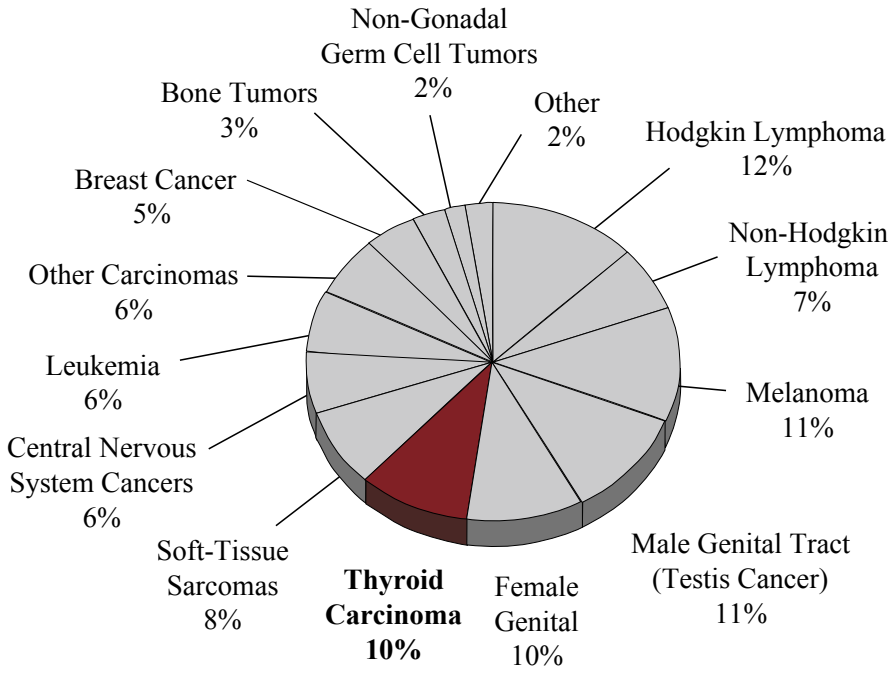
Chapter 12

Thyroid Cancer

Cancer in 15- to 29-Year-Olds in the United States



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HIGHLIGHTS

Incidence

- In the United States from 1975 to 2000, thyroid cancer accounted for about 10% of all malignancies diagnosed in individuals 15 to 29 years of age and was the 4th most common cancer in this age group.
- Nearly 2,400 individuals 15 to 29 years of age were diagnosed with a malignant thyroid neoplasm in the U.S. during the year 2000.
- Thyroid cancer, as a percentage of all cancer, peaked between 20 and 24 years of age, and represented more than 11% of malignancies in this age group.
- The incidence of thyroid cancer increased rapidly between 15 and 29 years of age, and reached a plateau by the 5th to 6th decades.
- Differentiated thyroid cancer (papillary and follicular carcinoma – PTC and FTC) accounted for the vast majority of cases occurring before 30 years of age, and medullary thyroid carcinoma (MTC) accounted for most of the rest.
- More than 80% of the cases of thyroid cancer occurred in females.
- Between 1975 and 2000 the incidence of thyroid cancer increased steadily, at a statistically significant rate. Most of the increase occurred during the 1990s.
- The increase in incidence occurred in localized and regional—but not distant—presentations of disease.

Mortality & Survival

- The mortality rate of thyroid cancer increased above age 10, and continued to rise as a function of age.
- Thyroid cancer has been one of the most curable malignancies, with 5-year survival rates exceeding 99% in 15- to 29-year-olds. This holds true even in patients with disseminated disease at diagnosis.
- Patients with MTC have not fared as well as those with PTC and FTC.
- Although the survival difference between males and females was small, males had a consistently lower survival rate than females.

Risk Factors

- Appreciating the major histologic distinction between PTC and MTC is fundamental to understanding the differences in the biologic behavior and treatment applicable to these very different thyroid cancers.
- The major established environmental risk factor for the development of malignant thyroid neoplasms, particularly PTC, is ionizing radiation. This can result from exposure to both external beam radiotherapy and internal radiation as delivered by the ingestion of radioiodine.
- The *RET* proto-oncogene is implicated in the development of PTC.
- Most young individuals diagnosed with MTC have one of three hereditary cancer syndromes: familial MTC, multiple endocrine neoplasia type 2A, or multiple endocrine neoplasia type 2B.
- MTC in the context of a familial syndrome is caused by germline mutations in the *RET* proto-oncogene.
- Sporadic MTC is rare in the adolescent and young adult population.

INTRODUCTION

Although uncommon, thyroid carcinoma is not an unusual finding in the adolescent and young adult population. Between 1975 and 2000, it represented approximately 7.8% of all cancers diagnosed in the 15- to 19-year age group, 11.5% in patients 20 to 24 years old, and 10.1% in individuals from ages 25 to 29 (Figure 12.1). In children younger than 15 years of age it is very rare, with very few cases diagnosed before 10 years of age. Fortunately, the long-term prognosis is excellent for most

children and young adults diagnosed with thyroid carcinoma. Due to the limited number of cases diagnosed each year and because of the extended follow-up needed to obtain meaningful outcome data, thyroid carcinoma in the adolescent and young adult population remains a poorly studied disease. In contrast to thyroid cancer in older individuals, thyroid carcinomas in patients younger than 30 years of age have notable differences in tumor biology and clinical presentation. Despite the likelihood of having more widespread disease at presentation, adolescents and young adult patients with thyroid cancer typically have a better outcome than older adults who present with a similar extent of disease.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

Thyroid cancer is classified in the International Classification of Childhood Cancer (ICCC) in category XI(b) as Thyroid Carcinoma, a category within Carcinomas and Other Epithelial Neoplasms (X). The ICCC thyroid category specifies that thyroid carcinoma includes International Classification of Disease for Oncology (ICD-O) categories 8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8155, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8573. These categories include general carcinomas and adenocarcinomas and specific cancers of the thyroid. ICCC group XI(b) also includes follicular carcinomas (8330-8350) of any cancer site.

Three major types of thyroid cancer exist in the adolescent and young adult population. The differentiated thyroid carcinomas (DTC)—papillary thyroid carcinoma (PTC) (ICD-O categories 8050, 8260, 8340) and follicular thyroid carcinoma (FTC) (ICD-O categories 8330-8334)—arise from the thyroid follicular epithelium. In contrast, medullary thyroid carcinoma (MTC) (ICD-O category 8510) arises from the parafollicular C cell, which has a distinct embryologic origin from neural crest cells.

The diagnosis of PTC and FTC is based upon histopathological features that are unique to each type of carcinoma. Within the broader classification of PTC and FTC, there are subtypes of each. Follicular cell, tall cell, diffuse sclerosing, columnar cell, and encapsulated are variants of PTC whereas subtypes of FTC include Hürthle-cell (oncocytic), clear cell, and insular carcinoma. Certain tumor subtypes, such as follicular and diffuse sclerosing variants of PTC, are more common in children and young adults as compared to older individuals.[1] Furthermore, in contrast to the classical type of PTC identified in older individuals, childhood PTC, particularly in the very young, may: 1) be unencapsulated and widely invasive throughout the gland and 2) have a solid and follicular architecture with unique nuclear features and abundant psammoma bodies.[2,3]

In general, MTC accounts for approximately 7-10% of all thyroid malignancies in the general population. PTC represents about 80% and follicular thyroid carcinoma accounts for approximately 20% of the differentiated thyroid carcinomas.[2,4,5] PTC and FTC account for the vast majority of cases before 30 years of age, and MTC accounts for almost all of the rest.

In contrast to DTC, MTC is often an inherited disease in the pediatric and young adult population, resulting from gain-of-function mutations in the rearranged during transfection (RET) proto-oncogene.[6] Sporadic cases of MTC are less common in the AYA age group. In patients with heritable disease, the MTC is virtually always bilateral, multicentric and located at the junction of the upper one-third and lower two-thirds of the thyroid lobes, which is where the greatest concentration of C cells exists. In contrast, only one thyroid lobe is typically involved in patients with sporadic tumors. In individuals with a familial form of MTC, clusters of C cells (C-cell hyperplasia) are routinely identified pathologically. This C-cell hyperplasia is believed to be one of the initial stages in the development and progression of MTC.[7]

Poorly differentiated and frankly anaplastic thyroid carcinomas arise from the differentiated thyroid carcinomas. Although they can occur in the adolescent and young adult population, they are exceedingly rare. Therefore, the main focus of this chapter will be the major categories of thyroid carcinoma identified in the adolescent and young adult age group: PTC, FTC, and MTC.

As explained in the Methods chapter, data are presented for 15- to 29-year-olds with comparisons to the age

Table 12.1: *Incidence of Thyroid Cancer in Persons Younger Than 30 Years of Age, U.S, 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	0	1.0	4.2	15.4	37.2	54.8
Average annual % change in incidence, 1975-2000, SEER	^	^	^	1.23	1.32	1.42
Estimated incidence per million, year 2000, U.S.	0	1.0	4.3	17.6	43.3	63.0
Estimated number of persons diagnosed, year 2000, U.S.	0	20	89	355	820	1,222

^ Too few for a reliable estimate

groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

INCIDENCE

Age-Specific Incidence

Based on incidence data collected from 1975 to 2000 in the United States, approximately 2,400 persons between 15 and 29 years of age were diagnosed each year with thyroid cancer (Table 12.1); this represents about 10% of all such cancers. More than half of these patients were 25 to 29 years of age. Over this same time period, more than 350 older adolescents in the 15- to 19-year age group were diagnosed annually to have thyroid cancer (Table 12.1).

Thyroid cancer as a percentage of all cancer reached a peak in those 20 to 24 years of age, and represented 11.5% of all malignancies in this age group. For those younger than age 10, it represented less than 1% of all cancers and for those 40 years and older, it represented 4% of all cancers (Figure 12.1).

DTC, MTC and other types of thyroid cancer peaked in incidence at 50, 70 and after 80 years of age, respectively, with DTC predominant at all ages (Figure 12.2). The incidence of DTC increased 3.5-fold from age 15 to 19 years to 25 to 29 years (Figure 12.3). In contrast, the incidence of MTC rose gradually over the life span, and there was no dramatic increase in the rate of diagnosis in the young adult population (Figure 12.4). In adolescents and young adults, MTC was an uncommon disease with an incidence of less than 1 case/million/year. Since PTC and FTC represented the vast majority of thyroid cancer cases, it is not surprising that the incidence of thyroid carcinomas as a whole (Figure 12.2) was parallel to that of DTC (Figure 12.3).

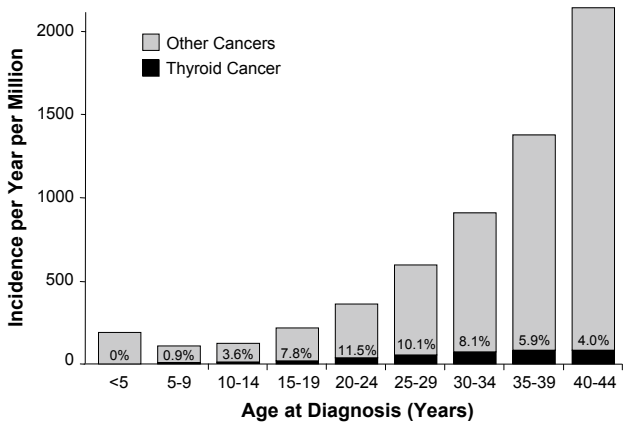

Figure 12.1: Incidence of Thyroid Cancer Relative to All Cancer, SEER 1975-2000

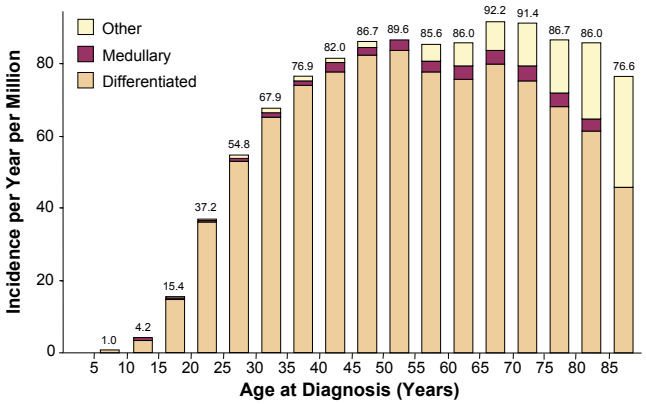

Figure 12.2: Incidence of Thyroid Cancer by Histology, SEER 1975-2000

Gender-Specific Incidence

Most cases of thyroid cancer occurred in females; peak incidence was between 45 and 50 years of age (Figure 12.5). In males, the peak incidence occurred at a much older age. The ratio of females to males with thyroid cancer was as high as 5-fold, and the maximum ratio was seen in the adolescent and young adult age group (Figure 12.5). This gender difference was not pronounced in children younger than 10 years of age.

When the types of thyroid cancer were reviewed by major subtype, the gender-specific incidence for DTC (Figure 12.6) was similar to that of the total group (Figure 12.5). However, MTC did not have as striking a difference in the female-to-male incidence ratio (Figure 12.7). Because MTC is frequently heritable via an autosomal dominant mode of transmission (see *Risk Factors and Etiology*), it is not surprising that the female-to-male ratio approximates one in many age groups.

Racial/Ethnic Differences in Incidence

Between 15 and 45 years of age, white non-Hispanics and Asians/Pacific Islanders were at highest risk of developing thyroid cancer, and African Americans/blacks and American Indians/Alaska Natives were at lowest risk (Figure 12.8). Among 15- to 29-year-olds in the U.S., African Americans/blacks were least affected, with an incidence less than one-half that of the other racial/ethnic groups. Hispanic persons had an intermediate incidence of thyroid cancer (Figure 12.8). Female-to-male ratios in the adolescent and young adult population were similar among the various racial/ethnic groups: 5.1 in African Americans/blacks; 5.4 in white non-Hispanics; 5.8 in Asians/Pacific Islanders; and 6.7 in Hispanics. The female-to-male ratio is not known for American Indians/Alaska Natives due to too few cases reported in males.

Trends In Incidence

Between 1975 and 2000, thyroid cancer increased steadily in all adolescent and young adult age groups, with a noticeable increase occurring in the 25- to 29-year-old and older age groups (Table 12.1, Figure 12.9). Most of the increase occurred during the 1990s (Figure 12.9). Overall, the most significant increase in incidence was observed in those individuals 45 years of age and older, but in all age groups these changes were statistically significant.

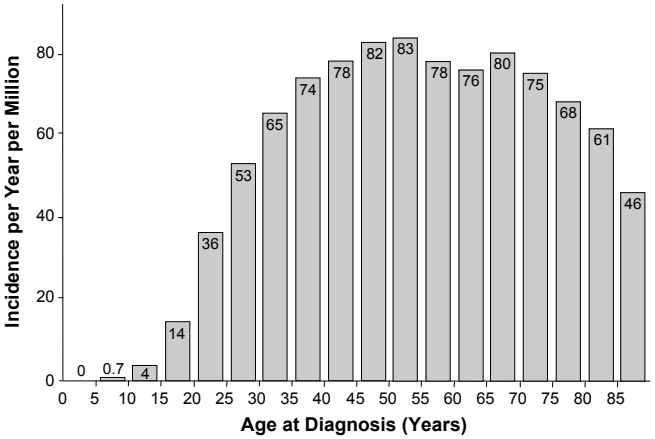

Figure 12.3: Incidence of Differentiated (Papillary and Follicular) Thyroid Cancer, SEER 1975-2000

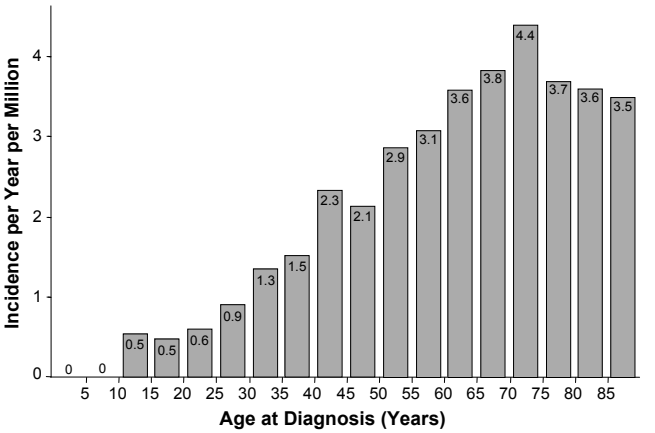

Figure 12.4: Incidence of Medullary Thyroid Cancer, SEER 1975-2000

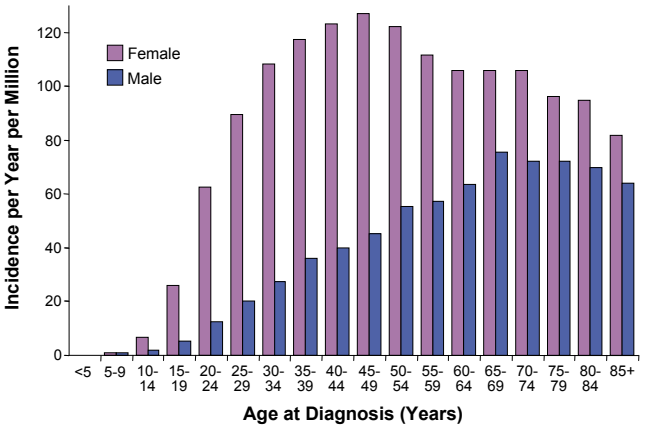

Figure 12.5: Incidence of Thyroid Cancer by Gender, SEER 1975-2000

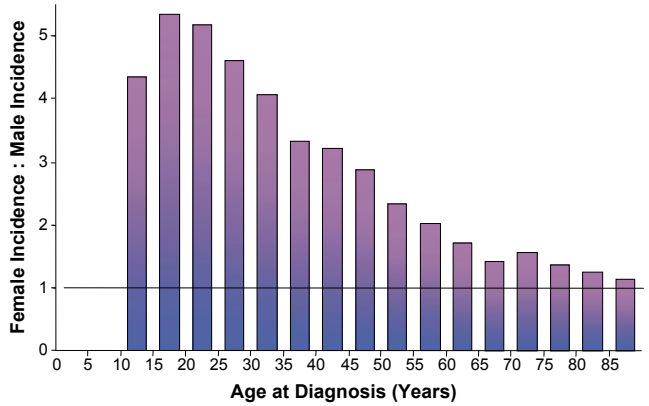

Figure 12.6: Ratio of Female to Male Incidence of Differentiated (Papillary and Follicular) Thyroid Cancer, SEER 1975-2000

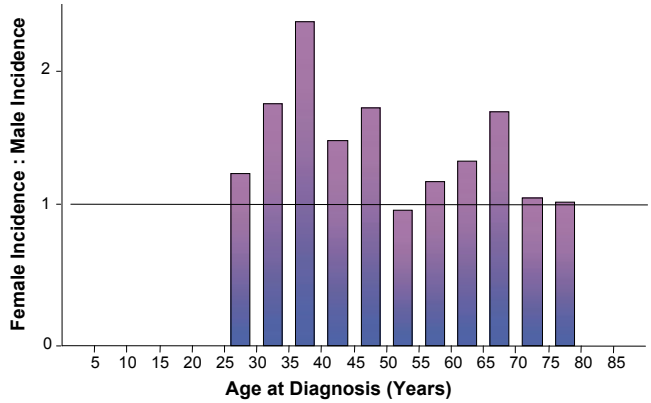

Figure 12.7: Ratio of Female-to-male Incidence of Medullary Thyroid Cancer, SEER 1975-2000

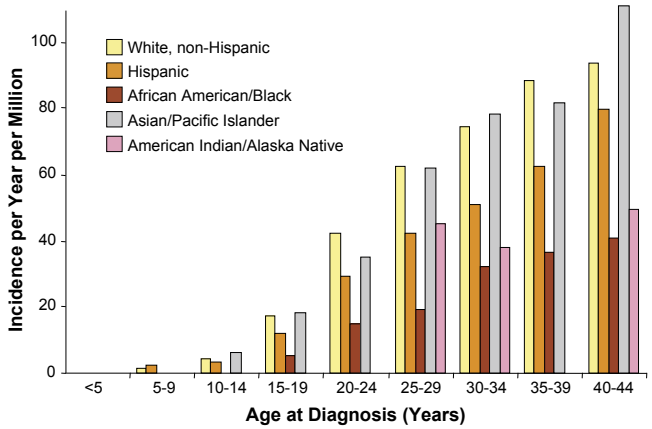

Figure 12.8: Incidence of Thyroid Cancer by Race/Ethnicity, SEER 1990-2000

Reasons for the significant changes in the incidence of thyroid cancer are unknown, but may include the increased use of diagnostic imaging, heightened awareness of cancer screening, or an environmental factor such as radiation (see *Risk Factors and Etiology*), to which the population as a whole has had increased exposure. There was an obvious increase in incidence of thyroid cancer in females (Figure 12.10) but not in males (Figure 12.11).

The increase in incidence was greater in regional presentations of disease than in either localized presentations or those with distant metastases (Figure 12.12). This may be a partial artifact due to better imaging and more complete lymph node dissections, which detect regional disease at a higher rate than in prior eras.

OUTCOME

Mortality

Overall, mortality for thyroid cancer remains low, since most cases in the adolescent and young adult population are cured after initial therapies or have an indolent clinical course. The death rate for those 15 to 24 years of age was 0.1 per year per million, and continued to rise as a function of age (Figure 12.13). The overall prognosis of DTC in young children, adolescents and young adults is favorable, even for patients with disseminated disease at diagnosis.[5,8] However some of these individuals may succumb to their disease or die from treatment-related complications decades after diagnosis, which underscores the importance of life-long follow up.[8]

Despite the remarkably higher incidence of thyroid cancer in females (Figure 12.5), mortality in females and males was essentially identical in the adolescent and young adult age group (Figure 12.14).

Mortality from thyroid cancer has not declined in the 15- to 29-year age group during the past quarter century, probably because of the high survival rates (see *Survival*). However, it has declined in older patients, probably representing an improvement in the diagnosis and treatment of these patients (Figure 12.15).

Survival

Thyroid cancer is one of the most curable of malignancies, particularly if identified early and treated appropriately. For all thyroid cancers, 5-year survival rates were 99% or greater in 15- to 29-year-olds (Figure 12.16). Although children diagnosed prior to age 10 had 5-year survival rates approaching 100% in the U.S (Figure 12.16), some still die from their disease many years to decades after diagnosis.[2,9]

It is known that MTC has a biological behavior that is more aggressive than PTC or FTC, but less aggressive than anaplastic or poorly differentiated thyroid carcinoma. Therefore patients with MTC have not fared as well as those with DTC, particularly those 15 to 24 years of age (Figure 12.17). Nonetheless, between 1975 and 2000, 5-year survival rates for MTC were still good overall, ranging between 85% and 95% among patients 10 to 44 years of age (Figure 12.17). For patients with MTC not diagnosed early, incurable yet indolent disease is often the norm. The biological aggressiveness of MTC also depends on the genetic background in which it develops. As compared to MEN2A and familial MTC (FMTC), MTC arising in the setting of MEN2B is more aggressive, presenting at a very early age in most cases. FMTC usually has a more benign clinical course, whereas MTC within MEN2A is somewhat capricious, following an indolent course in most patients but progressing rapidly in others. The reasons for this variable biological behavior of MTC in these different clinical entities are unknown. In adolescents and young adults it is difficult to assess the behavior of MTC in sporadic compared to familial cases.

Although the survival difference between males and females was small, males had a consistently lower survival rate than females (Figure 12.18).

Several prognostic scoring systems (AMES, MACIS, AGES, etc.) have been described for the thyroid carcinomas, chiefly PTC, but a thorough review of these is beyond the scope of the current discussion. The pathological TNM classification is used as an international reference staging system. Given that it takes into account the prognostic effects of lymph node metastases at presentation, it may be superior to the others, at least in PTC.[10] By definition, and reflecting the good prognosis in

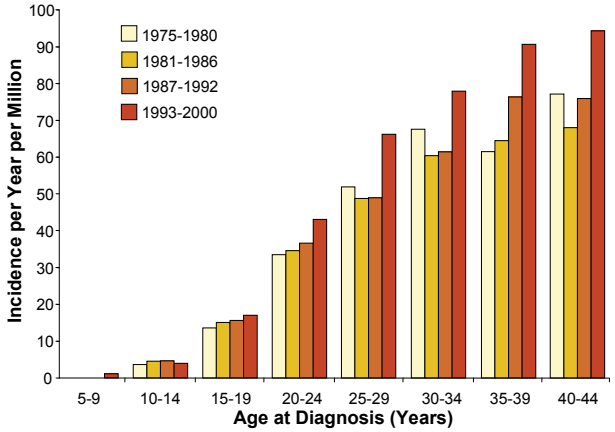

Figure 12.9: Incidence of Thyroid Cancer by Era, SEER 1975-2000

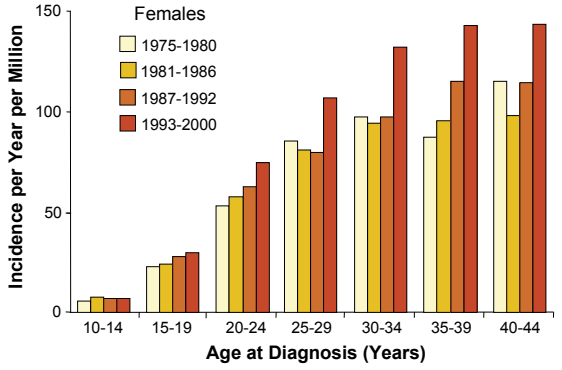

Figure 12.10: Change in Incidence of Thyroid Cancer in Females, by Era, SEER 1975-2000

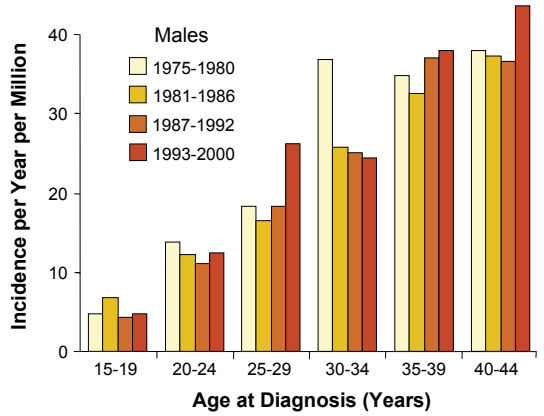

Figure 12.11: Change in Incidence of Thyroid Cancer in Males, by Era, SEER 1975-2000

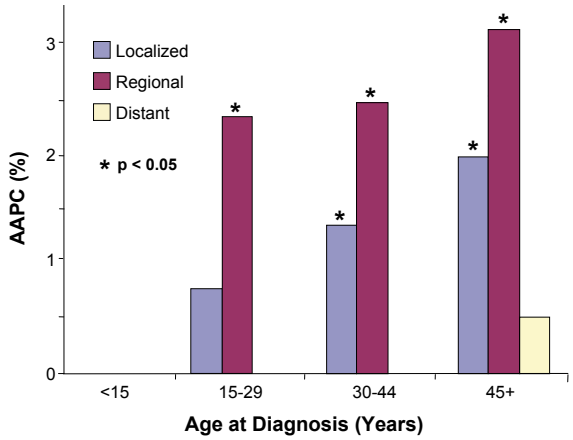

Figure 12.12: Average Annual Percent Change (AAPC) in Incidence of Thyroid Cancer by Extent of Disease, All Sites, SEER 1975-2000

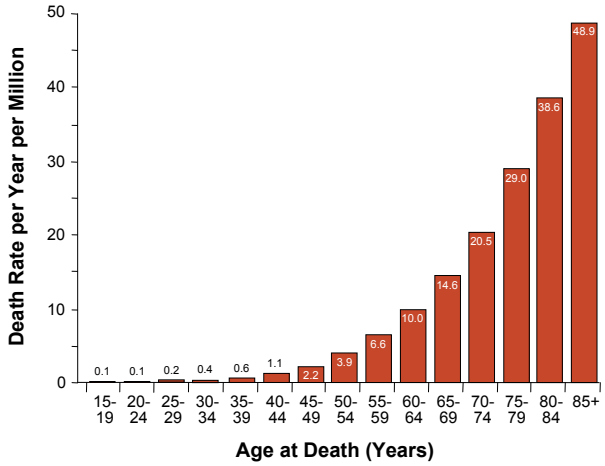

Figure 12.13: National Thyroid Cancer Mortality, U.S., 1975-2000

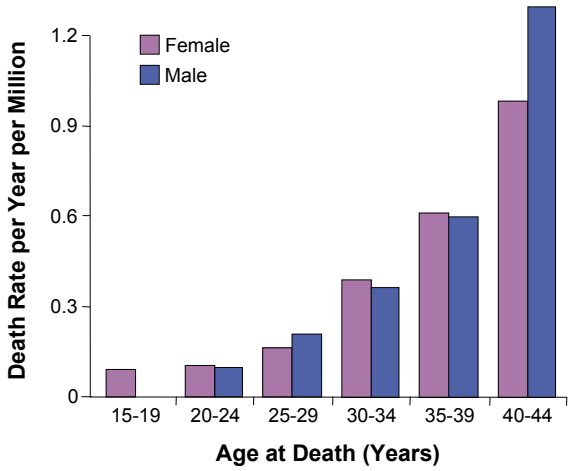

Figure 12.14: National Mortality for Thyroid Cancer by Gender, U.S., 1975-2000

adolescents and young adults, the highest TNM stage that anyone younger than age 45 can achieve is stage II, even with distant metastases. Therefore, utilizing the TNM staging system as a predictor of outcome or a determinant of treatment aggressiveness is not necessarily useful in children and young adults with thyroid cancer

RISK FACTORS AND ETIOLOGY

Differentiated Thyroid Carcinoma

The major established environmental risk factor for thyroid neoplasms, particularly PTC, is radiation exposure to the thyroid.[11,12] Younger individuals, particularly those under 5 years of age, are much more sensitive to the tumorigenic effects of irradiation.[12,13] In part, this may be due to the higher rate of thyroid cell replication in children as compared to adults.[1,14,15] Because children are no longer treated with external beam radiation therapy for benign conditions such as tonsillar hypertrophy, thymic enlargement, or acne, there are currently fewer adolescent and young adult thyroid cancer patients with this well-established risk factor. However the use of radiotherapy to treat malignancies (chiefly Hodgkin and non-Hodgkin lymphomas) remains a significant risk for thyroid carcinoma development, even many years after the completion of therapy.[16] Although there are some conflicting data, it appears that radiation-induced thyroid carcinoma is not more clinically aggressive as compared to sporadic, non-radiation induced tumors.[16,17]

Another well-documented risk factor for the development of PTC is internal ionizing radiation, such as occurred with the large environmental exposure to radioactive iodines from the Chernobyl nuclear accident.[18,19] The risk of thyroid cancer secondary to radioiodine is significantly higher the younger the age at the time of exposure, perhaps because the thyroid gland in younger children is better equipped to transport iodine as compared to older children.[15] The risk of thyroid cancer from the Chernobyl disaster has been demonstrated to be linearly correlated with radiation doses up to 1.5-2 Gy.[18] The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas than elsewhere. Administration of iodine as a dietary supplement reduced this risk of radiation-related thyroid cancer by a factor of 3, for consumption of

potassium iodide versus no consumption.[18] Fortunately, the doses of radioactive iodine used in diagnostic thyroid scans appear not to increase the rate of tumorigenesis.[11]

Researchers are beginning to understand the genetic and molecular basis of the differentiated thyroid carcinomas. One of the major early somatic events that is associated with the development of PTC is a chromosomal rearrangement linking the promotor region of an unrelated gene(s) (named "*PTC*") to the carboxyl terminus of the *RET* (rearranged during transfection) proto-oncogene.[1,6,14,19] Although it is widely believed that *RET/PTC* rearrangements are critical for the development of pediatric and radiation-induced PTC,[20-26] some recent reports have challenged these conclusions.[27] Mutational activation of the BRAF oncogene is commonly found in adult PTC. In children and young adults, mutations in BRAF do not occur frequently, although the prevalence of this genetic alteration appears to increase with age.[28-30]

Although PTC does not usually present as a familial disease, approximately 3-5% of patients with PTC do have a positive family history.[31] Having familial PTC may portend a worse prognosis, given previous data suggesting that these cases may have more aggressive disease with shorter disease-free intervals after initial therapy.[31,32] To date, the genetic basis for dominantly inherited non-medullary thyroid carcinoma has not been elucidated. Other familial tumor syndromes in which there is an increased risk of DTC include the Carney complex, Cowden disease, and familial adenomatous polyposis (Gardner syndrome).[1]

Figure 12.15: National Mortality for Thyroid Cancer by Era, U.S., 1975-2000

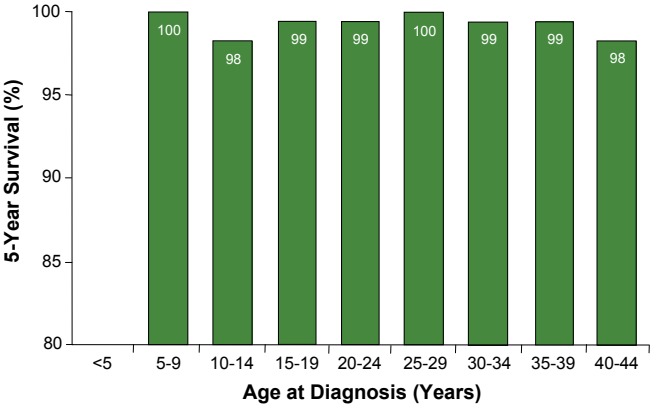

Figure 12.16: 5-year Survival Rate for Thyroid Cancer, SEER 1975-1999

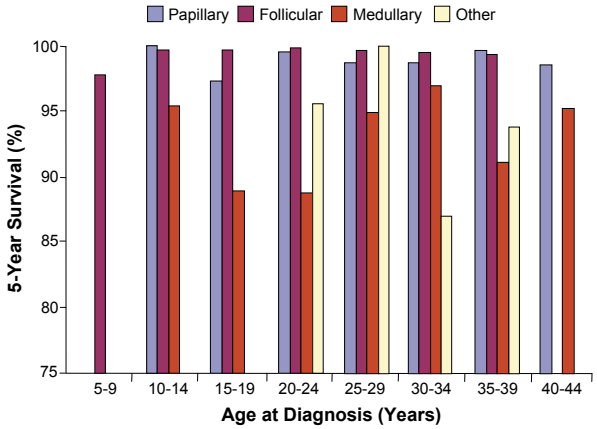

Figure 12.17: 5-year Survival Rate for Thyroid Cancer by Histologic Type, SEER 1975-1999

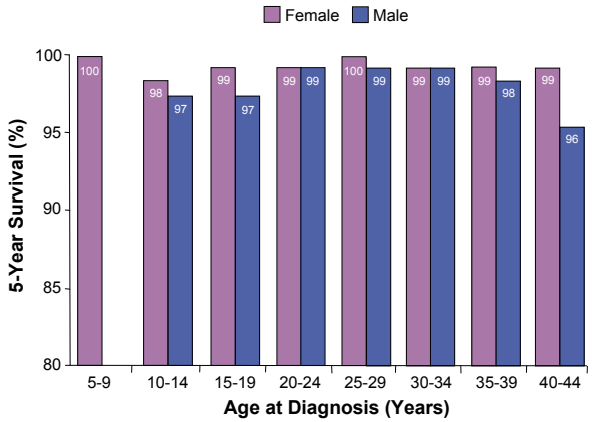

Figure 12.18: 5-year Survival Rate for Thyroid Cancer by Gender, SEER 1975-1999

Medullary Thyroid Carcinoma

Unlike PTC, medullary thyroid carcinoma does not have clearly identified environmental risk factors. On the other hand, the molecular basis of MTC in the context of the familial syndromes (see below) is very well understood. The development of MTC in this setting is also particularly relevant in young children because, with current methods of diagnosis and treatment, MTC is one of the few malignancies that can be prevented or cured (via total thyroidectomy) before it becomes clinically manifest. In the adolescent and young adult population, it is fair to say that the vast majority of cases of MTC will have a genetic basis, i.e. germline mutations in the *RET* proto-oncogene. Although sporadic (non-heritable) MTC can be seen in this age group, such cases are rare. Therefore, the focus of the subsequent discussion is on familial MTC, which is inherited in an autosomal dominant fashion.

Most children and young adults with MTC are afflicted with one of three hereditary cancer syndromes: FMTC, MEN2A, or MEN2B. Medullary thyroid carcinoma occurs in almost all patients with these familial syndromes, and it is the most common cause of death in affected individuals. Patients with FMTC only develop MTC. In MEN2A and MEN2B, 50% of patients develop pheochromocytoma; up to 20% of MEN2A patients develop hyperparathyroidism.[33] Individuals with MEN2A may also develop a pruritic cutaneous lesion on the upper back, termed "cutaneous lichen amyloidosis."[34] Other MEN2A kindreds can have associated Hirschsprung's disease.[35,36] All patients with MEN2B develop a generalized ganglioneuromatosis, manifested most obviously by the presence of oral mucosal neuromas. These individuals also manifest a Marfanoid body habitus and a characteristic facial appearance.

The exact etiology of sporadic MTC is unknown, although it too may have a genetic basis. After the discovery that germline mutations in the *RET* proto-oncogene cause heritable MTC, it was identified that somatic mutations in *RET* can be found in over 40% of sporadic cases of MTC.[37] However, due to the rarity of sporadic MTC in those younger than 30 years of age, it is unknown if this holds true for this age group.

SUMMARY

Malignant neoplasms of the thyroid were the fourth most commonly diagnosed cancer in the 15- to 29-year age group between 1975 and 2000. In the year 2000, nearly 2,400 individuals 15 to 29 years of age were diagnosed with a malignant thyroid neoplasm in the U.S., representing approximately 10% of all thyroid cancer cases. The incidence of thyroid carcinoma increased rapidly between 15 and 29 years of age and reached a plateau by the 5th—6th decades of life. Differentiated thyroid cancer (PTC and FTC) accounted for the vast majority of cases diagnosed before 30 years of age, and MTC accounted for almost all of the rest. Females were much more likely to develop thyroid cancer than males.

Between 1975 and 2000, the incidence of thyroid cancer rose steadily in all age groups between 15 and 30 years. In adolescent and young adult females this occurred at a statistically significant rate. Most of the increase in incidence occurred during the 1990s. The increase occurred in localized and regional, but not distant, presentations of disease, which may reflect changes in imaging modalities and surgical approaches to these diseases.

Overall, mortality from thyroid carcinoma was low, although it increased as a function of age. Despite the remarkably higher incidence of thyroid cancer in females, mortality for females and males was essentially identical and declined steadily during the past quarter century. Although the survival difference between males and females was small, males had a consistently lower survival rate than females. Thyroid cancer is one of the most curable malignancies, with 5-year survival rates exceeding 99% in the adolescent and young adult population, even in patients with disseminated disease at diagnosis. Patients with MTC have not fared as well as those with DTC, particularly those in the 15- to 24-year-old age group.

The major established environmental risk factor for the development of benign and malignant thyroid neoplasms, particularly PTC, is ionizing radiation exposure to the thyroid, whether from external (cancer radiotherapy) or internal (radioiodine exposure) sources. The genetic causes of DTC are now coming to light. Most adolescents and young adults with MTC are afflicted with one of three hereditary cancer syndromes—FMTC, MEN2A, or MEN2B—that are caused by activating mutations of the *RET* proto-oncogene.

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