Risk of Breast Cancer in Patients With Thyroid Cancer Receiving or Not Receiving I-131 Treatment: A Nationwide Population-based Cohort Study

Running title: Risk of Breast Cancer in Thyroid Cancer

Chun-Yi Lin¹², Cheng-Li Lin³⁴, Wen-Sheng Huang⁵, Chia-Hung Kao⁶⁷

¹Department of Nuclear Medicine, Show Chwan Memorial Hospital, Changhua, Taiwan;
²Research Assistant Center, Show Chwan Memorial Hospital, Changhua, Taiwan;
³Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan; ⁴College of Medicine, China Medical University, Taichung, Taiwan;
⁵Department of Nuclear Medicine, Changhua Christian Hospital, Changhua, Taiwan;
⁶Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan; and ⁷Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan
First author contact information: Chun-Yi Lin, Department of Nuclear Medicine, Show Chwan Memorial Hospital, Changhua, Taiwan. No. 542, Sec 1, Chung-shan Road, Changhua 500, Taiwan. Tel: 886-4-7256166, ext. 66322, Fax: 886-4-7073226, E-mail: amy36372215@yahoo.com.tw

For correspondence or reprints contact: Chia-Hung Kao, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan. No. 2, Yuh-Der Road, Taichung 404, Taiwan. Tel: 886-4-22052121, ext. 7412, Fax: 886-4-22336174, E-mail: d10040@mail.cmuh.org.tw

Wen-Sheng Huang and Chia-Hung Kao are equally contributory to this manuscript.

Author contributions:

Conception/Design: Chun-Yi Lin, Chia-Hung Kao

Provision of study materials: All authors

Collection and/or assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors
ABSTRACT

**Background:** An increased risk of second primary malignancy after I-131 therapy has been reported. The objective of this study was to determine the risk of breast cancer in patients with thyroid cancer receiving or not receiving radioiodine treatment in Taiwan.

**Methods:** This nationwide population-based cohort study was conducted using data obtained from the Taiwan National Health Insurance Database from 2000 to 2011. A total of 10 361 female patients with thyroid cancer (3292 did not receive I-131 treatment and 7069 received I-131 treatment) were enrolled, and 41 444 female controls were frequency matched to the thyroid cancer patients in a 1:4 ratio by age (5-y age group). A Cox proportional hazards model was applied to estimate the risk of breast cancer in thyroid cancer patients receiving or not receiving I-131 treatment in terms of hazard ratios (HRs), 95% and 98% confidence intervals.

**Results:** The incidence rates of breast cancer in patients with thyroid cancer receiving I-131 therapy, those not receiving I-131 therapy, and controls were 18.9, 17.7, and 13.1 per 10 000 person-years, respectively. Compared with patients with thyroid cancer treated with a cumulative I-131 dose of \( \leq 4.44 \) GBq, the risk of breast cancer was not significantly increased in those treated with a cumulative I-131 dose of \( > 4.44 \) GBq (adjusted HR = 0.78, 95% CI = 0.50-1.21, \( p = 0.26 \); 98% CI = 0.45-1.33, \( p > 0.02 \)).
**Conclusion:** The greatest increased risk of breast cancer in patients with thyroid cancer is associated with the fact that the patient has thyroid cancer regardless of I-131 administration. However, I-131 further increased that risk but not as much as just having thyroid cancer.

**Keywords:** I-131 therapy; breast cancer; thyroid cancer; Taiwan National Health Insurance Database
INTRODUCTION

The incidence of thyroid cancer is increasing worldwide (1-3). The Taiwan Cancer Registry Annual Report 2012 published by the Bureau of Health Promotion, Department of Health revealed that thyroid cancer is the fifth leading cause of death in women. The most common histological subtype of thyroid cancer is papillary carcinoma, followed by follicular carcinoma. The definitive therapy for differentiated thyroid cancer is surgical thyroidectomy, with or without adjuvant radioiodine therapy, depending on histological information and the presence of residual, unresectable, and metastatic disease (4-7). Chemotherapy or radiotherapy may also be used in cases of distant metastases or an advanced cancer stage (8). The 5-year survival rate of all people with thyroid cancer is approximately 98% (9,10).

The sodium-iodide symporter (NIS) is extremely relevant clinically, because it enables treating thyroid cancer patients with radioiodine (11-13). The NIS is also found in the breasts, salivary lacrimal glands, gastric mucosa, and ovaries (14,15). However, concerns have been raised regarding radioactive iodine therapy, because of the potential for the development of second primary malignancy, including breast cancer (16). In Taiwan, the malignancy with the highest incidence in women was breast cancer in 2012 (17). Because of a long life expectancy in most thyroid cancer survivors, it is crucial to
comprehensively evaluate the risk of breast cancer in patients with thyroid cancer receiving or not receiving I-131 therapy. Hence, we conducted a nationwide cohort study of patients with thyroid cancer identified from the Taiwan National Health Insurance Database (NHIRD) to investigate the risk of breast cancer in patients with thyroid cancer receiving or not receiving I-131 therapy.

MATERIALS AND METHODS

Data Source

The National Health Insurance (NHI) program was established in Taiwan in 1995 to provide comprehensive health care to the nation’s residents. The NHI program covers approximately 99% of the Taiwanese population (approximately 23.75 million) (18). The National Health Research Institutes (NHRI) is responsible for managing NHI claims data. It has established the NHIRD and releases this database annually to the public for research purposes. The NHRI encrypts all information that may potentially identify any individual patient. For this study, we used a subset of the NHIRD that contains health care data including files in the Registry for Catastrophic Illness Patient Database, Longitudinal Health Insurance Database 2000 (LHID 2000), and registry for beneficiaries.
Disease diagnoses are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the institutional review board of China Medical University (CMUH-104-REC2-115). The institutional review board also specifically waived the consent requirement.

**Sampled Patients**

From the Registry for Catastrophic Illness Patient Database, we identified female patients aged older than 20 years who were newly diagnosed with thyroid cancer (ICD-9-CM code 193) from 2000 to 2008. These patients comprised the thyroid cancer cohort, which was divided into 2 groups on the basis of I-131 therapy status. The index date for each patient receiving I-131 therapy was the first date on which I-131 therapy was received. The index date for patients not receiving I-131 therapy were the date of randomly assigned month and day with the same index year of the patient receiving I-131 therapy. Finally, we extracted data on 10 361 female patients with thyroid cancer without any other cancer history (ICD-9-CM codes 140-208) before the index date. Among them, 7069 female patients received I-131 therapy and 3292 did not. Controls (without thyroid cancer or any other cancer at baseline) were identified from the LHID 2000. For each
thyroid cancer patient, four controls were randomly selected from the pool of participants without thyroid cancer and any other cancer at the baseline, frequency matched by the year of index date, and age (every 5-year span).

Outcome

All study patients were observed until they were diagnosed with breast cancer, lost to follow-up, died, or withdrew from the NHI program, or December 31, 2011.

Variables of Interest

Information extracted from the claims data included age and the Charlson comorbidity index (CCI) score. We categorized the CCI score into 4 levels: 0, 1, 2, and 3 or more. The CCI score was calculated for each patient according to the claims data for hospitalization at the baseline. The CCI score is a scoring system that includes weighting factors on crucial concomitant diseases and has been validated for use with ICD-9-CM-coded administrative databases (19,20). The adjusted factors included obesity (ICD-9-CM code 278), alcohol-related illness (ICD-9-CM code 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), diabetes (ICD-9-CM code 250), lung metastases (ICD-9-CM code 197), benign neoplasm of breast (ICD-9-CM code 217),
hormone therapy, mammography, and ultrasonography. We also considered thyroid-cancer-related treatments including radiotherapy, chemotherapy, and thyroxine.

Statistical Analysis

A chi-square test and Student $t$ test were used to evaluate differences in categorical and continuous variables, respectively, between the thyroid cancer and comparison cohorts. The incidence of breast cancer in the 3 cohorts was calculated during the follow-up period. Univariate and multivariate Cox proportional hazards regression analyses were used to estimate the association between the risk of breast cancer and the I-131 therapy status. Hazard ratios are presented with 95% and 98% confidence intervals using the Cox models. The Bonferroni adjustment was used in multiple comparisons. Further analysis was performed to assess the effect of the I-131 dose on the risk of breast cancer according to the cumulative I-131 dose (in GBq) for patients receiving I-131 during the study period. All data analyses were performed using SAS statistical software (Version 9.4 for Windows; SAS Institute, Inc, Cary, NC, USA). Two-tailed $P < .05$ and $P < .02$ were considered significant.
RESULTS

Table 1 presents the baseline demographic factors, co-morbidities, medication, imaging examinations, and treatments of patients in the 3 cohorts. Most patients in the 3 cohorts were aged ≤49 years. Significant differences were observed in the number of patients with a CCI score of ≥1 among the 3 cohorts (P < .001). The proportions of patients with a CCI score ≥1 were 11.45% in the thyroid cancer without I-131 therapy cohort, 7.86% in the thyroid cancer with I-131 therapy cohort, and 6.76% in the comparison cohort. The proportions of obesity, diabetes, lung metastases, benign neoplasm of breast, receiving hormone therapy, underwent mammography and ultrasound in thyroid cancer patients were significantly higher than the comparison cohort (all p<0.001). Compared with the patients with thyroid cancer receiving I-131 treatment, a significantly higher proportion of the patients with thyroid cancer not receiving I-131 treatment underwent radiotherapy and chemotherapy (P < .001). A significantly higher proportion of the patients with thyroid cancer receiving I-131 treatment took a thyroxine supplement. The overall incidence of breast cancer was higher in the thyroid cancer cohort than in the comparison cohort (18.6 vs 13.1 per 10000 person-y). The median follow-up time of comparison cohort was 6.58 (IQR=4.40-9.12) years and thyroid cancer cohort was 6.51(IQR=4.34-9.11) years. Compared with the comparison cohort, the risk of
breast cancer was significantly higher in the thyroid cancer cohort (adjusted HR [aHR] = 1.31, 95% CI = 1.07-1.61; 98% CI = 1.02-1.68). The risk of breast cancer was significantly higher in the patients with thyroid cancer treated with I-131 than in the controls (aHR = 1.34, 95% CI = 1.15-1.69; 98% CI = 1.01-1.78) (Table 2).

After stratification by age, in patients aged >65 years, the patients with thyroid cancer not receiving I-131 treatment had a significantly higher risk of breast cancer than that of the controls (aHR = 2.83, 95% CI = 1.15-6.93); however, the risk became not significant with Bonferroni adjustment (aHR = 2.82, 98% CI = 0.95-8.40) (Table 3). We compared the risk of breast cancer according to follow-up period. For a follow-up period >5 years, the patients with thyroid cancer receiving I-131 treatment had a significantly higher risk of breast cancer than that of the controls (aHR = 1.81, 95% CI = 1.27-2.57; 98% CI = 1.18-2.77) (Table 4). Compared with patients with thyroid cancer treated with a cumulative I-131 dose ≤4.44 GBq, those treated with a cumulative I-131 dose >4.44 GBq did not have a significantly increased risk of breast cancer (aHR = 0.78, 95% CI = 0.45-1.33; 98% CI = 0.45-1.33) (Table 5).

DISCUSSION
Thyroid cancer is the most common endocrine malignancy. It was estimated that more than 60,000 new cases of thyroid cancer would be diagnosed in the United States in 2014, and that almost 1900 patients would die from this disease (21,22). Multiple primary tumors account for 13.1% of cancers in men and 13.7% of cancers in women, and all cancer survivors have a 2-fold greater probability of developing a second primary cancer compared with that of cancer-free people. The co-occurrence of multiple malignancies could be random or associated with risk factors such as an environmental or genetic predisposition and therapy-related effects (16,23,24). Thyroid remnants ablation is not necessary in patients with low-risk thyroid cancer. An increased risk of second primary malignancy after I-131 therapy has been reported. In the previous study found the incidence of second primary malignancy may be radically increased in patients who have received an extremely high cumulative activity (> 40 GBq) of I-131 (25). Lang et al reported that the occurrence of second primary malignancy adversely affected the survival of differentiated thyroid cancer (26). Hsu et al reported that the incidence rate of co-occurring breast cancer and thyroid cancer in women was 1.59%, and the strength of the association was intermediate (16).

In our study, patients with thyroid cancer treated with I-131 had a significantly increased risk of breast cancer compared with controls. After excluding patients with a
follow up duration < 3 years, the results were still the same (Supplemental Table 1) (25).

Physicians may propose patients with thyroid cancer performing breast self-exam periodically and undergoing ultrasonic mammography regularly. It has been reported that there was the association between breast cancer and thyroid cancer which may attribute to that these two cancer share common etiological features, pathologic processes and/or treatment-related factors (27,28). In the previous studies suggested the relationship between serum levels of thyroid hormones or thyroid peroxidase autoantibodies and the risk or prognosis of breast cancer (29-32). Radioiodine therapy is the main postoperative treatment for patients with differentiated thyroid cancer. The presence of the NIS in thyroid cancer cells enables highly efficient iodine accumulation, which facilitates using radioactive substrates for therapeutic purposes (33). Stimulating NIS expression by elevating thyroid-stimulating hormone levels is therefore required before I-131 administration (34,35). Studies have reported that enhanced NIS expression caused by hyperprolactinemia or individual variations might be a mechanism of radioiodine uptake in nonlactating breasts (36,37). The seminal study in which NIS expression in lactating breasts was discovered showed that this protein was expressed in more than 80% of both invasive and in situ breast cancers (33,38). The stimulation of NIS expression in patients with thyroid cancer before I-131 therapy may motivate NIS expression in the breast,
resulting in an increased risk of breast cancer. Previous reports have indicated that women and men with thyroid cancer have a risk of breast cancer (33).

We found that the risk of breast cancer was significantly higher in young (≤49 y) patients with thyroid cancer treated with I-131; this increased risk may be attributable to the stimulation of NIS expression before I-131 therapy and the long latency of radiogenic malignancy. In the past decade, thyroid cancer was found to be the leading malignancy incidentally detected using fluorodeoxyglucose positron emission tomography during health checkups or for staging or restaging patients with cancer. Another possible reason for detecting breast cancer in young patients with thyroid cancer is aggressive examination after the primary cancer was found (39,40).

Rubino et al found a correlation between the I-131 dose and number of second primary malignancies per number of person-years of follow-up. They concluded that the risk of solid tumors and leukemia is increased in patients with an increased cumulative administered dose of I-131 (41). Lang et al reported that the cumulative radioiodine therapy activity was the only independent risk factor for second primary cancer in thyroid cancer survivors (42). The risk of second primary malignancies including hematological cancer, head and neck cancer, cancer in the abdomen except in the genitourinary system, cancer out of the abdomen, uterine cancer, prostate cancer, urinary system cancer and
other cancer type receiving I-131 treatment were compare with those not receiving I-131
treatment in Ko’s study (43). Ko et al reported that I-131 treatment resulted in marginally
higher secondary cancer incidence, which was not related to the cumulative I-131 dose
(43). We found that the risk of breast cancer was not significantly increased in patents
with thyroid cancer treated with a cumulative I-131 dose >4.44 GBq compared with
patients treated with a cumulative I-131 dose ≤4.44 GBq. According to our study findings,
we hypothesize that the stimulation of NIS expression before I-131 treatment may have
stronger effects on the risk of breast cancer in patients with thyroid cancer than radiation
exposure does. Further research is required to confirm our hypothesis.

This study has the limitations. First, the NHIRD provides no detailed information on
patients regarding factors such as their lifestyle, behavioral habits, body mass index,
physical activity, socioeconomic status, and family history, all of which are possible
confounding factors in this study. Second, the evidence derived from a retrospective
cohort study is typically lower in statistical quality because of many sources of inherent
bias and the necessary adjustments for confounding factors. Third, the registries in the
NHI claims are primarily used for administrative billing and have not been verified for
scientific purposes. Fourth, under the regulations of the Personal Information Protection
Act in Taiwan, no individual patient’s medical chart and data could be allowed to directly
check, because of the anonymity of the identification number for every patient. Therefore, we can’t obtain additional information such as the I-131 absorbed dose, I-131 post therapy scintigraphy or the findings on the radioiodine scan with no uptake in the breast, focal uptake in the breast, and/or diffuse uptake in the breast by directly contacting the patients. However, the data on diagnoses in the NHIRD are highly reliable. The insurance program has mechanisms for monitoring insurance claims.

CONCLUSION

The greatest increased risk of breast cancer in patients with thyroid cancer is associated with the fact that the patient has thyroid cancer regardless of I-131 administration. However, I-131 further increased that risk but not as much has just having thyroid cancer.

ACKNOWLEDGMENTS

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**DISCLOSURE**

All authors state that they have no conflicts of interest.
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17. http://www.hpa.gov.tw/BHPNet/Portal/File/StatisticsFile/201504290915220898/101%E5%B9%B4%E7%99%8C%E7%97%87%E7%99%BB%E8%A8%98%E5%B9%B4%E5%A0%B1.pdf, Accessed on June 29th 2015


43. Ko KY, Kao CH, Lin CL, Huang WS, Yen RF. (131)I treatment for thyroid cancer and the risk of developing salivary and lacrimal gland dysfunction and a second primary
Table 1. Demographic factors, co-morbidities, medication and imaging examinations of study participants according to thyroid cancer status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control N=41,444</th>
<th>Thyroid cancer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=10,361</td>
<td>Without I-131 treatment N=3,292</td>
<td>With I-131 treatment N=7,069</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤49</td>
<td>26184</td>
<td>6546</td>
<td>1996</td>
</tr>
<tr>
<td>50-64</td>
<td>10740</td>
<td>2685</td>
<td>861</td>
</tr>
<tr>
<td>&gt;65</td>
<td>4520</td>
<td>1130</td>
<td>435</td>
</tr>
<tr>
<td>Means (SD)</td>
<td>46.0</td>
<td>46.2</td>
<td>47.2</td>
</tr>
<tr>
<td>CCI index score*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>38642</td>
<td>9429</td>
<td>2915</td>
</tr>
<tr>
<td>1</td>
<td>1812</td>
<td>630</td>
<td>235</td>
</tr>
<tr>
<td>2</td>
<td>514</td>
<td>183</td>
<td>80</td>
</tr>
<tr>
<td>3+</td>
<td>476</td>
<td>119</td>
<td>62</td>
</tr>
<tr>
<td>Obesity</td>
<td>643</td>
<td>283</td>
<td>78</td>
</tr>
<tr>
<td>Alcohol-related illness</td>
<td>519</td>
<td>113</td>
<td>42</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2405</td>
<td>820</td>
<td>269</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>8</td>
<td>95</td>
<td>17</td>
</tr>
<tr>
<td>Benign neoplasm of breast</td>
<td>1173</td>
<td>599</td>
<td>171</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>12443</td>
<td>3627</td>
<td>1074</td>
</tr>
<tr>
<td>Mammography</td>
<td>3412</td>
<td>1406</td>
<td>409</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>1498</td>
<td>781</td>
<td>237</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>479</td>
<td>179</td>
<td>179</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>240</td>
<td>112</td>
<td>112</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>6960</td>
<td>1771</td>
<td>1771</td>
</tr>
</tbody>
</table>

*Charlson comorbidity index score; * Comparison between breast cancer and control; † Comparison between thyroid cancer without I-131 treatment and thyroid cancer with I-131 treatment
Table 2. Crude and adjusted hazard for breast cancer among the thyroid cancer and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Thyroid cancer</th>
<th>Thyroid cancer without I-131 treatment</th>
<th>Thyroid cancer with I-131 treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of breast cancer</td>
<td>368</td>
<td>129</td>
<td>38</td>
<td>91</td>
</tr>
<tr>
<td>person-years</td>
<td>280940</td>
<td>69554</td>
<td>21439</td>
<td>48115</td>
</tr>
<tr>
<td>incidence rates</td>
<td>13.1</td>
<td>18.6</td>
<td>17.7</td>
<td>18.9</td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>1.00</td>
<td>1.41(1.16, 1.73)</td>
<td>1.35(0.97, 1.89)</td>
<td>1.44(1.15, 1.81)</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>1.00</td>
<td>1.31(1.07, 1.61)</td>
<td>1.26(0.90, 1.76)</td>
<td>1.34(1.06, 1.69)</td>
</tr>
<tr>
<td>Crude HR (98% CI)</td>
<td>1.00</td>
<td>1.41(1.11, 1.81)</td>
<td>1.35(0.90, 2.03)</td>
<td>1.44(1.09, 1.91)</td>
</tr>
<tr>
<td>Adjusted HR (98% CI)</td>
<td>1.00</td>
<td>1.31(1.02, 1.68)</td>
<td>1.26(0.84, 1.89)</td>
<td>1.34(1.01, 1.78)</td>
</tr>
</tbody>
</table>

Abbreviation: IR, incidence density rates, per 10,000 person-years; HR, hazard ratio; CI, confidence interval
Adjusted for age, all co-morbidities, hormone therapy, mammography, and ultrasonography
<table>
<thead>
<tr>
<th>Age</th>
<th>Control Adjusted HR (95% CI)</th>
<th>Thyroid cancer Adjusted HR (95% CI)</th>
<th>Thyroid cancer Without I-131 treatment Adjusted HR (95% CI)</th>
<th>Thyroid cancer With I-131 treatment Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤49</td>
<td>1.00</td>
<td>1.18 (0.89, 1.55)</td>
<td>0.94 (0.57, 1.57)</td>
<td>1.27 (0.94, 1.73)</td>
</tr>
<tr>
<td>50-64</td>
<td>1.00</td>
<td>1.36 (0.98, 1.90)</td>
<td>1.43 (0.85, 2.40)</td>
<td>1.33 (0.91, 1.96)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>1.00</td>
<td>1.74 (0.86, 3.52)</td>
<td>2.83 (1.15, 6.93)</td>
<td>1.18 (0.45, 3.09)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Control Adjusted HR (98% CI)</th>
<th>Thyroid cancer Adjusted HR (98% CI)</th>
<th>Thyroid cancer Adjusted HR (98% CI)</th>
<th>Thyroid cancer Adjusted HR (98% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤49</td>
<td>1.00</td>
<td>1.17 (0.84, 1.64)</td>
<td>0.94 (0.51, 1.75)</td>
<td>1.27 (0.87, 1.84)</td>
</tr>
<tr>
<td>50-64</td>
<td>1.00</td>
<td>1.38 (0.93, 2.06)</td>
<td>1.43 (0.76, 2.70)</td>
<td>1.36 (0.85, 2.16)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>1.00</td>
<td>1.69 (0.71, 3.98)</td>
<td>2.82 (0.95, 8.40)</td>
<td>1.14 (0.35, 3.66)</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio; CI, confidence interval
Adjusted for all co-morbidities, hormone therapy, mammography, and ultrasonography
Table 4. Adjusted hazard ratios for breast cancer according to thyroid cancer status stratified by follow-up time

<table>
<thead>
<tr>
<th>Follow-up time, years</th>
<th>Control</th>
<th>Thyroid cancer</th>
<th>Thyroid cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Thyroid cancer</td>
<td>Without I-131 treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>1.00</td>
<td>1.14(0.87, 1.48)</td>
<td>1.25(0.82, 1.88)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>1.00</td>
<td>1.65(1.20, 2.26)</td>
<td>1.28(0.72, 2.26)</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio; CI, confidence interval
Adjusted for: age, all co-morbidities, hormone therapy, mammography, and ultrasonography.
Table 5 Incidence rates and hazard ratios of breast cancer in thyroid patients with different dose of I-131 treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Event</th>
<th>Person-year</th>
<th>IR</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted HR (98% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted HR (98% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without I-131 treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-131 treatment Cumulative I-131 dose (GBq)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤4.44GBq</td>
<td>4221</td>
<td>61</td>
<td>29117</td>
<td>21.0</td>
<td>1.18(0.79, 1.77)</td>
<td>1.18(0.72, 1.93)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;4.44GBq</td>
<td>2848</td>
<td>30</td>
<td>18998</td>
<td>15.8</td>
<td>0.90(0.56, 1.46)</td>
<td>0.90(0.50, 1.63)</td>
<td>0.78(0.50, 1.21)</td>
<td>0.78(0.45, 1.33)</td>
</tr>
</tbody>
</table>

Abbreviation: IR, incidence density rates, per 1,000 person-years; HR, hazard ratio; CI, confidence interval
Adjusted for age, all co-morbidities, hormone therapy, mammography, ultrasonography, radiotherapy, chemotherapy, and thyroxine supplement.
Risk of Breast Cancer in Patients With Thyroid Cancer Receiving or Not Receiving I-131 Treatment: A Nationwide Population-based Cohort Study

Chun-Yi Lin, Cheng-Li Lin, Wen-Sheng Huang and Chia-Hung Kao

J Nucl Med.
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