Research

Explaining the increasing incidence of differentiated thyroid cancer

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The thyroid is the largest of the endocrine glands and by far the most common site of all primary endocrine cancers. However, thyroid cancer is relatively rare, accounting for only 1% of all cancers. The number of new cases diagnosed each year is comparable to that of leukemia, pancreatic cancer and oropharyngeal cancer.[1] Published in this issue of *CMAJ* are the results of a study in which Kent and colleagues[2] used the Ontario Cancer Registry to identify 7422 cases of differentiated thyroid cancer from 1990 to 2001. Their results show that the incidence of this type of thyroid cancer increased by 146% over the 12-year study period, for an overall increase of 13% per year. Similar findings have been reported lately in many countries, including the United States.[3] Earlier studies included one by Liu and colleagues,[4] who studied the incidence of thyroid cancer in Canada (excluding Quebec) from 1970 to 1996 using the Canadian Cancer Registry. They reported an increasing trend: the overall age-adjusted incidence rates of thyroid cancer doubled from 3.3 per 100 000 in 1970–1972 to 6.6 per 100 000 in 1994–1996 among female patients, and from 1.1 per 100 000 to 2.2 per 100 000 among male patients in the same time frame. There is a remarkable and impressive congruency among these worldwide reports, which identified that the increased incidence occurred almost exclusively with papillary thyroid carcinoma, particularly the microlesions (< 1 cm).

Given the unequivocal evidence that the incidence of papillary thyroid carcinoma has increased over the past number of decades, the obvious question is why. One explanation is that we may be witnessing a true increase in the incidence of thyroid cancer, which has been termed "an epidemic of micropapillary thyroid cancers." A second is that the rising number of cases is apparent only because of changes in medical practice, particularly the increased use of ultrasonography and fine-needle aspiration biopsy. Alternatively, the reason for the increased incidence may be a combination of both of these explanations. The answer will be fundamentally important, since an understanding of the basic causes and related risk factors — especially previously unrecognized ones — for thyroid cancer may lead to novel therapeutic interventions and preventive measures.

Similar to previous studies,[3,5] Kent and colleagues conclude from their Ontario data, that the increased incidence of thyroid cancer is due to increased detection of small, subclinical tumours through the use of medical imaging. Davies and Welch[3] attributed this apparent increase to the phenomenon of "increased diagnostic scrutiny." However, these studies lack clinical data, such as the proportion of patients in each tumour-size group who underwent neck imaging and fine-needle aspiration biopsy, and the proportion of patients with incidentally detected thyroid cancer. Nevertheless, there is consensus to support their conclusions.

Potential explanations for the increasing incidence of papillary thyroid carcinoma

- Increased incidence of small, subclinical papillary thyroid carcinoma
- Changes in medical practice such as increased use of neck imaging and fine-needle aspiration biopsy
- Greater exposure to radiation associated with increased use of computed tomography scanning

Studies in France for the period 1980–2000 have correlated the increased incidence of thyroid cancer with the increased use of ultrasonography (from 3% to 84% of patients) and cytological procedures (from 8% to 36% of patients).[6] More recently, Burgess and Tucker[7] provided evidence that, in Tasmania, increasing use of preoperative fine-needle aspiration biopsy led to an increase in the incidence of papillary thyroid carcinoma, especially tumours 1 cm or smaller. They also observed an increase in the incidence of tumours larger than 1 cm in patients without a history of preoperative fine-needle aspiration biopsy, which suggests that the occurrence of clinically relevant tumours has increased. Interestingly, Kent and colleagues found that the incidence of medium-sized tumours (2–4 cm) remained stable over time, but were surprised to discover a slight increase in large tumours (> 4 cm) among patients 45 years and younger.

These findings are surprising since modern imaging should help diagnose clinical lesions earlier. However, the

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opportunity and need for neck imaging for both thyroid disorders and nonthyroid indications vary for different age groups and for men and women. Moreover, if medical imaging and fine-needle aspiration biopsy are the only factors facilitating the recognition of an increasing number of micropapillary thyroid carcinomas, why is it that other thyroid cancer histotypes, such as follicular and medullary carcinomas, do not follow a similar trend? Admittedly, nonpapillary thyroid cancers occur much less frequently than papillary thyroid cancers. Perhaps even more important is the fact that a large number of undiagnosed, clinically occult cases of papillary thyroid carcinoma exist in the community, as deduced from autopsy studies that revealed a rate of 2.7%–36% of such cancers.[2] Indeed, in an informative and often-quoted autopsy study by Harach and colleagues[8] reported that close to 36% of individuals who had thyroid cancer that was undiagnosed during their lifetimes harboured 1 or more foci of thyroid cancer.

Seeking theoretical support for their findings and interpretation, Kent and colleagues allude to the increasing number and use of computed tomography and magnetic resonance imaging scanners in Canada, which should further inflate the number of incidentally detected cases of thyroid cancer. Paradoxically, there is a concern that the radiation exposure incurred through computed tomography scanning will increase the risk of cancer. In a provocative but thoughtful editorial, Baker and Bhatti[9] recently suggested that the rapid increase in computed tomography use could, at least in part, account for the increasing incidence of thyroid cancer. In addition, they offered a plausible explanation as to why the thyroid may be at particular risk: iodine, which is trapped by the thyroid gland, blocks photons more readily, so that the radiant energy that reaches the thyroid is more apt to be deposited locally instead of passing through. The situation is exacerbated following the intravenous administration of iodine-contrast media, and such increased energy deposition can cause DNA breaks that lead to mutations.[9]

Irrespective of the precise causes of the increasing incidence of papillary thyroid carcinoma, particularly microlesions, we are faced with therapeutic dilemmas about how to manage the ever-increasing number of patients presenting with malignant thyroid microlesions. The majority of micropapillary thyroid cancers have very good long-term prognoses, but some do give rise to metastases and require more aggressive treatment. Unfortunately, we currently do not have reliable means to predict which of these tumours will be harmless and which will become troublesome. Kent and colleagues argue that the management of these small thyroid tumours may be based on an outdated model culminating in unnecessary investigations and overly aggressive surgery. This conclusion echoes that of Davies and Welch,[3] who emphasized the risks of "overdiagnosis" and, in addition, made the bold, but highly controversial, statement that papillary thyroid cancers smaller than 1 cm could be classified as a normal finding. We would find it hard, if not impossible, to use such an approach in our office when confronted with a patient who has a cytologically proven micropapillary thyroid carcinoma. In an accompanying editorial to the paper by Davies and Welch, Mazzaferri[10] made a plea that we should not be too complacent with regard to the management of small papillary thyroid carcinoma. Papillary thyroid carcinoma is highly heterogeneous, and despite similar histological appearances, its biology and clinical behaviour can vary remarkably from one patient to another. The discovery and development of specific and sensitive markers, especially molecular and genetic, is urgently needed to facilitate the understanding of the basic biology and allow a clinically meaningful risk stratification of each subgroup and variant of papillary thyroid carcinoma. We agree with the philosophy of Colonna and colleagues[5] that we need to find a compromise between overdiagnosis and beneficial early screening.

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