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ORIGINAL REPORT

Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A Meta-Analysis

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ABSTRACT

Purpose

Differentiated thyroid cancer (DTC) incidence has been reported to have increased three- to 15-fold in the past few decades. It is unclear whether this represents overdiagnosis or a true increase in incidence. Therefore, the current study aimed to estimate the prevalence of incidental DTC in published autopsy series and determine whether this prevalence has been increasing over time.

Materials and Methods

PubMed, Embase, and Web of Science were searched from inception to December 2015 for relevant studies. Two authors searched for all autopsy studies that had included patients with no known history of thyroid pathology and reported the prevalence of incidental DTC (iDTC). Two authors independently extracted the data, and discrepancies were resolved by another author. The pooled prevalence of iDTC was assessed using a fixed-effects meta-analysis model with robust error variance. The time effect was studied using an inverse-variance weighted logit-linear regression model with robust error variance and a time variable.

Results

Thirty-five studies, conducted between 1949 and 2007, met the inclusion criteria and contributed 42 data sets and 12,834 autopsies. The prevalence of iDTC among the partial and whole examination subgroups was 4.1% (95% CI, 3.0% to 5.4%) and 11.2% (95% CI, 6.7% to 16.1%), respectively. Once the intensiveness of thyroid examination was accounted for in the regression model, the prevalence odds ratio stabilized from 1970 onward, and no time effect was observed.

Conclusion

The current study confirms that iDTC is common, but the observed increasing incidence is not mirrored by prevalence within autopsy studies and, therefore, is unlikely to reflect a true population-level increase in tumorigenesis. This strongly suggests that the current increasing incidence of iDTC most likely reflects diagnostic detection increasing over time.

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INTRODUCTION

In 2006, Davies and Welch[1] first flagged the increasing incidence of differentiated thyroid cancer (DTC) in the United States and suggested that this may be predominantly a result of the increased detection (overdiagnosis) of small papillary cancers. They tagged this as possible overdetection because it was felt that the two prerequisites (presence of a subclinical thyroid cancer reservoir and activities leading to increased detection of patients from the disease reservoir)[2] had been met. In particular, thyroid cancer is well known for subclinical cancers that may not progress or have such a slow progression that the patient is more likely to die of other causes.

There is evidence of activities leading to increased detection and a possible association with incidence rates; in one study between 2000 and 2012, a doubling of thyroid cancer incidence was also associated with a nearly five-fold increase in the use of thyroid ultrasound and a nearly seven-fold increase in the use of thyroid fine-needle aspiration.[3] One contributor to the increased use of fine-needle aspiration may be the investigation of incidental findings of imaging of the neck (eg, carotid ultrasound, neck computed tomography) or chest regions (eg, chest computed tomography).[4]

Although such data suggest overdiagnosis, one way to confirm this would be through population-level trends that document a mismatch in rates of change between thyroid cancer incidence and mortality on a large scale. Analyses by Davies and

Welch[5] have demonstrated this; they reported that between 1973 and 2009, mortality from thyroid cancer in the United States remained stable, but incidence was increasing, particularly in women. They found that the increased incidence of thyroid cancer was almost completely attributable to DTC, in particular, small ($\leq$ 2 cm) papillary thyroid cancers, with the incidence of subcentimeter thyroid cancers increasing at the fastest rates.

Although the increased incidence of thyroid cancer and stable mortality rates point to likely overdiagnosis, the reality is that thyroid cancer–specific mortality, especially of small papillary thyroid cancer, is so low anyway that it would be hard to show a difference.[6] This is because smaller thyroid cancers tend to remain subclinical and may not progress or will progress so slowly that the patient is more likely to die of other causes.[6,7] Therefore, it is imperative that we confirm the potential overdiagnosis using another approach. Given that the increasing incidence is mainly of subcentimeter tumors, a truly increasing incidence should be reflected by an expanding incidental thyroid cancer reservoir. The status of this reservoir can be examined using data from case series of autopsies performed on patients who were not known to have thyroid disease at the time of death. There are dozens of published reports of such studies documenting incidental thyroid cancers on autopsy, and individual studies confirm that a significant number of adults harbor occult papillary thyroid cancers.[8] Pooling these data over similar time periods would allow a determination of whether the incidental thyroid cancer reservoir has changed over time. If the reservoir has remained stable over time, then the apparent increases in the incidence of small (especially subcentimeter) thyroid cancers may be explained by activities leading to overdetection, rather than any true change in the underlying incidence (at least for the smaller cancers that are on the rise). Therefore, we undertook to combine all published autopsy series to estimate the time trend in pooled prevalence and to evaluate possible factors related to the differences in prevalence across studies.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

A systematic review and meta-analysis was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines. A systematic search was run in PubMed, Embase, and Web of Science from inception to December 2015 for autopsy studies that reported the prevalence of incidental DTC (iDTC). The complete details of the search strategies are available in the Appendix (online only).

Inclusion was restricted to autopsy studies that included patients with no known history of thyroid pathology. No language or date restrictions were used. Irrespective of the medical indication, data from surgical thyroid removal or fine-needle aspiration biopsies were excluded. Studies that reported atomic bomb or Chernobyl nuclear disaster survivors were excluded. Exclusions were also made for conference presentations, abstracts, and publications with incomplete information about the method of examination of the thyroid and the age of the patients at death.

Study Selection and Data Extraction

Two authors (L.F.-K. and J.C.) independently assessed the eligibility of studies and collated the data from the qualifying studies. Authors (L.F.-K. and K.J.L.B.) independently extracted the data, and discrepancies were resolved through discussion and consensus after independent evaluation by another author (S.A.R.D.). Data from the included studies were extracted and summarized in a spreadsheet. The recorded fields included study identifiers (authors, publication year), study population characteristics (median age, sex proportion, country), autopsy procedure (years when the autopsies were performed, number of autopsies performed, thyroid examination methodology), and outcome (thyroid weight, histologic findings [number of iDTCs]).

Quality Assessment

A modification of the validated scale proposed by Hoy et al[9] was used to assess study quality. This assessment of methodologic quality assesses risk of bias and does not refer to reporting quality, and therefore, the tool lists common safeguards against which the studies were assessed. The higher the number of safeguards present, the more assurance there is that the iDTC prevalence had been measured in a manner that is free from bias. Nine safeguards were assessed and reported for each study; these included both internal and external validity items, and although the recommendation has been to focus on internal validity for risk of bias assessments,[10] an exception applies to prevalence studies.[9]

Statistical Analysis

The primary effect measure of interest was the prevalence of iDTC in autopsies. The double arcsine square root transformed[11] (to stabilize the variance) prevalence of iDTC across studies was pooled using the inverse-variance heterogeneity model[12] (which uses robust error variances) stratified by method of thyroid examination and median age group at autopsy. For ease of interpretation, results were reported after back-transformation to natural proportions. The random-effects model was also used to run the meta-analysis, and results are reported in the Appendix (online only). Cochran Q test and I^2 were used to assess heterogeneity among studies. Because I^2 tends to increase for the same level of heterogeneity as precision of study estimates increase,[13] we also looked at the clinical relevance of any heterogeneity present, as well as the between-study heterogeneity measured through τ^2.

A linear model was used to gain additional insight into the time trend of the autopsy-based iDTC prevalence by analysis of the association of logit prevalence with year and other important variables that were defined a priori, including period when the autopsies were performed (before 1970, 1970 to 1975, 1976 to 1980, 1981 to 1985, 1986 to 1990, and after 1990), median age at death, and whether the whole thyroid was examined or only areas where macroscopic anomalies were observed. The linear model was fit using logit prevalence as the response variable, weighted by the inverse of each study's variance to allow the observations with the least variance to provide the most information to the model, and using robust error variances. As a sensitivity analysis, two additional models, a random-effects weighted logit-linear regression model and a mixed-effects linear model, were run, with intensiveness of thyroid examination as the random effect. Because these two models provided similar results to the inverse-variance weighted logit-linear regression model with robust error variance, we report only the latter model in this analysis.

All tests were two-tailed, and $P < .05$ was deemed statistically significant. Pooled analyses were conducted using MetaXL version 4.0 (EpiGear International, Sunrise Beach, Queensland, Australia), and the regression models were run using Stata SE version 14 (Stata Corp, College Station, TX).

RESULTS

Yield of Search Strategies

The search strategies identified 1,745 unique publications, the titles and abstracts of which were screened for inclusion. The full texts of 95 articles were retrieved, of which 35 studies[8,14-45,47,48] met the inclusion criteria and contributed with 42 data sets.

Table 1. Characteristics of the Included Studies

Study and Year of Publication	Location	Median Year When Autopsies Were Performed	Study Population	Median Age at Death (years)	Female (%)	Whole/Partial Examination of the Gland and No. of Slices Examined per Gland	No. of Autopsies Examined	No. of iDTCs	Prevalence of iDTC (%)
Arellano and Ibarra,[14] 1984	Santiago de Chile, Chile	1982	Unselected autopsies at Chile Medical School Hospital	55	47	Partial, 2*	274	9	3.28
Autelitano et al,[15] 1984	Rome, Italy	1984	Consecutive hospital autopsies	> 60	38	Partial, 4*	202	7	3.47
Autelitano et al,[16] 1990	Rome, Italy	1990	Consecutive autopsies without clinical evidence of thyroid cancer performed over 1 year	> 60	NR	Whole, NR	507	37	7.30
Bisi et al,[17] 1989	Brazil (city NR)	1989	Autopsies with no clinical evidence of thyroid disease	49	33	Partial, 3-4*	300	7	2.33
Bondeson et al,[18] 1984	Malmo, Sweden	1984	Consecutive hospital and forensic autopsies in patients without history of thyroid surgery	61	48	Partial, 2*	430	34	7.91
Brierre and Dickson,[19] 1964	Maryland, United States	1964	Consecutive autopsies in adults	55	38	Partial, NR	100	3	3.00
Chong et al,[20] 1994	Singapore	1984	Coronial cases with no history of thyroid disease	54	26	Whole, NR	444	43	9.68
de Matos et al,[8] 2006	Sao Paulo, Brazil	1999	Routine hospital autopsies in patients with a cause of death other than thyroid diseases	47	35	Partial, 8*	166	13	7.83
Delides et al,[21] 1987	Athens, Greece	1980	Autopsies without history of thyroid disease or extended hospitalization	41	85	Partial, 3*	200	3	1.50
Fleischmann and Hardmeier,[22] 1999	Canton of Thurgau, Switzerland	1995	Consecutive adult autopsies	71	44	Partial, NR	392	8	2.04
Franssila and Harach,[23] 1986	Helsinki, Finland	1984	20 consecutive autopsies for each 10-year age group of patients < 40 years of age	16	32	Whole, 20	57	13	22.81
Fukunaga and Yatani,[24] 1975 (1)	Ontario, Canada	1975	NR	63	38	Whole, NR	100	6	6.00
Fukunaga and Yatani,[24] 1975 (2)	Sendai, Japan	1975	Unselected thyroid glands were removed at autopsies performed at the Tohoku University Hospital	58	42	Whole, NR	102	29	28.43
Fukunaga and Yatani,[24] 1975 (3)	Gliwice, Poland	1975	NR	62	49	Whole, NR	110	10	9.09
Fukunaga and Yatani,[24] 1975 (4)	Cali and Medellin, Colombia	1975	Consecutive autopsies from Hospital Universitario Del Valle and Cali's Medicolegal Office	39	27	Whole, NR	607	34	5.60
Fukunaga and Yatani,[24] 1975 (5)	Hawaii, United States	1975	NR	72	44	Whole, NR	248	60	24.19
Harach et al,[25] 1985	Helsinki, Finland	1985	Consecutive hospital autopsies	67	48	Whole, 30	101	36	35.64
Hazard and Kaufman,[26] 1952	Ohio, United States	1950	Consecutive hospital autopsies in adults	62	34	Partial, NR	408	2	0.49
Hull,[27] 1955	Colorado, United States	1953	Consecutive necropsies; patients < 10 years of age were excluded	71	43	Partial, 3*	221	3	1.36
Komorowski and Hanson,[28] 1988	Wisconsin, United States	1988	Hospital autopsies of patients 20-40 years of age with clinical evidence of thyroid disease	30	38	Whole, NR	138	4	2.90
Kovacs et al,[29] 2005 (1)	Budapest, Hungary	2005	Consecutive autopsy series in an iodine-deficient area	75	51	Partial, 8*	222	11	4.95
Kovacs et al,[29] 2005 (2)	Szolnok, Hungary	2005	Consecutive autopsy series in an iodine-sufficient area	68	40	Partial, 8*	221	10	4.52

(continued on following page)

Table 1. Characteristics of the Included Studies (continued)

Study and Year of Publication	Location	Median Year When Autopsies Were Performed	Study Population	Median Age at Death (years)	Female (%)	Whole/Partial Examination of the Gland and No. of Slices Examined per Gland	No. of Autopsies Examined	No. of iDTCs	Prevalence of iDTC (%)
Lang et al,[30] 1988	Hannover, Germany	1987	Autopsies in patients > 15 years of age with no clinically manifest carcinoma of the thyroid	61	44	Partial, NR	1,020	62	6.08
Martinez-Tello et al,[31] 1993 (1)	Madrid, Spain	1993	Autopsies performed at the Hospital Central de la Cruz Roja	68	45	Partial, 2*	625	31	4.96
Martinez-Tello et al,[31] 1993 (2)	Madrid, Barcelona, and Zaragoza, Spain	1993	Consecutive autopsies with no thyroid-related diseases	58	34	Whole, 35	100	22	22.00
Mitselou et al,[32] 2002	Epirus, Greece	1999	Forensic cases without any clinical thyroid disease history	56	26	Partial, 4-6*	160	12	7.50
Mortensen et al,[33] 1955	Minnesota, United States	1952	Hospital routine consecutive postmortem examination; excluded patients with clinical evidence of thyroid disorder	> 60	32	Partial, 1*	821	13	1.58
Neuhold et al,[34] 2001	Vienna, Austria	2001	Consecutive hospital autopsies with no clinical manifestation of thyroid carcinoma	66	52	Whole, NR	118	10	8.47
Nielsen and Zetterlund,[35] 1985	Jonkoping, Sweden	1981	Consecutive hospital autopsies without prior surgery	72	42	Partial, 2*	498	27	5.42
Ottino et al,[36] 1989	La Plata, Argentina	1986	Consecutive hospital autopsies	58	41	Whole, 24*	100	11	11.00
Pingitore,[37] 1982	Tuscany and Liguria, Italy	1980	Consecutive hospital autopsies in adults with clinically normal thyroid	65	29	Partial, NR	111	4	3.60
Sampson et al,[38] 1974	Minnesota, United States	1970	Autopsies of Olmsted County residents	65	37	Partial, 2*	157	8	5.10
Seta and Takahashi,[39] 1976	Iwate, Japan	1976	Unselected autopsies	40	52	Whole, 120-180	379	58	15.30
Siegal and Modan,[40] 1981	Tel-Hashomer and Kfar Saba, Israel	1977	Consecutive hospital autopsies in adults	68	46	Partial, 6*	260	17	6.54
Silverberg and Vidone,[41] 1966	Connecticut, United States	1965	Unselected hospital autopsies in patients > 20 year of age	64	39	Partial, 5-6*	300	8	2.67
Sobrinho-Simoes et al,[42] 1979	Porto, Portugal	1975	Consecutive hospital autopsies in which entire thyroid gland was available	53	44	Partial, 2*	600	40	6.67
Solares et al,[43] 2005	Guatemala City, Guatemala	2000	Consecutive autopsies with a cause of death not related to thyroid disease	41	23	Partial, 1*	150	3	2.00
Tanriover et al,[44] 2011	Marmara, Turkey	2007	Forensic autopsies in people with no history of thyroid disease	45	14	Partial, 2*	108	4	3.70
Thorvaldsson et al,[45] 1992	Reykjavik, Iceland	1985	Consecutive forensic autopsies in people without history of thyroid surgery or radiation treatment	52	20	Whole, 19	199	13	6.53
Yamamoto et al,[47] 1990	Tokushima, Japan	1984	Hospital consecutive autopsies	61	39	Partial, 2*	408	46	11.27
Yatani et al,[48] 1981 (1)	Mie, Japan	1981	Unselected autopsies; routine autopsy examination	50	40	Partial, NR	1,102	27	2.45
Yatani et al,[48] 1981 (2)	Mie, Japan	1981	Unselected autopsies; exhaustive autopsy examination	50	44	Whole, NR	68	18	26.47

Abbreviations: iDTC, incidental differentiated thyroid cancer; NR, not reported.
*Number of slices examined when no grossly macroscopic lesions were visible; additional slices were examined when macroscopic lesions were present.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram summarizes the results of the literature searches (Appendix Fig A1, online only).

Characteristics of the Included Data Set

The included data sets accounted for 12,834 autopsies performed between 1949 and 2007. Forty percent of the autopsies were conducted in females, and the median age of study participants at death ranged between 16 and 75 years of age. Sixteen data sets examined the whole thyroid irrespective of the presence or absence of macroscopic evidence of disease. The autopsies were conducted before 1970 in five data sets,[19,26,27,33,42] between 1970 and 1975 in seven data sets,[24,38,42] between 1976 and 1980 in four data sets,[21,37,39,40] between 1981 and 1985 in 11 data sets,[14,15,18,20,23,25,35,45,47,48] between 1986 and 1990 in five data sets,[16,17,28,30,36] and after 1990 in 10 data sets[8,22,29,31,32,34,43,44] (Table 1).

Of the nine deficiencies assessed in terms of risk of bias (quality assessment), the studies had between one and four deficiencies (Appendix Table A1, online only). The most common deficiencies were nonrepresentativeness of the national population in 30 studies, nonsystematic cancer detection method in 25 studies, and no clearly stated DTC definition in 12 studies.

Quantitative Synthesis

The pooled prevalence among the partial examination subgroup was 4.1% (95% CI, 3.0% to 5.4%), whereas it was 11.2% (95% CI, 6.7% to 16.1%) when whole thyroids were examined irrespective of the macroscopic findings (Fig 1). With the second period (1970 to 1975) as the reference, the iDTC prevalence odds were much lower only in the first period, and no difference from the reference was seen over subsequent time periods (Table 2 and Fig 2). Results using random effects weights were comparable (Appendix Table A2, online only). The best predictor accounting for almost all of the model-explained variance in prevalence was whole or partial gland examination. Discrimination of studies with iDTC prevalence $< 10\%$ compared with $\geq 10\%$ with this single variable was excellent (area under the curve, 0.82; 95% CI, 0.69 to 0.96) and comparable to discrimination using the linear predictor from the logit-linear regression model, which also included the time period variables (area under the curve, 0.83; 95% CI, 0.70 to 0.95). This suggests that the time period when autopsies were conducted added little to the prediction of iDTC prevalence beyond that of whole or partial gland examination.

Heterogeneity was evident across all subgroups in Figure 1, with I^2 ranging between 89% and 92% and the Cochran Q χ^2 $P < .1$ across the subgroups and overall. Nevertheless, τ^2 was 0.014 for the partial examination group and 0.053 for the whole examination group. The overall τ^2 was 0.038. The clinical relevance of heterogeneity was therefore deemed to be low in the partial-gland groups but moderate in the whole-gland groups. This increase in heterogeneity was related to some members of the whole examination group having a relatively higher prevalence of iDTC or a higher number of thyroid slices examined (Fig 1 and Appendix Figs A2 and A3, online only).

DISCUSSION

Thyroid cancer incidence has substantially increased in many countries,[49] with uncertainty about whether this is a real biologic increase or simply an increased detection of a stable reservoir of incidental cancer. One of the most dramatic reports of such an increase comes from South Korea where, between 1993 and 2011, there was a 15-fold increase in thyroid cancer incidence, mainly of the papillary type.[50] The regional incidence correlated with the penetration of thyroid cancer screening in that area, suggesting overdetection.

Our results suggest that the prevalence of iDTC is stable across time, which provides evidence for overdetection as the mechanism

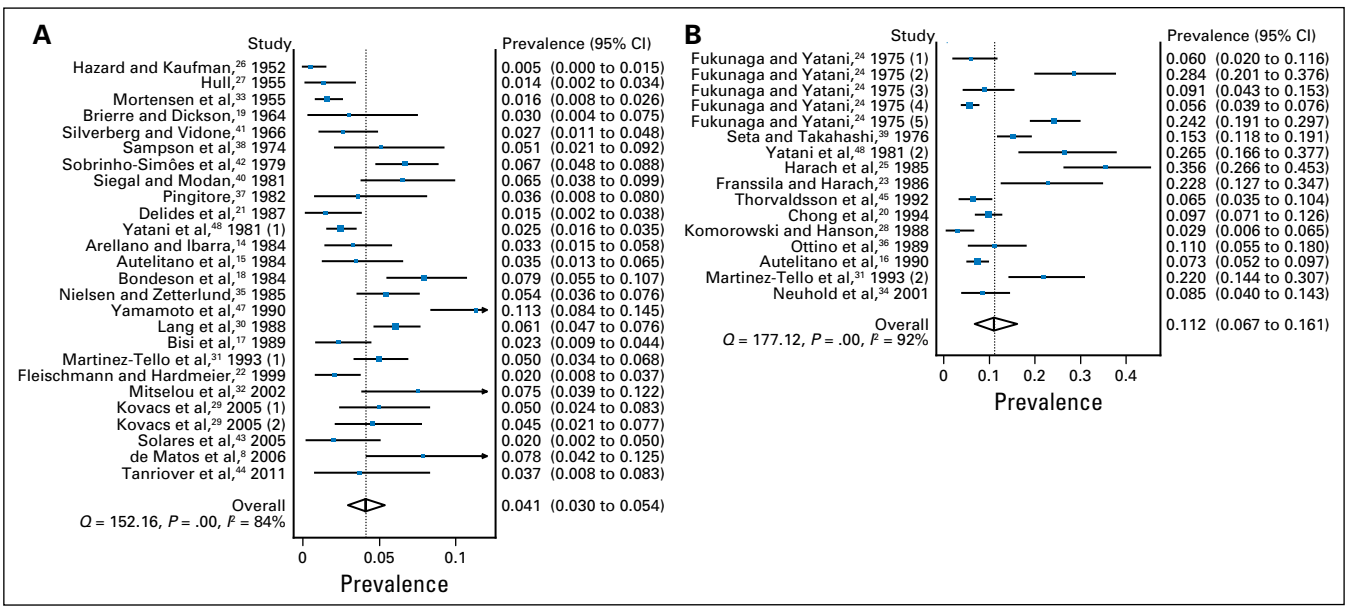

Fig 1. Forest plot (IVhet model) depicting the prevalence of incidental differentiated thyroid cancer in the (A) partial and (B) whole thyroid examination subgroups and sorted by period when the autopsies were conducted.

Table 2. Potential Predictors of Incidental Differentiated Thyroid Cancer: Univariable and Multivariable Regression

Predictors in Model	Univariable				Multivariable			
	POR	95% CI	*P*	R^2	POR	95% CI	*P*	R^2
Period when autopsies were conducted								
Before 1970	0.16	0.07 to 0.34	< .001	0.403	0.21	0.08 to 0.51	.001	0.598
1970-1975	1.00				1.00			
1976-1980	0.78	0.23 to 2.63	.677		0.91	0.35 to 2.37	.849	
1981-1985	0.67	0.29 to 1.51	.323		0.90	0.44 to 1.85	.773	
1986-1990	0.65	0.34 to 1.23	.179		0.68	0.32 to 1.45	.306	
After 1990	0.55	0.28 to 1.06	.073		0.75	0.35 to 1.61	.443	
Median age at death > 60 years	0.84	0.45 to 1.58	.585	0.009	1.56	0.99 to 2.43	.052	
Examined the whole thyroid	3.05	1.82 to 5.12	< .001	0.315	2.54	1.55 to 4.17	.001	

Abbreviation: POR, prevalence odds ratio (relative prevalence odds of incidental differentiated thyroid cancer per unit increase in each predictor).

for the rapidly increasing incidence of micropapillary DTC in recent times. Apparent differences in the iDTC prevalence over different time periods were found to be explained almost entirely by differences in the use of whole or partial gland examination. Averaged across all studies undertaking whole-gland examination, the prevalence of autopsy-detected thyroid cancers was just greater than 10%. This prevalence is well in excess of the lifetime cumulative incidence of thyroid cancer, which was 1.1% in the United States on the basis of data from 2010 to 2012.[51] The prevalence varied across studies; it was higher when more intensive evaluation of the thyroid was performed, suggesting that the baseline prevalence is detection method dependent and < 10% in meticulously examined thyroids.

Thyroid cancer death rates have remained stable over the past three decades, and recent data suggest only a slight change from 0.51 in 2007 to 0.52 in 2011 among men and from 0.48 to 0.49 among women in the United States (per 100,000 population).[52] Yet, the largest annual increases in incidence were for thyroid cancers (5.3% and 4.5% in men and women, respectively) in the same period.[52] We could attribute this stable mortality to the fact that thyroid cancer progresses slowly, but this cannot be the sole reason because that would imply extraordinarily long lead times (> 30 years) in which mortality has been stable.[5] It is also unlikely that improvements in diagnosis and treatment over the past 30 years are the main explanation of this stable thyroid cancer mortality rate,[49,53] because, as pointed out by Davies and Welch,[5] these improvements would have had to exactly match the change in incidence rate. A more reasonable explanation is what we demonstrate here, which is that there is a vast reservoir of subclinical cancer that remains stable; the evidence suggests that thyroid cancer is increasingly being detected without being destined to cause death. In addition, the increase in incidence of thyroid cancer is not recent; from data presented by Davies and Welch,[5] it is clear that the incidence has steady increased since the 1980s, yet we did not find an increase in the size of the reservoir from autopsies conducted 20 years later. If we assume that thyroid cancer evolves from this reservoir and the reservoir remains stable, then the most parsimonious conclusion is that increase in carcinogenesis is an unlikely culprit here.

It has been reported that at least one third of adults harbor small papillary thyroid cancers, the vast majority of which will not produce symptoms during a person's lifetime.[25] This substantial reservoir has been long recognized,[54] and given our results, the evidence for the reservoir representing a subclinical phase of iDTC

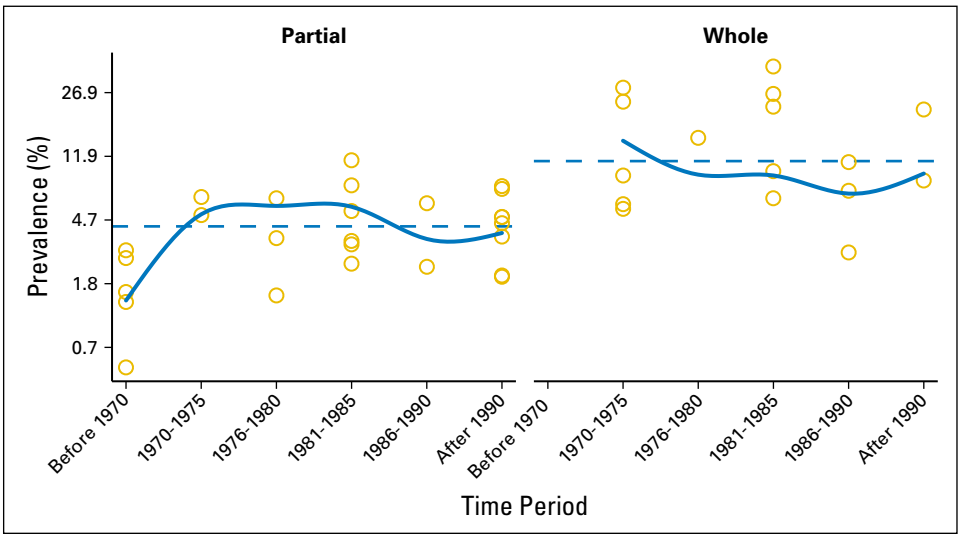

Fig 2. Modeled prevalence of incidental differentiated thyroid cancer over time (cubic spline fit using the cross-medians as knots) stratified by method of gland examination. The dashed lines depict the meta-analytic estimates of the overall prevalence of incidental differentiated thyroid cancer in the partial examination (4.1%) and whole examination (11.2%) subgroups. Please note that the *y*-axis is logit not linear, and hence, the labeled prevalence (percentage) increases are much larger in the upper part of the scale.

is strong. The question then is as follows: What can be done to reduce the problems from overdetection? Ideally, we would like not to detect such subclinical latent cancers in the first place, for example, by identifying and reducing overtesting.[55] However, when subclinical DTC has been detected, it seems reasonable to selectively defer offering treatment. This view is supported by clinical studies of DTC,[46,56,57] and the first of these studies observed 340 patients with untreated papillary microcarcinomas over a 10-year period and found no cancer deaths and few new nodal metastases (in only 3% of patients).[56] A second study described a group of 244 patients with incidentally detected papillary microcarcinoma who received ultrasounds every 6 to 12 months for up to 17 years.[46] No patients developed extrathyroidal invasion or distant metastases; only 5% of patients were ultimately recommended for surgery because of increase in size of the primary tumor or new nodal metastases. In a more recent study, 1,235 patients with subclinical DTC were observed for an average of 75 months.[57] Clinical progression (tumor size reaching 12 mm or new nodal metastases) occurred in $<$ 10% of patients at 10 years. Tumor size ($>$ 9 mm) and age ($<$ 40 years of age) were independent predictors of progression, and in young patients, progression occurred at twice the overall rate, but interestingly, none of the patients who had thyroid-stimulating hormone suppression experienced clinical progression.[57] The authors conclude that it may not be too late to intervene after detecting progression to clinical disease in younger patients,[57] and indeed, across all three clinical studies, patients who were treated after progression still had excellent outcomes with only one patient with recurrent disease.[46,56,57]

Our findings have limitations, principally the unknown validity of pathologic assessment at autopsy. For example, although not reported in these studies, thyroid glands may show autolysis on histologic examination, and because it is difficult to evaluate subtle nuclear details that are only present in a few cells of specimens subjected to a certain degree of autolysis, tiny lesions may have the potential to mimic cancer and might falsely elevate estimates of iDTC prevalence. Although the completeness of thyroid assessment varied, we tried to capture this through the extent of pathologic examination reported in each study. Interestingly, there were as many studies in the 5 years from 1981 to 1985 as in the 25 years from 1990 to 2015, which may be a result of the 1986 Chernobyl nuclear disaster; however, studies that might have been directly impacted by the disaster were excluded from the analysis. Another limitation was missing detail of methods and prevalence of cancer stratified by age and other factors; because many studies were old, contact with authors for clarifications was not possible. Insufficient data also meant we were unable to test for differences in prevalence by geography and race. Higher levels of risk can certainly explain why, in areas where thyroid cancer is highly prevalent, we also found high prevalence of the cancer reservoir in autopsies. However, the level of scrutiny when examining the gland seems to be more important than the location where the study was conducted. For example, Yatani et al[48] conducted a study in the same Japanese population but with different levels of scrutiny and found 2.5% and 26.5% of iDTCs with a routine examination and an exhaustive examination, respectively.

In conclusion, this study affirms the presence of a substantial reservoir of incidental thyroid cancer that, importantly, has not increased over the past several decades. Therefore, it is likely that the increasing incidence of DTC is related to increasing detection of stable incidental disease. Strategies to reverse such overdetection and the consequent overtreatment will require methods to both decrease inappropriate imaging and better manage small nodules when detected.[58] This situation had previously been compounded by older guidelines such as those from the American Thyroid Association that endorsed biopsy of thyroid nodules as small as 5 mm.[59] More recently, in the wake of this controversy, the American Thyroid Association has updated its guidelines to recommend that, in general, only nodules $>$ 1 cm should be evaluated, because they have a greater potential to be clinically significant cancers (with exceptions for nodules $<$ 1 cm with suspicious ultrasound findings, associated lymphadenopathy, or other high-risk clinical factors).[60] Similarly, the American College of Radiology recommends further evaluation only if the incidental nodule is $>$1 cm in those $<$ 35 years of age or $>$ 1.5 cm in those $\geq$ 35 years of age, unless there is evidence of focal metabolic activity in the thyroid.[61] We look forward to prospective studies examining outcomes of patients with subcentimeter nodules undergoing active surveillance only.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A Meta-Analysis

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Appendix

Search Strategy

The search strategy was built by a health librarian (J.C.) and included the following keywords and subject terms "thyroid cancer," "autopsy," "prevalence," and "incidental." A second, different, title/subject term (Medical Subject Headings [MeSH] and Emtree) search was done in order to find studies performed before 1975. This was deemed necessary because of the lack of pre-1975 results found in our initial search, which we surmised was a result of the lack of abstracts in the early literature. To achieve a comprehensive evaluation of the published evidence, the systematic searches were combined with a forward and backward citation search, and the first 20 similar articles from PubMed for each of the articles included from the searches were retrieved.

PubMed Search

"Thyroid Neoplasms"[MeSH] OR "Adenocarcinoma, Follicular"[MeSH] OR "Adenocarcinoma, Papillary"[MeSH] OR OPTC OR ((Thyroid[tiab] OR Follicular[tiab] OR Papillary[tiab] OR hurtle cell[tiab]) AND (cancer[tiab] OR cancers[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Adenocarcinoma[tiab] OR Adenocarcinomas[tiab] neoplasm[tiab] OR neoplasms[tiab] OR nodule[tiab] OR nodules[tiab] OR tumor[tiab] OR tumour[tiab] OR Tumors[tiab] OR Tumours[tiab] OR cyst[tiab] OR cysts [tiab]))

AND

"Autopsy"[MeSH] OR "Autopsy"[tiab] OR "Autopsies"[tiab] OR "Postmortem"[tiab] OR Post-mortem[tiab] OR (Post[tiab] AND mortem[tiab])

AND

"Prevalence"[MeSH] OR "Epidemiology"[MeSH] OR "Prevalence"[tiab] OR "Prevalences"[tiab] OR Epidemiology[tiab] OR Epidemiological[tiab] OR Frequency[tiab]

AND

"Incidental Findings"[MeSH] OR Incidental[tiab] OR Unsuspected[tiab] OR Discovery[tiab] OR Discoveries[tiab] OR Findings[tiab] OR Finding[tiab] OR Occult[tiab] OR Hidden[tiab]

PubMed Title/MeSH Search (for Finding Article Before 1975)

"Thyroid Neoplasms"[MeSH] OR

(Thyroid[ti] AND (cancer[ti] OR cancers[ti] OR carcinoma[ti] OR carcinomas[ti] OR Tumor[ti] OR Tumors[ti] OR Tumor [ti] OR Tumours[ti] OR Neoplasm[ti] OR Neoplasms[ti]))

AND

("Autopsy"[MeSH] OR pathology[sh] OR Autopsy[ti] OR Autopsies[ti] OR Pathology[ti])

AND

(epidemiology[sh] OR Epidemiology[ti] OR Prevalence[ti] OR Patterns[ti] OR Cases[ti])

Embase Search

'thyroid cancer'/exp OR 'adenocarcinoma'/exp OR OPTC OR (Thyroid OR Follicular OR Papillary OR hurthle cell) AND (cancer OR cancers OR carcinoma OR carcinomas OR Adenocarcinoma OR Adenocarcinomas neoplasm OR neoplasms OR nodule OR nodules OR tumor OR tumour OR Tumors OR Tumours OR cyst OR cysts)

AND

'Autopsy'/exp OR Autopsy OR Autopsies OR Postmortem OR Post-mortem OR (Post AND mortem)

AND

'prevalence'/exp OR 'epidemiology'/exp OR Prevalence OR Prevalences OR Epidemiology OR Epidemiological OR Frequency

AND

'incidental finding'/exp OR Incidental OR Unsuspected OR Discovery OR Discoveries OR Findings OR Finding OR Occult OR Hidden

Embase Title/Emtree Search (for Finding Articles Before 1975)

'thyroid cancer'/exp OR

((Thyroid:ti AND (cancer:ti OR cancers:ti OR carcinoma:ti OR carcinomas:ti OR Tumor:ti OR Tumors:ti OR Tumor:ti OR Tumours:ti OR Neoplasm:ti OR Neoplasms:ti)))

AND

('Autopsy'/exp OR 'pathology'/exp OR pathology:lnk OR Autopsy:ti OR Autopsies:ti OR Pathology:ti)

AND

('epidemiology'/exp OR epidemiology:lnk OR Epidemiology:ti OR Prevalence:ti OR Patterns:ti OR Cases:ti)

Web of Science Search

OPTC OR (Thyroid AND (cancer OR cancers OR carcinoma OR carcinomas OR Adenocarcinoma OR Adenocarcinomas neoplasm OR neoplasms OR nodule OR nodules OR tumor OR tumour OR Tumors OR Tumours OR cyst OR cysts))

AND

Autopsy OR Autopsies OR Postmortem OR Post-mortem OR (Post AND mortem)

AND

Prevalence OR Prevalences OR Epidemiology OR Epidemiological OR Frequency

AND

Incidental OR Unsuspected OR Discovery OR Discoveries OR Findings OR Finding OR Occult OR Hidden

Web of Science Title Search (for Finding Articles Before 1975)

((Thyroid AND (cancer OR cancers OR carcinoma OR carcinomas OR Tumor OR Tumors OR Tumor OR Tumours OR Neoplasm OR Neoplasms)))

AND

(Autopsy OR Autopsies OR Pathology)

AND

(Epidemiology OR Prevalence OR Patterns OR Cases)

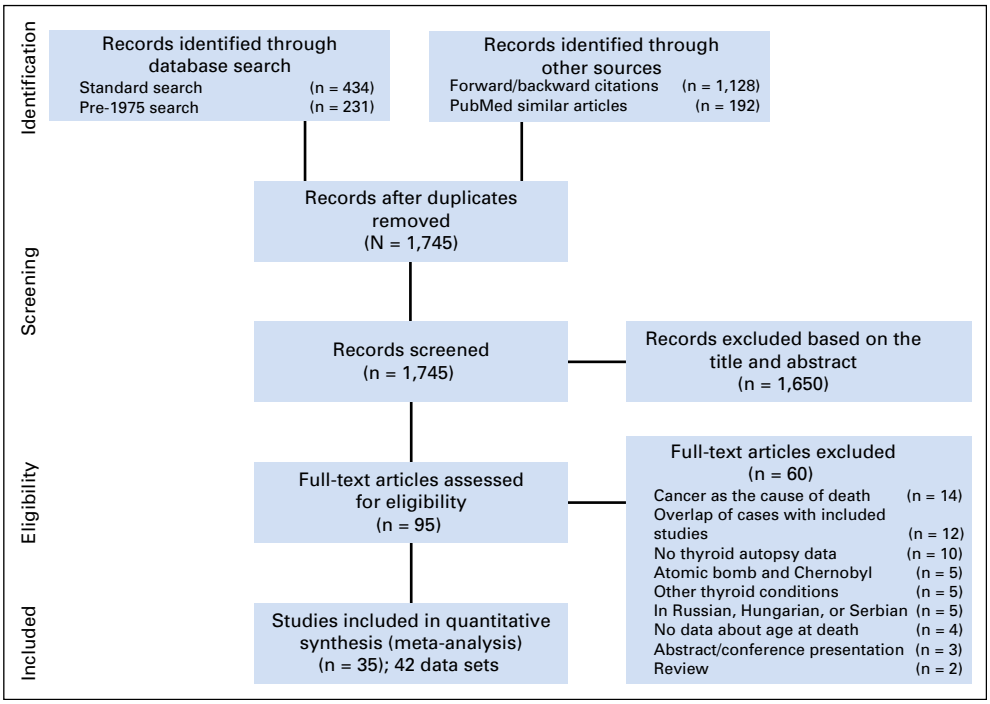

Fig A1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection for quantitative synthesis.

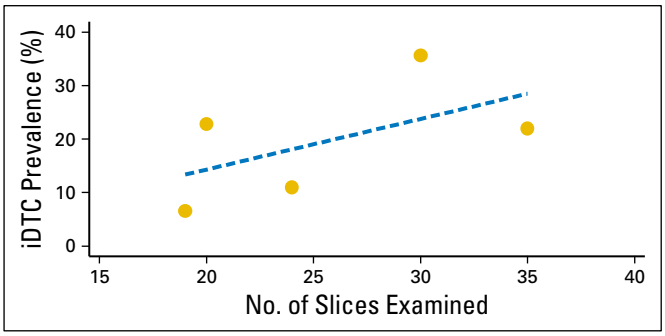

Fig A2. Scatterplot of the number of slices examined per gland and the prevalence of incidental differentiated thyroid cancer. There were six whole-gland examinations that reported slice numbers, and there seemed to be a general trend toward more slices having a higher prevalence. Five of the examinations have been plotted, with the sixth excluded because it reported 120 to 180 slices and was considered as an outlier.

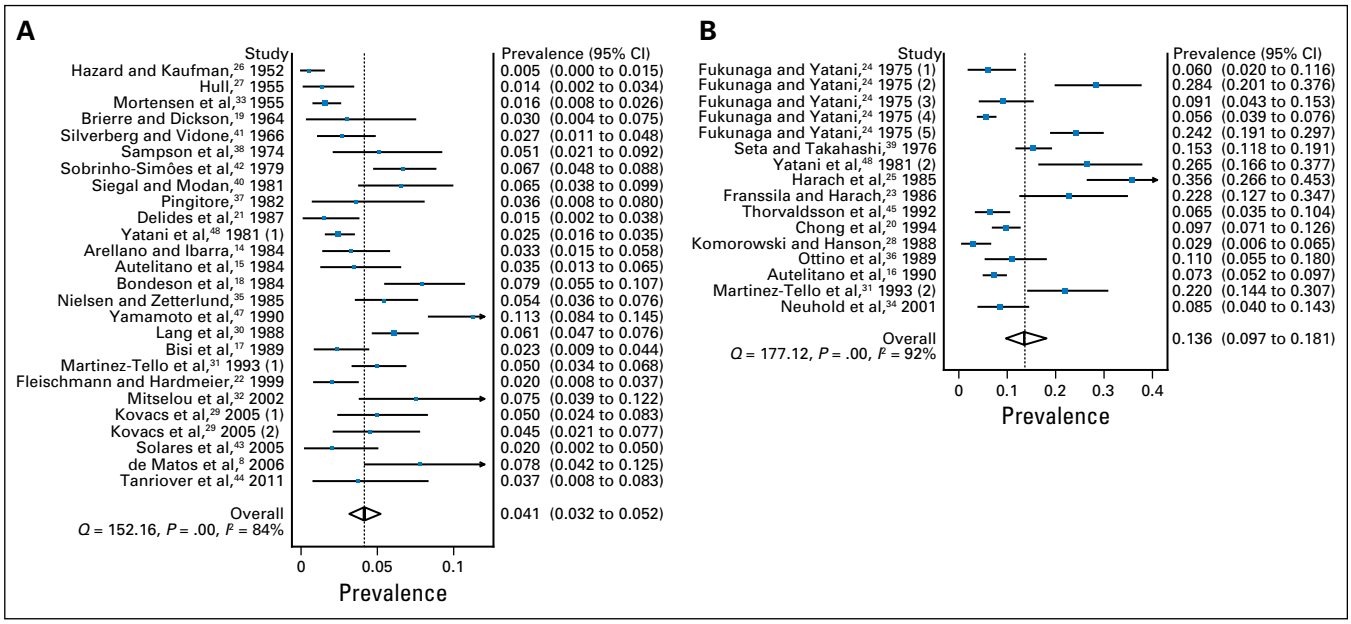

Fig A3. Forest plot for the prevalence of incidental differentiated thyroid cancer in the (A) partial and (B) whole thyroid examination subgroups, sorted by period when autopsies were conducted (random-effects model; note this represents a nonweighted synthesis because the weights are more or less equal).

Table A1. Quality Assessment of the Included Studies

Study and Year	External Validity				Internal Validity				
	Autopsy Service Received Participants Who Were a Close Representation of the National Population	Autopsy Service Did Not Deliberately Restrict Study Participants in Any Way (eg, age, sex) Except for Previous History of Thyroid Disease	Some Form of Random Selection Was Used or a Census (eg, consecutive participants) to Select the Participants	Nonavailability of Data Was < 20% Among the Selected Participants	Data Collected Directly From the Histopathology (not autopsy notes)	An Acceptable Case Definition Was Used for DTC (must have stated criteria)	Cancer Detection Method Was Reliable and Valid (ie, whole gland with fine slices was examined)	Same Mode of Thyroid Examination for All Participants in the Study	Numerator and Denominator Match the Reported Results
Arellano and Ibarra,[14] 1984	N	Y	Y	Y	Y	Y	N	Y	Y
Autelitano et al,[15] 1984	N	Y	Y	N	Y	N	N	Y	Y
Autelitano et al,[16] 1990	N	Y	Y	N	Y	N	Y	Y	Y
Bisi et al,[17] 1989	N	Y	Y	Y	Y	Y	N	Y	Y
Bondeson et al,[18] 1984	N	N	Y	Y	Y	Y	N	Y	Y
Brierre and Dickson,[19] 1964	N	Y	Y	Y	Y	N	N	Y	Y
Chong et al,[20] 1994	Y	Y	Y	Y	Y	N	Y	Y	Y
de Matos et al,[8] 2006	N	Y	Y	Y	Y	Y	N	Y	Y
Delides et al,[21] 1987	Y	N	N	Y	Y	Y	N	Y	Y
Fleischmann and Hardmeier,[22] 1999	N	N	Y	Y	Y	N	N	Y	Y
Franssila and Harach,[23] 1986	N	N	Y	Y	Y	Y	Y	Y	Y
Fukunaga and Yatani,[24] 1975	N	N	N	N	Y	Y	Y	Y	Y
Harach et al,[25] 1985	N	Y	Y	Y	Y	Y	Y	Y	Y
Hazard and Kaufman,[26] 1952	N	Y	Y	Y	Y	N	N	Y	Y
Hull,[27] 1955	N	Y	Y	Y	Y	Y	N	Y	Y
Komorowski and Hanson,[28] 1988	N	N	N	Y	Y	Y	Y	Y	Y
Kovacs et al,[29] 2005	Y	Y	Y	Y	Y	Y	N	Y	Y
Lang et al,[30] 1988	N	Y	Y	Y	Y	N	N	Y	Y
Martinez-Tello et al,[31] 1993	N	Y	N	Y	Y	Y	Y/N	N	Y
Mitselou et al,[32] 2002	N	Y	N	Y	Y	N	N	Y	Y
Mortensen et al,[33] 1955	N	Y	Y	Y	Y	N	N	Y	Y
Neuhold et al,[34] 2001	N	Y	Y	Y	Y	Y	Y	Y	Y
Nielsen and Zetterlund,[35] 1985	N	Y	Y	Y	Y	Y	N	Y	Y
Ottino et al,[36] 1989	N	Y	Y	Y	Y	Y	Y	Y	Y
Pingitore,[37] 1982	N	Y	Y	Y	Y	N	N	Y	Y
Sampson et al,[38] 1974	N	Y	Y	Y	Y	Y	N	Y	Y
Seta and Takahashi,[39] 1976	N	Y	Y	N	Y	N	Y	Y	Y
Siegal and Modan,[40] 1981	N	Y	Y	Y	Y	Y	N	Y	Y
Silverberg and Vidone,[41] 1966	N	Y	Y	N	Y	N	N	Y	Y
Sobrinho-Simoes et al,[42] 1979	N	N	Y	Y	Y	Y	N	Y	Y
Solares et al,[43] 2005	Y	N	Y	Y	Y	Y	N	Y	Y
Tanriover et al,[44] 2011	N	N	N	Y	Y	Y	N	Y	Y
Thorvaldsson et al,[45] 1992	Y	N	Y	Y	Y	Y	Y	Y	Y
Yamamoto et al,[47] 1990	N	Y	Y	Y	Y	Y	N	N	Y
Yatani et al,[48] 1981	N	Y	Y	Y	Y	Y	Y/N	N	Y

Abbreviations: DTC, differentiated thyroid cancer; N, no; Y, yes.

Table A2. Regression Model Investigating the Predictors of Logit Prevalence of Incidental Differentiated Thyroid Cancer (random-effects model weights)

	Univariable				Multivariable			
Independent Variable	OR	95% CI	*P*	R^2	OR	95% CI	*P*	R^2
Period when autopsies were conducted								
Before 1970	0.14	0.05 to 0.39	< .001	0.349	0.31	0.12 to 0.75	.012	0.592
1970-1975	1.00				1.00			
1976-1980	0.50	0.17 to 1.47	.198		0.83	0.33 to 2.08	.683	
1981-1985	0.85	0.37 to 1.97	.692		1.19	0.59 to 2.41	.617	
1986-1990	0.50	0.18 to 1.37	.169		0.58	0.25 to 1.34	.197	
After 1990	0.52	0.22 to 1.23	.133		0.95	0.45 to 2.02	.896	
Median age at death > 60 years	0.77	0.42 to 1.44	.403	0.018	1.17	0.74 to 1.85	.500	
Examined the whole thyroid	3.72	2.26 to 6.13	< .001	0.416	3.19	1.89 to 5.37	< .001	

NOTE. Weights are all equal and hence this represents a nonweighted analysis
Abbreviation: OR, odds ratio (relative odds of incidental differentiated thyroid cancer per unit increase in each predictor).