Screening as a cause of the thyroid cancer epidemic in Korea: Evidence from a nationwide study

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Screening as a cause of the thyroid cancer epidemic in Korea: Evidence from a nationwide study

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ABSTRACT

Objectives: Thyroid cancer incidence has been rapidly increasing, resulting in an unprecedented epidemic of thyroid cancer in Korea. Overdiagnosis is considered to be the most plausible explanation; however, some sceptics remain unconvinced.

Design: We reviewed the medical records of nationally representative samples of thyroid cancer patients diagnosed in 1999, 2005, and 2008.

Setting: From the nationwide cancer registry of Korea, sample cases were randomly selected using a systematic sampling method after stratification by region.

Participants: A total of 5,796 thyroid cancer patients were included in this study (891 in 1999; 2,355 in 2005; and 2,550 in 2008).

Main Outcome Measures: The age-standardized incidence of thyroid cancer was estimated, and the changes in incidence between 1999 and 2008 were examined according to the route of tumour detection.

Results: Between 1999 and 2008, there was a 6.4-fold increase in thyroid cancer incidence, from 6.3 to 41.3 per 100,000 people. Overall, 94.4% of the increase was due to thyroid cancer <20 mm in size, mainly due to screening. Even among clinically detected cases, the great majority (99.9%) of the increase was due to increased detection of tumours <20 mm in size. According to SEER summary staging, almost all (97.1%) of the increase in the incidence of thyroid cancer was due to detection of localized (35.5%) and regional stage tumours (61.6%).

Conclusions: The current epidemic of thyroid cancer in Korea is due to an increase in the detection of small-sized tumours, most likely resulting from the overdetection, which

warrants drastic change in thyroid cancer screening practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- An increase in the incidence of thyroid cancer with little change in mortality rate has been observed in most countries.
- Increased incidence of thyroid cancer is mainly due to detection of small-sized well-differentiated thyroid carcinoma.
- Ultrasound examination is a sensitive screening tool that detects very small-sized thyroid nodules, as well as indolent large tumours.

WHAT THIS STUDY ADDS

- This is the nationwide study that correlates the increase in thyroid cancer incidence with the routes of tumour detection, directly extracted by a review of medical records.
- The great majority of increased thyroid cancer was attributed to the increase in the incidence of small-sized tumours, detected mainly by screening.
- Thyroid cancer screening can detect notably small-sized tumours, but also clinically indolent asymptomatic tumours with local extension and lymph node involvement.
- Our study provides clear evidence that the increase in the incidence of thyroid cancer in Korea was mainly due to overdiagnosis.

INTRODUCTION

Over the past decades, incidence of thyroid cancer has increased steadily and consistently in most developed countries.[1] The most notable increase was reported in Korea, where the incidence of thyroid cancer increased steeply more than 7 times from 6.3 per 100,000 in 1999 to 47.5 per 100,000 in 2009.[2] During that short time span, thyroid cancer has become the most frequently diagnosed cancer for women since 2004, and for men and women combined in 2009.[2, 3] In fact, Korea has the highest incidence rate of thyroid cancer in the world.[4] This raised great public concern about its potential cause and also the financial burden to the national health care system. The economic burden of thyroid cancer in Korea increased about 7 times from $257 million in 2000 to $1,724 million in 2010.[5] In the United States, the incidence of thyroid cancer is expected to surpass the incidence of colorectal cancer and become the fourth most common cancer by 2030.[6] As such, the estimated economic burden of well-differentiated thyroid cancer in the United States was expected to increase to over $3.5 billion in 2030 from over $1.6 billion in 2013.[7]

Regarding the cause of this unprecedented epidemic of thyroid cancer in Korea and around the world, overdiagnosis is considered the most plausible.[8, 9] First of all, the thyroid cancer mortality rate remained stable for several decades,[1, 2] despite the fact that there was no dramatic improvement in thyroid cancer therapy, as exemplified by the trend in thyroid cancer incidence and mortality in Korea (Figure 1) [10]. Further evidence demonstrates a close correlation between the thyroid cancer incidence rate and thyroid cancer screening by ultrasonography. In Korea, Ahn et al. reported a good correlation between the thyroid cancer incidence rate of 2009 and the thyroid cancer screening rates of 2008 and 2009.[8] Also, using an age-period-cohort analysis tool, Oh et al. reported prominent period effects on the

incidence of thyroid cancer in Korea,[11] which suggests cancer screening as a cause of the Korean thyroid cancer epidemic.[11]

However, some investigators remain unconvinced and have raised questions about the idea of overdiagnosis being the main cause of the current thyroid cancer epidemic.[12-14] In a registry-based cancer study,[12] investigators observed that the incidence of not only small-sized but also large-sized thyroid cancers significantly increased from 1983 to 2006 in the United States, as well as the incidence of both intra-thyroidal and extra-thyroidal cancers.[12] They claimed that improved detection does not fully explain the rising incidence of thyroid cancer.[12] In Australia, the increase in thyroid cancer was observed across sociodemographic characteristics in both early and advanced stages.[13] Furthermore, there were no significant differences in tumour size, invasion, lymph node involvement, or distant metastasis between the incidentally diagnosed and the non-incidentally diagnosed thyroid cancers in the United States.[14]

To better elucidate the cause of the steep increase in the incidence of thyroid cancer in Korea and other countries, we need more sophisticated epidemiologic studies. Here, we report the nationwide epidemiologic study results that provide further supporting evidence for increased screening as the main cause of the thyroid cancer epidemic in Korea by demonstrating the changes in thyroid cancer incidence over time according to the routes of tumour detection.

METHODS

Data sources

To investigate the cause of the rapidly rising incidence of thyroid cancer in Korea, in 2010 the Korea Central Cancer Registry (KCCR) conducted the National Epidemiologic Survey of Thyroid cancer (NEST), which was designed to collect a nationally representative sample of thyroid cancer patients diagnosed in the years 1999, 2005, and 2008. The detailed study methods have been described previously,[15] and the dataset is available to the public (http://kccrsurvey.cancer.go.kr/index.do).

Briefly, from the registry database of all thyroid cancer patients registered (3,342 in 1999; 12,659 in 2005; and 26,890 in 2008), we selected the study population using a two-stage sampling method. We first selected 24 hospitals using a probability proportional to size method stratified by region in a given year. Then, sample cases were randomly selected within each hospital using a systematic sampling method. Because the number of cases diagnosed in 1999 and 2005 was smaller than that in 2008, different sampling proportions were applied for each study year (33% in 1999, 22% in 2005, and 11% in 2008).

Using a pre-designed data collection form, we collected basic demographic variables, such as age and sex, and tumour-related variables, such as tumour size, histologic type, status of nodal and distant metastases, tumour stage (AJCC 6th stage,[16] SEER summary stage[17]), and routes of tumour detection, through a review of medical records. The SEER summary stage grouped thyroid cancers in 3 major categories – localized stage, regional stage and distant stage and the regional stage includes 1) regional by direct extension only, 2) regional lymph nodes involved only and 3) regional by both direct extension and regional lymph node involved.[17] In our study, the regional stage was further categorized into 5 categories by the lymph node involvement status (yes, no) and the degree of extrathyroidal extension (none, minimal, gross) [16, 18]. The route of tumour detection was classified into three categories as

recorded in medical records: screen detection (detected by cancer screening as recorded in medical records), clinical detection (detected by symptom associated with thyroid disease, including thyroid cancer), and unspecified (or unknown). The histological subtypes of thyroid cancer were classified according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3)[19] as papillary carcinoma, medullary carcinoma, follicular carcinoma, anaplastic carcinoma, and others.[20]

Out of 6,846 patients selected at the first stage (1,103 patients in 1999, 2,785 patients in 2005, and 2,958 patients in 2008), 1,050 cases were excluded from the final analysis, including 960 cases owing to refusal of the hospital to disclose medical records and 90 cases owing to inadequate data available on medical records reviews. A total of 5,796 patients were included in this study (891 in 1999, 2,355 in 2005, and 2,550 in 2008). Ethics approval for the research protocol was approved by the institutional review board (IRB No: NCC2015-0152).

Statistical analysis

The age-standardized incidence rate of thyroid cancer was estimated for each route of tumour detection (screen detection vs. clinical detection vs. unspecified) by tumour size, SEER summary stage, and AJCC 6th stage for the years 1999, 2005, and 2008, separately. To estimate the age-standardized incidence of thyroid cancer, we calculated a weighted frequency for each 5-year age group for each study year, and then divided the weighted frequency by the corresponding mid-year population. The age-standardized incidence rate was estimated using the weights for the proportions of corresponding 5-year age groups of

the world standard of Segi as standard population. The 95% confidence interval was calculated per 100,000 people using the binomial method. We also calculated the absolute difference and relative risk of the incidence rate of thyroid cancer according to the route of tumour detection by tumour size, SEER summary stage, and AJCC 6th stage between 1999 and 2008.

The baseline characteristics were presented as means ± standard deviation or number (percentage) by year of detection. The one-way analysis of variance (ANOVA) was used to compare the differences of continuous variables by year and chi-squared test was used to compare the differences of categorical variables by year. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata 12.0 (StataCorp LP, TX, U.S.A.) and SAS 9.3 (SAS Institute, Cary, NC, U.S.A.).

RESULTS

Characteristics of the study population

The characteristics of the study population are shown for each study year in Table 1. Overall, 84.5% of study participants (N = 5,796) were women, and the mean (± SD) age of study was 46.9 ± 12.4 years. The most common histologic type (94.9%) was papillary carcinoma. Most notably, the tumour size of thyroid cancer steadily decreased from 1999 to 2008. With regard to the routes of tumour detection, the proportion of screen detection increased from 15.0% in 1999 to 56.1% in 2008, whereas the proportion of clinical detection decreased from 50.2% in 1999 to 22.1% in 2008. In terms of SEER summary staging, the proportion of regional stage thyroid cancer increased from 47.7% in 1999 to 59.1% in 2008,

whereas the proportion of distant stage thyroid cancer decreased from 5.4% in 1999 to 1.3% in 2008.

Changes in tumour size over time by routes of tumour detection

Overall, the median tumour size of thyroid cancer decreased from 18 mm in 1999 to 8 mm in 2008, and the size of screen-detected tumours was smaller than that of clinically detected tumours (Figure 2, Supplementary Table 1). For the clinically detected tumours, the median tumour size of thyroid cancer decreased from 20 mm in 1999 to 9 mm in 2008. For the screen-detected tumours, the median tumour size of thyroid cancer decreased from 14.5 mm in 1999 to 8 mm in 2008.

Regional lymph node involvement by tumour size and routes of tumour detection

The regional lymph node involvement status by tumour size according to the routes of tumour detection is shown in Supplementary Table 2. Overall, even the small tumours <10 mm in size were found to have regional lymph node involvement in more than one-fifth of the cases: 22.8% in 1999, 24.2% in 2005, and 28.4% in 2008. As the tumour size increased, the proportion of cases with positive regional lymph node involvement increased to 34.1%, 48.8%, and 44.2% in 1999; 40.4%, 53.4%, and 51.4% in 2005; and 48.8%, 58.7%, and 56.5% in 2008 for tumours 10–20 mm, 20–30 mm, and ≥30 mm in size, respectively.

Change in the thyroid cancer incidence over time by tumour size

Changes in estimated thyroid cancer incidence according to tumour size for each route of tumour detection from 1999 to 2008 are shown in Table 2 and Figure 3A. The most remarkable change is the incidence rate of small thyroid cancer <10 mm in size detected by cancer screening, which increased steeply from 0.27 per 100,000 in 1999 to 15.00 per 100,000 in 2008 with an absolute difference (AD) of 14.73 per 100,000. The incidence rate of small thyroid cancer <10 mm in size detected by clinical detection showed only a modest increase from 0.49 in 1999 to 4.88 in 2008 (AD of 4.39 per 100,000). There was also a small fractional increase in the incidence rate of thyroid cancer of large tumours ≥30 mm in size detected by cancer screening (AD of 0.44 per 100,000), with no significant increase in the incidence rate of such tumours diagnosed by clinical detection (AD of 0.00 per 100,000). About 94.4% of the incidence of thyroid cancer was attributed to the increase in the incidence rate of thyroid tumours <20 mm in size. In screen-detected cases, more than 94% of the increase in thyroid cancer was attributed to the increase of detected tumours <20 mm in size. Among clinically detected cases, the great majority (99.9%) of the increase in thyroid cancer was attributed to the increase of detected tumours <20 mm in size.

Figure 3A shows the ADs in the magnitude of the increase in thyroid cancer incidence by tumour size according to the route of tumour detection between 1999 and 2008, as well as between 2005 and 2008. It is striking to note that about 60% of the absolute increase in thyroid cancer incidence rates between 1999 and 2008 occurred over a short period of time between 2005 and 2008, especially for screen-detected cases with tumours <20 mm in size.

Change in the thyroid cancer incidence over time by SEER summary stage

Changes in estimated thyroid cancer incidence are shown according to the SEER summary stage in Table 2 & Figure 3B. Overall, there was 8.1 fold increase in regional stage tumours (AD of 21.2 per 100,000) and 6.7 fold increase in localized stage tumours (AD of 12.2 per 100,000) between 1999 and 2008. This increase in the incidence of regional stage tumour accounted for 61.6% of the total increase in thyroid cancer incidence between 1999 and 2008 and the increase in localized stage tumours accounted for additional 35.5% of the total increase. On the other hand, there was very little increase in the incidence of distant stage thyroid cancer between 1999 and 2008 (AD of 0.2 per 100,000).

According to the route of detection, the incidence of screen-detected regional stage thyroid cancer increased steeply by 38.2 fold from 0.37 per 100,000 in 1999 to 14.15 per 100,000 in 2008 (AD of 13.78 per 100,000). The incidence of clinically detected regional stage thyroid cancer also increased by 3.5 fold from 1.57 in 1999 to 5.51 in 2008 (AD of 3.94 per 100,000). On the other hand, the incidence of screen-detected distant stage thyroid cancer showed only a fractional increase (AD of 0.08 per 100,000) while there was no significant change in the incidence of clinically detected distant stage thyroid cancer (AD of −0.02 per 100,000).

Subgroup analysis of regional SEER summary stage tumours

The regional SEER summary stage encompasses both the tumours with regional lymph node involvement and the tumours with extrathyroidal extension. To better understand the true nature of the increase in the incidence of regional stage tumour over time, we further analysed the regional stage thyroid tumours by the lymph node involvement status (yes, no)

and the degree of extrathyroidal extension (none, minimal, gross) according to the route of tumour detection by year (Table 3 & Figure 3C). The majority of the increase in the incidence of regional stage thyroid cancer was due to lymph node involvement (AD of 12.8 per 100,000 in total; 4.3 of which without extrathyroidal extension, 8.4 with minimal extrathyroidal extension, and 0.05 with gross extrathyroidal extension). For the tumours without lymph node involvement, minimal extrathyroidal extension accounts for virtually all of the increase between 1999 and 2008 (AD of 8.4 per 100,000). By the route of tumour detection, there was more increase in screen-detected regional stage thyroid cancer than the clinical-detected regional stage tumour (AD of 13.8 *vs.* 3.9 per 100,000), even for the tumours with lymph node involvement (AD of 8.3 *vs.* 2.2 per 100,000).

DISCUSSION

Our study showed that the great majority of the recent increases in the incidence of thyroid cancer in Korea was due to more detection of small-sized (<20 mm) tumours, which accounted for 94.4% of the overall increase in the estimated thyroid cancer incidence between 1999 and 2008. By the SEER summary stage, 97.1% of the increase in the estimated thyroid cancer incidence was due to increased detection of regional stage tumours (61.6%) and localized stage tumours (35.5%), for which 5-year relative survival rates were 100.1% and 100.4%, respectively in Korea.[21] Obviously, a large portion of this increase was attributed to the widespread practice of thyroid cancer screening with ultrasonography, which started around the turn of the century in Korea. [8, 22]

By the route of tumour detection, the increase in the estimated incidence of screen-detected

tumours only accounted for 66.1% of the total increase in thyroid cancer incidence between 1999 and 2008 and clinical-detected tumours accounted for additional 18.7% of the increase. Although some might argue that this finding is inconsistent with the idea of overdiagnosis as a cause of recent thyroid epidemic, the truth seems to be the opposite. In fact, a large proportion of the increase between 1999 and 2008 in the screen-detected and the clinically-dectected tumours as well were due to more detection of small-sized (<20 mm) tumours, (Figure 3A) and the most of them were localized or regional SEER summary stage tumours (Figure 3B). Furthermore, 99% of the increase in the estimated incidence of clinically detected tumours between 1999 and 2008 was due to the increase in the incidence of small tumours less than 20mm in size, with no increase in the incidence of tumours with distant metastases.

This raises serious questions about the true nature of clinical-detected thyroid cancer. Practically, it is impossible to see so many clinically detected thyroid tumours less than 20 mm in size unless it is disguised as such for insurance reimbursement purpose. In fact, routine ultrasound examination and biopsy of any thyroid nodule <10 mm in size is not recommended without high risk clinical features.[23] Interestingly, the median size for clinically-detected tumours was only 9 mm in 2008 (it was 20 mm in 1999), which was quite similar to the median size of 8 mm for the tumours detected by screening in 2008 (Figure 2).

Taken together with the accumulating data that showed the thyroid cancer mortality rates remained stable for decades despite of the rapid increase in its incidence rate (Figure 1),[8, 24] our findings provide further supporting evidence for the overdiagnosis as a cause of thyroid cancer epidemic in Korea. Otherwise, there is no better explanation for the findings that about 60% of the total increase in thyroid cancer incidence between 1999 and 2008 occurred in a

short time span of 3 years between 2005 and 2008, and the rising trend continued even thereafter as shown in Figure 1.

Strengths and weakness of the study

Our study is one of the first to show a direct association between the routes of thyroid cancer detection and an increase in thyroid cancer rates. Our study is meaningful as a nationwide examination of the association between increased thyroid cancer incidence and thyroid cancer screening using a representative random sample of thyroid cancer patients from cancer registry data. In addition, our study also showed that the increase in thyroid cancer incidence was associated with increase in screen-detected tumour, directly extracted by a review of medical records.

However, there are some limitations in this study. Our data may have a misclassification bias regarding the routes of tumour detection, which may cause either underestimation or overestimation of incidence rate in specific subgroups. However, in our study, sample weights were used to calculate an unbiased estimate after adjusting for the non-response units. Therefore, it is unlikely to introduce any significant bias in estimation of overall thyroid cancer incidence due to misclassification of the detection route. Indeed, the estimated mean age and sex distribution from NEST data were similar to the mean age and sex distribution (Supplementary Table 2) from the Korea National Cancer Incidence Database (KNCI DB), and the estimated incidence rate from NEST data was similar to the nationally representative incidence rate of thyroid cancer from KNCI DB (Supplementary Table 3). Nevertheless, because of relatively short duration of follow-up, we could not secure the long-term survival

outcome data, which is the inherent limitation for the study of thyroid cancer.

Comparison with other studies

There have been debates regarding the cause of the rising incidence of thyroid cancer in the past decade. Although many experts suggested that the increase in the incidence of thyroid cancer was mainly due to the increasing utilization of imaging tools for thyroid cancer screening,[8-10, 24, 25] others remained sceptical and called upon more epidemiologic studies searching for yet unidentified causal factors.[12-14]

Some studies have shown that the incidence of small-sized as well as large-sized, and advanced stage thyroid cancer have increased.[12, 26] Furthermore, the proportion of incidentally detected thyroid cancer without symptoms did not increase in tertiary referral hospitals in the United States, despite the increasing number of thyroid cancer cases.[27] Yoo et al. also showed that patients with incidentally detected thyroid cancer showed no difference in tumour size, invasion, lymph node involvement and distant metastasis compared with patients with non-incidentally detected thyroid cancer.[14] However, these findings could well be explained by the indolent nature of a well-differentiated thyroid cancer, the basic premise of the overdiagnosis concept. Because of the indolent nature itself, well-differentiated thyroid cancer might grow to be large and undiagnosed, even with lymph node involvement as shown in this study and extra-thyroidal extension, until it is discovered incidentally by imaging study, [28] which are further substantiated by our study.

If the steep increase in Korean thyroid cancer incidence is not due to overdetection, it is very hard to find a reasonable explanation for our findings of a 20.1-fold increase in small

tumours <10 mm in size, and an 8.1-fold increase in regional stage tumours, over a short 9-year-time span between 1999 and 2008.

The timing of the increase in thyroid cancer incidence coincides with the timing of widespread use of ultrasound examination in local clinics following Korean health care reform in 2000. Many hospitals and clinicians encouraged routine health check-up programs, which include thyroid cancer screening as an option with a small additional cost. In a hospital-based study of 10 major hospitals, the annual numbers of thyroid ultrasound examinations almost doubled between 2001 and 2004, and the annual number of ultrasound-guided fine needle aspiration examinations almost quadrupled during the same period.[22] Generally, only nodules >1 cm were recommended for further evaluation, since they have a greater potential to be clinically significant cancers [23]. If there is no evidence of clinical progression of tumour, some investigators recommended clinical observation for small-sized papillary thyroid cancers because they do not usually become more aggressive form.[29, 30]

In Korea, there had been no discrete guideline for further evaluation of thyroid nodules until 2010, when the Korean Endocrine Society published a new guideline. The Korean Endocrine Society established the new guideline for fine needle aspiration cytology for thyroid nodule by nodule size to take account of these [31] considering the rising incidence of thyroid cancer in Korea. However, because of the same reason, there have been growing concerns about potential harms and side effects related to the unnecessary evaluation and subsequent treatments. Recently, a multidisciplinary expert committee, organized by the National Cancer Center Korea, developed a guideline for thyroid cancer screening. A consensus was that thyroid ultrasonography is not routinely recommended for healthy subjects.[32]

Conclusion and policy implications

Our study provides clear evidence that the increase in the incidence of thyroid cancer in Korea was mainly due to overdiagnosis that resulted from widespread utilization of sensitive imaging tools such as ultrasound. Considering increasing worldwide trends in thyroid cancer incidence,[1, 2] the financial burdens resulting from ultrasound detection of small-sized tumours and subsequent surgery for thyroid cancer are expected to rise more rapidly.[5-7] These problems are not limited to Korea. This happens in England and U.S., as well [1, 6, 7]. Conserted efforts are needed at local and global levels to discourage the routine thyroid ultrasound examination in asymptomatic general population unless clinically indicated.

Details of contributors:

Contributors: All authors contributed to the data analysis and interpretation of the results, and reviewed and approved the final manuscript. J Lee, the guarantor, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S Park coordinated the study, and wrote the manuscript. C-M Oh analyzed the data and wrote the manuscript. S.Park, Y.-J. Won, H-J Kong and Y-J. Lee collected and interpreted the data. H. Cho, K.-W. Jung, Y.-J.Won, H.-J.Kong, K.-S.Choi., Y.-J.Lee. and J. Lee contributed to the discussion as well as reviewed and edited the manuscript.

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Ethical approval: Ethics approval for the research protocol was approved by the National Cancer Center institutional review board (IRB No: NCC2015-0152).

Data sharing: The dataset for NEST study is freely available to public with open access (Available from: http://kccrsurvey.cancer.go.kr/index.do**)**. Informed consent was not obtained but the presented data are anonymised and the risk of identification is low.

Transparency: J Lee (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies with the study as planned (and, if relevant, registered) have been explained.

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Table 1. Characteristics of study population across the period

Variables	Total	Year			*p*-value‡
		1999	2005	2008	
Overall	5,796	891	2,355	2,550	
Age (year)*	46.9 ± 12.4	46.0 ± 14.3	47.3 ± 12.5	46.8 ± 11.6	0.03
Tumour size (mm) *	13.3 ± 11.7	21.5 ± 15.9	13.6 ± 11.1	10.5 ± 9.0	<0.01
Sex†					0.01
Men	898 (15.5)	136 (15.3)	328 (13.9)	434 (17.0)	
Women	4,898 (84.5)		2,027 (86.1)	2,116 (83.0)	
Routes of detection†					<0.01
Screen detection	2,655 (45.8)	134 (15.0)	1,090 (46.3)	1,431 (56.1)	
Clinical detection	1,784 (30.8)	447 (50.2)	773 (32.8)	564 (22.1)	
Unspecified	1,357 (23.4)	310 (34.8)	492 (20.9)	555 (21.8)	
Histologic type†					<0.01
Follicular carcinoma	173 (3.0)	62 (7.0)	66 (2.8)	45 (1.8)	
Papillary carcinoma	5,500 (94.9)	779 (87.4)	2,243 (95.2)	2,478 (97.2)	

Medullary carcinoma	43 (0.7)	13 (1.4)	19 (0.8)	11 (0.4)	
Anaplastic carcinoma	26 (0.5)	15 (1.7)	6 (0.3)	5 (0.2)	
Others	54 (0.9)	22 (2.5)	21 (0.9)	11 (0.4)	
Regional lymph node involvement[†]					<0.01
No	2,466 (42.6)	268 (30.1)	1,012 (43.0)	1,186 (46.5)	
Yes	2,047 (35.3)	319 (35.8)	799 (33.9)	929 (36.4)	
Unknown	1,283 (22.1)	304 (34.1)	544 (23.1)	435 (17.1)	
Distant metastasis[†]					<0.01
No	5,380 (92.8)	774 (86.9)	2,196 (93.3)	2,410 (94.5)	
Yes	34 (0.6)	15 (1.7)	14 (0.6)	5 (0.2)	
Unknown	382 (6.6)	102 (11.4)	145 (6.1)	135 (5.3)	
Extrathyroidal extension [†]					<0.01
No	2,783 (48.0)	397 (44.5)	1,194 (50.7)	1,192 (46.7)	
Yes	2,593 (44.7)	357 (40.1)	993 (42.2)	1,243 (48.8)	
Unknown	420 (7.3)	137 (15.4)	168 (7.1)	115 (4.5)	
Focality[†]					<0.01
Unifocal	3,810 (66.7)	554 (62.2)	1,553 (65.9)	1,703 (66.8)	
Multifocal	1,697 (29.3)	234 (26.3)	689 (29.3)	774 (30.3)	

Unknown	289 (5.0)	103 (11.5)	113 (4.8)	73 (2.9)	
AJCC 6th stage†					<0.01
Stage Ⅰ	3,038 (52.4)	428 (48.0)	1,249 (53.0)	1,361 (53.3)	
Stage Ⅱ	49 (0.9)	14 (1.6)	23 (1.0)	12 (0.5)	
StageⅢ	1,036 (17.9)	97 (10.9)	373 (15.8)	566 (22.2)	
StageⅣ	426 (7.3)	101 (11.3)	178 (7.6)	147 (5.8)	
Unknown	1,247 (21.5)	251 (28.2)	532 (22.6)	464 (18.2)	
SEER summary stage†					<0.01
Localized	2,125 (36.6)	302 (33.9)	919 (39.0)	904 (35.5)	
Regional	3,176 (54.8)	425 (47.7)	1,243 (52.8)	1,508 (59.1)	
Distant	126 (2.2)	48 (5.4)	45 (1.9)	33 (1.3)	
Unknown	369 (6.4)	116 (13.0)	148 (6.3)	105 (4.1)	

*Continuous variables were expressed as mean±standard deviation.
†Categorical variable were expressed as number (percentage).
‡*p*-values were calculated by ANOVA for continuous variables and chi-square test for categorical variables.

Table 2. Estimated age standardized incidence rate* of thyroid cancer by routes of tumour detection, tumour size and SEER summary stage, 1999-2008

Variables	Year								
	1999			2005			2008		
	Routes of tumour detection			Routes of tumour detection			Routes of tumour detection		
	SD	CD	UNK	SD	CD	UNK	SD	CD	UNK
Tumour size									
<10mm	0.27 (0.22, 0.31)	0.49 (0.43, 0.55)	0.43 (0.37, 0.49)	4.80 (4.63, 4.97)	2.37 (2.25, 2.49)	1.59 (1.49, 1.69)	15.00 (14.70, 15.29)	4.88 (4.71, 5.05)	4.00 (3.84, 4.15)
10 - 20mm	0.32 (0.27, 0.37)	0.82 (0.74, 0.90)	0.50 (0.44, 0.56)	3.39 (3.25, 3.54)	2.41 (2.28, 2.54)	1.00 (0.92, 1.08)	6.86 (6.66, 7.06)	2.85 (2.72, 2.98)	1.63 (1.53, 1.73)
20 - 30mm	0.13 (0.10, 0.16)	0.76 (0.68, 0.83)	0.30 (0.26, 0.35)	0.67 (0.60, 0.73)	1.09 (1.00, 1.17)	0.39 (0.34, 0.44)	0.97 (0.90, 1.05)	0.89 (0.81, 0.96)	0.45 (0.40, 0.50)
≥30mm	0.17 (0.13, 0.21)	0.97 (0.88, 1.06)	0.32 (0.27, 0.37)	0.32 (0.28, 0.37)	1.05 (0.97, 1.13)	0.32 (0.28, 0.37)	0.61 (0.55, 0.68)	0.97 (0.89, 1.05)	0.42 (0.37, 0.47)
Unspecified	0.13 (0.10, 0.16)	0.30 (0.25, 0.35)	0.47 (0.41, 0.53)	0.21 (0.17, 0.24)	0.26 (0.21, 0.30)	0.59 (0.53, 0.65)	0.27 (0.23, 0.31)	0.18 (0.15, 0.21)	0.76 (0.69, 0.83)
SEER summary stage									
Localized	0.42 (0.36, 0.48)	1.16 (1.07, 1.25)	0.56 (0.49, 0.62)	4.16 (4.00, 4.32)	2.80 (2.66, 2.93)	1.19 (1.10, 1.27)	8.84 (8.61, 9.07)	3.76 (3.60, 3.91)	1.73 (1.63, 1.83)
Regional	0.37 (0.32, 0.42)	1.57 (1.46, 1.68)	1.04 (0.95, 1.13)	4.74 (4.57, 4.91)	3.90 (3.74, 4.06)	2.01 (1.89, 2.12)	14.15 (13.86, 14.44)	5.51 (5.33, 5.70)	4.50 (4.33, 4.66)
Distant	0.09 (0.06, 0.12)	0.21 (0.17, 0.25)	0.06 (0.03, 0.08)	0.17 (0.14, 0.21)	0.20 (0.17, 0.24)	0.03 (0.02, 0.04)	0.17 (0.14, 0.20)	0.19 (0.16, 0.23)	0.15 (0.12, 0.18)
Unknown	0.13 (0.10, 0.16)	0.39 (0.33, 0.45)	0.37 (0.32, 0.42)	0.32 (0.27, 0.36)	0.27 (0.23, 0.31)	0.67 (0.60, 0.73)	0.55 (0.49, 0.60)	0.30 (0.26, 0.35)	0.87 (0.80, 0.95)
Total	1.01 (0.89, 1.13)	3.34 (3.13, 3.55)	2.02 (1.86, 2.18)	9.39 (9.07, 9.71)	7.17 (6.89, 7.45)	3.89 (3.68, 4.10)	23.71 (23.22, 24.20)	9.76 (9.44, 10.09)	7.25 (6.98, 7.52)

SD=Screen detection; CD=Clinical detection; UNK=Unknown

Age-specific incidence was estimated by dividing the weighted frequency by the corresponding 5-year mid-year population.

*Standard population used for age-standardization was Segi's world standard population and age-standardized incidence rate was calculated per 100,000 people.

Table 3. Estimated age-standardized incidence rate* of thyroid cancer with regional stage by the degree of extension and lymph node involvement according to the routes of tumour detection, 1999-2008

Regional stage		Year								
		1999			2005			2008		
Lymph node involvement	Extrathyroidal extension	Routes of tumour detection			Routes of tumour detection			Routes of tumour detection		
		SD	CD	UNK	SD	CD	UNK	SD	CD	UNK
No	Minimal extension	0.09 (0.05, 0.12)	0.44 (0.36, 0.52)	0.38 (0.30, 0.45)	1.76 (1.62, 1.90)	1.31 (1.19, 1.43)	0.75 (0.66, 0.84)	5.53 (5.30, 5.77)	2.18 (2.03, 2.33)	1.56 (1.43, 1.69)
	Gross extension	0.01 (0.00, 0.02)	0.03 (0.01, 0.05)	0.01 (0.00, 0.01)	0.11 (0.08, 0.15)	0.10 (0.07, 0.13)	0.00 (0.00, 0.00)	0.05 (0.03, 0.08)	0.02 (0.01, 0.04)	0.02 (0.01, 0.04)
	Subtotal	0.10 (0.06, 0.13)	0.47 (0.39, 0.55)	0.38 (0.31, 0.45)	1.87 (1.73, 2.01)	1.41 (1.28, 1.53)	0.75 (0.66, 0.84)	5.59 (5.35, 5.82)	2.20 (2.05, 2.35)	1.58 (1.46, 1.71)
Yes	None	0.13 (0.09, 0.18)	0.52 (0.43, 0.60)	0.16 (0.11, 0.20)	1.33 (1.21, 1.45)	0.89 (0.79, 0.99)	0.46 (0.39, 0.53)	3.05 (2.87, 3.23)	1.14 (1.02, 1.25)	0.89 (0.80, 0.99)
	Minimal extension	0.13 (0.09, 0.17)	0.53 (0.44, 0.61)	0.49 (0.41, 0.57)	1.43 (1.30, 1.55)	1.46 (1.33, 1.59)	0.77 (0.68, 0.86)	5.48 (5.24, 5.72)	2.06 (1.91, 2.21)	2.00 (1.86, 2.15)
	Gross extension	0.01 (0.00, 0.02)	0.05 (0.03, 0.08)	0.01 (0.00, 0.02)	0.12 (0.08, 0.15)	0.14 (0.10, 0.19)	0.03 (0.01, 0.05)	0.04 (0.02, 0.05)	0.11 (0.08, 0.15)	0.02 (0.00, 0.03)
	Subtotal	0.27 (0.21, 0.33)	1.10 (0.98, 1.22)	0.66 (0.57, 0.75)	2.87 (2.70, 3.05)	2.49 (2.32, 2.66)	1.26 (1.14, 1.38)	8.56 (8.27, 8.86)	3.31 (3.12, 3.50)	2.91 (2.74, 3.09)

Total	0.37 (0.32, 0.42)	1.57 (1.46, 1.68)	1.04 (0.95, 1.13)	4.74 (4.57, 4.91)	3.90 (3.74, 4.06)	2.01 (1.89, 2.12)	14.15 (13.86, 14.44)	5.51 (5.33, 5.70)	4.50 (4.33, 4.66)

SD=Screen detection; CD=Clinical detection; UNK=Unknown

Age-specific incidence was estimated by dividing the weighted frequency by the corresponding 5-year mid-year population.

*Standard population used for age-standardization was Segi's world standard population and age-standardized incidence rate was calculated per 100,000 people.

Figure legends

Figure 1. Trends in thyroid cancer inicidence and mortality rate between 1999 and 2013

The age-standardized rates are presented as number of thyroid cancer cases per 1,000,000 people using Segi's world standard population as standard population.

The solid line indicates the age-standardized incidence rates for thyroid cancer between 1999 and 2012 in Korea.

The dashed line indicates the age-standardized mortality rates for thyroid cancer between 1999 and 2013 in Korea.

Figure 2. Change in the tumour size of thyroid cancer by the diagnostic year according to the detection routes

The median tumour size of thyroid cancer are presented as the numeric value above the line in the middle of the box for each year.

The Y-axis represents tumour size (mm) and transformed using a 10 logarithmic scale.

Figure 3A. Absolute change over time in thyroid cancer incidence by tumour size according to the detection routes

This graph presented the absolute differences of age-standardized incidence rate of thyroid cancer per 100,000 people by tumor size according to the detection routes.

Tumor size is classified into <10 mm, 10-20 mm, 20-30 mm, ≥30 mm and unspecified.

The white bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 1999 and 2008.

The gray bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 2005 and 2008.

Figure 3B. Absolute change over time in thyroid cancer incidence by SEER summary stage according to the detection routes

This graph presented the absolute differences of age-standardized incidence rate of thyroid cancer per 100,000 people by SEER summary stage according to the detection routes.

SEER summary stage is classified into localized stage, regional stage, distant stage and unspecified stage.

The white bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 1999 and 2008.

The gray bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 2005 and 2008.

Figure 3C. Absolute change over time in incidence rate of regional stage thyroid cancer by degree of extension and lymph node involvement according to the detection routes

This graph presented the absolute differences of age-standardized incidence rate of regional stage thyroid cancer per 100,000 people by by the lymph node involvement status (yes, no) and the degree of extrathyroidal extension (none, minimal, gross) according to the detection routes.

Regional stage is classified into none extrathyroid extension with lymph node involvement, minimal extrathyroid extension with lymph node involvement, gross extrathyroid extension with lymph node involvement, minimal extrathyroid extension without lymph node

involvement, gross extrathyroid extension without lymph node involvement.

The white bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 1999 and 2008.

The gray bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 2005 and 2008.

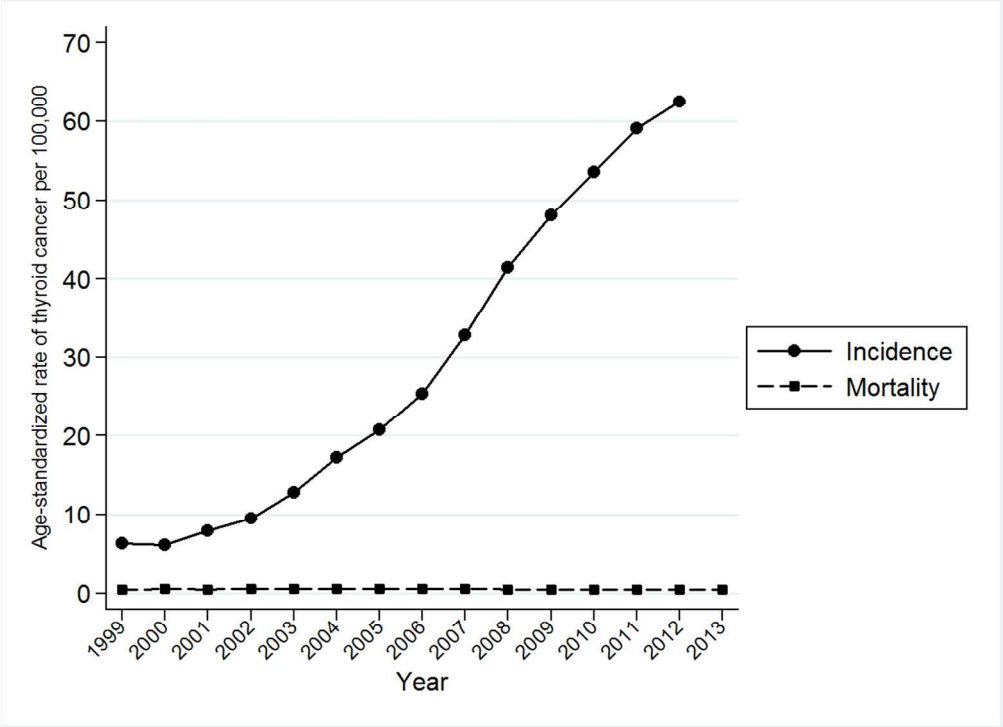

Figure 1. Trends in thyroid cancer inicidence and mortality rate between 1999 and 2013
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The solid line indicates the age-standardized incidence rates for thyroid cancer between 1999 and 2012 in Korea.
The dashed line indicates the age-standardized mortality rates for thyroid cancer between 1999 and 2013 in Korea.

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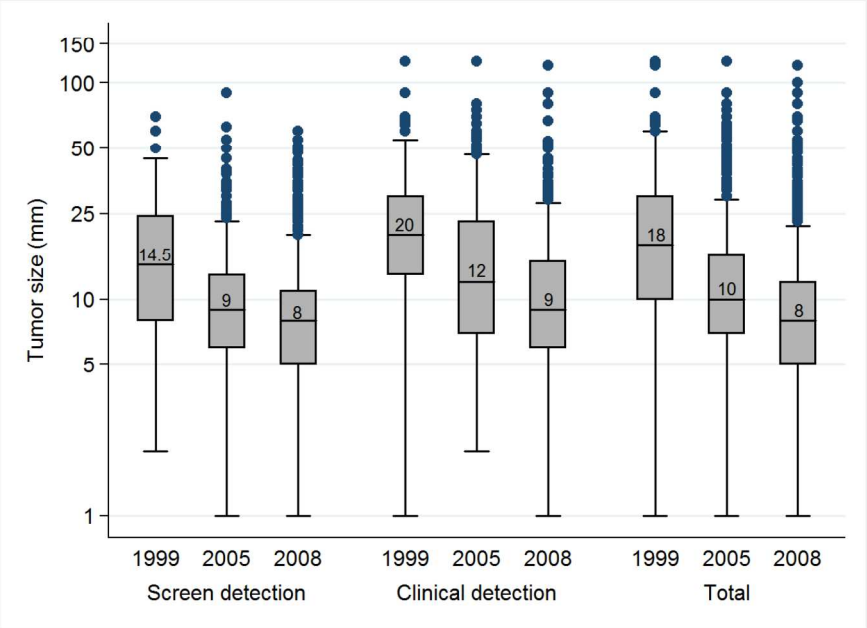

Figure 2. Change in the tumour size of thyroid cancer by the diagnostic year according to the detection routes

The median tumour size of thyroid cancer are presented as the numeric value above the line in the middle of the box for each year.

The Y-axis represents tumour size (mm) and transformed using a 10 logarithmic scale.

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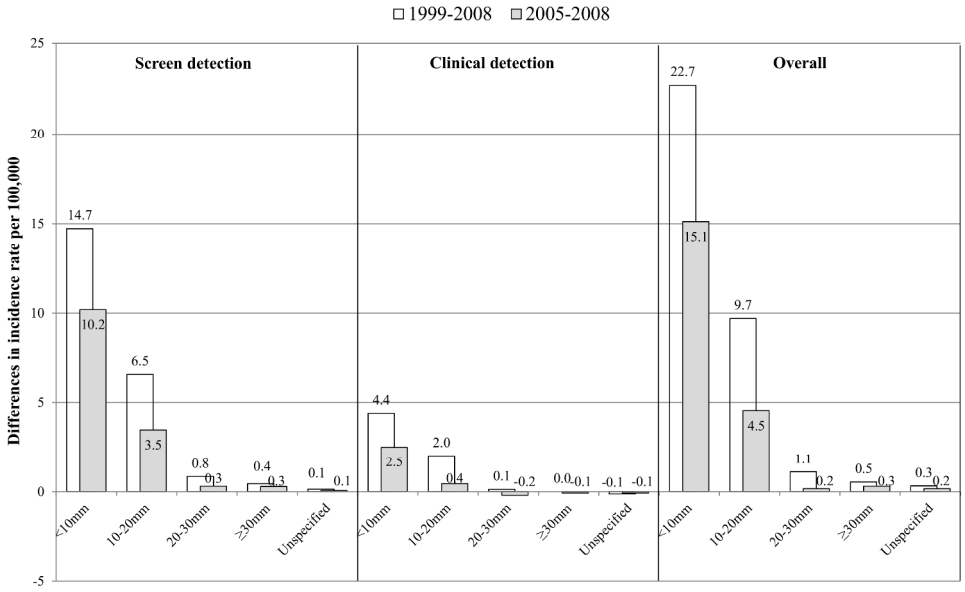

Figure 3A. Absolute change over time in thyroid cancer incidence by tumour size according to the detection routes

This graph presented the absolute differences of age-standardized incidence rate of thyroid cancer per 100,000 people by tumor size according to the detection routes.

Tumor size is classified into <10 mm, 10-20 mm, 20-30 mm, ≥30 mm and unspecified.

The white bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 1999 and 2008.

The gray bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 2005 and 2008.

254x190mm (300 x 300 DPI)

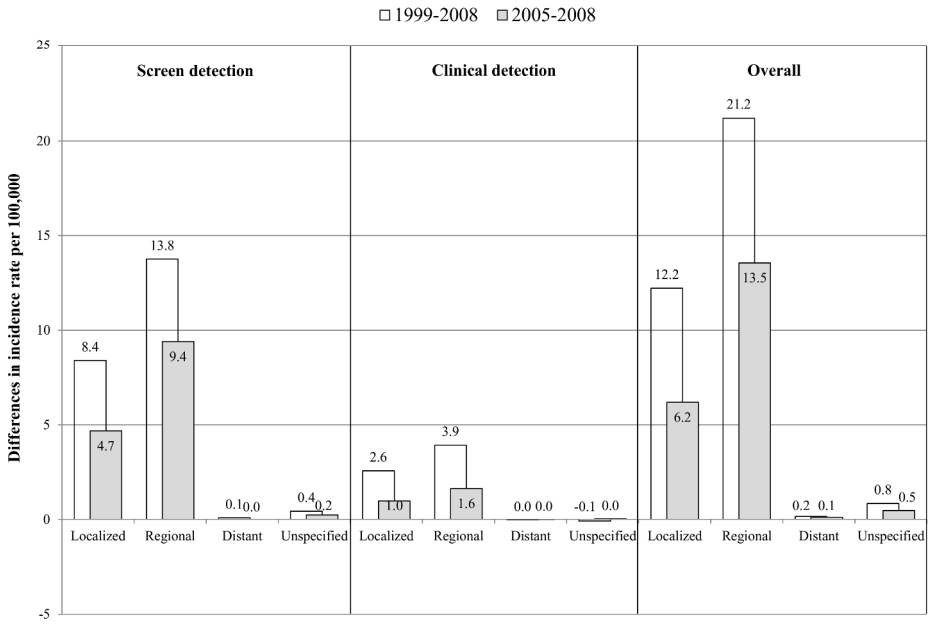

Figure 3B. Absolute change over time in thyroid cancer incidence by SEER summary stage according to the detection routes

This graph presented the absolute differences of age-standardized incidence rate of thyroid cancer per 100,000 people by SEER summary stage according to the detection routes.

SEER summary stage is classified into localized stage, regional stage, distant stage and unspecified stage.

The white bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 1999 and 2008.

The gray bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 2005 and 2008.

254x190mm (300 x 300 DPI)

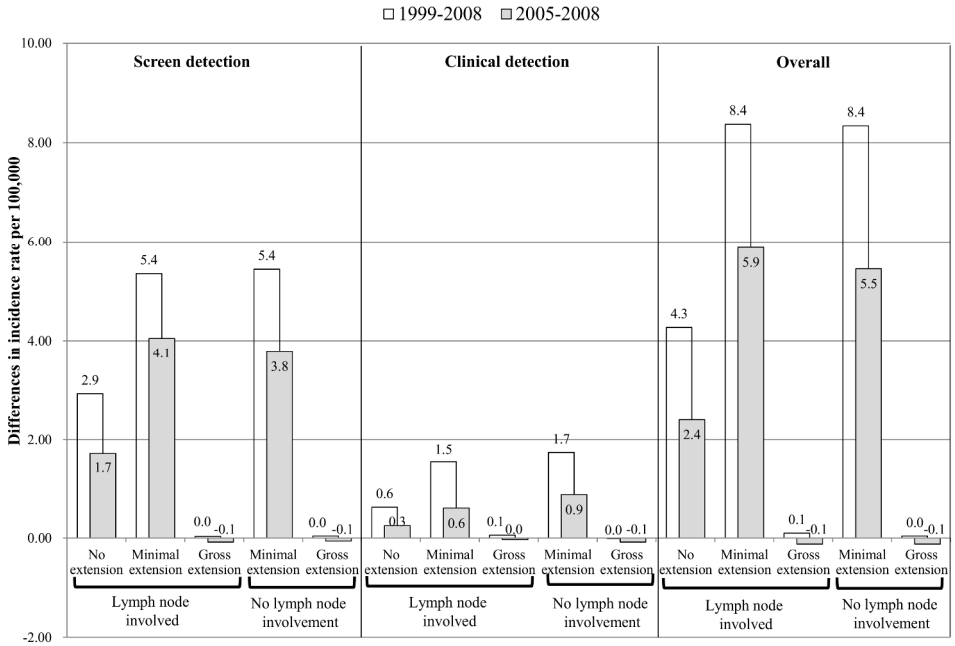

Figure 3C. Absolute change over time in incidence rate of regional stage thyroid cancer by degree of extension and lymph node involvement according to the detection routes

This graph presented the absolute differences of age-standardized incidence rate of regional stage thyroid cancer per 100,000 people by by the lymph node involvement status (yes, no) and the degree of extrathyroidal extension (none, minimal, gross) according to the detection routes.

Regional stage is classified into none extrathyroid extension with lymph node involvement, minimal extrathyroid extension with lymph node involvement, gross extrathyroid extension with lymph node involvement, minimal extrathyroid extension without lymph node involvement, gross extrathyroid extension without lymph node involvement.

The white bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 1999 and 2008.

The gray bars indicate the differences of age-standardized incidence rate of thyroid cancer per 100,000 people between 2005 and 2008.

254x190mm (300 x 300 DPI)

Supplementary table 1. Changes in median tumour size of thyroid cancer according to the routes of tumour detection and, 1999-2008

Variables	1999						2005						2008					
	Routes of tumour detection						Routes of tumour detection						Routes of tumour detection					
	SD		CD		Total		SD		CD		Total		SD		CD		Total	
Tumour size	n	Tumour size	n	Tumour size	n	Tumour size	n	Tumour size	n	Tumour size	n	Tumour size	n	Tumour size	n	Tumour size	n	Tumour size
Total	120	14.5 (8-24.5)	409	20 (13-30)	891	18 (10-30)	1,090	9 (6-13)	773	12 (7-23)	2,355	10 (7-16)	1,431	8 (5-11)	564	9 (6-15)	2,550	8 (5-12)
Men	19	15 (10-30)	66	25 (13-35)	136	20.5 (12-35)	163	9 (7-15)	87	20 (8-40)	328	11 (7-21)	257	9 (6-13)	81	10 (7-26)	434	9 (6-15)
Women	115	14 (8-20)	381	20 (13-30)	755	18 (10-30)	927	9 (6-13)	686	12 (7-20)	2,027	10 (7-15)	1,174	8 (5-11)	483	8 (6-14)	2,116	8 (5-12)

SD=Screen detection; CD=Clinical detection; LN=Lymph node involvement

Total include cases detected by screen detection, clinical detection and unknown routes of detection

Supplementary table 2. proportion of regional lymph node involvement by tumour size according to the routes of tumour detection and, 1999-2008

Variables	1999						2005						2008					
	Routes of tumour detection						Routes of tumour detection						Routes of tumour detection					
	SD		CD		Total		SD		CD		Total		SD		CD		Total	
Tumour size	n	LN(+)	n	LN(+)	n	LN(+)	n	LN(+)	n	LN(+)	n	LN(+)	n	LN(+)	n	LN(+)	n	LN(+)
<10mm	33	6 (18.2)	59	12 (20.3)	162	37 (22.8)	558	120 (21.5)	255	68 (26.7)	1,013	245 (24.2)	906	262 (28.9)	294	56 (19.1)	1,512	430 (28.4)
10- 20mm	43	16 (37.2)	112	33 (29.5)	232	79 (34.1)	392	168 (42.9)	250	95 (38.0)	768	310 (40.4)	421	208 (49.4)	159	68 (42.8)	707	345 (48.8)
20-30mm	21	10 (47.6)	100	45 (45.0)	168	82 (48.8)	73	36 (49.3)	112	60 (53.6)	234	125 (53.4)	57	30 (52.6)	48	28 (58.3)	138	81 (58.7)
≥30mm	23	8 (34.8)	138	60 (43.5)	208	92 (44.2)	43	22 (51.2)	128	63 (49.2)	212	109 (51.4)	32	12 (37.5)	50	29 (58.0)	115	65 (56.5)
Unspecified	14	6 (42.9)	38	10 (26.3)	121	29 (24.0)	24	3 (12.5)	28	3 (10.7)	128	10 (7.8)	15	2 (13.3)	13	2 (15.4)	78	8 (10.3)

SD=Screen detection; CD=Clinical detection; LN=Lymph node involvement

Total include cases detected by screen detection, clinical detection and unknown routes of detection

Supplementary table 3. Comparison between estimated mean age and sex distribution of thyroid cancer patients and mean age and sex distribution of thyroid cancer patients

	Year					
	1999		2005		2008	
	NEST data	KNCI DB	NEST data	KNCI DB	NEST data	KNCI DB
Age (year)	46.3 (44.8 – 47.9)	46.6 ± 15.2	47.3 (46.7 – 47.9)	47.2 ± 12.8	47.0 (46.0 – 47.9)	47.6 ± 12.1
Sex						
Men	136 (15.8)	521 (15.6)	328 (13.6)	1,779 (14.0)	434 (17.2)	4,336 (15.9)
Women	755 (84.2)	2,823 (84.4)	2,027 (86.4)	10,975 (86.1)	2,116 (82.8)	22,905 (84.1)

Mean ages and proportion of the sex from NEST data were estimated considering the weights and sample design.

Supplementary table 4. Comparison between estimated age-standardized incidence rate of thyroid cancer and true age-standardized incidence rate of thyroid cancer

	Year					
	1999		2005		2008	
	Estimated incidence rate	Real incidence rate	Estimated incidence rate	Real incidence rate	Estimated incidence rate	Real incidence rate
Total	6.37 (6.08 – 6.66)	6.3	20.45 (19.97 – 20.92)	20.7	40.73 (40.08 – 41.38)	41.3
Men	2.18 (1.93 – 2.43)	2.1	5.68 (5.33 – 6.04)	5.9	13.97 (13.43 – 14.51)	13.3
Women	10.48 (9.96 – 11.00)	10.4	35.04 (34.17 – 35.92)	35.3	67.61 (66.43 – 68.80)	69.3

Standard population used for age-standardization was Segi's world standard population and age-standardized incidence rate was calculated per 100,000 people.
Age-specific incidences were estimated by dividing the weighted frequency by the corresponding mid-year population.
Estimated incidence rates from NEST data were calculated considering the weights and sample design.