

## Executive Summary

### □ Part 1 : the current status of thyroid cancer screening

#### I. National Survey

A survey was conducted among 3,633 subjects with ages over twenty and less than seventy in order to examine their experience or plan for receiving thyroid cancer screening tests and their recognition on the risk of thyroid cancer.

846 (23.3%) subjects received thyroid ultrasonography. The examination rate was higher in women (31.3%) and those in their 50s (28.8%). 70.7% was found to be normal, 23.6% showed findings of thyroid nodules, and 1.9% was confirmed as cancer. As for the subjects found to have thyroid cancer, 87.5% among those with a nodule or tumor sized less than 0.5cm~1cm received thyroidectomy while those with a lesion over 1cm all received surgery for thyroid removal. Among patients with thyroid nodules, thyroidectomy was performed in 12.0% of the group with a nodule or tumor sized over 1cm, 6.7% in the group sized less than 0.5 cm, and 3.9% in sizes less than 0.5cm~1cm.

A group with plans to receive examination within 2 years and a potential group who wishes to receive examination within 2 years or sometime in the future were defined to examine factors that affect thyroid examination plans. In sociodemographic factors, women, married persons, and those with a higher income level tended to receive examination. In the potential group, a tendency for examination was remarkable especially in those with an educational level of college graduate or higher and in public health officers. As for health behavior factors, those with a past medical history or

family history of cancer and the group who experienced examinations such as national cancer screening, personal cancer screening, or thyroid ultrasonography showed a higher tendency to receive examination. Also, smokers compared to non-smokers, those who exercised 1~2 times per week, sleep 6 hours or less, and think they are not healthy tended to have plans for receiving examination. The group that actively searches for health information was more interested in health examination. When analyzing based on the Theory of Planned Behavior, people who are worried about thyroid cancer, who were recommended by family, friends, or doctors, and those who meet requirements on cost, time, and distance tended to receive examination. The potential group especially showed a tendency to receive examination if the cost, time and distance conditions are satisfied. A survey was conducted among the general population to examine their knowledge on thyroid cancer. As a result, over half of the subjects were aware of the survival rate, difference in occurrence by gender, and prognosis of thyroid cancer. Those who knew more accurately about the information tended to receive examination.

The recognition level of the risk of thyroid cancer was rather lower than other malignancies such as gastric cancer, colon cancer, lung cancer, liver cancer, cervical cancer, prostate cancer, but was higher than breast cancer. Among factors affecting the recognition of thyroid cancer risk, women, age group in their 30s, married people, educational level of college graduate or higher, office workers and housewives showed a higher recognition of risks. In terms of health behavior, the group with a past medical history or experience of examination including those with a family member with a past medical history of cancer, those who received personal cancer screening or thyroid ultrasonography, smokers, frequent drinkers, those who do not exercise often, those with an irregular diet habit, those who sleep 6 hours or less, and people who considered themselves as unhealthy showed a higher recognition of risks of thyroid cancer. People who actively searched for health information appeared to have a higher recognition of thyroid cancer risk. Other factors that were relevant with thyroid cancer risk

recognition were following: 1) people who were concerned and worried about thyroid cancer, 2) people who were negative about their own health, 3) people who had faith in their physicians and considered early screening as beneficial, 4) people referred by surroundings, 5) and those whose time, distance, and cost conditions were satisfied. Also, a structural equation model was created with 8 potential variables (pursuing media information, risk attitude (fatalism), socioeconomic status, faith, health condition, understanding risks, and recognition of risks) and 21 observatory variables to analyze determinants of receiving thyroid ultrasonography. As a result, recognition of risks was the most decisive factor for thyroid cancer screening and risk attitude (fatalism) was the most greatly affected factors that created risk recognition.

## 2. Health Screening Center Survey

An investigation was conducted among health examination centers to identify the status of thyroid ultrasonography tests. A percentage quota extraction by region was done for the questionnaire completion rate which was 10% in clinics and 19% in hospitals. As for the subject who carried out the thyroid ultrasonography, medical specialists took part in 81.3% at clinics and in 72.0% at hospitals, while the percentage of the chief engineer performing the test appeared relatively higher as 14.0% at hospitals compared to 5.6% at clinics. The response to the question on ultrasonography test period varied from 1980 to 2011. 35.2% of tests were performed at clinics while 41.3% were done at hospitals in year 2002. This changed to 58.2% and 41.3%, respectively after 2002. It appeared that ultrasonography was introduced relatively earlier in hospitals. The number of ultrasound machines ranged from a minimum of 1 to 12 at maximum. 92.8% of clinics had one machine, 5.7% had two, while 65.0% of hospitals occupied one machine, 17.5% had two, 8.4% had three, 4.2% had four, and 3.5% had five. Hospitals appeared to have more machines than clinics. The

number of doctors performing ultrasonography ranged from one to seven. 86.4% of clinics had one doctor, 10.4% had two, and 2.5% had three. 53.8% of hospitals occupied one doctor, 25.9% had two, 11.2% had three, 3.5% had four, and 2.1% had five. Over 95% of clinics and about 80% of hospitals had 1~2 medical examination doctors. The response for the presence of radiology specialists ranged from none to six. 88.3% of clinics appeared not to have any radiology specialist, while 9.5% had one, 1.6% had two. 18.2% of hospitals did not have a radiology specialist while 49.0% had one, 18.9% had two, and 7.7% had three. About 81% of hospitals appeared to have at least one radiology specialist compared to the 11% in clinics. The average number of patients receiving thyroid ultrasonography in the recent month was  $30.92 \pm 90.47$  at clinics and  $80.87 \pm 129.97$  at hospitals. The monthly average number of office workers among patients was  $7.28 \pm 69.54$  at clinics and  $22.08 \pm 61.22$  at hospitals. The average amount that a person pays for a thyroid ultrasound examination was 38,420±17,830 won in average (32,670±12,680 won at clinics, 54,650±20,160 at hospitals).

### 3. Physicians Survey

In order to examine the status of thyroid ultrasonography of medical examination doctors, a telephone survey was done to inquire about the consent on the questionnaire. The survey was conducted among 102 medical examination doctors. Doctors in their 40s (63.73%), men (82.35%), and radiology specialists (46.08%) were dominant. 93.14% appeared to have less than 10 thyroid ultrasonography patients per day in average. A low percentage of 35.29% of doctors responded that they performed thyroid ultrasonography in 'less than 5%' of asymptomatic patients, but 15.69% responded that they performed the test in 'over 50%' of asymptomatic cases, showing a different tendency depending on the doctor. 44.12% responded to have been performing thyroid ultrasonography before 2002.

49.02% answered that they learned to perform thyroid ultrasonography during their training period. 79.41% answered that the examination time per patient was 'less than 10 minutes' while all doctors responded as less than 20 minutes.

#### **4. Estimate the cost of Thyroid ultrasonography for screening**

Korea expends from 121 billion to 1,490.5 billion won annually for thyroid ultrasonography tests. 132.1 billion won is spent as an annual thyroid ultrasonography expenditure. Abnormal findings are detected in 858,205 among 3,232,560 patients. The average expected cost for one abnormal thyroid finding in a patient from thyroid ultrasonography appeared as 153,938 won.

Also, at least 125 billion won to a maximum of 1,516.6 billion won is expended when including additional tests (FNAC) after thyroid ultrasonography. When the sum of thyroid ultrasonography cost and additional test cost is 136 billion won, the number of patients confirmed as thyroid cancer appeared as 15,494 persons. The average expected cost for the detection of one thyroid cancer patient through thyroid ultrasonography and additional tests was 8.78 million won. The expected cost of detecting one thyroid cancer patient ranged from 3.87 million to 27.62 million won.

#### **5. Data Analysis of Health Insurance Review and Assessment Service**

As a result of analyzing the Health Insurance Review and Assessment Service claim data from 2006 to 2010, new thyroid nodule patients including benign thyroid tumors increased about 21% (10.5% annually) from 283,844 in 2008 to 343,532 in 2010. It increased 16% (8.0% annually)

after the population structure revision from 7.5 to 8.7 persons per 1,000.

111,262 patients (39.2%) received fine needle aspiration biopsy within 1 year of follow-up period among the 283,844 new thyroid nodule patients in 2008. Among those patients, 16,398 patients (14.7%) were diagnosed as thyroid cancer.

As for the risk factors of cancer in thyroid nodule patients, the young age group from 20-49 years of age showed a relatively higher cancer rate than the older group. Analysis of risk factors was limited due to the absence of information on the size or shape of the nodule.

In this study, about 400 thousand won was spent as the cost due to the thyroid nodule within 6 months after diagnosis, excluding the past average medical expenses. About 100 thousand won was additionally expended every 6 months for 18 months afterwards. When calculating as 281,006 patients excluding the top 1% of costs in the total thyroid nodule patients, about 200 billion won was assumed as health insurance expenses due to thyroid nodules. The cost for thyroid nodules was higher in the older age group than in the younger group and it also appeared higher when accompanied diseases were more severe.

In this study, the occurrence of post-surgical adverse effects and its costs were also investigated among thyroid cancer patients in 2008. Hypoparathyroidism occurred in 5.7% of patients who received surgery, while vocal cord paralysis developed in 1.7%. As for the comparison by surgical technique, complications occurred the most in patients who received radical resection of malignant thyroid tumors and total thyroidectomy (radical resection of malignant thyroid tumors : hypoparathyroidism: 6.7%, vocal cord paralysis 1.8%, both total thyroidectomy : hypoparathyroidism: 5.7%, vocal cord paralysis 1.6%).

The health insurance benefits due to thyroid cancer in new thyroid cancer patients excluding the past average medical expenses were 2 million won within 2 months, and then 4 million, 6 million, and 3 million won every 6 months.

## □ Part 2 : Effectiveness of ultrasonographic screening for thyroid cancer

An issue of whether early diagnosis and early treatment of thyroid cancer are beneficial to patients is being suggested, as the occurrence of thyroid cancer has rapidly increased in Korea recently and is appearing higher than other countries. In this study, the effects of thyroid cancer screening using ultrasonography which is the representative screening test were investigated.

### I. Study Methods

The purpose of this study is to evaluate whether thyroid cancer screening tests using ultrasonography are effective in healthy subjects. A systematic review was done based on studies published until now.

A scale evaluating the effects of the USPSTF was used for this study to establish Key Questions 1~4.

Key Question 1 : Would ultrasound thyroid screening and treatment raise the likelihood of early detection of thyroid cancer and reduce the risk of recurrence and death?

Key Question 2 : Is ultrasonography an accurate test for thyroid cancer screening?

Key Question 3 : Is the natural death of thyroid cancer detected from screening different from that of thyroid cancer found with symptoms?

Key Question 4 : Is delayed treatment different from early treatment effective in reducing mortality rate or preventing recurrence of papillary thyroid microcarcinoma (PTMC)?

We carried out a systematic review about each key question. Research was done through Ovid-Medline, Ovid-EMBASE, Cochrane Library(CENTRAL) and five Korean domestic databases. RoBANS was used for assessing risk of bias of studies in Key Questions 1,3, and 4, while QUADAS II was used

for Key Question 2. Quantitative synthesis was possible in Key Question 1 and meta-analysis was performed. This was not done in other Key Questions and results of selected studies were presented. Final conclusions were set by applying classification of evidence and recommendations of USPSTF for outcomes of each Key Question. GRADE was used in Key Questions 1 and 4 to proceed with additional classification of evidence and recommendations.

## 2. Study Results

### 2.1. Key Question 1

6 articles were chosen as final studies. These included 3 Korean articles, 1 was from Japan, 1 from the U.S, and 1 from Italy. 4 articles were cross-sectional studies and 2 were cohort studies. As for the risk of bias of studies assessed with RoBANS, 1 showed a low risk of bias and the other 5 were uncertain. When examined by domain, the risk of bias was rather low in the 'measurement of mediation' while 'low' and 'uncertain' was each 50% in the 'selection of participant'. The risk of bias was uncertain in the remaining domains. The percentage of stage I in detected cancers was 59-97% in the screening group and 53-81% in the control group. No studies showed a significant difference between the two groups. However, analysis of the three studies which were able to carry out meta-analysis indicated that the non-screening group had RR 1.14 times higher (95% CI 1.04-1.26) rate of stage I than the ultrasonography screening group. Cases of stage II~IV, recurrence, distant metastasis and other outcomes did not show any difference between the two groups. There were no studies that presented harm as an outcome. GRADE was used to classify the quality of evidence and recommendations. As a result, the quality of evidence was assessed as 'very low' in all outcomes. The level of recommendation of ultrasonography screening for thyroid cancer was 'low' and was 'not recommended'.



## 2.2. Key Question 2

11 articles were chosen as final studies. 1 study was held in Hong Kong while the other 10 were cross-sectional and follow-up studies held in Korea. 7 studies were held among breast cancer screening and follow-up patients, while subjects in 4 studies did not have any past medical history on the thyroid.

The studies included were all cross-sectional studies and their qualities were not low. Sensitivity and specificity values were required in order to examine whether ultrasonography was accurate for thyroid cancer screening. However, there were no articles that presented an accurate sensitivity and specificity. Only 3 articles indicated limited sensitivity and specificity values obtained from standard laboratory test subjects. In these 3 studies, the sensitivity values were all high being 0.94 while specificity varied from 0.33 to 0.66. Simple values of limited sensitivity may suggest that the test is very accurate for detecting cancer. However, this was only assumed by using limited data and there were only a few studies available. Evidence was insufficient for concluding whether thyroid ultrasonography is an appropriate thyroid cancer screening test.

According to the evidence level of USPSTF, previous studies on whether ultrasonography was an accurate test for thyroid cancer screening showed a relatively high quality but the evidence presented was inadequate.

## 2.3. Key Question 3

There were no appropriate articles for Key Question 3.

## 2.4. Key Question 4

One article was chosen as the final study. There were 2 more articles written by the same author, but subjects were included in the final article and only one was chosen. This was a prospective cohort study held in Japan. Ito et. al. gathered a patient group diagnosed with papillary thyroid microcarcinoma without any findings indicating poor prognosis and let them

choose between surgery or careful observation. The group of 340 patients (26M, 314F) that chose careful observation received thyroid ultrasonography once or twice a year to check tumor size changes and lymph node metastasis. Follow-up was done for 74 months (18~187). The 1055 patients who chose surgery (964F, 91M) received only surgery and a follow-up period of 76 months (1~183). Among the observation group, 109 patients (32.1%) received surgery during the follow-up period. 7 of the observation group (2.1%) and 9 of the surgery group (0.1%) showed novel LN metastasis during follow-up. The lymph node metastasis rate did not show any difference between the two groups during follow-up ( $p>0.05$ ). Harmful results were not presented as outcomes. The quality of study showed low in the measurement of mediation, incomplete outcome variable, and selective outcome report. The risk of bias was uncertain in blinding of subject selection, confounding variables, and outcome variables.

The level of evidence was assessed as very low when evaluated from GRADE. It was also assessed that evidence was inadequate for Key Question 4 in the USPSTF recommendation level assessment.

### 3. Level of Evidence and Strength of Recommendation

According to the USPSTF evidence level and recommendation grading assessment, all key questions except key question 3 which lacks a selected research outcome were evaluated as inadequate.

Taken these study results and evidence level together, the ultrasonography screening test of thyroid cancer in asymptomatic people corresponds to low among High/Moderate/Low in the certainty of net benefit. If it is assessed as low in the certainty of net benefit, the strength of evidence is evaluated as insufficient regardless of the magnitude of net benefit.

Therefore, we conclude that the current evidence is insufficient to assess the balance of benefits and harm of US thyroid cancer screening in the asymptomatic population.

## 4. Conclusion

Currently, there is insufficient evidence for assessing the effectiveness of thyroid cancer screening using ultrasonography among asymptomatic healthy population. Thus, studies presenting a basis on the effectiveness of thyroid cancer screening tests using ultrasonography would be required in the future.