Lower Thyroid Cancer Mortality in Patients Detected by Screening: A Meta-Analysis

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Background: Thyroid cancer screening has contributed to the skyrocketing prevalence of thyroid cancer. However, the true benefit of thyroid cancer screening is not fully understood. This study aimed to evaluate the impact of screening on the clinical outcomes of thyroid cancer by comparing incidental thyroid cancer (ITC) with non-incidental thyroid cancer (NITC) through a meta-analysis.
Methods: PubMed and Embase were searched from inception to September 2022. We estimated and compared the prevalence of high-risk features (aggressive histology of thyroid cancer, extrathyroidal extension, metastasis to regional lymph nodes or distant organs, and advanced tumor-node-metastasis [TNM] stage), thyroid cancer-specific death, and recurrence in the ITC and NITC groups. We also calculated pooled risks and 95% confidence intervals (CIs) of the outcomes derived from these two groups.
Results: From 1,078 studies screened, 14 were included. In comparison to NITC, the ITC group had a lower incidence of aggressive histology (odds ratio [OR], 0.46; 95% CI, 0.31 to 0.7), smaller tumors (mean difference, −7.9 mm; 95% CI, −10.2 to −5.6), lymph node metastasis (OR, 0.64; 95% CI, 0.48 to 0.86), and distant metastasis (OR, 0.42; 95% CI, 0.23 to 0.77). The risks of recurrence and thyroid cancer-specific mortality were also lower in the ITC group (OR, 0.42; 95% CI, 0.25 to 0.71 and OR, 0.46; 95% CI, 0.28 to 0.74) than in the NITC group.
Conclusion: Our findings provide important evidence of a survival benefit from the early detection of thyroid cancer compared to symptomatic thyroid cancer.

Keywords: Thyroid neoplasms; Mass screening; Ultrasonography

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INTRODUCTION

The incidence of thyroid cancer has risen worldwide during the last three decades [1]. The observed increase in thyroid cancer may be attributable to the increase in incidentally detected subclinical microcarcinomas, rather than a real change in incidence [2,3]. The rapid increase in the incidence of thyroid cancer in the Korean population has been substantial, and a previous study argued that 90% of thyroid cancer cases in South Korean women between 2008 and 2012 were attributable to overdiagnosis, despite the non-inclusion of thyroid cancer screening in the national screening program [4]. In recent years, there has been intensified debate regarding the role of thyroid ultrasound screening in detecting thyroid cancer.

The importance of a cancer screening program relies on its proven net benefit. According to the United States Preventive Services Task Force (USPSTF), the benefit is assessed in terms of five aspects: the screening effectiveness or accuracy, the benefits or harms of screening, and the benefits and harms of treatment [5]. To evaluate the benefits of thyroid cancer screening, associated experts reviewed references in the literature and assessed the evidence; however, few studies dealing with the benefits and harms of thyroid cancer screening were found [6]. Furthermore, the most important question—whether screening leads to a reduced risk of thyroid cancer-specific mortality—could not be answered yet [7].

The necessity or uselessness of thyroid cancer screening has been investigated using outcomes derived from retrospective observational studies, but the extraordinarily good prognosis of thyroid cancer, the wide spectrum of definitions of thyroid incidentalomas, and the diverse sociomedical circumstances of the studied populations have yielded inconsistent results. This study aimed to evaluate the impact of screening on the outcomes of thyroid cancer through a comparison between the outcomes of incidental thyroid cancer (ITC) and non-incidental thyroid cancer (NITC). First, we estimated the prevalence of aggressive histologic features in ITC and NITC. Second, we compared the thyroid cancer-specific mortality and recurrence rates between ITC and NITC.

METHODS

For the purposes of this study, ITC was defined as an unexpected thyroid cancer incidentally detected by imaging methods (ultrasound, computed tomography [CT]/magnetic resonance imaging [MRI], and ^{18}F-fludeoxyglucose [FDG] positron emission tomography [PET]/CT) or an analysis of a surgical pathology specimen. NITC was defined as thyroid cancer that had been detected due to clinical signs or symptoms (palpable thyroid lump, voice change or difficulty in swallowing, abnormality on a physical examination by a physician, and so on). This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Supplemental Tables S1, S2) [8]. The flow diagram is shown in Fig. 1. The study protocol was registered in the Prospective Register of Systematic Reviews (number CRD42022365478).

Search strategy and selection criteria

We performed a systematic literature search through Ovid-MEDLINE, Embase, and the Cochrane Library for studies published since 2012. Studies prior to 2012 that were included in the 2012 National Evidence-based Healthcare Collaborating Agency (NECA) report [9] (*n*=3) and studies included in a recent systematic review [10] but not included in our search results (*n*=3) were manually added. The search started on August 29, 2022 and finished on September 7, 2022. Previous reviews were evaluated, and individual articles included therein were eligible for the present review. Search terms were created using the PICO structure as follows. The patients (P) were all individuals diagnosed with thyroid cancer. The intervention (I) was a thyroid imaging test with the intention of screening or another purpose. The comparator (C) was palpation of the thyroid gland or thyroid imaging test due to thyroid disease-related symptoms. The outcomes (O) comprised findings on clinicopathologic reports, including histology, tumor size, extrathyroidal extension (ETE), lymph node metastasis, distant metastasis, and tumor-node-metastasis (TNM) stage, as well as the recurrence and thyroid cancer-specific mortality rates. The study design was a case-control design. The search terms and electronic search strategy are summarized in Supplemental Table S3.

Duplicates were filtered through an automated function of the Endnote X9 citation manager and then manually searched. After removing duplicates, the titles and abstracts of the initial search results were screened, and non-English language publications were excluded. The full texts of the remaining articles were independently assessed by four investigators (S.M., Y.S.S., K.Y.J., and E.K.L.). Any discrepancies were resolved by discussion and consensus between the two researchers.

Data extraction and management

Data sets were extracted from each eligible study by four independent reviewers (S.M., Y.S.S., K.Y.J., and E.K.L.). The re-
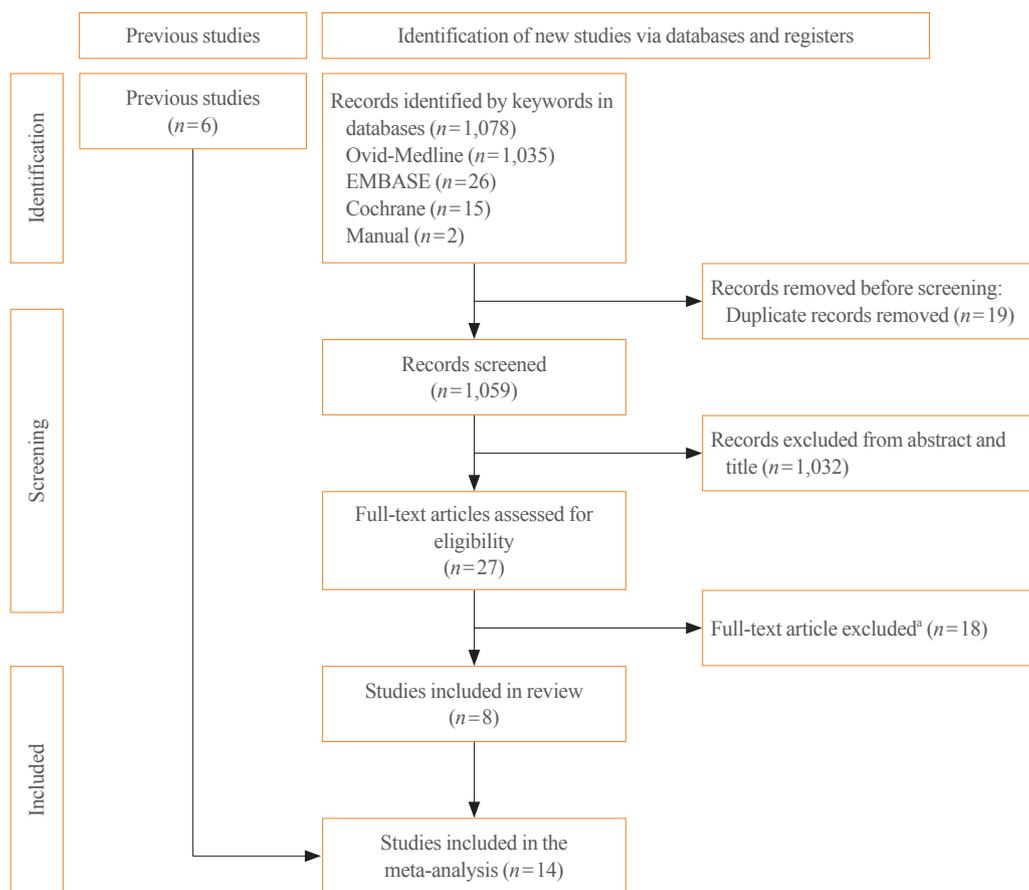
Fig. 1. Flow diagram of study selection. [a]Studies that did not report the mortality/recurrence or pathologic characteristics of incidental thyroid cancer were excluded. Additionally, studies of patients with thyroid cancer risk factors, such as nuclear accidents and radiation exposure, were excluded.

quired information included author name, publication year, study design, country, the total number of patients and controls, the mean age of subjects, the sex ratio, histology, clinicopathologic characteristics, recurrence, and thyroid cancer-specific mortality for both groups. Discrepancies between the reviewers regarding study eligibility were resolved by discussion.

Quality assessment and risk of bias
The quality of the included studies and the risk of bias were assessed using the Cochrane risk of bias criteria (Risk of Bias Assessment of Non-randomized Studies [RoBANS] version 2.0), which included: (1) selection of participants, (2) confounding variables, (3) measurement of intervention, (4) blinding for outcome assessment, (5) incomplete outcome data, and (6) selective outcome reporting; these parameters were independently assessed by four reviewers (S.M., Y.S.S., K.Y.J., and E.K.L.). Any discrepancies were resolved by discussion. The quality of the 14 included studies was evaluated using RoBANS version 2.0 (Fig. 2).

Statistical methods
Comparisons of pathologic staging, recurrence rate, and thyroid cancer mortality were expressed as risk ratios and 95% confidence intervals (CIs). The heterogeneity of the studies was tested using the Higgins I^2 statistic. I^2 values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively. If the I^2 value was ≥50%, a random-effect model was used; if I^2 was <50%, a fixed-effect model was used. Publication bias was investigated with the Egger test and by a visual evaluation of the funnel plot (Supplemental Fig. S1). A sensitivity analysis was conducted to determine the robustness of outcomes through repeated meta-analyses after excluding each study (Supplemental Fig. S2). Statistical analyses were performed with Comprehensive Meta-Analysis software version 3 (Biostat Inc., Englewood, NJ, USA) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). P values <0.05 were considered statistically significant.
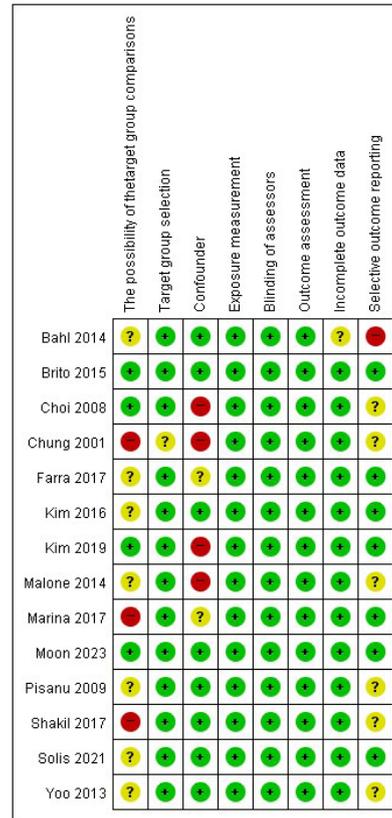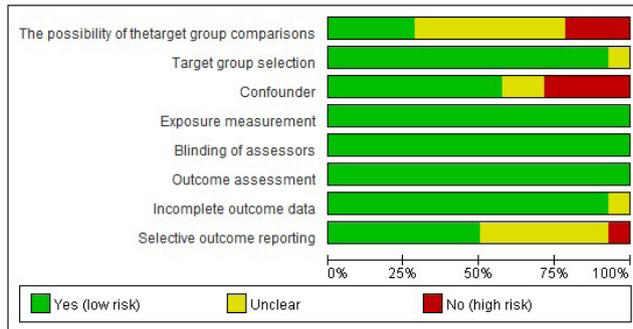
Fig. 2. Risk of bias assessment within studies using Risk of Bias Assessment of Non-randomized Studies (RoBANS).

RESULTS

Study characteristics

The literature search yielded 1,078 studies. After the exclusion of 19 duplicate studies and 1,032 studies that did not meet the inclusion criteria, 14 studies [11-24] were finally included in the meta-analysis (Fig. 1). The characteristics of each study are summarized in Table 1. A total of 9,432 participants with thyroid cancer were enrolled, of whom 5,091 (53.9%) were incidentally diagnosed with thyroid cancer. Among them, 13 studies reported clinicopathologic results and six studies provided longitudinal data for recurrence or thyroid cancer-specific mortality in ITC and NITC. Five studies were conducted in Korea, six in America, and three in Europe.

Risk of bias assessment

The results of the risk of bias assessment using RoBANS are summarized in Fig. 2. (1) Regarding participant selection, four of the 14 case-control studies had a low risk in selection of participants, while three studies had a high-risk of bias due to an inadequate control group. The remaining seven studies were un-

clear. (2) Eight studies had a low-risk of bias due to confounders, while four had high-risk. Two studies were unclear. (3) All studies had a low-risk of bias due to measurement of intervention. (4) All studies showed a low-risk of bias due to blinding for outcome assessment or inadequate outcome assessment. (5) Thirteen studies had a low-risk of bias due to incomplete outcome data, and one was unclear. (6) For selective outcome reporting, seven studies were at a low-risk of bias, one at high-risk, and six at unclear risk.

Comparison of pathologic characteristics between ITC and NITC

To compare the distribution of aggressive histology between ITC and NITC, 10 studies were analyzed. The incidence of aggressive histology of thyroid cancer (medullary thyroid cancer or anaplastic thyroid cancer) was significantly lower in ITC than in NITC (odds ratio [OR], 0.46; 95% CI, 0.31 to 0.7) (Fig. 3A). Heterogeneity was not significant among these studies ($I^2 = 21\%$).

Nine studies were included in the meta-analysis of tumor size in ITC and NITC. The mean difference between ITC and NITC

Table 1. Summary of Studies Included in the Meta-Analysis

Study	Country, recruitment years	Group[a]	Method of incidental detection	No. of patients	Mean age, yr	PTC, %	Mean tumor size, cm	Lymph node metastasis at diagnosis %	Distant metastasis at diagnosis %	No. of recurrence (%)	No. of thyroid cancer-specific death (%)	Overall follow-up, mo (range)
Moon et al. (2023) [21]	Korea, 1999, 2005, 2008	ITC	Imaging	2,655	46.8	95.3	1.0	42	0.6	NR	23 (0.9)	164
		NITC		1,784	47.0	92.7	1.7	46.8	1	NR	74 (4.1)	179
Solis-Pazmino et al. (2021) [22]	Ecuador, 2014–2017	ITC	Imaging, pathology	246	46.3	NR	2.23	43.8	NR	NR	NR	NR
		NITC		206	43	NR	3.57	53.7	NR	NR	NR	NR
Kim et al. (2019) [18]	Korea, 1994–2013	Before 2004	Imaging, pathology	33	44.2	54.5	3.5	51.5	100	NR	16 (48.5)	72 (0–276)
		ITC		13					100	NR	6 (46.2)	
		NITC[b]		20					100	NR	10 (50.0)	
		After 2004		94	50.7	52.1	3.7	64.5	100	NR	29 (30.9)	72 (0–276)
		ITC		64					100	NR	11 (17.2)	
		NITC[b]		30					100	NR	18 (60.0)	
Shakil et al. (2017) [11]	USA, 2005–2014	ITC NITC	Imaging, pathology	46	53.0	95.5	NR	13	NR	3 (6.7)[d]	NR	27.0 (6–55)
				126	45.3	94.4	NR	29.4	NR	25 (20.8)[d]	NR	26.5 (6–58)
Marina et al. (2017) [13]	Italy, 1998–2015	ITC NITC	Imaging	99	50.0	92.9	1.3	13.3	1.0	4 (4)	1 (1.0)	67.2 (32.4–114)
				62	44.0	87.1	2.5	23.3	6.5	7 (11)	1 (1.6)	67.2 (32.4–114)
Farra et al. (2017) [23]	USA, 2010–2016	ITC NITC	Imaging	65	54	91	NR	47	NR	NR	NR	NR
				401	50	92	NR	33	NR	NR	NR	NR
Kim et al. (2016) [12]	Korea, 2006–2009	ITC	Imaging	1,259	55.0	100	0.9	40.2	0	41 (3.3)	0	95.0 (24–119)
		NITC		160	55.0	100	1.1	52.5	1.9	17 (10.6)	2 (1.3)	96.0 (24–118)
Brito et al. (2015) [17]	USA, 2000–2012	1935–1999	Imaging, pathology									
		ITC		59	52.3	89.8	0.98	NR	NR	NR	NR	NR
		NITC		203	44.2	79.8	2.3	NR	NR	NR	NR	NR
		2000–2012										
		ITC		113	49.6	95.6	1.3	NR	NR	NR	NR	NR
		NITC		100	42.7	91	2.3	NR	NR	NR	NR	NR
Malone et al. (2014) [15]	USA, 2007–2010	ITC	Imaging	184	51	NR	1.6	39	NR	NR	NR	NR
		NITC		218	46	NR	2.1	58	NR	NR	NR	NR
Bahl et al. (2014) [16]	USA, 2003–2012	ITC	Imaging	101	57	84.2	1.8	24.7	0	NR	NR	NR
		NITC		485	46	82.7	2.2	32.4	1.0	NR	NR	NR
Yoo et al. (2013) [24]	USA, 2008–2009	ITC	Imaging	31	56.4	83.9	2.15	22.6	0	NR	NR	NR
		NITC		207	41.8	87.9	2.11	20.8	0.5	NR	NR	NR
Pisanu et al. (2009) [14]	Italy, 1998–2007	ITC	Pathology	73	52.5	100	0.4	1.4	NR	0	0	65.2
		NITC		76	49.5	100	0.7	34.1	NR	3 (3.9)	0	65.2
Choi et al. (2008) [20]	Korea, 2006–2008	ITC	Imaging	46	51.1	93.5	0.6	28.3	NR	NR	NR	NR
		NITC		157	48.1	97.5	1.6	29.9	NR	NR	NR	NR

(Continued to the next page)

Table 1. Continued

Study	Country, recruitment years	Group[a]	Method of incidental detection	No. of patients	Mean age, yr	PTC, %	Mean tumor size, cm	Lymph node metastasis at diagnosis %	Distant metastasis at diagnosis %	No. of recurrence (%)	No. of thyroid cancer-specific death (%)	Overall follow-up, mo (range)
Chung et al. (2001) [19]	Korea, 1997–1998	ITC[c]	Imaging	37	46.5	97.3	1.0	40.5	NR	NR	NR	NR
		NITC		106	45.3	92.5	1.9	78.3	NR	NR	NR	NR

PTC, papillary thyroid carcinoma; ITC, incidental thyroid cancer; NR, not reported; NITC, non-incidental thyroid cancer.
[a]Incidental thyroid cancer was defined as an unexpected thyroid cancer incidentally detected by imaging methods (ultrasound, computed tomography/magnetic resonance imaging, and 18-fludeoxyglucose positron emission tomography/computed tomography) or analysis of a surgical pathology specimen. Non-incidental thyroid cancer was defined as thyroid cancer that had been detected due to clinical signs or symptoms (palpable thyroid lump, voice change or difficulty in swallowing, abnormality on physical examination by a physician, and so on); [b]The enrolled patients had thyroid cancer with initial distant metastasis. The NITC group included both patients with local symptoms and patients with systemic symptoms; [c]Women who were scheduled to undergo either a breast cancer screening or a follow-up examination for breast cancer were screened for thyroid cancer; [d]Recurrence or residual.

was −7.9 mm (95% CI, −10.2 to −5.6), and I^2 was 94%, indicating significant heterogeneity (Fig. 3B). The funnel plot was symmetrical, and publication bias was not detected (Egger test, $P=0.315$) (Supplemental Fig. S1). In the sensitivity analysis, the significance of the results did not change even after each study was removed, and no outliers were observed (Supplemental Fig. S2).

To compare the proportion of ETE in ITC and NITC, seven studies were included. The ITC group had a lower risk of ETE (OR, 0.88; 95% CI, 0.79 to 0.98) (Fig. 3C). Heterogeneity was not significant among these studies ($I^2=0\%$); however, the funnel plot was asymmetrical and significant publication bias was detected (Egger test, $P=0.019$). The trim-and-fill method was conducted to adjust for publication bias and showed that statistical significance disappeared after adding three estimated missing studies (OR, 0.91; 95% CI, 0.82 to 1.01) (Supplemental Fig. S1). The sensitivity analysis showed robust results from repeated analyses after excluding each study (Supplemental Fig. S2).

Twelve studies were included in the meta-analysis of lymph node metastasis. The ITC group had a lower risk of lymph node metastasis (OR, 0.64; 95% CI, 0.48 to 0.86) compared to the NITC group, and I^2 was 74%, indicating significant heterogeneity (Fig. 3D). The funnel plot was symmetrical, and publication bias was not significant (Egger test, $P=0.134$) (Supplemental Fig. S1). In the sensitivity analysis, the significance of the results did not change even after each study was removed, and no outliers were observed (Supplemental Fig. S2). In addition, lymph node metastasis was divided into central and lateral metastasis, and a meta-analysis was performed of the four studies that contained this information. The risk of central lymph node metastasis was not significantly different between the two

groups (OR, 0.69; 95% CI, 0.38 to 1.24), but that of lateral lymph node metastasis was lower in the ITC group (OR, 0.31; 95% CI, 0.21 to 0.44) (Supplemental Fig. S3).

Five studies were included in the meta-analysis of distant metastasis. The ITC group had a lower risk of distant metastasis (OR, 0.42; 95% CI, 0.23 to 0.77) than the NITC group, without significant heterogeneity ($I^2=43\%$) (Fig. 3E).

Seven studies were included in the meta-analysis of TNM stage. The OR for advanced TNM stage (III to IV) was not significantly higher in the ITC group than in the NITC group, and there was significant heterogeneity (OR, 0.99; 95% CI, 0.73 to 1.33; $I^2=59\%$) (Fig. 3F).

Mortality and recurrence rate in ITC and NITC
Four studies were included in the meta-analysis of the recurrence rate in the ITC and NITC groups. The overall recurrence rate was 3.4% in the ITC group, versus 11.4% in the NITC group. In comparison with the NITC group, the ITC group had a significantly lower risk of recurrence (OR, 0.42; 95% CI, 0.25 to 0.71) (Fig. 4). Although no significant heterogeneity was found among these studies ($I^2=0\%$), the funnel plot was asymmetrical, and significant publication bias was detected (Egger's test, $P=0.01$). The trim-and-fill method was conducted to adjust for publication bias and showed that statistical significance remained after adding two estimated missing studies (OR, 0.46; 95% CI, 0.28 to 0.74) (Supplemental Fig. S1). The sensitivity analysis showed robust results from repeated analyses after excluding each study (Supplemental Fig. S2).

Five studies with eight datasets were included in the meta-analysis of thyroid cancer-specific mortality. In comparison with the NITC group, the ITC group had a lower risk of thyroid
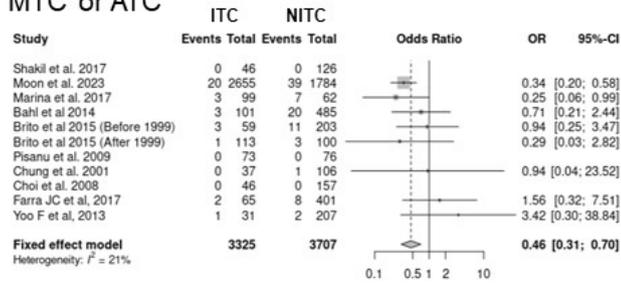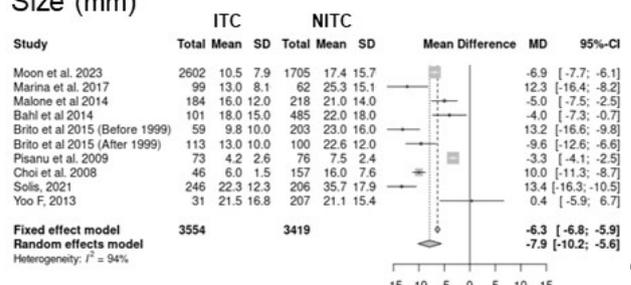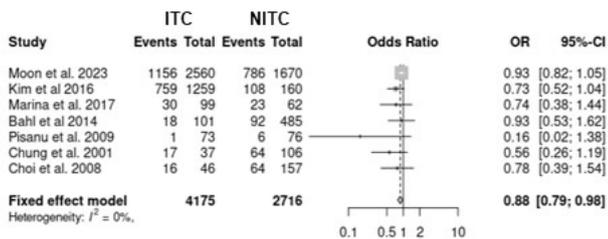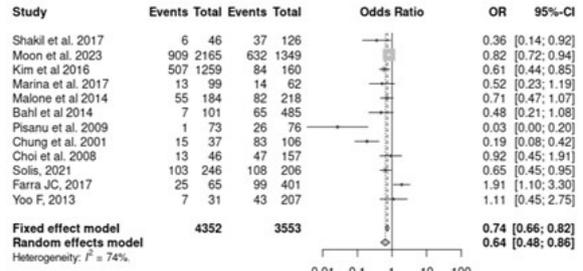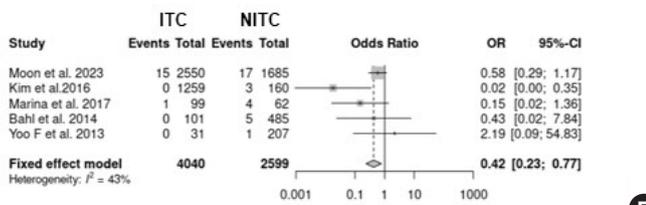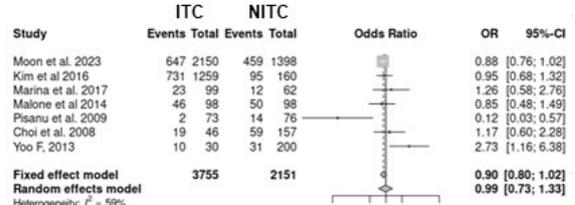
Fig. 3. Results of the meta-analysis for pathologic characteristics between the incidental thyroid cancer (ITC) and non-incidental thyroid cancer (NITC) groups. (A) Medullary thyroid cancer (MTC) or anaplastic thyroid cancer (ATC), (B) size, (C) extrathyroidal extension (ETE), (D) lymph node metastasis (LNM), (E) distant metastasis, and (F) advanced stage III to IV. OR, odds ratio; CI, confidence interval; SD, standard deviation; MD, mean difference.
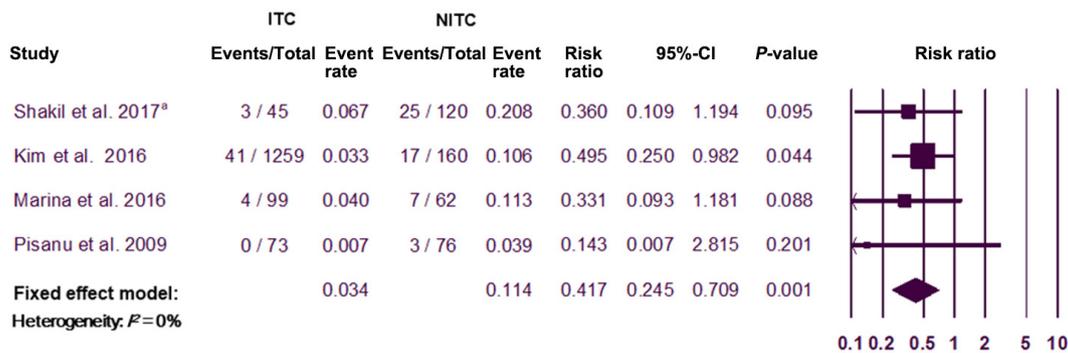
Fig. 4. Results of the meta-analysis for recurrence between the incidental thyroid cancer (ITC) and non-incidental thyroid cancer (NITC) groups. CI, confidence interval. [a]Recurrence and residual cancer.

cancer-specific mortality (OR, 0.28; 95% CI, 0.18 to 0.43) (Fig. 5). Heterogeneity was not significant among these studies ($I^2=0\%$). The funnel plot analysis and the Egger test revealed no significant publication bias ($P=0.503$) (Supplemental Fig.

S1). The sensitivity analysis showed robust results from repeated analyses after excluding each study (Supplemental Fig. 2).

Regarding postoperative complications, only two articles were included, which was insufficient to perform a meta-analysis. A
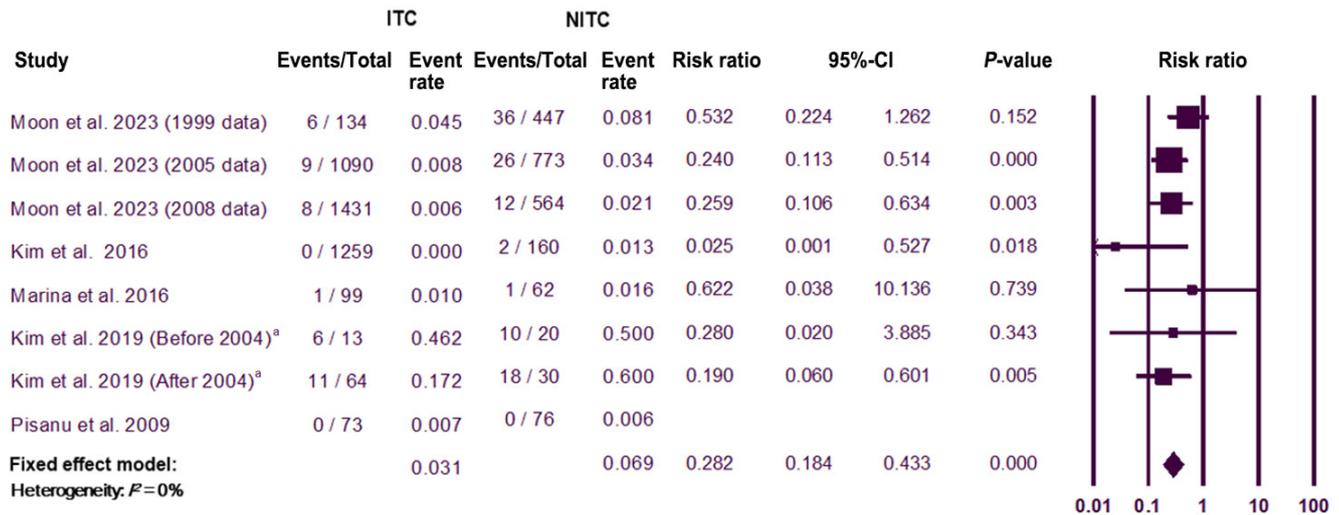
Fig. 5. Results of the meta-analysis for mortality between the incidental thyroid cancer (ITC) and non-incidental thyroid cancer (NITC) groups. CI, confidence interval. [a]Thyroid cancer with distant metastasis.

summary derived from systematic reviews is presented in Supplemental Table S4, revealing no significant differences in the prevalence of postoperative complications between ITC and NITC.

DISCUSSION

This meta-analysis demonstrated that ITC patients had lower risks of unfavorable clinicopathologic characteristics, such as aggressive histology, large tumor size, ETE, lymph node metastasis, distant metastasis, and advanced TNM stage, than NITC patients. Furthermore, in ITC patients, the risks of recurrence and mortality were significantly lower than in NITC patients, confirming the effectiveness and benefits of thyroid cancer screening.

In the 2017 USPSTF report [5], there was insufficient evidence to conclude whether thyroid cancer screening for adults leads to a reduced risk of thyroid cancer-specific morbidity, mortality, and/or all-cause mortality. Recently, Chooi et al. [10] reported a systematic review on the prognosis of thyroid incidentalomas. Although a meta-analysis could not be performed for the prognosis due to heterogeneity in the inclusion criteria, prognosis marker assessments, and follow-up duration, they reviewed 14 studies on the prognosis or various prognostic markers, such as histological characteristics and cancer staging in ITC and NITC. Four studies on recurrence—not mortality—were included to compare the thyroid cancer prognosis of ITC and NITC. All included studies showed a lower risk of recurrence in ITC than in NITC [11,12,22,25], although some studies did not

reach statistical significance. Meanwhile, in our study, we added more studies through a thorough systematic review and performed a meta-analysis with recent studies, including the National Epidemiological Survey of Thyroid cancer (NEST) [21].

We analyzed the NEST study [21] as three separate populations according to the time period, because the study randomly sampled Korean thyroid cancer patients at three time points (1999, 2005, and 2008) [26]. As Kim et al. [18] described previously, the early detection of thyroid cancer by ultrasound in Korea started in earnest in 2004 [27]. Moreover, the incidence of thyroid cancer increased dramatically in 2009 [28]. Therefore, to reflect heterogeneity in the clinicopathological features of thyroid cancer over time, each population from these three time points was analyzed as an independent group in this study.

The increased incidence of thyroid cancer coincided with the introduction and widespread use of imaging modalities such as ultrasound, and the improved sensitivity of diagnostic tools since the 2000s [4,29]. Despite the rising incidence of thyroid cancer, mortality from thyroid cancer remained stable, which has been interpreted as reflecting overdiagnosis [30,31]. However, according to a recent study of Surveillance, Epidemiology, and End Results (SEER) data, thyroid cancer incidence decreased during 2014 to 2018, but incidence-based mortality continued to increase [32]. Given the results of our study, which showed that thyroid cancer screening can reduce mortality, overdiagnosis alone might not be sufficient to explain the increased incidence of thyroid cancer.

The current meta-analysis revealed that patients with ITC had

more indolent tumor behaviors and better prognoses, suggesting that early detection improves the clinical outcomes of thyroid cancer. For patients with locally advanced or high-risk thyroid cancer, early diagnosis and treatment can prevent serious disease progression [33]. Therefore, to solve the issues of overdiagnosis and overtreatment caused by thyroid cancer screening, it is necessary to minimize the harms of screening and treatment while maintaining the benefits of screening. Moreover, it is critical to develop appropriate diagnosis and management guidelines for incidentally detected thyroid nodules. In this context, the Korean Society of Thyroid Radiology revised the indications for fine-needle aspiration to be stricter [34,35] to reduce unnecessary diagnostic tests. In addition, active surveillance for low-risk thyroid cancers has been introduced [36] and large-scale multicenter prospective clinical studies are currently being conducted in Korea, thereby minimizing the risk of unnecessary surgery [37,38].

Our study has several strengths. First, this is the first meta-analysis to comprehensively compare the clinicopathological characteristics and prognosis of ITC and NITC. Second, we demonstrated that ITC had better thyroid cancer-specific survival. The ultimate goal of cancer screening, which generally aims to detect cancer at an early stage rather than to prevent cancer occurrence, is to reduce cancer-related mortality [39,40]. Thus, it is meaningful that this study revealed a survival benefit, reflecting the purpose of cancer screening. However, this study has certain limitations. First, the spectrum of ITC was wide, including incidentalomas detected by various imaging modalities (ultrasound, carotid Doppler, neck CT/MRI, and ^{18}F-FDG PET/CT) or occult tumors found in the surgical pathology specimens of benign tumors. Furthermore, NITC covered various symptoms or signs, mostly neck symptoms, but one study [18] included patients with systemic symptoms due to distant metastasis in the NITC category. Second, no prospective randomized clinical trials were included in the meta-analysis, and retrospective cohort studies harbor a high probability of bias, as is widely recognized [41,42]. Nevertheless, the included studies were assessed as having a low-risk of bias, considering the large number of participants and well-controlled design.

In conclusion, our findings provide important evidence for a survival benefit from the early detection of thyroid cancer compared to symptomatic thyroid cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

Conception or design: E.K.L., Y.J.P. Acquisition, analysis, or interpretation of data: S.M., Y.S.S., K.Y.J., E.K.L. Drafting the work or revising: S.M., Y.S.S., K.Y.J., E.K.L. Final approval of the manuscript: S.M., Y.S.S., K.Y.J., E.K.L., Y.J.P.

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