Radiotherapy and Oncology 123 (2017) 394–400

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

NPC and hypothyroidism

Risk of hypothyroidism among patients with nasopharyngeal carcinoma treated with radiation therapy: A Population-Based Cohort Study

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ARTICLE INFO

Article history:
Received 21 February 2017
Received in revised form 21 April 2017
Accepted 25 April 2017
Available online 19 May 2017

Keywords:
Nasopharyngeal carcinoma
Hypothyroidism
Radiation therapy

ABSTRACT

Background and purpose: This study aimed to assess the incidence and risk of hypothyroidism among patients with nasopharyngeal carcinoma (NPC) after radiation therapy (RT).
Material and methods: We identified 14,893 NPC patients and 16,105 other head and neck cancer (HNC) patients treated with RT without thyroidectomy from the National Health Insurance Research Database in Taiwan between 2000 and 2011. Each NPC patient was randomly frequency-matched with four individuals without NPC by age, sex, and index year. Competing-risk regression models were used to estimate hazard ratios (HRs) of hypothyroidism requiring thyroxin associated with NPC after RT.
Results: The risk of developing hypothyroidism was significantly higher in the NPC cohort than in the matched cohort (adjusted HR = 14.35, 95% CI = 11.85–17.37) and the HNC cohort (adjusted HR = 2.06, 95% CI = 1.69–2.52). Independent risk factors for hypothyroidism among NPC patients included younger age, female sex, higher urbanization level, autoimmune disease, and receipt of chemotherapy.
Conclusion: The risk of hypothyroidism requiring thyroxin was significantly higher in NPC patients after RT than in the general Taiwanese population and HNC patients. Regular clinical and serum thyroid function tests are essential among NPC survivors after RT.
 Radiotherapy and Oncology 123 (2017) 394–400

The thyroid gland is the major endocrine gland regulating metabolism and its hormones facilitate some of the most fundamental physiologic processes in the body, including substrate use, energy expenditure, growth, and development. Hypothalamic thyrotropin-releasing hormone stimulates the pituitary gland to produce thyroid-stimulating hormone, which in turn stimulates triiodothyronine and thyroxine production in the thyroid. Damage to the hypothalamus-pituitary-thyroid axis may result in hypothyroidism, with overt symptoms including weight gain, dry skin, hair loss, cold intolerance, general weakness, muscle cramps, depression, irritability, and memory loss. Hypothyroidism can also lead to coagulopathy, diastolic hypertension, dyslipidemia, and atherosclerosis, which in turn increase the risk of cardiovascular events and mortality [1,2].

Nasopharyngeal carcinoma (NPC) is a malignant tumor arising from the nasopharynx, the narrow tubular passage behind the nasal cavity. NPC is a highly curable disease owing to its inherent radiosensitivity and chemosensitivity [3]. Because a large population of NPC survivors is expected after curative radiation therapy (RT), long-term RT-related complications will gradually emerge.

For external beam RT of NPC, bilateral neck lymphatics are routinely included in the target volume because over 75% of patients present with clinically positive or occult cervical lymphadenopathy [4]. As an organ situated in the anterior neck, the thyroid gland is often entirely or partially included in the high-dose region. Many related studies on lymphoma and head and neck cancers (HNC) have reported that high-dose radiation to the thyroid can induce primary hypothyroidism [5–7].

The pituitary gland is situated at the sella turcica, which is just superior to the nasopharynx, and therefore, it may also be irradiated with high doses during RT for NPC. Radiation injury to the hypothalamic–pituitary (H–P) axis can result in dysfunction of the H–P axis followed by central hypothyroidism in NPC patients after RT. Hence, NPC patients receiving RT may have a higher risk of developing hypothyroidism than HNC patients receiving RT without thyroidectomy.

Radiation-induced hypothyroidism after RT for NPC has been reported in previous studies [8–12]. However, there has been no

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http://dx.doi.org/10.1016/j.radonc.2017.04.025
0167-8140/

nationwide epidemiological study of NPC patients after RT and the subsequent risk of hypothyroidism until recently. In the present study, we investigated the risk of long-term clinical hypothyroidism in NPC patients after RT compared with the general population and other HNC patients who did not receive thyroidectomy using a population-based cohort design. The study analyzed possible factors that affect the development of hypothyroidism in NPC patients. Furthermore, we evaluated the risk of RT-induced H–P dysfunction between NPC patients and HNC patients not receiving thyroidectomy.

Methods

Data source

The study population was derived from the National Health Insurance Research Database (NHIRD) [13]. The NHIRD contains data from the NHI program, a single-payer health insurance program mandatory for all citizens (23.74 million residents) with a coverage rate of approximately 99%. The NHIRD includes the Registry of Catastrophic Illness Patient Database to protect vulnerable beneficiaries by exempting these patients from copayments for the corresponding medical services. All medical histories can be linked through an encrypted patient identification number for each subject. Diagnoses of diseases were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

Ethics statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR1). The IRB also specifically waived the consent requirement.

Sampled participants

Patients with newly diagnosed NPC (ICD-9-CM 147) and other HNC (oral cavity, ICD9-CM 140, 141, 143–145; oropharynx, ICD9-CM 146; hypopharynx, ICD9-CM 148; larynx, ICD9-CM 161) without thyroidectomy were identified from the registry data for catastrophic illness patients between January, 2000 and December, 2011. The ICD-9-procedure codes 06, 29, 30, and 31 indicate the following procedures: thyroidectomy, operations on the pharynx, excision of the larynx, and other operations on the larynx or trachea, respectively. We used these codes to identify and exclude patients who may receive thyroidectomy. We further selected patients who receive RT within 3 months after diagnosis of cancer. The index date of the cancer cohort was defined as the first date of RT. For each NPC patient, 4 control subjects without cancer were propensity score matched according to the year of NPC diagnosis, sex, and age. The control subjects (matched cohort) were extracted from 1 million people randomly selected from the NHIRD. Individuals in the study with a history of cancer, hypothyroidism (ICD-9-CM 244), taking thyroxine, receiving I-131 therapy, withdrawal from the insurance program before the index date, or age <18 years were excluded.

Outcome and relevant variables

The event of the study was defined as subsequent hypothyroidism based on the diagnosis code (ICD-9-CM 244) with the prescription of thyroxine. The prescription of thyroxine was used to ensure the accuracy of the diagnosis of hypothyroidism. All subjects were followed up from the index date until the date of hypothyroidism requiring thyroxine, withdrawal from the NHI program, or December 31, 2011, whichever came first. The percentage of patients developing H–P dysfunction (ICD-9-CM 253) was calculated for NPC and HNC cohorts. The urbanization of Taiwan cities was grouped into seven levels based on the following indexes: (1) population density (people/km^2); (2) the population ratio of different educational levels; (3) the population ratio of elderly persons; and (4) the population ratio of agricultural workers and the number of physicians per 100,000 people [14]. The numbers of subjects in levels 5, 6, and 7 were small so that these levels were combined with level 4. Level 1 was considered to represent the highest degree of urbanization, and level 4 represented the lowest. The following diagnoses were recorded in order to establish the baseline comorbidity history for each participant: hypertension, diabetes, chronic obstructive pulmonary disease, alcohol-related illness, and autoimmune disease. Cancer treatments, including chemotherapy and radical excision of cervical lymph nodes among NPC and HNC cohorts, were also noted.

Statistical analysis

The differences in baseline characteristics between the NPC cohort and matched/HNC cohorts were examined by chi-square tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated by Cox regression. Considering the competing risk, we applied the %CIF macro in SAS 9.4 to plot the cumulative incidences of the three cohorts and performed Gray's test to examine the differences in cumulative incidence among them. The chi-square test was used to test differences in H–P dysfunction between the NPC and HNC cohorts. All statistical analyses were performed using SAS software version 9.4 (SAS Institute INC., Carey, NC). A two-tailed p-value below 0.05 was defined as significant.

Results

This study included 18,919 NPC patients and 62,436 other HNC patients without thyroidectomy (Fig. 1). Among them, 15,713 NPC patients and 30,857 other HNC patients received RT within 3 months of diagnosis. Patients with a history of cancer, hypothyroidism, taking thyroxine, receiving I-131 therapy, withdrawal from the insurance program before the index date, or age <18 years were excluded (n = 820 in the NPC cohort, n = 14,752 in the HNC cohort). Eventually, there were 14,893 patients in the NPC cohort, 16,105 patients in the HNC cohort, and 59,572 subjects in the matched cohort.

Table 1 shows a comparison of the baseline characteristics of the study cohorts. The distributions of age and sex between the NPC cohort (mean age: 50.1 years; 75.5% male) and matched cohort (mean age: 50.2 years; 75.3% male) were similar. The HNC cohort was significant older (mean age: 53.6 years) and had a higher male-predominant ratio (92.3% male) compared with the NPC cohort. NPC patients had a median follow-up time of 3.4 years, shorter than the matched participants (5.2 years) but longer than the HNC patients (1.5 years). The rates of living in urbanized areas were 58.8%, 59.6%, and 53.3% in the NPC, matched, and HNC cohorts, respectively. Comorbidities, except for alcohol-related illness, were more frequent in the NPC cohort than in the matched cohort. The NPC cohort had a higher rate of receiving chemotherapy ($p < 0.0001$), but a lower rate of undergoing radical excision of cervical lymph nodes ($p < 0.0001$) than the HNC cohort.

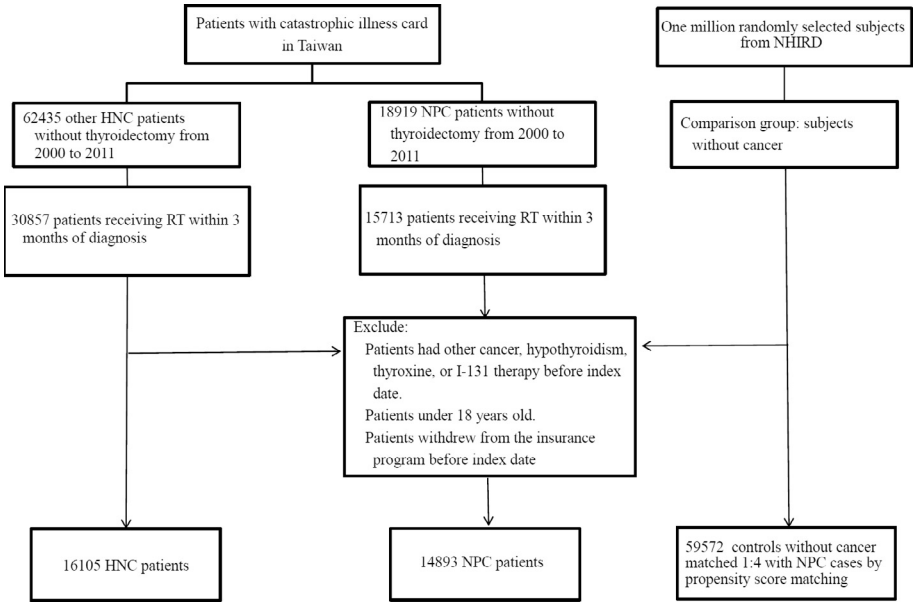


Fig. 1. Flowchart for case and control selection. Abbreviations: NHIRD, National Health Insurance Research Database; HNC, head and neck cancer; NPC, nasopharyngeal carcinoma; RT, radiation therapy.

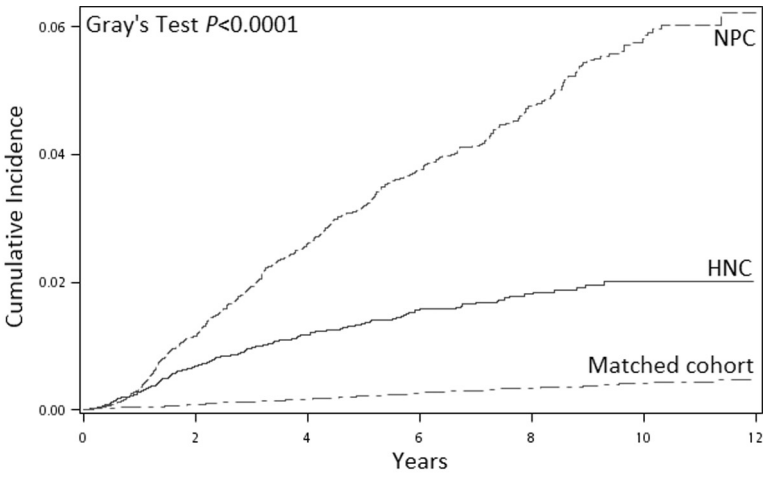
Table 1
Comparisons of clinical characteristics.

	NPC (n = 14893)	Matched cohort[#] (n = 59572)	p value[†]	HNC (n = 16105)	p value[§]
Age					
Mean ± SD	50.1 (12.6)	50.2(14.2)	0.217	53.6 (12.0)	<0.0001
Sex, n (%)					
Female	3647 (24.5)	14733(24.7)	0.5378	1245 (7.7)	<0.0001
Male	11246 (75.5)	44839(75.3)		14860 (92.3)	
Urbanization level[‡]					
1	4167(28.0)	17253(29.0)	0.0109	3741(23.2)	<0.0001
2	4582(30.8)	18244(30.6)		4841(30.1)	
3	2542(17.1)	10309(17.3)		2901(18.0)	
4	3602(24.2)	13726(23.0)		4622(28.7)	
Follow-up time, years					
Median (Q1, Q3)	3.4 (1.5, 6.4)	5.2 (2.4, 8.3)	<.0001	1.5 (0.7,3.8)	<0.0001
Comorbidities, n (%)					
Hypertension	4304 (28.9)	16054(26.9)	<.0001	5490 (34.1)	<0.0001
Diabetes	2068 (13.9)	7873(13.2)	0.0316	3137 (19.5)	<0.0001
COPD	1894 (12.7)	6607(11.1)	<.0001	2153 (13.4)	0.0891
Alcohol-related illness	523 (3.5)	2057(3.5)	0.7258	2259 (14.0)	<0.0001
Autoimmune disease	783 (5.3)	2890(4.9)	0.0406	707 (4.4)	0.0004
Treatment, n (%)					
Chemotherapy	11,898 (79.9)	0		11306 (70.2)	<0.0001
Radical excision of cervical lymph nodes	389 (2.6)	0		5945 (36.9)	<0.0001

NPC, nasopharyngeal carcinoma; HNC, head and neck cancer; COPD, chronic obstructive pulmonary disease.
Matched cohort[#]: propensity score matched.
p-Value[†]: NPC vs. Matched cohort.
p-Value[§]: NPC vs. HNC.
Urbanization level[‡]: The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

The median period for the development of clinical hypothyroidism requiring thyroxine in NPC patients was 3.11 years (Q1, 1.56; Q3, 5.23). Among NPC patients after RT, 1.87%, 3.31%, and 5.73% of them developed hypothyroidism requiring thyroxine by 3, 5, and 10 years, respectively. As shown in Fig. 2, the highest cumulative incidence of hypothyroidism was observed in the NPC cohort followed by the HNC cohort and then the matched cohort (Gray's test, $p < 0.0001$).

Overall, the incidence density rates of hypothyroidism were 7.86, 0.43, and 4.41 per 1000 person-years for the NPC, matched, and HNC cohorts, respectively (Table 2). After adjusting for all confounding factors, the NPC patients had a 14.35-fold higher risk of hypothyroidism than the matched cohort (adjusted HR [aHR] = 14.35, 95% CI = 11.85–17.37). The overall incidence and risk of hypothyroidism were compared between the NPC and matched cohorts with regards to several variables including sex, age, urban-



Number at risk							
NPC	14893	10008	6606	4202	2310	972	0
HNC	16105	6704	3774	2099	1113	440	0
Matched cohort	59572	47058	35936	25597	16227	7591	0

Fig. 2. Comparison of the cumulative incidence of hypothyroidism (accounted for competing events) among the nasopharyngeal carcinoma (NPC), head and neck cancer (HNC), and matched cohort groups.

Table 2
The incidence density and hazard ratio of hypothyroidism in the nasopharyngeal carcinoma cohort compared with the matched cohort and the head and neck cancer cohort.

	NPC		Matched cohort		Adjusted HR[§] (95% CI)	HNC		Adjusted HR[†] (95% CI)
	Event	Incidence	Event	Incidence		Event	Incidence	
All	491	7.86	138	0.43	14.35(11.85, 17.37)***	186	4.41	2.06(1.69, 2.52)***
Sex								
Female	198	12.26	67	0.85	12.01(9.08, 15.88)***	21	5.66	2.21(1.35, 3.61)**
Male	293	6.33	71	0.29	16.43(12.61, 21.4)***	165	4.29	2.06(1.66, 2.57)***
Age, years								
<50	297	8.13	49	0.26	25.23(18.61, 34.2)***	83	4.3	2.02(1.52, 2.67)***
50–65	159	8.17	51	0.54	11.42(8.28, 15.75)***	81	4.85	2.25(1.63, 3.11)***
>65	35	5.44	38	0.89	4.03(2.57, 6.33)***	22	3.55	1.74(0.99, 3.07)
Urbanization level[‡]								
1	161	9.04	37	0.4	18.88(13.17, 27.06)***	36	3.56	2.61(1.74, 3.91)***
2	160	8.26	44	0.44	14.59(10.4, 20.45)***	58	4.58	1.96(1.38, 2.79)***
3	88	8.32	22	0.4	15.55(9.66, 25.03)***	40	5.42	2.18(1.37, 3.46)**
4	82	5.58	35	0.47	8.8(5.88, 13.15)***	52	4.32	1.74(1.16, 2.61)**
Comorbidities[#]								
No	285	7.32	55	0.26	22.77(17.03, 30.44)***	93	4.2	1.87(1.43, 2.43)***
Yes	206	8.75	83	0.73	8.92(6.92, 11.52)***	93	4.64	2.29(1.7, 3.07)***
Follow-up duration, years								
<1	45	3.29	24	0.43	7.45(4.51, 12.32)***	40	3.03	0.81(0.49, 1.33)
1–3	195	9.64	41	0.44	20.65(14.75, 28.92)***	84	6.05	1.35(1.01, 1.79)*
3–5	118	8.90	30	0.42	19.43(13.02, 28.99)***	34	4.45	1.76(1.09, 2.83)*
5–10	128	8.90	41	0.44	18.58(13.04, 26.48)***	28	3.96	1.96(1.21, 3.19)**
≥10	5	5.57	2	0.29	22.05(4.64, 104.67)***	0	0.00	-

NPC, nasopharyngeal carcinoma; HNC, head and neck cancer; HR, hazard ratio; CI, confidence interval.
Incidence: incidence rate, per 1000 person-years.
Adjusted HR[†]: NPC vs. Matched cohort; models adjusted for sex, age, urbanization level, and comorbidities of hypertension, diabetes, chronic obstructive pulmonary disease, alcohol-related illness, and autoimmune disease.
Adjusted HR[§]: NPC vs. HNC; models adjusted for sex, age, urbanization level, radical excision of cervical lymph nodes, chemotherapy, and comorbidities of hypertension, diabetes, chronic obstructive pulmonary disease, alcohol-related illness, and autoimmune disease.
Urbanization level[‡]: The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.
Comorbidities[#]: patients with any one of the comorbidities of hypertension, diabetes, chronic obstructive pulmonary disease, alcohol-related illness, and autoimmune disease.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

ization level, presence or absence of comorbidities, and follow-up period. The risk of hypothyroidism in NPC patients regardless of stratification was higher than in the matched cohort. The risk of hypothyroidism was 2.06-fold higher (95% CI = 1.69–2.52) in the NPC cohort than in the HNC cohort. The proportion of hypothyroidism patients differed significantly between the NPC and HNC

Table 3
Hazard ratio of hypothyroidism in association with baseline characteristics among nasopharyngeal carcinoma patients in Cox model with competing risks.

Variable	Crude Hazard ratio (95% CI)	*p* value	Adjusted Hazard ratio (95% CI)	*p* value
Age	0.99(0.98, 0.99)	<.0001	0.99(0.98, 0.99)	0.0014
Sex (Female vs. Male)	2.09(1.74, 2.5)	<.0001	2.03(1.69, 2.43)	<.0001
Urbanization level‡				
1	1.75(1.34, 2.28)	<.0001	1.65(1.26, 2.17)	0.0002
2	1.55(1.18, 2.02)	0.0013	1.49(1.14, 1.95)	0.0037
3	1.55(1.15, 2.09)	0.0045	1.52(1.12, 2.06)	0.0071
4	1 (reference)		1 (reference)	
Comorbidities (yes vs. no)				
Hypertension	0.95(0.78, 1.16)	0.6385	1.15(0.9, 1.47)	0.2536
Diabetes	0.91(0.7, 1.2)	0.5201	0.99(0.73, 1.33)	0.938
COPD	0.86(0.65, 1.14)	0.3058	1.02(0.75, 1.38)	0.9052
Alcohol-related illness	0.97(0.57, 1.65)	0.9049	1.14(0.67, 1.95)	0.6291
Autoimmune disease	1.95(1.41, 2.69)	<.0001	1.69(1.21, 2.35)	0.002
Treatment (yes vs. no)				
Chemotherapy	1.31(1.05, 1.65)	0.0187	1.27(1, 1.6)	0.0488
Radical excision of cervical lymph nodes	0.86(0.5, 1.5)	0.6025	0.87(0.5, 1.51)	0.6253

COPD, chronic obstructive pulmonary disease.
Urbanization level‡: The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

groups after 1 year of follow-up. There were 213 patients (1.43%) that developed H–P dysfunction in the NPC cohort, significantly higher than the 56 patients (0.35%) in the HNC cohort ($p < 0.0001$).

The results of the univariable and multivariable Cox proportional hazards regression models for analyzing the risk of variables contributing to hypothyroidism in NPC patients are shown in Table 3. The aHR of hypothyroidism decreased 0.99-fold (95% CI = 0.98–0.99) with age (every year) and increased 2.03-fold for women relative to men (95% CI = 1.69–2.43). The aHR of hypothyroidism was significant increased 1.49–1.65 fold for NPC patients living in areas with a higher level of urbanization (level 1–3), compared with those living in the least urbanized area. The risk of hypothyroidism was greater in NPC patients with autoimmune disease (aHR = 1.69, 95% CI = 1.21–2.35) and NPC patients treated with chemotherapy had a higher risk of developing hypothyroidism than those without chemotherapy (aHR = 1.27, 95% CI = 1.00–1.60). The addition of radical excision of cervical lymph nodes was not a significant risk factor for developing hypothyroidism on either univariate or multivariate analysis.

Discussion

In this study, we observed the estimated incidences for clinical hypothyroidism requiring thyroxine were 1.87%, 3.31%, and 5.73% at 3, 5, and 10 years in NPC patients after the start of RT. The risk was significantly higher among NPC patients after RT than among the matched cohort (adjusted HR = 14.35) and HNC patients who received RT without thyroidectomy (adjusted HR = 2.06). In the multivariable Cox model with competing risks, younger age, female sex, higher urbanization level, autoimmune disease, and receiving chemotherapy were risk factors for hypothyroidism among NPC patients after RT, but receiving radical excision of cervical lymph nodes was not. The strengths of this study include its large sample size, long-term follow-up period (12 years), adequate controls for comorbidities, use of clinical hypothyroidism diagnoses defined according to ICD-9-CM codes, and the prescription of thyroxine. Thyroxine is the most common treatment for hypothyroidism and has no other approved indications in Taiwan. We focused on clinical hypothyroidism requiring medication with thyroxine, which may reflect the actual conditions of NPC patients under the care of clinical oncologists.

The mechanism of radiation-induced hypothyroidism remains unclear. It is believed to involve damage to the small thyroid vessels, direct thyroid cell injury, and immune-mediated damage, all of which subsequently lead to insufficient production of thyroid hormones [15,16]. Wu et al. [8] presented a prospective study of 408 patients who had received RT for NPC; the estimated incidences for clinical hypothyroidism were 5.3%, 9.0%, and 19.1% at 3, 5, and 10 years after radiotherapy, respectively. Lee et al. [11] noted that 21 of 149 NPC patients (14.1%) developed clinical hypothyroidism after RT with a median follow-up duration of 3.1 years. Peng et al. [17] compared the RT consequences of 616 patients who received conventional RT (CRT) and intensity-modulated RT (IMRT) treatment and found that hypothyroidism was 2.9% in the CRT group and 1.3% in the IMRT group with a median follow-up duration of 3.5 years. In the studies by Wu et al. [8] and Lee et al. [11], serum thyroid function tests were regularly monitored and the definition of hypothyroidism did not include the prescription of thyroxine; therefore, their incidence of hypothyroidism is higher than ours. However, Peng et al. [17] used clinical symptoms to evaluate the function of the thyroid without regular detection of hormone values, so their abnormal rates were similar to our study and lower than previously reported. Even though we may underestimate the incidence of hypothyroidism, in particular subclinical hypothyroidism, we still found a significantly higher risk of developing hypothyroidism in NPC patients after RT compared with the matched cohort. The adjust HR increased over time, and our results show a more than 18-fold increased risk when follow-up longer than 5 years.

Radiation damage is a potent cause of H–P dysfunction and is highly dose-dependent [18]. Neuronal cell death and degeneration due to the direct effects of radiation appear to play a major role [19]; nevertheless, vascular damage has also been proposed [20]. Lin and associates [12] found that NPC patients who were treated with high (>50 Gy) thyroid and pituitary doses of RT had the highest incidence (83.3%) of hypothyroidism, followed by those who received high (>50 Gy) thyroid doses and low (<50 Gy) pituitary doses of RT (50%). Our results showed NPC patients after RT had significantly higher incidences of hypothyroidism as well as H–P dysfunction compared to HNC patients without thyroidectomy after RT. This can be partially explained by the effect of an H–P axis injury causing central hypothyroidism, because the H–P axis lies within the field of RT for NPC. The H–P axis received a higher RT dose in the NPC than the HNC patients. Further studies on the association between NPC patients after RT and the subsequent risk of central hypothyroidism are warranted.

Age has been surveyed as an independent factor for hypothyroidism after RT with the risk of hypothyroidism decreasing by a

factor of 0.99 with each additional year of age in this study. The thyroid glands of children and adolescents are sensitive to radiation. For example, Zubizarreta et al. [21] suggested a higher incidence of radiation-induced hypothyroidism with 8 (73%) of 11 young patients treated for NPC. Similar to our study, Wu et al. [8] reported that younger age (<30 years) was a significant predictor of clinical hypothyroidism after RT.

Female sex has also been identified as an independent risk factor for radiation-induced hypothyroidism; however, this result is controversial. Sklar et al. [22] observed that female patients had a higher risk of developing hypothyroidism among the 1,791 evaluated Hodgkin's disease patients receiving RT, with a 1.7:1 female/male ratio. In contrast, some studies [23,24] have reported no sex differences among patients with hypothyroidism. In the present study, female sex was a risk factor for developing hypothyroidism.

Chemotherapy, such as 5-fluorouracil and l-asparaginase therapy, may modify circulating thyroid hormone levels; however, whether chemotherapy combined with RT aggravates the damage to the thyroid function remains controversial [6]. Some authors suggested that the addition of chemotherapy increases the risk of hypothyroidism [5] but others disagree [7,10,23–25]. Our data support the former conclusion. Combined therapy of RT and surgery is a risk factor for hypothyroidism in HNC patients [7,24,26]. The cause is believed to be thyroidectomy or hemithyroidectomy performed with laryngectomy or laryngopharyngoesophagectomy, or from damage to the feeding vessels of the thyroid gland [7]. However, radical excision of cervical lymph nodes without thyroidectomy did not increase the risk of hypothyroidism in NPC patients in the present study.

Our study also showed that NPC patients living in higher urbanization areas tended to have a significantly higher risk for hypothyroidism, which may be partially explained by the higher availability of medical resources in urbanized areas.

There are limitations to our findings. First, the NHIRD does not contain detailed information on potential confounding factors, such as family history of hypothyroidism, diet, smoking, and alcohol consumption. Second, because there is no link between the NHIRD and the cancer registry, we did not have access to information regarding NPC stage. Furthermore, the NHIRD provided no information on RT dose level, energy level, technique, or distribution. Treated volumes of RT to the thyroid, pituitary gland, and hippocampus were not available. This precluded us from performing any analysis involving these variables. Third, not all of our participants had regular serum thyroid function tests until overt symptoms occur. In addition, we used taking thyroxine to confirm the diagnosis of hypothyroidism, which means we may have underestimated the incidence of hypothyroidism, in particular subclinical hypothyroidism. Furthermore, the follow-up period of the HNC cohort was relatively short (median, 1.5 years). Radiation-induced hypothyroidism may occur after a longer follow-up period. Owing to the short follow-up, the real incidence of hypothyroidism in HNC patients might have been underestimated. Fourth, we could not collect sufficient numbers of other NHC patients to be propensity score matched with the NPC patients according to sex and age. Hypothyroidism is generally considered more common in women than in men [27]. In the present cohort, the NPC group was significantly younger and had a higher female-predominant ratio than the other HNC group. This pattern may have influenced the obtained results.

Conclusion

To the best of our knowledge, this is the first study using a large-scale nationwide cohort study to investigate the incidence and risk of hypothyroidism among NPC patients receiving RT. The risk of hypothyroidism was higher among NPC patients after RT than the general population as well as the HNC patients who received RT without thyroidectomy. RT-related central hypothyroidism should be considered, because we noted a significantly higher incidence of H–P axis dysfunction among NPC patients after RT relative to the HNC patients. Based on our data, we suggest that additional attention be focused on NPC patients with a younger age, female sex, comorbidities from autoimmune disease, and those treated with chemotherapy. Regular clinical and serum thyroid function tests are recommended to ensure early diagnosis of hypothyroidism and appropriate prescription of hormone replacement therapy or other therapeutic interventions.

Author contributions

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Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW106-TDU-B-212-113004), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037), NRPB Stroke Clinical Trial Consortium (MOST105-2325-B-039-003), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan, and Health and welfare surcharge of tobacco products, China Medical University Hospital Cancer Research Center of Excellence (MOHW105-TDU-B-212-134003, Taiwan). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.

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