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

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Complete List of Authors:	Park, Sohee; Yonsei University Graduate School of Public Health, Department of Biostatistics Oh, Chang-Mo; National Cancer Control Institute, Cho, Hyunsoon; National Cancer Center, Department of Cancer Control and Policy Lee, Joo Young; Yonsei University, Department of Preventive medicine Jung, Kyu-Won; Natl Canc Ctr Res Inst, Jun, Jae Kwan; National Cancer Center Won, Young-Joo; National Cancer Center Kong, Hyun-Joo; National Cancer Center choi, kui son; National Cancer Center, Lee, You Jin; National Cancer Center, Center for Thyroid Cancer Lee, Jin soo; National Cancer Center, Center for lung cancer
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Screening as a cause of the thyroid cancer epidemic in Korea: Evidence from a nationwide study

Running title: Increase in thyroid cancer by screening

Sohee Park,[1] Chang-Mo Oh,[2] Hyunsoon Cho, [2,3] Joo Young Lee,[4] Kyu-Won Jung,[2]Jae Kwan Jun,[2,3] Young-Joo Won,[2,3] Hyun-Joo Kong,[2] Kui Son Choi, [2,3] You Jin Lee,[5], Jin soo Lee[6*]

[1]Department of Biostatistics, Yonsei University Graduate School of Public Health, Seoul, Korea

[2]National Cancer Control Institute, National Cancer Center, Goyang, Korea

[3]Department of Cancer Control and Policy, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Korea

[4]Department of Preventive medicine, Yonsei University, College of Medicine, Seoul, Korea

[5]Center for Thyroid Cancer, National Cancer Center, Goyang, Korea

[6]National Cancer Center Research Institute & Hospital, National Cancer Center, Goyang, Korea

[*]**Sohee Park and Chang-Mo Oh contributed equally to this work, and should be considered as first co-authors.**

* *Correspondence to:* Jin soo Lee, MD, PhD

National Cancer Center Research Institute & Hospital, National Cancer Center, 111, Jungbalsan-ro, Ilsandong-gu, Goyang, Gyeonggi-do 410-769, Korea.

E-mail: jslee@ncc.re.kr

Tel: +82-31-920-1601

Fax: +82-31-920-

Author's Email addresses:

Sohee Park: soheepark@yuhs.ac

Chang-Mo Oh: kachas@ncc.re.kr

Hyunsoon Cho: hscho@ncc.re.kr

Joo Young Lee: battery79@daum.net

Kyu-Won Jung: ara@ncc.re.kr

Jae Kwan Jun: jkjun@ncc.re.kr

Young-Joo Won: astra67@ncc.re.kr

Hyun-Joo Kong: bscr@ncc.re.kr

Kui Son Choi: kschoi@ncc.re.kr

You Jin Lee: eulee@ncc.re.kr

Jin soo Lee: jslee@ncc.re.kr

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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, 86.5% 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 large tumours.

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 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. 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,[10] which suggests cancer screening as a cause of the

Korean thyroid cancer epidemic.[10]

However, some investigators remain unconvinced and have raised questions about the idea of overdiagnosis being the main cause of the current thyroid cancer epidemic.[11-13] In a registry-based cancer study,[11] 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.[11] They claimed that improved detection does not fully explain the rising incidence of thyroid cancer.[11] In Australia, the increase in thyroid cancer was observed across sociodemographic characteristics in both early and advanced stages.[12] 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.[13]

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,[14] 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 (TNM 6th stage,[15] SEER summary stage[16]), and routes of tumour detection, through a review of medical records. 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)[17] as papillary carcinoma, medullary carcinoma, follicular carcinoma, anaplastic carcinoma, and others.[18]

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 TNM 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, a 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 TNM 6th stage between 1999 and 2008.

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 (mm) of screen-detected tumours was smaller than that of clinically detected tumours (mm) (Figure 1, 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 over time by tumour size

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 is shown in Table 2 and Figure 2A. 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 tumour such tumours diagnosed by clinical detection (AD of 0.00 per 100,000). About 86.5% 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 2A shows the absolute differences 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 two-thirds 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

Regarding SEER summary staging, the incidence rate of screen-detected regional stage thyroid cancer increased steeply from 0.37 per 100,000 in 1999 to 14.15 per 100,000 in 2008 (AD of 13.73 per 100,000) as shown in Table 2 and Figure 2B. For the incidence of clinically detected regional stage thyroid cancer, there was also a modest increase 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 no significant increase was observed in the incidence of clinically detected distant stage thyroid cancer (AD of −0.02 per 100,000).

The absolute differences in the magnitude of the increase in thyroid cancer incidence by SEER summary stage were shown in Figure 2B according to the route of tumour detection between 1999 and 2008. The majority of the increase in thyroid cancer (97.1%) comprised increases in localized (35.5%) and regional stage tumours (61.6%). Furthermore, there was little increase in the incidence of distant stage thyroid cancer between 1999 and 2008.

DISCUSSION

Our study showed that the great majority of the recent increases in the incidence of thyroid cancer in Korea was attributed to the increase in the incidence of small-sized tumours detected mainly by screening. A large proportion of screen-detected cases were associated with a sharp increase in small-sized (<20 mm) thyroid tumours (Figure 2A) and most of them were localized or regional SEER summary stage tumours (Figure 2B). In addition, clinically detected tumours <20 mm in size, which accounts for 99% of the increase in clinically detected cases, should be considered as screen detected rather than true clinically detected cases. Furthermore, a recent increase in the thyroid cancer incidence rate between 2005 and 2008 accounts for 63% of the total increase in thyroid cancer incidence between 1999 and 2008. Moreover,

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 to this study. Our data may have a misclassification bias regarding the routes of detection. Data regarding detection methods may be incomplete, potentially resulting in 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. Indeed, the estimated mean age and sex distribution from NEST data were similar to the mean age and gender 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). Despites the overall distribution of our study was similar with the national representative incidence rate of thyroid cancer, the caution should be needed for interpreting the results by subgroups.

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 owing to the increasing utilization of imaging tools for thyroid cancer screening,[8-10, 20] others remained sceptical and called upon more epidemiologic studies searching for yet unidentified causal factors.[11-13]

Some studies have shown that the incidence of small-sized as well as large-sized, and advanced stage thyroid cancer have increased.[11, 21] 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.[22] 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.[13] 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, a well-differentiated thyroid cancer might grow to be large and undiagnosed, even with extra-thyroidal spread, until it is discovered incidentally by screening.[23]

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.

Some may argue that there was also a significant increase in the incidence rates of clinically detected thyroid cancer over the same time period, especially with small tumour size (<20 mm). Although true, the magnitude of this increase was rather small compared to

that of screen-detected cases over the same time period between 1999 and 2008: 14.73 per 100,000 vs. 4.39 per 100,000 for tumours <10 mm in size, and 6.54 per 100,000 vs. 2.03 per 100,000 for tumours 10–20 mm in size, respectively. In addition, this seemingly contradictory finding has a very plausible explanation. Practically, it is impossible to see so many clinically detected thyroid tumours <10 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.[19] Overdetection appears to be the best explanation for the sharp increase in the incidence of thyroid cancer in Korea.

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.[24] There has been no guideline for the fine needle aspiration cytology for thyroid nodules by nodule size in Korea before 2010. However, as the number of thyroid nodules and cancer increase, the Korean Endocrine Society established the new guideline for fine needle aspiration cytology for thyroid nodule by nodule size to take account of these increases.[25] While there has been no guideline for the screening the asymptomatic thyroid nodule yet.

Conclusion and policy implications

Our study provides clear evidence that the increase in the incidence of thyroid cancer in Korea was mainly owing to overdetection 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 level 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 J.-Y.Lee collected and interpreted the data. H. Cho, K.-W. Jung, Y.-J.Won, H.-J.Kong, K.-S.Choi., Y.-J.Lee., K.-Y.Chung, and J. Lee contributed to the discussion as well as reviewed and edited the manuscript.

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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	Year			Total
	1999	2005	2008	
Overall	891	2,355	2,550	5,796
Age (year)*	46.0 ± 14.3	47.3 ± 12.5	46.8 ± 11.6	46.9 ± 12.4
Tumour size (mm) *	21.5 ± 15.9	13.6 ± 11.1	10.5 ± 9.0	13.3 ± 11.7
Sex†				
Men	136 (15.3)	328 (13.9)	434 (17.0)	898 (15.5)
Women	755 (84.7)	2,027 (86.1)	2,116 (83.0)	4,898 (84.5)
Routes of detection†				
Screen detection	134 (15.0)	1,090 (46.3)	1,431 (56.1)	2,655 (45.8)
Clinical detection	447 (50.2)	773 (32.8)	564 (22.1)	1,784 (30.8)
Unspecified	310 (34.8)	492 (20.9)	555 (21.8)	1,357 (23.4)
Histologic type†				
Follicular carcinoma	62 (7.0)	66 (2.8)	45 (1.8)	173 (3.0)

Papillary carcinoma	779 (87.4)	2,243 (95.2)	2,478 (97.2)	5,500 (94.9)
Medullary carcinoma	13 (1.4)	19 (0.8)	11 (0.4)	43 (0.7)
Anaplastic carcinoma	15 (1.7)	6 (0.3)	5 (0.2)	26 (0.5)
Others	22 (2.5)	21 (0.9)	11 (0.4)	54 (0.9)
Regional lymph node involvement[†]				
No	268 (30.1)	1,012 (43.0)	1,186 (46.5)	2,466 (42.6)
Yes	319 (35.8)	799 (33.9)	929 (36.4)	2,047 (35.3)
Unknown	304 (34.1)	544 (23.1)	435 (17.1)	1,283 (22.1)
Distant metastasis[†]				
No	774 (86.9)	2,196 (93.3)	2,410 (94.5)	5,380 (92.8)
Yes	15 (1.7)	14 (0.6)	5 (0.2)	34 (0.6)
Unknown	102 (11.4)	145 (6.1)	135 (5.3)	382 (6.6)
Extrathyroidal invasion[†]				
No	397 (44.5)	1,194 (50.7)	1,192 (46.7)	2,783 (48.0)
Yes	357 (40.1)	993 (42.2)	1,243 (48.8)	2,593 (44.7)
Unknown	137 (15.4)	168 (7.1)	115 (4.5)	420 (7.3)
Focality[†]				
Unifocal	554 (62.2)	1,553 (65.9)	1,703 (66.8)	3,810 (66.7)

Multifocal	234 (26.3)	689 (29.3)	774 (30.3)	1,697 (29.3)
Unknown	103 (11.5)	113 (4.8)	73 (2.9)	289 (5.0)
TNM stage†				
Stage Ⅰ	428 (48.0)	1,249 (53.0)	1,361 (53.3)	3,038 (52.4)
Stage Ⅱ	14 (1.6)	23 (1.0)	12 (0.5)	49 (0.9)
StageⅢ	97 (10.9)	373 (15.8)	566 (22.2)	1,036 (17.9)
StageⅣ	101 (11.3)	178 (7.6)	147 (5.8)	426 (7.3)
Unknown	251 (28.2)	532 (22.6)	464 (18.2)	1,247 (21.5)
SEER summary stage†				
Localized	302 (33.9)	919 (39.0)	904 (35.5)	2,125 (36.6)
Regional	425 (47.7)	1,243 (52.8)	1,508 (59.1)	3,176 (54.8)
Distant	48 (5.4)	45 (1.9)	33 (1.3)	126 (2.2)
Unknown	116 (13.0)	148 (6.3)	105 (4.1)	369 (6.4)

*Continuous variables were expressed as mean±standard deviation.
†Categorical variable were expressed as number (percentage).

Table 2. Estimated age standardized incidence rate* of thyroid cancer by routes of tumour detection, tumour size and SEER summary stage, 1999-2011

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)

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

Figure 2A. Absolute change over time in thyroid cancer incidence by tumour size according to the detection routes

Figure 2B. Absolute change over time in thyroid cancer incidence by SEER summary stage according to the detection routes

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

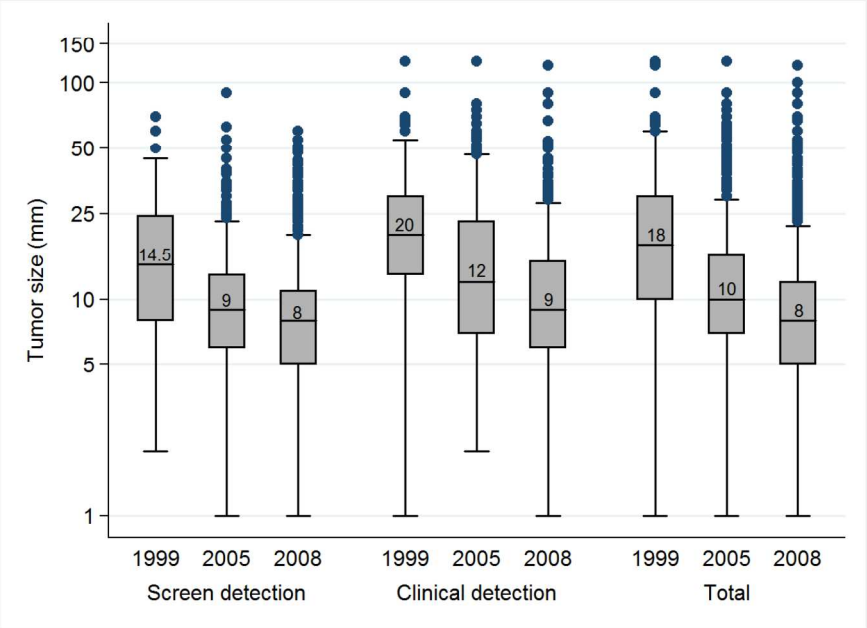


Figure 1. Change in the tumour size of thyroid cancer by the diagnostic year according to the detection routes
Figure 1
254x190mm (300 x 300 DPI)

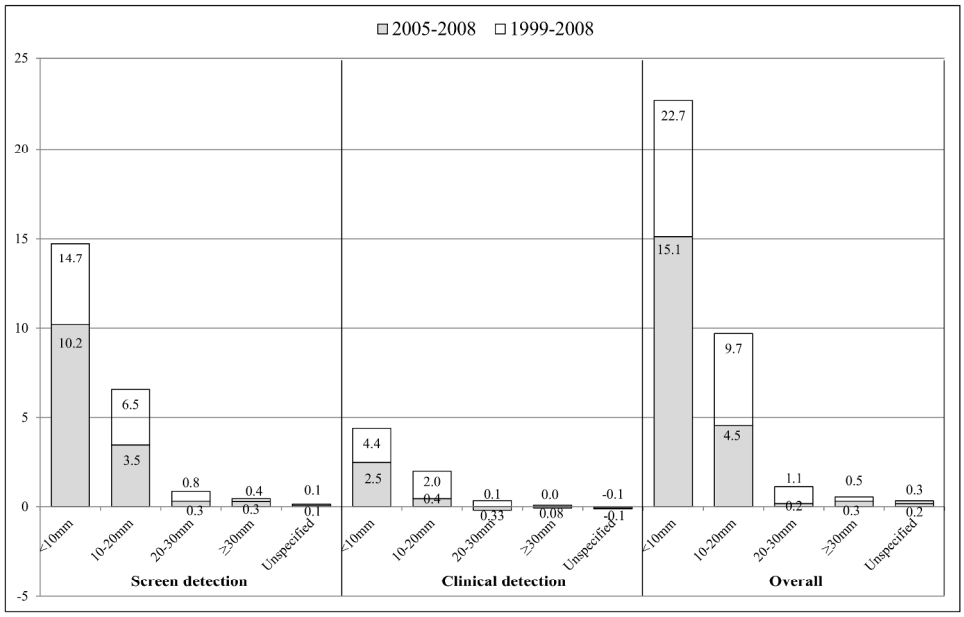


Figure 2A. Absolute change over time in thyroid cancer incidence by tumour size according to the detection routes

Figure2A

254x190mm (300 x 300 DPI)

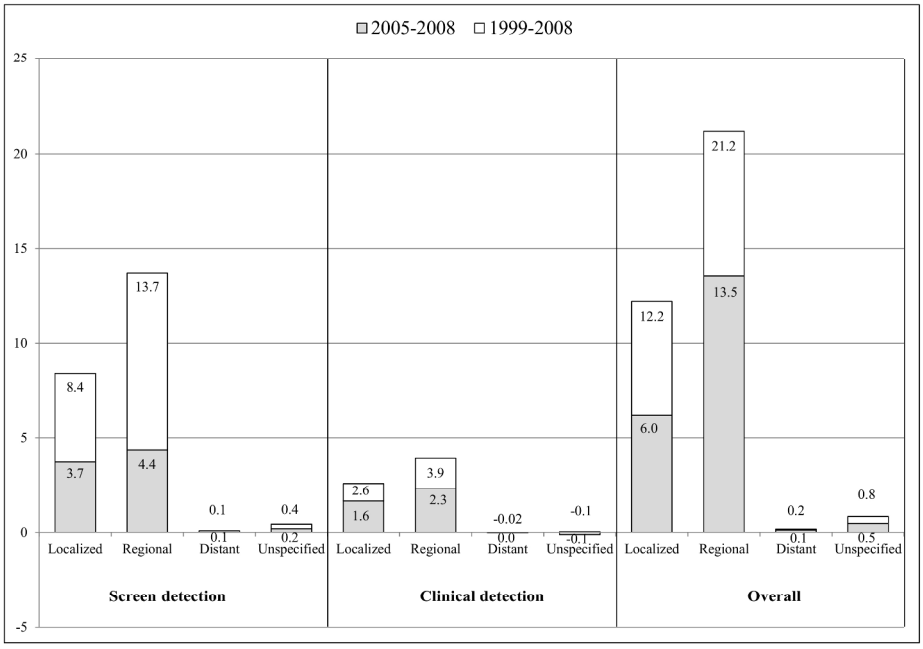
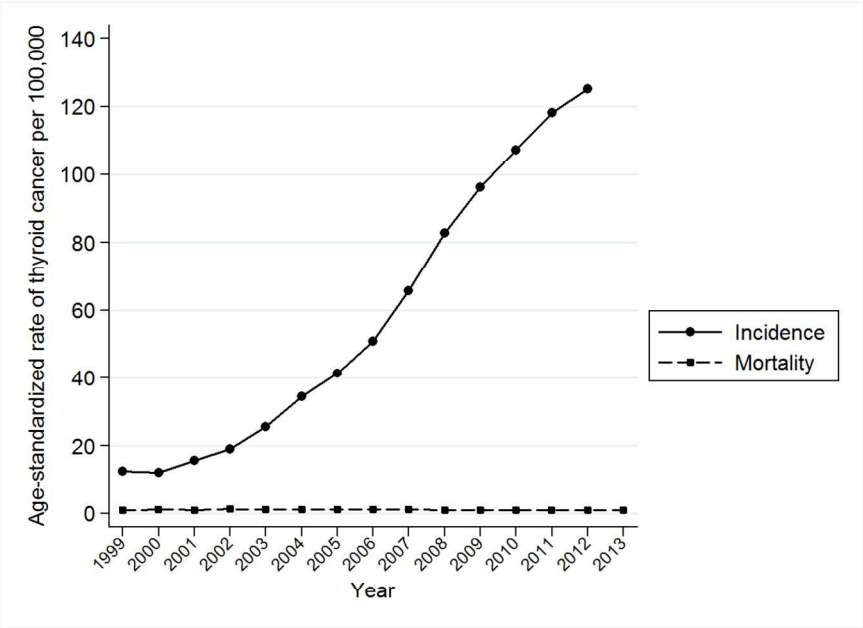


Figure 2B. Absolute change over time in thyroid cancer incidence by SEER summary stage according to the detection routes

Figure2B

254x190mm (300 x 300 DPI)



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