The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, 2945–2952
https://doi.org/10.1210/clinem/dgac468
Advance access publication 10 August 2022
Meta-Analysis

Prevalence of Subclinical Papillary Thyroid Cancer by Age: Meta-analysis of Autopsy Studies

Natalia Arroyo,[1] Katy J. L. Bell,[2] Vivian Hsiao,[3] Sara Fernandes-Taylor,[1] Oguzhan Alagoz,[4] Yichi Zhang,[4] Louise Davies,[5] and David O. Francis[1,6]

[1]Wisconsin Surgical Outcomes Research Program (WiSOR), Department of Surgery, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53792, USA
[2]School of Public Health, Faculty of Medicine and Health, University of Sydney, Camperdown NSW 2050, Sydney, New South Wales, Australia
[3]Department of Surgery, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53792, USA
[4]Department of Industrial and Systems Engineering, College of Engineering, University of Wisconsin-Madison, Madison, WI 53706, USA
[5]The VA Outcomes Group, Department of Veterans Affairs Medical Center, White River Junction, VT 05009, USA; Section of Otolaryngology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA; The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, USA; and
[6]Division of Otolaryngology, Department of Surgery, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53792, USA

Correspondence: David O. Francis, MD, MS, K6/130 CSC, 600 Highland Avenue, Madison, WI 53792, USA. Email: dofrancis@wisc.edu

Abstract

Context: It is not known how underlying subclinical papillary thyroid cancer (PTC) differs by age. This meta-analysis of autopsy studies investigates how subclinical PTC prevalence changes over the lifetime.

Methods: We searched PubMed, Embase, and Web of Science databases from inception to May 2021 for studies that reported the prevalence of PTC found at autopsy. Two investigators extracted the number of subclinical PTCs detected in selected age groups and extent of examination. A quality assessment tool was used to assess bias. Logistic regression models with random intercepts were used to pool the age-specific subclinical PTC prevalence estimates.

Results: Of 1773 studies screened, 16 studies with age-specific data met the inclusion criteria (n = 6286 autopsies). The pooled subclinical PTC prevalence was 12.9% (95% CI 7.8-16.8) in whole gland and 4.6% (2.5- 6.6) in partial gland examination. Age-specific prevalence estimates were ≤40 years, 11.5% (6.8-16.1); 41-60 years, 12.1% (7.6-16.5); 61-80 years, 12.7% (8-17.5); and 81+ years, 13.4% (7.9-18.9). Sex did not affect age-specific prevalence and there was no difference in prevalence between men and women in any age group. In the regression model, the OR of prevalence increasing by age group was 1.06 (0.92-1.2, $P = .37$).

Conclusion: This meta-analysis shows the prevalence of subclinical PTC is stable across the lifespan. There is not a higher subclinical PTC prevalence in middle age, in contrast to higher observed incidence rates in this age group. These findings offer unique insights into the prevalence of subclinical PTC and its relationship to age.

Key Words: thyroid cancer, papillary, prevalence, meta-analysis, autopsy

Abbreviation: PTC, papillary thyroid cancer.

Solid tumors are typically diagnosed in adults 65 years and older in the United States and other high-income countries. For instance, the median age at diagnosis of lung, colorectal, prostate, and breast cancer in the United States ranged from 63 to 71 years during 2014-2018 (1). A number of biological mechanisms may explain the association of age with increased risk of cancer development including cumulative environmental exposures, accumulation of damage to DNA, genome instability, immunosenescence, and other changes to the tissue microenvironment (2-5). Age-restricted cancer screening programs may also contribute (6).

Rates of thyroid cancer diagnosis also change with increasing age, but not in the same way as these other common cancers (7-12). Papillary thyroid cancer (PTC), in particular, is more often diagnosed in middle-aged adults (45-64 years) (1). It is unknown why there is a peak in middle age. Two hypotheses have been advanced to explain this observation: (1) increased diagnostic scrutiny resulting in the detection of subclinical cancers, and (2) a true increase in cancer incidence in middle age. A body of evidence suggests that the large rise in PTCs in recent decades is attributable to detection of subclinical cancers from greater exposure to diagnostic testing (diagnostic scrutiny) (9, 10). How that may differentially affect the middle-aged group, and especially women (who are disproportionately diagnosed with PTC), is an active investigation. The pooled prevalence of thyroid cancer at autopsy is 11% among people who died of other causes (13); it is plausible that the reservoir of subclinical cancer grows and peaks in middle-aged individuals. It is also possible that there is a biological explanation for higher PTC detection rates in middle age (8).

Received: 17 February 2022. **Editorial Decision:** 28 July 2022. **Corrected and Typeset:** 26 August 2022

Recognizing the plausibility of these hypotheses, we sought to investigate whether the prevalence of subclinical PTC differs by age group. The pooled prevalence of subclinical thyroid cancer at autopsy is known; however, age-specific prevalence is not. Herein we performed a meta-analysis of autopsy studies to investigate whether the prevalence of subclinical thyroid cancer changes by age group, and, if so, whether its peak corresponds to the increased incidence observed in middle age.

Materials and Methods

Study Selection

We updated the published systematic review protocol created by Furuya-Kanamori et al (13). We searched PubMed, Embase, and Web of Science databases for autopsy studies that reported the prevalence of thyroid cancer from database inception through May 2021. Conference abstracts and proceedings were also reviewed for relevant studies. Excluded were studies examining patients with a history of thyroid disease or thyroid cancer treatment, studies of populations with known radiation exposure (ie, Hiroshima and Nagasaki atomic bombings, Chernobyl nuclear power plant accident), studies with incomplete information about the method of thyroid examination, studies that did not report age at death, and studies that did not provide age-specific data. After performing the updated search, independent investigators (N.A. and V.H.) screened and reviewed all abstracts for inclusion and exclusion, and subsequently evaluated selected full texts for inclusion in data extraction (Fig. 1).

Data Extraction

Two investigators (N.A. and V.H.) extracted the number of PTCs within age groups and by sex, if reported. Other data extracted included authors, publication year, study population characteristics (age, sex, and country), years autopsy was performed, whether the whole or partial thyroid gland was examined, and cause of death. Uncertainties about study inclusion or data extraction were resolved by a senior investigator (D.O.F.).

Quality Assessment

Rigorous risk of bias assessment was performed using a modified validated quality assessment tool specific to prevalence studies (14), as used in the published protocol (13). Using this tool, studies were evaluated for the presence of 9 external and internal validity safeguards to minimize bias in reporting of subclinical thyroid cancer prevalence. Examples of the risk

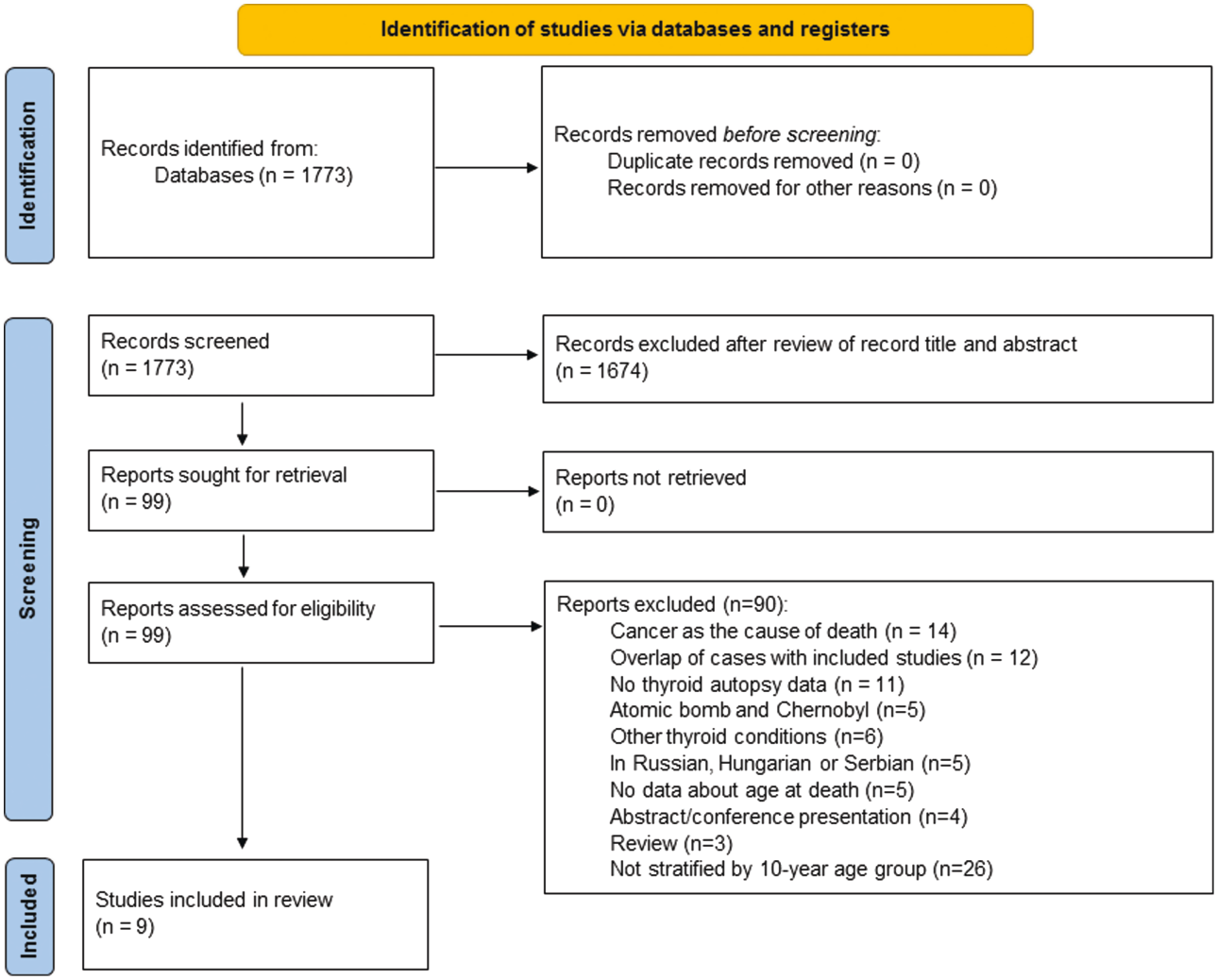

Figure 1. PRISMA flow diagram.

of bias items include population representativeness (Was the study's target population a close representation of the national population in relation to relevant variables?), randomization (Was some form of random selection used to select the sample?), data collected directly from histopathology reports (Were data collected directly from the subjects? [as opposed to a proxy]), and reliability of gland examination method (Was the same mode of data collection used for all subjects?).

Statistical Analysis

A subclinical PTC was defined as PTC detected at autopsy. The primary outcome measure was the prevalence of PTC in autopsied people by age. If other thyroid cancer subtypes (eg, medullary, follicular) were identified during autopsy, they were excluded from final analysis, as these were not the subject of the study. The number of autopsies and detected PTCs were divided into 4 age groups (ie, ≤40, 41-60, 61-80, 81+ years). The age groups were created to include at least 500 individuals in each age group to ensure stable coefficient estimates. Logistic regression models with random intercepts were fit to estimate the pooled subclinical PTC prevalence using a nonlinear mixed effects model (NLMIXED procedure, SAS version 9.4; Cary, NC). As used in previous meta-analyses (15-17), this validated approach is recommended and accounts for heterogeneous age-specific prevalence estimates across the studies (18). We first fitted models where age and extent of examination (partial vs whole thyroid) were included separately as covariates and then were included together in the model. Finally, we estimated the age-specific prevalence, with an upward adjustment if studies examined partial rather than whole glands. The upward adjustment was made by including the model parameter for the extent of examination in age-specific ESTIMATE statements in PROC NLMIXED. All statistical analyses were performed using SAS version 9.4 (Cary, NC)).

Results

Of 1773 studies screened, 99 full-text articles were reviewed, and 16 studies met the inclusion criteria (ranges: year of autopsy 1975-2005, age of decedents 16-75 years, 20-85% female; Fig. 1) (19-34). All but 3 studies analyzed consecutive autopsies, and across all included studies, only 6 decedents were excluded from original analyses due to history of thyroid cancer treatment. Table 1 describes characteristics of included studies, which included 6286 autopsies, 7 studies examining whole glands, and 9 examining partial glands. Included studies originated from 8 countries across 4 continents (Europe, North and South America, and Asia). The nonthyroid cause of death of decedents was not reported in any study.

The overall, reported prevalence rates ranged from 1.5% to 35.6%. One study identified other thyroid cancer subtypes and these cancers were excluded from final analysis (n = 4). Age-specific prevalence of subclinical PTC estimates varied across included studies (Table 1). Pooled analyses across the 16 studies found overall prevalence of subclinical PTC was 12.9% (95% CI 7.8-16.8) in whole gland and 4.6% (2.5-6.6) with partial gland examination. Age-specific prevalence of subclinical PTC estimates adjusted for partial vs whole gland examination were ≤40 years, 11.5% (6.8-16.1); 41-60 years:, 12.1% (7.6-16.5); 61-80 years, 12.7% (8-17.5); and 81+ years, 13.4% (7.9-18.9) (Fig. 2). Thirteen of 16 included studies reported the number of PTCs by both sex and age group. Prevalence of subclinical PTC estimates did not differ across the lifespan in females (10.8-13.9%) or in males (11.1-13.2%), or between sexes. In the regression model, the OR for prevalence by increasing age was 1.06 (0.92-1.2, $P = .37$). In other words, there was no change by increasing age group. All studies had deficiencies in 1 to 3 risk of bias domains, most commonly lack of assurance of representativeness of the target population (n = 12) and nonsystematic cancer detection method (ie, partial gland examination; n = 9) (Table 2).

Discussion

Our meta-analysis of autopsy studies found no association between the prevalence of subclinical PTC and age across the adult lifespan. Specifically, subclinical PTC prevalence of among autopsied individuals did not increase with age and did not peak in the middle-aged group, which is when PTC is most often diagnosed. These findings are surprising. They contrast with autopsy studies of other common solid tumors, like prostate (15), whose known subclinical reservoir peaks later in life, the time period when most of these cancers are diagnosed. Thyroid cancer incidence peaks in middle-aged individuals (45-64 years) globally (35-38); however, our results do not show a corresponding peak and suggest that prevalence of subclinical PTC remains relatively flat across all ages. Two potential explanations may contribute to this phenomenon in thyroid cancer: (1) variability in clinical detection patterns, and/or (2) biological factors. Although not definitive, these findings do suggest support for variability in clinical detection patterns.

Clinical Detection Patterns

PTCs are present in greater than 10% of autopsies in patients who died from other causes (13) and our findings show that the prevalence of subclinical PTCs is stable over the lifespan. The dramatic increase in thyroid cancer rates over the last 30 years has been largely due to the increased diagnosis of small PTCs (<2 cm) (10, 39-41). Small PTCs are usually too small to cause symptoms and therefore likely represent tumors identified from the subclinical reservoir through increased diagnostic imaging and testing. Recognizing the existence of the subclinical reservoir and the potential risk of identifying indolent cancers, the US Preventive Services Taskforce (USPSTF) recommends against screening for thyroid cancer. The USPSTF cited that the risks of subclinical disease detection outweighed the potential benefits (42, 43). This recommendation was supported by epidemiologic studies from South Korea showing a strong positive correlation between the use of screening ultrasound examinations and thyroid cancer incidence, without a mortality benefit (44, 45).

It is less clear how, in the setting of stable prevalence of subclinical PTC, detection patterns explain PTC incidence being highest in middle-aged individuals. This apparent disparity may be related to timing. SEER data show that an incidence peak in middle age was not present in the 1980s (1), which was prior to the rise of widespread imaging and ultrasound technology. Thus, higher observed incidence in middle-aged individuals since the 1990s could be a consequence of increased diagnostic scrutiny and, in particular,

Table 1. Characteristics of 16 included studies

Study, publication year	Country	Median year of autopsies	Median age at death (years)	Female (%)	Whole/partial examination of the gland	Reported overall prevalence (%)	Number of subclinical PTCs/ total autopsies (%)			
							<40 years	41-60 years	61-80 years	81+ years
Bondeson and Ljungberg, 1984 (19)	Sweden	1984	61	48	Partial	7.91	10/129 (7.8)	8/89 (9)		14/212 (6.6)
Chong et al, 1994 (20)	Singapore	1984	54	26	Whole	9.68	6/92 (6.5)	19/148 (12.8)	18/161 (11.2)	2/19 (10.5)
Delides et al, 1987 (21)	Greece	1980	41	85	Partial	1.5	1/80 (1.3)	2/97 (2.1)	0/14 (0)	
Franssila and Harach, 1986 (22)	Finland	1984	16	32	Whole	22.81	13/93 (14)			
Fukunaga and Yatani, 1975 (1) (23)	Canada	1975	63	38	Whole	6	2/9 (22.2)	4/37 (10.8)	0/45 (0)	0/9 (0)
Fukunaga and Yatani, 1975 (2) (23)	Japan	1975	58	42	Whole	28.43	3/13 (23.1)	11/46 (23.9)	15/41 (36.6)	0/2 (0)
Fukunaga and Yatani, 1975 (3) (23)	Poland	1975	62	49	Whole	9.09	2/8 (25)	3/40 (7.5)	5/59 (8.5)	0/3 (0)
Fukunaga and Yatani, 1975 (4) (23)	Colombia	1975	39	27	Whole	5.6	17/355 (4.8)	13/162 (8)	6/80 (7.5)	0/10 (0)
Fukunaga and Yatani, 1975 (5) (23)	United States	1975	72	44	Whole	24.19	1/11 (9.1)	21/62 (33.9)	27/116 (23.3)	11/59 (18.6)
Harach et al, 1985 (24)	Finland	1985	67	48	Whole	35.64	2/5 (40)	8/21 (38.1)	21/59 (35.6)	5/16 (31.3)
Kovács et al, 2005 (25)	Hungary	2005	75 (ID); 68 (IS)	51 (ID); 40 (IS)	Partial	4.95 (ID); 4.52 (IS)	0/16 (0)	8/97 (8.2)	10/220 (4.5)	3/110 (2.7)
Mitselou et al, 1999 (26)	Greece	1999	56	26	Partial	7.5	0/36 (0)	3/39 (7.7)	4/69 (5.8)	2/17 (11.8)
Neuhold et al, 2001 (27)	Austria	2001	66	52	Whole	8.47	1/11 (9.1)	2/18 (11.1)	7/68 (10.3)	0/21 (0)
Nielsen and Zetterlund, 1981 (28)	Sweden	1981	72	42	Partial	5.42	0/12 (0)	0/58 (0)	10/300 (3.3)	4/128 (3.1)
Ottino et al, 1989 (29)	Argentina	1986	58	41	Whole	11	0/7 (0)	4/18 (22.2)	6/53 (11.3)	0/22 (0)
Siegal and Modan, 1981 (30)	Israel	1977	68	46	Partial	6.54		3/50 (6)	12/169 (7.1)	2/41 (4.9)
Sobrinho-Simões et al, 1979 (31)	Portugal	1975	53	44	Partial	6.67	3/141 (2.1)	11/204 (5.4)	25/250 (10)	
Thorvaldsson et al, 1992 (32)	Iceland	1985	52	20	Whole	6.53	2/57 (3.5)	5/60 (8.3)	6/71 (8.5)	1/11 (9.1)
Yamamoto et al, 1990 (33)	Japan	1984	61	39	Partial	11.27	4/45 (8.9)	14/126 (11.1)	25/211 (11.8)	3/26 (11.5)
Yatani et al, 1981 (34)	Japan	1981	50	40	Partial	2.45	3/382 (0.8)	11/347 (3.2)	7/373 (1.9)	

Fukunaga and Yatani; 1975 (23) examined samples from 5 geographic locations and reported prevalence by country.
Abbreviations: PTC, papillary thyroid cancer; ID, iodine-deficient area; IS, iodine-sufficient area.

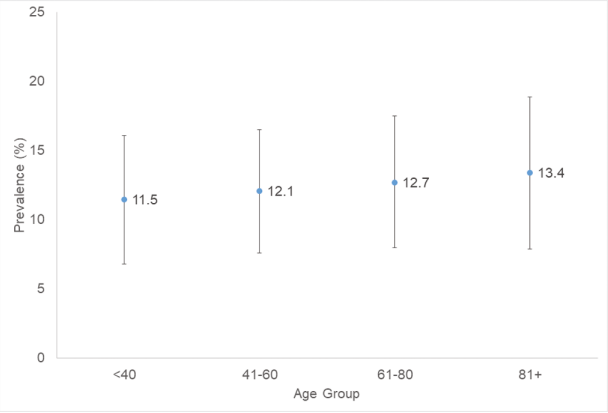

Figure 2. Age group–specific prevalence in logistic regression model; error bars represent 95% CI.

ultrasound detecting small PTCs previously attributed to the subclinical reservoir. Diagnostic scrutiny refers to the pathways through which thyroid cancer may be detected in addition to imaging. Other pathways include (1) presenting with constitutional (eg, fatigue) and/or compressive symptoms (eg, globus, dysphagia) or for a routine health maintenance visit, (2) having a palpable neck mass or enlarged thyroid (by patient or physician), (3) having thyroid cancer risk factors (eg, family history), or (4) having metabolic thyroid disease (46). Additionally, there are circumstances in middle age during which healthcare utilization may systematically differ between men and women; the latter having higher utilization and higher incidence during this period (eg, perimenopause) (47). Consequently, the likelihood of detecting smaller cancers (<1 cm) via thyroid ultrasound may be greater in middle-aged adults (45-54 years) and in women (48). It is also possible there has been a different birth cohort effect, with people who were born between about 1930 and 1960 disproportionately affected. The United States performed nuclear bomb testing in Nevada in the 1950s and 1960s, and this could affect thyroid cancer rates for those in the highest risk age groups at that time. These represent potential explanations; the reasons why middle-aged individuals are disproportionately affected by thyroid cancer remains an active investigation.

Biological Factors

Biology could also explain the discrepancy between a stable prevalence of subclinical PTC and observed peak in PTC incidence in the middle-aged individuals. It is possible that PTCs in this age group become more active and thus more likely to present and be treated surgically. "Treated" cancers would, by definition, be removed from the subclinical reservoir and autopsy studies and their omission may flatten the curve in this age group. Thus, it is possible there is a true increase in clinically relevant PTC among middle-aged individuals, despite the stable prevalence of subclinical disease over the lifespan. It is important to reiterate the PTC incidence peak in middle-aged individuals was first observed in the 1990s after the included autopsy studies were published. As such, newer risk factors affecting thyroid carcinogenesis overall and by age would not be captured in these studies.

There are a number of reasons why thyroid cancer behavior and prognosis may change with age. Specifically, age affects thyroid architecture, nodularity, and cancer behavior. Multiple epidemiologic studies demonstrate a positive association between thyroid nodule prevalence (ie, precursors to thyroid cancer) and advancing age (49-52). Thus, the likelihood of detecting thyroid disease increases with age due to greater nodularity. Moreover, studies examining the relationship of advancing age and thyroid cancer prognosis find that *symptomatic* thyroid cancers in older individuals (>60 years of age) tend to be more aggressive (eg, aggressive papillary histology variants, medullary, anaplastic, poorly differentiated, distant metastatic) (53) and have higher associated mortality (54-56). Yet, the incremental risk of malignancy of each individual nodule decreases with advancing age, even as suspicious features of nodules (eg, larger size, solid) become more common. Thus, malignancy risk differences exist between older and middle-aged adults.

Thyroid cancer incidence differs by sex, while thyroid cancer mortality and subclinical PTC do not (38, 57). Our current study shows that there are also no differences in age-specific prevalence of subclinical PTC between men and women. While women have higher incidence rates during life, the data do not support a larger reservoir of subclinical thyroid cancer. Studies have reported sex disparity in thyroid cancer detection, observing that sex amplified differences in age-specific incidence rates; however, more lethal cancers tend be detected at similar rates in both men and women (12, 57). Nonetheless, sex-based risk factors for developing thyroid cancer (eg, dietary, environmental, molecular) are poorly characterized and would benefit from further elucidation (58).

Limitations

This study has limitations related to autopsy study representativeness, sample sizes, and study period. First, those who die in younger age groups may not be representative of the population under 40 years of age, whereas autopsy data are more likely to representative in the older-aged population. Other risk factors for death at younger ages (eg, obesity, smoking) may also affect representativeness and present differences in the deceased and living populations of younger age groups. Also, there is greater uncertainty in the estimates for younger age groups as fewer young individuals undergo autopsies. The use of consecutive autopsies in all but 3 studies does mitigate but does not eliminate the risk of selection bias, but does improve representativeness of included data. Second, we may not have sufficient data to detect small differences in subclinical PTC prevalence across the lifespan. Third, it is important to note that autopsy studies were conducted between 1975 and 2005 and data may not represent more recent trends in observed incidence. We used all available autopsy data to evaluate the prevalence of subclinical PTC. Most studies (13 of 16) were performed prior to the advent of widespread ultrasound availability and the observed rising incidence (ie, mid to late 1990s). Nonetheless, the findings remain relevant since there has not been any known change in underlying biological risk of thyroid cancer since these data were published. The Furuya-Kanamori meta-analysis did examine 10 studies published after 1990, including 6 studies published in 2001-2011, and found no evidence that the prevalence of subclinical thyroid cancer had changed significantly since the 1970s (13).

Table 2. Risk of bias assessment

Study, publication year	Autopsy samples were a close representation of the national population in relation to age and sex	Autopsy samples were a close representation of the target population (eg, only restricted by history of thyroid disease)	Samples were selected randomly (eg, consecutive autopsies)	Likelihood of nonresponse Bias Was Minimal (ie, nonavailability of data was < 20% among the selected samples)	Data were collected directly from subjects (eg, histopathology)	An acceptable case definition was used for thyroid cancer	Sample examination method was reliable and valid (ie, whole gland examined)	Same mode of thyroid examination for all samples in the study	Numerator and denominator match the reported results
Bondeson et al, 1984 (19)	N	N	Y	Y	Y	Y	N	Y	Y
Chong et al, 1994 (20)	Y	Y	Y	Y	Y	N	Y	Y	Y
Delides et al, 1987 (21)	Y	N	N	Y	Y	Y	N	Y	Y
Franssila and Harach, 1986 (22)	N	N	Y	Y	Y	Y	Y	Y	Y
Fukunaga and Yatani, 1975 (23)	N	N	N	N	Y	Y	Y	Y	Y
Harach et al, 1985 (24)	N	Y	Y	Y	Y	Y	Y	Y	Y
Kovács et al, 2005 (25)	Y	Y	Y	Y	Y	Y	N	Y	Y
Mitselou et al, 1999 (26)	N	Y	N	Y	Y	N	N	Y	Y
Neuhold et al, 2001 (27)	N	Y	Y	Y	Y	Y	Y	Y	Y
Nielsen and Zetterlund, 1981 (28)	N	Y	Y	Y	Y	Y	N	Y	Y
Ottino et al, 1989 (29)	N	Y	Y	Y	Y	Y	Y	Y	Y
Siegal and Modan, 1981 (30)	N	Y	Y	Y	Y	Y	N	Y	Y
Sobrinho-Simões et al, 1979 (31)	N	N	Y	Y	Y	Y	N	Y	Y
Thorvaldsson et al, 1992 (32)	Y	N	Y	Y	Y	Y	Y	Y	Y
Yamamoto et al, 1990 (33)	N	Y	Y	Y	Y	Y	N	N	Y
Yatani et al, 1981 (34)	N	Y	Y	Y	Y	Y	N	N	Y

Adapted from Furuya-Kanamori, et al (13).
Abbreviations: Y, yes; N, no.

Conclusions

This meta-analysis shows the prevalence of subclinical PTC is stable across the lifespan. There is not a higher subclinical PTC prevalence in middle age, in contrast to higher observed incidence rates in this age group. These findings offer unique insights into the prevalence of subclinical PTC and its relationship to age.

Funding

This work is supported by National Institutes of Health (NIH), National Cancer Institute grants 1R01CA251566 and 3R01CA251566-02S1, NIH, National Institute on Deafness and Other Communication Disorders grant T32DC009401, and by the Australian National Health and Medical Research Council (NHMRC Investigator Grant #1174523).

Disclosure Summary

The authors have nothing to disclose.

Data Availability

All data analyzed during this study are included in this published article.

References

1. Surveillance, Epidemiology, and End Results (SEER) Program. *National Cancer Institute, DCCPS, Surveillance Research Program*. August, 8, 2021. www.seer.cancer.gov
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646-674.
3. Vijg J, Suh Y. Genome instability and aging. *Annu Rev Physiol*. 2013;75(1):645-668.
4. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health*. 2003;57(10):778-783.
5. Belpomme D, Irigaray P, Hardell L, *et al*. The multitude and diversity of environmental carcinogens. *Environ Res*. 2007;105(3):414-429.
6. Welch HG, Kramer BS, Black WC. Epidemiologic signatures in cancer. *N Engl J Med*. 2019;381(14):1378-1386.
7. Aschebrook-Kilfoy B, Ward MH, Sabra MM, Devesa SS. Thyroid cancer incidence patterns in the United States by histologic type, 1992-2006. *Thyroid*. 2011;21(2):125-134.
8. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974-2013. *JAMA*. 2017;317(13):1338-1348.
9. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA*. 2006;295(18):2164-2167.
10. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg*. 2014;140(4):317-322.
11. Enewold L, Zhu K, Ron E, *et al*. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. *Cancer Epidemiol Biomarkers Prev*. 2009;18(3):784-791.
12. Kilfoy BA, Devesa SS, Ward MH, *et al*. Gender is an age-specific effect modifier for papillary cancers of the thyroid gland. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1092-1100.
13. Furuya-Kanamori L, Bell KJL, Clark J, Glasziou P, Doi SAR. Prevalence of differentiated thyroid cancer in autopsy studies over six decades: a meta-analysis. *J Clin Oncol*. 2016;34(30):3672-3679.
14. Hoy D, Brooks P, Woolf A, *et al*. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol*. 2012;65(9):934-939.
15. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: a systematic review of autopsy studies. *Int J Cancer*. 2015;137(7):1749-1757.
16. Cénat JM, Blais-Rochette C, Morse C, *et al*. Prevalence and risk factors associated with attention-deficit/hyperactivity disorder among US Black individuals: a systematic review and meta-analysis. *JAMA Psychiatry*. 2021;78(1):21-28.
17. Thomas ET, Del Mar C, Glasziou P, Wright G, Barratt A, Bell KJL. Prevalence of incidental breast cancer and precursor lesions in autopsy studies: a systematic review and meta-analysis. *BMC Cancer*. 2017;17(1):808.
18. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. *J Clin Epidemiol*. 2008;61(1):41-51.
19. Bondeson L, Ljungberg O. Occult papillary thyroid carcinoma in the young and the aged. *Cancer*. 1984;53(8):1790-1792.
20. Chong PY. Thyroid carcinomas in Singapore autopsies. *Pathology*. 1994;26(1):20-22.
21. Delides GS, Elemenoglou J, Lekkas J, Kittas C, Evthimiou C. Occult thyroid carcinoma in a Greek population. *Neoplasma*. 1987;34(1):119-125.
22. Franssila KO, Harach HR. Occult papillary carcinoma of the thyroid in children and young adults. A systemic autopsy study in Finland. *Cancer*. 1986;58(3):715-719.
23. Fukunaga FH, Yatani R. Geographic pathology of occult thyroid carcinomas. *Cancer*. 1975;36(3):1095-1099.
24. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer*. 1985;56(3):531-538.
25. Kovács GL, Gonda G, Vadász G, *et al*. Epidemiology of thyroid microcarcinoma found in autopsy series conducted in areas of different iodine intake. *Thyroid*. 2005;15(2):152-157.
26. Mitselou A, Vougiouklakis T, Peschos D, Dallas P, Agnantis NJ. Occult thyroid carcinoma. A study of 160 autopsy cases. The first report for the region of Epirus-Greece. *Anticancer Res*. 2002;22(1a):427-432.
27. Neuhold N, Kaiser H, Kaserer K. Latent carcinoma of the thyroid in Austria: a systematic autopsy study. *Endocr Pathol Spring*. 2001;12(1):23-31.
28. Nielsen B, Zetterlund B. Malignant thyroid tumors at autopsy in a Swedish goitrous population. *Cancer*. 1985;55(5):1041-3.
29. Ottino A, Pianzola HM, Castelletto RH. Occult papillary thyroid carcinoma at autopsy in La Plata, Argentina. *Cancer*. 1989;64(2):547-551.
30. Siegal A, Modan M. Latent carcinoma of thyroid in Israel: a study of 260 autopsies. *Isr J Med Sci*. 1981;17(4):249-253.
31. Sobrinho-Simões MA, Sambade MC, Gonçalves V. Latent thyroid carcinoma at autopsy: a study from Oporto, Portugal. *Cancer*. 1979;43(5):1702-1706.
32. Thorvaldsson SE, Tulinius H, Björnsson J, Bjarnason O. Latent thyroid carcinoma in Iceland at autopsy. *Pathol Res Pract*. 1992;188(6):747-750.
33. Yamamoto Y, Maeda T, Izumi K, Otsuka H. Occult papillary carcinoma of the thyroid. A study of 408 autopsy cases. *Cancer*. 1990;65(5):1173-1179.
34. Yatani R, I K, Ito M, Ogawa M. Prevalence of carcinoma in thyroid glands removed in consecutive autopsy cases. *Mie Med J*. 1981;30:273-277.
35. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. *N Engl J Med*. 2016;375(7):614-617.
36. James BC, Mitchell JM, Jeon HD, Vasilottos N, Grogan RH, Aschebrook-Kilfoy B. An update in international trends in incidence rates of thyroid cancer, 1973-2007. *Cancer Causes Control*. 2018;29(4-5):465-473.
37. Kilfoy BA, Zheng T, Holford TR, *et al*. International patterns and trends in thyroid cancer incidence, 1973-2002. *Cancer Causes Control*. 2009;20(5):525-531.
38. Li M, Dal Maso L, Vaccarella S. Global trends in thyroid cancer incidence and the impact of overdiagnosis. *Lancet Diabetes Endocrinol*. 2020;8(6):468-470.

39. Brito JP, Davies L. Is there really an increased incidence of thyroid cancer? *Curr Opin Endocrinol Diabetes Obes*. 2014;21(5):405-408.
40. Smith-Bindman R, Lebda P, Feldstein VA, *et al*. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. *JAMA Intern Med*. 2013;173(19):1788-1796.
41. Haymart MR, Banerjee M, Reyes-Gastelum D, Caoili E, Norton EC. Thyroid ultrasound and the increase in diagnosis of low-risk thyroid cancer. *J Clin Endocrinol Metab*. 2019;104(3):785-792.
42. Bibbins-Domingo K, Grossman DC, Curry SJ, *et al*. Screening for thyroid cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;317(18):1882-1887.
43. Lin JS, Bowles EJA, Williams SB, Morrison CC. Screening for thyroid cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;317(18):1888-1903.
44. Ahn HS, Kim HJ, Kim KH, *et al*. Thyroid cancer screening in South Korea increases detection of papillary cancers with no impact on other subtypes or thyroid cancer mortality. *Thyroid*. 2016;26(11):1535-1540.
45. Oh CM, Jung KW, Won YJ, Shin A, Kong HJ, Lee JS. Age-period-cohort analysis of thyroid cancer incidence in Korea. *Cancer Res Treat*. 2015;47(3):362-369.
46. Davies L, Ouellette M, Hunter M, Welch HG. The increasing incidence of small thyroid cancers: where are the cases coming from? *Laryngoscope*. 2010;120(12):2446-2451.
47. Avis NE, McKinlay SM. Health-care utilization among mid-aged women. *Ann N Y Acad Sci*. 1990;592:228-238; discussion 257-62.
48. Esfandiari NH, Hughes DT, Reyes-Gastelum D, Ward KC, Hamilton AS, Haymart MR. Factors associated with diagnosis and treatment of thyroid microcarcinomas. *J Clin Endocrinol Metab*. 2019;104(12):6060-6068. Doi: 10.1210/jc.2019-01219
49. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest*. 2009;39(8):699-706.
50. Reiners C, Wegscheider K, Schicha H, *et al*. Prevalence of thyroid disorders in the working population of Germany: ultrasonography screening in 96 278 unselected employees. *Thyroid*. 2004;14(11):926-932.
51. Brander A, Viikinkoski P, Nickels J, Kivisaari L. Thyroid gland: US screening in a random adult population. *Radiology*. 1991;181(3):683-687.
52. Bartolotta TV, Midiri M, Runza G, *et al*. Incidentally discovered thyroid nodules: incidence, and greyscale and colour Doppler pattern in an adult population screened by real-time compound spatial sonography. *Radiol Med*. 2006;111(7):989-998.
53. Kwong N, Medici M, Angell TE, *et al*. The influence of patient age on thyroid nodule formation, multinodularity, and thyroid cancer risk. *J Clin Endocrinol Metab*. 2015;100(12):4434-4440.
54. Mazzaferri EL. Papillary thyroid carcinoma: factors influencing prognosis and current therapy. *Semin Oncol*. 1987;14(3):315-332.
55. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 1990;71(2):414-424.
56. Ganly I, Nixon IJ, Wang LY, *et al*. Survival from differentiated thyroid cancer: what has age got to do with it? *Thyroid*. 2015;25(10):1106-1114.
57. LeClair K, Bell KJL, Furuya-Kanamori L, Doi SA, Francis DO, Davies L. Evaluation of gender inequity in thyroid cancer diagnosis: differences by sex in US thyroid cancer incidence compared with a meta-analysis of subclinical thyroid cancer rates at autopsy. *JAMA Intern Med*. 2021;181(10):1351-1358.
58. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. *Future Oncol*. 2010;6(11):1771-1779.