1. Epidemiology and Etiology of Thyroid Nodules and Thyroid Cancers

Thyroid nodules are very common but thyroid cancers are not. The data that follow relate predominantly to the United States (US). Between 5% to 7% of adults have a clinically detectable nodule in the thyroid and 30% to 50% of adults have one or more nodules in the thyroid when the gland is examined by ultrasound. Therefore, in the adult population, approximately 10^7 and 10^8 have thyroid nodules that are palpable, or ultrasonically visible. In contrast, there are approximately 30,000 new cases of thyroid cancer annually in the US.[1] Physicians should have an algorithm for management of nodules to identify the small proportion that are malignant from the very large proportion that are benign (Chapter 4). Thyroid nodules are more common in women and in regions of low intake of iodine. External radiation increases the incidence. There are families in which there is an increased incidence of clinically palpable nodules and some of these are part of syndromes such as Cowden's syndrome. There are also familial aggregations of medullary thyroid cancer and occasionally papillary cancer.

Epidemiology of Thyroid Cancer

Approximately 1.1% of all cancers arise from the thyroid and 1.7% of cancers in women compared with 0.5% in men are primary thyroid cancers. Thus, thyroid cancer is about three times more common in women. This gender difference is found in almost all countries. One exception to the gender difference occurs in prepubertal children, in whom the incidence in boys and girls is about equivalent. The average age of the patient with differentiated thyroid cancer is 35–40 years. The peak incidence at about 40 years is different from most malignancies that are more prevalent with advancing age. Hispanic men are the exception to the relatively young median age and their highest incidence is more than 70 years and the frequency is 9.2 per 100,000. Other significant differences among ethnic groups are discussed below. Figure 1.1 shows the overall number of cases and deaths in the US from 1970 to 2006. Reasons for the increasing incidence include a true increase that might in part be caused by radioactive fallout from atomic bomb testing and from medical radiation. Alternatively, physicians might be identifying small cancers that would have been overlooked in earlier decades and the almost stable death rate supports this point of view.[2] Small papillary cancer makes up almost all of the increase in cases. The prognosis is good and 6% of patients die from the

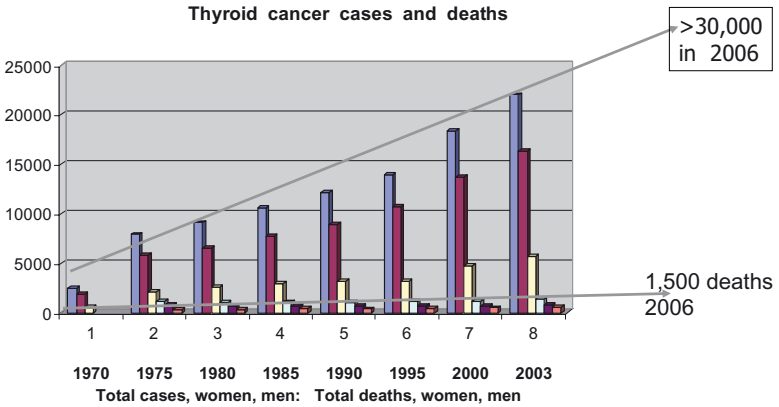

Figure 1.1. The graph shows increases in cases of thyroid cancer between 1976 and 2003 in the US. The increases in mortality are less marked. (Adapted from McDougall IR. Management of Thyroid Cancer and Related Nodular Disease. London: Springer-Verlag; 2006:2.)

cancer but the genders are more equally represented with about 850 women and 650 men expected to die annually (43,000 die of road traffic accidents and 30,000 from gunshots in US annually!). Less than 0.5% of all cancer deaths are from carcinomas of the thyroid. Because the large majority of patients who are diagnosed with thyroid cancer have an excellent prognosis, there are several hundred thousand people in the US who are living with a diagnosis of thyroid cancer.

There are substantial differences in the prevalence of thyroid cancer among ethnic groups. In women, the lowest incidence is 3.3 cancers per 100,000 in African Americans. By comparison, women from Hawaii, Vietnam, and the Philippines represent 9.1, 10.5, and 14.6 cases per 100,000.[3] White and Hispanic women have similar incidences of 6.5 and 6.2 cancers per 100,000. When age is also considered, Filipino women between 55 and 69 years have an incidence of 32.5 cancers per 100,000. Filipino men also have a higher incidence of thyroid cancer with 4.1 per 100,000 compared with 1.4 per 100,000 for African Americans. A multiethnic study in the San Francisco Bay area tried to answer whether there were environmental differences, but no compelling factor was identified.

The 5-year survival for white Americans over time has been 92% (1974–1976), 94% (1980–1982), and 95% (1989–1995); in contrast, the outcomes for African Americans were 88%, 94%, and 89%.

The incidence in the United Kingdom (UK) (1000 new cases annually) is proportionately about one fifth of that of the US based on the respective populations. There are 2.3 thyroid cancers per 100,000 women and 0.9 per 100,000 men. Two hundred fifty (25%) die annually in the UK (25%) and the 5-year survival for women and men is 75% and 64%.[4] The lower incidence and higher mortality in the UK might be attributable to delayed diagnosis.

Summary

Thyroid cancer is not common and there are significant differences in the incidence based on ethnicity. It is not clear whether the increasing incidence is attributable to diagnosis of earlier cases, or a true increase attributable to environmental factors. The use of a staging system such as tumor, node, metastasis (TNM; see Chapter 5) of every new case would allow this point to be resolved. Within one country, the survival is also dependent on ethnicity. The 5-year survival for white Americans was 95% for the period 1989–1995. Over the same time, the outcome for African Americans was lower at 89%.

Etiology of Thyroid Nodules and Cancer

Radiation and genetics are two important causal factors. Radiation causes mutations that can be carcinogenic. There are also familial thyroid cancers that are associated with genetic abnormalities. This is best understood for familial medullary cancer and multiple endocrine neoplasia (MEN 2) syndromes. There is increasing evidence that some cancers of follicular cells are also familial.

Varying doses of radiation to the thyroid have different effects, with intermediate doses (10–1000 rad or 0.1–10 Gy) to tissues being carcinogenic and high doses causing death of cells and hypothyroidism. For many years, the majority of data supported that external radiations, predominantly X-rays, were more likely to induce thyroid cancer. The increased incidence of thyroid cancer in children who were exposed to internal radiation at the time of the Chernobyl incident has altered this concept. Table 1.1 classifies radiation under four main headings, medical, occupational, atomic bomb, and accidental and whether the radiation is external, internal, or a combination.

Terms and Definitions Related to Radiation, Radiation Doses, and Exposure

To define the units of radiation, there are two systems of nomenclature in common usage. This is confusing for patients and also for physicians. The international system (Systeme International d'unites, SI units) is used exclusively in Europe and the non–SI system, or standard system, is used predominantly in the US. There is an increased effort to use SI units universally and in scientific reports. There are also two meanings of radiation dose. One deals with the quantity of radiation absorbed by tissues and its potential damaging effects. The second deals with the dose that is administered to a patient for a specific procedure. Units used to describe absorbed radiation are discussed first. Radiation is energy. The energy of radiation results in ionization of atoms

Table 1.1. Potential situations that could result in exposure of humans to radiation and cause radiation to the thyroid

Major	
Medical	Diagnostic Diagnostic X-rays CT scan Nuclear medicine, thyroid scan Therapeutic: external Treatment of tinea capitis Treatment of acne Treatment of hemangioma Treatment of Hodgkin's disease Treatment of head and neck cancer Total-body radiation Therapeutic: internal Treatment with ^{131}I Graves' disease Toxic nodular goiter Thyroid cancer
Occupational	Medical Radiology Radiation oncology Nuclear medicine Nuclear power plant Other
Atomic bomb	War Hiroshima and Nagasaki Testing Marshall Islands Nevada
Accidental	Three Mile Island "Hanford" Chernobyl

and that causes damage to cellular materials such as DNA and cell membranes. Energy is usually measured in joules (J) (after James Prescott Joule, an English scientist, 1818–1889). One joule is the energy required to lift 1 kg to a height of 10 cm. In SI units, when 1 J of energy is delivered to 1 kg of tissue, it is defined as 1 gray (1 Gy, in recognition of the radiobiologist Louis H. Gray). One gray is equal to 100 rad (radiation absorbed dose) in the non–SI system. These are quantities of radiation absorbed by tissue. All types of radiation do not cause the same amount of damage to tissues. Photons, including X-rays and gamma (γ) rays and beta particles (electrons, β) are equivalent. Neutrons and alpha

(α) particles are considerably more damaging. This is because they have substantial mass. An α particle is a helium nucleus that has mass (2 protons and 2 neutrons) and also electric charge. Alpha particles released inside the body travel very short distances and because of their mass and charge they are very destructive to biologic molecules in their path. An α particle emitted adjacent to a chromosome causes many breaks in DNA. The breaks are in close proximity and are unlikely to be reparable. In contrast, a photon traversing DNA might cause a single break that would be amenable to one of the many repair mechanisms for DNA. Therefore, there are simple mathematical conversions that allow the damaging ability of the radiation to be considered. These are derived by multiplying the absorbed dose by a quality factor that depends on the type of radiation. The quality, or weighting factor, for most radiologic and nuclear medicine sources of radiation is 1, i.e., the quality factor is 1 for X-rays, γ rays, and electrons. The quality factor for neutrons is 10 (range 5–20) and for α particles is 20.

To describe absorbed radiation in man, in SI nomenclature, the sievert (Sv) is the basic unit and in the non–SI system it is the rem (roentgen-equivalent-man). For photons and electrons, the Sv and Gy are equivalent and they are equal to 100 rem and 100 rad, respectively, indicating that rem and rad are also equivalent. In the case of particles with mass such as α particles, 1 Gy is equivalent to 20 Sv, and for neutrons, 1 Gy is equal to 10 Sv. The dose equivalent expressed in Sv or rem is a more accurate index of the biologic effect of radiation.

Next, the units of administered radioactivity are described. That radiation will result in the absorbed radiation to tissues was described previously. In the SI system, the basic unit is the becquerel (Bq, named after Antoine H. Becquerel). It is equal to a source of radioactivity that decays at a rate of 1 disintegration per second. In clinical practice, mega becquerel (MBq, 10^6 Bq) or even giga becquerel (GBq, 10^9 Bq) are used. In the non–SI system, the basic quantity of radioactivity is the curie (Ci, named after Madame Marie Curie). One curie is a source of radioactivity that decays at a rate of 3.7×10^{10} disintegrations per second. Clinically, quantities such as microcurie (μCi, one millionth of a curie) and millicurie (mCi, one thousandth of a curie) are used. One millicurie is equal to 37 MBq and 1 MBq is equivalent to 27 μCi.

Radionuclides of Iodine

^{127}I is nonradioactive natural iodine. The best known radionuclides of iodine are ^{123}I, ^{124}I, ^{125}I, and ^{131}I. ^{131}I is used to treat thyroid cancer and hyperthyroidism and for diagnostic whole-body scintigraphy in patients who have thyroid cancer and have undergone thyroidectomy. ^{123}I is a diagnostic agent used for diagnostic imaging and ^{125}I is widely used in biologic laboratories for radioimmunoassays and for labeling proteins in vitro. ^{124}I is a positron emitter that has value in imaging called positron emission tomography (PET scanning). When ^{131}I is used for whole-body scanning in patients with thyroid

cancer, the quantity administered is 37–370 MBq (1–10 mCi) and for therapy 1.1 to >7.4 GBq (30 to >200 mCi). The dose of ^{123}I varies considerably from 7.4 MBq (200 μCi) for a routine thyroid scan to 37–185 MBq (1–5 mCi) for a whole-body scan.

Radiation in Everyday Activities

We are exposed to radiation from common everyday events. In the US, the average total radiation is approximately 3.6 mSv/y (360 mrem/y). This is made up by cosmic radiation, radiation from radon, internal radiation from natural radionuclides mostly ^{40}K, and medical sources including X-rays, computed tomography (CT scanning), and nuclear medicine procedures. In the US, it has been estimated that on average we receive 0.4 mSv/y (40 mrem/y) from diagnostic radiologic sources and 0.15 mSv/y (15 mrem/y) from nuclear medicine tests.

Medical Diagnostic Procedures from External Radiation

An X-ray delivers about 0.05–0.1 mSv (5–10 mrem) radiation. The dose to the thyroid in adults undergoing a helical CT of the cervical spine is 26 mSv (2.6 rem).[5] It has been demonstrated that 0.06–0.1 Sv (6–10 rem) from external radiation can cause an increase in thyroid cancer; therefore, physicians should be concerned when diagnostic radiologic procedures, or repeated diagnostic procedures, reach this dose.[6,7] This is most important in pediatric patients.

Medical Diagnostic Procedures from Internal Radiation

The thyroid receives radiation from diagnostic procedures using radionuclides of iodine and from ^{99m}Tc (pertechnetate). For routine diagnostic thyroid scintigraphy, ^{123}I, a pure γ emitter is preferred. In a normal adult, 200 μCi ^{123}I (7.4 MBq) delivers approximately 2 cGy (2 rad) to a normal-size thyroid; 100 μCi ^{131}I (3.7 MBq) delivers approximately 1 Gy (100 rad) because of its β and γ emissions. A multicenter trial in the US evaluated thyroid nodules and cancers arising in children who had a prior diagnostic procedure with ^{131}I. There were 5 cancers in the 3503 study patients and 1 cancer in 2594 control patients.[8] A study of 34,104 patients who had ^{131}I scans in Sweden showed 67 thyroid cancers when 49.7 were predicted.[9] The thyroids received an average of 1.1 Gy (110 rad). The population included adults and children and when patients younger than 20 years were analyzed there were 3 cancers versus 1.8 expected. The conclusion of these studies is there was no statistically signifi-

cant increase in thyroid cancer in adults who had a thyroid scan with ^{131}I that delivered on average 0.94 Gy (94 rad).[10]

Medical Therapeutic Procedures Using External Radiation

The doses of external radiation used to treat patients with cancer is usually in the range 40–60 Gy (4000–6000 rad). In the past, physicians prescribed lower doses of radiation to treat nonmalignant conditions. It was recognized that low-dose external radiation increases the incidence of thyroid cancer. The doses used were usually in the range of 1–10 Gy (100–1000 rad).[11] Maxon et al.[12] identified 16 cancers and 15 benign nodules from 1266 irradiated patients in contrast to 1 cancer and 2 benign nodules from the 958 controls. Other studies demonstrated that about 5%–10% of those exposed developed thyroid cancer. Almost all thyroid cancers associated with external radiation are papillary. The latent period between the external radiation treatment and identification of the cancer usually falls within 5–20 years. In one report, cancer was found in only 2 of 700 patients less than 5 years from radiation.[6] Young age is important and the risk decreased in patients 20 years of age or older at the time of exposure to external radiation. Those 5 years or younger are at the highest risk and women are about twice as likely to develop a radiation-related thyroid cancer. The natural history of radiation-related thyroid cancer is the same as in spontaneously occurring cancer. Higher doses of external radiation administered to treat nonthyroidal cancers cause hypothyroidism. There is also an increase in Graves' hyperthyroidism and Graves' orbitopathy after external radiation.[13] Probably the radiation alters thyroid antigens and the immune system produces antibodies some of which are thyroid-stimulating antibodies. Although thyroid cancer rarely follows high-dose external radiation, we found approximately a 20-fold increase in thyroid cancer 10–20 years after the exposure.[13] The high increase is attributable to the rarity of thyroid cancer in normal people.

Very low therapeutic doses of external radiation are also of concern, for example, treatment of tinea capitis (ringworm) of the scalp.[14] The thyroid received approximately 6–10 cGy.[14] Compared were 10,834 exposed children to 10,834 matched nonirradiated children and to 5392 siblings who were also not irradiated.[6,15] There were 44 cancers in the treated group versus an expected 10.7.

Taking all the information related to external radiation, it has been calculated that there is an excess relative risk of 7.7 per Gy (100 rad). The absolute risk is 4–5 cancers per 10,000 (10^4) per year per Gy. From the data available, there is a linear effect from low doses of 0.06 Gy (6 rad) to 5–10 Gy (500–1000 rad). This relationship holds true until the administered dose reaches 25 Gy or higher (2500 rad). At about this dose, the risk levels off but does not reach zero and has been estimated to be 0.4 cancer 10^4 per gray per year.[16] In addition to the radiation dose, the age of the patient at the time of radiation

is important. Most cancers arise after a latent period of 5 years and the incidence decreases but does not disappear after 20 years. Women are at greater risk.

Medical Therapeutic Procedures Using Internal Radiation

^{131}I has been used for treatment of hyperthyroidism for 60 years. One of the concerns about treating benign conditions with radiation is that there would be an increase in cancers in the organ being irradiated. Ron et al.[17] conducted a large follow-up study of 23,020 patients treated with ^{131}I; 9028 received only radioiodine treatment and the remaining patients were also treated with antithyroid medications (10,439), antithyroid medications and surgery (2661), or surgery (892). The investigators found 29 patients died from thyroid cancer when 10.47 deaths would have been expected [standardized mortality ratio (SMR) 2.77; confidence interval (CI) 1.85–3.98]. The cancers were more likely to be found in patients with nodular glands and to be found within 4 years of ^{131}I treatment. Because of the short latency period and increased number in patients with nodular glands, the small increase in thyroid cancer after ^{131}I treatment of thyrotoxicosis suggests the cancers were already present at the time of ^{131}I treatment.

Medical Occupational Exposure

I am aware of colleagues in nuclear medicine and radiologic specialties who have had thyroid cancer but the denominator is unknown. Cancer mortality in radiologists who worked in the UK between 1897 and 1997 showed no increase in specialists registered after 1954.[18] There was an increase in earlier years but radiation safety precautions were less rigorous at that time. In a different study, cancer mortality was studied in 146,000 radiology technologists.[19] There were 7 deaths from thyroid cancer, 6 in women, and this was the exact number expected in the general population. In summary, the published data show no increase in thyroid cancer deaths in medical personnel who work with radiation.

Occupational Exposure in Nuclear Power Plant Workers

There was an almost threefold increase in thyroid cancer deaths (6 identified versus 2.2 expected) in 14,319 people who had worked at Sellafield nuclear power plant.[20] The numbers are small and could be attributable to chance.

Other Occupational Exposures

The average radiation exposure in the US is 300–360 mrem (3–3.6 mSv). The radiation increases at higher altitude and pilots and cabin crew receive an addition 500–1000 mrem (5–10 mSv) annually. Therefore, a 20-year career could result in exposure to 20 rem (0.2 Sv). A study of 28,000 male pilots identified 5 thyroid cancer deaths, which was more than the 3.6 expected, giving an SMR of 1.48 but the 95% CI ranged from 0.47 to 3.48.[21]

War-Time Exposure to Atomic Bomb

There were two populations, both Japanese, that have been studied. They were citizens of Hiroshima and Nagasaki in whom there was an increase in thyroid cancer. One hundred twelve thyroid cancers (62 from Hiroshima) were identified from 98,610 exposed residents. Prentice et al.[22] conclude "A clear, predominantly linear, increase in thyroid cancer incidence corresponds to increasing levels of γ radiation to the thyroid gland."

Exposure from Atomic Bomb Testing

Testing of atomic bombs in the US was conducted in Nevada. It has been estimated that the US population received 0.5 mGy (0.05 rad) of external radiation from fallout.[23] Since radionuclides of iodine were released, the thyroid was a key organ and it has also been estimated that the thyroid of a child born in 1951 received 30 mGy (3 rad). This resulted in a report from the National Cancer Institute suggesting that this could result in 75,000 additional thyroid cancers.[24] This is one explanation for the increasing incidence of thyroid cancer in the US.

Accidental Exposure to Atomic Bomb

The US tested an atomic device in the region of the Bikini islands near ground level. Two hundred thirty-five occupants of the Marshall Islands were exposed to direct radiation (external) and internal radiation to the thyroid plus exposure to ^{137}Cs, ^{90}Sr, ^{210}Po, and ^{239,240}Pu. These noniodine radionuclides could cause both external and internal radiation. Ten thyroid cancers were identified as well as 53 thyroid nodules.[25] Six of the 10 cancers occurred in people who were 18 years of age or younger at the time of exposure. There were 39 islanders in this age category, therefore 15.4% developed thyroid cancer. In contrast, less than 2% of older people were identified with thyroid cancer.

Accidental Release of Radioactivity from Power Plants

In the US, the nuclear accident that is remembered best is Three Mile Island that occurred on May 28, 1979. In fact, the maximum radiation exposure to people in the surrounding region was only 0.1 rem (1 mSv) and the average dose was 1 mrem (1 μSv). These are inconsequential. From 1954 to 1957, there were releases of substantial quantities of ^{131}I from Hanford in South Central Washington State into the Snake River, which is a tributary of the Columbia River.[26] Hanford was a production site for manufacturing atomic weapons. Thus, it was not a "power" plant and the releases were not accidental. The general conclusion was that no increased incidence of thyroid cancer was measured. By contrast, the accident at Chernobyl on April 26, 1986 released substantial amounts of radioactivity into the atmosphere and resulted in an increase in thyroid cancer in children. It has been estimated that 1.8×10^{18} Bq of ^{131}I was released plus short-lived radionuclides of iodine. Chernobyl caused a change in the understanding of radiation-induced thyroid cancer:[27] First, internal radiation could be causal; second, although most of the patients who developed thyroid cancer were young when exposed, older persons could also be at risk; and third, the latent period between exposure and cancer could be less than 5 years.[28] The incidence of pediatric thyroid cancer in Belarus, an adjacent territory, increased from 2 per year in 1986 to 6 cases in 1989 to 114 cases in 1992.[29,30] Similarly, the incidence in Ukraine increased from 3 in 1986–1988 to 324 between the years 1990–1998.

Short-lived radionuclides of iodine contributed one-third radiation to those who did not take prophylactic inorganic iodine and for half the thyroid dose in those who took inorganic iodine. The paradoxic higher percentage is attributed to the reduced absorbed radiation from ^{131}I (half-life 8 days) which was trapped in smaller quantities because of prophylactic inorganic iodine.

Almost all of the cancers were papillary. There is an increased incidence of solid trabecular papillary cancer. Genetic analysis has demonstrated a consistent pattern of mutation. Rearrangements of the *RET* has been identified in 60%–90% of papillary cancers in children exposed to fallout from Chernobyl. This is a considerable increase over the findings in sporadic papillary cancer. The genetics are described later in the chapter.

Prophylaxis for Radioactive Fallout

When radionuclides of iodine are released into the atmosphere, the thyroid can be protected by ingesting an excess of nonradioactive iodine ^{127}I. The iodine dilutes the radioactive iodine and a smaller proportion of the radioactive nuclide is trapped by the gland. The main requirement is to ingest the ^{127}I before exposure to the radionuclides of iodine. This is usually not possible. A 130-mg potassium iodide (KI) pill is the most suitable preparation. There are liquid preparations including Lugol's iodine (1 mL, 30 drops, contains 130 mg of iodine) and saturated solution of KI that are effective. The liquid is not so

easy to store, it loses potency with time, and is more difficult to dispense. A dose of iodine between 100 and 200 mg reduces thyroidal uptake by 95%. Because of recent concern about terrorists detonating an atomic, or dirty bomb, there has been a run on the sale of KI pills. KI will not be useful for protection against dirty bombs unless radioactive iodine was attached to the explosive device.

Pregnant women are advised to take half of a 130-mg KI pill. The US recommendation for 12- to 18-year-old adolescents is a half pill (65 mg), but because most of these individuals are adult size and they are at more risk because of their youth, I would recommend the full dose.

It has been shown that taking the KI 96 hours before has no protective effect. Similarly, taking the KI 16 hours or more after the radioactive iodine has no beneficial effect. There is a short window of opportunity.

Genetic Mutations as a Cause of Thyroid Cancer

About one third of medullary cancers are familial and there are 3 phenotypic categories. 1) The affected family members have medullary cancer and no associated conditions. 2) Patients with MEN 2A have medullary cancer and about 50% develop pheochromocytoma and 20%–30% hyperparathyroidism. 3) Patients with MEN 2B have medullary cancer and pheochromocytoma in about 50%. They also have ganglioneuromas of the lips, tongue, intestines, abnormal nerves in the eyeball, plus a marphanoid appearance. A genetic cause for MEN 2 syndromes was identified in 1987.[31] Mutations in the *RET* (rearranged during transfection) protooncogene as the cause of medullary cancer were reported in 1993.[32] The *RET* protooncogene is a single transmembrane protein encoded by chromosome 10. The RET protein has a receptor on the extracellular end of the molecule and protein kinase function at the intracellular end. The extracellular segment adjacent to the cell membrane is rich in cysteine molecules. The presence of a ligand results in fusion of 2 *RET* receptor molecules and when a dimer is formed the enzyme tyrosine kinase is activated.

Point mutations in the gene for *RET* are associated with the three syndromes. The majority of mutations are on exons 10 (codons 609, 611, 618, and 620) and 11 (codon 630 and 634). The codon 634 mutation is present in the majority of MEN 2A and familial medullary cancer patients. The mutations are in the region of the chromosome that codes for the cysteine-rich segment of *RET*.[33] A base alteration in one of these codons results in a cysteine molecule being replaced by an alternative amino acid. The cysteine molecules within a strand of *RET* form intramolecular disulfide bonds and the absence of one of the pair allows disulfide bonding between *RET* molecules thus producing dimers. Thus, the protein kinase enzyme is activated without the presence of ligand. This is called constitutive activation. In MEN 2B, the point mutation is usually in exon 16, codon 918 which results in methionine being replaced by threonine. This mutation is in the tyrosine kinase segment and induces phosphorylation of alternative substrates.

The parafollicular cells with *RET* protooncogene mutations first develop C cell hyperplasia and then become frankly cancerous. Curative treatment of patients with one of these mutations requires total thyroidectomy before there is clinically significant cancer. It is of interest that many of the sporadic (nonfamilial) medullary cancers have similar mutations but they are restricted to the thyroid cancer cells and are not transmissible.

In contrast, the genetic changes in the *RET* protooncogene in papillary cancer are different. The active enzyme protein tyrosine kinase is intact but the extracellular component that binds ligands is lost. That segment is replaced by a fusion gene. These result in oncogenes called *RET-PTC-1*, *RET-PTC-2*, *RET-PTC-3*, etc. The fusion genes contain segments with three-dimensional configurations that produce dimers and when these are formed the tyrosine kinase is activated without the presence of ligand. These mutations are only found in the thyroid and have been identified in cancerous and benign nodules. These are not hereditary. Sixty to ninety percent of the papillary thyroid cancers in children who were exposed to radiation from Chernobyl have *RET-PTC* oncogenes. *RET-PTC-1* is frequently associated with "regular" papillary cancer. *RET-PTC-3* is strongly associated with solid trabecular papillary cancer found in children exposed to radiation from Chernobyl.

p53 is an important tumor suppressor gene. Mutations and deletions of this gene have been found in differentiated and anaplastic thyroid cancer. There is increasing evidence that this mutation in addition to other initiators could be the genetic defect that alters the phenotypes of thyroid cancers from slow-growing differentiated cancer to the rapidly aggressive and invasive behavior of anaplastic cancer. Recent reports identified point mutations in the *BRAF* gene in 38% of papillary cancers and 83% of anaplastic lesions.[34]

Familial Nonmedullary Thyroid Cancer

There is increasing evidence that there are familial clusters of differentiated thyroid cancer.[35,36] This was first reported in 1951 and a few case reports were published over the next 4 decades. It is possible that a genetic defect might make family members more susceptible to radiation. One investigation compared the probability of a second member of a family having thyroid cancer with the risk in families with no evidence of an index case.[37] There was a 10.6-fold increased risk of a second person having thyroid cancer in the former population. A somewhat similar study in Norway found a fivefold increased likelihood of cancer (men 5.2, women 4.9) compared with expected.[38] There are reports of several families with three or more first-degree relatives with papillary cancer and the chance of five family members with papillary cancer has been estimated at 1 in 2 billion.[39]

There is a definite coexistence of differentiated thyroid cancer with hereditary syndromes including familial adenomatous polyposis and the associated Gardner's syndrome and Cowden's syndrome. One group of investigators who have conducted extensive research in the field state, "familial nonmedullary

thyroid cancer is an emerging clinical phenotype that is genetically heterogeneous, and none of the currently identified genes accounts for the majority of families."[40]

Multifocal lesions and recurrences are more common.[41] Current data suggest that about 5% of papillary cancers are familial. This is similar to my experience with 34 families out of more than 1000 patients (3.4%).

Chemicals as a Cause of Thyroid Cancer

In humans, there is little evidence that chemicals can cause cancer of the thyroid. Goitrogens in doses sufficient to increase thyroid-stimulating hormone can augment the carcinogenic effects of radiation. A metaanalysis concluded there was a reduced risk of thyroid cancer in people who smoked.[42]

The Role of Iodine in the Etiology of Thyroid Cancer

Follicular cancer is more common in regions deficient in iodine and papillary cancer is less common. Laboratory animals fed a chronically iodine-deficient diet develop benign follicular tumors and with time follicular cancers.[43] Most studies show that follicular cancer is more common in areas of chronic low iodine intake. In the majority of reports, the ratio of papillary cancers increases in parallel with increasing dietary iodine. Lymphocytic thyroiditis is also more common in iodine-replete regions. Low iodine potentiates the effect of known thyroid carcinogens.

Estrogen and Thyroid Cancer

All reports of differentiated thyroid cancer with meaningful numbers of patients indicate that women are about 3 times more likely to be affected. However, there are few data regarding female sex hormones as a cause of thyroid cancer.

Geographic Factors

There are data from Sicily indicating an increased risk in regions near volcanoes. This could be attributable to higher levels of radiation. It could explain the higher risk in the Philippines and Hawaii, which are volcanic islands.

Summary and Key Facts

Most thyroid cancers are sporadic and no single cause can be identified. A proportion of thyroid cancers are associated with radiation as an etiologic factor and a proportion have a genetic link. The radiation is usually external and there is a linear relationship from about 0.05–0.1 Gy (50–100 mGy or 5–10 rad) to 5–10 Gy (500–1000 rad). There is an excess risk ×7.7 per Gy. Children exposed to internal radiation resulting from the accident at Chernobyl also have a definite increase in the incidence of thyroid cancer. Genetic defects in the *RET* protooncogene are the cause of 25%–30% of medullary cancers and 100% of the MEN 2A and 2B syndromes.

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