Epidemiology of Thyroid Cancer

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Incidence

Thyroid cancer is the most common endocrine malignancy, accounting for 3.6 % of all new malignant tumors (excluding basal and squamous cell skin cancers and in situ carcinomas except urinary bladder) diagnosed annually in the United States (1.7 % of cancers in men; 5.6 % in women; [1]. Annual incidence rates vary by geographic area, age, and sex [2–8]. The age-adjusted annual incidence (from 2006 to 2010) in the United States is 122 new cases per million [2], with a higher incidence in women (182/million) than men (61/million) [2]. Approximately 60,220 new cases of thyroid cancer are now diagnosed annually in the United States with a female to male ratio close to 3:1 [1]. Worldwide, incidence rates are highest in certain geographic areas, such as Sao Paulo, Brazil (149/million women and 39/million men) [5], Hawaii (223/million women and 63/million men) [2, 6], New Jersey (246/million women and 82/million men) [2, 7], Utah (247/million women and 75/million men) [2], and Connecticut (257/million women and 85/million men) [2, 4], probably as a result of local environmental influences. Rates in Poland are among the lowest recorded: 14 per million women and 4 per million men [8]. Thyroid cancer is very rare in children under age 15 [9]. The annual US incidence in children ages 10–14 is ten per million girls and three per million boys [2]. The annual incidence of thyroid cancer increases with age, peaking between 199 and 243 per million by the fifth through eighth decades [2].

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The incidence of thyroid cancer has increased over a period of several decades in the United States, as well as many other countries worldwide, particularly among women [2–4, 10–32]. 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, reaching 58 per million in 1990–1991, and 257 per million in 2006–2010 [2, 4]. The corresponding figures for men are 2 per million, 18 per million, 21 per million, 26 per million, and 85 per million, respectively [2, 4]. Davies and Welch [26] analyzed the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database and showed that the increasing incidence of thyroid cancer in the United States between 1973 and 2002 was almost exclusively attributable to an increase in the incidence of papillary thyroid cancer. According to their analysis, 49 % of the increase was restricted to cancers measuring 1 cm or smaller, and 87 % of the increase consisted of cancers measuring 2 cm or smaller [26]. The precise reasons for the increase are not clearly understood but might 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, 25, 26]. Hence, Davies and Welch concluded that "increased diagnostic scrutiny," reflecting an increased detection of subclinical disease, is the most likely reason for the apparent increase in thyroid cancer incidence. This is consistent with the epidemiologic concept of "overdiagnosis," which postulates that an increasing number of diagnoses reflect more effective detection of a subclinical reservoir of cancers, which, if left undetected, would not have caused symptoms or death [27]. Moris et al. [27] have provided further evidence from the SEER database demonstrating that markers for higher levels of health care access are associated with higher papillary thyroid cancer incidence rates, thus supporting the hypothesis that overdiagnosis explains much of the increase in thyroid cancer incidence. Some of these papillary carcinomas

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represent "incidentalomas," in the sense that they were detected as incidental findings during the course of an evaluation for an unrelated issue, such as a carotid ultrasound or a chest CT scan.

However, other detailed analyses of the SEER database have partially refuted the overdiagnosis hypothesis [28–33]. Devesa's group [28] compared thyroid cancer types by race/ethnicity, gender, and age and concluded that a detection effect cannot completely explain the observed increases in thyroid cancer incidence [28]. Age-specific incidence curves by gender for papillary carcinoma are notably similar across all SEER racial/ethnic groups despite known disparities among the groups in access to healthcare technologies such as ultrasound [28]. For papillary carcinoma, the age-specific rates for whites, Asians, and Hispanics are nearly identical, but the rates for black women and men are slightly lower across all age groups [28]. Additionally, ethnic variations in thyroid cancer incidence are minimal in cases of nonpapillary histology, arguing against differences in diagnostic scrutiny [28]. Li et al. [29] considered socioeconomic status (SES) as a surrogate for access to technology. In analyzing the SEER registry, Li et al. [29] confirmed higher thyroid cancer incidence rates in high- vs. low-SES counties, but only for tumors up to 4.0 cm. For larger tumors (>4.0 cm), the thyroid cancer incidence increased similarly for both high- and low-SES counties. Furthermore, Li et al. [29], Yu et al. [30], Chen et al. [31], Enewold et al. [32], and Morris and Myssiorek [33] have documented an increasing incidence of large (e.g., >4.0 cm) as well as small papillary thyroid carcinomas in the SEER database. Between 1992 and 2005, 50 % of the overall increase in papillary carcinoma incidence rates in SEER was due to papillary microcarcinomas (1.0 cm or less), 30 % to cancers 1.1–2 cm, and 20 % to cancers greater than 2 cm [32]. Among white females, the rate of increase for papillary cancers greater than 5 cm in diameter almost equals that for the smallest papillary cancers [32]. If the early detection hypothesis were entirely correct, then one would expect to see a decreasing, and not increasing, incidence of larger papillary cancers [30]. Thus, the "increased diagnostic scrutiny" hypothesis regarding clinical application of more sensitive diagnostic procedures cannot completely explain the observed increases in papillary thyroid cancer incidence. It is most likely that overdiagnosis contributes significantly to the observed increase in thyroid cancer incidence, but there is a true increase as well. Hence, other relevant factors must exist.

Radiation has been proposed as major factor to explain the increasing incidence of thyroid cancer. In the United States, the increased incidence between 1935 and 1975 may be a consequence of therapeutic radiation treatments administered to the head and neck region of children [11, 34]. However, elevations in thyroid cancer incidence were documented in other countries where childhood radiation treatments were never commonly employed [15, 17, 21]; therefore, other factors must also be involved. Exposure to fallout from nuclear weapon testing has been suggested as an influence in Europe, but epidemiological data indicate that there are still more important factors [16]. In the United States, a committee of the US National Academy of Sciences Institute of Medicine and National Research Council [35] estimated that an excess of 11,300 thyroid cancer cases could be attributed to exposure to fallout from the Nevada atomic bomb testing of the 1950s. Fallout from the Chernobyl accident in Connecticut, Utah, Iowa, and in parts of Europe has been suggested as another factor [24, 36]. Increasing population exposure to medical and dental diagnostic X-rays, particularly CT scans, has been postulated to be a factor [7, 29, 37, 38]. Finally, exposure to environmental pollutants has been proposed as a contributing factor [38]. The incidence of thyroid cancer is no longer rising in certain countries, such as Norway and Iceland [17–19], 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 [39–46]. Mortensen and colleagues [39] reported on 1,000 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 [39]. On routine clinical assessment, 61 % (17/28) of the cancers originated from thyroid glands that were apparently normal [40]. Similar prevalence rates (2.3–2.7 %) were reported by Bisi and colleagues [41] and Silverberg and Vidone [42]. 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" [47] and occur frequently in autopsy material (reviewed in ref. 48). Most papillary microcarcinomas measure between 4 and 7 mm [49]. These can be subdivided into "tiny" (5–10-mm diameter) and "minute" carcinomas (<5-mm diameter; [47, 50–53]). The term "occult" carcinoma has no pathological meaning and should be abandoned in favor of these more precisely defined terms, as advocated by LiVolsi [47]. 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 [54], with 33.7 % of 101 cases harboring this finding.

Rates over 20 % have been reported from Japan [55, 56], whereas the rate of papillary microcarcinoma is much lower in Sweden (6.4 %; [44]) and in Olmsted County, Minnesota (5.1 %; [57]). Minute papillary carcinomas (<5 mm) are rarely detected on physical exam 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 [58]. Mazzaferri has published an excellent review of the natural history of papillary microcarcinomas [59].

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 [60]. These data refer only to clinically apparent disease and are therefore lower than the rates in many autopsy series [39–46].

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 1,850 deaths from thyroid cancer annually in the United States [1], accounting for 0.32 % of all cancer deaths (0.26 % of cancer deaths in men; 0.38 % 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 years [2]. The reduced mortality is due to earlier diagnosis, improved treatment, and decreased incidence of anaplastic carcinoma. For example, 5-year relative survival rates for thyroid cancer have increased from 80 % in 1950–1954 to 98 % in 2003–2009 [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 [61]. 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 to 1984 [19]; in Bavaria, Germany, an iodine-deficient area, the proportions were 35 % papillary and 65 % follicular during 1960–1975 [61]. The introduction of iodine supplementation in an endemic goiter region results in an increased proportion of papillary cancers [62], coupled with an improved outcome relating to life expectancy [63].

In the United States, approximately 87 % of invasive thyroid cancers are papillary carcinomas [2, 64]. Papillary cancer has a peak incidence in the fourth through eighth decades of life and affects women three times more frequently than men [28]. Follicular carcinoma accounts for about 6 % of US cases [2, 64] and has a peak incidence in the seventh and eighth decades [28]. The tumor is two to three times more common in women than men. Medullary carcinomas comprise nearly 2 % of thyroid carcinomas [2]. Of these, 80 % are sporadic and 20 % are familial. The hereditary familial forms are classified under the multiple endocrine neoplasia type IIA (MEN IIA) syndrome, or the MEN IIB syndrome [65]. The sporadic form presents mostly in the fifth and sixth decades of life and affects females 1.5 times more than males [66]. Classical 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 [65]. Familial medullary thyroid carcinomas arising in families without pheochromocytomas or primary hyperparathyroidism (FMTC, now recognized to be a variant of MEN IIA) present in the sixth decade and beyond [65]. Familial forms of medullary carcinoma occur with equal frequency in females and males. Anaplastic cancers account for just under 1 % of cases [2]. 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 and beyond; the female to male ratio is approximately 1.5:1 [28]. Lymphomas represent about 5 % of thyroid malignancies, with a mean age of 60–65 at the time of presentation [67, 68]. 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 [67, 68].

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 [69–71].
3. Several genetic syndromes are associated with follicular cell-derived thyroid carcinomas: familial adenomatous polyposis (including Gardner syndrome), phosphatase, and tensin homolog deleted on chromosome ten (*PTEN*)-hamartoma tumor syndrome (including Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome), Carney complex type I, Pendred syndrome, Werner syn-

drome, and several familial papillary thyroid carcinoma (fPTC) syndromes (pure fPTC, with or without oxyphilia, fPTC with papillary renal cell carcinoma, and fPTC with multinodular goiter) [72–74]. Familial cancer syndromes that include medullary thyroid carcinoma (MTC) are multiple endocrine neoplasia IIA (MEN IIA) and MEN IIB. Pure familial MTC syndrome (FMTC) is now recognized to be a variant of MEN IIA.

4. Radiation exposure in childhood is the only factor that has been shown unequivocally to cause thyroid cancer.
5. A history of goiter and a history of benign nodules/adenomas are the strongest risk factors for thyroid cancer, apart from radiation in childhood (see discussion below).
6. Strong evidence indicates that individuals with Hashimoto's thyroiditis have an increased chance to develop thyroid lymphoma [75].

Epidemiology

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 [76], which may result in prolonged stimulation of thyroid tissue by elevated thyroid-stimulating hormone (TSH) levels. Data on this postulated relationship are inconsistent [71, 76–86]. 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 [86]. 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 [87–101], with reported cancer rates ranging from 0.06 % [90] to as high as 8.7 % [92] in glands affected by Graves' disease. Lower rates were reported in older studies [87–90], and several more recent studies [94–96] 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 [71, 75, 77, 81, 102–106]. 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 [107–111] has provided evidence that a large risk of thyroid cancer is associated with a history of goiter (pooled odds ratio [OR] = 5.9 in women; OR = 38.3 in men) or benign nodules/adenomas (OR = 29.9 in women; 18 cases vs 0 controls in men). This evidence was validated by a prospective study from Denmark [112, 113]. Thus, current data suggest that apart from radiation in childhood, goiter and benign nodules/adenomas are the strongest risk factors for thyroid cancer.

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