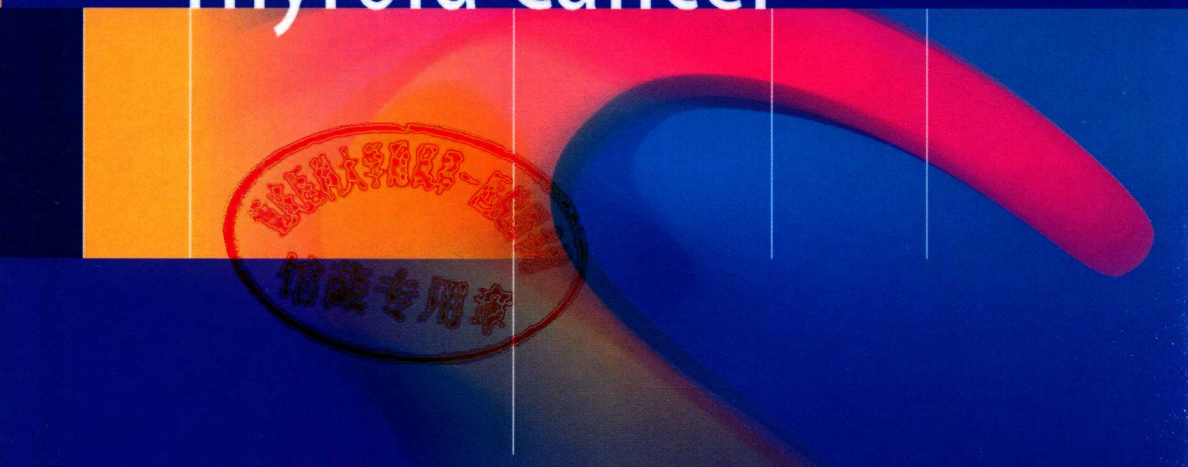
Management of Thyroid Nodules and Differentiated Thyroid Cancer



A Practical Guide

Sanziana A. Roman
Julie Ann Sosa
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Editors

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Preface

Thyroid nodules are a common problem in the USA and the world. They are present in nearly 5 % of women and 1 % of men in the iodine-sufficient areas and have a much higher incidence in iodine-deficient parts of the world. With the growing use of imaging studies, such as ultrasound and computed tomography, it is estimated that more than 70 % of the adult population in the USA harbors thyroid abnormalities and nodules. While most nodules are benign, patient and physician anxiety about their presence and possible lack of familiarity with thyroid disorders can lead to either unnecessary interventions or to misdirected and inadequate treatments. Understanding the meaning of detecting such abnormalities is important for alleviating patient anxiety and undertaking the most efficient and effective diagnostic work-up and treatment.

While much has been written about thyroid nodules, we realized that a comprehensive, easy-to-follow, organized approach to understanding thyroid nodules and thyroid cancer was needed. Whether you are a primary care clinician, family practitioner, pediatrician, obstetrician/gynecologist, general endocrinologist, general surgeon, otorhinolaryngologist, nurse practitioner, physician assistant, student, trainee, or fellow, this book is designed to address numerous questions about patients with thyroid nodules and cancer. We have organized the book in specific patient presentation scenarios, ranging from small and occult thyroid nodules detected incidentally to palpable, clinical multinodular goiters, patients with benign nodules, patients with indeterminate nodules, and those with clear malignant diagnoses. It encompasses easy-to-understand diagnostic approaches, including imaging, serologic testing, and fine needle biopsies; it seeks to clarify molecular testing and to describe appropriate surgical treatment, postoperative radioactive iodine administration for differentiated thyroid cancer, and adequate thyroid hormone replacement. It describes special and often anxiety-producing patient situations such as concomitant pregnancy and thyroid nodules and cancer in children. It includes aspects of the disease which are often not discussed, such as patient quality of life after thyroid surgery and common long-term problems, and dedicates a chapter to integrative medical approaches for patients who desire such interventions.

We have brought together experts and thought leaders from the USA in the fields of thyroidology, thyroid surgery, nuclear medicine, pathology, radiology, pediatrics, and integrative medicine and have edited an up-to-date book, which we feel speaks directly to the concerns of our colleagues and our patients.

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Contents

Chapter 1
Incidence and Epidemiology

Megan R. Haymart and Nazanene H. Esfandiari

Rise in Thyroid Cancer Incidence

The incidence of thyroid cancer has tripled over the past 30 years (Fig. 1.1), with thyroid cancer now the eighth most common cancer in the United States and the fifth most common cancer in women [1–3]. Although thyroid cancers of all sizes have increased in incidence, 87 % of the rise in thyroid cancer is attributed to small papillary thyroid cancers (2 cm or smaller), which have an excellent prognosis [1]. It is estimated that in 2015, there will be 62,450 new cases of thyroid cancer but only 1,950 deaths [4]. Because of this rising incidence, thyroid cancer is projected to be the fourth most common cancer by 2030 [2, 5–9]. Not only has the incidence risen in the United States, the rise in thyroid cancer incidence has been seen across the world [10]. This rise in thyroid cancer incidence is most marked in Korea, where thyroid cancer is now the most common cancer and the incidence is close to 70/100,000 [11]. This worldwide unexplained rise in thyroid cancer incidence remains a major concern for physicians treating thyroid cancer.

The greatest rise in thyroid cancer incidence has been seen in women [12]. Women represent close to 75 % of all thyroid cancer cases and the incidence has

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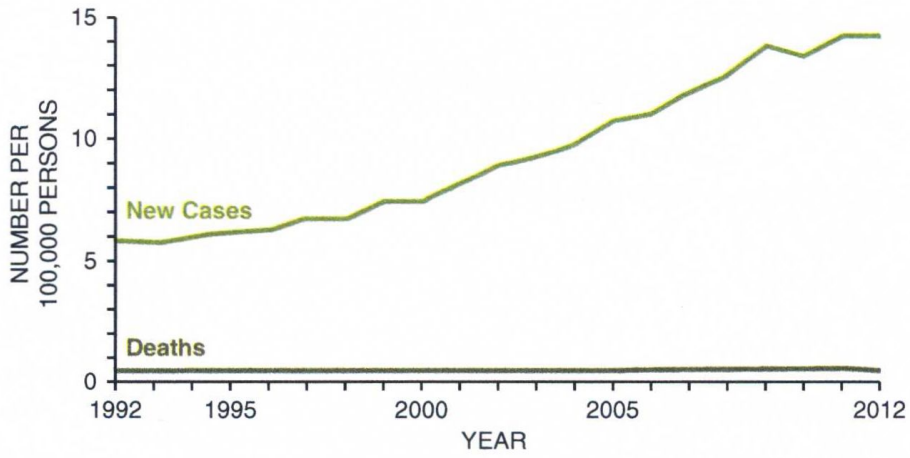

Fig. 1.1 Based on SEER data, the number of new cases of thyroid cancer was 13.5 per 100,000 men and women per year. The number of deaths was 0.5 per 100,000 men and women per year. These rates are age adjusted and based on 2008–2012 cases and deaths [5]

risen in both men and women but at a greater rate in women. From 1980 to 1983 versus 2003 to 2005, papillary thyroid cancer rates tripled among white and black females and doubled among white and black males [12]. Although two-thirds of thyroid cancers occur in patients < age 55, the fastest rise in incidence has been seen in adults over age 65 [13, 14]. Older adults have the highest incidence of thyroid cancer per 100,000, with 25.84 new cases diagnosed in patients ages 65–74 years versus 15.16 diagnosed in patients ages 20–49 [5]. Adults aged ≥ 65 also have the greatest growth in incidence with an annual percentage change of 8.8 % versus 6.4 % for those aged < 65 years [5, 15]. The rise in incidence has been seen across race groups, but incidence rates tend to be higher among whites than blacks and among white non-Hispanics than white Hispanics and Asian Pacific Islanders [12]. Historically, thyroid cancer diagnosis has been more common in cohorts with higher socioeconomic status (SES). Based on Surveillance, Epidemiology and End Results (SEER) data from 497 counties in the United States, county papillary thyroid cancer incidence positively correlates with rates of college education, white-collar employment, and family income [15].

The Origin of Thyroid Cancer

Diagnosing thyroid cancer usually starts with identifying a thyroid nodule and/or occasionally lateral neck mass. Between 20 and 70 % of adults have thyroid nodules with older adults having a higher prevalence than younger [16, 17]. In patients with thyroid nodules, male gender, younger age, and high-risk ultrasound characteristics, such as irregular borders, solid, hypoechoic, larger size, and microcalcifications, are associated with greater likelihood of thyroid cancer [18–21].

The majority of thyroid cancers are identified with fine-needle aspiration of a thyroid nodule. Of the nodules that undergo fine needle aspiration (FNA), only 5–8 % are thyroid cancer [22–24]. Although most cancers are diagnosed by FNA, 6–21% of the thyroid operations planned for treatment of benign disease have incidental discovery of thyroid cancer postoperatively [25–27].

The most common thyroid cancer diagnosed is papillary thyroid cancer, which represents 85 % of all thyroid cancers [28]. Additional thyroid cancers include other well-differentiated cancers, such as follicular and Hürthle cell which represent approximately 10 and 3 % of thyroid cancers, respectively [28]. Medullary thyroid cancer arises from c-cells and accounts for less than 5 % of all thyroid cancers [28–30]. Anaplastic is rare and deadly and represents only 1 % of all thyroid cancers [31, 32].

Risk Factors for Thyroid Cancer

As shown in Table 1.1, there are two accepted risk factors for well-differentiated thyroid cancer: ionizing radiation and family history. Ionizing radiation is thought to cause cancer through somatic mutations and DNA strand breaks [14, 33]. When catastrophic events such as Chernobyl happen, the risk of thyroid cancer is dose and age related [34]. Children and young adults under age 20 years are most susceptible to radiation-induced thyroid cancers [14, 35, 36]. Similarly, children who underwent radiation therapy for childhood cancers, acne, treatment of enlarged thymus, etc. also have an increased risk for thyroid cancer [37]. In addition, to radiation exposure, familial nonmedullary thyroid cancer does exist. If two or more first-degree relatives have well-differentiated thyroid cancer, then it is presumed to be hereditary. However, this hereditary form of well-differentiated thyroid cancer cannot be tracked with genetic testing and is thought to represent just over 5 % of all well-differentiated thyroid cancers [38–41]. Recently, a germline variant in *HABP2* was identified in familial nonmedullary thyroid cancer [41]. Therefore, for the

Table 1.1 Accepted risk factors for thyroid cancer

Radiation
Nuclear events such as Chernobyl[a] or Fukushima[b]
Treatment of childhood cancers with ionizing (external beam) radiation Treatment of acne, thymus, etc., with ionizing (external beam) radiation Environmental exposures are currently under investigation by several researchers
Family history
RET mutations with MEN2A and MEN2B
Familial nonmedullary thyroid cancers and syndromes

[a]Chernobyl happened on April 25, 1986

[b]Meltdown of the reactor in Fukushima happened on March 11, 2011

RET RET proto-oncogene gain of function mutation is associated with the development of medullary thyroid cancer, *MEN* multiple endocrine neoplasias

majority of patients with well-differentiated thyroid cancer, there is no clear etiology of their thyroid cancer and the cancer thought to be sporadic.

In comparison, for medullary thyroid cancer, up to 1–7% of patients with apparently sporadic medullary thyroid cancer end up having germline mutations and associated syndromes MEN2A and MEN2B [42, 43]. Genetic testing can identify the RET mutation involved in development of the medullary thyroid cancer, and then subsequent testing can identify family members at risk. In addition to germline mutations, up to half of patients with sporadic medullary thyroid cancer patients have an unidentified somatic RET mutation [44].

There are no clear risk factors for anaplastic thyroid cancer. However, anaplastic thyroid cancer is thought to arise from a well-differentiated thyroid cancer, and it is more common in older adults [32]. There is an accepted "second hit" hypothesis that well-differentiated thyroid cancers typically need a second mutation, often p53, to develop anaplastic thyroid cancer [31].

Proposed Explanations for the Rise in Thyroid Cancer Incidence

Table 1.2 illustrates the two broad theories to explain the rise in thyroid cancer incidence [14]. One theory is that new or previously unidentified risk factors for thyroid cancer explain the rise in incidence. These proposed risk factors would include radiation exposure outside of known catastrophic events or treatment of childhood cancers, obesity/diabetes, autoimmune thyroid disease, and iodine deficiency or excess. Another conflicting theory is that we have detection bias or in essence overdiagnosis leading to the rise in thyroid cancer incidence. In principle, there is a large reservoir of indolent thyroid cancer, and the more we "look," the more we find. Based on this overdiagnosis theory, increased use of imaging, FNA, surgery, and

Table 1.2 Proposed explanations for the rise in thyroid cancer incidence

Novel risk factor
Background environmental radiation
Obesity/diabetes mellitus
Autoimmune thyroid disease
Iodine deficiency or excess Other environmental agents
Overdiagnosis
Greater use of neck imaging leading to more nodule detection and cancer diagnosis
More fine-needle aspirations of nodules leading to more cancer diagnosis
More surgery leading to more post op incidental cancer discovery
Greater pathologic inspection leading to more cancer diagnosis

[a]Adapted from Table 1.1. Potential Contributors to the Increasing Incidence of Thyroid Cancer in the United States, by Category [14]