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ANALYSIS

TOO MUCH MEDICINE

Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours

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This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies.

Thyroid cancer is the most common endocrine malignancy.[1] Worldwide, its incidence has increased substantially over the past 50 years. The Cancer Incidence in Five Continents report showed that the age standardised incidence of thyroid cancer in women rose from 1.5 cases/100 000 population in 1953 to 7.5 cases/100 000 in 2002, with a similar relative increase in men (fig 1⇓).[2] Behind these averages hide important and surprising differences between and within countries. In the US, the incidence of thyroid cancer has tripled in the past 30 years, increasing from 3.6 cases/100 000 in 1973 to 11.6 cases/100 000 in 2009,[3] making it one of the fastest growing diagnoses. By contrast, in Sweden, Japan, and China, the increase in incidence has been minimal.[2]

Not all thyroid cancers are equal

Malignant cells are detected in only 10% of patients who present with thyroid nodules.[4] To identify which nodules are malignant, current guidelines recommend that patients with thyroid nodules have thyroid ultrasonography followed by fine needle aspiration biopsy if ultrasongraphy shows suspicious features (microcalcifications, hypoecogenecity, infiltrative margins) or if the patient has a family history of thyroid cancer or has had significant radiation exposure (box).

The histology of malignant thyroid nodules provides the most important prognostic information. Thyroid cancer is divided into four types: papillary (comprising 85% of the total detected), follicular (11%), medullary (3%), and anaplastic (1%).[5 6] Anaplastic thyroid cancer is associated with the worst prognosis, with most patients dying within a year of diagnosis (table⇓).[7]This contrasts with the excellent prognosis of papillary cancers, especially in patients with nodules <20 mm in diameter: 99% of these patients will be alive at 20 years.[8] Patients with small (<15-20 mm) lesions, no family history of thyroid cancer or personal history of radiation exposure, and no evidence of extraglandular invasion on ultrasonography are considered to be at low risk of progression.[9 10]

Autopsy series have shown a large reservoir of subclinical papillary thyroid cancers. One study found that a third of people who died from other causes had this type of thyroid cancer. These tumours (most <1 mm) were discovered through interval sectioning every 2 to 3 mm,[11] raising the possibility that many more may have been missed between interval cuts. The presence of this subclinical reservoir is consistent with the asymptomatic nature of most diagnosed cases of papillary thyroid cancer.

Increased imaging has fuelled epidemic in diagnosis

Small papillary thyroid cancers account for 90% of cases in countries in which the incidence is increasing rapidly.[12] Until two decades ago most thyroid cancers were found in patients who presented with nodules causing compression symptoms on the neck, visible neck masses, or through regular physical examinations in patients with no thyroid complaints. Nodules bigger than 20 mm were assessed by palpation and biopsy. The advent of neck ultrasonography in the 1980s and ultrasound guided biopsy in the late 1990s enabled detection and biopsy of nodules as small as 2 mm. Ready access to portable ultrasound machines together with policies which reimburse physicians for imaging have promoted the routine use of neck ultrasonography, which has increased by 80% in general endocrinological services over the past few decades.[13]

Increased diagnosis has also resulted from greater use of new imaging technology for other indications. In the US computed tomography (CT) more than tripled between 1995 and 2005 (rising to 173/1000 Medicare beneficiaries) and magnetic resonance imaging more than doubled (547/1000 Medicare beneficiaries).[14] Nearly 16% of CT and magnetic resonance images show incidental thyroid nodules, of which around three quarters are <15 mm.[15 16] This imaging (mostly chest CT to investigate cough and exclude pulmonary embolus and head

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Summary box

Clinical context—Thyroid cancer is the most common endocrine malignancy and one of the fastest growing diagnoses

Diagnostic change—Introduction of neck ultrasonography into routine endocrinological practice in the 1980s with guided biopsy in the late 1990s, plus increased use of computed tomography and magnetic resonance imaging for other conditions

Rationale for change—New imaging methods allow the detection and biopsy of thyroid nodules as small as 2 mm

Leap of faith—Patients with small papillary cancers will benefit from their removal

Increase in disease—Worldwide increase in incidence of thyroid cancer since the early 1980s but with considerable variation between countries. In the US the incidence of thyroid cancer has increased from 3.6 cases/100 000 population in 1973 to 11.6 cases/100 000 in 2009. Small papillary thyroid cancers, the most indolent form of thyroid cancer, account for 90% of cases

Evidence of overdiagnosis—The expanding gap between the incidence of thyroid cancer and stable death rates from papillary thyroid cancer (0.5/100 000 in 1979 and 2009). Observational evidence shows that small papillary thyroid cancers, which are a common autopsy finding, may never progress to cause symptoms or death

Harms from overdiagnosis—Patients having thyroidectomy experience physical complications, financial and psychosocial burdens, and need lifelong thyroid replacement therapy

Limitations—Inference about overdiagnosis of thyroid cancer is based on epidemiological and observational evidence

Conclusion – The incidence of small and indolent thyroid cancer is increasing, exposing patients to treatments inconsistent with their prognosis. We suggest a term that conveys the favourable prognosis for low risk thyroid cancers (micropapillary lesions of indolent course or microPLICs) and call for research to identify the appropriate care for these patients

Recommendations for investigation and management of thyroid nodule and cancer

Guideline recommendations [5]

Investigation

- Avoid thyroid cancer screening in the general population
- All thyroid nodules should be evaluated by ultrasonography
- CT/MRI should not be used for evaluation of thyroid nodules
- Thyroid nodules ≥5 mm and with ultrasound features suggestive of thyroid cancer and nodules in patients with a family history of thyroid cancer or a history of radiation exposure should be investigated by fine needle aspiration biopsy
- Thyroid nodules ≥10-15 mm (if solid) and ≥20 mm (if cystic-solid) should also be investigated by fine needle aspiration biopsy regardless of any risk factor or ultrasound feature

Treatment

- Surgery is indicated for thyroid nodules with positive cytology for any type of thyroid cancer regardless of nodule size
- Radioactive iodine treatment should be selectively considered but is not recommended for low risk papillary cancers
- Thyroxine suppression therapy is recommended for all patients after thyroid surgery
- Follow-up every 6-12 months with neck ultrasonography, tumour markers, and selective use of whole body scans

Our suggestion for the management of low risk papillary thyroid cancer

- Enrol patients in trials of immediate treatment versus surveillance
- If no trial is available, engage patients in designing a course of action consistent with their clinical condition and personal preferences

and neck MRI to evaluate cervical radiculopathy[17]) has contributed to a 2.4-fold increase in the reported incidence of thyroid nodules over the past 30 years[18] and a threefold increase in biopsies between 1995 and 2005.[18 19] Today, more patients receive a diagnosis of thyroid cancer after an evaluation of an incidentally found thyroid nodule than after evaluation of a symptomatic or palpable nodule**.** More women than men are diagnosed (ratio 3:1) and most are in their 40s or 50s at the time of diagnosis.[3]

The link between imaging and increased incidence is supported by a correlation with access. In an analysis across 18 regions in the US markers for higher levels of healthcare access, both sociodemographic and age based, were associated with higher incidences of papillary thyroid cancer.[20] In New Jersey,[21] Los Angeles,[22] and Wisconsin,[23] thyroid cancer incidence rates were higher among people with higher socioeconomic status. In Wisconsin, for each 5% rise in the population covered by health insurance, the incidence of thyroid cancer increased, on average, by 1.4 cases/100 000 people for the years 1980-2004. In the same population, for each increase of $10 000 (£6400; €7500) in county median income, thyroid cancer incidence increased on average 0.5 cases/100 000 a year. Counties in Wisconsin with a higher percentage of residents with a college degree also tended to have higher incidences of thyroid cancer.

Evidence suggests overtreatment

Detection of small papillary thyroid cancers in patients without a family history of thyroid cancer or exposure to radiation usually triggers intensive treatment, even though these are unlikely to cause morbidity or premature mortality. In an observational study conducted between 1993 and 2004, 1395 patients with low risk papillary thyroid cancer were given the choice of surgery or active surveillance.[9] Less than a quarter (340) opted for active surveillance with ultrasonography. Patients in the surveillance group had repeat ultrasonography at six months and a year and then annually for an average of 74 months. Nodules enlarged by >3 mm in only 31 patients during follow-up. Of these, 18 subsequently had surgery and 13 chose to continue surveillance. In seven of the 13, the tumour shrank. No one died in the surveillance group. This suggests that small papillary cancers may never progress to cause symptoms or death. To back this view, analysis of the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database, which includes 32 years of data, showed no significant difference in the death rate from thyroid cancer in patients who did not receive immediate surgery (n=440) for low risk papillary thyroid cancers compared with those who did (n=35 663).[24]

The most compelling evidence that patients with low risk cancers are being overtreated is that despite a threefold increase

in incidence of papillary thyroid cancer over the past 30 years, the death rate has remained stable (0.5/100 000 in 1979 and 0.5/100 000 in 2009, fig 2⇓).

Unnecessary thyroidectomy is costly and harms patients

The number of thyroidectomies for thyroid cancer in the US has risen by 60% over the past 10 years, from 16 377 in 1996 to 27 493 in 2006.[25] The increase has been associated with costs estimated at $416m (£270m; €316m) in 2006.[25] Thyroidectomy requires hospital admission and carries a 1-6% risk of complications, including permanent hypoparathyroidism and hypocalcaemia requiring calcium supplementation and laryngeal nerve injury. The risk of complications depends on whether the patient has total or partial thyroidectomy (more risk with the former, which is the recommended procedure) and on the skill of the surgical team.[26] Patients who have had total thryroidectomy and some who have had partial thyroidectomy, also require lifelong thyroid replacement therapy, which carries its own burden of monitoring and treatment, costs, and the risk of complications from over-replacement and under-replacement.

Despite recommendations against using radioactive iodine in patients with low risk thyroid cancer, its use increased from one in 300 patients to two in five patients between 1973 and 2006 in the US, perhaps because of a suggestion that it makes it easier to follow-up patients because the tumour markers are more reliable.[27] The short term side effects of radioactive iodine include altered taste and inflammation of salivary glands in a third of patients, and dry eyes and transient fertility reduction in a fifth.[28-31] In the long term, it is associated with reduced quality of life[27 32] and a risk of secondary malignancies. Among 14 589 patients who received radioactive iodine from 1973 to 2007, there was a 13% increase in the risk of salivary gland malignancies and a 5.7-fold increase in the risk of leukaemia compared with a reference cohort without thyroid cancer.[27]

Limitations of the evidence

The evidence supporting overdiagnosis and overtreatment of low risk papillary thyroid cancer is drawn from epidemiological and observational evidence. Such evidence is often affected by confounding and selection and reporting biases. Large randomised trials are required comparing immediate thyroidectomy with surveillance. Although trials in patients with low risk thyroid cancer might be challenging to plan, fund, and execute, the example from prostate cancer, shows us that it is possible.[33]

How to do better

Cancer raises fear and anxiety in patients and clinicians, and labelling indolent lesions as papillary thyroid cancer causes unnecessary distress. We suggest renaming low risk lesions (< 20 mm in patients with no family history or radiation exposure and no ultrasound evidence of extraglandular invasion[9]) as micropapillary lesions of indolent course (microPLICs) to convey their favourable prognosis. A change in nomenclature could reframe the care of these patients and avoid their overtreatment. It might also improve recruitment into trials in which one arm entails active surveillance rather than immediate treatment. Renaming has already occurred in other "cancers": papillary urothelial neoplasia of low malignant potential (from grade 1 papillary transitional cell carcinoma of the bladder), atypical lipomatous tumour (from well differentiated liposarcoma), and cervical intraepithelial neoplasia (from cervical cancer).

Patients with low risk lesions should be offered the option of surveillance to detect changes suggestive of progression (for example, tumour growth causing compression symptoms, lymph node metastasis). Although there is currently no evidence based surveillance schedule, it might follow a similar path to the one used after thyroidectomy, including yearly neck ultrasonography and physical examination. Patients with lesions that are stable or shrink could then be followed up less often than those whose nodules increase in size (change in volume >20%).

What to discuss with patients

Uncertainty about the benefits and harms of immediate treatment for low risk papillary thyroid carcinoma should spur clinicians to engage patients in shared decision making. This will ensure treatment is consistent with the evidence for the subtype of cancer that they have and with their preferences. Some patients may prefer not to have aggressive treatment of small, low risk thyroid cancers, especially those patients where the risk clearly outweighs the benefits of treatment (for example, older patients, patients with other malignancies, or patients with severe comorbidities). Patients can be reassured that if nodules later show more aggressive behaviour the evidence suggests no additional harm from delayed surgical treatment.[9]

Unresolved questions

The proportion of the gap between thyroid cancer incidence and mortality that is explained by overdiagnosis remains unclear. Part of the discrepancy may be due to new risk factors for thyroid cancer such as radiation exposure from CT, nutritional factors,[34] and menstrual and reproductive factors.[35] While the association between these risk factors and the incidence of thyroid cancer is weak and inconsistent, further research should clarify their relative contribution. Furthermore, the differing rates of thyroid cancer between countries (fig1⇓) suggest that other factors (such as healthcare system coverage, access to care, or expenditure per capita) may have a role in the incidence of thyroid cancer and warrant investigation. Why, for example, do Ecuador and Iceland have high rates but not Norway, Sweden, and Japan? The role of new biomarkers (such as the BRAF V0600E mutation) in identifying and monitoring indolent thyroid cancers also needs to be clarified.[36]

Conclusion

The incidence of small and indolent thyroid cancer is increasing at different rates among countries. The incongruity between the increased incidence and stable mortality is most likely an effect of overdiagnosis. This is exposing patients to treatments inconsistent with their prognosis. Both the overdiagnosis and overtreatment of this form of cancer need to be fully recognised. A change in nomenclature for low risk cancers, as we have suggested, here, could help this and make it easier to give patients the choice of active surveillance.

Contributors and sources: JPB is an endocrine fellow and healthcare delivery scholar at Mayo Clinic. JCM is a professor of medicine, thyroidologist, and previous chair of the endocrinology department at Mayo Clinic. VMM is a health service researcher and director of the healthcare delivery research programme at the Mayo Clinic. All authors contributed to the concepts and structure of this manuscript. VMM is the guarantor.

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Table

Thyroid cancer	Proportion of all thyroid cancers	Change in incidence over past three decades	Change in mortality over past three decades	Mortality	Treatment		
					Type of intervention	Benefits	Harms
Papillary	85%	3-fold increase	Unchanged	1-2% at 20 years	Thyroidectomy/radioactive iodine/thyroid hormone replacement	Unclear, possible decrease in mortality from 0 to 2/1000 patients compared with active surveillance	Anxiety, insurability, need for lifelong thyroid replacement, cost, burden of follow-up, complication from surgery and radioactive iodine
Follicular	11%	Unchanged	Unchanged	10-20% at 10 years	Thyroidectomy/radioactive iodine/thyroid hormone replacement	Clear benefit in mortality (50% reduction in cancer death rate on average)	
Medullary	3%	Unchanged	Unchanged	25-50% at 10 years	Thyroidectomy/thyroid hormone replacement	Some patients can be cured with surgery	Anxiety, insurability, need for lifelong thyroid replacement, cost, burden of follow-up, complication from surgery
Anaplastic	1%	Unchanged	Unchanged	90% at 5 years	Thyroidectomy/chemotherapy/thyroid hormone replacement	Some benefit (prolongs survival by months)	As above plus side effects from chemotherapy

Figures

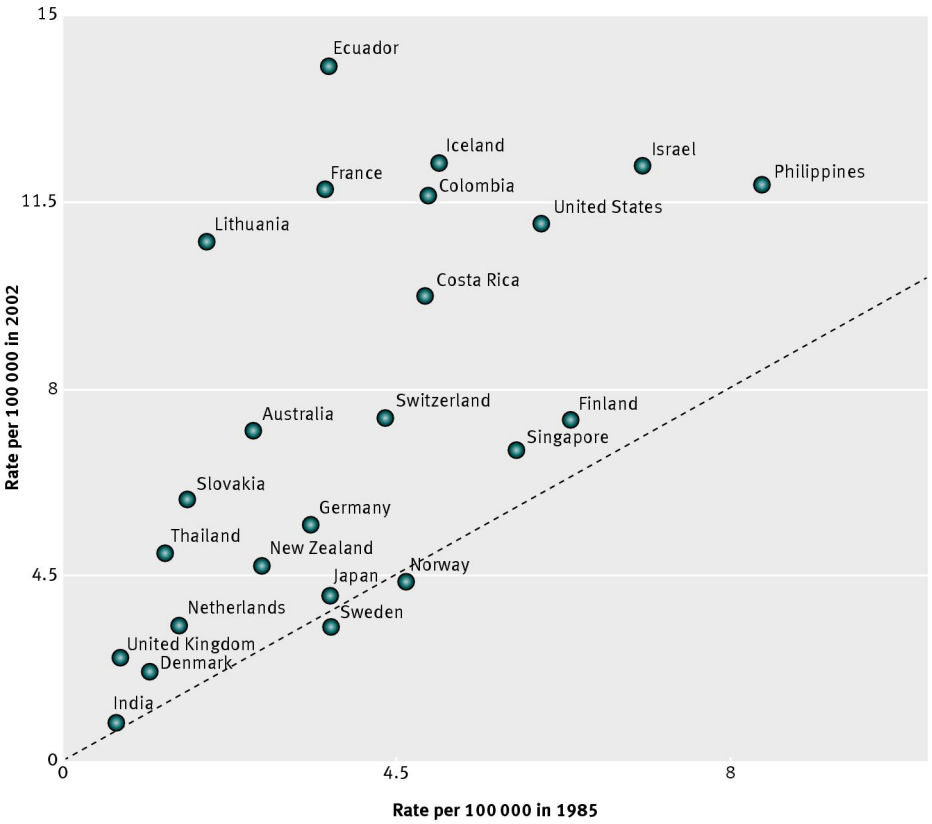

Fig 1 Incidence of thyroid cancer by country. Countries above the dotted line experienced a rise in incidence between 1985 and 2002[2]

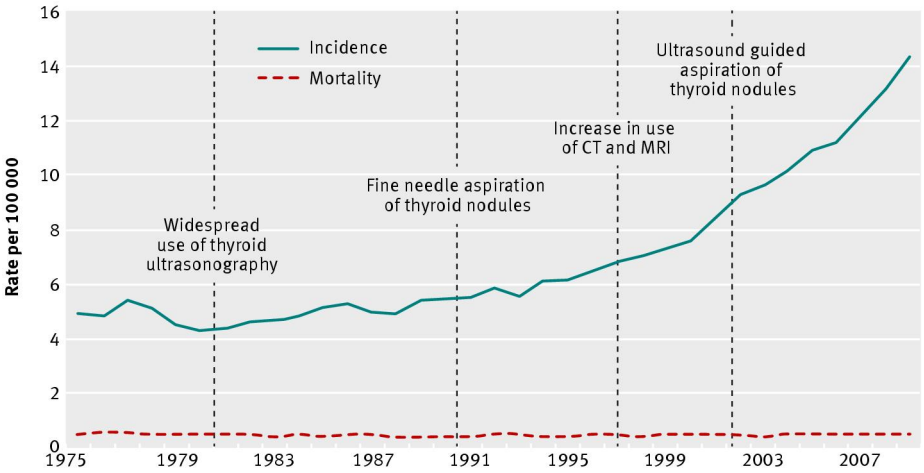

Fig 2 Incidence of and mortality from thyroid cancer in the US, 1975-2009[3] and advent of new technologies