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TITLE PAGE

Title

Association between ^{131}I treatment for thyroid cancer and risk of receiving cataract surgery—a cohort study from Taiwan

Running title

^{131}I therapy and cataract

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ABSTRACT

The risk of cataract following ^{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 (HRs) 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 8221 patients were eligible for the final analysis (mean age 43.2 years, mean follow-up 5.9 years). 69% received ^{131}I with a median cumulative activity of 3.7 GBq. 200 patients received cataract surgery. The adjusted HRs were 0.77 (95%CI = 0.54 to 1.09), 0.92 (95%CI = 0.64 to 1.31) and 1.06 (95%CI = 0.58 to 1.94) for cumulative ^{131}I activity of 0.1-3.6 GBq, 3.7-7.3 GBq and ≥7.4 GBq respectively, compared to a cumulative activity = 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). **Conclusions:** ^{131}I treatment for thyroid cancer did not increase the risk of receiving cataract surgery up to 10-years following 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 years.

Key words: cataract; iodine radioisotopes; thyroid neoplasms

INTRODUCTION

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 US, the prevalence of cataract was estimated to be 22% for aged 65 to 69 years and up to 71% for those aged more than 80 years (*2*). The number of cataract surgeries continues to rise steadily and poses a substantial financial burden (*3*). In Taiwan, the prevalence of cataract was estimated to be 51% for people older than 50 years (*4*) and 59% for those older than 65 years (*5*).

Aging is the most common cause of cataract, which also develops more frequently following 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 cataract at a much earlier age (*13*).

Radiation cataract used to be classified as a deterministic effect with threshold of 2 Gy for acute exposure and 5 Gy for chronic exposure (*14*). Recent epidemiological studies on atomic bomb survivors (*15*,*16*), Chernobyl accident clean-up workers (*17*), interventional cardiologists and staff (*18-20*), radiological 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 cataract. 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 year period and less than 50 mSv in any one year (*25*).

Radiation cataract had not been considered as an important adverse long term effect of ^{131}I therapy probably because radiation cataract 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 to 5 Gy (*14*). However, as mentioned above the new threshold has recently been revised to 0.5 Gy and there may be a linear non-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 cataract after ^{131}I therapy for thyroid cancer, despite being clinically and scientifically important for assessment of treatment safety.

Lens extraction surgery is the only effective treatment for cataract and indicates late stage of cataract 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 three or five diagnoses coded by the International Classification of Disease, Ninth Revision (ICD-9), prescription drugs and doses, orders, and dates, were obtained for each outpatient visit or hospital admission. This database has been used for epidemiological research, and information on prescription use, diagnoses and hospitalizations is of high quality (*27-29*). The authors have previously used this database to assess the link between ^{131}I therapy for thyroid cancer and primary hyperparathyroidism (*30*).

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 has also been 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 received any ^{131}I whole body scan before the index date, since they were more likely to be prevalent cases.

Patients were excluded if they had received first ^{131}I before, or greater than 6 months after, the index date; had missing information on sex or address; had been followed up equal to or less than 2 years from the index date; or had received extraction surgery before or within two years after index date. Patients who had received radiotherapy, chemotherapy, or certain kinds of fluoroscopic examination ([*31*]) (see the footnotes of Figure 1 for details) two years 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 two years or more before cataract surgery or last clinical visit. ICD-9 codes, the Anatomical Therapeutic Chemical codes of drugs, and drug or order codes used in Taiwan NHI dataset were listed in Supplemental Table 1-3.

Statistics

All statistical analyses were performed using SAS software (release v.9.4; SAS Inc., Cary NC). *P* values were two-sided and a value < 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 two years was used to calculate cumulative ^{131}I activity and person years at risk. Cumulative ^{131}I activity was treated as a four-level covariate (0, 0.1-3.6, 3.7-7.3, ≥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 which would affect the risk of developing cataract, 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 computerized tomography) and nuclear medicine examinations (^{99m}Tc-methyldiphosphonate bone scan, ^{201}Tl whole body scan, ^{67}Ga scan, ^{99m}Tc labelled red blood cell scan, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography scan, parathyroid scan, sialoscintigraphy, ^{131}I thyroid scan, ^{99m}Tc thyroid scan). Each diagnostic radiation examination was treated as a binary variables (0 = no, 1 = yes). Slitlamp 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 carried out to investigate bias. First, an alternate analysis (Model 2) was performed for cataract with less visual impairment: at least one inpatient admission or three 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 aged less than 50 years only since 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 one ^{131}I ablation therapy. Fourth, the analysis (Model 5) was repeated using a latency of five years (rather than 2 years) to investigate possible later biological 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 per cent of patients received ^{131}I. The median cumulative ^{131}I activity was 3.7 GBq and ^{131}I was given on average 1.5 months after the index date. The mean follow-up period was 5.9 years. 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 years, $P < 0.001$), were slightly younger (42.9 vs. 44.0 years, $P < 0.001$), had a slightly lower female to male ratio (men % = 21% vs. 16 %, $P < 0.001$), their thyroid cancers 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 steroid (2% vs. 3%, $P = 0.01$), more likely to receive computerized tomography (CT) scanning (37% vs. 32%, $P < 0.001$) and many nuclear examinations particularly ^{99m}Tc-methyldiphosphonate bone scan (13% vs. 8%, $P < 0.001$) and ^{201}Tl whole body scan (14% vs. 6%, $P < 0.001$).

Figure 2 shows the incidence rate and adjusted HRs in the primary analysis (Model 1) and sensitivity analyses (Model 2 to 6). Of the 8,221 patients, 200 received cataract extraction surgery during the 30,512 person-years. There were 72 patients receiving cataract extraction surgery during 9,354 person-years for cumulative ^{131}I activity = 0 GBq and 128 patients receiving cataract extraction surgery during 22,405 person-years for >0 GBq. The overall rate of receiving cataract extraction surgery was 655 per 10^5 person-years (700 and 571 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%CI = 0.54 to 1.09), 0.92 (95%CI = 0.64 to 1.31) and 1.06 (95%CI = 0.58 to 1.94) for cumulative ^{131}I activity of 0.1-3.6 GBq, 3.7-7.3 GBq and ≥7.4 GBq respectively, compared to a cumulative activity = 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 (Model 2 to 6) the findings remained negative.

DISCUSSION

Although radiation-induced lens opacities with varying degrees of severity were found in many epidemiological 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 years 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 radiological technologists (occupational lens dose, median = 28.1 mGy) (*21*). From the study of 6,066 atomic bomb survivors exposed at age 20 years, the RR per Gy was 1.32 (95% CI = 1.17 to 1.52) after a follow-up period of 50 years. After nearly 20 years follow-up of 35,705 radiologic technologists aged 23-44 years, the risk of self-reported cataract extraction for those with number of x-rays ≥25 was 1.5 times that for those with number of x-rays <5 (95% CI = 1.09 to 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 methodological 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, unmeasured, radiation exposure. Lens dose from head CT was estimated 50 mGy (*32*). 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 results from a long latency period since the latency seems to be inversely related to dose (*9*,*33*). An average latency of 2 to 3 years, ranging from 6 months to 35 years, was noted for radiation-induced lens opacities following acute low-dose X-ray exposure (*34*). We used latencies of 2 and 5 years in the analyses and the results remained similar. We were not, however, able to examine the long-term effects beyond 10 years 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 rhTSH 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 non-differential, and its effect would tend to move the effect estimate towards to 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*,*33*,*35*)—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 diagnosis using direct eye slit lamp examination. Therefore, we could not rule out the possibility that ^{131}I therapy induces mild cataract. Our final concern was that the follow-up period of up to ten years might be too short for occurrence late stage of cataract.

Having considered limitations, we recognise 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. As 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. Lastly, being prospective in nature, we were able to study 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-years after treatment. Our negative findings indicate that medical costs spent on cataract surgery would not increase following ^{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 years.

DISCLOSURE

No conflicts.

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FIGURE LEGENDS

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, percutaneous gall bladder drainage), percutaneous transluminal angioplasty, transarterial embolization, percutaneous nephrostomy, hysterosalpingography, myelography, percutaneous vertebroplasty and venography.

Figure 2. Incidence, and adjusted HRs of cataract associated with ^{131}I treatment in the patients with thyroid cancer and sensitivity analyses. Model 2: Different cataract definition—Cataract defined as at least one inpatient admission or three 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, alcoholic related diseases), drug use (estrogen, statin, oral steroid, steroid eye drops), receiving radiologic examinations (head x-ray, computerized tomography), examinations of nuclear medicine (^{99m}Tc- methyldiphosphonate bone scan, ^{201}Tl whole body scan, ^{67}Ga scan, ^{99m}Tc labelled red blood cell scan, ^{18}F-FDG positron emission tomography scan, parathyroid scan, sialoscintigraphy, ^{131}I thyroid scan, ^{99m}Tc thyroid scan), and slitlamp examination. Cumulative ^{131}I activity was used as a continuous variable in trend test. CI: confidence interval; HR: hazard ratio.

TABLES

Table 1. Characteristics of patients with thyroid cancer by ^{131}I activity

	Patients with thyroid cancer (No. = 8,221)		^{131}I activity = 0 (No. = 2,549)		^{131}I activity >0 (No. = 5,672)		
	No.	%	No.	%	No.	%	*P* value§
Cumulative ^{131}I activity, median (IQR), GBq						3.7 (4.4)	
Interval between index date and ^{131}I ablation therapy, mean (SD), months						1.5 (1.0)	
Follow-up period, mean (SD), years		5.9 (2.6)		5.5 (2.7)		6.1 (2.5)	<0.001
Age at index date, mean (SD), years		43.2 (13.7)		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 <15840 New Taiwan dollars/month	3,139	38%	993	39%	2,146	38%	0.33
Rural area	1,598	19%	488	19%	1,110	20%	0.65
Slip-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
Alcoholic related disease	45	1%	14	1%	31	1%	0.99
Drug use							
Aspirin ≥180 days	410	5%	140	5%	270	5%	0.16
Statin ≥180 days	413	5%	115	5%	298	5%	0.15
Metformin ≥180 days	405	5%	129	5%	276	5%	0.71
Angiotensin converting enzyme inhibitor ≥180 days	554	7%	168	7%	386	7%	0.72
Angiotensin receptor blocker ≥180 days	557	7%	162	6%	395	7%	0.31
Estrogen (female) ≥180 days	764	12%	230	11%	534	12%	0.18
Progesterone (female) ≥180 days	311	5%	86	4%	225	5%	0.08
Steroid, oral ≥180 days	172	2%	68	3%	104	2%	0.01
Steroid, inhaled or nasal, amount ≥6	178	2%	67	3%	111	2%	0.05
Steroid, eyedrops, 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 & GI 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 labelled red blood cell scan	107	1%	21	1%	86	2%	0.01
^{18}F-FDG positron emission tomography 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

* Abbreviations: CT, computerized tomography; GI series, gastrointestinal series; IQR, interquartile range; SD, standard deviation

† 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 positron emission tomography scans have been reimbursed by Taiwan National Health Insurance System since 2004.

§ t-tests or chi-squared tests

Patients with thyroid cancer diagnosed in 1997-2008
n = 18,111

Excluded:

Prevalent cases
- Thyroid cancer diagnosed before 1998, *n* = 1,572
- No thyroidectomy on date of first inpatient diagnosis of thyroid cancer (index date), *n* = 2,290
- Any ^{131}I whole body scan before index date, *n* = 70

Patients with any I-131 given before index date or >6 mo after index date
- Any ^{131}I given before index date, *n* = 20
- First ^{131}I given >6 mo after index date, *n* =443

Information on sex or urbanization missing, *n* = 201
Period of follow-up ≤2 y, *n* = 4,099
Cataract surgery before or in 2 y after index date, *n* = 342
Radiotherapy ≥2 y before cataract surgery or last clinical visit, *n* = 308
Chemotherapy ≥2 y before cataract surgery or last clinical visit, *n* = 90
Fluoroscopy ≥2 y before cataract surgery or last clinical visit, *n* = 416
Muscular dystrophies and other myopathies, *n* = 21
Patients receiving capsulectomy for cataract, *n* = 1
Diseases or surgery of eyes ≥2 y before cataract surgery or last clinical visit
- Inflammation of uvea, *n* = 5
- Intraocular cancer, *n* = 0
- Ocular trauma, *n* = 0
- Intraocular surgery, *n* = 12

Patients eligible for final analysis
n = 8,221

^{131}I activity (GBq)	No. of patients	Person-years at risk	No. of cataract	Rate (per 10^5 person-years)	Adjusted HR (95% CI)
Model 1: Primary analysis					
0	8,221	9,354	72	770	1.00
0.1-3.6	3,124	10,622	57	537	0.77 (0.54 to 1.09)
3.7-7.3	2,986	8,493	57	671	0.92 (0.64 to 1.31)
≥7.4	936	3,043	14	460	1.06 (0.58 to 1.94)
					P for trend = 0.85
Model 2: Different cataract definition					
0	7,741	8,670	156	1,799	1.00
0.1-3.6	2,972	9,944	141	1,418	0.88 (0.70 to 1.11)
3.7-7.3	2,787	7,822	104	1,330	0.81 (0.63 to 1.04)
≥7.4	874	2,884	27	936	0.71 (0.46 to 1.09)
					P for trend = 0.05
Model 3: Patients of age <50 years					
0	5,784	6,829	11	161	1.00
0.1-3.6	2,252	8,052	5	62	0.59 (0.19 to 1.85)
3.7-7.3	2,116	6,334	7	111	1.22 (0.43 to 3.45)
≥7.4	663	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					
0	5,653	8,185	140	1,710	1.00
0.1-3.6	1,921	6,886	105	1,525	1.04 (0.80 to 1.35)
3.7-7.3	1,537	5,434	75	1,380	0.92 (0.68 to 1.23)
≥7.4	72	401	6	1,496	1.13 (0.49 to 2.61)
					P for trend = 0.78
Model 5: Latency = 5 years					
0	4,831	4,069	36	885	1.00
0.1-3.6	1,887	4,606	24	521	0.64 (0.37 to 1.09)
3.7-7.3	1,685	3,462	15	433	0.55 (0.29 to 1.04)
≥7.4	491	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					
0	8,221	9,354	72	770	1.00
0.1-3.6	3,124	10,622	57	537	0.75 (0.52 to 1.07)
3.7-7.3	2,986	8,493	57	671	0.88 (0.61 to 1.26)
≥7.4	936	3,043	14	460	0.88 (0.48 to 1.61)
					P for trend = 0.74