Radioactive Iodine Therapy Did Not Significantly Increase the Incidence and Recurrence of Subsequent Breast Cancer

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Context: Previous studies on the extent to which radioactive iodine (RAI) therapy for thyroid cancer increases the risk of subsequently developing breast cancer have given conflicting results.

Objective: This study aimed to evaluate the effect of RAI treatment on breast cancer development and recurrence among female patients with primary thyroid cancer.

Design: This was a retrospective cohort study. The risk of subsequent breast cancer associated with RAI and its dose in hazard ratios (HRs) with 95% confidential intervals (CIs) were calculated using time-dependent Cox proportional hazard models.

Patients: A total of 6150 patients with thyroid cancer enrolled between 1973 and 2009 were followed until December 2012. Of these, 3631 (59.0%) received RAI therapy. During the follow-up period, 99 primary breast cancers were diagnosed.

Main Outcome Measure: Risk of breast cancer development according to RAI therapy and RAI dose during treatment for primary thyroid cancer.

Results: RAI therapy did not significantly increase the incidence of subsequent breast cancer among female patients (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.22–1.06) when a 2-year latency period was accounted for. High-dose RAI (≥120 mCi) was associated with a reduced incidence of subsequent breast cancer (HR, 0.17; 95% CI, 0.05–0.62) in the cohort with a 2-year latency period.

Conclusions: The long-term follow-up results of this study suggest that RAI treatment for patients with thyroid cancer may not increase the risk or recurrence of breast cancer. **(*J Clin Endocrinol Metab* 100: 3486–3493, 2015)**

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Abbreviations: BMI, body mass index; CI, confidence interval; CT, computed tomography; fluorodeoxyglucose–positron emission tomography; FDG-PET, HR, hazard ratio; IQR, interquartile range; NIS, sodium-iodine symporter; RAI, radioactive iodine; RR, relative risk.

Well-differentiated thyroid cancer and breast cancer are common in women. According to a recent annual report on cancer statistics in Korea, thyroid cancer was the most common female cancer and breast cancer was the second most common (1). An association between thyroid and breast cancer in women was first suggested in 1966 (2). Since then, several studies have suggested that breast cancer is diagnosed more frequently than expected in patients who were diagnosed with and received therapy for thyroid cancer (3–5). Genetic or environmental factors, young age (3, 5), nulliparity (6), and receipt of radioactive iodine (RAI) therapy (7) have been suggested as potential risk factors for the development of breast cancer in patients with thyroid cancer.

With regard to the breast cancer risk associated with RAI therapy, it has also been suggested that exposure to ionizing radiation during childhood could increase the risk of this malignancy (8, 9). Edmonds et al (7) reported that the risk of breast cancer in women who were previously treated using RAI for thyroid cancer was approximately 2.4 times higher than in those who did not undergo this therapy. In addition, the incidence of breast cancer in patients with thyroid cancer or other thyroid diseases is increasing (10–13). As RAI therapy is commonly used in the treatment of thyroid cancer, the possibility of this being a risk factor for breast cancer is of growing concern.

Despite a number of studies that suggested a link between RAI treatment and breast cancer, a recent meta-analysis of multicenter studies showed that the risk of a second primary breast cancer was not related to the use of RAI (14). These contrasting results suggest that the relationship between RAI therapy and the development of breast cancer among patients with thyroid cancer needs to be further evaluated.

In this study, we aimed to evaluate the effect of RAI treatment and its dosage on the occurrence and recurrence of breast cancer in patients previously diagnosed with well-differentiated thyroid carcinoma.

Subjects and Methods

Subjects

Between January 1973 and December 2009 at Seoul National University Hospital, 6150 female patients with pathologically confirmed, well-differentiated thyroid carcinoma who had not been diagnosed with any other cancer prior to thyroid cancer diagnosis were enrolled. Of these, 84 subjects were excluded because their RAI dose at baseline was unknown. To assess the outcome of breast cancer, we reviewed medical records and included subjects who were diagnosed with breast cancer subsequently to, or on the same day as they were diagnosed with thyroid cancer, up to December 31, 2012. On this basis, we identified 99 breast cancer cases from the whole cohort. In the 2-year latency period cohort, we excluded 58 breast cancer cases because the malignancy was diagnosed within the first 2 years following the diagnosis of thyroid cancer. Fourteen breast cancer cases were further excluded because their first RAI exposure was within the 2-year period before the diagnosis of breast cancer. However, we added one death certificate–only case of breast cancer in the analysis of the cohort with a 2-year latency period, and thus a total of 28 breast cancer cases were finally included in this cohort. To exclude prevalent breast cancer cases at baseline and clarify the issues related to the latency period of breast cancer, we calculated breast cancer risks in subgroups of patients who were followed-up for at least 2 or 5 years in the whole cohort. The diagnosis of both thyroid and breast cancer was confirmed by pathologists.

To evaluate the effect of breast irradiation resulting from RAI therapy and other sources of radiation used in diagnostic imaging studies, we examined the dose of each RAI therapy and the number of times various diagnostic imaging studies were conducted (chest x-rays, spine x-rays, computed tomography [CT] scans of the chest, neck, coronary vasculature, abdomen, and breasts, fluorodeoxyglucose-positron emission tomography [FDG-PET] scans, bone scans, and thallium-201 scans) from medical records. We also examined the history of thyroid radiation therapy and interventional fluoroscopy to exclude the effect of high-dose radiation. The cumulative RAI dose was calculated as the sum of all RAI doses in each patient, or the sum of doses prior to breast cancer diagnosis in patients who developed this malignancy. The total absorbed radiation dose to the breast from diagnostic imaging studies was calculated by multiplying the number of studies by the known absorbed dose to breast tissue during each diagnostic imaging study (15–17). We also examined the history of estradiol, estrogen, and progesterone administration to evaluate the effect of this potential confounder. The data collection and analytical methods were approved by the Seoul National University Hospital Institutional Review Board (H-0912-009-302 and H1204-077-406).

Statistical analysis

Descriptive statistics of the RAI and no-RAI group were tested using the χ^2 test and Student t test, or the Wilcoxon Rank-Sum test for numerical variables. The breast cancer risk in hazard ratios (HRs) and their 95% confidence intervals (CIs) for the two groups were estimated using time-dependent Cox proportional hazard models.

All models were adjusted for age at diagnosis of thyroid cancer, body mass index (BMI) (<25 or ≥ 25 kg/m^2), smoking (never or ever), family history of breast cancer (yes or no), T stage and N stage, cumulative medical diagnostic radiation exposure (none, 0–4, 5–9, 10–49, 50–99, 100–199, or ≥ 200 cGy), the number of mammography visits (none, 1, 2, or ≥ 3), hormone replacement therapy (yes or no) and year of thyroid cancer diagnosis (1973–1994, 1995–2004, or 2005–2009). To account for a 2-year latency period, we calculated the person-years at risk from 2 years after thyroid cancer diagnosis, and RAI therapy was counted when it was administered 2 years before the last followup or the date of breast cancer diagnosis. To determine the association between RAI therapy and the risk of breast cancer, and to confirm the results after accounting for the latency period of breast cancer, we estimated HRs in the total cohort as well as the cohort with a 2-year latency period (2, 3, 5, 7, and 10 y). Moreover, the risk of breast cancer was estimated in groups with high- and low-dose RAI (high dose, ≥ 120 mCi; low dose, <120 mCi). Among the patients

with breast cancer, the risk of recurrence of breast cancer by RAI was analyzed using Cox proportional hazard models after adjusting for age at diagnosis, tumor size, nuclear and histologic grade, and the administration of chemotherapy, hormone therapy, and radiation therapy. The at-risk period for recurrence was defined as the time from the date of diagnosis of primary breast cancer to the date of recurrence or the last followup. All analyses were two-tailed tests based on an alpha value of 0.05 and were conducted using SAS version 9.4 (SAS Institute).

Results

General characteristics of cohort participants

Table 1 summarizes the general characteristics of the whole cohort, as well as the cohort with a 2-year latency period. The whole cohort (median followup, 6 y; interquartile range [IQR], 6 y) was classified into two groups: 3631 patients (59.0%) who received RAI therapy (RAI group), and 2519 patients (41.0%) who did not (no-RAI group). The cohort with a 2-year latency period was also classified into these two groups (RAI group, 3591 patients [59.1%]; no-RAI group 2489 patients [41.9%]). The median follow-up period was 7.0 years (IQR, 6.0 y) in the no-RAI group and 6.0 years (IQR, 5.0 y) in the RAI group. During the follow-up period, 18 patients in the no-RAI group and 10 in the RAI group were diagnosed with breast cancer when we accounted for a 2-year latency period.

Table 1. General Characteristics of Cohort Participants With Primary Thyroid Cancer According to Radioactive Iodine Therapy

	Total Thyroid Cancer Cohort (n = 6150)			Cohort With 2-Year Latency Period (n = 6080)		
Characteristic	No RAI Therapy (n = 2519)	RAI Therapy (n = 3631)	*P* Value[e]	No RAI Therapy (n = 2489)	RAI Therapy (n = 3591)	*P* Value[e]
Age at diagnosis of thyroid cancer, y, mean (SD)	44.3 (12.1)	46.9 (12.6)	<.01	44.2 (12.1)	46.9 (12.6)	<.01
Age at diagnosis of thyroid cancer among patients with breast cancer, y, mean (SD)[a]	45.8 (10.3)	47.3 (11.6)	<.01	42.6 (7.4)	40.0 (12.0)	<.01
Age at diagnosis of breast cancer, y, mean (SD)[a]	49.5 (9.8)	52.3 (9.8)	<.01	50.7 (7.3)	48.8 (7.6)	<.01
Follow-up periods, y, median (IQR)	7.0 (6.0)	6.0 (5.0)	<.01	5.0 (6.0)	5.0 (5.0)	<.01
RAI dose, mCi, median (IQR)	—	90.0 (90.0)	—	—	90 (90.0)	—
Cumulative medical diagnostic radiation exposure, except mammography cGy, median (IQR)[b]	2.0 (97.0)	4.0 (92.0)	<.01	2.0 (96.9)	4.0 (92.7)	<.01
Frequency of mammography among those ever exposed (n = 1089), median (IQR)	3.0 (4.0)	3.0 (4.0)	.26	2.0 (4.0)	3.0 (3.0)	.24
Ever smokers, %	1.7	1.5	.66	1.7	1.5	.76
Family history of breast cancer, %	1.0	0.9	.85	1.0	0.9	.96
Menarche age ≤14 y, %	36.5	33.2	.49	37.0	33.3	.46
Menopause age ≥55 y, %[c]	5.4	7.5	.33	5.5	7.2	.42
BMI ≥25 kg/m^2, %	24.7	30.0	<.01	24.6	29.9	<.01
Papillary thyroid cancer, %	91.0	94.4	<.01	91.0	94.3	<.01
Thyroid tumor size ≥2 cm, %	18.7	30.0	<.01	18.7	30.1	<.01
Extrathyroid involvement, %	29.6	74.1	<.01	29.5	74.0	<.01
T stage 3–4, %	26.2	74.8	<.01	26.1	74.7	<.01
N stage 3–4, %	12.1	51.5	<.01	12.0	51.7	<.01
Ever exposed to medical diagnostic radiation exposures, except mammography, %[b]	76.0	82.8	<.01	75.7	82.7	<.01
Ever exposed to mammography, %	19.2	17.2	.05	18.6	16.5	.03
Hormone replacement therapy, %[d]	2.7	3.7	.04	2.7	3.7	.04
Year at the diagnosis of thyroid cancer, %						
1973–1994	11.3	6.1	<.01	11.4	6.2	<.01
1995–2004	38.9	29.1		38.8	29.2	
2005–2009	49.7	64.8		49.8	64.7	

Abbreviation: Tl-201 scan, radioactive thallium-201 scan.

[a] Included breast cancer cases in total cohort (n = 99) and cohort with 2-year latency period (n = 28).

[b] Radiation exposures from diagnostic medical devices including chest x-ray, spine x-ray, chest CT, neck CT, coronary CT, abdomen and pelvis CT, mammography, FDG-PET scan, bone scan, and Tl-201 scan.

[c] The proportion was calculated among menopausal women in total cohort (n = 563) and cohort with 2-year latency period (n = 548).

[d] Hormone replacement therapy including estradiol, estrogen and progesterone.

[e] Tested for group differences by RAI therapy using Student *t* test (Wilcoxon Rank-Sum test) for numerical variables and χ^2 test for categorical variables.

Table 2. The Hazard Ratio (95% CI) of Breast Cancer Development According to RAI Therapy and its Dose During the Followup of Patients With Primary Thyroid Cancer

	Cohort With 2-Year Latency Period (n = 6080)[d]			Cohort With 2-Year Latency Period ≥5-Year Followup (n = 3344)[d]		
	Thyroid Cancer Cohort, n	Breast Cancer Cases, n	HR (95% CI)	Thyroid Cancer Cohort, n	Breast Cancer Cases, n	HR (95% CI)
All patients[a]						
RAI therapy						
No	2471	18	1.00 (Reference)	1479	10	1.00 (Reference)
Yes	3581	10	0.49 (0.22–1.06)	1848	7	1.22 (0.36–4.19)
Total dose of RAI, mCi[b]						
No RAI	2471	18	1.00 (Reference)	1479	10	1.00 (Reference)
<90	1700	3	0.77 (0.30–1.99)	657	1	0.91 (0.10–8.03)
90–120	632	3	0.81 (0.25–2.66)	323	2	2.64 (0.44–15.72)
≥120	1168	3	0.17 (0.05–0.63)	821	3	0.78 (0.16–3.86)
No RAI	2471	18	1.00 (Reference)	1479	10	1.00 (Reference)
<120	2332	6	0.78 (0.34–1.83)	980	3	1.57 (0.35–7.00)
≥120	1168	3	0.17 (0.05–0.62)	821	3	0.74 (0.15–3.64)
Patients age < 30 y[c]						
RAI therapy						
No	299	1	1.00 (Reference)	208	1	1.00 (Reference)
Yes	364	5	1.52 (0.10–22.74)	238	5	1.52 (0.10–22.74)
Total dose of RAI, mCi						
No RAI	299	1	1.00 (Reference)	208	1	1.00 (Reference)
<120	165	2	1.37 (0.07–26.36)	83	2	1.37 (0.07–26.36)
≥120	182	3	1.82 (0.08–44.14)	147	3	1.82 (0.08–44.14)

[a] Time-dependent Cox hazard models were adjusted for age at diagnosis of thyroid cancer, BMI (<25 or ≥25 kg/m^2), smoking (never or ever), family history of breast cancer (yes or no), T stage, N stage, cumulative medical diagnostic radiation exposure (no, 0–4, 5–9, 10–49, 50–99, 100–199, or ≥200 cGy), frequencies of mammography (no, 1, 2, or ≥3) and hormone replacement therapy (yes or no) and year of the diagnosis of thyroid cancer (1973–1994, 1995–2004, or 2005–2009).

[b] Subjects undergone RAI therapy (cohort with 2-y latency period: one breast cancer among 82 patients with thyroid cancer; cohort with 5-y latency period: one breast cancer among 48 patients with thyroid cancer) but with missing information for RAI dose were excluded.

[c] Included patients with thyroid cancer age ≤30 y.

[d] HRs and 95% CIs were estimated in the cohorts including subjects with 2-y latency period (n = 6080) and 2-y latency period ≥5-y followup (n = 3344).

In the whole cohort, compared with the no-RAI group, patients in the RAI group were on average older when thyroid cancer was diagnosed (age: mean ± SD, 46.9 ± 12.6 vs 44.3 ± 12.1 y, $P < .01$), and had been exposed to more medical diagnostic radiation (median radiation dose: 4.0 vs 2.0 cGy; $P < .01$). Patients in the RAI group were more likely to be overweight (BMI ≥25 kg/m^2) (30.0 vs 24.7%; $P < .01$). The proportion of patients with thyroid cancer with papillary thyroid cancer (94.4 vs 91.0%; $P < .01$), a larger thyroid tumor (size ≥2 cm) (30.0 vs 18.7%; $P < .01$), extrathyroidal invasion (74.1 vs 29.6%; $P < .01$), an advanced T stage (stage 3 or 4) (74.8 vs 26.2%, $P < .01$), or lymph node metastasis (51.5 vs 12.1%, $P < .01$) was higher in the RAI group compared with the no-RAI group. We found statistical differences in terms of exposure to mammography (19.2 vs 17.2%; $P = .05$) and the administration of hormone replacement therapy (2.7 vs 3.7%; $P = .04$) between the no-RAI and RAI group. The general characteristics of the cohort with a 2-year latency period were similar to those of the whole cohort (Table 1). The mean age at diagnosis of breast cancer in the RAI and no-RAI group was 49.5 and 52.3 years, respectively. The clinicopathologic characteristics of patients with breast cancer were also similar between the RAI and no-RAI groups (Supplemental Table 1).

Hazard ratios for occurrence and recurrence of breast cancer by RAI therapy and RAI dose in patients with primary thyroid cancer

After accounting for a latency period of 2 years, the adjusted HRs of breast cancer occurrence in patients with primary thyroid cancer are given in Table 2. The risk of breast cancer was not significantly higher in the RAI group (HR, 0.49; 95% CI, 0.22–1.06). The adjusted HR was estimated in the cohort with 5-year followup (HR, 1.22; 95% CI, 0.36–4.19). The HRs were also estimated for lower doses (<120 mCi: HR, 0.78; 95% CI, 0.34–1.83) and higher doses (≥120 mCi: HR, 0.17; 95% CI, 0.05–0.62) in the cohort with a 2-year latency period.

For patients with thyroid cancer younger than 30 years old, the risk of breast cancer was also not significantly higher in the RAI group (HR,1.52; 95% CI, 0.10–22.74),

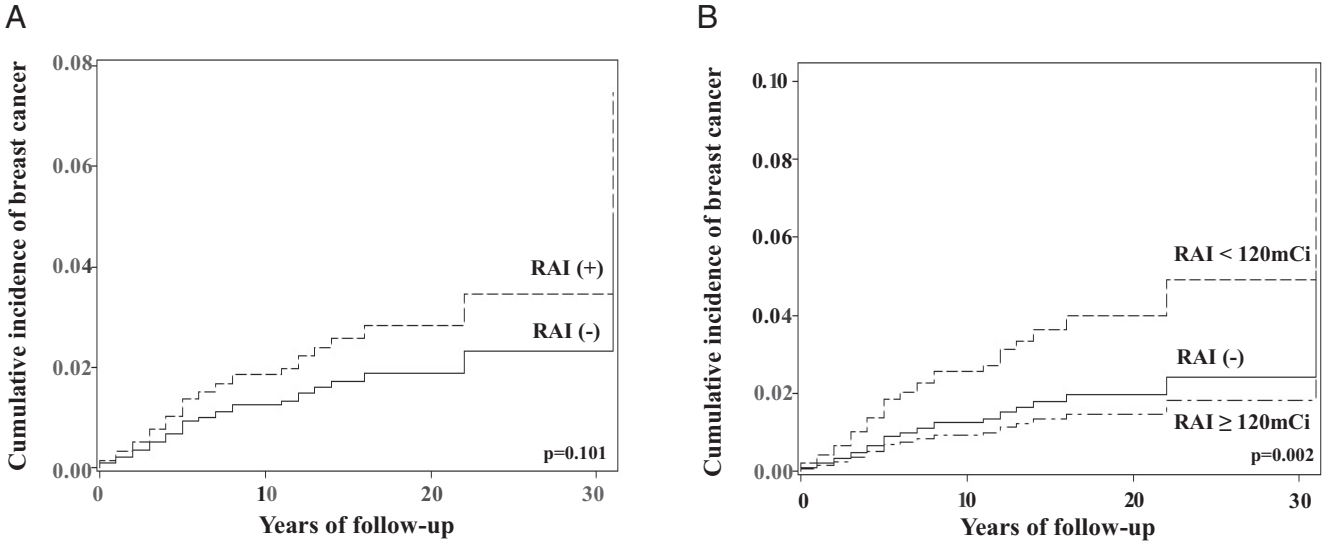

Figure 1. Cumulative breast cancer incidence curve with respect to subsequent breast cancer RAI exposure (A) and its dose (B), high dose (≥120 mCi; low dose <120 mCi) relative to non-RAI exposure among a cohort with a 2-y latency period (n = 6080).

and a high RAI doses (≥120 mCi: HR,1.82; 95% CI, 0.08–44.14) also did not increase the risk of breast cancer in these patients (Table 2). When we restricted the cohort to those who were followed up for at least 5 years, a similar result was obtained (Table 2). When we did the same analysis without accounting for a latency period in the whole cohort, there were 53 and 46 patients with breast cancer in the RAI and no-RAI group, respectively (Supplemental Table 2).

In the cohort with a 2-year latency period, the cumulative incidence curves for subsequent breast cancer did not differ significantly according to RAI exposure (Figure 1A; $P = .101$). However, when we did the same analysis for low-dose (<120 mCi) and high-dose (≥120 mCi) subgroups, the cumulative incidence was significantly different (Figure 1B; $P = .002$). The cumulative incidence curve of the low-dose group was more increased during follow-up period compared with no-RAI group, whereas that of the high-dose group was not significantly different than the no-RAI group incidence (Figure 1B).

The results for sensitivity analyses by follow-up years (2, 3, 5, 7, and 10 y) are presented in Figure 2, A and B. The risk of breast cancer occurrence by RAI exposure increased as the follow-up period lengthened, although the increase was not significant when its CI was considered (Figure 2A). In addition, we analyzed the effect of RAI dose on the occurrence of breast cancer (Figure 2B) during the follow-up period, and this was also not significant. With regard to the recurrence of breast cancer, RAI exposure did not affect the recurrence of breast cancer regardless of the length of the follow-up period (Figure 3).

Discussion

An increase in the risk of breast cancer in patients with thyroid cancer has been reported, and RAI therapy has

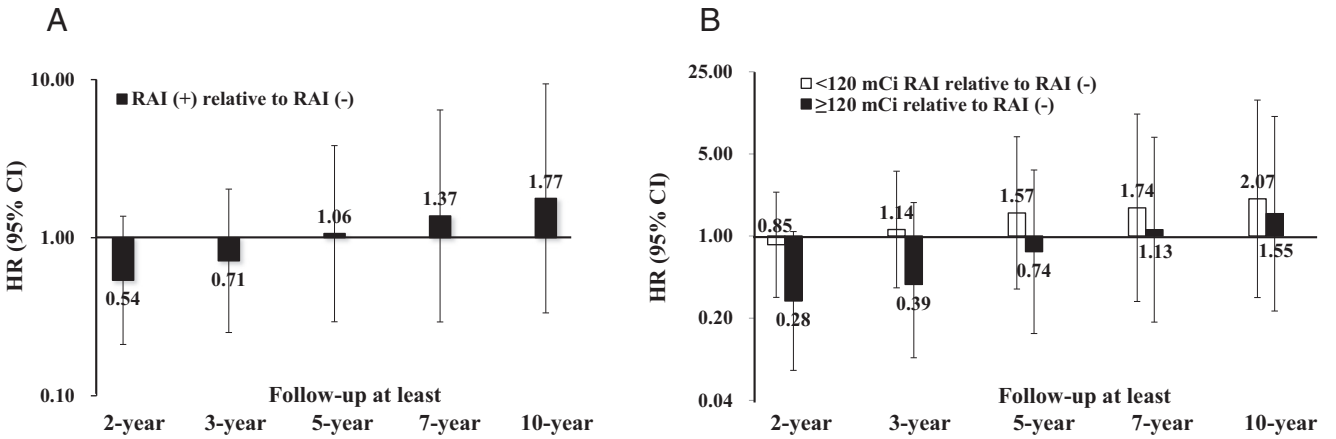

Figure 2. The risk of subsequent breast cancer with respect to RAI exposure (A) and its dose (B), high dose (≥120 mCi; low dose <120 mCi) relative to non-RAI exposure among a cohort with a 2-y latency period (n = 6080). The vertical bar shows the (95% CI) of HRs.

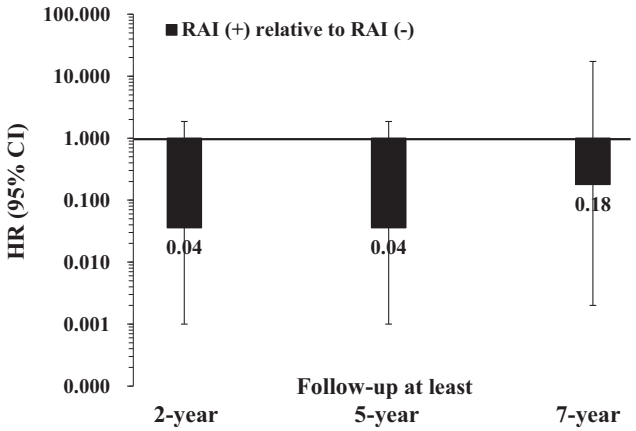

Figure 3. The risk of breast cancer recurrence with respect to RAI exposure relative to non-RAI exposure among a cohort with a 2-y latency period (n = 6080). The HRs were adjusted for age at breast cancer diagnosis, tumor size, nuclear and histologic grade, and the administration of chemotherapy, hormone therapy, and radiation therapy. The vertical bar shows the 95% CI of the HRs.

been proposed as a potential risk factor (7). However, a recent study suggested that RAI therapy might not be the only risk factor (14), and we undertook this study in light of these conflicting findings. The results from our study based on a large cohort of patients with thyroid cancer clearly demonstrated that RAI treatment in these patients did not increase the risk of development nor worsen the recurrence of breast cancer.

Moderate to high levels of radiation are known to cause many cancers (18). In particular, bone marrow, breast, lung, and thyroid are possibly sensitive to radiation, especially when patients are exposed at a young age (19). Among these malignancies, the incidence of breast cancer has been reported to be higher among women who were previously treated with radiation for childhood Hodgkin's disease or other cancers (20, 21), and among atomic bomb survivors (8, 22). In addition, exposure to multiple diagnostic x-rays was related to an increased risk of breast cancer in women less than 20 years old in a scoliosis cohort study conducted in the United States (23). It has been suggested that RAI therapy during thyroid cancer is a risk factor for breast cancer, and Metso and colleagues (24) recently reported that the incidence of breast cancer was higher in patients treated with RAI for hyperthyroidism. However, other studies gave conflicting results, as the incidence of breast cancer after administration of RAI for hyperthyroidism did not increase after a follow-up period of more than 10 years (25–27).

Previous studies reported an overall increased risk of breast cancer among women treated for thyroid cancer (28–31). The study from three major European cohorts showed an higher incidence of breast cancer among women treated for thyroid cancer compared with women in the general population; however, the relative risk (RR) of breast cancer associated with RAI treatment was not significant (RR, 0.8; 95% CI, 0.5–1.1) (28). Analysis of a large U.S. population database covering the period 1973–2002 revealed a significantly elevated risk of breast cancer after a primary thyroid cancer (observed/expected, 1.22; 95% CI, 1.13–1.32), although the risk of breast cancer was not significantly elevated in the radioisotope cohort (observed/expected, 1.14; 95% CI, 0.92–1.39) compared with the general population (29). Verkooijen et al (30) reported that the risk of a second primary breast cancer was not increased after RAI therapy among RAI-treated patients with thyroid cancer in The Netherlands. Our study also confirmed that the risk of breast cancer was not increased among RAI-treated patients with thyroid cancer after a followup of more than 2 years.

To exclude the effect of other potential confounders, we analyzed the HR of RAI for breast cancer occurrence after adjusting for the cumulative radiation dose of diagnostic imaging studies, the number of times a patient underwent mammography, and the use of hormone replacement therapy. We found that a smaller proportion of patients in the RAI group received mammography screening for breast cancer in the whole thyroid cancer cohort (Table 1, proportions of ever-exposed to mammography: 17.2% in the RAI group vs 19.2% in the no-RAI group; $P = .05$), the difference was statistically significant in the cohort with a 2-year latency period (16.5% in the RAI group vs 18.6% in the no-RAI group; $P = .03$) (Supplemental Table 3). However, mammography was less frequently administered in the RAI group, and the HR of breast cancer was not increased after adjusting for cumulative diagnostic radiation, frequencies of mammography, and hormone replacement therapy. To confirm the direct effect of RAI on the risk of breast cancer, the HR of breast cancer was analyzed after exclusion of subjects who had been exposed to high-dose radiation from radiotherapy and interventional fluoroscopies (Supplemental Table 4). In this analysis, the HR was still insignificant in the RAI group (HR, 0.99; 95% CI, 0.43–2.24) and the high-dose RAI group (≥120 mCi: HR, 0.50; 95% CI, 0.15–1.68).

The biological mechanism underlying the effect of RAI on breast cancer is unclear. Radiation hormesis mediated by the sodium-iodine symporter (NIS) could be one possible mechanism, if RAI therapy dose not increase the risk of breast cancer development. In the hormesis hypothesis, a low-level stress such as ionizing radiation can stimulate protective processes at the cellular, molecular, and organismic levels, reducing the incidence of cancer and other disease below the level at which they occur spontaneously (33).

As NIS mediates the active transport of iodide into thyroid follicular cells, RAI treatment can be effective only in

NIS expressing thyroid cancer (34). As in the thyroid gland, active iodide transport occurs in the lactating mammary gland (35) and in NIS-expressing breast cancer (36, 37), but not in normal breast tissues (36). A low dose of ionizing radiation from RAI therapy could therefore suppress the occurrence of breast cancer if normal breast tissue or pre-existing, undiscovered small breast cancers can take up RAI through mammary gland NISs. However, because the incidence of breast cancer did not decrease after RAI therapy in our study, we should consider the possibility of other, as-yet unidentified mechanisms as an alternative to radiation hormesis.

Our study has several limitations. First, due to its retrospective nature, some clinical and related epidemiologic data were missing. However, we addressed this by a thorough review of medical charts and nursing records with the standardized data collection protocols. A sensitivity analysis was performed to compare all subjects and, even with some missing information for the RAI dose, the results were robust. There were, however, advantages of using this data with respect to the efficient national data linkage for long-term followup based on the retrospective study design. A second potential study limitation is a possible selection bias due to the inclusion of patients from only a single institute. However, Seoul National University Hospital is one of the largest hospitals in the country, and the most renowned facility among the few hospitals providing RAI therapy in Korea. Despite these limitations, our results are important because there are only a few previous reports regarding the effects of RAI treatments on the prognosis of second primary breast cancer.

In summary, there was no increase in the occurrence or recurrence of breast cancer in patients with primary thyroid cancer who had undergone RAI treatment. These results suggest that RAI treatment can be used without increasing the risk of breast cancer.

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