Association Between ^{131}I Treatment for Thyroid Cancer and Risk of Receiving Cataract Surgery: A Cohort Study from Taiwan

Chien-Mu Lin[1,2], Po-Ting Yeh[3,4], Pat Doyle[5], Yu-Tse Tsan[6,7], and Pau-Chung Chen[8,9], Health Data Analysis in Taiwan (hDATa) Research Group

[1]Department of Nuclear Medicine, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan; [2]Department of Radiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [3]Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan; [4]Department of Ophthalmology, School of Medicine, National Taiwan University, Taipei, Taiwan; [5]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; [6]Division of Occupational Medicine, Department of Emergency Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [7]School of Medicine, Chung Shan Medical University, Taichung, Taiwan; [8]Department of Public Health and Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan; and [9]Department of Environmental and Occupational Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

The risk of cataracts after ^{131}I therapy for cancer is unknown. The objective of this study was to evaluate the association between ^{131}I therapy for thyroid cancer and risk of receiving cataract surgery in Taiwan. **Methods:** This was a nationwide population-based cohort study of patients with thyroid cancer diagnosed during the period 1998–2008. The data were obtained from the Taiwan National Health Insurance Research dataset. The cumulative ^{131}I activity in each patient was calculated. Hazard ratios were calculated using a time-dependent survival analysis to estimate the effect of ^{131}I therapy on the risk of receiving cataract surgery. **Results:** A total of 8,221 patients were eligible for the final analysis (mean age, 43.2 y; mean follow-up, 5.9 y); 69% received ^{131}I with a median cumulative activity of 3.7 GBq. Two hundred patients received cataract surgery. The adjusted hazard ratios were 0.77 (95% confidence interval, 0.54–1.09), 0.92 (95% CI, 0.64–1.31), and 1.06 (95% CI, 0.58–1.94) for cumulative ^{131}I activities of 0.1–3.6, 3.7–7.3, and 7.4 GBq or more, respectively, compared with a cumulative activity of 0. No trend was noted ($P = 0.85$). No interaction between ^{131}I activity and age or between ^{131}I activity and sex was noted (all $P > 0.05$). **Conclusion:** ^{131}I treatment for thyroid cancer did not increase the risk of receiving cataract surgery up to 10 y after treatment. However, further research with direct lens examination and a longer follow-up period is needed to assess subtle and late adverse effects beyond 10 y.

Key Words: cataract; iodine radioisotopes; thyroid neoplasms

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A cataract is opacity of the ocular lens that results in visual impairment. It is a leading cause of blindness and accounts for 51% of global blindness, about 20 million people (*1*). In the United States, the prevalence of cataracts was estimated to be 22% for people aged 65–69 y and up to 71% for those older than 80 y (*2*). The number of cataract surgeries continues to rise steadily and poses a substantial financial burden (*3*). In Taiwan, the prevalence of cataracts was estimated to be 51% for people older than 50 y (*4*) and 59% for those older than 65 y (*5*).

Aging is the most common cause of cataracts, which also develop more frequently after uveitis (*6*), intraocular cancer, ocular trauma (*7*), and intraocular surgery. Well-established risk factors include diabetes, smoking, exposure to ionizing radiation or ultraviolet B light, and use of steroids (*8–10*). Less well-established risk factors include myopia, drinking, obesity, hypertension, nutrition, exogenous estrogen, and statin use (*8,10,11*). Children with congenital cataracts are usually diagnosed at birth and receive combined lens extraction and posterior capsulectomy (*12*). Patients with myotonic dystrophy are more likely to develop cataracts at a much earlier age (*13*).

Radiation cataracts used to be classified as a deterministic effect with a threshold of 2 Gy for acute exposure and 5 Gy for chronic exposure (*14*). Recent epidemiologic studies on atomic bomb survivors (*15,16*), Chernobyl accident clean-up workers (*17*), interventional cardiologists and staff (*18–20*), radiologic technologists (*21*), astronauts and airline pilots (*22,23*), and Taiwanese residents in radiocontaminated buildings (*24*) suggested a linear no-threshold relationship at low doses for radiation cataracts. Accordingly, a new occupational exposure guideline has considerably lowered the radiation cataract threshold to 0.5 Gy and the occupational lens equivalent exposure limit to a mean of 20 mSv per year over a 5-y period and less than 50 mSv in any 1 y (*25*).

Radiation cataracts had not been considered as an important adverse long-term effect of ^{131}I therapy probably because radiation cataracts had been regarded as a deterministic effect and a dose to the lens, estimated to be about 60 mGy per 3.7 GBq (*26*), was well below the old threshold of 2–5 Gy (*14*). However, as

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For correspondence contact: Pau-Chung Chen, Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, 17 Xuzhou Rd., Taipei 10055, Taiwan
E-mail: pchen@ntu.edu.tw
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mentioned above, the new threshold has recently been revised to 0.5 Gy and there may be a linear no-threshold relationship (*25*). Furthermore, some thyroid cancer patients received repeated ^{131}I therapy for recurrence or metastases, giving a lens dose of hundreds of mGy. Currently there is no information on radiation cataracts after ^{131}I therapy for thyroid cancer, despite being clinically and scientifically important for the assessment of treatment safety.

Lens extraction surgery is the only effective treatment for cataracts and indicates late stage of cataracts when vision is severely affected. In this study, a nationwide cohort of thyroid cancer patients from the Taiwan National Health Insurance (NHI) database was used to investigate the association between ^{131}I therapy for thyroid cancer and risk of receiving cataract surgery.

MATERIALS AND METHODS

Taiwan NHI Research Database

The database used was from the NHI reimbursement system of Taiwan, which was launched in March 1995 and covers more than 98% of the population. Detailed information concerning health care services, including up to 3 or 5 diagnoses coded by the International Classification of Diseases, Ninth Revision (ICD-9) (*27*), prescription drugs and doses, orders, and dates, were obtained for each outpatient visit or hospital admission. This database has been used for epidemiologic research, and information on prescription use, diagnoses, and hospitalizations is of high quality (*28–30*). The authors have previously used this database to assess the link between ^{131}I therapy for thyroid cancer and primary hyperparathyroidism (*31*).

The NHI reimbursement data of Taiwan is anonymized and maintained by the National Health Research Institute with strict confidentiality in accordance with the Personal Electronic Data Protection Law. This study was also approved by the Ethics Review Board of the National Taiwan University College of Public Health.

Study Design and Population Selection

This was a nationwide population-based cohort study. A total of 18,111 patients with a diagnosis of thyroid cancer (ICD-9 code 193) made between 1997 and 2008 were identified from the Registry of Catastrophic Illnesses Patients, which includes people diagnosed with cancer, serious autoimmune diseases, end-stage renal disease, and chronic mental disorders. Patients with such illnesses are exempt from medical costs, so the registry database is comprehensive, with excellent validity.

Figure 1 shows population selection. The date of the first inpatient diagnosis of thyroid cancer, typically at the date of the first cancer surgery, was used as the index date. We excluded patients who had a diagnosis of thyroid cancer before 1998 and those who had no thyroidectomy on the index date or had undergone any ^{131}I whole-body scanning before the index date, because they were more likely to be prevalent cases.

Patients were excluded if they had received first ^{131}I activity before, or more than 6 mo after, the index date; had missing information on sex or address; had been followed up 2 y or less from the index date; or had received extraction surgery before or within 2 y after the index date. Patients who had received radiotherapy, chemotherapy, or certain kinds of fluoroscopic examination (*32*) (the footnotes of Fig. 1 provide details) 2 y or more before cataract surgery or last clinical visit were also excluded. This was to minimize confounding and to ensure that the main radiation source was ^{131}I therapy.

We further excluded patients who had been diagnosed as muscular dystrophy or other dystrophy; had received capsulectomy for congenital cataract; had been diagnosed as inflammatory disorders of uvea, intraocular tumor, or ocular trauma; or had received intraocular surgery 2 y or more before cataract surgery or last clinical visit. ICD-9 codes, the Anatomic Therapeutic Chemical codes of drugs, and drug or order codes used in the Taiwan NHI dataset are listed in Supplemental Tables 1–3 (supplemental materials are available at http://jnm.snmjournals.org).

Statistics

All statistical analyses were performed using SAS software (release v.9.4; SAS Inc.). *P* values were 2-sided, and a value of less than 0.05 was considered statistically significant. A Cox proportional hazards model was used to estimate the effect of ^{131}I therapy on the risk of receiving extraction surgery using a time-dependent covariate for cumulative ^{131}I activity by the SAS PHREG procedure. A latency of 2 y was used to calculate cumulative ^{131}I activity and person-years at risk. Cumulative ^{131}I activity was treated as a 4-level covariate (0, 0.1–3.6, 3.7–7.3, $\geq$ 7.4 GBq). Patients with 0 GBq were used as the reference group.

The potential confounding factors considered in the primary analysis (model 1) included sociodemographic characteristics (sex, age and calendar year at diagnosis of thyroid cancer, income, and urbanization degree of a residential area). We also considered comorbidities that would affect the risk of developing cataracts, particularly diabetes. Prescription drugs that could potentially confound the association between ^{131}I therapy and cataract risk were identified, including statin, estrogen, and steroid use. Other radiation sources from diagnostic radiation examinations were controlled for, including diagnostic radiology (head x-ray and CT) and nuclear medicine examinations (^{99m}Tc-methyldiphosphonate bone scan, ^{201}Tl whole-body scan, ^{67}Ga scan, ^{99m}Tc-labeled red blood cell scan, ^{18}F-FDG PET scan, parathyroid scan, sialoscintigraphy, ^{131}I thyroid scan, ^{99m}Tc thyroid scan). Each diagnostic radiation examination was

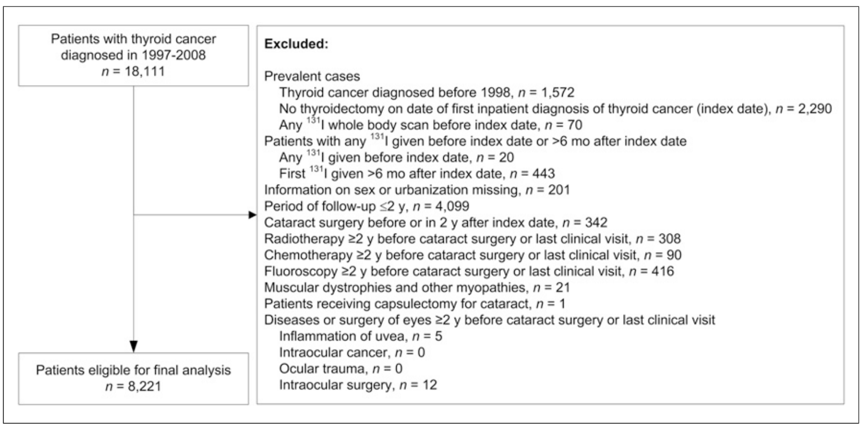

FIGURE 1. Population selection. Fluoroscopy includes coronary angiography, aortography/noncardiac angiography, procedures related to biliary system (t-tube cholecystography, operative cholangiography, endoscopic retrograde cholangiopancreatography, endoscopic retrograde pancreas drainage, percutaneous transhepatic cholangiography, percutaneous transhepatic cholangiography-drainage, and percutaneous gallbladder drainage), percutaneous transluminal angioplasty, transarterial embolization, percutaneous nephrostomy, hysterosalpingography, myelography, percutaneous vertebroplasty, and venography.

TABLE 1
Characteristics of Patients with Thyroid Cancer by ^{131}I Activity

Characteristic	Patients with thyroid cancer (total no. = 8,221)		^{131}I activity = 0 (total no. = 2,549)		^{131}I activity > 0 (total no. = 5,672)		P*
	No.	%	No.	%	No.	%	
Median cumulative ^{131}I activity (GBq)						3.7 (interquartile range, 4.4)	
Mean interval between index date and ^{131}I ablation therapy ± SD (mo)						1.5 ± 1.0	
Mean follow-up period ± SD (y)		5.9 ± 2.6		5.5 ± 2.7		6.1 ± 2.5	<0.001
Mean age at index date ± SD (y)		43.2 ± 3.7		44.0 ± 14.1		42.9 ± 13.5	<0.001
Men	1,585	19%	409	16%	1,176	21%	<0.001
Calendar year, 2003–2008	4,143	50%	1,436	56%	2,707	48%	<0.001
Income < 15,840 New Taiwan dollars/mo	3,139	38%	993	39%	2,146	38%	0.33
Rural area	1,598	19%	488	19%	1,110	20%	0.65
Slit-lamp examination	2,390	29%	702	28%	1,688	30%	0.04
Comorbidities							
Diabetes	1,041	13%	314	12%	727	13%	0.53
Hypertension	2,232	27%	707	28%	1,525	27%	0.42
Hyperlipidemia	1,482	18%	418	16%	1,064	19%	0.01
Chronic kidney disease	168	2%	74	3%	94	2%	<0.001
Chronic obstructive pulmonary disease	686	8%	235	9%	451	8%	0.05
Alcohol-related disease	45	1%	14	1%	31	1%	0.99
Drug use							
Aspirin ≥ 180 d	410	5%	140	5%	270	5%	0.16
Statin ≥ 180 d	413	5%	115	5%	298	5%	0.15
Metformin ≥ 180 d	405	5%	129	5%	276	5%	0.71
Angiotensin-converting enzyme inhibitor ≥ 180 d	554	7%	168	7%	386	7%	0.72
Angiotensin receptor blocker ≥ 180 d	557	7%	162	6%	395	7%	0.31
Estrogen (female) ≥ 180 d	764	12%	230	11%	534	12%	0.18
Progesterone (female) ≥ 180 d	311	5%	86	4%	225	5%	0.08
Steroid, oral ≥ 180 d	172	2%	68	3%	104	2%	0.01
Steroid, inhaled or nasal, amount ≥ 6	178	2%	67	3%	111	2%	0.05
Steroid, eye drops, amount ≥ 6	1,729	21%	523	21%	1,206	21%	0.44
Diagnostic radiology							
Head x-ray	4,266	52%	1,282	50%	2,984	53%	0.05
CT	2,913	35%	827	32%	2,086	37%	<0.001
Esophagography and gastrointestinal series†	634	8%	215	8%	419	7%	0.10
Nuclear medicine							
^{99m}Tc-methyldiphosphonate bone scan	955	12%	214	8%	741	13%	<0.001
^{201}Tl whole-body scan	930	11%	159	6%	771	14%	<0.001
^{67}Ga scan	39	0%	6	0%	33	1%	0.03
^{99m}Tc-labeled red blood cell scan	107	1%	21	1%	86	2%	0.01
^{18}F-FDG PET scan‡	153	2%	11	0%	142	3%	<0.001
Parathyroid scan	51	1%	20	1%	31	1%	0.20
Sialoscintigraphy	78	1%	13	1%	65	1%	0.006
^{131}I thyroid scan	777	9%	219	9%	558	10%	0.07
^{99m}Tc thyroid scan	1,458	18%	410	16%	1,048	18%	0.009

*t tests or χ^2 tests.

†Gastrointestinal (GI) series includes upper GI series, small bowel series, upper GI and small bowel series, lower GI series, double-contrast study of lower GI series, and double-contrast small bowel series.

‡^{18}F-FDG PET scans have been reimbursed by Taiwan National Health Insurance System since 2004.

treated as a binary variable (0 = no, 1 = yes). Slit-lamp examination was included in the model to consider potential detection bias. A trend was assessed by treating ^{131}I activity as a continuous covariate. Interaction between ^{131}I activity and age and between ^{131}I activity and sex was examined.

Sensitivity analyses were performed to investigate bias. First, an alternate analysis (model 2) was performed for cataracts with less visual impairment: at least 1 inpatient admission or 3 outpatient visits with diagnosis coded as ICD-9 366, prescription of relevant eye drops (pirenoxine, azapentacene), or receiving extraction surgery. Second, the analysis (model 3) was repeated, focusing on patients younger than 50 y only because younger patients exposed to radiation were likely to be at more risk (*16,21,24*). Third, the analysis (model 4) was conducted focusing on patients receiving only 1 ^{131}I ablation therapy. Fourth, the analysis (model 5) was repeated using a latency of 5 y (rather than 2 y) to investigate possible later biologic effects of ^{131}I activity. Lastly, we repeated the analysis (model 6), treating both cumulative ^{131}I activity and age as time-dependent variables to consider a possible aging effect.

RESULTS

In total, there were 8,221 thyroid cancer patients eligible for the primary analysis. Their characteristics are shown in Table 1. Sixty-nine percent of patients received ^{131}I. The median cumulative ^{131}I activity was 3.7 GBq, and ^{131}I was given on average 1.5 mo after the index date. The mean follow-up period was 5.9 y. Compared with patients with zero ^{131}I activity, those with ^{131}I activity were followed up for a slightly longer period (6.1 vs. 5.5 y, $P < 0.001$), were slightly younger (42.9 vs. 44.0 y, $P < 0.001$), had a slightly lower female-to-male ratio (men % = 21% vs. 16%, $P < 0.001$), had thyroid cancers that were diagnosed earlier in the decade (48% vs. 56% in 2003–2008, $P < 0.001$), were more likely to have hyperlipidemia (19% vs. 16%, $P = 0.01$), were less likely to have chronic kidney disease (2% vs. 3%, $P < 0.001$), were less likely to take oral steroids (2% vs. 3%, $P = 0.01$), and were more likely to receive CT scanning (37% vs. 32%, $P < 0.001$) and many nuclear examinations particularly ^{99m}Tc-methyldiphosphonate bone scanning (13% vs. 8%, $P < 0.001$) and ^{201}Tl whole-body scanning (14% vs. 6%, $P < 0.001$).

Figure 2 shows the incidence rate and adjusted hazard ratios (HRs) in the primary analysis (model 1) and sensitivity analyses (models 2–6). Of the 8,221 patients, 200 received cataract extraction surgery during the 31,512 person-years. There were 72 patients receiving cataract extraction surgery during 9,354 person-years for a cumulative ^{131}I activity of 0 GBq and 128 patients receiving cataract extraction surgery during 22,158 person-years for more than 0 GBq. The overall rate of receiving cataract extraction surgery was 635 per 10^5 person-years (770 and 578 per 10^5 person-years for ^{131}I activity = 0 and > 0 GBq, respectively).

In the primary analysis (model 1), the adjusted HRs were 0.77 (95% confidence interval [CI], 0.54–1.09), 0.92 (95% CI, 0.64–1.31), and 1.06 (95% CI, 0.58–1.94) for cumulative ^{131}I activity of 0.1–3.6, 3.7–7.3, and 7.4 GBq or more, respectively, compared with a cumulative activity of 0. No trend with dose was noted ($P = 0.85$). No interaction between cumulative ^{131}I activity and age or between ^{131}I activity and sex was noted (all $P > 0.05$, data not shown). In the sensitivity analyses (models 2–6), the findings remained negative.

^{131}I activity (GBq)	Person-years at risk	No. of cataract	Rate (per 10^5 person-years)	Adjusted HR (95% CI)
Model 1: Primary analysis (no. of patients = 8,221)				
0	9,354	72	770	1.00
0.1-3.6	10,622	57	537	0.77 (0.54 to 1.09)
3.7-7.3	8,493	57	671	0.92 (0.64 to 1.31)
≥7.4	3,043	14	460	1.06 (0.58 to 1.94)
				P for trend = 0.85
Model 2: Different cataract definition (no. of patients = 7,741)				
0	8,670	156	1,799	1.00
0.1-3.6	9,944	141	1,418	0.88 (0.70 to 1.11)
3.7-7.3	7,822	104	1,330	0.81 (0.63 to 1.04)
≥7.4	2,884	27	936	0.71 (0.46 to 1.09)
				P for trend = 0.05
Model 3: Patients of age <50 years (no. of patients = 5,784)				
0	6,829	11	161	1.00
0.1-3.6	8,052	5	62	0.59 (0.19 to 1.85)
3.7-7.3	6,334	7	111	1.22 (0.43 to 3.45)
≥7.4	2,327	2	86	0.94 (0.18 to 4.95)
				P for trend = 0.78
Model 4: Patients with only one ^{131}I ablation therapy (no. of patients = 5,653)				
0	8,185	140	1,710	1.00
0.1-3.6	6,886	105	1,525	1.04 (0.80 to 1.35)
3.7-7.3	5,434	75	1,380	0.92 (0.68 to 1.23)
≥7.4	401	6	1,496	1.13 (0.49 to 2.61)
				P for trend = 0.78
Model 5: Latency = 5 years (no. of patients = 4,831)				
0	4,069	36	885	1.00
0.1-3.6	4,606	24	521	0.64 (0.37 to 1.09)
3.7-7.3	3,462	15	433	0.55 (0.29 to 1.04)
≥7.4	1,052	6	571	1.04 (0.40 to 2.72)
				P for trend = 0.17
Model 6: ^{131}I activity and age as time-dependent variables (no. of patients = 8,221)				
0	9,354	72	770	1.00
0.1-3.6	10,622	57	537	0.75 (0.52 to 1.07)
3.7-7.3	8,493	57	671	0.88 (0.61 to 1.26)
≥7.4	3,043	14	460	0.88 (0.48 to 1.61)
				P for trend = 0.74

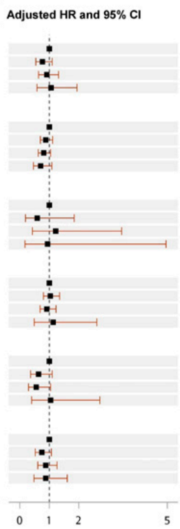

FIGURE 2. Incidence and adjusted HRs of cataracts associated with ^{131}I treatment in patients with thyroid cancer and sensitivity analyses. Model 2: different cataract definition—cataract defined as at least 1 inpatient admission or 3 outpatient visits with diagnosis coded as ICD-9 366, prescription of relevant eye drops (pirenoxine, azapentacene), or receiving extraction surgery. HR adjusted for sex, age, and calendar year at diagnosis of thyroid cancer, income, degree of urbanization, comorbidities (diabetes, hypertension, hyperlipidemia, chronic kidney disease, chronic obstructive pulmonary diseases, alcohol-related diseases), drug use (estrogen, statin, oral steroid, steroid eye drops), receiving radiologic examinations (head x-ray, computerized tomography), nuclear medicine examinations (^{99m}Tc-methyldiphosphonate bone scan, ^{201}Tl whole-body scan, ^{67}Ga scan, ^{99m}Tc labeled red blood cell scan, ^{18}F-FDG PET scan, parathyroid scan, sialoscintigraphy, ^{131}I thyroid scan, ^{99m}Tc thyroid scan), and slit-lamp examination. Cumulative ^{131}I activity was used as continuous variable in trend test.

DISCUSSION

Although radiation-induced lens opacities with varying degrees of severity were found in many epidemiologic studies, whether such opacities affect vision is rarely reported (*16,21*). In this study, we assessed clinically relevant visual impairment as quantified by the risk for receiving cataract surgery and obtained negative findings for patients receiving ^{131}I therapy (median, 3.7 GBq) in an average of 5 y of follow-up per patient using the NHI claims dataset.

Our negative findings were not consistent with the results of the studies using cataract surgery as an outcome among atomic bomb survivors (lens dose, range = 0 to > 3 Gy) (*16*) and radiologic technologists (occupational lens dose, median = 28.1 mGy) (*21*). From the study of 6,066 atomic bomb survivors exposed at age 20 y, the RR per Gy was 1.32 (95% CI, 1.17–1.52) after a follow-up period of 50 y. After a nearly 20-y follow-up of 35,705 radiologic technologists aged 23–44 y, the risk of self-reported cataract extraction for those with number of x-rays 25 or greater was 1.5 times that for those with number of x-rays less than 5 (95% CI, 1.09–2.06). Explanations for the disparity between these studies and the current analysis might relate to differences in the radiation dose received, in the age at exposure, or in the follow-up period.

Several methodologic issues need to be clarified before any conclusion can be made. There is a concern that patients receiving ^{131}I therapy usually had more advanced-stage thyroid disease and may have been examined more by diagnostic radiology and nuclear medicine, which would be a source of additional and unmeasured radiation exposure. Lens dose from head CT was estimated to be 50 mGy (*33*). However, additional radiation exposure would tend to overestimate the effect of ^{131}I therapy and cannot explain the negative results found.

There is an issue whether the negative findings reported result from a long latency period because the latency seems to be inversely related to dose (*9,34*). An average latency of 2–3 y, ranging from 6 mo to 35 y, was noted for radiation-induced lens opacities after acute low-dose x-ray exposure (*35*). We used latencies of 2 and 5 y in the analyses, and the results remained similar. We were not, however, able to examine the long-term effects beyond 10 y in this dataset.

We recognize that the administered ^{131}I activity used in our study could not be a precise indicator of absorbed doses to lenses. Doses may depend on different clinical situations, such as recombinant human thyroid-stimulating hormone use, presence of thyroid remnants or metastases, renal clearance, and use of techniques to increase ^{131}I excretion such as lemon juice intake, hydration, frequency of urination, and laxative use. Such misclassification would be nondifferential, and its effect would tend to move the effect estimate toward null. Information on the type of cataract was not available in the NHI dataset, so that the effects on specific radiation-induced types—posterior subcapsular cataract and cortical cataract (*9,34,36*)—could not be further analyzed. Also, several potential confounders such as smoking, alcohol, diet, sunlight exposure, and use of self-paid radiation modalities were not measured, and myopia was not validly coded in the NHI reimbursement dataset, raising concern about uncontrolled confounding.

Cataract surgery was used as the main outcome in this study and although a different definition was used in the sensitivity analysis we recognize that this was not as sensitive as diagnosis using direct eye slit-lamp examination. Therefore, we could not rule out the possibility that ^{131}I therapy induces mild cataracts. Our final concern was that the follow-up period of up to 10 y might be too short for occurrence of late-stage cataracts.

Having considered limitations, we recognize that this study had several strengths. The large sample size in this nationwide study gave excellent statistical power, minimized the problem of losing cohort members at follow-up, and allowed accurate calculation of ^{131}I activity. Treatment of patients at different hospitals was not an issue because the NHI database includes more than 98% of the population in Taiwan. Because cataract surgery was validly coded due to the nature of insurance reimbursement, misclassification bias was minimized. In addition, the NHI database allowed us to deal with as many potential confounders as possible to obtain unbiased results. Last, because the study was prospective, we were able to investigate the causal relationship between radiation exposure from ^{131}I therapy and the risk of receiving cataract surgery.

CONCLUSION

Overall, we did not find that ^{131}I treatment for thyroid cancer in Taiwanese patients increased their risk of receiving cataract surgery up to 10 y after treatment. Our negative findings indicate that medical costs spent on cataract surgery would not increase after ^{131}I therapy and may have clinical implications for assessing the safety of ^{131}I therapy. However, further research with direct lens examination and a longer follow-up period is needed to assess subtle and late adverse effects beyond 10 y.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

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