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The association between iodine, ionizing radiation, hormonal factors and thyroid cancer in the Korean population

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김경식

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Abstract

Introduction: The debate over thyroid cancer in South Korea is still controversial, and the age standardization incidence rate has continued to decrease since 2012 but has been on the rise again since 2015. In 2019, thyroid cancer was the most common cancer in the Korean population, with a standardized incidence rate of 52.3 per 100,000 people and higher in women than men (79.6 per 100,000 women; 25.9 per 100,000 men).

In the meantime, several studies have reported risk factors for thyroid cancer, but only ionizing radiation is sufficient evidence in the world. Also, the association between reported other factors and thyroid cancer differed all over the world. Therefore, high thyroid cancer in the Korean population issue needs to be considered for specific factors in Koreans.

This study aims to evaluate the risk of thyroid cancer based on the iodine intake status which considered the Korean specific dietary habits and medical ionizing radiation exposure. In addition, we would like to estimate the detailed dose to the thyroid organ which is a more accurate radiation exposure dose. Based on the tumorigenesis according to the ionizing radiation exposure, this study aimed to assess the DNA methylation and lead to thyroid

cancer. Plus, considering the association between breast cancer and thyroid cancer, national big data analysis was conducted. Based on the hypothesized common etiology between the two cancers, estrogen receptor-related markers were assessed both in breast cancer and thyroid cancer in DNA methylation analysis. Also, the association between reproductive factor and thyroid cancer was considered.

Ultimately, it is expected that effective prevention policies for high Korean thyroid cancer will be implemented and contribute to reducing the incidence of thyroid cancer.

Methods: A case-control study was conducted in the papillary thyroid cancer cases from the hospital-based thyroid cancer prospective cohort. Controls were selected from the community-based population which did not diagnose thyroid cancer. As the study population, the cases defined 427 patients with papillary thyroid cancer who were identified as having urine iodine information and tumor size of 0.5cm or more, and 479 controls with no history of thyroid cancer and other cancers were included. Logistic regression analysis was applied to determine the association between thyroid cancer according to the iodine

exposure level, and the odds ratio and 95% confidence interval were calculated accordingly.

In addition, to understand the association between thyroid cancer due to therapeutic radiation exposure, second thyroid cancer risk in childhood patients was assessed as a systematic literature review and meta-analysis. In addition, the association between medical ionizing radiation of thyroid cancer was assessed in the general population between 2006-2009, and cancer incidence and death followed until December 31, 2019. In this study, medical ionizing radiation exposure is defined as computerized tomography and estimated the thyroid exposure dose from the tool of the Korean Disease Control and Prevention Agency. In addition, we tried to assess the dose-response relationship by categorizing them into categories based on a continuous scale according to the annual dose limits, and other reference values. In addition, the previously reported epigenetic markers related to ionizing radiation were identified in thyroid cancer and assessed the linked mechanism.

Considering the common environmental exposure of breast cancer and thyroid cancer, the association between breast cancer and thyroid cancer was identified in the general population (Korea

National Health Insurance Database as both cohort, nested case-control study) and DNA methylation analysis both in breast cancer (Illumina 850K, 24 Korean women) and papillary thyroid cancer (Illumina 850K, 40 Korean women) and additional functional assessment based on Kyoto Encyclopedia of Genes and Genomes, Gene Ontology, Reactome, and WikiPathway.

Furthermore, a case-control study was conducted to assess the association between reproductive factors and thyroid cancer.

Results: When evaluating the association between thyroid cancer and the iodine intake status, more than 90% of papillary thyroid cancer patients were exposed to excessive iodine, and only 50% of the control group were exposed to excessive iodine. The papillary thyroid microcarcinoma group (tumor size, 0.5-1 cm) showed a strong association (OR, 8.97; 95% CI, 5.07-15.90), and papillary thyroid cancer (> 1 cm) showed a stronger association (OR, 31.49; 95% CI, 13.02-76.16). Considering both iodine intake level and thyroid function, the association between thyroid cancer was strong when the iodine intake level was high and free thyroxine was high, and a similar tendency was shown at high thyroid stimulating hormone levels.

In the case of secondary thyroid cancer following therapeutic radiation exposure in childhood patients, a total of 7 studies were found to be significant in both the overall study (RR, 5.09; 95% CI, 3.51−7.37). In the case of thyroid cancer risk from ionizing radiation exposure, the hazard ratio was statistically significant as 1.16, 95% CI, and 1.12−1.30 in CT exposure. In detail, it showed the dose−response relationship considered in radiation exposure frequency (1−2 times, HR, 1.04; 95% CI, 0.97−1.11; 3−10 times, HR, 1.21; 95% CI, 1.14−1.26; more than 10 times, HR, 2.90; 95% CI, 2.24−3.76) and CT dose (3−5 mSv, reference; 5−9.9 mSv was not associated with thyroid cancer risk (1.46; 1.15−1.82) and over 10 mSv only associated with thyroid cancer risk (5.20; 3.10−8.68). Also, in the case of DNA methylation change from the ionizing radiation exposure, 10 genes were identified in thyroid cancer methylation data in which ldelta m−valuel is higher than 0.25 and FDR less than 0.10. In the functional assessment, GO molecular function (histone deacetylase activity, protein lysine deacetylase activity), GO biological process (peptidyl−lysine deacetylation, skeletal muscle fiber development, histone H4 deacetylation, histone H3 deacetylation), CORUM (HDAC4−ERK2 complex), and

WikiPathway (Ethanol effects on histone modifications) were identified.

In the general population, thyroid cancer according to breast cancer was associated (HR, 3.26; 95% CI, 2.44−4.36), and in 2-year lag periods, it was consistently associated, HR, 2.13; 95% CI, 1.45−3.13). Considering the share etiology based on the estrogen receptor five common estrogen receptor binding site gene was identified both in thyroid cancer and breast cancer, and IQGAP1 is related to the ERK signaling pathway.

In this study, menarche after 16 years old was protectively associated with thyroid cancer compared to before 13 years old menarche (OR, 0.38; 95% CI, 0.26−0.48). Oral contraception use and hormone replacement treatment both were protectively associated with thyroid cancer (Oral contraception, OR, 0.79; 95% CI, 0.61−0.97; hormone replacement treatment, OR, 0.68; 95% CI, 0.54−0.96).

Conclusion: According to the findings of this study, excessive iodine intake had a significantly higher risk of developing PTC and PTMC compared to people whose iodine intake was adequate. The combination of an excessive iodine intake and a high level of free T4 had a synergistic effect on raising the risk of PTC and PTMC;

on the other hand, the combination of an excessive iodine intake and TSH resulted in a rapid increase in the risk of PTC and PTMC at excessive iodine intake.

In the meta-analysis, the risk of secondary thyroid cancer from therapeutic radiation exposure was evaluated for pediatric and adolescent patients, and the association was identified. Also, in low-dose medical radiation and thyroid cancer risk, CT exposure was associated with thyroid cancer risk. Plus, along with the simple exposure status, the frequency of CT exposure and exposed CT dose classification was associated with thyroid cancer. In DNA methylation change according to ionizing radiation exposure, markers which ldelta m-valuel over 0.25 and FDR less than 0.10 were related to histone deacethylase activity, protein lysine deacethylase activity, histone H4 deacethylation, histone H3 deacethylation, HDAC4-ERK2 complex, and ethanol effects on histone modification. The tumorigenesis mechanism from the ionizing radiation would be followed as above, but there would be a specific mechanism based on the previous studies. First, the FMO1 gene is related to PTC occurrence and free survival, therefore FMO1 expression is protectively associated with recurrence-free survival in PTC. However, due to ionizing radiation exposure, it

would not work properly (FMO1 gene expression independently predicts favorable recurrence-free survival of classical papillary thyroid cancer). Also, the HDAC9 gene which affects histone deacetylase is known to affect the dysregulation of the thyroid gland and autoimmune thyroid disease. (Analysis of Expression of Different Histone Deacetylases in Autoimmune Thyroid Disease). A previous study reported that it related to the expression of transcription factor activation of NF-kB and the synthesis of pro-inflammatory cytokines.

In Korean National Health Insurance Database, the association between breast cancer and thyroid cancer was identified, and it can hypothesize the share link between breast cancer and thyroid cancer. Lastly, the common DNA methylation markers based on the estrogen receptor were considered both in breast cancer and thyroid cancer. Between thyroid cancer and breast cancer, IQGAP1 is activated by estrogen receptor alpha activation, which then leads to ERK1/2 activity increases, ultimately affecting PTC. Also, IQGAP1 plays an important role in cell proliferation and invasion in human breast cancer cells.

Consequently, the association between various factors and thyroid cancer considering the Korean environment was evaluated, and it is

necessary to organize Korea's own specific cancer management and prevention. Additionally, epigenetics markers could provide some clues for cancer treatment based on the specific mechanisms in thyroid patients.

Keywords: Thyroid neoplasms, iodine intake, ionizing radiation, DNA methylation, hormone factors, estrogen receptor, big-data analysis. Epidemiological study

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Contents

List of tables and figures

Introduction

1.1. Thyroid cancer incidence and mortality worldwide

The incidence of thyroid cancer worldwide is increasing. On the other hand, thyroid cancer mortality has been decreasing. In 2020, thyroid cancer incidence is the ninth most common cancer in the world, and half of the cancer cases occurred in the East Asian population. Also, more than 90% of all cases consisted of high-development index countries. But, only 30% of all mortality cases are from the East Asian population (1).

The detailed incidence rates in each country, Canada showed the highest age-standardized incidence rate (17.4 cases per 100,000) in North America. Italy was the highest in Europe (16.1 cases per 100,000), and Australia, China, and Brazil (11 cases per 100,000, Globocan). Considering gender, women show a different incidence between about 2-9 times that of men (2). For men, Canada and Italy (7.8 cases per 100,000) showed high incidences except for South Korea. The United States showed 6.1 cases per 100,000, and 5,4 cases per 100,000 in China. This trend was similar in women (Canada, 26.9 cases per 100,000; Italy, 24.6 cases per 100,000; France, 23.1 cases per 100,000, Globocan).

In the case of mortality rate, Samoa showed the highest age-standardized mortality rate (2.7 cases per 100,000) and followed by Vanuatu (2.1 cases per 100,000) and Papua New Guinea (1.9 cases per 100,000). Compared to these countries, the United States, China, and Italy's mortality rate showed lower than 0.5 cases per 100,000. In men's thyroid cancer age-standardized mortality rate, only Togo and Nepal exceeded 1 case per 100,000 worldwide, while the United States, Italy, China, and Brazil showed lower than 0.3 cases per 100,000. In women, their mortality rate showed a similar pattern as the overall population, and the order of Samoa (5 cases per 100,000), Vanuatu (4.2 cases per 100,000), and Papua New Guinea (3.2 cases per 100,000) showed the highest mortality rate in the world. Similar to the overall population, (1).

1.2. TC incidence and mortality in Korea

As of 2019, there were 30,676 thyroid cancer patients in South Korea, and it ranked as the most common cancer (52.3 cases per 100,000). According to the men and women, the age-standardized incidence rate was 25.9 cases and 79.6 cases per 100,000, respectively. Based on the thyroid cancer trend, the incidence rate increased sharply in the 2000s and gradually decreased in 2012.

During the period, the annual percent change between 1999 and 2009 increased by 26.3% annually in the total population and increased by 15.2% and 10.9% for both men and women between 2009–2012 (3). Compared to the previous period, in 2012–2016, it had decreased by 11.8% and 16.3%, both men and women every year. But between 2015 and 2019, it increased again by 8.5% and 3.1% for both men and women.

The 5-year survival rate of thyroid cancer was 94.5% in 1993–1995, 95% in 1996–2000, 98.4% in 2001–2005, and almost 100% after 2006. Along with the good prognosis, most thyroid cancer in the Korean population consists of papillary thyroid cancer (PTC). In the case of thyroid cancer mortality, 365 people died of thyroid cancer in 2020, which was 0.7 cases per 100,000 in South Korea. Compared to gastric cancer, gastric cancer showed 20 times higher than thyroid cancer in 2020 (7,510 cases of death from gastric cancer; 14.6 cases per 100,000) (4).

1.3. Basic treatment and alternative treatment for TC

In the case of differentiated thyroid cancer, including papillary thyroid cancer, thyroidectomy, radioactive iodine treatment, and thyroid stimulating hormone suppression are commonly treated.

Except for these treatments, removal of metastatic lesions, high-frequency removal, and ethanol injection is conducted as additional treatments. The main surgery treatment consists of lobectomy, total thyroidectomy, and near total thyroidectomy, and total thyroidectomy was the usual surgery in the past. In current papillary thyroid cancer, which the tumor size is less than 1cm, no capsule invasion, a good prognosis, and without metastasis, lobectomy can be conducted on the patients. In the case of total thyroidectomy and near-total thyroidectomy, both usually conduct for residual thyroid tissue. Also, thyroid active treatment aims to reduce thyroid cancer recurrence and progression. In the case of hormone therapy, it aims to make stable metabolic status and suppress the TSH level, because usual differentiated thyroid cancer cell growth depends on TSH level, so its recurrence could be restricted.

Instead of universal treatment from the past, an alternative treatment has recently emerged. Active surveillance in thyroid cancer was first recommended as an alternative treatment by the thyroid society in 2015 and 2016. As a treatment, the following patients can be considered active surveillance instead of surgery; 1) very low-risk cancer patients (clinically no metastasis and invasion in papillary thyroid microcarcinoma); 2) not available for surgery due

to other comorbidities; 3) short life expectancy. Except for 2) and 3) most papillary thyroid microcarcinoma patients can be applied active surveillance but there was no evidence for that. To present the optimal treatment between surgery and active surveillance for papillary thyroid cancer patients, objective evidence should be considered based on the real-world situation (8).

1.4. Economic burden of TC

Although alternative treatment is suggested in the real world, along with the thyroid cancer incidence increasing, the economic burden is increasing during this time. Evaluating the economic burden of thyroid cancer patients from 1992 to 2009 based on The Surveillance, Epidemiology, and End Results Program, $1.4 billion was spent in 2010 and $2.38 billion was spent in 2019 (5). Domestic treatment cost based on the National Health Insurance Database, the first year of diagnosis spent 1,654,438 won in 2014, and 3,267,792 won. In the second year, 495,535 won were spent in 2004, and 708,602 won were spent in 2010, and the medical expense seemed to decrease after 5 years of diagnosis. In addition, the patient's burden of thyroid cancer treatment according to the national medical insurance system

also tended to increase compared to the past. Based on the social perspective, the increasing economic burden of thyroid cancer is due to 1) an increase in the number of thyroid cancer patients; 2) an extended life expectancy and high survival rate, and 3) inflation and currency value differences. However, based on the Korean National Health Insurance Database which can access the overall Korean population, it is difficult to consider the detailed thyroid cancer pathologic information. Therefore, it cannot evaluate the definite economic burden of papillary thyroid cancer patients. In addition to surgery treatment, active surveillance has recently been suggested as an alternative treatment, and there is no evidence of the lifetime economic burden for thyroid cancer patients (6,7).

1.5. Known risk factors of TC and other possible risk factors

1.5.1. Gender

Thyroid cancer incidence varies according to gender. In the United States, thyroid cancer is more common in women than men and it differed by three times from men (2). But it varied slightly depending on the thyroid cancer type. In the case of anaplastic thyroid cancer or medullary thyroid cancer, the incidence was not different between

men and women, and only follicular thyroid cancer and papillary thyroid cancer were mainly different. In South Korea, female thyroid cancer was seven times higher than male thyroid cancer in 2004, and it has decreased to three times difference (2005, 6.3 times difference; 2008, 5.5 times difference; 2013, 3.6 times difference) (9).

1.5.2. Ionizing radiation

Among the various risk factors, ionizing radiation is a risk factor known as sufficient evidence for thyroid cancer. The main mechanism of thyroid cancer the ionizing radiation, and the break of the double helix leads to mutation as oncogenesis (10). In detail, thyroid cells exposed to ionizing radiation, RET/PTC rearrangement is induced, and BRAF or RAS mutation occurs as a mutation. The source of ionizing radiation classifies natural radiation and artificial radiation. Recently, due to the device development and longer life expectancy, the frequency of artificial radiation exposure especially diagnostic radiation has been increasing. Among the diagnostic radiation exposure, previous studies reported that computer tomography and dental X-ray exposure were associated with thyroid cancer incidence. The childhood population is more susceptible to radiation exposure than adulthood, and much more people developed thyroid

cancer (11-13). In this situation, the childhood population is concerned about the second health effects of radiation therapy. Therefore, it is necessary to assess second health effects such as thyroid cancer. In addition, the health effects of low-dose radiation exposure (< 100 mSv) have been continuously reported, but it is still controversial. In the previous studies, they usually considered radiation exposure status, so the detailed exposed dose of the organ from each examination is needed

1.5.3. Obesity

For decades, several studies have reported the association between obesity and thyroid cancer. One of the studies suggested that there was a 30% increase in thyroid cancer risk by an increase in body mass index (BMI) 5 and a 14% increase in thyroid cancer risk by an increase in waist-hip ratio 0.1. Also, 10-year follow-up of 22 cohort studies from North America, Europe, Australia, and Asia, baseline BMI, waist-hip ratio, BMI in childhood, and BMI in adulthood were strongly associated with thyroid cancer. Especially, baseline BMI and an increase in the gap in BMI were strongly associated with ATC and overall thyroid mortality. Also, Korean population aged ≥ 18, both men and women with BMI ≥ 25 kg/m^2 were associated with

papillary thyroid cancer compared to BMI lower than 25 kg/m^2. (14–16). In addition, 450,000 USA population aged between 50–70, overweight and obese group were associated with papillary thyroid cancer compared to the normal group (17).

1.5.4. Alcohol consumption and smoking status

The association between thyroid cancer and alcohol consumption is controversial. A recent meta–analysis reported that alcohol consumption is protectively associated with thyroid cancer (RR, 0.74; 95% CI, 0.67–0.83), and it was consistently associated according to the study design. The possible mechanism is that alcohol consumption could reduce TSH levels, and animal studies reported that chronic alcohol consumption could decrease the response of the hypothalamus to central stimulation. Another possible mechanism was alcohol's direct toxicity to thyroid cells could reduce the thyroid's volume size, and it could protectively associate with thyroid cancer decrease (18). However, a recent study suggested that excessively high alcohol consumption associated with thyroid cancer increasing, and both men (OR, 2.21; 95% CI, 1.27–3.85) and women (OR, 3.61; 95% CI, 1.52–8.58) were consistently significant. Also, it was associated with papillary thyroid cancer but not with follicular

thyroid cancer (19). Along with alcohol consumption, smoking is also protectively associated with thyroid cancer (OR, 0.80; 95% CI, 0.68–0.94) in the previous meta–analysis. The related mechanism is smoking could increase the T3 and T4 levels and it consequently decreases the TSH level and the thyroid stimulation (20).

1.5.5. Family history of thyroid cancer

Along with other factors, a family history of thyroid cancer also suggested thyroid cancer risk factors, but there are few studies based on the Asian population (21). Some studies suggested it is a protective association, but other study suggested it is a risk factor. The Korean population–based study suggested that thyroid cancer history in each family member associated with thyroid cancer (father, OR, 6.59; 95% CI, 2.05–21.21; mother, OR, 4.76; 95% CI, 2.59–8.74; siblings, OR, 9.53; 95% CI, 6.92–13.11).

1.5.6. Genetic alteration

Even though many environmental factors and genetic factors are related to thyroid cancer, and it differed according to thyroid cancer differentiation. For example, RET, TRK alteration, and BRAF, RAS mutation are associated with papillary thyroid cancer (22). All of

them induced the oncogenesis based on the MEK-ERK signal pathway (23). Also, the genetic biomarkers could apply to thyroid cancer prevention as pre-diagnosis or prognosis prediction. In papillary thyroid cancer in the Korean population, BRAF mutation is common. Also, to assess the cancer association, many studies referred that epigenetic change could affect cancer development or progression (24). But there is a lack of studies based on the Korean-specific population.

1.5.7. Breast cancer and other factors

In the case of breast cancer, the incidence rate is increasing similar to thyroid cancer. According to the cancer statistics, the trend of incidence rate according to the age group was similar between thyroid cancer and breast cancer (4). Therefore, several studies suggested that it is linked as hormonal factors. Some studies assessed the association between thyroid cancer and breast cancer, but it was controversial. Also, there is lack of studies based on the Korean population, and it was conducted only in a small sample size. Therefore, additional study is needed. If two cancers are linked to each other, the most of paths would be based on hormone factors.

Therefore, it is necessary to identify the pathway which links to the estrogen receptor.

1.5.8. Iodine intake

Recently, iodine intake suggested as an additional risk factor for thyroid cancer. Iodine is an essential element of thyroid hormone synthesis which regulates metabolism or biochemical activity in humans (25). In previous studies, iodine deficiency or excessive status affects thyroid function and leads to thyroid diseases or cancer. But most of the studies focused on iodine deficiency and thyroid disease (25-27). Even though some studies assessed the association between excessive iodine levels and thyroid, it was controversial (28-30). The main reasons for the debate were as follows; 1) information bias of exposure assessment; 2) measurement errors in iodine intake; 3) non-consideration of detail race or population. For example, the Korean population intakes seaweed soup or other seaweeds on a regular diet, so their iodine intake could be higher than other populations and it can be exposed in a chronic lifetime. Also, considering the thyroid function affected by iodine intake, the association between thyroid diseases or thyroid

cancer needs and iodine intake needs to consider thyroid function simultaneously.

In addition, the iodine intake distribution in the general population, including adolescents varied by district (31, 32). Especially, most adolescents intake excessive iodine intake. In all districts more than half of the adolescents consumed excessive iodine intake, and Gwangju and Incheon consumed the highest iodine intake than other districts. Therefore, it is important to understand the iodine intake level in the general population.

1.5.9. Thyroid cancer in nuclear power plant

Thyroid cancer is a big issue for the entire Korean population, but many health issues have been raised population living near the nuclear power plants, after Fukushima nuclear power plant accident. After the accident, a high incidence of thyroid cancer has been reported in the surrounding area (33, 34). Also, several reports of thyroid cancer incidence from the residents around the Korean nuclear power plant have been reported (35–37). Even though continuous disputes and lawsuits of thyroid cancer incidence according to the nuclear power plant report, the association between thyroid cancer and living near the nuclear power plant is

not clear. Therefore, it is necessary to consider the thyroid cancer incidence in the community population living near nuclear power plants as well as the general population.

1.5.10. Detection bias

In addition to the factors mentioned, detection bias should be considered as an additional risk factor for Korean thyroid cancer. Detection bias was identified due to the diagnostic devices development and increasing medical use in current environments. Especially, it is one of the major health issues in South Korea. In the previous report in 2009, 16% of female thyroid cancer patients were diagnosed due to the screening, and its rate had been increasing over the years. Plus, a previous study suggested a high correlation between regional screening rate and thyroid cancer incidence (38). Also, a high proportion of thyroid cancer which a tumor size lower than 1cm in the South Korean population (39). In detail, between 1999 and 2008, thyroid cancer due to the screening detection consisted between 2005 and 2008. Therefore, consideration of detection bias in South Korea is one of the important factors to understand the high thyroid cancer incidence rate.

1.6. Imperativeness of the study

Situation of the high incidence rate of thyroid cancer and the increasing economic burden, a new cancer management strategy and identification of Korean-specific risk factors is needed. In this study, iodine intake was considered as the Korean-specific factor based on Korean dietary habits. Also, compared to the previous studies, it considered both iodine intake and thyroid function to assess thyroid cancer as iodine metabolism in humans.

In the case of ionizing radiation, there was a lack of systematic review on the second thyroid cancer on high-dose radiation (radiation therapy). In low-dose radiation exposure, most of the medical radiation exposure did not consider the detailed exposed dose except for radiation exposure status. Plus, due to the lack of a detailed exposed dose in each organ, exact health effect assessment was limited in previous studies. Therefore, this study considered the systematic review of the high-dose effect on second thyroid cancer and low-dose radiation exposure on medical radiation (computed tomography) considering detailed organ dose. In addition, there is no study about an epigenetic marker according

to radiation exposure which leads to papillary thyroid cancer development, so it aimed to conduct the in-silico DNA methylation. Although the high incidence of thyroid cancer and breast cancer seem to have similar incidence trends, the association is controversial and there was a lack of studies on the Korean population and a small sample size. So, this study aimed to conduct big-data analysis based on more subjects. Furthermore, to identify the pre-biomarkers which shared the same path based on the estrogen receptor between thyroid cancer and breast cancer, DNA methylation was conducted in this study.

Purpose and hypothesis

2.1. Objective

First of all, in assessing the potential risk factors of thyroid cancer in the Korean population, the association between iodine intake and thyroid cancer based on urinary iodine concentration was considered. In addition, combined effect of both iodine intake and thyroid function was considered. Thus, it can contribute to the Korean-specific thyroid cancer risk factor for cancer management.

In the case of ionizing radiation, it is known as Group 1 carcinogen by the International Agency for Research Cancer. However, considering the radiation susceptibility in the childhood population and the second health effect of high-dose radiation such as radiation therapy is needed. Thus, it aims to assess the overall radiation therapy effect on thyroid cancer as a systematic review and meta-analysis. As low-dose radiation exposure, considering the increase in medical use, it aims to assess the thyroid cancer risk according to CT exposure. In detail, exposed dose and detailed treatment type were considered. As an epigenetics aspect, it aims to evaluate the genomic aberration in thyroid cancer due to ionizing radiation exposure as DNA methylation.

In addition, for the still controversial association between thyroid cancer and breast cancer, this study aims to identify sharing epigenetics markers and path through population-based big data analysis and DNA methylation analysis as estrogen receptor mechanisms.

2.2. Hypothesis

(1) Hypothesis of the association between iodine intake and thyroid cancer

① Excessive iodine intake would significantly associate with thyroid cancer.

② Both excessive iodine intake and thyroid dysfunction would significantly play a role in thyroid cancer

(2) Hypothesis of the ionizing radiation and thyroid cancer

① High-dose medical radiation (radiation therapy) would significantly associate with second thyroid cancer in the childhood population

② Low-dose medical radiation (CT) would be associated with thyroid cancer risk in both exposure status and detailed organ exposure dose estimation could apply to assess thyroid cancer risk

③ Based on the epigenetic aberration according to ionizing radiation, specific markers would lead to the thyroid cancer

(3) Hypothesis of breast cancer and thyroid cancer

① Several reproductive factors would associate with thyroid cancer

② Breast cancer would associate with thyroid cancer in the Korean population

③ There would be sharing pathway between thyroid cancer and breast cancer at the epigenetic level especially the estrogen receptor path

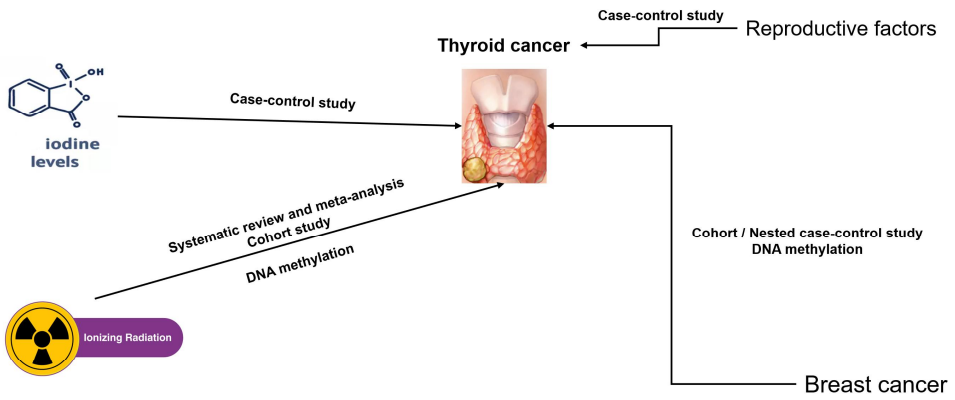

Figure 1. Research diagram of the association between iodine, ionizing radiation, other factors and thyroid cancer in Korean population based on environmental and epigenetic bio-markers.

Figure 1. Research flow of the study.

Methods & Material

Part 1. Iodine intake and thyroid cancer

3.1. Iodine intake and TC in case-control study

3.1.1. Data and study design

This study is a case-control study between papillary thyroid cancer cases and the general population who did not have any cancer history. All of the cases were derived from the Thyroid Cancer Longitudinal Study, which consisted of 5,000 thyroid cancer prospective cohort studies (40). The baseline registration was from April 2010 to December 2014, and they were recruited from Seoul National University of the hospital, Seoul National University of Bundang hospital, and the National Cancer Center. Eligible cases were subjects who identified pathological information and voluntarily participated over 20 years. Also, subjects can collect both urine and blood samples with a baseline questionnaire.

As a questionnaire, demographic factors, individual history, lifestyle, medical history, family history, and food frequency were included. Also, each subject collected 16 ml of a blood sample which is fasting glucose status and divided it into serum, plasma, DNA, and

10 ml of urine in the deep freezer at −70 C. The control group was a community population that lived in four cities and treated check−ups at medical institutions (hospitals, public health centers). The eligible population aged from 20 up to 80, and people who did not have any cancer history including thyroid cancer and hormone therapy could affect thyroid function. Among all thyroid cancer patients, cases did not have blood or urine samples (n=987), insufficient confounder information (n=1,565); unavailable matched cases based on sex and age (n=132). Remaining 500 papillary thyroid cancer patients, there were 427 papillary thyroid cancer patients were selected without tumor sizes less than 5mm and hemolysis samples. Among the cases, 199 cases were defined as papillary thyroid cancer whose tumor size was over 1cm, and 228 cases were defined as papillary thyroid microcarcinoma whose tumor size was between 0.5 cm and 1 cm. Among the overall controls, people who did not have blood or urine samples, had insufficient information, history of cancer, and were unmatched people were excluded. Therefore, there were 479 controls in this study. All of the study population got a research consent form from the Seoul National hospital IRB.

3.1.2. Exposure assessment

3.1.2.1. Iodine intake

This study collected urine samples at the study registration used to assess iodine intake. In the case of thyroid cancer cases, their urine samples were collected before thyroid cancer diagnosis. In the case of controls, their urine samples were collected when they visited the medical institutions for a check-up at the study registration. All of the samples were stored in the deep freezer at -70 degrees, and used 7900x, Agilent for the measurement with the Inductively Coupled Plasma-Mass Spectrometry method. According to the urinary iodine concentration, iodine intake level was defined by the World Health Organization and International Council for the Control of Iodine Deficiency Disorders as follows (41,42).

(a) UIC < 100 ug/L (Iodine deficiency)

(b) UIC, 100-199 ug/L, (Adequate iodine intake)

(c) UIC, 200-299 ug/L, (Above adequate level)

(d) UIC, 300 ug/L +, (Excessive iodine intake)

This classification is the universal standard for assessing the iodine intake status. 300 μg/L of urinary iodine concentration is the same as

450 μg/L iodine intake, indicating six plain yogurt or eight cups of milk, or 20 white slices of bread (43,44). Additional iodine intake definition, this study considered individual excretion and creatinine-adjusted iodine concentration level.

(a) UIC, < 85 ug/gCr (Iodine deficiency)

(b) UIC, 85-219 ug/gCr (Adequate iodine intake)

(c) UIC, 220 ug/gCr + (Excessive iodine intake)

In addition, the stability of individual urine samples due to being stored in the deep freezer for a long time was assessed. As a method, repeated variance analysis was conducted on the urinary iodine concentration difference from the first day to 180 days. According to the analysis, the iodine urinary concentration was not significantly different according to time (p-value, 0.82). Therefore, the possibility of using long-term stored urine samples was confirmed.

3.1.2.2. Thyroid function

To assess thyroid function, this study used stored serum samples. The detailed thyroid function test consisted of thyroid stimulation hormone (TSH), free thyroxine (Free T4), and triiodothyronine (T3).

The criteria of thyroid function are classified into two definitions first is the diagnosis criteria of Seoul National University hospital, and the second was the average value reported in the Korean National Health and Nutrition Examination Survey (KNHANES, 45). Due to the none reported value of T3, the mean value of the control population was used as the criteria. Each thyroid function criteria in this study were as follows.

[Diagnostic criteria]

(a) Thyroid stimulation hormone, Low, <0.4 uIU/mL; Normal, 0.4−4.1 uIU/mL; High, ≥ 4.2 uIU/mL

(b) Free thyroxine, Low, <0.70 ng/dL; Normal, 0.70−1.80 ng/dL; High, ≥1.81 ng/dL

(c) Triiodothyronine, Low, 0.87 ng/mL; Normal, 0.87−1.84 ng/mL; High ≥1.85 ng/mL

[Criteria in general population]

(a) Thyroid stimulation hormone, Low, 0.4−2.15 uIU/mL; High, ≥2.16 uIU/mL

(b) Free thyroxine, Low, 0.70−1.24 ng/dL; High, ≥1.25 ng/dL

(c) Triiodothyronine, Low, 0.87−1.19 ng/mL; High ≥1.20 ng/mL

Blood samples were collected at the recruitment of the study population used in this study. As a method, repeated variance analysis was conducted on the thyroid function different from the first day to 180 days. According to the analysis, the thyroid function was not significantly different according to time. Therefore, the possibility of using long−term stored blood samples was confirmed.

3.1.3. Statistical analysis

Analysis of all thyroid cancer patients, including papillary thyroid cancer and papillary thyroid microcarcinoma patients, was conducted by multiple logistic regression analysis, and potential confounding variables were included in this study. To assess the association between iodine intake and papillary thyroid cancer, a visual spline analysis was conducted. Additionally, stratified analysis is based on sex, body mass index, and menopausal status. Also, to assess the thyroid cancer progression according to the iodine intake, a case−only analysis was conducted. The selected progression indicators, in

this study, considered BRAF mutation status, lymph node metastasis, and extra-thyroidal extension. In addition, considering both iodine intake and thyroid function, a combined analysis was conducted. For that, urinary iodine concentration is classified into 'adequate' and 'high', and thyroid function is considered both TSH and Free T4 ('Low' and 'High') based on the general population criteria. In addition, for subjects who had an abnormal creatinine level, this study considered both dilute urine excretion rate (<0.3 g/L) and very concentrated level (> 3.0 g/L). Sas version 9.4 and R software version 4.0 are used as statistical analysis programs.

Part 2. Ionizing radiation and thyroid cancer

3.2. Childhood therapeutic radiation exposure and second thyroid cancer: A therapeutic radiation

3.2.1. PICOT definition

The definition of PICOT, it is defined as shown in the table below.

Table 1. PICOT of childhood therapeutic radiation exposure and thyroid cancer

Population: Childhood patients Outcome 1) Sufficient evidence from the International Agency for Research on Cancer: thyroid cancer (C73) Intervention: Childhood patients who are treated with radiation therapy Comparison: General population (not treated radiation therapy); Other therapy-treated groups except radiation therapy Time: 1990.01.01-2020.03.31 If there has the same source study, the recently published study was included

3.2.2. Search strategy

For the literature search, Pubmed, KoreaMed, The Cochrane Library were used. To find additional studies, the IARC monograph which evaluated the carcinogenicity of ionizing radiation in IARC as a group 1 was used in this study. As search keywords, 'childhood radiation exposure' was applied to identify the exposure, and 'thyroid cancer' as outcome factors. If there was a meta-analysis or a systematic review through the search strategy, possibly included studies were included for meta-analysis. After excluding documents deemed not to be related to this study based on the title and abstract of the documents searched in each database, the full text was reviewed to finally select documents that meet the selection and exclusion criteria of this study. The documents retrieved from each database were exported to the Endnote X9 bibliography management program and then duplicated. Even in the same paper, if the forms of bibliographic information are different, duplicate verification is not possible, so the bibliographic management program sorts the titles alphabetically and checks bibliographic information for similar titles.

Table 2. Inclusion and exclusion criteria of systematic review and meta-analysis

Category	Description
Inclusion criteria	1) Childhood patients-based study 2) Research which described cancer incidence, mortality according to the radiation therapy 3) Standardized incidence (mortality) ratio (SIR, SMR), Odds ratio (OR), relative risk (RR), hazard ratio (HR) reported studies
Exclusion criteria	1) Not human based study 2) Commentary, letter case-report or series, in vivo, in vitro study, radiation therapy technology study 3) Published language without Korean or English 4) Not reported in SIR (SMR), OR, RR from the studies

3.2.3. Data extraction

As data extraction, author, publication year, study district, study population, exposed and unexposed group, the number of the entire study population, thyroid cancer cases, SIR (SMR), OR RR, HR and 95% CI were extracted.

3.2.4. Statistical analysis

If two or more studies reported the same indicator such as SIR (SMR), OR, RR or HR, a meta-analysis was conducted to present the summarized estimates in thyroid cancer. If summarized estimates could divide into men and women, a subgroup analysis was conducted. The main model for meta-analysis was the random effect model. Also, if the 95% confidence interval was not reported, the below equation was applied for the meta-analysis.

Table 3. Confidence interval equation for the meta-analysis

SIR = O/E; O: Observed number of cases, E: Expected number of cases
SIR (lower 95% CI) = SIR $(1-\frac{1}{9O}-\frac{1.96}{3\sqrt{O}})^3$
SIR (upper 95% CI) = SIR $SIR(\frac{O+1}{O})(1-\frac{1}{9(O+1)}+\frac{1.96}{3\sqrt{(O+1)}})^3$

As a subgroup analysis, radiation exposure status and category of exposed dose were considered. Also, the latency period between the first treatment and second thyroid cancer, fist diagnosis of the disease was considered as a subgroup analysis. To assess the heterogeneity, higgin's I^2 statistics was used, and 25-49% defined as low heterogeneity, 50-74% defined as moderate heterogeneity,

and over 75% was defined as high heterogeneity (46). To minimize the heterogeneity, various subgroups, or sensitivity analysis (considered quality of the study or study design). Also, a publication bias assessment was conducted based on the egger and Begg test (a p-value lower than 0.05 is defined as significant publication bias, 47,48). All the statistical analyses were conducted by Stata SE 14 and R software.

3.3. Medical diagnostic radiation exposure and thyroid cancer risk in the general population

3.3.1. Data source and study population

The Korean Health Insurance Database (KNHID, customized database) consisted of a qualification database (gender, age, location, income, type of subscription), death database (death date), treatment database (statement, details of treatment, type of disease), and medical check-up database (including laboratory, lifestyle and other questionnaires). In this study, subjects included qualification database between 2006-2009 are the source population (N=4,205,833). Then excluded subjects who did not have health check-up information (N=269,436) between 2006-2009. After that, any cancer history including thyroid cancer

between 2006-2009 and previous record subjects was excluded (N=51,624). To identify the thyroid cancer record during the time, history of cancer in health check-up questionnaire and International Classification of Diseases (ICD) 10 code as C73 in main-sick or sub-sick with surgery treatment. Finally, there were 3,884,773 subjects in this study as study population.

3.3.1.1 Exposure and outcome variable

In this study, diagnostic medical radiation is defined as the main exposure. Specifically, computed tomography (CT) defined the main medical radiation exposure in this study. In detail, CT exposure status, CT exposure frequency, type of the treatments, and each exposed dose from the treatments. All the exposure information was extracted from the KNHID based on the treatment database. In the case of the thyroid cancer definition, firstly ICD-10 code as 'C73' in main sick or sub sick was extracted. Among the subjects, who can identify the thyroid surgery record included thyroid cancer in this study.

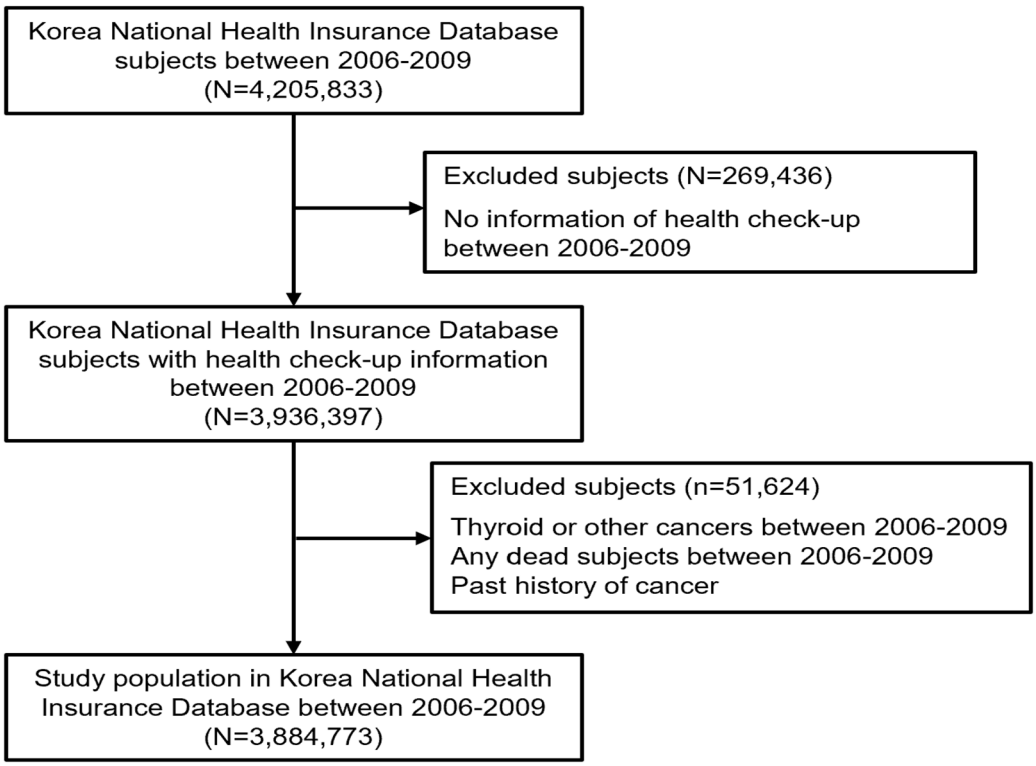

Figure 2. Flow chart of study population selection in KNHID study.

3.3.2. Thyroid exposed dose estimation

In this study, low as reasonably achievable (ALARA) CT, a patient dose calculation program for CT treatment developed by the Korea Disease Control and Prevention Agency used to estimate the dose of CT. This program considered 102 CT devices in South Korea and exposed doses could estimate both in childhood and adulthood population. Also, the exposed dose defines as the effective dose

which reflects the actual patient's exposure, not the radiation dose generated by the CT device.

In detail, the head, and neck (including the brain, face, and skull), spine, chest, and abdominal CT were included as CT treatments that can affect the thyroid organ. This accounted for 92.8% of the total CT tests in the medical use rate survey. According to the each treatment dose, the frequency of individual treatments, and each type of treatment, the total exposed dose was estimated.

3.3.3. Statistical analysis

As statistical analysis, general characteristics between CT exposed group and the non-exposed group were assessed by t-test and chi-square test. In the multivariate cox analysis, age, gender, residence, income level, history of hypertension, and family history of cancer were included as confounding variables. To assess the thyroid cancer risk according to the CT exposure, the latent period of at least 1 year to 5 years was considered. In detail, this study conducted various CT exposure statuses to assess thyroid cancer (simple CT exposure (e.g., none or yes), the frequency of individual CT exposure, and CT dose classification). In the case of CT dose, it was classified based on the personal dose limit (1 mSv),

the natural radiation exposure (3 mSv), and the abdominal CT exposure (10 mSv). In addition, stratification analysis was conducted according to gender and living near metropolitan are due to medical use. All statistical analyses were conducted by SAS 9.4.

3.4. DNA methylation on ionizing radiation-related markers to thyroid cancer

3.4.1. Ionizing radiation markers selection data source and information extraction

In this study, two data sources were considered to identify epigenetic markers according to the ionizing radiation from Clin var. Clin var contains genomic alteration and various phenotype information and is a database managed by the National Institutes of Health. Among the studies, this study focused on epigenetic change at the DNA level. In addition, studies on DNA methylation change and genomic alteration according to ionizing radiation exposure were derived from the Pubmed database. From the selected studies, CpG id, position, Gene label, chromosome, delta m-value, and p-value were extracted from the studies.

3.4.2. Application data source to thyroid cancer tumorigenesis according to ionizing radiation

The thyroid cancer DNA methylation data source consisted of 24 papillary thyroid cancer cases and 16 controls without any cancer. Cases were selected from the T-CALOS study that identified papillary thyroid cancer with BRAF mutation. Also, all cases have other information such as sex, age, history, anthropometric measurement, urinary iodine concentration, and thyroid function. Controls were selected from the community population who did not have any cancer history, hypertension, diabetes, or dyslipidemia. Also, all of the population have information the same as cases. Two groups consisted of a minimum age of 20 to 70. Two groups matched their sex and age (± 5) to conduct a DNA methylation analysis.

Both DNA samples used the sample stored at the study registration. For DNA purity measurements in DNA samples, nanodrop (Thermo Fisher Scientific Inc) A260/A280 ratio was used. After that, the samples were separated into agarose gels, and the subject without a smear in the gel was included as an eligible population. Then DNA was diluted by Quant-iT Picogreen quantitative method as 50 ng/uL. Bisulfite conversion is used by the EZ DNA methylation kit (Zymo Research Corp) according to the manufacturing manual. Statistical

analysis of illumine Beadchip array is based on Bioconductor and 'Minfi' package for sample quality assessment, 'RnBeads' for exclusion of the non-informative CpG, excluding CpG which is the detection p-value over 0.05. Also, CpGs underlying on the Sex chromosome, minor allele frequency over 0.01, poor CpG, and cell component were considered as additional exclusion criteria.

3.4.3. Analysis flow of thyroid cancer tumorigenesis according to ionizing radiation

The analysis process to find the DNA methylation marker affecting thyroid cancer is as follows. First, identify the significant epigenetic markers at the DNA methylation level then assess the markers in the thyroid cancer DNA methylation group which conducted the normalization and quality assessment. After that, to have the consistency of biological plausibility, the same direction of delta m-value was included as candidate epigenetic markers between the previous studies and thyroid cancer DNA methylation data source. Plus, based on the tumorigenesis mechanism of thyroid cancer especially PTC, candidate epigenetic markers are described as a result. Ultimately, the effect of epigenetics changes on PTC due to the ionizing radiation was functionally assessed and described the

detailed information of the markers such as hypo, hypermethylated status, promoter region or island region. All the analyses were conducted by R software 4.2.1.

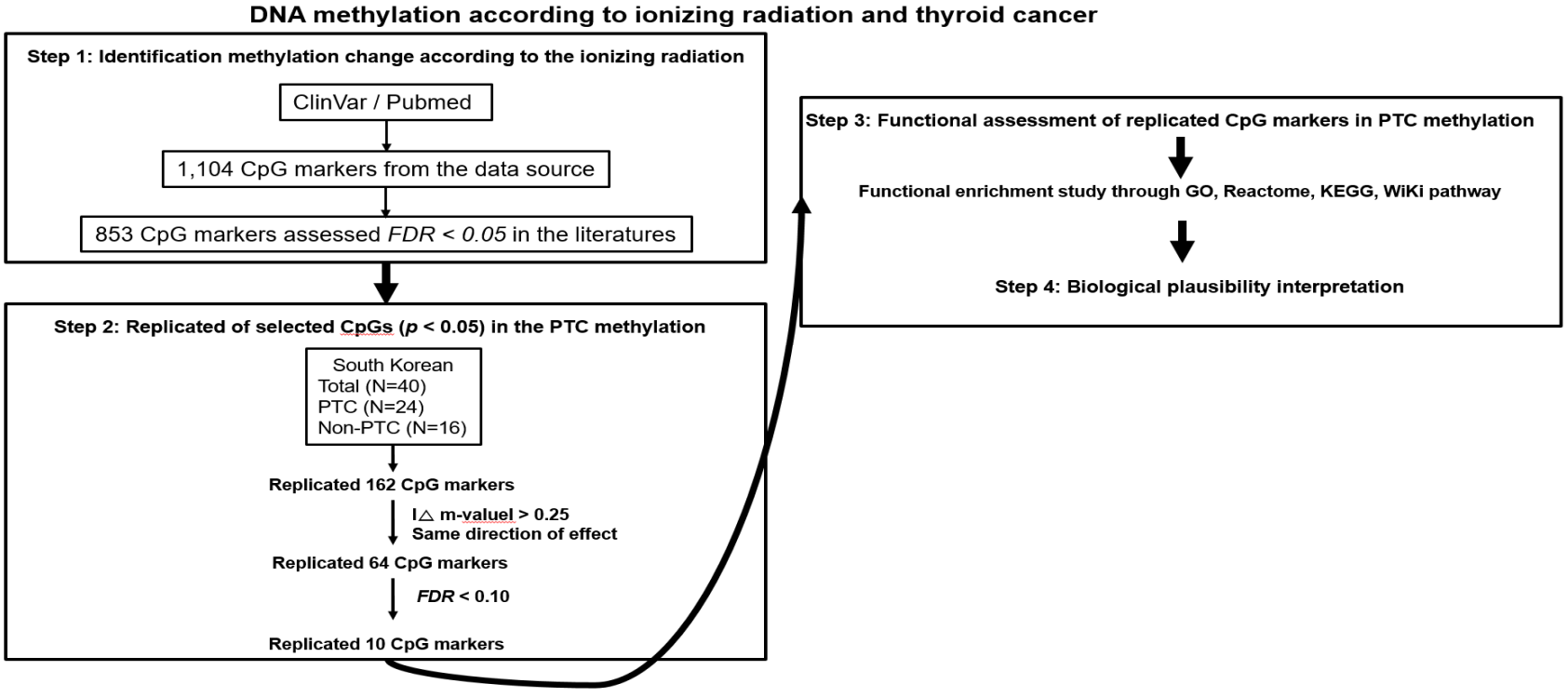

Figure 3. Research flow of thyroid cancer related epigenetic markers according to the ionizing radiation-related epigenetic change.

3.5. Thyroid cancer risk according to the breast cancer

3.5.1. Study design, data source and study population

It is a cohort study based on the Korean population from the KNHID. Especially, sample cohort selected 2.2% from the overall Korean population which has national health insurance information. The overall population of the sample cohort consisted of nearly 1 million subjects who has health insurance recipients in 2002. Subjects were monitored from 2002 to 2013, and their socioeconomic variables including death, disability, and other qualification information were included. In addition, treatment (main sick, sub sick, and others), prescription information at the medical institutions, surgery, and other treatment records. Also, medical check-ups and clinic information (Status, facility, equipment, and personnel data of clinics by type, and establishment,) were included. A study population, men in 2002 (N=513,258), age lower than 30 (N=216,648), thyroid diagnosis in 2002 (N=536), thyroid cancer incidence before the breast cancer incidence (N=517) and missing the basic information at the baseline (N=12,010). Therefore, finally, 282,371 women subjects were included in the study population.

3.5.2. Breast cancer and thyroid cancer definition

Among the subjects, the breast cancer at baseline defines who had breast cancer as main sick or sub-sick according to the ICD-10 (C50) in the treatment record with treated surgery or radiation therapy or chemotherapy at the treatment record. Therefore, there were 1,164 breast cancer Status, facility, equipment, and personnel data of clinics by type, establishment,) was included. As the study population, men in 2002 (N=513,258), age lower than 30 (N=216,648), thyroid diagnosis in 2002 (N=536), thyroid cancer incidence before the breast cancer incidence (N=517) and missing the basic information at the baseline (N=12,010). Therefore, finally, 282,371 women subjects were included in the study population.

3.5.3. Statistical analysis

To assess the general characteristics between breast cancer and non-breast cancer group, t-test and chi-square tests were conducted. For cox regression analysis, the cox proportional hazard assumption was assessed in advance. The thyroid cancer risk according to breast cancer was assessed in overall subjects and considered 2 years of the latent period. Furthermore, to assess the consistent association under the screening effect of thyroid cancer,

sensitivity analysis was conducted except for the group which treated fine needle aspiration. In addition, thyroid cancer risk assessment is considered a follow-up period in the breast group. Also, stratification analysis was conducted on age, income level, smoking status, physical activity, and alcohol consumption status. The confounding variables included in this study included age, income level, smoking status, physical activity, alcohol consumption status, and history of hypertension which were assessed in various models. All analyses were conducted by SAS 9.4.

Part 3. Other factors related to thyroid cancer

3.6. The association between breast cancer and thyroid cancer (Estrogen receptor-based epigenetics markers)

3.6.1. Study population of thyroid cancer

The thyroid cancer DNA methylation data source consisted of 24 papillary thyroid cancer cases and 16 controls without any cancer. Cases were selected from the T-CALOS study that identified papillary thyroid cancer with BRAF mutation. Also, all cases have other information such as sex, age, history, anthropometric measurement, urinary iodine concentration, and thyroid function. Controls were selected from the community population who did not have any cancer history, hypertension, diabetes, or dyslipidemia. Also, all of the population have information the same as cases. Two groups consisted of a minimum age of 20 to 70. Two groups matched their sex and age (± 5) to conduct a DNA methylation analysis.

Both DNA samples used the sample stored at the study registration. For DNA purity measurements in DNA samples, nanodrop (Thermo Fisher Scientific Inc) A260/A280 ratio was used. After that, the samples were separated into agarose gels, and the subject without a smear in the gel was included as an eligible population. Then DNA

was diluted by Quant-iT Picogreen quantitative method as 50 ng/uL. Bisulfite conversion is used by the EZ DNA methylation kit (Zymo Research Corp) according to the manufacturing manual. Statistical analysis of illumine Beadchip array is based on Bioconductor and 'Minfi' package for sample quality assessment, 'RnBeads' for exclusion of the non-informative CpG, excluding CpG which is the detection p-value over 0.05. Also, CpGs underlying on the Sex chromosome, minor allele frequency over 0.01, poor CpG, and cell component were considered as additional exclusion criteria. The difference in methylation between cases and controls was assessed through delta M-value, and multiple comparisons to CpG sites were corrected. Finally, FDR less than 0.20 and llogFcl 0.25 or more were defined as differentially methylated markers in this study.

3.6.2. Study population of breast cancer

In the case of the breast cancer group, women aged at least 20 years were included. There are 16 breast cancer cases and 8 controls. Among the cases, eight subjects were BRCA carriers and others were BRCA non-carrier. At the subject registration, basic questionnaires such as socioeconomic, lifestyle, and laboratory information were assessed. In this study, control is defined as non-

breast cancer cases. For DNA purity measurements in DNA samples, nanodrop (Thermo Fisher Scientific Inc) A260/A280 ratio was used. After that, the samples were separated into agarose gels, and the subject without a smear in the gel was included as an eligible population. As chip sequencing, Illumina HumanMethylation 850K array was considered. To assess significant epigenetic markers, FDR less than 0.20 and llogFcl 0.25 or more are defined as differentially methylated markers in this study.

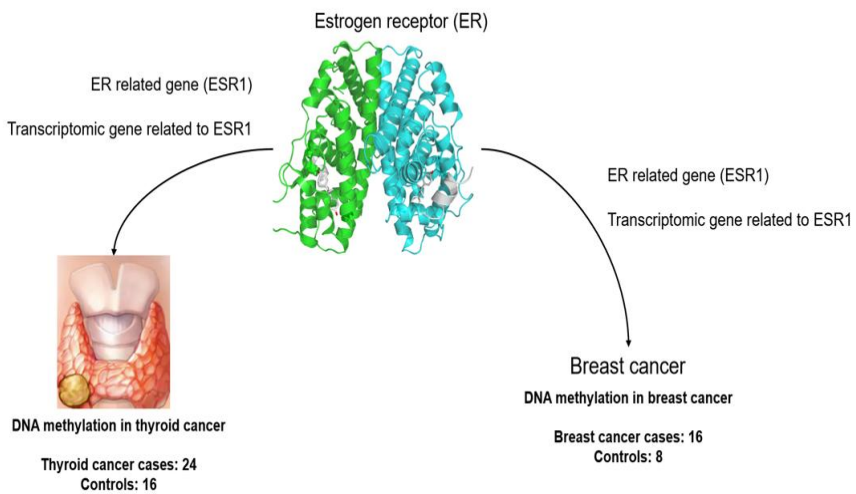

Figure 4. Shared link identification between breast cancer and thyroid cancer as ER.

3.6.3. Statistical analysis

It aimed to identify estrogen receptor-related markers in each cancer data and evaluate the biological plausibility. First, it intended to evaluate gene (ESR1) which is directly related to estrogen receptors in each data and significant level. If it is not available to assess the gene which directly related to the estrogen receptor, markers that were affected in transcription level were assessed. In this study, the directly affected gene was considered ESR1 based on the previous studies and the Genecard database, and transcriptomic genes were considered from the Genecard database. In addition, if it is confirmed in each data, its delta m-value and p-value are compared to the breast cancer and thyroid cancer.

3.7. Reproductive factors and thyroid cancer

3.7.1. Study population of thyroid cancer

This study was based on the case-control study, and between 2010-2015, 1,205 female PTC subjects were selected from the T-CALOS study which was the prospective cohort study of thyroid cancer patients at the Seoul National University Hospital. All the subjects answered the basic questionnaire and reproductive factor questions. As a control group, women who did not diagnose with

thyroid cancer and thyroid disease living in Seoul and Kyunggi province between 2009 and 2014 were selected as the eligible control group.

For matching, 1,205 control groups were selected as 1:1 matching. As considered variables age ± 5 years, an education level (not educated, the elementary school graduated, the middle school graduated, high school graduated, over university), income levels (< 1 million won, 1−2 million won, 2−3.9 million won, over 4 million won).

The detailed information on the reproductive factors was confirmed by a structured questionnaire. Reproductive factors were as follows: 1) age at menarche, 2) menopausal status, 3) age at menopause, 4) pregnancy, 5) delivery experience, 6) age at pregnancy, 7) age at first birth, 8) a number of live births, 9) history of spontaneous abortion, 10) breastfeeding, 11) duration of breastfeeding, 12) a number of breastfeeding children, 13) oral contraception use, and 14) hormone replacement treatment.

3.7.2. Statistical analysis

To assess the general characteristics between breast cancer and non−breast cancer group, chi−square tests were conducted. In the

case-control study, smoking habits, drinking habits, body mass index, and marital status were. In detail, conditional logistic regression was conducted to assess the association between reproductive factors and thyroid cancer. As stratification analysis, menopausal status was considered, and multi-level categories, p-trend was conducted. All analyses were conducted by SAS 9.4.

Results

4.1 Iodine intake and TC in case-control study

4.1.1 General characteristics of the study population

Table 4 presents the traits of the controls and cases of PTC and PTMC. Patients with PTC or PTMC had greater levels of education (both $P < 0.001$) compared to controls, and only those with PTMC had higher rates of family history of cancer ($P=0.003$), dyslipidemia (both $P< 0.001$), and benign thyroid disease ($P=0.01$, P, 0.001). The proportion of postmenopausal women was lower in PTMC patients than in the control group ($P=0.03$), and the mean BMI ($P=0.01$) and percentage of women who had ever been pregnant were lower in PTC patients than in the control group ($P=0.001$). Between the PTC patients and the controls or between the PTMC cases and the controls, there were no differences in the distribution of the two matching variables (age and sex).

Table 4. Selected characteristics between controls and PTC cases or controls and PTMC cases

	Controls (N=479)	PTC (N=199)		PTMC [1] (N=228)	
	Mean (SD)	Mean (SD)	*p-value* [2]	Mean (SD)	*p-value* [2]
Age (years)	47.8 (11.3)	47.7 (12.5)	0.91	47.8 (11.3)	0.96
Body mass index (kg/m^2)	24.0 (3.1)	23.3 (3.4)	0.01	23.6 (3.3)	0.08
	N (%)	N (%)	*p*-value [2]	N (%)	*p*-value [2]
Females	356 (74.5)	147 (73.9)	0.87	180 (79.0)	0.19
Education (≥ college)	99 (20.7)	103 (51.8)	<0.001	134 (58.8)	<0.001
Ever cigarette smokers	103 (21.6)	41 (20.6)	0.77	35 (15.4)	0.051
Ever alcohol drinkers	245 (51.3)	96 (48.2)	0.47	124 (54.4)	0.44
Family history of cancer	119 (24.9)	62 (31.1)	0.09	81 (35.7)	0.003
Past history of					
Hypertension	78 (16.3)	51 (25.6)	0.01	34 (14.9)	0.63
Dyslipidemia	18 (3.8)	33 (16.6)	<0.001	31 (13.7)	<0.001
Benign thyroid disease	14 (2.9)	15 (7.5)	0.01	22 (9.7)	<0.001
Diabetes	38 (8.0)	12 (6.0)	0.38	15 (6.6)	0.52
Females only					
Pregnancy	324 (91.0)	116 (80.0)	0.001	159 (88.8)	0.42
Post-menopausal	174 (48.9)	68 (46.3)	0.59	70 (38.9)	0.03

Abbreviations: PTC, Papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma
1. PTMC with 5 mm ≤ tumor size < 10 mm
2. Pearson's Chi-square tests for categorical variables and Student's t-tests for continuous variables.

4.1.2 Association between iodine intake and thyroid cancer

The relationship between case status and UIC is displayed in Table 5. In comparison to controls, PTC cases and PTMC cases had a greater prevalence of excessive iodine intake (UIC 220 g/gCr; UIC 300 g/L). Additionally, both PTC cases and PTMC cases seldom had insufficient iodine consumption (UIC 85 g/gCr; UIC 100 g/L), but it was slightly higher in the control group. High risk of PTMC and PTC were both linked to excessive UIC (220 g/gCr) (odds ratio [OR], 8.97; 95% confidence interval [CI], 5.07−15.90; and OR, 31.49; 95% CI, 13.02–76.16, respectively), with PTC having a stronger correlation than PTMC (P−ordinal 0.05). In addition, a high unadjusted UIC was linked to a higher risk of PTC and PMTC analyses based on sex, BMI, and a woman's menopausal status. Spline analysis revealed a strong correlation between UIC and PTC risk, confirming the findings of excessive UIC.

Table 5. Urinary iodine concentration for the risk of PTC and PTMC

		Controls (N=479)	PTC (N=199)		PTMC [1] (N=228)	
		N (%)	N (%)	OR (95% CI)[2]	N (%)	OR (95% CI)[2]
UIC (μg/gCr)						
< 85	Insufficient iodine intake	37 (7.7)	0 (0.0)	0.25 (0.01–4.42)[3]	1 (0.4)	0.19 (0.02–1.57)
85–219	Adequate	195 (40.7)	6 (3.0)	1.00	20 (8.8)	1.00
≥ 220	Excessive	247 (51.6)	193 (97.0)	31.49 (13.02–76.16)	207 (90.8)	8.97 (5.07–15.90)
UIC (μg/L)						
20–99	Insufficient	51 (10.7)	1 (0.5)	0.38 (0.04–3.35)	2 (0.9)	0.38 (0.08–1.90)
100–199	Adequate	141 (29.4)	6 (3.0)	1.00	13 (5.7)	1.00
200–299	Above requirements	79 (16.5)	5 (2.5)	1.09 (0.31–3.89)	11 (4.8)	1.38 (0.53–3.56)
≥ 300	Excessive	208 (43.4)	187 (94.0)	19.70 (8.28–46.89)	202 (88.6)	10.33 (5.34–19.99)

Abbreviations: UIC, Urinary iodine concentration; PTC, Papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma

1. PTMC with 5 mm ≤ tumor size < 10 mm
2. Adjusted for age, sex, education level, family history of cancer, past history of chronic disease (dyslipidemia and benign thyroid disease), and total energy intake
3. Logit estimation in Cochran–Mantel–Haenszel method

Table 6. Urinary iodine concentration except insufficient group for the risk of PTC and PTMC according to sex based on exclusion of insufficient iodine intake

	Male (52 PTC, 47 PTMC [1] vs. 114 Controls) [3]					Female (147 PTC, 180 PTMC [1] vs. 336 Controls) [3]				
	Controls	PTC		PTMC		Controls	PTC		PTMC	
	N	N	OR (95% CI) [2]	N	OR (95% CI) [2]	N	N	OR (95% CI) [2]	N	OR (95% CI) [2]
UIC (μg/gCr)										
85–219	59	1	1.00	6	1.00	136	5	1.00	14	1.00
≥ 220	47	51	79.67 (7.75–818.52)	41	7.38 (2.47–22.04)	200	142	26.99 (10.12–71.98)	166	9.92 (5.01–19.63)
UIC (μg/L)										
100–299	69	1	1.00	4	1.00	151	11	1.00	22	1.00
≥ 300	45	51	114.32 (11.16–983.48)	44	18.60 (5.38–64.34)	163	136	16.98 (8.50–33.92)	158	9.64 (5.46–17.02)

Abbreviations: UIC, Urinary iodine concentration; PTC, papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma

1. PTMC with 5 mm ≤ tumor size < 10 mm

2. Adjusted for age, sex, total energy intake, education level, family history of cancer, and each past history of dyslipidemia and benign thyroid disease

3. Total numbers of each category in the study population

Table 7. Urinary iodine concentration except insufficient group for the risk of PTC and PTMC according to BMI levels based on exclusion of insufficient iodine intake

	BMI < 25 kg/m^2 (138 PTC, 166 PTMC [1] vs. 286 Controls) [3]					BMI ≥ 25 kg/m^2 (61 PTC, 61 PTMC [1] vs. 156 Controls) [3]				
	Controls	PTC		PTMC		Controls	PTC		PTMC	
	N	N	OR (95% CI)[2]	N	OR (95% CI)[2]	N	N	OR (95% CI)[2]	N	OR (95% CI)[2]
UIC (μg/gCr)										
85–219	129	4	1.00	11	1.00	66	2	1.00	9	1.00
≥ 220	157	134	18.03 (7.70–42.21)	155	10.17 (5.04–20.50)	90	59	34.36 (6.62–178.33)	52	7.13 (2.53–20.10)
UIC (μg/L)										
100–299	144	9	1.00	15	1.00	76	3	1.00	11	1.00
≥ 300	135	129	19.04 (8.62–42.07)	152	13.95 (6.92–28.12)	73	58	30.10 (7.87–115.07)	50	6.46 (2.70–15.46)

Abbreviations: UIC, Urinary iodine concentration; PTC, papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma

1. PTMC with 5 mm ≤ tumor size < 10 mm

2. Adjusted for age, sex, total energy intake, education level, family history of cancer, and each past history of dyslipidemia and benign thyroid disease

3. Total numbers of each category in the study population

Table 8. Urinary iodine concentration except insufficient group for the risk of PTC and PTMC according to women's menopausal status based on exclusion of insufficient iodine intake

	Premenopausal women (79 PTC, 115 PTMC [1] vs. 166 Controls) [3]					Postmenopausal women (68 PTC, 71 PTMC [1] vs. 170 Controls) [3]				
	Controls	PTC		PTMC		Controls	PTC		PTMC	
	N	N	OR (95% CI)[b]	N	OR (95% CI)[b]	N	N	OR (95% CI)[b]	N	OR (95% CI)[b]
UIC (μg/gCr)										
85–219	72	3	1.00	9	1.00	64	2	1.00	5	1.00
≥ 220	94	76	44.10 (11.65–166.99)	101	11.22 (4.60–27.38)	106	66	17.63 (3.83–81.16)	65	5.95 (2.01–17.61)
UIC (μg/L)										
100–299	81	4	1.00	12	1.00	70	6	1.00	9	1.00
≥ 300	82	75	35.34 (11.44–109.23)	103	14.97 (6.54–34.27)	81	61	8.93 (3.63–21.97)	59	5.05 (2.23–11.47)

Abbreviations: UIC, Urinary iodine concentration; PTC, papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma

1. PTMC with 5 mm ≤ tumor size < 10 mm

2. Adjusted for age, sex, total energy intake, education level, family history of cancer, and each past history of dyslipidemia and benign thyroid disease

3. Total numbers of each category in the study population

4.1.3 Association between thyroid function and thyroid cancer

High free T4 levels were related to a higher risk of PTMC and PTC (population cutpoints: OR, 3.11; 95% CI, 2.08 to 4.66; and OR, 1.92; 95% CI, 1.31 to 2.80). This is in comparison to normal levels of free T4, which were found to have low free T4 levels. When utilizing the clinical cutpoint, the strength of the associations was shown to be significantly higher than when using the population cutpoint. TSH was positively linked with the risk of PTC in only females in the analyses that were stratified according to sex, BMI, and women's menopausal state; T3 was not associated with PTC or PTMC in either males or females. TSH and free T4 revealed a U-shaped connection with PTC when plotted, however, this association was not significant for people whose levels of PTC were low. Regarding the T3 level, there was no significant correlation with the PTC in the total level. In addition, the interaction between iodine intake and thyroid function was assessed. There was a significant interaction between iodine intake and free T4 (p, 0.04), but there was no significant interaction between iodine intake and TSH level (p, 0.13).

Table 9. Thyroid function for the risk of PTC and PTMC

	Controls (N=479)	PTC (N=199)		PTMC [2] (N=228)	
	N (%)	N (%)	OR (95% CI)[3]	N (%)	OR (95% CI)[3]
TSH (μIU/mL)					
Clinical cutpoint [1]					
< 0.4	14 (2.9)	6 (3.0)	1.42 (0.50–4.02)	10 (4.4)	0.93 (0.33–2.63)
0.4–4.1	437 (91.2)	172 (86.4)	1.00	200 (87.7)	1.00
≥ 4.2	28 (5.9)	21 (10.6)	1.59 (0.81–3.12)	18 (7.9)	1.11 (0.54–2.28)
Population cutpoint [1]					
0.4–2.15	322 (67.2)	118 (59.3)	1.00	133 (58.3)	1.00
≥ 2.16	143 (32.8)	75 (40.7)	1.34 (0.93–2.01)	85 (41.7)	1.32 (0.89–1.96)
Free T4 (ng/dL)					
Clinical cutpoint [1]					
< 0.7	2 (0.4)	1 (0.5)	2.01 (0.18–22.76)	1 (0.4)	1.65 (0.14–18.94)
0.7–1.7	473 (98.8)	182 (91.5)	1.00	209 (91.7)	1.00
≥ 1.8	4 (0.8)	16 (8.0)	10.24 (3.12–33.59)	18 (7.9)	11.25 (3.28–38.60)
Population cutpoint [1]					
0.7–1.24	254 (53.0)	73 (36.7)	1.00	65 (28.5)	1.00
≥ 1.25	223 (47.0)	125 (63.3)	1.92 (1.31–2.80)	162 (71.5)	3.11 (2.08–4.66)
T3 (ng/mL)					
Clinical cutpoint [1]					
< 0.87	16 (3.3)	8 (4.0)	0.73 (0.27–2.01)	9 (4.0)	1.05 (0.40–2.77)
0.87–1.84	459 (95.8)	189 (95.0)	1.00	215 (94.3)	1.00
≥ 1.85	4 (0.8)	2 (1.0)	1.05 (0.17–6.54)	3 (1.7)	0.85 (0.15–4.87)
Population cutpoint					
0.87–1.19	204 (42.6)	99 (49.8)	1.00	108 (47.4)	1.00
≥ 1.20	259 (54.1)	92 (46.2)	0.82 (0.57–1.20)	110 (48.3)	0.96 (0.66–1.40)

Abbreviations: PTC, Papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma; TSH, thyroid stimulating hormone; T4, thyroxine; T3, triiodothyronine

1. Clinical cutpoint and population cutpoint for each thyroid hormone are referenced in the [20], and the [21] (mean value based on the data from KNHANE VI (Korea National Health and Nutrition Examination Survey in 2013–2015), respectively. 2. PTMC with 5 mm ≤ tumor size < 10 mm, 3. Adjusted for age, sex, education level, family history of cancer, past history of chronic disease (dyslipidemia and benign thyroid disease), and total energy intake

Table 10. Thyroid function except insufficient group for the risk of PTC and PTMC according to sex based on exclusion of low thyroid function

	Male (52 PTC, 48 PTMC [1] vs. 121 Controls) [3]					Female (146 PTC, 179 PTMC [1] vs. 355 Controls) [3]				
	Controls	PTC		PTMC		Controls	PTC		PTMC	
	N	N	OR (95% CI) [2]	N	OR (95% CI) [2]	N	N	OR (95% CI) [2]	N	OR (95% CI) [2]
TSH (μIU/mL)										
0.4–2.15	95	42	1.00	34	1.00	227	76	1.00	99	1.00
≥ 2.16	25	9	0.75 (0.26–2.13)	10	1.12 (0.43–2.91)	118	66	1.54 (1.00–2.37)	75	1.31 (0.84–2.04)
Free T4 (ng/dL)										
0.7–1.24	44	14	1.00	7	1.00	210	59	1.00	58	1.00
≥ 1.25	78	38	1.60 (0.65–3.92)	41	3.88 (1.30–11.54)	145	87	2.09 (1.37–3.19)	121	3.04 (1.95–4.73)
T3 (ng/mL)										
0.87–1.19	41	19	1.00	20	1.00	163	80	1.00	88	1.00
≥ 1.20	80	29	1.09 (0.47–2.56)	28	0.81 (0.35–1.89)	179	63	0.80 (0.52–1.21)	82	0.96 (0.63–1.48)

Abbreviations: UIC, Urinary iodine concentration; PTC, papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma

1. PTMC with 5 mm ≤ tumor size < 10 mm

2. Adjusted for age, sex, total energy intake, education level, family history of cancer, and each past history of dyslipidemia and benign thyroid disease

3. Total numbers of each category in the study population

Table 11. Thyroid function except insufficient group for the risk of PTC and PTMC according to body mass index based on exclusion of low thyroid function

	BMI < 25 kg/m^2 (137 PTC, 166 PTMC [a] vs. 307 Controls) [c]					BMI ≥ 25 kg/m^2 (61 PTC, 61 PTMC [a] vs. 165 Controls) [c]				
	Controls	PTC		PTMC		Controls	PTC		PTMC	
	N	N	OR (95% CI)[2]	N	OR (95% CI)[2]	N	N	OR (95% CI)[2]	N	OR (95% CI)[2]
TSH (μIU/mL)										
0.4–2.15	205	79	1.00	97	1.00	117	39	1.00	36	1.00
≥ 2.16	95	54	1.47 (0.91–2.35)	63	1.41 (0.88–2.26)	48	21	1.04 (0.50–2.17)	22	1.18 (0.55–2.54)
Free T4 (ng/dL)										
0.7–1.24	168	55	1.00	46	1.00	86	18	1.00	19	1.00
≥ 1.25	139	82	1.79 (1.13–2.83)	120	3.70 (2.25–6.10)	84	43	2.80 (1.35–5.81)	42	2.64 (1.22–5.70)
T3 (ng/mL)										
0.87–1.19	135	68	1.00	81	1.00	69	31	1.00	27	1.00
≥ 1.20	164	67	0.89 (0.57–1.39)	78	0.90 (0.57–1.41)	95	25	0.68 (0.33–1.39)	32	1.08 (0.51–2.28)

Abbreviations: UIC, Urinary iodine concentration; PTC, papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma
1. PTMC with 5 mm ≤ tumor size < 10 mm
2. Adjusted for age, sex, total energy intake, education level, family history of cancer, and each past history of dyslipidemia and benign thyroid disease
3. Total numbers of each category in the study population

Table 12. Thyroid function except insufficient group for the risk of PTC and PTMC according to menopausal status based on exclusion of low thyroid function

	Premenopausal women (79 PTC, 110 PTMC[a] vs. 182 Controls)[c]					Postmenopausal women (68 PTC, 69 PTMC[a] vs. 182 Controls)[c]				
	Controls	PTC		PTMC		Controls	PTC		PTMC	
	N	N	OR (95% CI)[2]	N	OR (95% CI)[2]	N	N	OR (95% CI)[2]	N	OR (95% CI)[2]
TSH (μIU/mL)										
0.4–2.15	113	38	1.00	56	1.00	114	38	1.00	43	1.00
≥ 2.16	64	36	1.53 (0.84–2.80)	50	1.11 (0.62–2.00)	54	30	1.82 (0.95–3.47)	25	1.51 (0.74–3.11)
Free T4 (ng/dL)										
0.7–1.24	107	35	1.00	36	1.00	109	24	1.00	22	1.00
≥ 1.25	75	44	1.91 (1.08–3.38)	74	3.08 (1.70–5.60)	73	43	2.50 (1.32–4.75)	47	3.27 (1.60–6.68)
T3 (ng/mL)										
0.87–1.19	87	38	1.00	60	1.00	76	42	1.00	28	1.00
≥ 1.20	87	40	1.18 (0.66–2.11)	46	0.94 (0.52–1.70)	92	23	0.52 (0.27–0.99)	36	1.29 (0.64–2.60)

Abbreviations: UIC, Urinary iodine concentration; PTC, papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma
1. PTMC with 5 mm ≤ tumor size < 10 mm
2. Adjusted for age, sex, total energy intake, education level, family history of cancer, and each past history of dyslipidemia and benign thyroid disease
3. Total numbers of each category in the study population

4.1.4 Aggressiveness of thyroid cancer according to the iodine intake and thyroid function

According to the aggressiveness of PTC in case-only analysis, there were no significant differences seen between the two subgroups in terms of UICs or thyroid function. A significantly greater increase in OR of PTC and PTMC was associated with excessive UIC in combination with a high free T4 level than the risk associated with either excessive UIC or a high free T4 level alone. This was the case regardless of which risk factor was evaluated separately. The cumulative effect of high levels of free T4 and excessive levels of UIC had a more pronounced negative impact on risk for PTC than it did for PTMC. Based on these findings, it appeared that high levels of free T4 and excessive UIC had a synergistic effect. In the same vein, the combination of an adequate UIC and a TSH level posed a risk of PTC that was moderately high when compared to the risk posed by a high TSH level alone. Regardless of the levels of TSH present, an elevated risk of PTC and PTMC was observed in patients who had excessive UIC.

Table 13. Urinary iodine concentration and thyroid function for the likelihood of aggressive overall PTC [1] in case-only study

	BRAF mutation			LN metastasis			Extra-thyroidal extension		
	Yes	No		Yes	No		Yes	No	
	N	N	OR (95% CI)[2]	N	N	OR (95% CI)[2]	N	N	OR (95% CI)[2]
UIC (μg/gCr)									
< 85	1	0	1.77 (0.07-47.14)[3]	0	1	0.28 (0.01-7.36)[3]	1	0	2.31 (0.09-61.41)[3]
85-219	15	9	1.00	13	13	1.00	15	9	1.00
≥ 220	192	101	1.12 (0.47-2.69)	120	210	0.59 (0.26-1.36)	154	130	0.72 (0.30-1.73)
UIC (μg/L)									
20-99	3	0	8.14 (0.39-72.1)[3]	1	2	1.38 (0.10-18.94)	2	1	1.25 (0.09-18.01)
100-199	10	9	1.00	7	12	1.00	8	6	1.00
200-299	9	7	1.10 (0.28-4.36)	7	9	1.40 (0.35-5.70)	11	5	1.42 (0.31-6.48)
≥ 300	186	94	1.86 (0.70-4.94)	118	201	0.82 (0.31-2.21)	149	127	0.78 (0.26-2.35)
TSH (μIU/mL)									
0.4-2.15	126	57	1.00	81	134	1.00	99	80	1.00
≥ 2.16	77	43	0.86 (0.51-1.44)	47	80	1.05 (0.65-1.71)	65	53	1.08 (0.66-1.78)
Free T4 (ng/dL)									
0.7-1.24	56	35	1.00	35	72	1.00	52	42	1.00
≥ 1.25	151	75	1.33 (0.78-2.28)	98	151	1.26 (0.76-2.09)	117	97	1.01 (0.61-1.69)
T3 (ng/mL)									
0.87-1.19	104	43	1.00	68	99	1.00	76	66	1.00
≥ 1.20	98	64	0.63 (0.39-1.04)	62	116	0.74 (0.47-1.17)	88	69	1.09 (0.68-1.74)

Abbreviations: UIC, Urinary iodine concentration; PTC, papillary thyroid cancer; BRAF, v-raf murine sarcoma viral oncogene homolog B1; LN, Lymph node; TSH, thyroid stimulating hormone; T4, thyroxine; T3, triiodothyronine

1. Overall PTC meant PTC + papillary thyroid microcarcinoma (PTMC)

2. Adjusted for age, sex, total energy intake, education level, family history of cancer, and each past history of dyslipidemia and benign thyroid disease

3. Logit estimation in Cochran-Mantel-Haenszel method

4.1.5 Combined effect of iodine intake and thyroid function on thyroid cancer

A significantly greater increase in OR of PTC and PTMC was associated with excessive UIC in combination with a high free T4 level than the risk associated with either excessive UIC or a high free T4 level alone. This was the case regardless of which risk factor was evaluated separately. The cumulative effect of high levels of free T4 and excessive levels of UIC had a more pronounced negative impact on risk for PTC than it did for PTMC. Based on these findings, it appeared that high levels of free T4 and excessive UIC had a synergistic effect. In the same vein, the combination of an adequate UIC and a TSH level posed a risk of PTC that was moderately high when compared to the risk posed by a high TSH level alone. Regardless of the levels of TSH present, an elevated risk of PTC and PTMC was observed in patients who had excessive UIC.

Table 14. Combined effect of urinary iodine concentration and thyroid function for the risk of PTC and PTMC based on adequate and excessive iodine intake

		Controls (N=463)	PTC (N=199)		PTMC [2] (N=227)	
		N (%)	N (%)	OR (95% CI)[3]	N (%)	OR (95% CI)[3]
UIC [1] (μg/gCr)	Free T4[1] (ng/dL)					
Adequate	Low	92	3	1.00	6	1.00
	High	103	3	0.94 (0.18–4.98)	14	2.79 (0.93–8.36)
Excessive	Low	150	71	18.75 (5.41–64.97)	60	7.81 (2.92–20.97)
	High	97	122	46.35 (13.39–160.46)	147	28.18 (10.63–74.71)
UIC [1] (μg/gCr)	TSH [1] (μIU/mL)					
Adequate	Low	155	2	1.00	12	1.00
	High	40	4	6.25 (1.05–37.16)	8	2.32 (0.81–6.68)
Excessive	Low	153	122	74.15 (17.36–316.73)	130	11.99 (5.86–24.51)
	High	94	71	66.0815.20–287.26)	77	11.20 (5.27–23.81)

Abbreviations: UIC, Urinary iodine concentration; PTC, Papillary thyroid cancer; PTMC, Papillary thyroid microcarcinoma; TSH, thyroid stimulating hormone; T4, thyroxine

1. UIC levels were divided into two groups: 'Adequate' meant 'UIC 85–219 μg/gCr', and 'Excessive' meant 'UIC ≥ 220 μg/gCr'. Free T4 and TSH levels were divided into two groups using population cutpoints: 'Low' and 'High' Free T4 levels meant '< 1.25 ng/dL' and '≥ 1.25 ng/dL', respectively; 'Low' and 'High' TSH levels meant '< 2.16 μIU/mL' and 'High TSH' ≥ 2.16 μIU/mL', respectively.

2. PTMC with 5 mm ≤ tumor size < 10 mm

3. Adjusted for age, sex, education level, family history of cancer, past history of chronic disease (dyslipidemia and benign thyroid disease), and total energy intake

Part 2. Ionizing radiation and thyroid cancer

4.2 Childhood therapeutic radiation exposure and second thyroid cancer: A systematic review and meta-analysis

4.2.1 Study selection flow

Totally 445 studies were identified from the core database including PubMed. Among them, duplicated studies were excluded first (N=75). After that, 146 studies were excluded as titles and abstracts. As eligible studies, there were 224 studies for assessing the entire contents. The main reasons were as follows; 1) studies not reported thyroid cancer as an outcome (N=48), 2) review or letter types of studies (N=33), 3) Insufficient studies which not described effect size for the meta-analysis (N=43). Finally, there were seven cohort studies, to assess the association between radiation therapy and thyroid cancer risk in the childhood population.

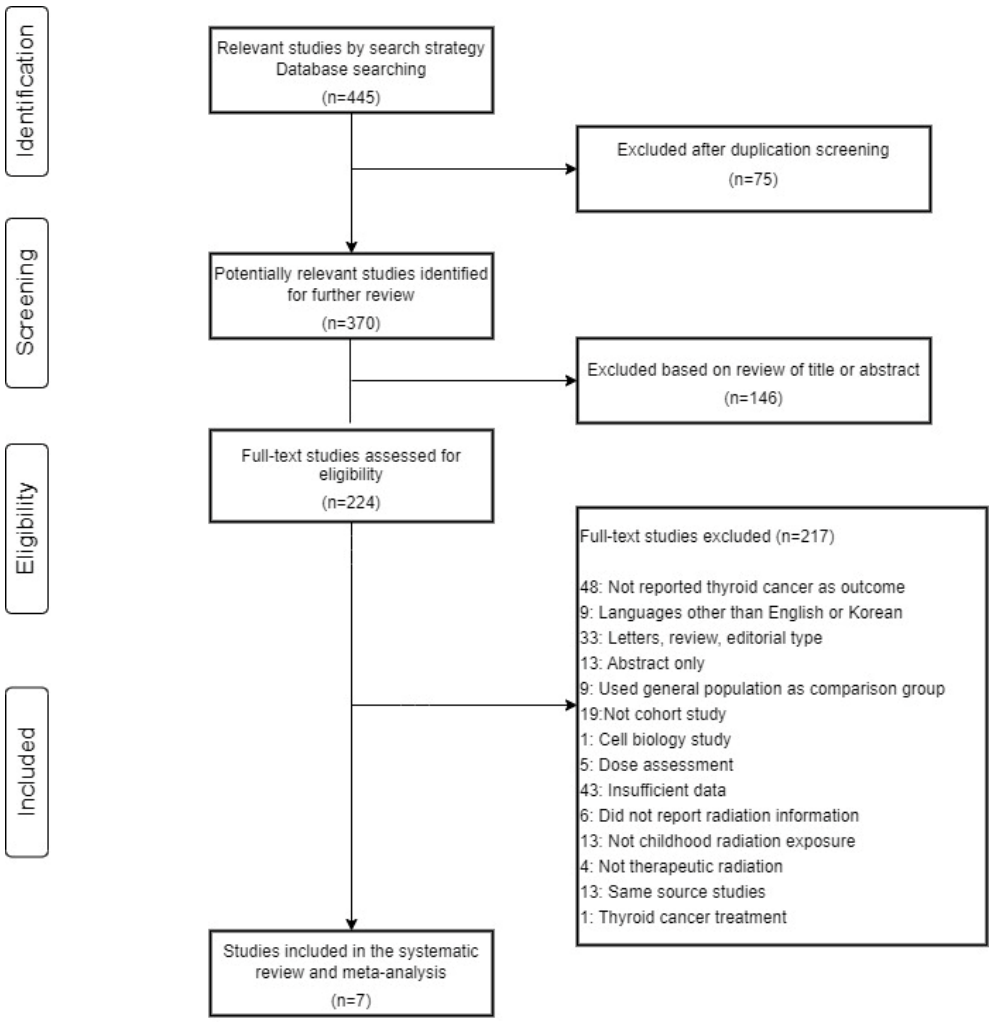

Figure 5. Study selection flow chart in systematic review and meta-analysis.

4.2.2 Association between therapeutic radiation exposure and second thyroid cancer

Among the selected seven studies, four studies were conducted in North America, including the United States and Canada, and the other three were studies conducted in Europe, and no studies were

conducted in Asia or other countries. All the childhood population aged less than 20 years and at least 3,000 to 13,000 subjects consisted in each study. The overall summary relative risk was 5.09 and the 95% CI was (3.51−7.37), so radiation therapy was statistically significant for thyroid cancer. Also, the heterogeneity was moderate. In the case of the females group, there were only four studies, and the summary relative risk was 1.40 and the 95% CI was 0.84−2.34, so it was not statistically significant. To identify the reason for the heterogeneity, several factors were considered. They were 1) the treated age of the subjects; 2) minimum years of follow−up; 3) countries of research; 4) the first type of the disease. According to the mete−regression and subgroup analysis, the treated age of the subjects and minimum years of follow−up were not associated with significant heterogeneity in this study. However, in the meta−analysis, which conducted based on Europe and American studies, only American studies showed significant heterogeneity, and it would be originated from the subjects who diagnosed with leukemia.

Table 15. General characteristics of studies included in the meta-analysis (49-55)

Author (year)	Study population	Exposed period	Follow-up period	Sex	Category	Cohort N.	Case N.	RR (95% CI)
Adams (2010)	Chest radiation therapy for thymus as exposed group and their siblings as unexposed group from USA (age < 1 year)	1926-1957	2008	Total	Ever	3,071	50	5.60 (3.10-10.80)
				Female	Ever	1,650	36	1.50 (0.93-2.50)
Bhatti (2010)	The Childhood Cancer Survivor Study from US and Canada, survived over 5 years (age < 21 years)	1970-1986	2005	Total	Ever	12,547	103	6.28 (4.73-8.35)
				Female	Ever	Not reported	79	2.30 (1.60-3.40)
Vathaire (2015)	Solid cancer patients from France and UK who treated radiation therapy (age < 16 years), and 8 years of latency	1985-1995	2012	Total	Ever	4,338	49	5.49 (3.23-9.34)
				Female	Ever	1,919	30	1.50 (0.90-2.50)
Ronckers (2002)	Irradiated patients of ear, nose and throat from Netherlands (age < 20 years), 30 years of latency	1945-1981	1997	Total	Ever	8,443	4	3.80 (0.50-76.0)
Taylor (2009)	Childhood Cancer Survivor Study of Britain, survived over 5 years (age < 15 years)	1940-1991	2004	Total	Ever	13,211	41	4.60 (1.40-15.10)
				Female	Ever	Not reported	31	0.60 (0.30-1.20)
Rose (2012)	Patients who diagnosed various cancers (ALL, AML, CML, lymphoma, CNS cancer) from USA	1973-1988	2008	Total	Ever	7,670	35	2.22 (1.15-4.29)
				Female	Ever	3,263	19	1.67 (0.73-3.85)
Bhatia (2002)	Acute lymphobalstics leukemia survivors from the cohort study in US and Canada	1983-1995	1999	Total	Ever	8,831	Not reported	30.8 (1.20-62.90)

Abbreviation, ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, Chronic myeloid leukemia

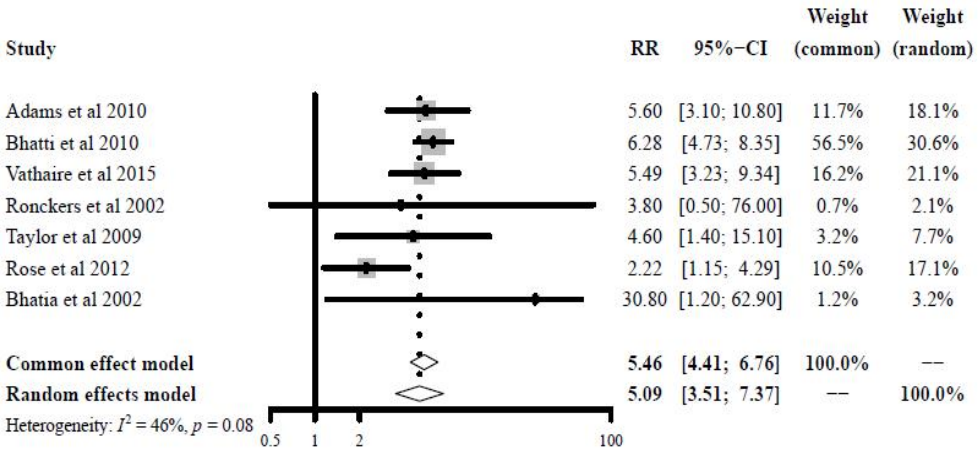

Figure 6. Meta−analysis of the entire studies in the meta−analysis.

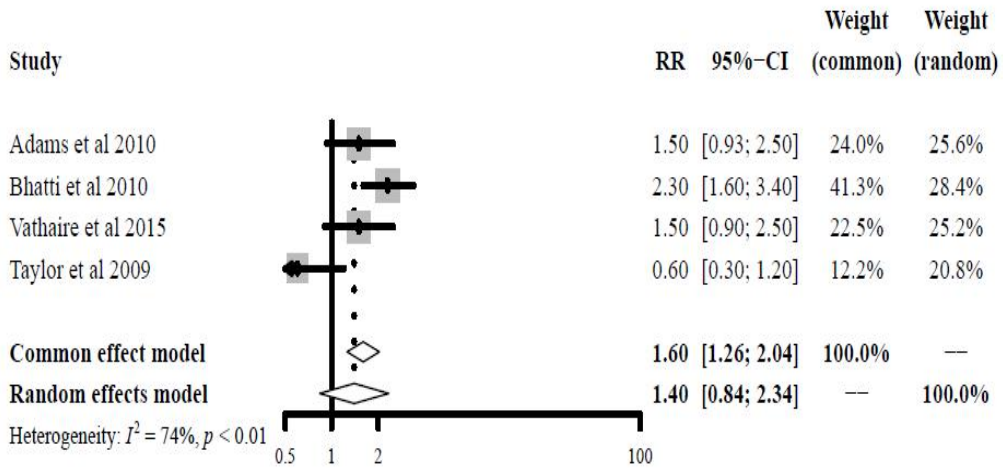

Figure 7. Meta−analysis of the women studies in the meta−analysis.

4.3 Medical diagnostic radiation exposure and thyroid cancer risk in the general population

4.3.1 General characteristics of the study population

Of the total of 3,884,773 subjects, 246,281 subjects were exposed to CT between 2006–2009, and 3,638,492 subjects were not exposed to CT. As general characteristics, body mass index and age were statistically significant between groups. The mean age of the exposed group was 48.9 years and 43.7 years in the non-exposed group. Also, women consisted of more than half in the exposed group (N=124,500, 50.6%) and men consisted of more than half in the unexposed group (N=1,969,295, 54.1%).

In the case of the income levels, the overall distribution was similar between groups but there was a significant difference. For smoking and alcohol consumption, much more smokers (exposed group, N=51,183, 21%; non-exposed group, N=902,742, 24.8%) and current drinkers (exposed group, 101,851, 41.3%; non-exposed group, N=1,785,779; 49.1%) in the exposed group than the unexposed group. As per individual history, diabetes and hypertension were significantly higher in the exposed group than in the unexposed group.

In the case of Chest CT, pneumonia, bronchitis, pulmonary nodules, asthma, and obstructive lung diseases accounted for 62.1% of all chest CT treatments and followed by benign tumors such as lungs bronchus, and trachea (9.0%), injury including thoracic and ribs (6.5%), and cardiovascular diseases including angina (3.4%).

In abdominal CT, 48.2% accounted for abdominal pain, appendicitis, gastric and esophageal reflux disease, gastroenteritis, pancreatitis, and cholecystitis, and 21.6% accounted for urinary system-related diseases including kidney, ureter stones, gallstones, and hematuria, and a benign tumor on liver, kidney, pancreas, and gallbladder accounted for 14.7%. In the head and neck (including brain, face, and skull) CT, 38.4% accounted for cerebral infarction, cerebral hemorrhage, stroke, headache, and dizziness were the main cause, and injuries including head trauma, nasal fracture, eye, and scalp accounted for 21.1%. In addition, sinusitis, maxillary sinusitis, nasal septum, and otitis media from the face and skull CT accounted for 13.9%. Others as dementia, Parkinson's disease, and hydrocephalus accounted for 6.8%. As for Spinal CT, fractures of the cervical, thoracic, and lumbar vertebrae, and musculoskeletal disorders such as intervertebral disc exodus, spinal stenosis, and sprain accounted for 92.8%.

Table 16. General characteristics between exposed and unexposed group

Characteristics	Total (N=3884773)	Exposed group (N=246281)	Non-exposed group (N=3638492)	p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Body mass index (kg/m^2)	23.62 (3.15)	24.02 (3.02)	23.62 (3.09)	*<0.001*
Age	44.2 (13.2)	48.9 (12.8)	43.7 (13.0)	*<0.001*
	N (%)	N (%)	N (%)	
Residence (metropolitan)	1754060 (45.1)	93164 (37.8)	1660896 (45.6)	*<0.001*
Sex				*<0.001*
Male	2091076	121781 (49.4)	1969295 (54.1)	
Female	1793697	124500 (50.6)	1669197 (45.9)	
Income level				*<0.001*
Q1	5354 (0.1)	449 (0.2)	4905 (0.1)	
Q2	1613056 (42.5)	103668 (42.1)	1509388 (41.5)	
Q3	1997035 (52.6)	129778 (52.7)	1867257 (51.3)	
Q4	181148 (4.8)	12386 (5.0)	168762 (4.6)	
Smoking status				
Non-smoker	2592698 (66.7)	175982 (71.5)	2416716 (66.4)	
Ex-smoker	338150 (8.7)	19116 (7.8)	319034 (8.8)	
Current-smoker	953925 (24.6)	51183 (21.0)	902742 (24.8)	
Alcohol consumption				*<0.001*
Yes	1887630 (48.6)	101851 (41.3)	1785779 (49.1)	
Past history of disease				
Hypertension				*<0.001*
Yes	274518 (7.1)	27482 (11.2)	247036 (6.8)	
Diabetes				*<0.001*
Yes	71750 (1.8)	6581 (2.7)	65169 (1.8)	
Family history of cancer				*<0.001*
Yes	452708 (11.6)	30187 (12.3)	422521 (11.6)	

Table 17. Major diseases of CT according to the various CT type

Major disease of Chest CT	Details	Proportion (%)
Lung, and bronchus-related diseases	Pneumonia, bronchiectasis, pulmonary nodule, asthma, COPD, pulmonary emphysema, bronchitis., and others	62.1
Benign tumor	Lung, bronchus, trachea	9
Injury	Thorax injury, lumbar fracture, wound of the thoracic caviaty, a strain of ribs, sternum, back pain., others	6.5
Cardiac diseases	Angina pectoris, unstable angina, congestive heart failure	3.4
Infection	Sequelae of respiratory tuberculosis, sepsis, bacterial infection, pulmonary mycobacterial infection and others	2.5
Major disease of Abdomen CT		
Digestsystem-relatedated diseases	Abdominal pain, Acute appendicitis, gastro-oesophageal reflux disease, gastroenteritis and colitis, calculus of gallbladder, acute pancreatitis	48.2
Urinsystem-relatedated diseases	Calculus of ureter, kidney, gross hematuria, retubulointerstitialtial disease, cyst of kidney, hyperplasia of prostate, hydronephrosis, urinary tract infection	21.6
Benign tumor	Liver, kidney, pancreas, gallbladder, colon	14.7
Injury (bone, muscle)	Pubis, pelvis, femur fracture, abdominal wall contusion, sprain and strain of l-spine and pelvis	3.8

Table 17. Major diseases of CT according to the various CT type

(Continued)

Major disease of Chest CT	Details	Proportion (%)
Major disease of Head, Brain, Neck CT		
Circulatory system disease	Cerebral infarction, hemorrhage, aneurysm, cerebral arteries, stroke, sequelae of intracerebral hemorrhage, headache, dizziness, epilepsy., and others	38.4
Trauma (injury)	Concussion, diffuse brain injury, nasal bone fracture, open wound of eyelid, scarp, orbital floor	21.1
Ear, nose, ear, tonsil	Sinusitis, pansinusitis, otitis media, maxillary sinusitis, nasal septum, vestibular function disorder, hearing loss	13.9
Behavioral disorder and nervous system	Dementia, hemiplegia, Parkinson' s disease, hydrocephalus	6.8
Benign tumor	Thyroid gland, cerebral meanings, pituitary gland	3.3
Major disease of Spine CT		
Musculoskeletal system and connective tissue-related diseases included fracture	Lumbar and other intervertebral disc disorders with radiculopathy, spinal stenosis lumbar region, other specified intervertebral disc displacement, fracture of the lumbar spine, and pelvis fracture of rib(s), sternum and thoracic spine	92.8

4.3.2 Medical diagnostic radiation exposure and thyroid cancer

There were 2,703 thyroid cancer cases according to the CT exposure and it was statistically significant (HR, 1.21; 95% CI, 1.14−1.27). Considering the latent period of more than 5 years, it was consistently significant (HR, 1.17; 95% CI, 1.13−1.40).

Also, in the frequency of CT exposure, there was dose−response relationship was identified in each category (1−2 times, HR, 1.04; 95% CI, 0.97−1.11; 3−10 times, HR, 1.21; 95% CI, 1.14−1.26; more than 10 times, HR, 2.90; 95% CI, 2.24−3.76).

Additionally, the radiation dose received at the thyroid according to the CT treatment was classified into various groups and it showed a dose−response relationship. Compared to the natural ionizing radiation level (3−5 mSv), 5−9.9 mSv is associated with thyroid cancer risk (1.46; 1.15−1.82), and over 10 mSv also associated with thyroid cancer risk (5.20; 3.10−8.68), and other groups (never exposed group, 0.1−0.99 mSv, 1.0−2.9 mSv) were not associated with thyroid cancer.

Table 18. Association between medical diagnostic radiation exposure and thyroid cancer in overall population

Overall	Non-TC		TC		HR (95% CI)[1]	Non-TC		TC		HR (95% CI)[1]
	Over 1 year lag period					5-year lag period				
Radiation exposure status	N	PY	N	PY	HR (95% CI)[1]	N	PY	N	PY	HR (95% CI)[1]
Never	3607156	50464112	32659	248098	1.00	3538916	50149186	29147	240815	1.00
Ever	244098	3414931	2703	20619	1.21 (1.14-1.27)	228178	3318912	2389	18561	1.16 (1.12-1.30)
Radiation exposure frequency										
Never	3607156	50464112	32659	248098	1.00	3538916	50149186	29147	240815	1.00
1-2	92757	1298598	939	7089	1.12 (1.06-1.20)	87851	1228815	834	6199	1.04 (0.97-1.11)
3-9	148921	2082453	1692	13027	1.23 (1.16-1.31)	138296	2061716	1491	11924	1.21 (1.14-1.26)
≥ 10	2420	33880	72	503	2.84 (2.15-3.58)	2031	28381	64	438	2.90 (2.24-3.76)
Exposed dose (CT, mSv)										
Never	3607156	50464112	32659	248098	0.75 (0.61-0.93)	3538916	50149186	29147	240815	0.75 (0.62-0.95)
0.10-0.99	73284	1027092	748	5676	0.88 (0.74-1.04)	67395	1012916	639	5098	0.86 (0.72-1.02)
1.00-2.99	145170	2030958	1539	11753	0.94 (0.86-1.12)	138292	1969727	1385	10624	0.96 (0.79-1.13)
3.00-4.99	12495	175812	172	1328	1.00	10398	162324	147	1198	1.00
5.00-9.99	12768	177629	221	1689	1.44 (1.13-1.79)	11738	170719	200	1499	1.46 (1.15-1.82)
≥ 10.0	381	3440	23	173	5.41 (3.19-9.04)	355	3226	18	142	5.20 (3.10-8.68)

Abbreviation, TC, Thyroid cancer; PY, Person-year; HR, Hazard ratio; CT, Computed tomography

1. Adjusted by age, sex, residence, income, past history of hypertension and family history of cancer
2. CT dose classification defined as annual radiation dose limit (1 mSv), annual exposed natural radiation (3 mSv), and abdominal CT dose (10 mSv)

Table 19. Association between medical diagnostic radiation exposure and thyroid cancer in men

Men	Non-TC		TC		HR (95% CI)[1]	Non-TC		TC		HR (95% CI)[1]
	Over 1 year lag period					5-year lag period				
Radiation exposure status	N	PY	N	PY	HR (95% CI)[1]	N	PY	N	PY	HR (95% CI)[1]
Never	1959826	27436985	8615	70752	1.00	1898533	27149020	7820	67395	1.00
Ever	121179	1695382	577	4509	1.08 (1.03-1.19)	112787	1645892	503	4217	1.09 (1.03-1.20)
Radiation exposure frequency										
Never	1959826	27436985	8615	70752	1.00	1898533	27149020	7820	67395	1.00
1-2	44807	624982	216	1676	1.16 (1.03-1.32)	42085	605005	188	1569	1.07 (0.92-1.26)
3-9	74979	1051015	342	2693	1.09 (0.95-1.17)	69471	1022928	298	2522	1.02 (0.86-1.18)
≥ 10	1393	19385	19	140	3.40 (1.97-3.93)	1231	17959	17	126	3.51 (2.15-4.01)
Never	1959826	27436985	8615	70752	0.58 (0.41-0.80)	1898533	27149020	7820	67395	0.64 (0.47-0.95)
0.10-0.99	36849	514786	174	1396	0.76 (0.52-1.06)	33651	481209	146	1265	0.81 (0.55-1.21)
1.00-2.99	71594	1003075	320	2486	0.70 (0.52-0.98)	67853	994460	286	2379	0.78 (0.63-1.14)
3.00-4.99	6300	87843	41	302	1.00	5574	84123	33	269	1.00
5.00-9.99	6287	87695	37	289	0.97 (0.63-1.55)	5567	84086	34	271	1.14 (0.71-1.86)
≥ 10.0	149	1983	5	36	5.08 (2.04-14.36)	142	2014	4	33	4.92 (1.67-15.44)

Abbreviation, TC, Thyroid cancer; PY, Person-year; HR, Hazard ratio; CT, Computed tomography

1. Adjusted by age, sex, residence, income, past history of hypertension and family history of cancer
2. CT dose classification defined as annual radiation dose limit (1 mSv), annual exposed natural radiation (3 mSv), and abdominal CT dose (10 mSv)

Table 20. Association between medical diagnostic radiation exposure and thyroid cancer in women

Women	Non-TC		TC		HR (95% CI)[1]	Non-TC		TC		HR (95% CI)[1]
	Over 1 year lag period					5-year lag period				
Radiation exposure status	N	PY	N	PY	HR (95% CI)[1]	N	PY	N	PY	HR (95% CI)[1]
Never	1647330	23027127	24044	177346	1.00	1640383	23000166	21327	173420	1.00
Ever	122919	1719549	2126	16110	1.19 (1.11-1.27)	115391	1673020	1886	14344	1.18 (1.10-1.27)
Radiation exposure frequency										
Never	1647330	23027127	24044	177346	1.00	1640383	23000166	21327	173420	1.00
1-2	47950	673616	723	5413	1.08 (1.00-1.18)	45766	623810	646	4630	1.06 (0.98-1.15)
3-10	73942	1031438	1350	10334	1.33 (1.26-1.43)	68825	1038788	1193	9402	1.29 (1.23-1.38)
≥10	1027	14495	53	363	3.32 (2.49-4.15)	800	10422	47	312	3.30 (2.46-4.11)
Never	1647330	23027127	24044	177346	0.71 (0.55-0.98)	1640383	23000166	21327	173420	0.69 (0.52-0.95)
0.1-0.99	36435	512306	574	4280	0.80 (0.65-1.06)	33744	531707	493	3833	0.74 (0.55-1.14)
1.0-2.9	73576	1027883	1319	9267	0.92 (0.74-1.13)	70439	975267	1099	8245	0.90 (0.72-1.09)
3.0-4.9	6195	87969	131	1026	1.00	4824	78201	114	929	1.00
5.0-9.9	6481	89934	814	1400	1.41 (1.05-1.84)	6171	86633	166	1228	1.40 (1.04-1.85)
≥10	232	1457	18	137	7.63 (5.36-11.31)	213	1212	14	109	6.85 (4.47-10.20)

Abbreviation, TC, Thyroid cancer; PY, Person-year; HR, Hazard ratio; CT, Computed tomography

1. Adjusted by age, sex, residence, income, past history of hypertension and family history of cancer
2. CT dose classification defined as annual radiation dose limit (1 mSv), annual exposed natural radiation (3 mSv), and abdominal CT dose (10 mSv)

Table 21. Association between medical diagnostic radiation exposure and thyroid cancer living in metropolitan

Living in metropolitan	Non-TC		TC		HR (95% CI)[1]	Non-TC		TC		HR (95% CI)[1]
	Over 1 year lag period					5-year lag period				
Radiation exposure status	N	PY	N	PY	HR (95% CI)[1]	N	PY	N	PY	HR (95% CI)[1]
Never	1646214	23042815	14196	111036	1.00	1637628	22934805	12471	103299	1.00
Ever	92059	1286180	1011	7552	1.25 (1.18-1.33)	87604	1268852	886	7084	1.20 (1.14-1.29)
Radiation exposure frequency										
Never	1646214	23042815	14196	111036	1.00	1637628	22934805	12471	103299	1.00
1-2	44389	620720	471	3534	1.16 (1.04-1.28)	41192	607891	396	3264	1.12 (1.01-1.25)
3-9	46988	655812	520	3815	1.24 (1.13-1.36)	45837	651913	471	3666	1.20 (1.10-1.31)
≥ 10	682	9648	23	203	3.68 (2.35-5.49)	575	9048	19	154	3.80 (2.52-5.79)
Never	1646214	23042815	14196	111036	0.75 (0.53-1.02)	1637628	22934805	12471	103299	0.77 (0.56-1.05)
0.10-0.99	34951	487185	364	2675	0.83 (0.59-1.16)	32028	475149	312	2519	0.82 (0.57-1.15)
1.00-2.99	48868	683894	537	4029	0.91 (0.74-1.26)	47590	679635	478	3788	0.92 (0.74-1.36)
3.00-4.99	4417	61582	54	411	1.00	4283	61149	46	369	1.00
5.00-9.99	3767	52739	50	384	1.16 (0.77-1.74)	3651	52200	44	355	1.18 (0.80-1.77)
≥ 10.0	56	780	6	53	9.83 (4.01-26.51)	52	719	6	53	11.59 (5.05-29.12)

Abbreviation, TC, Thyroid cancer; PY, Person-year; HR, Hazard ratio; CT, Computed tomography

1. Adjusted by age, sex, residence, income, past history of hypertension and family history of cancer
2. CT dose classification defined as annual radiation dose limit (1 mSv), annual exposed natural radiation (3 mSv), and abdominal CT dose (10 mSv)

Table 22. Association between medical diagnostic radiation exposure and thyroid cancer non-living in metropolitan

Non-living in metropolitan	Non-TC		TC		HR (95% CI)[1]	Non-TC		TC		HR (95% CI)[1]
	Over 1 year lag period					5-year lag period				
Radiation exposure status	N	PY	N	PY	HR (95% CI)[1]	N	PY	N	PY	HR (95% CI)[1]
Never	1960942	27421297	18463	137062	1.00	1901288	27214381	16676	137516	1.00
Ever	152039	2128751	1692	13067	1.26 (1.20-1.33)	140574	2050060	1503	11477	1.26 (1.19-1.32)
Radiation exposure frequency										
Never	1960942	27421297	18463	137062	1.00	1901288	27214381	16676	137516	1.00
1-2	48368	677878	468	3555	1.06 (0.95-1.15)	46659	620924	438	2935	1.05 (0.94-1.15)
3-9	101933	1426641	1172	9212	1.25 (1.17-1.34)	92459	1409803	1020	8258	1.28 (1.15-1.32)
≥ 10	1738	24232	49	300	2.43 (1.86-3.39)	1456	19333	45	284	2.40 (1.83-3.35)
Never	3572205	49976927	32295	245423	0.78 (0.64-0.97)	1901288	27214381	16676	137516	0.77 (0.63-0.95)
0.10-0.99	24416	343198	211	1647	0.87 (0.73-1.04)	35367	537767	327	2579	0.88 (0.75-1.03)
1.00-2.99	140753	1969376	1485	11342	0.95 (0.82-1.24)	90702	1290092	907	6836	0.97 (0.83-1.26)
3.00-4.99	8728	123073	122	944	1.00	6115	101175	101	829	1.00
5.00-9.99	12712	176849	215	1636	1.37 (1.08-1.77)	8087	118519	156	1144	1.40 (1.10-1.81)
≥ 10.0	3572205	49976927	32295	245423	4.01 (2.01-8.66)	303	2507	12	89	3.53 (1.62-7.59)

Abbreviation, TC, Thyroid cancer; PY, Person-year; HR, Hazard ratio; CT, Computed tomography

1. Adjusted by age, sex, residence, income, past history of hypertension and family history of cancer
2. CT dose classification defined as annual radiation dose limit (1 mSv), annual exposed natural radiation (3 mSv), and abdominal CT dose (10 mSv)

4.3.3 Stratification of medical diagnostic radiation exposure and thyroid cancer

There were 577 thyroid cancer cases according to the CT exposure in men and it was statistically significant (HR, 1.08; 95% CI, 1.03−1.19). Considering the latent period of more than 5 years, it was consistently significant (HR, 1.09; 95% CI, 1.03−1.20). Also, in the frequency of CT exposure, there was dose−response relationship was identified in each category (1−2 times, HR, 1.07; 95% CI, 0.92−1.26; 3−9 times, HR, 1.02; 95% CI, 0.86−1.18; more than 10 times, HR, 3,51; 95% CI, 2.15−4.01).

Additionally, the radiation dose received at the thyroid according to the CT treatment was classified into various groups and it showed a dose−response relationship. Compared to the natural ionizing radiation level (3−5 mSv), 5−9.9 mSv was not associated with thyroid cancer risk (1.14; 0.71−1.86), and over 10 mSv only associated with thyroid cancer risk (4.92; 1.67−15.44), and other groups (never exposed group, 0.1−0.99 mSv, 1.0−2.9 mSv) were not associated with thyroid cancer.

In women, there were 2,126 thyroid cancer cases according to the CT exposure and it was statistically significant (HR, 1.19; 95% CI, 1.11−1.27). Considering the latent period of more than 5 years,

it was consistently significant (HR, 1.18; 95% CI, 1.10−1.27). Also, in the frequency of CT exposure, there was dose−response relationship was identified in each category (1−2 times, HR, 1.06; 95% CI, 0.98−1.15; 3−10 times, HR, 1.29; 95% CI, 1.23−1.38; more than 10 times, HR, 3.30; 95% CI, 2.46−4.11).

Additionally, the radiation dose received at the thyroid according to the CT treatment was classified into various groups and it showed a dose−response relationship. Compared to the natural ionizing radiation level (3−5 mSv), 5−9.9 mSv was associated with thyroid cancer risk (1.40; 1.04−1.85), and over 10 mSv only associated with thyroid cancer risk (6.85; 4.47−10.20), and other groups (never exposed group, 0.1−0.99 mSv, 1.0−2.9 mSv) were not associated with thyroid cancer.

In the case of living in a metropolitan, radiation exposure status, radiation exposure frequency, and CT dose were associated with thyroid cancer and both radiation exposure frequency and CT dose showed a dose−response relationship. Although non−living in the metropolitan area showed a consistent result, the strength of the living in the metropolitan area, thyroid cancer risk showed higher in 10 more frequency and over 10 mSv exposed dose.

4.4 DNA methylation on ionizing radiation-related markers to thyroid cancer

4.4.1 Identified ionizing radiation-related markers from the database

A total of 1,104 gene markers were included which related to ionizing radiation exposure through Clin Var and Pubmed database. In detail, studies on CpG methylation and DNA methylation according to radioactive, X-ray, and linac accelerators were considered. Also, the exposed targets were human epithelial cells or human cells such as skin or lung cells.

4.4.2 Radiation markers related to thyroid cancer in DNA methylation

Of the 1,104 genes related to CpG and DNA methylation according to ionizing radiation exposure, 162 genes were found. Among them, 64 genes were identified as ldelta m-valuel 0.25 or higher. In addition, significant gene markers are summarized in several combinations according to FDR, CpG island location, and promoter region. Specifically, ten markers were significant FDR lower than 0.10 in thyroid cancer DNA methylation.

4.4.3 Functional assessment of thyroid cancer risk according to the ionizing radiation exposure

The biological function assessment from the identified markers both DNA methylation from ionizing radiation and thyroid cancer was conducted. The considered database for functional assessment was 'Gene Ontology molecular function, cellular component, biological process', 'Biological pathways; KEGG, Reactome, WikiPathways', 'Regulatory motifs in DNA, TRANSFAC, miRTarBase' and 'Protein database, Human Protein Atlas, CORUM'. Also, identified 10 genes that are ldelta m−valuel higher than 0.25 and FDR less than 0.10 conducted the functional assessment. During the process GO molecular function (histone deacetylase activity, protein lysine deacetylase activity), GO biological process (peptidyl−lysine deacetylation, skeletal muscle fiber development, histone H4 deacetylation, histone H3 deacetylation), CORUM (HDAC4−ERK2 complex), and WikiPathway (Ethanol effects on histone modifications) were identified.

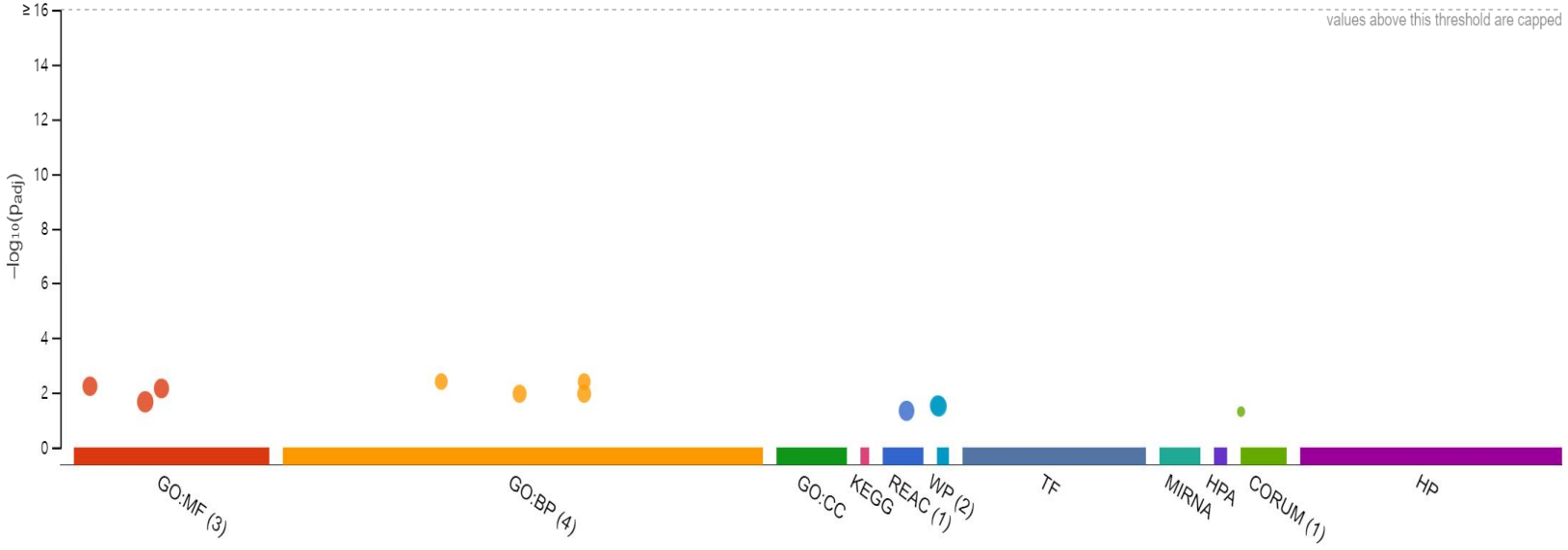

Figure 8. Functional assessment of selected 10 Gene markers both associated with ionizing radiation exposure and Papillary thyroid cancer.

Table 23. Gene description of associated both ionizing radiation epigenetic change and thyroid cancer

Gene name	Description
MAGI2	Diseases associated with MAGI2 include Nephrotic Syndrome, Type 15 and Genetic Steroid-Resistant Nephrotic Syndrome. Among its related pathways are Cell junction organization and Endometrial cancer. Gene Ontology (GO) annotations related to this gene include obsolete signal transducer activity and SMAD binding.
XYLT1	Diseases associated with XYLT1 include Desbuquois Dysplasia 2 and Pseudoxanthoma Elasticum. Among its related pathways are Glycosaminoglycan metabolism and Chondroitin sulfate/dermatan sulfate metabolism. Gene Ontology (GO) annotations related to this gene include acetylglucosaminyltransferase activity and protein xylosyltransferase activity.
ZNF671	Among its related pathways are Gene expression (Transcription). Gene Ontology (GO) annotations related to this gene include nucleic acid binding and transcription coregulator activity.
SDPR	(Caveolae Associated Protein 2) is a Protein Coding gene. Diseases associated with CAVIN2 include Seckel Syndrome 1. Among its related pathways are Nuclear receptors meta-pathway and Glucocorticoid receptor pathway.
HSPA2	Diseases associated with HSPA2 include Crohn's Disease and Varicocele. Among its related pathways are Meiosis and Cellular responses to stimuli. Gene Ontology (GO) annotations related to this gene include enzyme binding and glycolipid binding.
HDAC9	Diseases associated with HDAC9 include Primary Cutaneous T-Cell Non-Hodgkin Lymphoma and Cryptogenic Organizing Pneumonia. Among its related pathways are Constitutive Signaling by NOTCH1 HD+PEST Domain Mutants and Gene expression (Transcription). Gene Ontology (GO) annotations related to this gene include transcription factor binding and histone deacetylase binding
SH3BGRL3	Diseases associated with SH3BGRL3 include Prune Belly Syndrome. Among its related pathways are VEGFA-VEGFR2 signaling pathway. Gene Ontology (GO) annotations related to this gene include GTPase activator activity and protein-disulfide reductase activity
FMO1	Diseases associated with FMO1 include Trimethylaminuria and Thyroid Dyshormonogenesis 6. Among its related pathways are Metapathway biotransformation Phase I and II and "Busulfan Pathway, Pharmacodynamics

	". Gene Ontology (GO) annotations related to this gene include oxidoreductase activity and monooxygenase activity
TBCD	Diseases associated with TBCD include Encephalopathy, Progressive, Early-Onset, With Brain Atrophy And Thin Corpus Callosum and Seborrhea-Like Dermatitis With Psoriasiform Elements. Among its related pathways are Chaperonin-mediated protein folding and Metabolism of proteins. Gene Ontology (GO) annotations related to this gene include binding and chaperone binding
HDAC4	Diseases associated with HDAC4 include Neurodevelopmental Disorder With Central Hypotonia And Dysmorphic Facies and Chromosome 2Q37 Deletion Syndrome. Among its related pathways are Constitutive Signaling by NOTCH1 HD+PEST Domain Mutants and Gene expression (Transcription). Gene Ontology (GO) annotations related to this gene include sequence-specific DNA binding and transcription factor binding

Table 24. Results of functional assessment for relating genes both ionizing radiation and thyroid cancer to confirm biological function

Relating genes	Description	p-value
HDAC4:HDAC9	Histone deacetylase activity	0.0059
HDAC4:HDAC9	Protein lysine deacetylase activity	0.0071
HDAC4:HDAC9	Deacetylase activity	0.0021
HDAC4:HDAC9	Peptidyl-lysine deacetylation	0.0040
HDAC4:HDAC9	Histone H4 deacetylation	0.0040
HDAC4:HDAC9	Regulation of skeletal muscle fiber development	0.0113
HDAC4:HDAC9	Histone H3 deacetylation	0.0113
HDAC4:HDAC9	Notch-HLH transcription pathway	0.0464
HDAC4:HDAC9	Ethanol effects on histone modification	0.0298
HDAC4:HDAC9	Initiation of transcription and translation elongation at the HIV-1 LTR	0.0318
HDAC4	HDAC4-ERK2 complex	0.0496

Part 3. Other factors related to thyroid cancer

4.5 Thyroid cancer risk according to breast cancer

4.5.1 General characteristics of study population

Baseline general characteristics between 1,164 breast cancer and 281,207 non-breast cancer, 63.9% (N=744) of breast cancer cases were 40–59-year-old and it was statistically significant between groups (p <0.001). In addition, income level was statistically significant between groups (p <0.001). But the family histories were not significant between groups and only individual hypertension history was associated with between groups (p=0.013). Also, smoking status (p=0.002), alcohol consumption (p <0.001), and physical activities (p <0.001) were statistically significant. Plus, baseline smoker and drinker prevalence were higher in the breast cancer group (Ever smoker, 1.98%; Ever drinker, 11.6%) than non-breast cancer group (Non-smoker, 3.91%; Ever drinker, 16.9%).

Table 25. General characteristics between breast cancer patients (N=1,164) and non-breast cancer (N=281,207) from the Korea National Health Insurance Database (KNHID)

	Non-breast cancer (N=281,207)	Breast cancer (N= 1,164)	P-value[1]
	N (%)	N (%)	
Age			
< 40	89,900 (31.97)	225 (19.33)	
40-59	126,763 (45.08)	744 (63.92)	<0.001
60 +	64,544 (22.95)	195 (16.75)	
Income level			
1-2quintile	82,650 (29.39)	292 (25.09)	
3 quintile	51,965 (18.48)	197 (16.92)	<0.001
4-5quintile	146,592 (52.13)	675 (57.99)	
Family history of diabetes			
No	87,723 (31.20)	358 (30.76)	
Yes	110,318 (39.23)	417 (35.82)	0.288
Unknown	83,166 (29.57)	389 (33.42)	
Family history of cancer			
No	83,669 (29.75)	322 (27.66)	
Yes	114,659 (40.77)	458 (39.35)	0.609
Unknown	82,879 (29.47)	384 (32.99)	
Family history of hypertension			
No	84,023 (29.88)	332 (28.52)	
Yes	114,576 (40.74)	442 (37.97)	0.742
Unknown	82,608 (29.38)	390 (33.51)	
Concomitant diabetes			
No	257602 (91.61)	1068 (91.62)	0.857
Yes	24,634 (5.07)	96 (8.38)	
Concomitant hypertension			
No	207,139 (73.66)	895 (76.89)	0.013
Yes	74,068 (26.34)	269 (23.11)	
Smoking status			

Never smokers	206058 (73.28)	812 (69.76)	
Ever	11,006 (3.91)	23 (1.98)	0.002
Unknown	64,143 (22.81)	329 (28.26)	
Alcohol drinking habit			
Never	168,717 (60.00)	701 (60.22)	
Ever	47,680 (16.96)	135 (11.60)	<0.001
Unknown	64,810 (23.04)	328 (28.18)	
Walking frequency in a week at least 30 minutes			
Never	120,066 (42.70)	412 (35.40)	
Ever	97,475 (34.66)	424 (36.43)	<0.001
Unknown	63,666 (22.64)	328 (28.18)	
Concomitant dyslipidemia			
No	277,506 (98.68)	1,142 (98.11)	0.09
Yes	3,701 (1.32)	22 (1.89)	

1 P-values were calculated using t-test for fasting blood glucose and chi-square test for the other variables.
2. Income level (monthly) divides by quintile
(1 quintile = 1,598,817 KRW, 2 quintile = 1,927,149 KRW, 3 quintile = 2,569,499 KRW, 4 quintile = 3,368,899 KRW and 5 quintile = 5,809,644 KRW)

4.5.2 Thyroid cancer risk according to the breast cancer

Follow-up during 2003 to 2013, there were 48 thyroid cancer cases according to the breast cancer, and it was statistically significant with thyroid cancer (HR, 3.26; 95% CI, 2.44-4.36) in the fully adjusted model. Considered over 2 years lag period, breast cancer is associated with thyroid cancer (HR, 2.13; 95% CI, 1.45-3.13). Stratification according to age, breast cancer cases were associated with thyroid cancer in all age groups (< 40 years; 4.13; 2.14-7.96; 40-50 years, 2.94; 2.08-4.17; over 60 years, 4.25; 1.76-10.25) compared to non-breast cancer group).

In addition, stratification according to income level showed a significant risk of thyroid cancer according to the breast in all groups. Also, compared to the high-income level (5 quartile, 2.49; 1.65-3.76), quartile 3 (4.62; 2.48-8.64) and quartiles 1 and 2 (4.65; 2.69-8.05) showed higher thyroid cancer risk. Lifestyle stratification such as smoking, alcohol consumption, and physical activities, and individual history of hypertension was associated with thyroid cancer in the breast cancer group. In the case of the breast cancer-only group analysis, most of the variables were not associated but only smoking status was associated compared to never smoker group (HR, 6.60; 95% CI, 2.34-18.59).

Table 26. Subsequent primary thyroid cancer risk between breast cancer patients and non-breast cancer subjects at baseline from the Korea National Health Insurance Database (KNHID)

Breast cancer	Person-year	TC cases (N=4,626)	HR[1] (95% CI)	HR[2] (95% CI)	HR[3] (95% CI)
Total subjects					
Non-BC	3,233,094	4,578	1.00	1.00	1.00
BC patients	9,827	48	**3.64 (2.72-4.86)**	**3.23 (2.42-4.32)**	**3.26 (2.44-4.36)**
2-year lag periods					
Non-BC	3,227,123	4,157	1.00	1.00	1.00
BC patients	9,720	26	**2.28 (1.55-3.36)**	**2.11 (1.44-3.10)**	**2.13 (1.45-3.13)**

1. Crude value
2. Adjusted for such as age, income levels, smoking status, walking frequency in a week at least 30 minutes
3. Adjusted for [3] + alcohol consumption and hypertension

Table 27. Stratification and combination analyses according to baseline age, income levels for the subsequent primary thyroid cancer risk between breast cancer patients and non-breast cancer subjects from the Korea National Health Insurance Database (KNHID)

Total cohort	Person-year	TC cases (N=4,626)	Stratification HR[2] (95% CI)	Stratification HR[3] (95% CI)	Combination HR[2] (95% CI)	Combination HR[3] (95% CI)
According to baseline age						
Age < 40 years						
Non-BC	1,068,979	1,419	1.00	1.00	1.00	1.00
BC patients	1,840	9	**4.19 (2.17-8.08)**	**4.13 (2.14-7.96)**	**3.97 (2.06-7.64)**	**3.93 (2.04-7.57)**
Age 40-59						
Non-BC	1,493,655	2,664	1.00	1.00	**1.29 (1.21-1.38)**	**1.23 (1.15-1.32)**
BC patients	6,417	33	**2.92 (2.05-4.13)**	**2.94 (2.08-4.17)**	**3.81 (2.68-5.40)**	**3.69 (2.60-5.24)**
Age 60+						
Non-BC	670,460	495	1.00	1.00	0.58 (0.53-0.65)	0.53 (0.47-0.59)
BC patients	1,570	6	**4.24 (1.76-10.22)**	**4.25 (1.76-10.25)**	**2.59 (1.08-6.23)**	2.34 (0.97-5.63)
According to income levels[3]						
Quintile 1-2						
Non-BC	947,103	1,150	1.00	1.00	1.00	1.00
BC patients	2,360	15	**4.61 (2.66-7.96)**	**4.64 (2.68-8.02)**	**4.48 (2.59-7.74)**	**4.49 (2.60-7.75)**
Quintile 3						
Non-BC	600,868	749	1.00	1.00	1.02 (0.93-1.11)	1.02 (0.93-1.11)
BC patients	1,723	10	**4.55 (2.44-8.51)**	**4.59 (2.46-8.58)**	**4.71 (2.53-8.77)**	**4.73 (2.54-8.80)**
Quintile 4-5						
Non-BC	1,685,123	2679	1.00	1.00	**1.30 (1.22-1.40)**	**1.30 (1.22-1.40)**
BC patients	5,744	23	**2.43 (1.61-3.66)**	**2.47 (1.64-3.72)**	**3.27 (2.16-4.93)**	**3.30 (2.19-5.00)**

1. Adjusted for age
2. Adjusted for age, income levels, smoking status, walking frequency in a week at least 30 minutes [1]
3. Adjusted for [1] + alcohol consumption and concomitant hypertension
4. Income levels (average monthly household income): Quintile 2= 1,927,149 KRW, Quintile 3 = 2,569,499 KRW, and Quintile 4 = 3,368,899 KRW

Table 28. Stratification and combination analyses according to cigarette smoking, exercise, alcohol drinking and concomitant hypertension for the subsequent primary thyroid cancer risk between breast cancer patients and non-breast cancer subjects at baseline from the Korea National Health Insurance Database

Total cohort	Person-year	Thyroid cancer cases	Stratification HR[1] (95% CI)	Stratification HR[2] (95% CI)	Combination HR[1] (95% CI)	Combination HR[2] (95% CI)
Smoking status[2]						
Never						
Non-BC	2,430,320	3,877	1 (reference)	1 (reference)	1 (reference)	1 (reference)
BC patients	7,288	36	**2.96 (2.12-4.12)**	**2.96 (2.12-4.11)**	**2.95 (2.11-4.12)**	**2.96 (2.12-4.13)**
Ever (experienced)						
Non-BC	129,403	140	1 (reference)	1 (reference)	0.70 (0.59-0.83)	0.72 (0.61-0.86)
BC patients	154	4	**28.2 (10.38-76.9)**	**28.3 (10.38-77.5)**	**18.36 (6.88-48.95)**	**19.37 (7.26-51.69)**
Exercising status						
Never						
Non-BC	1,410,837	2,069	1 (reference)	1 (reference)	1 (reference)	1 (reference)
BC patients	3,631	21	**3.70 (2.38-5.76)**	**3.73 (2.40-5.80)**	**3.69 (2.37-5.73)**	**3.71 (2.39-5.76)**
Ever [3]						
Non-BC	1,154,334	1,954	1 (reference)	1 (reference)	**1.09 (1.03-1.17)**	**1.10 (1.03-1.17)**
BC patients	3,809	19	**2.88 (1.83-4.53)**	**2.87 (1.83-4.52)**	**3.16 (2.01-4.97)**	**3.18 (2.03-5.00)**
Alcohol consumption[2]						
Never						
Non-BC	1,986,092	3,162	1 (reference)	1 (reference)	1 (reference)	1 (reference)
BC patients	6,293	33	**3.09 (2.18-4.37)**	**3.11 (2.20-4.41)**	**3.09 (2.18-4.37)**	**3.12 (2.20-4.42)**
Ever [3]						
Non-BC	565,539	841	1 (reference)	1 (reference)	0.91 (0.84-0.99)	0.91 (0.84-0.99)
BC patients	1,150	7	**4.16 (1.98-8.76)**	**4.16 (1.98-8.76)**	**3.73 (1.78-7.83)**	**3.75 (1.79-7.88)**
Concomitant hypertension						
No						
Non-BC	2,410,386	3,435	1 (reference)	1 (reference)	1 (reference)	1 (reference)
BC patients	7,648	38	**3.32 (2.40-4.59)**	**3.30 (2.39-4.57)**	**3.30 (2.39-4.57)**	**3.29 (2.38-4.54)**
Yes						
Non-BC	822,708	1,143	1 (reference)	1 (reference)	**1.19 (1.11-1.28)**	**1.19 (1.11-1.28)**
BC patients	2,179	10	**2.99 (1.55-5.76)**	**2.98 (1.54-5.75)**	**3.76 (1.95-7.24)**	**3.75 (1.95-7.23)**

1. Adjusted for age, income levels, smoking status, walking frequency in a week at least 30 minutes
2. Adjusted for [2] + alcohol consumption and concomitant hypertension
3. Income levels (average monthly household income): Quintile 2= 1,927,149 KRW, Quintile 3 = 2,569,499 KRW, and Quintile 4 = 3,368,899 KRW

Table 29. Stratification and combination analyses according to baseline age, income levels for the subsequent primary thyroid cancer risk among 1,164 breast cancer patients at baseline from the Korea National Health Insurance Database (KNHID)-representative cohort study, 2002-2013

BC patient' s cohort	Person-year	Thyroid cancer cases (N=48)	HR[1] (95% CI)	HR[2] (95% CI)	HR[3] (95% CI)
According to baseline age					
Age < 40 years	1,840	9	1.59 (0.62-4.08)	1.52 (0.51-4.54)	1.55 (0.52-4.61)
Age 40 -59	6,417	33	1.53 (0.51-4.58)	1.46 (0.57-3.73)	1.47 (0.57-3.78)
Age 60+	1,570	6	1 (reference)	1 (reference)	1 (reference)
According to income levels[3]					
Quintile <= 3	2,360	15	1.40 (0.79-2.50)	1.40 (0.79-2.50)	1.39 (0.78-2.48)
Quintile > 3	7,467	33	1 (reference)	1 (reference)	1 (reference)
Smoking status[2]					
Never	7,288	36	1 (reference)	1 (reference)	1 (reference)
Ever [3]	154	4	5.75 (2.04-16.18)	6.24 (2.22-17.57)	6.60 (2.34 -18.59)
Exercising status					
Never	3,631	21	1 (reference)	1 (reference)	1 (reference)
Ever [3]	3,809	19	0.88 (0.47-1.64)	0.86 (0.46-1.61)	0.86 (0.46-1.61)
Alcohol consumption[2]					
Never	6,293	33	1 (reference)	1 (reference)	1 (reference)
Ever [3]	1,150	7	1.18 (0.52-2.67)	1.22 (0.54-2.77)	1.21 (0.54-2.75)
Concomitant hypertension					
No	7,648	38	1 (reference)	1 (reference)	1 (reference)
Yes	2,179	10	1.02 (0.49-2.11)	1.12 (0.54-2.33)	1.13 (0.54-2.33)

1. Adjusted for age
2. Adjusted for age, income levels, smoking status, walking frequency in a week at least 30 minutes [1]
3. Adjusted for [1] + alcohol consumption and concomitant hypertension
4. Income levels (average monthly household income): Quintile 2= 1,927,149 KRW, Quintile 3 = 2,569,499 KRW, and Quintile 4 = 3,368,899 KRW

Table 30. Association between breast cancer and thyroid cancer in nested case-control study

Female cancer type	Cases (Thyroid cancer) N = 6,339	Controls (Non-thyroid cancer) (N = 25,356)	OR[1] (95% CI)
Past-history of Breast cancer			
Non-Breast cancer	6,088	24,990	1.00
Breast cancer patients	251	366	2.76 (2.34 – 3.25)

Model 1: Income level, smoking status, exercising status, alcohol consumption, family history of cancer, body mass index + concomitant hypertension, diabetes

According to income levels[2]	Cases (Thyroid cancer) N = 6,339	Controls (Non-thyroid cancer) (N = 25,356)	Combination OR[1] (95% CI)
Past-history of Breast cancer			
Decile 0-3			
Non-Brest cancer	1,427	6,139	1.00
Breast cancer patients	54	64	3.57 (2.47 – 5.16)
Decile 4-7			
Non-Brest cancer	1,915	9,440	0.86 (0.80 – 0.93)
Breast cancer patients	82	137	2.54 (1.92 – 3.36)
Decile 8-10			
Non-Brest cancer	2,746	9,411	1.24 (1.15 – 1.33)
Breast cancer patients	115	165	2.97 (2.32 – 3.79)

Model 1: Income level, smoking status, exercising status, alcohol consumption, family history of cancer, body mass index + concomitant hypertension, diabetes

1. Income levels (average monthly household income): (Decile 3 = 1,481,706 KRW, Decile 7 = 2,893,173 KRW, Decile 10 = 6,585,130 KRW)

4.5.3 Thyroid cancer risk according to the breast cancer (Sensitivity analysis)

Additionally, sensitivity analysis was conducted for assessing the screening effects on thyroid cancer. In detail, fine-needle aspiration (FNA) treatment is considered a screening effect for thyroid cancer. Among the study population, 268 subjects were treated for FNA, and we excluded the subjects for sensitivity analysis. Among the subjects, seven subjects consisted of the breast cancer group (1.7% of overall breast cancer diagnosis), and others were non-breast cancer group (5.6% of overall non-breast cancer subjects).

Except for them, thyroid cancer according to breast cancer was associated (HR, 2.82; 95% CI, 2.31-3.78) and it was consistently associated based on the 2-year lag period (HR, 2.03; 95% CI, 1.22-2.74). Stratification of age and income levels is consistently associated similarly to the overall group.

In the case of income levels, breast cancer patients with low-income levels were more strongly associated with thyroid cancer than middle- or high-income levels (Quintile 1-2, HR, 5.32; 95% CI, 3.18-9.12).

Table 31. The association between breast cancer and thyroid cancer according to the consideration of FNA examination

Breast cancer	Non-TC (N=277,745)	TC (N=4,358)	HR[1] (95% CI)
Total subjects			
Non-BC	276,629	4,317	1.00
BC patients	1,116	41	2.82 (2.31-3.78)
2-year lag periods			
Non-BC	272,381	3,954	1.00
BC patients	995	22	2.03 (1.22-2.74)

Table 32. The stratification of age and income levels, consideration of FNA examination

	Non-TC (N=277,745)	TC (N=4,358)	Stratification HR (95% CI)
Baseline age			
Age < 40 years			
Non-BC	91,485	1,345	1.00
BC patients	227	8	3.76 (1.96-7.22)
Age 40 -59			
Non-BC	130,741	2,505	1.00
BC patients	696	28	2.83 (1.90-4.02)
Age 60+			
Non-BC	54,403	467	1.00
BC patients	193	5	4.81 (2.33-11.58)
Income levels[1]			
Quintile 1-2			
Non-BC	86,189	1,058	1.00
BC patients	2,360 267	14	5.32 (3.18-9.12)
Quintile 3			
Non-BC	600,868	708	1.00
BC patients	1,723,208	8	3.86 (1.84-7.08)
Quintile 4-5			
Non-BC	1,685,123	2551	1.00
BC patients	5,744,641	19	2.41 (1.46-3.30)

4.6 The association between breast cancer and thyroid cancer (Estrogen receptor-based epigenetics markers)

4.6.1 General characteristics of each study population

The general characteristics of the subjects included the thyroid cancer DNA methylation consisting of 24 thyroid cancer cases and 16 controls. The mean age of the thyroid cancer cases was 42.1 years old; the control group was 44.9 years old, and BMI in thyroid cancer cases was 22.9 (standard deviation, 2.5) and 21.2 (standard deviation, 1.3) in the control group, which was statistically significant. In addition, education level was statistically significant, and lifestyle factor was not different. Also, the control group did not have any history of diseases such as diabetes, hypertension, dyslipidemia, and thyroid disease. In the clinical pathology of thyroid cancer cases, nine cases had lymph node metastasis, and 14 cases with extrathyroidal extension. Also, tumor sizes less than 1cm and more than 1cm consisted of 12 cases in each group, respectively.

Table 33. General characteristics of thyroid cancer DNA methylation data

	Thyroid cancer cases (N=24)	Controls (N=16)	p-value
	Mean (SD)	Mean (SD)	
Age (years)	42.1 (8.7)	44.9 (9.7)	0.39
Body mass index (kg/m^2)	22.9 (2.5)	21.2 (1.3)	0.01
	N (%)	N (%)	
Education (≥ college)	12 (50.0)	3 (18.8)	0.04
Ever cigarette smokers	1 (4.4)	3 (18.8)	0.14
Ever alcohol drinkers	17 (73.9)	9 (56.3)	0.25
Regular exercised	6 (25.0)	6 (37.5)	0.45
Family history of cancer	8 (33.3)	3 (18.8)	0.27
Pregnancy	17 (73.9)	12 (75.0)	0.95
Post-menopausal	6 (25.0)	5 (31.3)	0.89
Lymph node meta	9 (37.5)	NA	NA
Extra thyroidal extension	14 (60.9)	NA	NA
Tumor size			
< 1 cm	12 (50.0)	NA	NA
≥ 1 cm	12 (50.0)		

There were 16 breast cancer cases, and 8 control in breast cancer DNA methylation. In the cases of age, the mean age of the breast cancer cases was 44.5 (SD, 9.6) and controls were 36.9 (SD, 9.2). BMI level was not statistically significant between group

(breast cancer, 22.4; controls, 20.9). Also, lifestyle factor and individual history of diseases were not statistically significant, but only post-menopausal status was significant between groups. It would be due to the age difference.

Table 34. General characteristics of breast cancer DNA methylation data

	Breast cancer cases (N=16)	Controls (N=8)	p-value
	Mean (SD)	Mean (SD)	
Age (years)	44.5 (9.6)	36.9 (9.2)	0.08
Body mass index (kg/m^2)	22.4 (2.5)	20.9 (3.4)	0.30
Education (≥ college)	8 (50.0)	2 (25.0)	0.65
Ever cigarette smokers	2 (12.5)	0 (0.0)	0.19
Ever alcohol drinkers	4 (25.0)	4 (50.0)	0.16
Regular exercised	6 (37.5)	1 (12.5)	0.18
Past history of			
Diabetes	1 (6.3)	1 (12.5)	0.61
Hypertension	0 (0)	1 (12.5)	0.13
Dyslipidemia	1 (6.3)	0 (0)	0.36
Thyroid disease	0 (0)	0 (0)	1.00
Pregnancy	14 (87.5)	6 (75.0)	0.45
Post-menopausal	9 (56.3)	0 (0)	0.001

4.6.2 Estrogen receptor related markers in thyroid cancer population

The ESR1 gene is an estrogen receptor-encoding gene and ligand-activated transcription factor. But it was not identified in the thyroid cancer DNA methylation database (Illumina EPIC array 850K). Therefore, 52 transcriptome binding sites with the highest association score of the ESR1 gene from the 'Genecard' database were applied to assess thyroid cancer DNA methylation. Among the 52 transcriptome binding sites, 246 CpG (45 Genes) were identified in the thyroid cancer database and 42 CpGs (16 Genes) were validated in breast cancer. Consequently, based on ldelta m-valuel > 0.25 and FDR < 0.20, there were six CpGs and six genes were validated both in thyroid cancer and breast cancer. If validated in the breast cancer database, 524 CpG (42 Genes) were identified, and 36 CpGs (16 Genes) were validated in thyroid cancer. Consequently, based on ldelta m-valuel > 0.25 and FDR < 0.20, there were six CpGs and six genes were validated both in thyroid cancer and breast cancer.

4.7 Reproductive factors and thyroid cancer

4.7.1. Association between reproductive factors and thyroid cancer in overall group

In the overall population, ORs of thyroid cancer according to menarche tended to decrease, if the first age of menarche was later. In this study, menarche after 16 years old was protectively associated with thyroid cancer compared to before 13 years old menarche (OR, 0.38; 95% CI, 0.26−0.48). In addition, menopausal status women were associated with thyroid cancer compared to premenopausal women (OR, 1.37; 95% CI, 1.05−1.54). If the menopausal age was getting later, thyroid cancer risk tended to increase than early age.

In the case of pregnancy status, pregnancy history was protectively associated with thyroid cancer (OR, 0.45; 95% CI, 0.32−0.59). Regardless of pregnancy age, all age groups were protectively associated with thyroid cancer.

In groups who had a history of spontaneous abortion, their thyroid cancer was protectively associated (OR, 0.65; 95% CI, 0.50−0.78). In the case of breastfeeding, it tended to decrease the thyroid cancer risk, but it was not significant, and a longer period of breastfeeding tended to decrease the thyroid cancer risk, it was not significant.

Lastly, oral contraception use and hormone replacement treatment both were protectively associated with thyroid cancer (Oral contraception, OR, 0.79; 95% CI, 0.61−0.97; hormone replacement treatment, OR, 0.68; 95% CI, 0.54−0.96).

According to the stratification based on the menopausal status, the association was similar to the overall population. Delivery experience in the postmenopausal status group, although thyroid cancer was not significant, it was marginally associated. Also, age in the pregnancy, postmenopausal group was not associated with thyroid cancer. In the case of breastfeeding, a longer period of breastfeeding is protectively associated with thyroid cancer. In addition, oral conception use was protectively associated with the postmenopausal group only.

Table 35. Association between reproductive factors and thyroid cancer

		Overall group		
Reproductive factors		Cases (N=1,205)	Controls (N=1,205)	OR (95% CI)
		N (%)	N (%)	
Age at menarche	≤ 13	458 (38.0)	284 (23.6)	1.00
	14-15	528 (43.8)	559 (46.4)	0.58 (0.43-0.72)
	≥ 16	219 (18.2)	362 (30.0)	0.38 (0.26-0.48)
Menopausal status	Pre	629 (52.2)	698 (57.9)	1.00
	Post	571 (47.4)	500 (41.5)	1.37 (1.05-1.54)
Age at menopause	≤ 47	138 (24.2)	171 (34.2)	1.00
	48-51	249 (43.6)	200 (40.0)	1.51 (1.12-2.11)
	≥ 52	184 (32.3)	127 (25.4)	1.75 (1.24-2.57)
Pregnancy	Never	136 (11.3)	63 (5.2)	1.00
	Ever	1067 (88.5)	1142 (94.8)	0.45 (0.32-0.59)
Delivery experience	No parity	136 (11.3)	60 (5.0)	3.06 (1.44-6.64)
	Never	14 (1.2)	19 (1.6)	1.00
	Ever	1052 (87.3)	1126 (93.4)	1.27 (0.63-2.60)
Age at pregnancy	Never	136 (11.3)	60 (5.0)	1.00
	≤ 25	454 (37.7)	507 (42.1)	0.42 (0.25-0.68)
	26-27	251 (20.8)	319 (26.5)	0.37 (0.20-0.52)
	≥ 28	359 (29.8)	315 (26.1)	0.52 (0.30-0.75)
Age at first birth	Never	14 (1.3)	19 (1.7)	1.00
	≤ 25	248 (23.2)	272 (23.7)	1.21 (0.55-2.74)
	26-27	366 (34.3)	481 (42.0)	1.03 (0.48-2.26)
	≥ 28	436 (40.8)	367 (32.1)	1.61 (0.75-3.53)
Number of live births	Never	14 (1.3)	19 (1.7)	1.00
	1	166 (15.5)	136 (11.9)	1.61 (0.70-3.71)
	2	650 (60.9)	643 (56.2)	1.30 (0.56-3.10)
	≥ 3	234 (21.9)	343 (29.9)	0.94 (0.61-1.47)
History of SAB	Never	969 (80.4)	874 (72.5)	1.00
	Ever	231 (19.2)	330 (27.4)	0.65 (0.50-0.78)

Table 35. Association between reproductive factors and thyroid cancer (Continued)

		Overall group		
Reproductive factors		Cases (N=1,205)	Controls (N=1,205)	OR (95% CI)
		N (%)	N (%)	
Breastfeeding	No parity	136 (11.3)	60 (5.0)	2.04 (1.39−3.05)
	No gravity	12 (1.0)	16 (1.3)	0.71 (0.27−1.53)
	Never	184 (15.3)	169 (14.0)	1.00
	Ever	867 (71.9)	955 (79.3)	0.89 (0.60−1.11)
Duration of breastfeeding	Never	184 (17.4)	169 (15.0)	1.00
	≤ 25	374 (35.4)	408 (36.1)	0.87 (0.62−1.20)
	26−27	268 (25.4)	278 (24.6)	0.90 (0.56−1.20)
	≥ 28	224 (21.2)	266 (23.6)	0.77 (0.59−1.03)
Number of breastfeeding children	Never	184 (17.4)	169 (15.0)	1.00
	1	229 (21.7)	193 (17.1)	1.08 (0.72−1.62)
	2	439 (41.5)	480 (42.5)	0.83 (0.57−1.19)
	≥ 3	201 (19.0)	283 (25.1)	0.65 (0.48−0.89)
Oral contraception use	Never	986 (81.8)	936 (77.7)	1.00
	Ever	211 (17.5)	258 (21.4)	0.79 (0.61−0.97)
HRT	Never	433 (75.8)	333 (66.6)	1.00
	Ever	133 (23.3)	167 (33.4)	0.68 (0.54−0.96)

Table 36. Association between reproductive factors and thyroid cancer according to the menopausal status

		Pre-menopausal status			Pre-menopausal status		
Reproductive factors		Cases (N=629)	Controls (N=698)	OR (95% CI)	Cases (N=571)	Controls (N=500)	OR (95% CI)
		N (%)	N (%)		N (%)	N (%)	
Age at menarche	≤ 13	319 (50.7)	205 (29.3)	1.00	137 (24.0)	72 (14.4)	1.00
	14-15	244 (38.8)	335 (48.0)	0.48 (0.33-0.62)	283 (49.5)	223 (44.6)	0.69 (0.42-0.96)
	≥ 16	66 (10.5)	158 (22.7)	0.27 (0.15-0.41)	151 (26.5)	205 (41.0)	0.41 (0.23-0.58)
Pregnancy	Never	121 (19.2)	47 (6.7)	1.00	14 (2.4)	11 (2.1)	1.00
	Ever	506 (80.5)	651 (93.3)	0.30 (0.17-0.46)	557 (97.6)	489 (97.8)	0.90 (0.35-2.06)
Delivery experience	No parity	121 (19.3)	47 (6.7)	2.02 (0.68-5.70)	14 (2.4)	11 (2.2)	3.69 (0.82-20.47)
	Never	9 (1.5)	7 (1.0)	1.00	3 (0.6)	9 (1.7)	1.00
	Ever	496 (78.9)	644 (92.3)	0.60 (0.21-1.66)	554 (97.0)	480 (95.9)	3.47 (0.97-15.92)
Age at pregnancy	Never	121 (19.2)	47 (6.7)	1.00	14 (2.5)	11 (2.1)	1.00
	≤ 25	157 (24.9)	249 (35.7)	0.28 (0.12-0.41)	297 (52.0)	255 (50.9)	0.93 (0.35-2.21)
	26-27	112 (17.7)	194 (27.8)	0.25 (0.10-0.39)	135 (23.6)	127 (25.4)	0.84 (0.30-2.10)
	≥ 28	236 (37.5)	207 (29.6)	0.44 (0.29-0.66)	123 (21.5)	106 (21.1)	0.91 (0.36-2.27)
Age at first birth	Never	9 (1.8)	7 (1.1)	1.00	3 (0.5)	9 (1.8)	1.00
	≤ 25	75 (14.8)	111 (17.1)	0.56 (0.10-1.51)	173 (31.1)	161 (33.0)	3.20 (0.80-12.16)
	26-27	145 (28.5)	286 (43.9)	0.42 (0.12-1.22)	220 (39.5)	194 (39.6)	3.42 (0.88-12.77)
	≥ 28	277 (54.6)	242 (37.1)	0.91 (0.30-2.46)	159 (28.6)	124 (25.3)	3.85 (1.01-17.90)
Number of live birth	Never	9 (1.8)	7 (1.1)	1.00	3 (0.5)	9 (3.0)	1.00
	1	128 (25.2)	94 (14.4)	1.13 (0.31-4.39)	38 (6.9)	41 (8.4)	2.56 (0.46-15.51)
	2	327 (64.4)	441 (67.7)	0.61 (0.16-2.20)	323 (58.0)	202 (41.4)	4.20 (0.93-29.17)
	≥ 3	42 (8.3)	106 (16.3)	0.49 (0.11-1.27)	191 (34.3)	237 (48.4)	2.15 (0.31-13.74)
History of SAB	Never	513 (81.5)	506 (72.5)	1.00	453 (79.3)	366 (73.1)	1.00
	Ever	114 (18.2)	192 (27.5)	0.59 (0.43-0.78)	117 (20.5)	134 (26.8)	0.72 (0.51-0.95)

Table 36. Association between reproductive factors and thyroid cancer according to the menopausal status (Continued)

Reproductive factors		Pre-menopausal status			Pre-menopausal status		
		Cases (N=629)	Controls (N=698)	OR (95% CI)	Cases (N=571)	Controls (N=500)	OR (95% CI)
		N (%)	N (%)		N (%)	N (%)	
Breastfeeding	No parity	121 (19.3)	47 (6.7)	2.95 (1.91-4.62)	14 (2.4)	11 (2.2)	0.83 (0.32-2.18)
	No gravity	9 (1.8)	8 (1.3)	1.21 (0.37-3.55)	3 (0.6)	8 (1.6)	0.24 (0.02-1.12)
	Never	102 (16.2)	119 (17.0)	1.00	76 (13.3)	49 (9.8)	1.00
	Ever	391 (62.2)	520 (74.5)	0.85 (0.62-1.22)	476 (83.4)	432 (86.3)	1.01 (0.58-1.72)
Duration of breastfeeding	Never	102 (20.5)	119 (18.5)	1.00	76 (13.7)	49 (10.2)	1.00
	≤ 25	254 (51.3)	302 (47.0)	0.92 (0.63-1.27)	120 (21.7)	105 (21.8)	0.75 (0.44-1.21)
	26-27	102 (20.5)	157 (24.5)	0.71 (0.45-1.04)	165 (29.8)	118 (24.4)	0.91 (0.55-1.41)
	≥ 28	34 (6.9)	57 (8.9)	0.81 (0.48-1.18)	190 (34.3)	209 (43.3)	0.62 (0.36-0.92)
Number of breastfeeding children	Never	102 (20.5)	119 (18.6)	1.00	76 (13.7)	49 (10.2)	1.00
	1	151 (30.5)	137 (21.4)	1.30 (0.89-1.87)	78 (14.1)	56 (11.6)	0.90 (0.51-1.55)
	2	212 (42.7)	312 (48.6)	0.81 (0.57-1.12)	227 (40.9)	167 (34.6)	0.88 (0.56-1.35)
	≥ 3	29 (5.9)	72 (11.2)	0.48 (0.25-0.83)	172 (31.0)	208 (43.2)	0.55 (0.30-0.96)
Oral contraception use	Never	508 (80.8)	583 (83.5)	1.00	476 (83.4)	354 (70.8)	1.00
	Ever	116 (18.4)	110 (15.8)	1.22 (0.85-1.67)	95 (16.6)	141 (28.1)	0.53 (0.33-0.74)

Discussion

5.1 Iodine intake and TC in case-control study

According to the findings of this study, people whose iodine intake was excessive had a significantly higher risk of developing PTC and PTMC compared to people whose iodine intake was adequate. A higher risk of both PTC and PTMC was associated with high levels of free T4, the researchers found. A high level of free T4 had a more marked effect on increasing the risk of PTMC than it did on increasing the risk of PTC, but an excessive amount of UIC had a more marked effect on increasing the risk of PTC than it did on increasing the risk of PTMC. The combination of an excessive iodine intake and a high level of free T4 had a synergistic effect on raising the risk of PTC and PTMC; on the other hand, the combination of an excessive iodine intake and TSH resulted in a rapid increase in the risk of PTC and PTMC at excessive iodine intake.

Previous results on the association between dietary iodine intake and thyroid cancer were difficult to interpret because of inconsistencies between studies caused by factors such as differences in measurement methods and measurement bias in measuring iodine intake (56, 57). This made it difficult to conclude

the strength of the relationship between the two. The measurement of the 24-hour urinary iodine concentration (UIC) is considered the gold standard for assessing iodine intake; however, it is difficult to apply at the population level (58). As a result, urinary iodine concentration (UIC) from a random spot has been proposed as an alternative indicator (42, 58). Although UIC varies dependent on dietary iodine intake, including the consumption of ionized water, it has been used as a surrogate marker in the population (42, 58).

The association between thyroid cancer and UIC has been the subject of a great number of studies in the past; however, some of these studies have concentrated on determining the median difference in UIC between cases and controls (59, 60). Although a meta-analysis reported the odds ratios for papillary thyroid cancer in comparison to normal controls that were associated with excessive iodine intake (61), we were unable to compare their findings directly with those of our study for the following reasons: The OR that was reported in the meta-analysis for one study was not reported in the original article (61); for a different study, the OR that was reported in the meta-analysis was not reported in the original article (61); and for the fourth study, the UIC reference value that was used was different from the standards set by the

World Health Organization (WHO) (61). According to the findings of one study (62), the PTC risk associated with an excessive UIC did not significantly vary between the cases and the controls. In addition, four studies used patients with thyroid nodules as the control group. Because iodine and thyroid hormones are involved in the growth and differentiation of the thyroid, these studies may have underestimated the effect that UIC has on the risk of developing PTC (62-64).

Several earlier studies, including our own, have reported the effect of excessive UIC on the clinicopathological aggressiveness of PTC; however, the results of these studies have been inconsistent. Some studies found a relationship between excessive iodine intake and an increased risk of lymph node metastasis (64), larger tumor size (65), capsular invasion (65, 66), bilateral location (64]) extra-thyroid metastasis (67), and BRAF V600E or T17799A mutation (67, 68), while other studies have not found an association between excessive iodine intake and lymph node metastasis (65, 66), tumor size (66, 67), multifocal tumors or bilaterality (65, 66), extracapsular extension (65) or BRAF mutations (60).

A high free T4 level was found to be associated with both PTC and PTMC when looking at the correlation between thyroid function and

the risk of PTC. Previous research found that a high level of free T4 was linked to an increased risk of developing thyroid cancer. When looking at the TSH level, thyroid cancer was found to be associated with a moderate TSH level; however, it was difficult to determine whether or not the thyroid cancer was pathologically PTC [14]. In addition, several studies looked at thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) in conjunction with thyroid stimulating hormone (TSH) and thyroid hormone (62, 63, 69, 70). We found a correlation between high free T4 levels, excessive iodine intake, and an increased risk of both papillary thyroid cancer and papillary thyroid microcarcinoma (PTC and PTMC). However, we were unable to find any previous studies that looked at the relationship between consuming an excessive amount of iodine and having a poorly functioning thyroid and how that relates to the risk of developing PTC.

There are a few potential biological mechanisms that could explain a relationship between high levels of thyroid hormone and excessive iodine consumption, which both increase the risk of papillary thyroid cancer (PTC). (71) An in vitro study found that thyroid hormone makes a direct contribution to the plasma membrane–initiated activation of the mitogen–activated protein

kinase (MAPK) cascade, which means that it plays a role in the proliferation of thyroid cancer cells. In addition to this, it has been demonstrated that both TPOAb and TGAb are linked to a significantly elevated probability of developing PTC (70). However, the association between the presence of autoantibodies and the risk of PTC had been inconsistent in previous studies (62, 67, 69, 71). This suggested that autoimmune pathogenesis was associated with excessive iodine intake (71). In the case of TSH, an increase in TSH levels and an effect on the progression of PTC can be caused by either an insufficient or an excessive intake of iodine (72). During this stage of the process, TSH is responsible for stimulating thyroid cells, which ultimately results in genetic changes as well as cell proliferation (72). When a person consumes a diet that is low in iodine, their thyroid produces more type 1 iodothyronine deiodinase, which in turn stimulates TSH and causes an increase in the amount of type 2 deiodinase activity in the thyroid (73). However, consuming an excessive amount of iodine can inhibit the activity of the pituitary type 2 deiodinase, which can cause an increase in serum TSH (74). It has been demonstrated that an abnormal intake of iodine can result in thyroid dysfunction by disrupting the homeostasis of the body (25–27).

There are a few problems with this study. In the first place, we did not consider nutritional supplements as a source of additional iodine intake (75). Second, TPOAb and TGAb levels were not evaluated, which means that we do not have any information regarding thyroid autoimmunity. In addition, a single measurement using the UIC might not consider changes in diet. On the other hand, a previous study that was based on KNHANES discovered that individual dietary changes in iodine intake tend to vary less than that of other nutrients such as foods that are high in fat or sugar-based. Many foods that are sources of iodine are typically served as condiments or side dishes rather than as the primary course (76). Even though insufficient UIC and low hormone levels (clinical cut) were observed in some of the group's members, the possibility of bias could be ruled out because our findings agreed with those of the ordinal logistic regression analysis, which has been suggested as a correction method for sparse data bias (77). Even though some rare cases were observed in the group with insufficient UIC and low hormone levels, the clinical cut, and the possibility of bias could have. In addition, given the lack of perfect matching in our data, we analyzed it with the help of an unconditional logistic regression model, which is highly unlikely to be biased (78, 79). Nevertheless,

there was a possibility of variance inflation in the analyses that looked at the combined effect of UIC and hormones. This was because the reference group consisted of a small number of cases, and the models contained many covariates. In the future, a larger study is going to be required to verify the effect of UIC and hormones together on the risk of PTC.

Despite its restrictions, this study does have several favorable aspects. On PTC and PTMC, we took into consideration several pathologically aggressive behaviors, as well as the combined effects of thyroid function and iodine consumption. In addition, the fact that the PTC and PTMC results were generally comparable suggests that there is a continuous risk of both PTMC, and PTC associated with high levels of UIC. The personal total calorie intake was controlled for all statistical models analyzing the association with iodine intake (80), which was done because there are a lot of different eating habits that can act as a confounding variable in the relationship between high iodine intake and thyroid cancer. We determined the UIC by using the ICP-MS method, which is the gold standard for determining the UIC, and we used the creatinine-adjusted UIC as the primary explanatory variable to account for variations in both dietary intake and excretion (81). Creatinine-

adjusted urine creatinine concentration is a better indicator than unadjusted urine creatinine concentration since it is less prone to variability. Previous studies have provided evidence supporting the validity and reliability of creatinine-adjusted urine creatinine concentration (82, 83). Due to the widespread application of the unadjusted UIC results in the interpretation of WHO standards, we also reported on those.

5.2. Childhood therapeutic radiation exposure and second thyroid cancer: A systematic review and meta-analysis

In this study, the risk of secondary thyroid cancer from therapeutic radiation exposure was evaluated for pediatric and adolescent patients, and the association was identified. In the case of the included studies, studies from the United States, France, Germany, and other European countries were centered, and no studies were reported in Asia or other regions. In addition, all documents were cohort-based studies, so the risk of selection bias is somewhat low. In addition, the long latent period as solid cancer could be considered in consideration of the latent period of at least 5 years to secondary cancer because of radiation exposure. In the case of summary

statistics, the significance could be confirmed, but a significant interpretation is needed due to moderate heterogeneity.

However, it is important to pay attention to the interpretation because the number of documents is small in the overall literature as well as in the subgroup analysis, and there has been no research in Asia, including Korea. In addition, treatment radiation has been defined, but due to the nature of cancer or some treatments, it is difficult to consider exposure to individual factors due to complex treatments such as anticancer drugs or other drug exposure in addition to radiation. In addition, the first diagnostic disease was considered, but the severity of the disease could not be determined, so caution should also be taken. However, this study is meaningful in that it not only evaluated the presence or absence of ionizing radiation exposure in pediatric and adolescent patients, but also considered various factors such as first diagnosis age, gender, radiation dose, and latent period.

In addition, in a follow-up study, a more accurate cancer risk assessment is expected only when the above factors are reflected to evaluate secondary cancer following radiation treatment in pediatric and adolescent patients.

5.3. Medical diagnostic radiation exposure and thyroid cancer risk in the general population

In this study, it was confirmed that the association between medical diagnostic radiation (CT) and thyroid cancer in the general population. Also, considering the latent period of at least 5 years, it showed a consistent association. Plus, along with the simple exposure status, the frequency of CT exposure and exposed CT dose classification was associated with thyroid cancer.

Many previous studies have reported thyroid cancer risk due to diagnostic radiation, but there were some differences from this study. 1) Usually, simple X-ray exposure was considered and 2) radiation workers were the main study population in previous studies (84, 85). Although, some study conducted in the Korean general population according to CT exposure, it was a nested case-control study (86). Thus, lack of studies on the Korean population and controversial association, and it needs additional studies at the national general population level.

This study considered the detailed individual frequency of CT exposure and total exposed dose. In addition, it considered the detailed exposure dose to the thyroid organ, so it would be the most exact study in dose estimation for thyroid cancer. Moreover, it has

sufficient statistical power due to the 100 times much more samples than the previous study. Furthermore, CT exposure and thyroid cancer definition would be similar to the cancer statistics and national utilization, so it would represent the Korean population.

Nevertheless, there are some limitations, first, there was still a concern about misclassification bias due to operational definition. In addition, this study considered a maximum of 14 years of follow-up duration, it might be a short period for thyroid cancer risk according to the radiation exposure. Also, the KNHID was not available to evaluate the pathological information or severity of thyroid cancer patients. However, this study considered various categories of CT exposure and much more samples than previous studies. One of the important points, considering the thyroid organ-specific dose in the Korean national database. Cancer definition would be like the cancer statistics and national utilization, so it would represent the Korean population.

5.4. DNA methylation on ionizing radiation related markers to thyroid cancer

In this study, the genes which reported methylation change due to the ionizing radiation exposure were derived from a few databases and validated in thyroid cancer DNA methylation. As result, validated markers were conducted for functional assessment and literature review. Especially, markers which ldelta m-valuel over 0.25 and FDR less than 0.10 were related to histone deacethylase activity, protein lysine deacethylase activity, histone H4 deacethylation, histone H3 deacethylation, HDAC4-ERK2 complex, and ethanol effects on histone modification. The general biological mechanism of tumorigenesis from ionizing radiation exposure and activation of tyrosine kinase/RAS/mitogen-activated protein kinase (MAPK) signaling pathway through RET/PTC rearrangement is suggested (87). Various gene rearrangements (RET/PTC, NTRK) in chromosome 10 or 1 RET genes can form tumors through tyrosine kinase activity, which is known to activate the MAPK signaling pathway, causing thyroid papillary cancer to 10-40%. It is estimated that RET/PTC rearrangement will play an important role in the radiogenic thyroid cancer mechanism in that the frequency of RET/PTC rearrangement of radiation-related papillary cancers is

higher and the higher dose is higher (88). However, for low-dose radiation, the biological basis for cancer induction is not clear, so there are several opinions on the LNT model. A low dose of 100 mGy is known to result in oxidative DNA damage, single-strand breaks (SSB), and DSB damage of more than 100 per cell, 100 or less, and 4 per cell, respectively (88). DNA damage signaling, cell cycle checkpoint activation, DNA repair, gene and protein expression, apoptosis, cell transformation, etc. differ in quality and quantity compared to high doses at low doses (89), and in several animal experiments and epidemiological studies (90). Therefore, further research is needed on the cancer development mechanism of low-dose ionizing radiation such as diagnostic radiation, and the carcinogenic effect of the thyroid due to additional exposed substances can be expected in chromosomal instability due to ionizing radiation exposure.

The tumorigenesis mechanism from the ionizing radiation would be followed as above, but there would be a specific mechanism based on the previous studies. First, the FMO1 gene is related to PTC occurrence and free survival, therefore FMO1 expression is protectively associated with recurrence-free survival in PTC (91).

However, due to ionizing radiation exposure, it would not work properly. Also, the HDAC9 gene which affects histone deacetylase is known to affect the dysregulation of the thyroid gland and autoimmune thyroid disease. (92). Previous studies reported that it is related to the expression of transcription factor activation of NF-kB and the synthesis of pro-inflammatory cytokines (83). This would relate to the inflammatory response due to ionizing radiation exposure. Lastly, another previous study reported that SH3BGRL3 is related to PTC compared to the normal thyroid (93). However, the association between ionizing radiation and SH3BGRL3 to thyroid cancer should be considered in further study.

However, the fact that most thyroid cancer according to ionizing radiation is based on gene fusion and BRAF mutation is not common under ionizing radiation exposure, additional possible mechanism consideration is needed. Previous studies suggested that low-dose radiation (< 100 mSv) exposure could increase the expression of PAX8 in PTC cells, and it led to BRAF mutants (94).

In detail, STAT3 activation decreased due to ionizing radiation exposure, which downregulates the expression of miRNA (144, 300), which induced the PAX8 upregulation. Consequently, it affected PTC through thyroglobulin, sodium iodine symporter, and

thyroid stimulating hormone receptors, so additional study is needed.

Also, to assess the gene fusion in the study population, gene expression studies such as whole-genome sequencing.

5.5. Thyroid cancer risk according to breast cancer

In this study, the association between breast cancer and thyroid cancer in the general population was assessed in KNHID. Both the overall period and at least 2 years latent period were associated with thyroid cancer consistently. In addition, stratification analysis in age and income level showed a consistently significant trend. However, the strength of the association tended to be high in groups under 40 and 40-59 years compared to the aged over 60 years. Also, compared to high-income level middle- or low-income level were higher associated with thyroid cancer risk. In the previous studies, they suggested that possible link between breast cancer and thyroid cancer, so few hypotheses were suggested (95, 96). Mainly, hormonal factors are likely to play a major role (97), given the similar incidence trend between the two cancers.

This study has several limitations. First, the follow-up period was short to identify the association between breast cancer and thyroid cancer. Also, due to the small study population, thyroid cancer incidence according to the breast cancer was insufficient. Additionally, it was limited to identifying a pathological record in the KNHID. However, this study suggested the possible association between breast cancer and thyroid cancer in the Korean population. In addition, it indicated the possible mechanism between breast cancer and thyroid cancer based on the shared etiology. As a further study, much more samples and longer follow-up duration could be conducted in the Korean general population.

5.6. Association between breast cancer and thyroid cancer

This study aimed to assess the common DNA methylation markers based on the estrogen receptor. As a hypothesis, there would be a common etiology between breast cancer and thyroid cancer. From previous studies, estrogen alpha accelerates cell proliferation in both breast cancer and thyroid cancer (98, 99). Especially, ESR1 which is estrogen alpha gene mRNA expression is high in PTC, and it is associated with PTC tumorigenesis (100). However, in this study, ESR1 was not identified in both thyroid

cancer and breast cancer. Therefore, 23 ESR1 transcription binding sites genes were identified in thyroid cancer, and one gene was identified in the breast cancer population. Among them, only one gene was identified in both breast cancer and thyroid cancer. A functional assessment of 23 transcription binding sites identified in thyroid cancer showed various biological plausibility including KEGG, Gene ontology, and others.

Considering the estrogen receptor biology in thyroid cancer, estrogen is controlled by P27 (a specific protein on estrogen alpha), and it affects PTC proliferation (101, 102). Also, ER alpha is expressed in PTC cells and ER alpha with ER beta imbalance increases ERK 1/2 activity (103). In addition, it is known that the estrogen receptor affects the BCL-2, and Bax expression then leads to an increase in the capacity of cell survival and cell proliferation (103). Plus, NF-kB expression and activity increase in PTC, and it directly relates to the regulation of inflammatory triggers (104). Also, inflammation-related genes activate various transcription factors in thyroid cancer proliferation and estrogen environment (105). In addition, the growth simulation of estrogen is associated with an increase in cyclin D1 expression, and a previous study reported that estrogen receptor alpha knock-down

suppressed the ERK 1/2 and cyclin D1 expression (106, 107). Among the described mechanisms, IQGAP1 is activated by estrogen receptor alpha activation, which then leads to ERK1/2 activity increases, ultimately affecting PTC (101, 107). Also, IQGAP1 plays an important role in cell proliferation and invasion in human breast cancer cells (108, 109). Based on this result, estrogen receptors would act as a common etiology both in breast cancer and thyroid cancer.

Nevertheless, there is some limitation in this study. The number of subjects in the thyroid cancer and breast cancer group would be a small population. However, this study found a shared marker in terms of estrogen receptors between thyroid cancer and breast cancer. In addition, the identified marker could be a clue to estrogen receptor–based treatment in patients who simultaneously suffer from breast cancer and thyroid cancer.

5.7. Reproductive factors and thyroid cancer

This study found that several reproductive factors were associated with thyroid cancer. In addition, the results according to the menopausal status were consistent with the overall population.

But few results suggested that it was different according to the menopausal status.

In the case of first age at menarche, previous studies suggested that late age at menarche in Asian countries seemed to be insignificant on thyroid cancer or increased risk (110). However, this study found it to be a protective factor. Perhaps it could be affected by other environmental, genetic, and nutritional factors, and it is complicated to discuss the cause (111).

Additionally, similar to previous studies, this study suggested that breastfeeding could be prevented thyroid cancer (112). Because breastfeeding can inhibit ovulation and ultimately reduce exposure to endogenic estrogen, and it prevents thyroid cancer (113,114). Also, hormonal fluctuation in pregnant women could affect their thyroid function. Previous studies reported that an increase in hCG hormones can affect clinical or subclinical hyperthyroidism (115).

This study reported that oral contraceptives were protectively associated with thyroid cancer. Also, many studies suggested that female hormones contained in oral contraceptives are related to various cancers such as ovarian and endometrial cancer (116).

Through this study, it was possible to assess the association between thyroid cancer and reproductive factors such as age at

menarche, menopausal status, pregnancy, breastfeeding, and oral contraceptives. However, to understand the underlying mechanism, additional genetic and nutritional–based studies are needed.

Conclusion

Through this study, iodine intake is considered as a specific thyroid cancer exposure in the Korean population, and this study identified the association between excessive iodine intake and thyroid cancer. Also, the dose-response relationship between iodine intake and thyroid was assessed. Plus, both thyroid function and iodine intake were simultaneously considered to assess thyroid cancer risk.

In the case of ionizing radiation, both high-dose medical radiation (radiation therapy) and low-dose medical radiation (CT) were associated with thyroid cancer. Under the high medical utilization environment in South Korea, detailed CT exposure was assessed in national big data and assessed the detailed exposure dose on thyroid organs with assessing thyroid cancer risk. Furthermore, the epigenetic changes caused by ionizing radiation and genes can affect PTC in the methylation level. Through this result, it could guess the mechanism which acts on PTC due to the radiation exposure.

As breast cancer was considered an additional risk factor for thyroid cancer due to the similar incidence trends and previous studies. Under the general population, the association between breast cancer and thyroid cancer was associated. Also, estrogen receptor-related markers based on DNA methylation levels in both thyroid cancer and

breast cancer were identified. It seems that there are shared environmental factors that can affect the estrogen receptor between two cancers.

Consequently, the association between various factors and thyroid cancer considering the Korean environment was evaluated, and it is necessary to organize Korea own specific cancer management and prevention. Additionally, epigenetics markers could provide some clues for cancer treatment based on the specific mechanisms in thyroid patients.

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‘Thyroid cancer according to the breast cancer’ used the National Health Insurance Service Database.

‘Childhood therapeutic radiation exposure and second thyroid cancer: A systematic review and meta-analysis’ aimed to conduct for ‘Fraction of Cancer Attributable to Lifestyle and Environmental Factors in Korea in 2015” project’ and several coauthors involve in the project (‘Kwang-Pil Ko, Jung Eun Lee, Inah Kim, Sungji Moon, Soseul Sung, Woojin Lim, Seokyung An, and Sue K. Park). This study was funded by the Korean Foundation for Cancer Research. (Grant Number. CB-2017-A-2)

As breast cancer cases, it derived from ‘The Korean Hereditary Breast Cancer (KOHBRA) study’. Reproductive factors and thyroid cancer, I thank to the effort for the research assist (Yunji Hwang, Yohwan Yeo).

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초 록

한국인 갑상선암에 있어 요오드, 전리방사선, 호르몬 요인과 후성유전체 마커의 연관성 평가

배경: 대한민국에서의 갑상선암에 대한 논쟁은 지속적으로 이어져 왔고 2012 년 이후 갑상선암 연령표준화발생률은 지속적으로 감소하였으나 2015 년 이후 다시 증가하는 추세를 보이고 있다. 2019 년 갑상선암은 한국인 집단에서 가장 많이 호발한 암이며, 표준화발생률은 10 만 명당 52.3 명이였고, 여성이 남성보다 많이 발생하였다. (여성, 10 만 명 당 79.6 명; 남성. 10 만 명당 25.9 명).

그 동안 여러 연구들에서 갑상선암의 위험요인들이 보고되었으나, 전리방사선 외 요인들의 경우 논쟁의 소지가 있으며 보고된 요인이 국가별로 그 유의성에 차이가 있거나 아직까지 불분명한 경우가 많다. 이를 비추어 보았을 때 한국인의 높은 갑상선암 발생은 한국인의 특이적 요인에 대한 고려가 필요한 실정이다.

이에 본 연구에서는 한국인 고유 식단을 고려하여 요오드 섭취에 따른 갑상선암의 위험 평가와 더불어 의료 전리방사선 노출에 따른 갑상선암 간의 연관성을 평가하고자 하였다. 구체적으로 전리방사선 노출 평가에 있어 의료방사선 가운데 고선량인 방사선치료와 저선량인 CT 노출을 고려하여 갑상선암 위험을 평가하고자 하였다. 특히 저선량 CT 노출에 따른 갑상선암 위험은 여전히 논쟁적이기에

본 연구에서는 전체 인구집단 수준의 국가빅데이터에서 CT 노출 유무와 빈도 및 갑상선에 노출되는 특이적인 선량을 고려하여 보다 정확한 노출 선량에 따른 연관성을 평가하고자 한다. 또 전리방사선 노출에 따른 후성유전체적 변화의 기존 문헌을 참고하여 한국인 갑상선암 DNA methylation data 내에서 갑상선암과 관련있는 후성유전체적 마커가 도출되는지를 확인하고 이를 생물학적 기능에 기반하여 평가하고자 하였다. 또 한국인에서의 유방암과 갑상선암의 높은 발생률, 유사한 발생 양상, 기존 연구를 고려하였을 때 유방암에 따른 갑상선암의 위험을 건강보험공단 빅데이터에서 확인하고자 하였다. 이후 공통적인 생리적 기전을 에스트로겐 수용체로서 고려하였을 때 두 암이 공통적으로 공유하는 마커가 있을 것이란 가정을 하였다. 이에 에스트로겐 수용체 유전자 및 해당 유전자의 전사인자로서 관련된 유전 마커들이 유방암 및 갑상선암 DNA methylation 수준에서 확인되는지를 평가하였다.

궁극적으로 이는 요오드 및 전리방사선, 호르몬 요인과 갑상선암의 연관성을 한국인 집단에서 파악함과 동시에 후속적으로 높은 한국인 갑상선암 발생에 대한 효과적인 예방 정책과 갑상선암 발생률 감소에 이바지할 수 있을 것으로 기대된다.

방법: 요오드와 갑상선암 간의 연관성을 평가하기 위해, 환자군은 병원 집단 기반의 갑상선암 전향적 코호트 내의 유두성갑상선암 환자를, 대조군의 경우는 지역사회 거주자 가운데 갑상선암을 가지고 있지 않은

대상자로 정의하여 환자-대조군 연구를 수행하였다. 구체적으로 환자군은 소변요오드 정보와 종양 크기 0.5cm 이상으로 확인된 유두성갑상선암 환자군 427 명과 지역사회 코호트 내에 갑상선암 및 기타 암 이력이 없는 479 명을 연구대상자로서 정의하였고 로지스틱 회귀분석과 이에 따른 오즈비와 95% 신뢰구간을 산출하여 통계적 분석을 수행하였다.

또한 방사선치료에 따른 갑상선암과의 연관성 파악을 위해 소아청소년환자에서 갑상선암의 위험을 체계적문헌고찰과 메타분석으로 평가하였으며 의료방사선 노출에 따른 갑상선암 간의 연관성 평가는 2006-2009 년 사이의 일반인을 대상으로 암 발생과 사망에 대해서는 2019 년 12 월 31 일까지 추적관찰하였다. 본 연구에서는 의료방사선 노출은 전산화단층촬영으로 정의하고 질병관리청에서 환자들의 전산화단층촬영 노출에 따른 환자피폭선량 산출을 위해 고안된 ALARA-CT 프로그램에서 각 검사법에 따른 갑상선암에 노출되는 장기선량 및 유효선량을 고려하였다. 구체적인 방사선 노출의 범주는 단순 노출 유무와 CT 노출의 횟수, 총 노출 선량을 기반으로 평가하였다. 그 외로 기존에 전리방사선 노출에 따른 후성유전체적 변화로서 보고된 마커를 한국인 갑상선암 DNA methylation 데이터에서 확인하여 실질적으로 전리방사선 노출이 갑상선암에 어떠한 후성유전체 마커로서 재현되는지를 파악하고자 하였다. 이후 해당 마커에 대에 대한 생물학적 기능분석을 수행하였다.

또 유방암과 갑상선암 간의 연관성 평가를 위해 우선 국민건강보험공단 표본코호트 자료를 이용하였고 추가적으로 공통적인 환경 노출을 고려하여 에스트로겐 수용체 유전자 및 이에 대한 관련 전사인자를 'Genecard'에서 선정하고 이를 갑상선암 및 유방암 methylation 데이터에서 도출되는지를 평가하였다.

결과: 요오드 노출에 따른 갑상선암 간의 연관성을 평가하였을 때 유두성갑상선암 환자의 90% 이상이 과다한 요오드 노출 상태였으며, 대조군의 경우 50% 만이 과다한 요오드 노출 상태였다. 미세유두성갑상선암 집단 (종양크기, 0.5-1 cm)의 경우 강한 연관성을 보였으며 (OR, 8.97; 95% CI, 5.07-15.90), 유두성갑상선암 (> 1cm)의 경우 더 강한 연관성을 보였다. (OR, 31.49; 95% CI, 13.02-76.16). 요오드 섭취 수준과 갑상선 기능을 모두 고려하였을 때, 요오드 섭취 수준이 높고 Free T4 가 높았을 때 갑상선암 간의 연관성이 강하게 나타났으며, 높은 TSH 수준에도 유사한 경향을 나타냈다.

소아청소년 환자에서 방사선 치료 노출에 따른 갑상선암 위험의 경우 RR, 5.09; 95% CI, 3.51-7.37 로 유의미하였으며, CT 노출에 따른 갑상선암 위험의 경우, 위해비가 1.16; 95% CI, 1.12-1.30 으로 통계적으로 유의하였다. 구체적으로 빈도에 따른 갑상선암 위험에서는 용량-반응 관계로 나타났으며 (1-2 회, HR, 1.04; 95% CI, 0.97-1.11; 3-10 회, HR, 1.21; 95% CI, 1.14-1.26; 10 회 이상, HR, 3.93; 95% CI, 2.37-6.53)로 유의하였다. CT 선량 3-5 mSv 를 기준으로 확인하였을

때 5-9.9 mSv 에서는 통계적으로 유의하였고 (HR, 1.46; 95% CI, 1.15-1.82), 10 mSv 이상에서도 유의하였다 (HR, 5.20; 95% CI, 3.19-8.68). 전리방사선 노출에 따른 후성유전체적 변화의 마커 가운데 10 개가 도출되었으며 이는 ldelta m-valuel 0.25 이상 및 FDR 0.10 미만으로서 유의하였으며 기능적 분석에서는 GO molecular function (histone deacethylase activity, protein lysine deacetylase activity), GO biological process (peptidyl-lysine deacetylation, skeletal muscel fiber development, histone H4 deacethylation, histone H3 deacethylation), CORUM (HDAC4-ERK2 complex), and WikiPathway (Ethanol effects on histone modifications)등이 관련있는 것으로 확인되었다.

유방암과 갑상선암 간의 연관성에 있어서는 국민건강보험공단 빅데이터에서 HR, 3.25; 95% CI, 2.44-4.36 으로 유의미하였고 이는 2 년 이상의 잠재기에서도 일관적으로 유의하였다 (HR, 2.13; 95% CI, 1.45-3.13). 갑상선암과 유방암 간의 공통적인 기전을 에스트로겐 수용체에서 고려하였을 때 에스트로겐 수용체 유전자의 전사 마커 가운데 1 개가 갑상선암과 유방암에서 공통적으로 나타났다.

추가적으로 생식요인과 갑상선암 간의 연관성을 평가하였을 때는 초경연령이 13 세 미만인 경우에 비해 초경 연령이 16 세 이후로 늦을수록 갑상선암 위험에 보호요인으로 나타났다 (OR, 0.38; 95% CI, 0.26-0.48). 또 경구피임약을 복용하였거나, 호르몬 대체요법을 받은

경우 또한 갑상선암에 보호적으로 연관이 있는 것을 나타냈을 때 호르몬 요인이 갑상선암에 영향을 미치는 것을 파악할 수 있었다.

결론: 본 연구결과에 따르면 요오드 섭취가 과다한 집단은 요오드 섭취가 적정한 집단에 비해 PTC 와 PTMC 발병 위험이 유의하게 높았다. 과도한 요오드 섭취와 높은 수준의 유리 티록신의 조합은 PTC 와 PTMC 의 위험성을 높이는 복합효과가 나타났으며, 과도한 요오드 섭취와 높은 수준의 갑상선자극호르몬은 이 수준을 훨씬 더 높게 높이는 효과를 보였다.

소아청소년 집단에서 방사선치료에 따른 갑상선암 위험에 대한 연관성을 파악하였으나 한국을 포함한 아시아 연구가 부족하였다. 또 저선량 의료방사선 노출에 따른 갑상선암의 위험은 노출 유무에서 유의미한 연관성을 나타냈으며 빈도와 노출선량 범주에 따라서는 용량-반응 관계를 나타냈다. 특히 전리방사선 노출에 따른 후성유전체적 변화와 이에 따른 갑상선암간의 연관성은 몇 가지 기전에서 고려할 수 있는데, FMO1 유전자의 발현은 PTC 재발과 free survival 과 보호적으로 연관되어 있으나 전리방사선 노출로 인하여 이것이 제대로 작동하지 않을 가능성이 존재한다. 또한 히스톤 탈아세틸화효소에 영향을 미치는 HDAC9 유전자는 갑상선의 조절 장애와 자가면역성 갑상선질환에 영향을 미치는 것으로 알려져 있다. 특히 이전 연구가 NF-kB 의 전사 인자 활성화의 발현 및 염증성

사이토카인의 합성과 관련이 있다고 보고하였는데 아마 전리방사선 노출로 인한 염증성 생화학 반응을 유발할 가능성이 있다.

역학적으로 인구집단 기반에서 유방암과 갑상선암 간의 연관성 파악을 통해 두 암 간의 연관성을 파악해볼 수 있었고 이를 통해 두 암 간의 공유하는 환경적, 생리적 바탕이 있을 것을 추측해 볼 수 있다. 본 연구에서 이를 에스트로겐 수용체에 기반하여 DNA methylation 마커를 갑상선암과 유방암에서 확인하였을 때 IQGAP1 를 공통적으로 확인하였고 이에 대한 생물학적 메카니즘은 에스트로겐 수용체 알파 활성화에 의해 활성화된 후 ERK1/2 활성 증가를 유도하여 궁극적으로 PTC 에 영향을 미치며 동시에 유방암세포에서는 세포 증식과 invasion 에 영향을 미치는 것으로 확인되었다.

결론적으로 본 연구를 통해 한국인 집단에서의 환경을 고려한 특이적인 요인 후보인 요오드 노출과 전리방사선, 호르몬 요인과 갑상선암 간의 연관성을 평가하였다. 또 본 연구 결과를 통해 한국인 갑상선암에 대한 새로운 관리 방법과 예방 체계를 정비를 촉구하며, 도출된 후성유전체적 마커는 갑상선 환자의 특정 메커니즘에 기초한 암 치료에 있어 몇 가지 실마리를 제시할 수 있을 것으로 보인다.

주요어: 갑상선암, 요오드, 전리방사선, DNA 메틸레이션, 호르몬 요인, 에스트로겐 수용체, 빅데이터 분석, 역학적 연구

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