

Even prior to the Chernobyl accident, there was concern about the potential carcinogenic potential of ^{131}I . In part, this came from experiments in animals, but it was unclear if these findings could be extrapolated to humans (29). Some people living on certain atolls of the Marshall Islands who were exposed to fallout from a nuclear test explosion in 1954 subsequently developed thyroid tumors, including carcinomas (24,30,31). However, their radiation exposure came from a combination of ^{131}I , other more rapidly decaying isotopes of iodine, and external gamma radiation.

Shortly after the accident at the Chernobyl power plant, which released an estimated 23 to 46 MCi of ^{131}I , reports began to appear of thyroid carcinoma occurring in exposed children. However, because of the unusually short latency and the intense thyroid screening performed in the area, it was not immediately

Dose-response by age at exposure

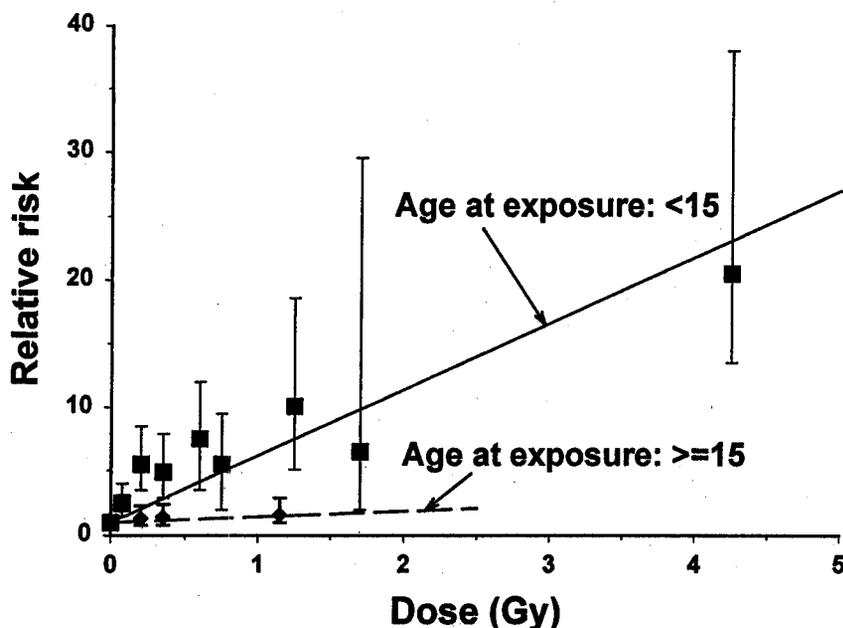


FIG. 77.2. Relative risk for thyroid carcinoma by age at radiation exposure. The dose-response relationship for age at exposure <15 years is compared to the dose-response relationship for age at exposure ≥ 15 years. (Data from Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995;141:259.)

clear whether these cancers were attributable to the ^{131}I exposure from the accident. The data collected during the more than 10 years since the accident now indicate that the sharp increase in childhood thyroid carcinoma is associated with exposure from Chernobyl (32–36). This conclusion is drawn from several lines of evidence. The cases have been reviewed by an international panel of pathologists, and the thyroid carcinoma diagnoses were confirmed in about 95% of the cases. The incidence of childhood thyroid neoplasms is far higher than the incidence prior to the accident, and the cases have been confined almost exclusively to children who were alive, or in utero, at the time of the accident. As demonstrated in studies of external radiation, the risk of developing thyroid carcinoma has increased with decreasing age at exposure. Furthermore, new studies have linked thyroid dose with thyroid carcinoma incidence (35,37,38). For example, a case-control study conducted in Belarus has demonstrated a statistically significant relationship between childhood thyroid carcinoma and individually estimated radiation doses (37). In addition, based on detailed dose reconstruction data from Ukraine, Belarus, and Russia, Jacob et al. (38) correlated mean regional thyroid doses with thyroid carcinoma incidence and found a linear dose-response relationship. The risk estimates were not significantly different from those reported for external radiation (17). However, only long-term studies will provide an accurate and complete account of the dose-response relationships. The roles of short-lived isotopes, iodine deficiency (34,39–43), and genetic predisposition need to be elucidated before the Chernobyl findings can be extrapolated to other settings.

There are several distinctive features of the Chernobyl-related cases of childhood thyroid carcinoma. The latency was shorter than previously reported for radiation-related cases. This may be a result of intense thyroid screening, the promotion of thyroid tumorigenesis by iodine deficiency, or the extremely large number of exposed individuals, which increases the chance to observe an uncommon disease. Furthermore, many of the cases had a unique histologic pattern of papillary carcinoma with a large solid component (44–46), and cases appeared to be rapidly growing and aggressive, with infiltration and lymph node involvement. Some of these findings are similar to those of thyroid carcinoma in children in general (47). Finally, the pattern of somatic mutations in the carcinomas, particularly in the *ret* proto-oncogene, appeared to be distinctive (see subchapter by Fagin on molecular genetics of tumors of thyroid follicular cells).

Following the Chernobyl accident, KI was widely administered to residents of Poland (48). The success of the program and the rarity of observed side effects support the distribution of KI as an effective means of reducing ^{131}I exposure in the event of a nuclear accident (49).

In addition to the Marshall Islands and Chernobyl, ^{131}I was widely dispersed into the environment in the United States and elsewhere by above-ground nuclear tests (50) and as a by-product of plants preparing isotopes for use in nuclear weapons (51). An epidemiologic study of children exposed to nuclear fallout from weapons testing at the Nevada Test Site found a significant association between all thyroid nodules and dose, but not for thyroid carcinoma separately (26). In a detailed evaluation of thyroid doses received by Americans during the testing period,

the estimated average collective dose was 2.0 cGy. For people under age 20 at the time of exposure, the mean dose was about 10 cGy (51). An ecologic study of U.S. thyroid carcinoma incidence and mortality rates and ^{131}I doses from the bomb tests was recently conducted (52). No association with cumulative dose was found, but associations were observed for children exposed under 1 year of age and those in the 1950 to 1959 birth cohort. Although it is impossible to determine the number of potential excess thyroid carcinomas caused by exposure to the tests, a U.S. National Academy of Sciences committee calculated that, if there is an excess, it is probably no more than 11,000 cases and that about 45% of them have already been diagnosed (53). In early 1999, the Hanford Thyroid Disease Study reported no evidence of an increased risk of developing benign or malignant thyroid neoplasms associated with childhood exposure to the atmospheric releases of radioactive iodine from the Hanford Nuclear site. In this study, the thyroid glands of 3,441 people who were born in the vicinity of the Hanford plant between 1940 and 1946 were thoroughly examined. Among the 3,193 participants who lived in the Hanford site region during the years of atmospheric emissions, the mean and median thyroid doses were 18.6 cGy and 10.0 cGy, respectively.

MEDICAL USES OF ^{131}I

A great deal of effort has gone into assessing the relationship between ^{131}I used for therapeutic or diagnostic medical purposes and the development of thyroid carcinoma (54–61). These studies generally have been reassuring about the use of ^{131}I . The most recent report of the U.S. Thyrotoxicosis Therapy Follow-up Study Group indicates that among 35,593 hyperthyroid patients treated during 1946 to 1964 and followed through 1990, 63% of whom were treated with ^{131}I , total cancer mortality was not associated with ^{131}I use (58). However, the standardized mortality rate for thyroid carcinoma was slightly, but significantly, elevated, resulting in a very small number of excess thyroid carcinomas (58). Most of the deaths occurred soon after ^{131}I treatment, suggesting that the underlying thyroid disease may have been involved in the development of thyroid carcinoma or may have influenced the surveillance or reporting on death certificates (62). In a study of 10,552 hyperthyroid patients treated with ^{131}I in Sweden, there was a nonsignificant 30% increased risk of thyroid carcinoma, which was more pronounced among the toxic nodular goiter patients (61). No dose response was demonstrated.

Among 34,104 patients administered diagnostic ^{131}I and followed through 1990, the absorbed thyroid dose was estimated to be 1.1 Gy (56). Thyroid carcinoma incidence was slightly elevated compared with the general population, but when patients who were scanned because of suspected thyroid tumors were eliminated from the analysis, the elevated risk disappeared. Furthermore, the usual patterns associated with radiation-induced thyroid carcinoma were not observed. There was no dose response or modifying effect of age at exposure. When a sample of approximately 1,005 female patients exposed to ^{131}I and 248 nonexposed female patients controls were examined for palpable thyroid nodularity, no excess was found among exposed women

compared with nonexposed women, but among the exposed women there was a significant relationship between dose and nodules (63).

In general, studies of adult ^{131}I exposure for therapeutic and diagnostic purposes continue to be reassuring, but some aspects of the studies suggest a small effect, apparently related to ^{131}I exposure, on thyroid nodularity, thyroid carcinoma incidence, and thyroid carcinoma mortality. Although a causal relationship is possible, it is more likely that the observations represent the nature of the underlying thyroid condition or an increase in surveillance and diagnostic misclassification.

The reasons for the apparent difference between external and internal radiation are not known with certainty. One factor is undoubtedly age at exposure, which has a very strong modifying effect for external radiation (Fig. 77.2). Because most of the patients included in studies of the medical uses of ^{131}I have been adults, the results cannot be extrapolated to children. Another factor is that compared with the instantaneous dose received from external radiation, the lower dose rate of ^{131}I may allow repair of radiation damage. Finally, when ^{131}I is administered, it results in a wide range of doses to different areas of the thyroid, whereas external radiation exposes the entire thyroid to the same dose, making it difficult to compare the two types of radiation. Exposures to ^{131}I , as occurs in the medical setting, may not be applicable to the more prolonged exposure generally received by people from fallout or living near nuclear production facilities.

Evaluation of Irradiated Patients

An essential part of evaluating a person with a history of irradiation is determining the type of radiation, the site or sites treated, the age at treatment, and the dose (15-17,64). Among the potential risk factors, the dose received by the thyroid is the most important. The patient's age at the time of therapy is an independent risk factor, with younger age associated with greater risk. The dose schedule may be a risk factor, with fractionation possibly reducing the risk. There is a greater spontaneous risk for women, but it is unclear whether radiation increases the risk of thyroid carcinoma differently for women and men.

External irradiation formerly was used to treat a wide range of benign conditions during childhood. These included enlargement of the thymus, tonsils, adenoids, and cervical lymph nodes, as well as pertussis, asthma, bronchitis, tinea capitis, and acne. It is important to distinguish between diagnostic and therapeutic radiation exposure. Although a diagnostic examination theoretically could confer some risk, a large case-control study in Sweden (484 cases of thyroid carcinoma and 484 controls) found no association with prior diagnostic x-rays (65). For acne it is important to distinguish between ultraviolet therapy and radiation therapy and then to distinguish superficial (grenz rays) from conventional radiation therapy. Another commonly used form of therapy was the local application of radioactive plaques to treat hemangiomas, other localized lesions, and enlarged tonsils. The dose received by the thyroid as a result of these therapies is probably less than with external radiation therapy. External radiation of the neck for malignant conditions such as Hodgkin's disease and carcinoma of the larynx continues in wide

use. Such treatment often results in subclinical or overt hypothyroidism (66-68), and sometimes in nodular thyroid disease and thyroid carcinoma (69,70). It is important to obtain the best radiation history possible because it is needed to decide whether further evaluation, particularly thyroid imaging, should be performed.

How to examine a patient with a history of radiation exposure is a deceptively simple question (71). Thyroid palpation has limited sensitivity, but whether imaging should be used and, if so, when, is a controversial matter. The limitations of palpation are shown by the following illustrative studies involving radiation-exposed individuals: in one small series, about half of the nodules found by ultrasonography that were larger than 1.5 cm were not palpable (72). In a larger series, about two thirds of the palpable nodules were not confirmed by ultrasonography (73). The use of imaging is supported by the observation that many people with nodular thyroid disease, including carcinoma, were discovered solely by imaging (72,74). Some clinicians believe that even if imaging discloses otherwise undetectable nodules, they are too small to be of clinical consequence and can be safely disregarded until they become evident by palpation. Ultrasonography is associated with considerable observer variation and may be too sensitive because approximately one third of adult women have ultrasonographically detectable thyroid nodules (75,76). Whether nonpalpable nodules are of clinical importance remains to be determined. For a nonpalpable nodule larger than 10 mm in diameter, ultrasound-guided fine-needle aspiration can be performed effectively (77). For a patient with a small nodule, the benefit of careful follow-up and thyroid suppression is likely to outweigh any risk from imaging. A reasonable approach is to reserve imaging for those patients who have especially high risk factors (71,78).

There is no evidence that subclinical or overt hypothyroidism or thyrotoxicosis results from the doses of radiation used to treat benign childhood conditions (79). However, there is some, as yet unconfirmed, data suggesting a relationship between autoimmune thyroid disease and radiation (80,81). The evaluation and treatment of patients with nodular disease is discussed further in Chapters 76 and 80.

Other tumors may arise in patients with a history of childhood radiation exposure to the head and neck, some of which can have equal or greater clinical consequence for the patient than thyroid tumors. Parathyroid adenomas have been reported in people who received radiation therapy. The Michael Reese tonsil study, a Japanese study of atomic bomb survivors, and a study of x-ray treatment for tuberculous cervical adenitis have demonstrated a significant dose-response relationship for hyperparathyroidism (82-84). Salivary gland tumors most commonly occur in the parotid glands and are usually readily evident to the patient. About two thirds are benign, and most of these are of the mixed cell variety. Mucoepidermoid carcinomas were the most common malignant form. In both the atomic bomb survivors and the Michael Reese patients, there was a dose-response relationship, although there were differences between the studies in specific categories of salivary neoplasms (85-87). Among Israeli patients irradiated to the head and neck for tinea capitis, a 4.5-fold risk of salivary gland malignancies was observed (88). Salivary gland neoplasms can occur many years after radiation

exposure. Neural tumors also occur after radiation exposure. In a large group of children treated for tinea capitis by radiation epilation, more brain tumors occurred than in a control group (89). Benign neural tumors, particularly neurilemmomas and acoustic neuromas, occasionally more than one in an individual, were more common in people who received childhood radiation therapy (90,91). An association between thymic irradiation in childhood and the subsequent occurrence of breast cancer in adult women was found in the Rochester study (92). Finally, an elevated risk of nonmelanoma skin cancer has been observed among several of the groups studied (23,93-95).

Clinical Features of Radiation-related Thyroid Neoplasms

A history of radiation exposure has two major clinical implications: the increased risk of developing thyroid nodules and the increased risk of a thyroid nodule being malignant. In the Michael Reese Hospital tonsil group, more than one third of radiation-exposed patients who had thyroidectomies had a thyroid carcinoma (96).

Follow-up studies so far indicate that external radiation-related thyroid carcinomas behave the same as other thyroid carcinomas in both children and adults (97-99). Therefore, therapy and follow-up should be similar to that provided to other patients with thyroid carcinoma. As mentioned above, the behavior of the Chernobyl-related carcinomas may be especially aggressive. Whether this behavior is due to the young age at diagnosis and iodine deficiency at the time of exposure remains to be determined.

The thyroid carcinomas that arise in relation to radiation treatment are almost all well-differentiated papillary or papillary-follicular carcinomas. Case reports of anaplastic thyroid carcinoma occurring after radiation treatment have appeared, but are rare (100). There is no evidence that the well-differentiated thyroid carcinomas found in patients who received radiation therapy are more likely to undergo transition to more aggressive or less differentiated forms. It is possible, however, that as the population ages, more aggressive carcinomas will be seen, as occurs in the general population (101).

All irradiated patients who have had nodular thyroid disease treated by thyroidectomy should receive thyroid hormone treatment, even if enough of the gland remains to maintain normal thyroid hormone secretion. This recommendation is based on the observation that nodules continue to occur in these patients with equal or greater frequency compared with patients who did not have surgery. When thyroid hormone therapy is given after thyroidectomy, the frequency of recurrence is reduced (102).

Patients with a currently normal thyroid and a history of irradiation should be examined periodically. Radiation-related nodular disease continues to occur for as long as it has been possible to study patients irradiated in 1939 to 1962 (19,96,103). Patients at especially high risk should have thyroid ultrasonographic imaging as part of their follow-up examination. Ultrasonography results should be interpreted with caution, given the high prevalence of abnormalities found in the general, adult population. Examples of high-risk patients are those with one or more of the factors listed in Table 77.2. An examination interval

TABLE 77.2. RISK FACTORS ASSOCIATED WITH RADIATION-INDUCED THYROID TUMORS

Amount of radiation exposure
Young age at exposure to radiation
High serum thyroglobulin concentration
Other radiation-related tumor(s)
First-degree relative with radiation-related tumor(s)

of 1 to 2 years and an imaging interval of 3 to 5 years, continued indefinitely, seem prudent.

Prophylactic therapy to prevent the occurrence of nodular thyroid disease should be considered in patients who received radiation treatment (104,105). One report demonstrated the effectiveness of thyroid hormone therapy in preventing the appearance of nodules in irradiated patients, but this was not confirmed by another report (106,107). In patients at high risk, thyroxine (T₄) therapy has potential benefits that probably outweigh its risks. In this instance a reasonable definition of high risk is more than one of the factors listed in Table 77.2. Also, an abnormal or equivocal thyroid imaging finding, such as a nodule seen by ultrasonography that is too small to aspirate, would contribute to a classification of high risk. Even if only benign nodules occur less frequently in T₄-treated patients, the reduction of both anxiety and the likelihood of surgery is important.

FAMILIAL THYROID CARCINOMA

The existence of two familial syndromes that include carcinoma of thyroid follicular cell origin supports the existence of genetic factors in the pathogenesis of thyroid carcinoma. Thyroid carcinomas occur in association with familial adenomatous polyposis (FAP) and its subtype, Gardner's syndrome, which is FAP associated with osteomas, epidermoid cysts, and desmoid tumors. Both are dominantly inherited conditions with mutations in the *APC* gene. In fact, thyroid carcinoma is considered to be the most common noncolonic malignancy in these syndromes. As reviewed by Hizawa et al. (108), the risk of thyroid carcinoma is increased by more than 100-fold over the general population. In the Leeds Castle Polyposis data base, 45 patients (1.2%) had thyroid carcinoma (109). Because there was only one death from thyroid carcinoma and the frequency was relatively low, Bulow et al. concluded that screening for thyroid carcinoma is not indicated. However, it seems prudent to perform careful palpation of the thyroid in any patient with these syndromes. The thyroid carcinomas in these syndromes have two distinguishing features. They tend to occur at an early age, often before 35 years (110), and they have a distinct histologic pattern (111). The carcinomas are papillary carcinomas with a cribriform pattern and solid, spindle cell-containing areas. A recent clue to the pathogenesis of these carcinomas comes from the observations of Cetta et al. that in three of four cases there was activation of the *ret/ptc1* oncogene. How the germline mutation in *APC* and the somatic mutation in *ret* are related remains to be determined.

The second familial syndrome associated with thyroid carcinoma is Cowden's disease, a rare autosomal-dominant disorder involving the development of multiple hamartomatous polyps,

mucocutaneous pigmentation, and extraintestinal manifestations. Thyroid abnormalities, including thyroid carcinomas, are common in these cases (112). Little is known about the thyroid carcinomas in this setting. Recently, it has been found that mutations in the *PTEN* gene, a tumor suppressor gene thought to be a protein phosphatase, cause the syndrome.

Studies of family patterns of nonmedullary thyroid carcinoma have provided increasing evidence supporting the existence of additional hereditary factors. In a systematic study of 576 people with thyroid carcinoma in Utah, using extensive family history records and the state tumor registry, 28 first-degree relatives were found to have thyroid carcinoma (113). The expected number of cases was only 3.3, and compared with 27 other sites of malignancy, this was the largest increase found. There have been multiple reports of family aggregates of papillary thyroid carcinoma. For example, in a clinical study, 6% of 226 patients with papillary carcinoma reported having at least one relative who also had a papillary thyroid carcinoma (114), and in a case-control study a fivefold increase of thyroid carcinoma was found in close relatives of patients with nonmedullary thyroid carcinoma (115). Recently, it was calculated that, given the observed prevalence of thyroid carcinoma in the general population, two members of a family could have thyroid carcinomas by chance alone (116). There is some debate about the behavior of the thyroid carcinomas found in family clusters. In one series, the high frequency of lymph node and local invasion was cited as a reason for aggressive treatment (117). In a review of 15 case series, containing 87 families with 178 cases, evidence for aggressive presentation was present in only 6 (118). Although the investigator did not advocate therapy more aggressive than usual, it should be noted that the overall frequency, where it was reported, of distant metastases (10%) and recurrences (29%) was high. So far, no gene (besides *APC* and *PTEN*, mentioned above) has been identified as a cause of familial thyroid carcinoma. One obvious candidate gene, *ret*, was excluded in a study of seven multiply affected families (119).

There may be genetic factors related to the probability of developing radiation-induced thyroid tumors. Patients with one radiation-induced tumor (thyroid, salivary, or benign neural) are more likely to develop another tumor than are patients with comparable risk factors exposed to the same amount of radiation (90,120). Furthermore, in sibling pairs in which both members were irradiated, thyroid tumor development was concordant more often than would be expected by chance (121). These findings are limited by the possibility that other unknown lifestyle risk factors might account for these observations.

PREEXISTING THYROID DISEASE

Thyroid carcinoma is often preceded by other thyroid abnormalities, including endemic and sporadic goiter, benign thyroid nodules, lymphocytic thyroiditis, and Graves' disease, all of which are common. Whether patients with these abnormalities should be considered at increased risk of developing thyroid carcinoma is uncertain. Despite considerable efforts to resolve this question, results remain inconclusive. Many case-control studies of thyroid carcinoma have revealed more preexisting benign

thyroid nodules and goiter in the carcinoma patients than in the control subjects (115,122-128). The risks have been high, especially for nodules. Most recently, a pooled analysis of 14 case-control studies (129-132) with 2,725 cases and 4,776 controls was conducted to allow a systematic approach to analyzing and interpreting major hypotheses for thyroid carcinoma etiology. In the analysis of benign thyroid diseases, the pooled analysis showed large risks associated with a history of goiter (odds ratio = 5.9) or benign nodules (odds ratio = 30) among women (132). Case-control studies, however, are especially subject to recall bias in which cases may mistakenly remember previous thyroid disease while controls may forget them. This is less of a problem in prospective studies. In one prospective study of women with benign thyroid conditions in Boston, there was a significant excess of thyroid carcinoma mortality among patients with thyroid adenomas (133). Perhaps the most convincing study is one from Denmark (134). In the period 1977 to 1991, 57,326 patients were discharged from Danish hospitals with a diagnosis of myxedema, thyrotoxicosis, or goiter. The subsequent incidence of thyroid carcinoma was ascertained through the Danish Cancer Registry and compared with thyroid carcinoma incidence in the general population. The incidence of thyroid carcinoma was increased among all three patient groups, but was substantially higher among goiter patients. However, prospective studies remain subject to potential ascertainment bias (i.e., one thyroid disorder could draw attention to another). In the Danish study, the thyroid carcinoma risk decreased with time following hospital discharge, but the risk remained elevated even 10 years later. The cumulative data now suggest that a history of goiter or benign thyroid nodules is a strong thyroid carcinoma risk factor.

Recent genetic data suggest that thyroid neoplasms may progress from benign tumors to well-differentiated carcinomas to anaplastic carcinomas, as somatic mutations accumulate (see next section). The epidemiologic data relating previous nodular thyroid disease to thyroid carcinoma are consistent with this model.

HORMONAL AND REPRODUCTIVE FACTORS

Thyroid carcinoma, like most other thyroid diseases, occurs more frequently in women than men, suggesting that hormonal factors are involved in its pathogenesis. In England and Wales, the female:male ratio was highest at the time of puberty. From puberty to menopause the difference between females and males declined consistently (10). In Switzerland, the female:male ratio at puberty for papillary carcinoma was very high, but for follicular carcinoma the ratio was highest between the ages of 25 to 44 years (5). This finding suggests that hormonal events occurring at puberty or the early reproductive years might be most important in influencing the development of papillary thyroid carcinoma, but few significant relationships between hormonal and reproductive factors and thyroid carcinoma have been found, and often the findings have not been consistent across studies (115, 123,124,126,127,135-138). In a more recent pooled thyroid carcinoma study, there was a small but significantly positive trend for risk to increase with age at menarche (130).

Results from some, but not all, epidemiologic studies indicate that parity may increase the risk of thyroid carcinoma (115,

123,124,126,139-141). The pooled analysis found only a slightly elevated risk associated with having had at least one child, but no relationship with number of children (130). The most convincing data come from a prospective study of 1.1 million Norwegian women of reproductive age. Based on almost 1,000 thyroid carcinomas, a significant trend for increasing risk with increasing parity was demonstrated (139). To determine whether this trend was related to life-style or environmental exposures, the influence of number of children on the thyroid carcinoma risk in men was studied (142). No trend was found, which led the researchers to conclude that the effect was due to biologic changes during pregnancy. Results from the pooled analysis also suggest that thyroid carcinoma occurs more often among women having a later age at first birth (130). Data from some studies suggest that women with a history of spontaneous or induced abortion, particularly during the first pregnancy, have an enhanced risk of thyroid carcinoma (25,115,123,137,138), that the risk of thyroid carcinoma may be elevated among women seeking medical care for fertility problems (143,144), and that women undergoing hysterectomy may be at increased risk of developing thyroid carcinoma (140,145), but these findings were not confirmed in the pooled analysis (130).

Other suggested risk factors for thyroid carcinoma in women are exogenous estrogens, including oral contraceptives (123,126,146), lactation-suppressant drugs (146), postmenopausal estrogen therapy (146), and fertility drugs (137). The associations, however, were usually weak and not dose dependent. For example, in a case-control study in the state of Washington where 410 women with papillary thyroid carcinoma and 510 controls were interviewed, no relationship was found with the use of birth control pills or hormone replacement therapy (HRT) in older women, and a negative association was found with birth control pills in younger women (147). In the recent pooled analysis, current oral contraceptive users had a moderately raised risk, which disappeared 10 or more years after discontinuing use (130). No significant risks were reported for use of HRT or fertility drugs, but the odds ratio for drugs used to suppress lactation was elevated. Therefore, although positive associations between hormonal and reproductive factors and the incidence of thyroid carcinoma have been found in some studies, they are generally weak and not always consistent across studies.

Two studies, both conducted among irradiated individuals, have examined reproductive factors and benign thyroid tumors (148,149). One study showed a protective effect of pregnancy, whereas, in apparent contradiction, both showed a nonsignificant increase in risk with number of pregnancies.

DIETARY FACTORS

Iodine

A relationship between iodine-deficient endemic goiter and thyroid carcinoma has been suspected since Wegelin (150) reported more thyroid carcinoma at autopsy in Bern, an endemic goiter area, compared with Berlin, a nonendemic goiter area. Since then, several studies of the effects of iodine supplementation on the incidence of thyroid carcinoma have, with at least one exception, failed to show a decline. In Switzerland, thyroid carcinoma

mortality decreased after the introduction of iodized salt (151), but it did not decrease in Italy or the United States (152,153). In Austria, the incidence continued to increase after the introduction of iodine prophylaxis (9). In Sweden, the incidence of thyroid carcinoma has continued to increase in both iodine-deficient and iodine-sufficient areas (154).

The effects of iodine intake on specific histologic types of thyroid carcinomas are clearer. In endemic goiter areas, follicular and, perhaps, anaplastic thyroid carcinoma predominate. When iodine supplementation is introduced, the proportion of papillary carcinomas increases and that of follicular carcinomas decreases (12,155). In Hawaii, where iodine intake is extremely high, the proportion of papillary carcinoma is also high (137). In Sweden, the risk of follicular carcinoma was higher in iodine-deficient areas than in iodine-sufficient areas, whereas the pattern was opposite for papillary carcinoma (4). Similar findings were reported in Sicily (156). These data suggest that follicular carcinomas are related to iodine deficiency and prolonged TSH stimulation.

There are a few studies in which iodine intake was evaluated. In a case-control study in Hawaii in which iodine intake from food sources and supplements was quantitated, iodine intake was higher in the patients with thyroid carcinoma than in the control subjects (137). There have been seven case-control studies in which fish and shellfish consumption was examined as a surrogate measure of iodine intake. In all but the Hawaiian study the dietary data were extremely limited; therefore, the findings should be interpreted with caution. Because shellfish generally have a higher iodine content than fish, they are a better indication of high iodine intake. Although the results were not always statistically significant, fish or shellfish consumption was reported more frequently among cases than controls in four studies (115,126,137,157). In a Norwegian population-based study, a similar conclusion was reached based on the observation that among women, being married to a fisherman was a risk factor for thyroid carcinoma (158). In contrast, results from northern Italy and Vaud, Switzerland, indicated a protective effect of fish (159). In a study conducted in northern Sweden, the results were equivocal: adult consumption of fish appeared to be associated with a slightly decreased risk of thyroid carcinoma, and shellfish intake with a higher risk (136).

Other Dietary Factors

Attempts to determine if there are other dietary factors related to thyroid carcinoma have yielded nearly consistent findings. Vegetables, particularly cruciferous ones, appear to be associated with a reduced risk of thyroid carcinoma (115,137,159). This is a somewhat surprising finding because these vegetables contain natural goitrogens. In fact, the one discordant finding was from a case-control study from Norway and Sweden, where cruciferous vegetables were associated with a higher risk, but only in iodine-deficient areas (160). However, cruciferous vegetables contain several constituents that could reduce tumor risk (161-163). In a pooled analysis of Italian and Swiss studies, pasta, bread, pastry, and potatoes were associated with an increased risk (159), and in the study from Norway and Sweden, consumption of butter and cheese was associated with an increased risk (160). In the Hawaiian study, the cases reported

eating more fat, protein, and carbohydrates than the control subjects. The higher total calorie intake among cases is consistent with patients being overweight seen in the Hawaiian study (137), as well as two other epidemiologic studies (115,146). Finally, in studies conducted in Greece and Japan, coffee consumption protected against thyroid carcinoma (164,165).

PHARMACEUTICAL AGENTS AND TOXINS

Although no pharmaceutical agent or toxin has been implicated in the etiology of thyroid carcinoma in humans, there is reason to remain open to this possibility. Drugs such as lithium and phenobarbital are known to cause goiter and increased serum TSH concentrations, making it reasonable to suspect that certain drugs could cause or promote the growth of thyroid carcinoma. In rodents, a variety of drugs and other chemicals cause thyroid growth and thyroid neoplasms (166). None of them has been shown to be thyroid mutagens. Rather, they appear to act by interfering with the synthesis of thyroid hormones or by altering the peripheral metabolism of thyroid hormones (167). In either case, the increased TSH secretion, possibly combined with subsequent random events or events promoted by the TSH stimulation, may lead to thyroid neoplasms (168,169). Patients with congenital goiter have thyroid glands that are subjected to intense TSH stimulation until appropriate treatment is given. Rarely, such patients develop thyroid carcinoma, supporting the possibility that intense TSH stimulation contributes to thyroid carcinogenesis in humans (170,171).

SUMMARY

Radiation is the clearest factor proven to cause thyroid carcinoma in humans. A history of goiter or benign nodules appears to significantly increase the risk of developing thyroid carcinoma. One of the major problems in understanding the pathogenesis of thyroid carcinoma is the need to take histology into account. The four major histologic types of thyroid carcinoma (papillary, follicular, anaplastic, and medullary) have different risk factors, and the rarity of the disease makes it extremely difficult to study the histologic types separately. Although pooling data from several studies of radiation-induced thyroid carcinoma has helped resolve many questions regarding the shape of the dose-response curve and effect modification, similar pooling of data from etiologic studies of thyroid carcinoma so far has been less informative. The roles of iodine, diet, reproductive and hormonal factors, and genetics still remain unclear.

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MOLECULAR GENETICS OF TUMORS OF THYROID FOLLICULAR CELLS

JAMES A. FAGIN

An estimated 16,100 patients were diagnosed with thyroid cancer in the United States in 1997. Of the two major forms of differentiated cancer derived from thyroid follicular cells, papillary carcinomas are by far the most common. By contrast, follicular thyroid carcinomas are now comparatively rare (1). Iodide intake is a key environmental factor determining the relative incidence of follicular and papillary cancers. The association of follicular carcinomas with iodine deficiency suggests that this type of tumor often develops within glands subjected to a chronic proliferative drive. Many of them probably arise from preexisting adenomas, and as such fit the paradigm of clonal evolution through a multistep process involving progressive transformation through somatic mutations of genes important

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