

ORIGINAL RESEARCH

The risk of cardiovascular disease and stroke in survivors of head and neck cancer in Korea

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Abstract

Background: Head and neck cancer (HNCA) survivors have a high risk of developing cardiovascular disease (CVD) or stroke because of sharing risk factors of disease. Therefore, we investigated the risk of CVD or stroke occurrence among HNCA survivors in Korea based on the Health Insurance Review and Assessment (HIRA) Service claims database.

Methods: We retrieved claims data of patients who were diagnosed with HNCA in 2014-2015 using ICD-10 code and followed up data until 2018. Patients with newly diagnosed with CVD or stroke after HNCA diagnosis during the follow-up period were detected. We analyzed the characteristics of patients with HNCA who were subsequently diagnosed with CVD or stroke. In addition, the risk factors of CVD or stroke occurrence were investigated using Cox proportional hazard regression analysis.

Results: Among the 8288 patients with HNCA, 477 and 404 patients were diagnosed with new-onset CVD and stroke, respectively. Patients with hypertension, diabetes mellitus (DM), and hyperlipidemia had a 3.25-fold higher risk of CVD comparing to patients without any underlying disease (95% confidence index [CI], 2.38-4.45). Patients with three underlying diseases had a 2.92-fold higher risk of stroke compared to patients without any underlying disease (95% CI 2.03-4.21).

Conclusions: HNCA survivors with hypertension, DM, and hyperlipidemia should be cautious of the risks of CVD and stroke.

KEYWORDS

cardiovascular disease, head and neck cancer, risk, stroke, survivorship

1 | INTRODUCTION

Head and neck cancer (HNCA) encompasses epithelial malignancies that develop in multiple anatomic sites, including the paranasal sinus, oral cavity, oropharynx, hypopharynx, and larynx. Histologically,

squamous cell carcinoma is the most common HNCA, and other cellular origins are rarely detected.

Recently, human papilloma virus (HPV) has been considered an important cause of oropharyngeal cancer, a subset of HNCA, and the incidence of HPV-related HNCA has been increasing. These

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HPV-related HNCA tends to occur in relatively young patients with a history of light smoking and their prognosis is relatively better, with a 5-year survival rate of 60%-90%.^{1,2} However, still the most common and important behavioral risk factors for HNCA are tobacco and alcohol consumption.³ Tobacco affects HNCA development in a dose-dependent manner and the concomitant use of tobacco and alcohol adds a strong synergistic risk.^{4,5} In addition, HNCA associated with classical risk factors tends to occur in older patients on the contrary to HPV-related HNCA. Because the incidence of HPV-related HNCA is still low with less than 20% of all HNCAs, still substantial proportion of patients are old-aged patients those have had a high exposure of smoking and alcohol drinking.^{6,7} Indeed, older age population has an

increased risk for HNCA and approximately 50% of HNCA diagnoses occur in patients over 60 years of age.⁷

Long-term exposure to smoking or alcohol can be the reason of other disease, such as other primary cancers, chronic obstructive pulmonary disease, and cerebrovascular or cardiovascular disease (CVD) which share risk factors. Because substantial patients with HNCA have had a long-term exposure to smoking and alcohol, they might suffer from CVD or stroke before or after HNCA diagnosis. In other words, even after the treatment of HNCA, HNCA survivors continue to have a high risk of developing other diseases. Sometimes, these diseases can be the cause of death after cure of cancer. Therefore, the present study investigated the risk of CVD or cerebral stroke, which

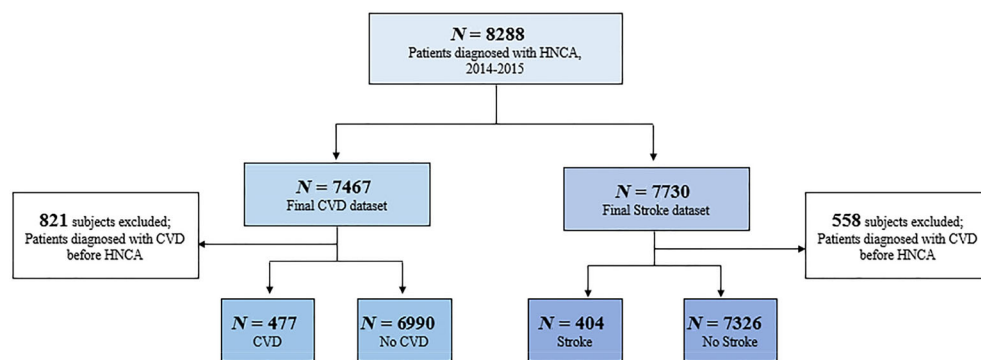


FIGURE 1 Flowchart of patient inclusion and exclusion for analysis. CVD, cardiovascular disease; HNCA, head and neck cancer

TABLE 1 Baseline patient characteristics

	Total CVD set		No CVD		CVD		P	Total stroke set		No stroke		Stroke		P
	N	%	N	%	N	%		N	%	N	%	N	%	
Total	7467	100.0	6990	93.6	477	6.4		7730	100.0	7326	94.8	404	5.2	
Primary site							.1843							.0164
Oral cavity	2092	28.0	1973	28.2	119	24.9		2163	28.0	2068	28.2	95	23.5	
Oropharynx	1358	18.2	1270	18.2	88	18.4		1382	17.9	1317	18.0	65	16.1	
Hypopharynx	866	11.6	812	11.6	54	11.3		881	11.4	837	11.4	44	10.9	
Larynx	2351	31.5	2179	31.2	172	36.1		2485	32.1	2324	31.7	161	39.9	
Others	800	10.7	756	10.8	44	9.2		819	10.6	780	10.6	39	9.7	
Sex							.0169							.0057
Male	5994	80.3	5591	93.3	403	6.7		6209	80.3	5863	80.0	346	85.6	
Female	1473	19.7	1399	95.0	74	5.0		1521	19.7	1463	20.0	58	14.4	
Age (years)							<.0001							<.0001
<70	5072	67.9	4797	68.6	275	57.7		5231	67.7	5004	68.3	227	56.2	
≥70	2395	32.1	2193	31.4	202	42.3		2499	32.3	2322	31.7	177	43.8	
Comorbidities														
Hypertension	2582	34.6	2347	33.6	235	49.3	<.0001	2759	35.7	2559	34.9	200	49.5	<.0001
Diabetes mellitus	1573	21.1	1438	20.6	135	28.3	<.0001	1667	21.6	1525	20.8	142	35.1	<.0001
Hyperlipidemia	1548	20.7	1403	20.1	145	30.4	<.0001	1685	21.8	1568	21.4	117	29.0	<.0003
CCI							.0101							.0744
0-2	6148	82.3	5776	82.6	372	78.0		6341	82.0	6023	82.2	318	78.7	
≥3	1319	17.7	1214	17.4	105	22.0		1389	18.0	1303	17.8	86	21.3	

Abbreviations: CCI, Charlson comorbidity index; CVD, cardiovascular disease.

can be regarded as life-threatening disease in patients with HNCA in Korea, especially after diagnosis with HNCA. We also analyzed the specific characteristics of this population and the risk factors to find predictable or preventable way.

2 | MATERIALS AND METHODS

2.1 | Data source

The data for this study were retrieved from the Database of the Korea Health Insurance Review and Assessment (HIRA) Claims for 2013-2018 (Study No. M20200409451). In South Korea, every resident is obligated to sign up in the National Health Insurance (KNHI) program and around 3% of the population is under the Medical Aid Program. According to the health insurance policies, healthcare providers should allow all the review of medical costs provided by the HIRA and the HIRA generated a big data platform using these medical claim data. Thus, the HIRA database contains information on all claims that were covered by KNHI for almost all Koreans, except for treatments or procedures that are not covered by national health insurance such as esthetic surgery.

HIRA has provided data to many Korean researchers to perform studies, for example, cost-effectiveness analysis, cohort studies, or investigations about specific disease characteristics in Korea. After IRB and HIRA approval, only approved person can access provided data for research. In addition, all claim data provided by HIRA should conceal individuals' identities according to the Act on the Protection of Personal Information Maintained by Public Agencies. Therefore, the claims database that we received consisted of an information on patient demographics, institution, main diagnosis and a list of prescribed drugs or procedures incorporating with unidentifiable code representing each individual person. This study was approved by institutional review board (IRB) of the Korea University Guro Hospital (IRB No. 2020GR0597).

2.2 | Study population

The diagnosis and procedure codes from the tenth version of the International Classification of Disease (ICD-10) were used to identify patients with HNCA. The HNCA population was defined as patients whose records were newly assigned the ICD-10 codes for HNCA (ICD-10: C01, C02, C03, C04, C05, C06, C09, C10, C12, C13, C14, C30, C31, C32) for 2 years between January 1, 2014, and December 31, 2015. Patients with salivary gland (ICD-10: C07, C08) or nasopharyngeal (ICD-10: C11) cancer were excluded from the evaluation of patients with head and neck squamous cell carcinoma. For the exact definition of the newly diagnosed patients during this time, we applied a 1-year washout window period before detecting the ICD-10 code for HNCA. Therefore, individuals assigned an ICD-10 code for HNCA in 2013 were not regarded as new patients who were diagnosed during 2014-2015 and were excluded from the analysis. In addition, we

applied an additional claim code, V193, which is specially used for all cancer patients in Korea to support medical expenses for cancer diagnosis and treatment. Finally, individuals who visited the hospital for cancer treatment more than twice were included in this analysis for more accurate extraction from the database.

2.3 | Outcome

This study investigates the incidence and risk factors of CVD and cerebral stroke after the diagnosis of HNCA. Additionally, we analyzed the characteristics of patients with HNCA who were subsequently diagnosed with CVD or stroke. The claim codes of the population were subsequently followed-up till December 31, 2018. During this follow-up period, patients with ICD-10 codes of CVD (ICD-10: I20, I21, I22, I23, I24, I25) who visited the hospital for the treatment of CVD at least once were regarded as having CVD. For the detection of newly onset CVD, patients assigned the ICD-10 codes for CVD before the diagnosis of HNCA were excluded. For the detection of new-onset stroke, we used the same method. The ICD-10 codes for stroke included I60, I61, I62, I63, I64, I65, I66, I67, I68, and I69, and only patients who visited the hospital for the treatment of stroke and were not previously assigned codes for stroke before the diagnosis of

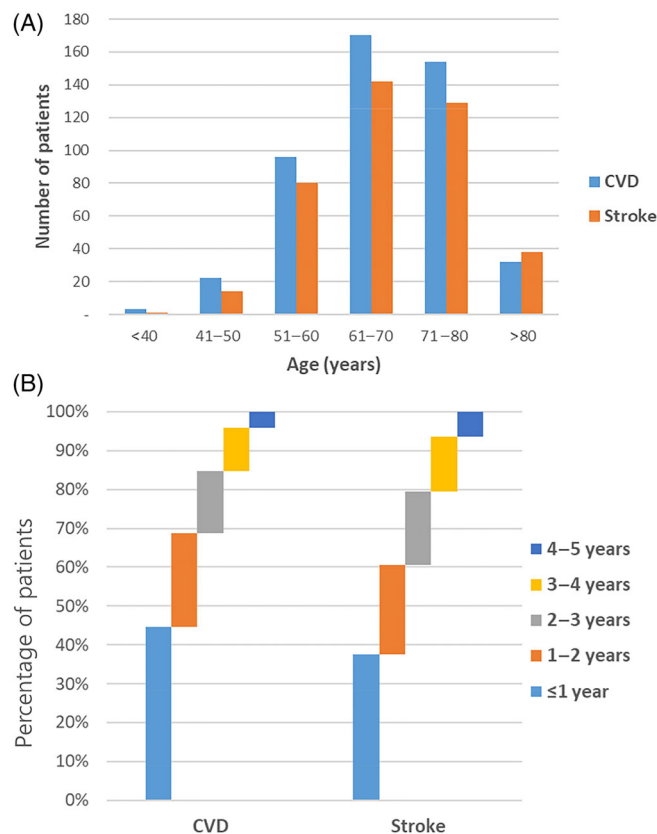


FIGURE 2 (A) Age distribution of patients diagnosed with CVD or stroke. (B) Percentages of patients diagnosed with CVD or stroke after head and neck cancer and the timing of diagnosis. CVD, cardiovascular disease

TABLE 2 Risk factors for the occurrence of CVD or stroke after head and neck cancer diagnosis

	CVD (N = 477)						Stroke (N = 404)					
	Model 1			Model 2			Model 1			Model 2		
	N	aHR	95% CI	N	aHR	95% CI	N	aHR	95% CI	N	aHR	95% CI
Sex												
Female	74	Ref.		74	Ref.		58	Ref.		58	Ref.	
Male	403	1.375	1.058–1.787	403	1.368	1.053–1.777	346	1.455	1.084–1.953	346	1.464	1.091–1.966
Age (years)												
<70	275	Ref.		275	Ref.		227	Ref.		227	Ref.	
≥70	202	1.470	1.215–1.778	202	1.483	1.228–1.792	177	1.546	1.259–1.898	177	1.538	1.255–1.884
Comorbidities												
Hypertension	235	1.578	1.300–1.916				200	1.424	1.154–1.758			
Diabetes mellitus	135	1.156	0.938–1.426				142	1.652	1.329–2.054			
Hyperlipidemia	145	1.425	1.162–1.748				117	1.178	0.941–1.474			
Number of comorbidities												
0				177	Ref.					126	Ref.	
1				138	1.478	1.179–1.852				136	1.963	1.536–2.509
2				109	1.633	1.281–2.081				103	2.050	1.575–2.670
3				53	3.254	2.379–4.451				39	2.922	2.028–4.212
CCI												
0–2	372	Ref.		372	Ref.		318	Ref.		318	Ref.	
≥3	105	1.271	1.019–1.587	105	1.247	0.999–1.556	86	1.176	0.941–1.500	86	1.173	0.920–1.497
Primary site												
Oropharynx	88	Ref.		88	Ref.		65	Ref.		65	Ref.	
Larynx	172	0.964	0.739–1.257	172	0.958	0.734–1.250	161	1.152	0.856–1.550	161	1.156	0.859–1.555
Hypopharynx	54	0.918	0.652–1.292	54	0.921	0.654–1.298	44	1.039	0.707–1.528	44	1.033	0.703–1.520
Oral cavity	119	0.907	0.680–1.209	119	0.910	0.683–1.213	95	1.000	0.721–1.387	95	1.008	0.727–1.398
Others	44	0.917	0.635–1.324	44	0.908	0.629–1.311	39	1.120	0.749–1.675	39	1.131	0.757–1.692

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; CVD, cardiovascular disease.

HNCA were included. The Charlson comorbidity index (CCI) was calculated according to the guidelines for estimates of comorbidities provided by HIRA.⁸

2.4 | Statistical analysis

We compared the distributions of demographic factors between the CVD and no-CVD groups and the stroke and no-stroke groups using chi-square and t-tests for categorical and continuous variables, respectively. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) describing the risks of CVD or stroke were calculated using Cox proportional hazard regression models. All statistical analyses were performed using R3.0.2.

3 | RESULTS

A total of 8288 patients were newly diagnosed with HNCA between 2014 and 2015. After excluding 821 patients with a history of CVD, 7467 patients were followed-up until 2018 for new-onset CVD after cancer diagnosis. In addition, 7730 patients were followed-up until 2018 for new-onset stroke after cancer diagnosis, excluding 558 patients with a history of CVD before cancer diagnosis (Figure 1). In the CVD dataset, the median follow-up duration was 3.8 years (range, 0.005-5.0 years). The baseline characteristics of the CVD and stroke datasets are described in Table 1. A total of 477 patients (6.4%) were diagnosed with new-onset CVD after the cancer diagnosis through 2018. The common primary sites were the larynx, oral cavity, and oropharynx. As shown in Figure 2A, patients in their 60s and 70s accounted for the largest portion of CVD or stroke cases. Among patients who experienced CVD, 42.3% were over 70 years of age, a higher proportion than that in the non-CVD group. Compared to the non-CVD group, the CVD group had a higher proportion of comorbidities including hypertension (HTN), diabetes mellitus (DM), and hyperlipidemia, as well as a higher proportion with CCI scores >3. In the stroke dataset, the median follow-up duration was 3.8 years (range, 0.016-5.0 years). A total of 404 patients (5.2%) were diagnosed with new-onset stroke after cancer diagnosis through 2018. The common primary sites were the same as in the CVD dataset. Among the patients who experienced a stroke, 43.8% were over 70 years of age, a proportion higher than that in the nonstroke group. Similar to the CVD dataset, the stroke group had a higher proportion of comorbidities compared to the nonstroke group.

We also analyzed the timing of CVD or stroke diagnosis after the diagnosis of HNCA. The occurrence of CVD or stroke was the highest within 2 years after the cancer diagnosis. Approximately 68.9% of CVD and 60.6% of stroke events occurred within 2 years after the cancer diagnosis (Figure 2B).

Analysis of the risk factors for the occurrence of CVD or stroke after HNCA diagnosis (Table 2) showed that male sex and age ≥ 70 years were the risk factors for CVD (HR 1.38, 95% CI 1.06-1.79, HR 1.47, 95% CI 1.22-1.78 in Model 1, HR 1.37, 95% CI 1.05-1.78,

HR 1.48, 95% CI 1.23-1.79 in Model 2). In the CVD data set, the presence of HTN and hyperlipidemia had 1.58-fold and 1.42-fold times higher risks of CVD, respectively. Because a substantial number of patients have these comorbidities, we analyzed the risk according to the number of underlying comorbidities including HTN, DM, and hyperlipidemia. Compared to patients without any underlying disease, patients with three underlying diseases had a 3.25-fold higher risk of CVD (95% CI 2.38-4.45). In the stroke dataset, 404 patients had new-onset stroke after the cancer diagnosis. Male patients and patients aged ≥ 70 years had a 1.5-fold higher risk for stroke (HR 1.46, 95% CI 1.08-1.95, HR 1.55, 95% CI 1.29-1.90 in Model1, HR 1.46, 95% CI 1.09-1.97, HR 1.54, 95% CI 1.26-1.88 in Model 2). The presence of HTN and DM showed 1.42-fold and 1.65-fold higher risks of stroke, respectively. Patients with three underlying diseases had a 2.92-fold higher risk of stroke compared to patients without underlying diseases (95% CI 2.03-4.21). A higher CCI score (≥ 3) was not a significant risk factor for the occurrence of CVD or stroke and no special primary site showed a higher risk for CVD or stroke occurrence.

4 | DISCUSSION

Our analysis of this nationwide, large cohort study identified patients who developed CVD or stroke and analyzed the risk factors for CVD or stroke after a diagnosis of HNCA during a median follow-up of 3.8 years. Male patients, elderly patients, or patients with comorbidities such as HTN, DM, or hyperlipidemia showed higher risks of CVD or stroke. Moreover, patients with three comorbidities; namely, HTN, DM, and hyperlipidemia, had an almost 3-fold higher risk of CVD or stroke compared to patients without these underlying comorbidities.

Several studies have reported increased risks of CVD or stroke after the diagnosis of HNCA.⁹⁻¹³ Kwon et al.¹² reported a 1.376-fold higher incidence of myocardial infarction (MI) and 1.483-fold higher incidence of stroke in the Korean population compared to the control group. In the Taiwanese population, the risk of stroke incidence was 1.44-fold higher than that in the control cohort.¹³ Moreover, the risk of CVD or stroke is important as the noncancer mortality that persists over the lifetime is increasing in patients with HNCA, while cancer-specific mortality is decreasing.¹⁴ Because coronary artery and cerebrovascular diseases are the most common causes of non-cancer mortality, it is important to identify the risk factors for the occurrence of CVD or stroke in the HNCA population to predict and prevent these events.^{15,16}

In this report, CVD and stroke occurred in 6.4% and 5.2% of the HNCA population, respectively, rates similar to those reported previously.^{12,13} Likewise, the risk factors associated with increased risk were male sex, older age, and related comorbidities, such as HTN or DM.¹¹⁻¹³ Among these related comorbidities, HTN, DM, and hyperlipidemia are also traditional risk factors for CVD or stroke.¹⁷⁻¹⁹ As these related comorbidities are included in metabolic syndrome, they tend to coincide. Thus, it is important to analyze the impact of multiple comorbidities on the risks of CVD or stroke, rather analyze the risk of

each comorbidity. However, no reports have assessed the risk of the coincidence of multiple traditional risk factors on the occurrence of CVD or stroke in patients with HNCA. In our analysis, 11.1% and 9.6% of patients in the CVD and stroke datasets, respectively, showed these three comorbidities. Therefore, approximately 10% of the subpopulation with these three comorbidities, both patients and their physicians should be aware of the occurrence of CVD or stroke after a cancer diagnosis. In many cases, the management of chronic underlying diseases tends to be neglected after cancer diagnosis as cancer treatment is the primary concern. However, HNCA is a curable disease in a substantial proportion of patients and cancer-specific mortality is decreasing.¹⁴ Therefore, HNCA survivorship requires the continuous management of chronic underlying comorbidities by physicians and patients. Moreover, this attention should be supervised, especially within the early years after a cancer diagnosis. Our analysis revealed that approximately 60% of the cases of CVD or stroke occurred within 2 years after a cancer diagnosis. Moreover, Chu et al. reported an increased risk of stroke within 2 years after a cancer diagnosis in Taiwan, similar to our findings. In their report, the risk decreased after 2-4 years of follow-up and increased again with more prolonged follow-up.¹³ Because a considerable proportion of patients with HNCA receive multimodal treatments including surgery, radiotherapy, or chemoradiotherapy, these treatments might trigger thrombogenic conditions and, consequently, CVD or stroke. Lee et al. and Arthurs et al. identified radiotherapy as a risk factor for CVD or stroke.^{10,11} Kwon et al. also reported the highest risk in patients who received chemotherapy alone,¹² those assumed to have metastatic disease, those unable to receive curative treatment, such as surgery or radiotherapy, or those who had a high risk of thrombogenic events, thus having the highest risk of MI or stroke.²⁰

As the survival of patients with HNCA is increasing, the multidirectional support of patients with cancer has become an essential part of survivorship care. Although the American Cancer Society HNCA survivorship care guideline has been endorsed by the American Society of Clinical Oncology, the guideline focused on the detection of recurrence and management of potential late and long-term complications and did not recommend the continuous management of underlying diseases, including chronic comorbidities.^{21,22} The results of the present analysis and other related studies indicate that the HNCA survivorship guidelines should include the importance of management and proper control of HTN, DM, or hyperlipidemia to reduce the risk of life-threatening diseases, such as CVD or stroke, to optimize survivorship care.

This study has several limitations. First, we could not obtain data on important risk factors for CVD or stroke, including smoking, alcohol consumption, and body mass index, and detailed clinical data, such as performance status, histologic diagnosis, cancer stage, and treatment modalities, as the HIRA data did not provide this information. Second, based on the Personal Information Protection Act of the Korean government, we could not perform survival analysis because the HIRA data did not provide the cause of death or the exact survival status of the included patients. Third, the long-term follow-up was not performed. However, almost all patients newly diagnosed with HNCA in Korea between 2014 and 2015 were

included and followed-up for 5 years; therefore, the results of this analysis should represent the characteristics of the Korean population with HNCA and reflect the status of recent patients. Further investigation, including a longer follow-up and analysis with more detailed data, combined with the clinical information of patients, would be valuable.

In conclusion, male and older patients showed increased risks of CVD or stroke after diagnosis of HNCA. Patients with HNCA and multiple comorbidities, including HTN, DM, and hyperlipidemia, had considerably a high increased risk of CVD or stroke after HNCA. Physicians and patients should pay particular attention to the occurrence of these life-threatening diseases as well as managing the risk factors in this subpopulation after a diagnosis of HNCA.

CONFLICT OF INTEREST

None of the authors have anything to disclose.

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