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

Shinje Moon1,*, Young Shin Song2,*, Kyong Yeun Jung3, Eun Kyung Lee4, Young Joo Park5,6

1Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul; 2Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam; 3Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University, Seoul; 4Department of Internal Medicine, Center for Thyroid Cancer, National Cancer Center, Goyang; 5Department of Internal Medicine, Seoul National University College of Medicine; 6Department of Molecular Medicine and Biopharmaceutical Sciences Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea

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
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-fluodeoxyglucose [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-
Lower Mortality by TC Screening: A Meta-Analysis

Fig. 1. Flow diagram of study selection. *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.

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 $\geq 50\%$, 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.
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 unclear. (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

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

(Continued to the next page)
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...
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. 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. *Recurrence and residual cancer.
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 of 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 18F-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

This study was supported by the Korean Thyroid Association, research funding from the National Cancer Center (Grant Number 2210521-2 and 2112570-3), and a grant from the National Research Foundation (NRF) of Korea (NRF-2020R1C1C1003924).

We acknowledge and thank Miyoung Choi (National Evidence-based Healthcare Collaborating Agency, Division of Health Technology Assessment Research) and Chang Hee Cho (The Korean Society of Radiology), who contributed to searching and interpreting the evidence.

AUTHOR CONTRIBUTIONS


ORCID

Shinje Moon https://orcid.org/0000-0003-3298-3630
Young Shin Song https://orcid.org/0000-0003-4603-1999
Kyong Yeun Jung https://orcid.org/0000-0003-4029-6312
Eun Kyung Lee https://orcid.org/0000-0003-0098-0873

REFERENCES


15. Malone MK, Zaggag J, Ogilvie JB, Patel KN, Heller KS. Thyroid cancers detected by imaging are not necessarily small or early stage. Thyroid 2014;24:314-8.


