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Head and Neck Cancers

Accelerated Risk of Premature Ischemic Stroke in 5-Year Survivors of Nasopharyngeal Carcinoma

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Key Words. Nasopharyngeal carcinoma • Stroke • Radiotherapy • Survivorship

Abstract

Background. Research on cancer survivorship associated with nasopharyngeal carcinoma (NPC) is rare. We aimed to elucidate the risk of ischemic stroke in 5-year survivors of NPC following radiotherapy (RT) or concurrent chemoradiation therapy (CCRT).

Subjects, Materials, and Methods. NPC survivors, defined as those who survived longer than 5 years after diagnosis, were identified and matched at a 1:5 ratio with normal controls from the Longitudinal Health Insurance Database 2005 of Taiwan. The stratified Cox regression models were used to access the risk of ischemic stroke, with adjustment for age, treatment modality, comorbidities, and socioeconomic characteristics.

Results. From 2000 to 2005, a total of 3,016 NPC survivors who had received RT (n = 959) or CCRT (n = 2,057) and 15,080 controls were matched for age, sex, income, and urbanization level. The risk of ischemic stroke was significantly higher in the NPC survivor cohort than in the control cohort. Stroke was positively related to death. Moreover, the age onset of stroke for NPC survivors was 10 years earlier than that for the general population.

Conclusion. Not only was the stroke risk in NPC survivors higher than that in the general population, but the onset age was also 10 years earlier. Future survivorship care should include ischemic stroke as a late complication, for its proper prevention and management. ***The Oncologist*** 2019;24:e891–e897

Implications for Practice: Nasopharyngeal carcinoma (NPC) is endemic in Taiwan, and its 5-year survival is 65.2%. With the increased 5-year cancer survivors, survivorship has become an important issue. However, research on NPC survivorship is very rare. To the authors' knowledge, this is the first population-based study on long-term NPC survivors. This study's results indicated that not only was the risk of ischemic stroke in NPC survivors at least triple that of the general population, but the onset age was also 10 years earlier. These results may provide solid evidence that survivorship care guidelines should include stroke as a late complication in 5-year NPC survivors, for its proper prevention and management.

Introduction

Survivorship care includes the management of late side effects in post-treatment cancer survivors. However, research on nasopharyngeal carcinoma (NPC) survivorship is rare. NPC has a distinct geographical distribution that is closely related to Epstein-Barr virus. It is endemic in Southern China, Hong Kong, and Taiwan. In North America and Europe, the age-standardized incidence of NPC is 0.4–0.9 per 100,000 person-years [1]. In Taiwan, the incidence rates of NPC are 7.21 and 2.29 per 100,000 person-years in males and females, respectively [2]. NPC is a disease with favorable overall survival owing to its inherent radiosensitivity and chemosensitivity. Concurrent chemoradiation therapy (CCRT) improves 5-year survival and has become the standard of care for locally advanced NPC [3]. The 5-year overall survival is reported to be 65.2% in Taiwan [4]. With more NPC survivors, concerns have been raised about the detrimental impact of late complications owing to treatment in their survivorship.

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Retrospective studies have shown that patients with head and neck cancer have a significantly higher risk of ischemic stroke [5–7]. Stroke risk is primarily related to radiotherapy of the head and neck region [8]. However, these studies included all the patients from diagnosis, so their results did not exactly represent those for long-term survivors. The risk of ischemic stroke in NPC survivorship remains unknown; moreover, the National Comprehensive Cancer Network and European Society for Medical Oncology have not yet incorporated stroke in their current survivorship care guidelines or recommendation. To address this issue, we conducted a nationwide population-based study to assess the risk of ischemic stroke in NPC survivors, strictly defined as patients who survived longer than 5 years after diagnosis. We also assessed whether age, treatment modality, income level, and comorbidities are associated with the risk of stroke.

Subjects, Materials, and Methods

Data Sources

The databases used in this study were sourced from the Registry of Catastrophic Illness (RCI) and Longitudinal Health Insurance Database 2005 (LHID2005), which are two subsets of records from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD is a nationwide database containing longitudinal medical records of beneficiaries enrolled in the National Health Insurance (NHI) program, which provides comprehensive health care coverage for more than 98% of the Taiwanese population. The RCI database was used to identify patients with NPC or other cancers, as it is meant to exempt vulnerable beneficiaries from copayments for medical services. Patients included in the RCI database are evaluated by a panel of specialists through a strict process of review of medical records, imaging, and pathology reports. The LHID2005 contains original claims data for 1,000,000 beneficiaries randomly sampled from the entire population in 2005. All information on comorbidities and treatment modalities (for NPC cases) during 1995–2012 was available for analysis from inpatient and outpatient databases. This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (approval number, 201600205B0).

Study Design

The primary endpoint in this study was ischemic stroke during the follow-up period (2005–2012). Ischemic stroke was identified if the participant was hospitalized with a major or minor diagnosis of the following International Classification of Diseases, Ninth Revision (ICD-9) Clinical Modification codes: 433.xx (occlusion and stenosis of precerebral arteries), 434.xx (occlusion of cerebral arteries), 436.xx (acute but ill-defined cerebrovascular disease), or 437.1 (other generalized ischemic cerebrovascular disease), accompanied by either computed tomography or magnetic resonance imaging examination.

To evaluate the risk of ischemic stroke in NPC survivors (ICD-9 code: 147), two study groups were compared: an NPC survivor group and a matched control group. NPC survivors were defined as those who survived for longer than 5 years after diagnosis; the first day after 5 years of survivorship was defined as the index date. Originally, the NPC group comprised 9,412 patients who were diagnosed between 2000 and 2005. However, 6,396 patients were excluded owing to any one of the following criteria: aged <20 or >80 years at diagnosis of NPC, survived for less than 5 years, developed second cancers during follow-up or ischemic stroke before the index date, incomplete individual information, and received treatment modalities other than radiotherapy (RT) alone and CCRT. Finally, 3,016 NPC survivors who had received RT alone (n = 959) or CCRT (n = 2,057) were eligible for our survivorship study. Normal controls were matched using propensity score, calculated as the probability of being a case (NPC) according to baseline variables, including age at index date (<35, 35–40, ..., 65–70, ≥70 years), sex, urbanization level (five levels), and income-related insurance payment (five levels). With a match ratio of 1:5, five corresponding normal controls were selected for each NPC case based on the closest propensity score. Thus, a total of 15,080 controls aged 25–85 years, without any history of cancers or ischemic stroke before the index date, were selected from the LHID2005. The index date of each control was assigned to be the same as that of the corresponding NPC survivor. The survival time to stroke for both groups was defined as the number of years from the index date to a new diagnosis of ischemic stroke, withdrawal from the NHI program (most owing to death, and a few owing to immigration, imprisonment, and others), or December 31, 2012, whichever came first. Comorbidities related to ischemic stroke included hypertension, diabetes, ischemic heart disease, atrial fibrillation, peripheral arterial occlusive disease, hyperlipidemia, and chronic kidney disease, and diagnoses of these comorbidities were confirmed by at least three clinical visits or at least one hospitalization during the 12 months prior to the index date.

Statistical Analysis

Demographic data and comorbidities in NPC survivors and matched controls are presented as mean with SD or frequency with percentage. Because the normal controls were matched instead of randomly selected, the comparisons between two groups were assessed using generalized estimating equations [9], which takes into account correlations within each cluster (one NPC case and five matched controls). Similarly, we used stratified Cox proportional hazards models to assess the risk of ischemic stroke between two groups by presenting crude hazard ratio (HR) and adjusted HR (aHR) with p values. In addition, the cumulative incidence rates of ischemic stroke were calculated and compared between groups by applying a competing risk model proposed by Kalbfleisch and Prentice [10] and Gray [11]. Factors related to death, defined as withdrawal from the insurance program, were assessed in 3,016 NPC survivors with ischemic stroke as a time-dependent variable. Data were managed and analyzed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All statistical tests were two-sided, and $p < .05$ was considered statistically significant.

Table 1. Characteristics of NPC survivors and matched normal controls

Characteristic	NPC survivors (n = 3,016)	Normal controls (n = 15,080)	p value
Male sex	2,165 (71.8)	10,825 (71.8)	.999
Age at index date, years	52.52 ± 11.41	52.59 ± 11.65	
25–35	138 (4.6)	690 (4.6)	1.000
35–45	582 (19.3)	2,910 (19.3)	
45–55	1,112 (36.9)	5,560 (36.9)	
55–65	720 (23.9)	3,600 (23.9)	
>65	464 (15.4)	2,320 (15.4)	
Urbanization			
1 (least urbanized)	859 (28.5)	4,279 (28.4)	.992
2	687 (22.8)	3,435 (22.8)	
3	861 (28.6)	4,305 (28.6)	
4 (most urbanized)	609 (20.2)	3,061 (20.3)	
Income-related insurance payment			.799
1 (lowest)	1,795 (59.5)	8,979 (59.5)	
2	472 (15.7)	2,354 (15.6)	
3	391 (13.0)	1,951 (12.9)	
4 (highest)	403 (13.4)	2,015 (13.4)	
Comorbidity			
Diabetes	171 (5.7)	1,463 (9.7)	<.001
Hypertension	454 (15.1)	3,232 (21.4)	<.001
Ischemic heart disease	98 (3.3)	1,031 (6.8)	<.001
Atrial fibrillation	10 (0.3)	112 (0.7)	.014
Peripheral arterial occlusive disease	4 (0.1)	63 (0.4)	.026
Hyperlipidemia	85 (2.8)	963 (6.4)	<.001
Chronic kidney disease	2 (0.1)	60 (0.4)	.012
Ischemic stroke (ICD 433.x, 434.x, 436.x, and 437.1)	115 (3.8); 880[a]	200 (1.3); 285[a]	<.001
Treatment modality			
RT alone	959 (31.8)		
CCRT	2,057 (68.2)		

Data are presented as n (%) or mean ± SD.
NPC survivors and the comparison group matched by 5-year age group, sex, urbanization level, and income-related insurance payment.
All p values were obtained from generalized estimating equations models.
[a]Incidence per 100,000 person-years.
Abbreviations: CCRT, concurrent chemoradiation therapy; ICD, International Classification of Diseases; NPC, nasopharyngeal carcinoma; RT, radiotherapy.

Results

Characteristics of Study Participants

From 2000 to 2005, a total of 3,016 eligible NPC 5-year survivors identified from the RCI and 15,080 controls selected from the LHID2005 were matched according to information on sex, age at index date, urbanization, and income-related insurance payment. The median follow-up time after the index date was 4.43 years. The baseline characteristics are listed in Table 1. Among NPC survivors, 71.8% were male and the mean age at the index date was 52.52 (±11.41) years. The percentages of NPC survivors in each urbanization level ranged from 20.2% to 28.6%, and nearly 60% of these survivors had the lowest income-related insurance payment. The matched cohort was comparable to NPC survivors with respect to sex, age, and income-related insurance payment (all $p \geq .799$). However, NPC survivors had lower proportions than matched controls of comorbidities, such as diabetes (5.7 vs. 9.7%, $p < .001$), hypertension (15.1 vs. 21.4%, $p < .001$), ischemic heart disease (3.3 vs. 6.8%, $p < .001$), atrial fibrillation (0.3 vs. 0.7%, $p = .014$), peripheral arterial occlusive disease (0.1 vs. 0.4%, $p = .026$), hyperlipidemia (2.8 vs. 6.4%, $p < .001$), and chronic kidney disease (0.1 vs. 0.4%, $p = .012$).

Risk Factors for an Ischemic Stroke Event

The overall stroke incidence was threefold higher in the NPC survivors than in the matched controls (880 vs. 285 per 100,000 person-years; Table 1), and this was also observed for cumulative incidence ($p < .001$; Fig. 1). Furthermore, it was found that those who were NPC survivors (HR = 2.93, $p < .001$) or had any one of the following comorbidities were at higher risk of developing ischemic stroke: diabetes (HR = 1.87, $p < .001$), hypertension (HR = 1.78,

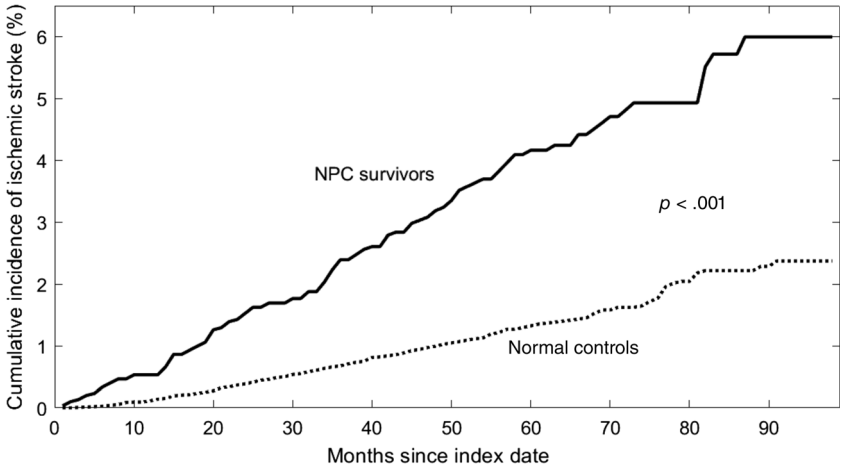

Figure 1. Cumulative incidence of ischemic stroke in survivors of NPC and normal controls. The overall stroke incidence was significantly higher in the NPC survivors than in the matched controls ($p < .001$).
Abbreviation: NPC, nasopharyngeal carcinoma.

Table 2. Crude and adjusted hazard ratios for the occurrence of ischemic stroke using a stratified Cox model with withdrawal as a competing risk

	Crude HR (95% CI)		*p* value	Adjusted HR[a] (95% CI)		*p* value
Group (controls)	1		<.001	1		<.001
NPC survivors[b]	2.93	(2.40–3.58)		3.53	(2.85–4.38)	
RT alone[c]				3.97	(2.89–5.44)	<.001
CCRT[d]				3.26	(2.43–4.38)	<.001
Comorbidity						
Diabetes	1.87	(1.40–2.50)	<.001	1.68	(1.21–2.34)	.002
Hypertension	1.78	(1.40–2.26)	<.001	1.65	(1.25–2.18)	<.001
Ischemic heart disease	1.81	(1.32–2.47)	<.001	1.54	(1.07–2.23)	.018
Atrial fibrillation	2.97	(1.52–5.81)	.001	3.38	(1.63–7.01)	<.001
Peripheral arterial occlusive disease	1.11	(0.27–4.58)	.882			
Hyperlipidemia	0.77	(0.46–1.31)	.332			
Chronic kidney disease	5.88	(2.07–16.73)	<.001	3.24	(1.22–8.59)	.016

[a]Adjusted HRs and *p* values obtained from a multiple Cox model, which included significant explanatory variables only.
[b]All NPC survivors, regardless of treatment modality.
[c]Subgroup analyses for treatment modalities (RT alone and CCRT) examined in the Cox model.
Abbreviations: CI, confidence interval; CCRT, concurrent chemoradiation therapy; HR, hazard ratio; NPC, nasopharyngeal carcinoma; RT, radiotherapy.

$p < .001$), ischemic heart disease (HR = 1.81, $p < .001$), atrial fibrillation (HR = 2.97, $p = .001$), and chronic kidney disease (HR = 5.88, $p < .001$; left panel, Table 2). The adjusted HRs also revealed that NPC survivors had at least triple the stroke risk of matched controls, after adjusting for confounders (aHR = 3.53, $p < .001$; right panel, Table 2). When treatment modalities were taken into account, both RT and CCRT subgroups were at higher risk of ischemic stroke than normal controls (aHR = 3.97 and 3.26, respectively, all $p < .001$).

Premature Stroke in NPC Survivorship

The age-specific incidence rates of stroke revealed that the risk of ischemic stroke was much higher in NPC survivors than in controls, for all age groups. Although the incidence of stroke increased with age in both cohorts, the incidence rate ratio of the NPC cohort to the control cohort decreased with age, suggesting that the younger the survivor, the higher the age-adjusted risk of stroke (Table 3). Furthermore, when basic characteristics (sex, urbanization level, income-related insurance payment) and comorbidities were treated as confounders, the onset age of stroke was found to be nearly 10 years earlier in NPC survivors than in controls (Fig. 2). For instance, NPC survivors <50 years of age had an adjusted risk of stroke similar to controls older than 55–60 years. Likewise, NPC survivors aged 50–55 years had a risk of stroke equivalent to that of controls older than 65 years. The risk among NPC survivors aged ≥60 years was even higher than that among controls aged ≥70 years. These results showed that premature stroke was a complication in NPC survivorship for all age groups, even the young patients.

Impact of Ischemic Stroke on Survival

When withdrawal from the NHI program was deemed to be owing to death, NPC survivors who developed ischemic

Table 3. Age-specific rates of stroke in NPC survivors and normal controls

	NPC survivors			Normal controls				
Age, years	Stroke, *n*	Person-years	Rate ($\times 10^{-5}$)	Stroke, *n*	Person-years	Rate ($\times 10^{-5}$)	Rate ratio[a]	95% CI of rate ratio
≤50	22	6,079.44	361.87	21	31,737.31	66.17	5.47	3.02–9.94
50–55	24	2,424.92	989.72	25	12,539.14	199.38	4.96	2.84–8.69
55–60	20	1,840.51	1,086.65	36	9,837.41	365.95	2.97	1.72–5.13
60–65	17	1,057.63	1,607.37	27	6,016.97	448.73	3.58	1.96–6.57
65–70	13	724.48	1,794.39	29	4,171.70	695.16	2.58	1.35–4.97
>70	19	936.75	2,028.30	62	5,767.086	1,075.07	1.89	1.13–3.15
Total	115	13,063.72	880.30	200	70,069.61	285.43	3.08	2.45–3.88

[a]Rate ratio of NPC cohort to control cohort.
Abbreviations: CI, confidence interval; NPC, nasopharyngeal carcinoma.

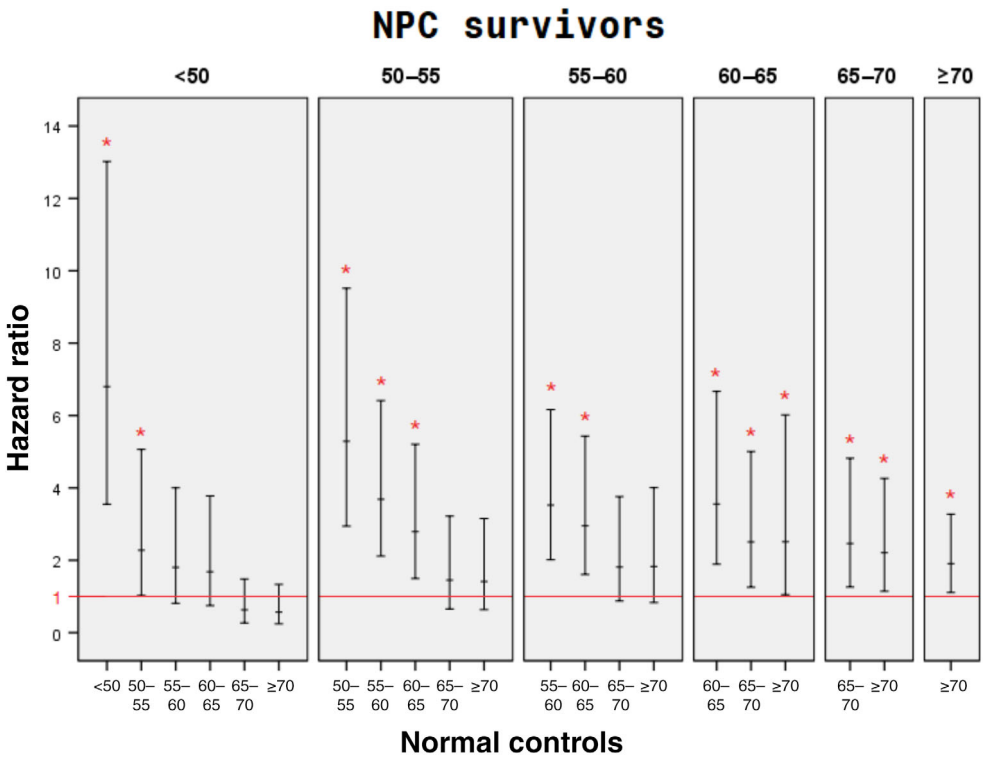

Figure 2. Adjusted hazard ratios with 95% confidence intervals: survivors of NPC versus normal controls in different age groups (*denotes $p < .05$). The onset age of stroke was found to be nearly 10 years earlier in all age groups of NPC survivors than in controls after adjusting for basic characteristics and comorbidities.
Abbreviation: NPC, nasopharyngeal carcinoma.

stroke were more likely to die than those who were free of ischemic stroke during follow-up (aHR = 1.60, $p = .012$). Furthermore, those who had received CCRT were at higher risk of death than those who received RT alone (aHR = 1.32, $p = .015$). Moreover, the risk of death was increased among participants who were male (aHR = 1.20, $p < .001$), older (age >55 years; all aHR ≥2.07, all $p < .001$), had at least one comorbidity (aHR = 1.28, $p = .038$), and had low income-related insurance payment (Table 4).

Discussion

The number of cancer survivors continues to increase as a result of earlier detection and treatment advances [12], but many survivors face distinct and serious health care issues. For example, an estimated 17% of people older than 60 years are cancer survivors in the U.S. [13]. Therefore, achieving a high quality of cancer survivorship care has become an important issue [14]. Salivation, hearing, and swallowing dysfunctions are the most common problems that affect health-related quality of life for NPC survivors. This study targeted on stroke, the most overwhelming complication. After adjusting for comorbidities, such as diabetes mellitus, hypertension, ischemic heart disease, atrial fibrillation, and chronic kidney disease, our results indicated a significantly higher risk of ischemic stroke among NPC survivors (aHR = 3.53, $p < .001$). In this study, we also highlighted the devastating impact of stroke on survival (aHR = 1.60,

Table 4. Adjusted hazard ratios for death as endpoint in nasopharyngeal carcinoma survivors (n = 3,016)

Variables	Adjusted HR	*p* value
Ischemic stroke (with)	1.60	.012
Treatment modality		
RT alone	1	
CCRT	1.32	.015
Gender (male)	1.20	<.001
Age at index date, years[a]		
<45	1	
45–55	1.20	.345
55–65	2.07	<.001
>65	4.35	<.001
Comorbidity		
0	1	
≥1	1.28	.038
Income-related insurance payment[b]		
1 (lowest)	1	
2	0.56	.004
3	0.49	<.001
4 (highest)	0.24	<.001

[a]Risk of death was significantly different among age groups <55, 55–65, and >65 years.
[b]Risk of death was significantly different in comparing between any two groups; risks could be ordered from highest to lowest: group 1 (lowest payment) > group 2 and 3 > group 4 (highest payment).
Abbreviations: CCRT, concurrent chemoradiation therapy; HR, hazard ratio; RT, radiotherapy.

p = .012). Because the NPC survivor cohort had lower proportions of comorbidities than the matched cohort, their real risk of stroke was estimated to be even higher. Therefore, survivorship care should involve a multidisciplinary approach to stroke surveillance and management of the abovementioned comorbidities.

The investigation of stroke in NPC survivors is appropriate because the radiation field is in proximity of the carotid arteries. The effect of ionizing radiation on atherosclerosis has been previously reported [15]. Radiation has a role in promoting plaque initiation and dose-related effects on plaque growth [16]. Despite the advent of *intensity-modulated radiotherapy*, the late effects of radiation resulting in vascular injury are inevitable from the viewpoint of radiation scattering. Significant stenosis of the internal and common carotid arteries was associated with age and time interval from radiotherapy [17]. In Figure 2, we compared the cumulative incidence of ischemic stroke between NPC survivors and normal controls. With longer periods of survival, the upward trend in the stroke incidence curve of survivors was more obvious than that of normal controls. This nonlinear incidence curve may be attributable to a combined effect of aging and the late vasculopathic properties of radiation exposure.

The accelerated effect of aging on blood vessels by radiation was validated by premature stroke found in NPC survivors. From our data (shown in Fig. 2), premature stroke occurred 10 years earlier among NPC survivors in all age groups, compared with the normal population. The effect was robust in patients aged <50 and 50–55 years, and this effect continued but became weaker in those aged 55–70 years. The influence of radiation on ischemic stroke became unobservable among those aged >70 years. This implies that most of the effect comes from the initiation of occlusion, for example, plaque formation. Once the patency of cerebral blood vessels is compromised because of aging, hypertension, or diabetes, the contribution of radiation to stroke risk becomes less apparent. Considering that NPC incidence peaks at a relatively young age, during the 40s to 50s, and the high likelihood of long-term remission after definitive treatment, our results suggest that the younger the survivor, the higher the age-adjusted risk of stroke, and this finding was similar to the results reported by Lee et al. [6] and Chu et al [7]. As cancer survivors are an important group with respect to providing risk assessment and prevention services, young NPC survivors should not be exempt from stroke surveillance. Moreover, age-specific preventive measures could be taken in accordance with their risk equivalents in normal individuals.

This study had the strengths of long follow-up duration, sizable and homogeneous population, and high certainty in the definitions of NPC survivors. Nevertheless, our work has some limitations. First, some potential confounding factors were not available for analysis. Smoking is an important risk factor for stroke [18], but the impact of this modifiable factor could not be evaluated in our study. In an attempt to eliminate the confounding effect of smoking, the smoking-associated comorbidities, such as hypertension, ischemic heart disease, atrial fibrillation, peripheral arterial occlusive disease, hyperlipidemia, and chronic kidney disease, were adjusted in the statistical models. Second, the details of treatment, such as volume of radiation and dosage of chemotherapy, were not provided in the NHIRD. Two thirds of patients in this study received CCRT, in which the most popular chemotherapy regimen is platinum alone or in combination with 5-fluorouracil.

Conclusion

This nationwide cohort study revealed that 5-year survivors of NPC are at increased risk for premature stroke, which adds to their burden of survival. Thus, future survivorship care plans should include stroke as a complication and its management. For example, carotid artery sonography should be performed regularly to detect the carotid artery stenosis [19], and early interventions such as antiplatelets or stent insertion could be applied, although the benefits are still undetermined [20].

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Disclosures

The authors indicated no financial relationships.

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