INCIDENCE

Thyroid cancer is the most common endocrine malignancy, accounting for 1.9% of all new malignant tumors (excluding skin cancer and in situ carcinomas) diagnosed annually in the United States (0.92% of cancers in men; 2.9% in women; 1). Annual incidence rates vary by geographic area, age, and sex. The age-adjusted annual incidence (from 1996 to 2000) in the United States is 68 new cases per million (2,7), with a higher incidence in women (99/million) than men (36/million) (2,4). Approximately 25,690 new cases of thyroid cancer are now diagnosed annually in the United States with a female/male ratio close to 3:1 (7). Worldwide, incidence rates are highest in certain geographic areas, such as Hawaii (119/million women and 45/million men), probably as a result of local environmental influences (2,5). Rates in Poland are among the lowest recorded: 14 per million women and four per million men (6). Thyroid cancer is very rare in children under age 15. The annual U.S. incidence in this population is 2.2 per million girls and 0.9 per million boys (7). The annual incidence of thyroid cancer increases with age, peaking between 100 and 120 per million by the fifth through eighth decades (2).

The incidence of thyroid cancer has increased over a period of several decades in the United States, as well as several other countries, particularly among women (2–4,8–20). For example, in Connecticut, the annual age-standardized incidence in women has progressively increased from 13 per million in 1935–1939, to 36 per million in 1965–1969, to 45 per million in 1985–1989, and reaching 58 per million in 1990–1991. The corresponding figures for men are two per million, 18 per million, 21 per million, and 26 per million, respectively (4). The precise reasons for the increase are not clearly understood but may be related, at least in part, to the introduction of improved diagnostic methodology (e.g., ultrasound, thyroid scans, and fine-needle aspiration biopsy) and improvements in cancer registration (4,20). In the United States, the increased incidence between 1935 and 1975 may also be a consequence of therapeutic radiation treatments administered to the head and neck region of children (9,21; see Chapter 7). However, elevations in thyroid cancer incidence were documented in other countries where childhood radiation treatments were never commonly employed (13,15,19); therefore, other factors must also be involved. Exposure to fallout from nuclear weapons testing has been suggested as an influence in Europe, but epidemiological data indicate that there are still more important factors (14). The incidence of thyroid cancer is no longer rising in certain countries, such as Norway and Iceland (15–17), but it continues to rise in the United States (2).

PREVALENCE

Thyroid cancer prevalence rates vary widely by geographic area, patient population, and method of survey. Autopsy rates ranging from 0.03% to over 2% have been reported (22–26). Mortensen and colleagues (22) reported on 1000 consecutive routine autopsies and found a 2.8% prevalence rate of thyroid carcinoma. The high cancer prevalence can be attributed to the meticulous histological evaluation protocol (22). On routine clinical assessment, 61% (17/28) of the cancers originated from thyroid glands that were apparently normal (23). Similar prevalence rates (2.3–2.7%) were reported by Bisi and colleagues (24) and Silverberg and Vidone (25). The high prevalence rates reported in the latter two studies may have also been influenced by the highly selected inpatient populations studied and may not reflect the prevalence in the general population.

Small foci of papillary thyroid carcinoma, measuring 1 cm or less in diameter, can be classified as “papillary microcarcinomas” (27) and occur frequently in autopsy material (reviewed in ref. 28). Most papillary microcarcinomas measure between 4 and 7 mm (29). These can be subdivided into “tiny” (5–10-mm diameter) and “minute” carcinomas (<5-mm diameter; 27,30–33). The term “occult”
carcinoma has no pathological meaning and should be abandoned in favor of these more precisely defined terms, as advocated by LiVolsi (27). Papillary microcarcinomas are usually detected by meticulous sectioning of the thyroid at 2–3-mm intervals, with detailed microscopic examination of each section. The highest prevalence rate of papillary thyroid microcarcinoma (≤1-cm diameter) was reported from Finland (34), with 33.7% of 101 cases harboring this finding. Rates over 20% have been reported from Japan (35,36), whereas the rate of papillary microcarcinoma in Olmsted County, Minnesota, is much lower (5.1%; 37). Minute papillary carcinomas (<5 mm) are rarely detected clinically and are believed to exhibit a relatively benign clinical course. However, there are occasional reports of distant metastases (e.g., pulmonary metastases) that arise from minute papillary carcinomas (38).

Thyroid cancer prevalence rates are significantly greater than incidence figures, reflecting that substantial numbers of patients survive several decades or longer. Data in the Connecticut registry show a prevalence rate of 677 cases per million in women and 237 cases per million in men (39). These data refer only to clinically apparent disease and are therefore lower than the rates in many autopsy series (22–25).

**Mortality**

The annual mortality from thyroid cancer is low—five deaths per million individuals per year (2), presumably reflecting the good prognosis for most thyroid cancers. Mortality rates are lowest in individuals under age 50 and increase sharply thereafter (2). There are about 1490 deaths from thyroid cancer annually in the United States (1), accounting for 0.26% of all cancer deaths (0.21% of cancer deaths in men; 0.31% in women).

Although the incidence of thyroid cancer has been increasing over time in both men and women, mortality has decreased over the past 50 yr (2). The reduced mortality is due to earlier diagnosis, improved treatment, and decreased incidence of anaplastic carcinoma. For example, 5-yr relative survival rates for thyroid cancer have increased from 80% in 1950–1954 to 96% in 1992–1999 (2).

**DISTRIBUTION BY HISTOLOGICAL TYPE**

The relative proportion of differentiated (follicular and papillary) thyroid cancers in a given geographic area depends on the dietary iodine intake (40). Papillary cancers predominate in iodine-sufficient areas. For example, in Iceland, which has ample iodine intake, the proportions were 85% with papillary and 15% with follicular cancer from 1955 through 1984 (17); in Bavaria, Germany, an iodine-deficient area, the proportions were 35% papillary and 65% follicular during 1960–1975 (40). The introduction of iodine supplementation in an endemic goiter region results in an increased proportion of papillary cancers (41), coupled with an improved outcome relating to life expectancy (42).

In the United States, approximately 80% of thyroid cancers are papillary carcinomas (43). Papillary cancer has a peak incidence in the fourth decade of life and affects women three times more frequently than men. Follicular carcinoma accounts for about 5–10% of U.S. cases (43) and has a peak incidence in the fourth or fifth decade. The tumor is three times more common in women than men.

Medullary carcinomas comprise nearly 5–10% of thyroid carcinomas (44). Of these, 80% are sporadic and 20% are familial, mostly multiple endocrine neoplasia type II (MEN II)-related (44). The sporadic form presents mostly in the fifth and sixth decades of life and affects females 1.5 times more than males (45). MEN Ila-related medullary carcinomas present in the first and second decades, and MEN IIb-associated medullary cancers present during the first decade of life (44). Familial non-MEN medullary thyroid carcinomas present in the sixth decade and beyond (44). Familial forms of medullary carcinoma occur with equal frequency in females and males.

Anaplastic cancers and lymphomas account for the remainder of cases. The incidence of anaplastic cancer has recently declined—a factor that has contributed to the reduction in overall thyroid cancer mortality. The peak incidence of anaplastic cancer is in the seventh decade; the female: male ratio is 1.5:1. Lymphomas represent about 5% of thyroid malignancies, with a mean age of 60–65 at the time of presentation (46,47). Females predominate at all ages: in patients under age 60, the ratio is 1.5:1; in patients over age 60, the ratio ranges from 3 to 8:1 (46,47).

**FACTORS ASSOCIATED WITH THYROID CANCER RISK**

There are several strong associations between thyroid cancer incidence and certain risk factors.

1. Thyroid cancer incidence increases with age.
2. Thyroid cancer is more common in females than males. The female predominance suggests that hormonal factors may be involved. Some studies suggest that biological changes that occur during pregnancy may increase the risk of thyroid carcinoma (48–50).
3. Several genetic syndromes (e.g., Gardner syndrome, adenomatous polyposis coli, and Cowden’s disease) are associated with an increased risk of thyroid cancer (discussed in Chapter 3).
4. Radiation exposure is the only factor that has been shown unequivocally to cause thyroid cancer (discussed in detail in Chapter 7).
5. Strong evidence indicates that individuals with Hashimoto’s thyroiditis have an increased chance to develop thyroid lymphoma (51).
In addition to these well-established associations, there are postulated risk factors for thyroid carcinoma that remain unproven. These include iodine deficiency and endemic goiter (52), which may result in prolonged stimulation of thyroid tissue by elevated thyroid-stimulating hormone (TSH) levels. Data on this postulated relationship are inconsistent (50,52–62). A major study comparing goiter prevalence and the effect of iodine supplementation with thyroid cancer rates in the United States failed to support a link between endemic goiter and thyroid cancer (62). Graves’ disease has also been postulated to be associated with an increased incidence of thyroid cancer. This hypothesis is of interest because of the TSH-like activity of thyroid-stimulating immunoglobulins. However, the data remain inconclusive (63–76), with reported cancer rates ranging from 0.06% (66) to as high as 8.7% (68) in glands affected by Graves’ disease. Lower rates were reported in older studies (63–66), and several recent studies (70–72) show rates in the range of 5.1–7.0%. The possibility that other benign diseases of the thyroid could increase the risk of cancer has also been considered (50,51,53,57,77–81). Given the strong possibility of ascertainment and recall bias, these data are difficult to interpret. Furthermore, it is well established that pathological examinations of thyroid tissue can reveal a high rate of unsuspected microcarcinomas that may be of little clinical significance. Nevertheless, a recent pooled analysis of 14 case-control studies (82–86) has provided evidence that a large risk of thyroid cancer is associated with a history of goiter or benign nodules among women. This evidence was validated by a prospective study from Denmark (87,88). Thus, current data tentatively suggest that apart from radiation in childhood, goiter and benign nodules/adenomas are the strongest risk factors for thyroid cancer.

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