

# Increased Incidence of Thyroid Cancer: A Real Up surge or Over diagnosis of Subclinical Cases

Ebtehal Khairallahs 

*Department Of Surgery and Surgical Operations, Faculty of Nursing, Tripoli university, Tripoli, Libya*

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## ABSTRACT

### Keywords:

Thyroid cancer  
Increased incidence  
Overdiagnosis  
Increased subclinical cases

Worldwide, the incidence of thyroid (TC)cancer has increased over the past few decades; however, the cause has been debated. Several theories have been proposed to explain this. Some have addressed over-detection and others have focused on the growing number of clinically relevant cases being detected and the possible increase in risk factors exposure. This study reviewed the possible reasons for the increase in the TC incidence rate, to determine the existence of a true increased incidence, to clarify the role of overdiagnosis and to elucidate the possible risk factors for TC. Articles in the following databases were systematically reviewed: Medline, the Cochran Library, CINAHL and Embase. The increase in incidence of TC over the past several decades has been well documented. The reviewed studies attributed the rise mainly to overdiagnosis, due to improved access to health care, and the development of higher-quality diagnostic techniques. However, a parallel increase in risk factors exposure and the increased incidence of clinically significant TC cases especially papillary type have been documented, which suggest a true increase of TC incidence rate. The surge in the TC incidence rate seemed to be multifactorial. It cannot be attributed to over diagnosis as a sole cause.

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**Citation info.** Khairallahs E. Increased Incidence of Thyroid Cancer: A Real Up surge or Over diagnosis of Subclinical Cases. *J Lib Sur Soc.* 2021;1(1):13-18. <https://doi.org/10.5281/zenodo.5735568>

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## INTRODUCTION

Thyroid carcinoma (TC) is the most common type of endocrine malignancy (1). Most thyroid nodules are small and subclinical, they are usually detected by diagnostic imaging techniques (2). Only 5% to 15% of the diagnosed nodules are malignant (3). For patients presenting with thyroid nodules, recent management guidelines recommend ultrasound for all nodules followed by fine-needle aspiration (FNA) if the results indicate any signs of malignancy, such as hyper vascularity and local invasion (4). With more than 97% specificity for malignant samples, FNA is the most important diagnostic tool for the evaluation of thyroid nodules (1).

TC has been the most rapidly increasing cancer diagnosis in several developed countries (5). For example, in the United States, a threefold increase in the TC incidence rates was documented between 1975 and 2009 (6). In Germany, the incidence was found to have almost doubled between 1981 and 2015 (7). TC incidence rate expected to grow by 50% to 60% between 2010 and 2020 worldwide (2). The reason for this upsurge is undetermined. Some studies have concluded that there is a true increase in the incidence of TC. Others have attributed it to improved detection by better diagnostic

techniques, such as ultrasonography and FNA.

Overdiagnosis has been defined as the detection of tumors that would be unlikely to progress to symptoms or death if left untreated (5). TC can easily be subject to overdiagnosis because of its slow progression. Symptoms usually appear in the late stages but rarely cause death (8).

The surge has been linked to improved access to healthcare and the expanded use of thyroid imaging techniques (9). The routine screening of healthy people in many countries has played a role in the detection of small TCs. For example, South Korea initiated a national TC screening program in 1999. The national diagnosis rate in 2011 was 15 times greater than that in 1993 (10). Furthermore, the use of cervical ultrasound and subsequent FNA for other conditions has led to the discovery of subclinical reservoir of TC nodules (11). In addition, the diagnostic techniques for TC have become more sensitive. Thyroid nodules as small as 0.2 mm can be detected (4). The role of over diagnosis has also been confirmed by the change in the stage distribution in favor of the earlier stages (12).

Other studies have attributed the recent surge in the TC

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\*Corresponding E-mail addresses: [eak1g19@southampton.ac.uk](mailto:eak1g19@southampton.ac.uk)

incidence to increased exposure to risk factors. For example, some radiation exposure has been strongly correlated with a higher TC incidence (8). Some cases between 1910 and 1960 might have been linked to the head and neck radiation therapy that was used to treat benign childhood conditions given that this group became adults during this documented surge (13). Iodine deficiency, familial TC and a history of goiter or thyroid nodules have been suspected to play a role in the recent surge (14). For instance, goiter and benign nodules were found to be strong TC risk factors (12).

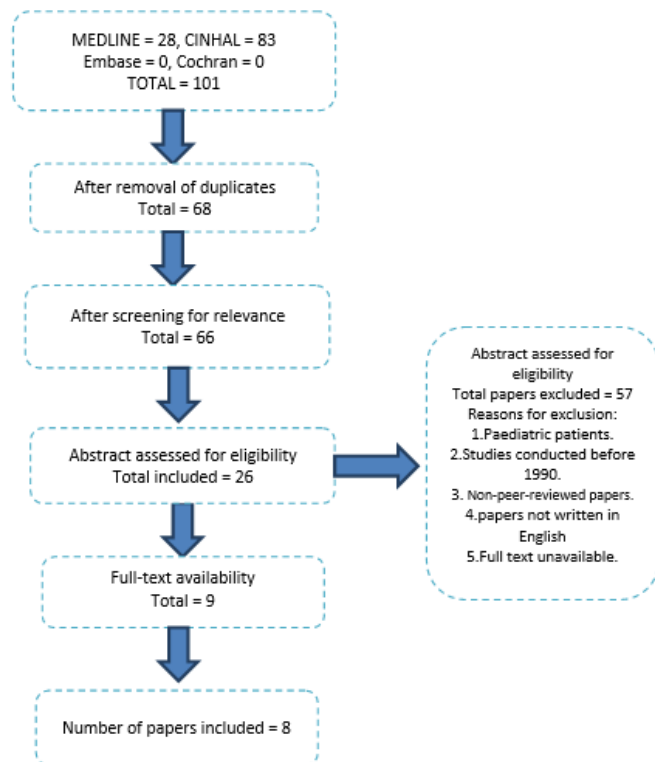
The recent increased incidence was documented for large tumors; thus, these cases cannot be attributed to over diagnosis. Moreover, the increase was noted in mainly PTC. If overdiagnosis were the only explanation for the recent surge, the increase would be seen in all types (8). the overdiagnosis could lead to unnecessary treatment and potential damage from unnecessary distress (6), possible adverse surgical consequences and the financial burden (8). The main treatment of TC is surgical. This includes partial or total thyroidectomy, which necessitates hospital admission and has a 1% to 6% risk of complications, including permanent hypoparathyroidism and hypocalcemia and laryngeal nerve injury (4).

It is crucial to understand the changes in the thyroid cancer incidence rates. Disease epidemiology has been found to have a significant effect on clinical reasoning, i.e., diagnosis and decision-making (15). Increased diagnostic activity has long been assumed to have contributed to the significant rise in the TC incidence (16). Therefore, awareness of the possible causes and risk factors is important to avoiding overdiagnosis and subsequent unnecessary treatment (8).

The overarching goal of the research is to determine whether there is a real increase in TC incidence, the role of overdiagnosis in the current spike, and to identify any potential risk factors and reasons of the surge.

## METHODS

Articles in the following databases were systematically reviewed: Medline, the Cochran Library, CINAHL and Embase. The study question served as the basis for the inclusion and exclusion criteria. Only peer-reviewed papers about adult patients were included, as were studies conducted after 1990, papers written in English, and papers about papillary and follicular carcinoma. The systematic review was developed in Accordance with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines Figure (1) illustrates the search process. Only eight studies were included based on inclusion/exclusion criteria in this review and full text availability. One meta-analysis (17), three systemic reviews (8, 10, 12), four cohorts (5,13,18,19) eligibility and quality of the selected papers were assessed with the Critical Appraisals Skills Programme tool (CASP) tool (20).



**Fig. 1:** Search process based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

## RESULTS

### Changes in Thyroid Cancer Incidence

Three studies confirmed that the TC incidence has increased worldwide at a rate higher than that of any other cancer over the past several decades (18), (5) and (19). This has had effects on the economies of and human resources in many countries. For example, the United States spent \$1.6 billion on care for TC patients. In China, the disability-adjusted life years and years of life lost because of the early mortality related to thyroid cancer was 133.5 thousand person-years and 114.2 thousand person-years, respectively (10).

A cohort study conducted by Lortet-Tieulent, J., et al (2019) in 55 countries worldwide from 2008 to 2012 found a significant increase in the TC incidence rate (9). The surge varied across countries. The Republic of Korea had the highest rate. Italy, Canada, France and the United States had very high rates. The high-income countries HIC with the lowest incidence were the United Kingdom, Denmark and the Netherlands.

One of the most significant observations of Lortet-Tieulent, J., et al was those low-income countries, also had higher TC incidence rates. However, the incidence was much lower than that in HICs (5). La Vecchia, C. and E. Negri (3) indicated that the incidence rates in HICs were more than 200% higher than those in low- and middle-income countries LMICs. Many African countries were included in Lortet-Tieulent, J., et al's cohort study (5). Vollmer emphasized that Africa was an exception in the 1984–1997 international TC incidence increase (18). Vollmer explained that the low detection during that period might have been caused by limited access to health services. Other studies have drawn similar conclusions

(5, 19).

There appeared to be a significant difference in the incidence for men and women in the recent surge. (18), (8,5,19,21) documented a much higher incidence increase in females than in males. Lortet-Tieulent, J., et al asserted that the incidence in men followed a similar trajectory (5); however, it was 25% of that in women. La Vecchia, C., et al. reported a similar result (12). For example, from 2000 to 2010, the incidence rates of TC in high- and middle-income countries were in women (11.10/100,000 and 4.70/100,000, respectively) and in men (3.60/100,000 and 1.40/100,000, respectively).

The papillary thyroid cancer PTC type accounted for a majority of the cases during TC surge. Other histological types, such as follicular and medullary TC increased at a much lower rate (5,13). For example, Vollmer indicated that from 1975 to 1999, the documented new cases during the surge were mainly PTC (18).

### **Thyroid Cancer Mortality During the Surge**

The mortality rates for other types of cancer decreased over the past two decades as a result of improvements in diagnoses and treatments (8). However, TC mortality rate did not improve but rather remained stable over the past three decades (17).

Some studies found a slight increase in the TC mortality rates (8). Vollmer asserted that the documented increase in mortality might be the result of a small group of TC patients with a fatal, rapidly progressive disease (18). Vollmer suggested that the indolent behavior of TC could lead to a delay in the changes in mortality during the TC surge (18).

### **Role of Over diagnosis in Increased TC Incidence**

The recent surge in the TC incidence has been attributed mainly to over diagnosis and improved cancer registration (8,17); Haymart et al estimated that 70% to 90% of the TC cases during the high-incidence period were the result of over diagnosis (5). TC can be discovered by physical examination when the nodule is larger than 1.5 cm. Only 40% of thyroid nodules less than 1.5 cm can be felt during palpation (8). Haymart et al provided evidence that at diagnosis, 39% of the thyroid tumours in the United States were  $\leq 1$  cm, and 50% in the Republic of Korea were  $< 0.8$  cm. In both countries, there was an element of over-detection and a strong correlation between ultrasound use and the increased incidence of TC (5).

The strong correlation between ultrasound uses and the increased TC incidence from 2003 to 2013 has been well-established (19). In their cohort study, Liu, Y., et al indicated that 1,833 patients would not have been diagnosed with TC if ultrasound had remained at the 2012 levels (19). The expanded use of ultrasound was more prevalent in some patient groups, such as women and elderly patients with comorbidities (19). TC was detected by ultrasound more often when doctors were compensated under a fee-for-service model (5).

Several studies have examined the relationship between health service access and TC surge. For example, the TC incidence was higher in countries where the healthcare system was generally private and market-oriented (5).

Kent, W. D., et al highlights a positive correlation between improved sociodemographic markers and an increased TC incidence (13). Furthermore, the incidence was related to the population density of endocrinologists and surgeons. Haymart et al termed this relationship 'screening pressure' (5). For example, in countries such as Brazil where diagnostic equipment, such as ultrasound, is widely available and the physician-to-population ratio is high, the surge was well documented. Furthermore, The incidence variations among and within countries were explained by differences in access to health services (5). Improved access to health services has led to increases in the histopathological diagnosis of TC. For example, the incidence of thyroidectomies has risen because of their increased application in benign diseases, such as goitre, and this has in turn resulted in the histopathological detection of subclinical TC (13). Furthermore, the guidelines for pathological examinations of thyroid specimens have changed to include entire glands rather than sections (10). Vollmer indicated that some pathologists changed the pathological criteria for TC by lowering the diagnostic threshold for diagnosis (18). The high incidence of TC was not associated with equivalent increases in mortality. This reinforced the over diagnosis conclusion (5). La Vecchia, C., et al explains that unlikely that TC incidence growth and treatment improvement changed in the same rate, although the growth of both were parallel during the previous century (12).

### **Other Possible Causes for the Surge in the Incidence of TC**

Kent, W. D., et al indicated evidence of a parallel increase in clinically significant cases and over diagnosis. For example, despite early detection and management (13), the incidence of large TC tumours and cancer-related mortality increased slightly (18). Vollmer's study also demonstrated the presence of rapidly growing and lethal forms of TC with high mortality rates within the first two years of diagnosis among the documented TC surge (18). The TC increased incidence was observed mainly in the papillary type, especially BRAF-positive (BRAF is a human gene that encodes the B-Raf protein) PTC suggested that might molecular abnormalities typical of papillary cancer had occurred, which rise the possibility of gene mutation role in the recent TC surge (8). thus, clarifies the inadequacy of the over diagnosis theory justifying TC incidence growth.

### **Radiation**

Pellegriti, Frasca et al reported that increases in the exposure of the thyroid to diagnostic and therapeutic radiation could have affected the TC incidence rate. For example (8), in the United States, the radiation dose per person doubled during the last three decades through medical and dental X-rays (10). Approximately 40% of diagnostic CT is performed in the head or neck region, and this has in turn led to higher radiation doses to the thyroid gland. Furthermore, the use of iodinated contrast agents augmented the thyroid radiation uptake (8). Radiation exposure might have played only a limited role

in the TC incidence surge because a history of radiation exposure was found in only a small proportion of thyroid cancers (10). Overall, the effects of radiation on the adult TC incidence are still inconclusive.

- **Possible Intake of Carcinogenic Substances (iodine and nitrates as food additives)**

The effects of iodine intake on the incidence of TC have been debated. TC diagnosis after a continued iodine deficiency has been well documented in animal experiments. In contrast, High iodine concentrations have been found to stimulate the growth of TC cells in vitro (10). Several studies have reported a higher TC incidence in regions with excessive iodine intake (10). In addition, the TC-related mortality rate varied between the regions with iodine deficiency and those with excessive iodine intake (12). An association between the introduction of universal salt iodization and TC was documented in several Chinese studies (10).

Nitrates as food additives have been considered a possible risk factor for TC. Liu, Y., et al explains that dietary nitrates prevent iodine uptake by the thyroid and are considered a probable risk factor for TC (10).

#### ***Relationship between TC and High Thyroid-Stimulating Hormone Levels and Autoimmune Hashimoto's Thyroiditis***

The relationship between TC and obesity has been well documented (8, 10). A meta-analysis of 21 observational studies conducted by J. Ma, et al (2015) showed an increase of PTC in obese individuals (10).

In another study, insulin resistance was documented in half of the PTC patients but only 10% of the control group (8). The relationship between TC in patients with obesity and those with insulin resistance is not well understood. Studies have examined the effects of high insulin levels on thyroid cells suggested that high insulin levels promote thyroid cell proliferation, which is considered to have carcinogenic effects (10).

## **DISCUSSION**

Overdiagnosis was presumed to be the main reason for the recent surge in TC; however, this was not confirmed as the sole reason. The increased incidence of large and clinically significant TC nodules, with a slight increase in mortality rate were documented during the surge suggesting a true increase of TC incidence (13).

This literature review suggests that the surge in the TC incidence rate can be explained by both over diagnosis and a true increase in clinically significant cases. For example, the incidence increase was observed mainly for PTC, particularly BRAF-positive PTC. This suggests a true rise in the incidence, as well as possible genetic mutations. In the other hand, PTC is the most common type of well-differentiated TC (22). Consequently, with improved diagnostic tools and more widely available health services, the PTC has been more frequently detected than other types. This can attribute the significant increase in the PTC incidence rate to over-detection because larger sample sizes and improved

diagnostic test sensitivity have been known to contribute to the detection of more cases and (23).

Women are more likely to have TC than men (12). The gender differences in incidence, aggressiveness and prognosis have been well documented is not well understood (24). In TC incidence surge, the rates for women were higher than those for males. This gender difference confirms the multifactorial nature of the increased TC incidence. Haymart, M. R., et al (19) concluded that the more frequent ultrasound indications in female patients played a role in the higher TC detection because thyroid nodules are more common in Female and TC incidence is threefold higher in females which rise the Likelihood of screening bias. However, high oestrogen levels in women have been linked to TC (10). Oestrogen and its receptors have been found to play an important role in thyroid cancer proliferation, migration and invasion at the cellular level (10).

Most studies on the TC surge were retrospective, and this might have affected the validity of the results. For example, the study by Haymart, M. R., et al. (2019) was based on retrospective data on the effects of expanded ultrasound use on the increased detection of TC over 12 years. This raised the possibility errors of coding and reporting bias (19). In Kent, W. D., et al cohort's study used retrospective reviews of pathology reports, which accounted for only 10% of the patients diagnosed with TC during the study period.

Disregarding approved evidence-based TC risk factors, such as obesity, iodine and nitrate intake and higher diagnostic and therapeutic radiation doses, as confounding factors is irrational. Several studies found direct relationships between these factors and TC during the surge (13) (19). However, more studies are needed to exclude excessive exposure to carcinogenic substances in the regions with a higher incidence. Conducting studies taking any possible risk factor as confound factors would have some limitations because measuring of behavioral factors, such as dietary intake would be almost inestimable in epidemiologic studies using traditional methods like self-reporting (10).

Interregional and urban-rural variations in the TC incidence rates have highlighted the importance of adopting an international policy to reduce over-detection. Some countries, such as the United Kingdom with a health system subjected to regulatory control, had a lower incidence rate increase than countries without such regulations (5).

The need to reduce the over-classification of small indolent TC nodules as cancer has been addressed (18). The over-detected subclinical TC, termed pseudo disease by Pellegriti, Frasca et al (8). For example, some studies observed that the prognosis and behavior of small PTC over prolonged periods did not result in cancer deaths, and only few new nodal metastases (17). Studies on small, well-capsulated follicular carcinoma have had favourable outcomes (18). However, there is a need for long-term prospective studies to examine the prognosis of small TCs diagnosed during the surge. Vollmer identified the indolent behaviour of TC as posing problems for conducting such studies (18). A broad research sample



and a time-consuming analysis cycle are required, and this could affect the statistical power (18).

The debate over the prognosis for small TCs and the causes of the recent surge provides clinicians and patients with a dilemma because of the uncertainty regarding the early treatment benefits of small, well-differentiated TCs. Most studies have suggested surveillance or a 'wait and see' approach to detect the changes that are indicative of progression in low-risk well-differentiated TCs (4) (8). Albeit the patients are reassured by the fact that the studies indicate that there is no harm in choosing observation to delay surgical intervention (4). Most patients decide to take the surgical option because of the distress associated with a cancer diagnosis (8).

Conversely, to reduce follow-up costs, some studies have recommended selective simplified surgical procedures (8). The most rational approach seems to follow the clinical guidelines, which include estimating the prognostic factors and engaging patients in decision-making to achieve the best possible outcomes (4). In addition, limiting the inappropriate use of ultrasound will reduce over detection and unnecessary surgical interventions (19).

## CONCLUSION

The review of the literature suggests that the surge in TC incidence is multifactorial. It is explained mainly by overdiagnosis. However, an increase in clinically significant TC cases and a slight increase in TC mortality rate were documented. In addition, the surge was considerably correlated with TC risk factors increased exposure suggesting a parallel true increase of TC incidence rate.

## Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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