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Original Article

Association of smoking status, duration and amount with the risk of head and neck cancer subtypes: a national population-based study

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Abstract: Smoking is positively associated with multiple cancer types including head and neck cancer (HNC). We sought to confirm the effect of smoking in HNC and subtypes through big data analysis. All data used in this study originated from the Korean National Health Insurance Service database. We analyzed subjects who had undergone health check-ups in 2009 with follow-up until 2018 (n=10,585,852). We collected data on smoking and other variables that could affect the risk of HNC. The overall incidence of HNC was highest in current smokers (HR: 1.822, 95% CI: 1.729-1.920), followed by ex-smokers (HR: 1.242, 95% CI: 1.172-1.317). Laryngeal cancer, hypopharynx cancer, oral cancer, oropharyngeal cancer, and salivary gland cancer showed increasing incidence rates from ex-smokers to current smokers. Smoking duration and amount showed a dose-dependent relationship with the occurrence of HNC. However, the incidence of HNC did not increase significantly when smoking duration was less than 10 years, or when the smoking amount was less than 10 pack-years in ex-smokers. Smoking is associated with the risk of HNC. Smoking cessation before 10 years or 10 pack-years can prevent the development of HNC.

Keywords: Head and neck neoplasms, smoking, epidemiology, Republic of Korea

Introduction

Head and neck cancer (HNC) is the sixth most common form of cancer worldwide [1]. About 550,000 people are diagnosed with HNC and about 380,000 people die from it every year [2]. Tobacco products cause several types of cancers such as pulmonary, esophageal, gastric, bladder, and pancreatic cancer as well as HNC. Specifically, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx cancer are known to have strong association with smoking [3, 4]. Although the incidence of HNC due to human papilloma virus (HPV) is increasing, a 2013 analysis of over 100,000 subjects showed that 66% of HNC diagnoses were tobacco- and alcohol-related [5, 6]. Thus, despite the increase in virus-related cancer, tobacco still remains a leading cause of HNC.

The relationship between HNC and smoking and the role of smoking in the development of HNC are well known from many studies. However, given the relative rarity of HNC compared to other cancers, especially when divided by anatomical subsite, previous studies were often not large in scale. Technological innovations combined with automation have created huge amounts of available data, also known as “big data” [7]. Recently, big data has been used in identifying risk factors for diseases to support the clinical decision-making process. Due to the difficulty of selecting optimal treatment modalities and the need for personalized therapy due to different biologic behavior in cancers, big data is a popular tool in oncology research and in HNC specifically [8, 9].

The Korean National Health Insurance Service (KNHIS) is the public medical insurance system

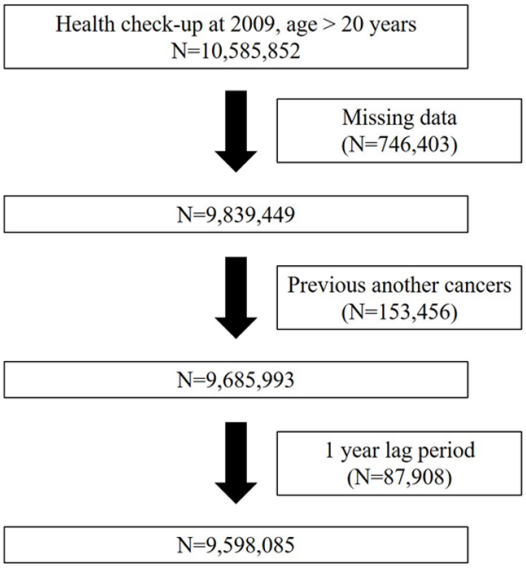

Figure 1. Flow chart of data enrollment.

administered by the Ministry for Health, Welfare and Family Affairs [10]. The National Health Insurance Corporation is a compulsory social insurance system, and about 97% of the total population is enrolled. The remaining 3% of the population are covered by a Medical Aid program. The KNHIS database contains patient demographics and records on diagnosis, interventions, and prescriptions. Therefore, the KNHIS data represent the entire Korean population without selection bias and are used in many epidemiological studies.

The aim of this study was to re-evaluate the effect of smoking in HNC and its subtypes, and to compare the effects of current and previous smoking, smoking amount and period using large-scale data.

Materials and methods

Study population and patient selection

All data used in this study came from the KNHIS database. We selected subjects who were >20 years and who had undergone a health check-up in 2009 (n=10,585,852). We monitored subjects until December 31, 2018. We excluded individuals with missing data (n=746,403) and those with a history of another cancer before health check-up (n=153,456). We also applied a 1-year lag period to minimize detection bias (n=87,908). Finally, 9,598,085 subjects were included in this study from baseline to the date of diagnosis of HNC (**Figure 1**). Participants were defined as having HNC if they had admission records for HNC in their KNHIS data from 2010 to 2018. Diagnoses were confirmed using the International Classification of Disease, Tenth Revision, Clinical Modification codes. HNC was defined according to subsite. We included oral cavity (codes C02, C03, C04, C05, and C06), oropharynx (codes C01, C051, C099, and C103), hypopharynx (codes C12 and C13), larynx (codes C32.0), nasopharynx (code C11), sinonasal cavity (code C10) and salivary gland (codes C07 and C08) cancers. Written informed consent was provided by all participants. The research protocol was approved by the Institutional Review Board of the Catholic University of Korea. Methods were performed in accordance with the relevant guidelines and regulations.

Classification of smoking status, duration and amount

We categorized subject smoking status into never smokers, ex-smokers, or current smokers. The period of smoking was classified into less than 10 years, from 10 to 20 years, and more than 20 years. The amount of smoking was expressed as pack-years (PYs), which was calculated by multiplying the smoking period by the number of packs smoked per day.

Statistical analysis

Variables were compared using the χ^2 test and one-way analysis of variance. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between smoking and the risk of HNC. Model 1 was adjusted for age, sex, income, BMI, alcohol consumption, regular exercise, diabetes, and hypertension. In addition to the variables in Model 1, adjustment was made in model 2 for hyperlipidemia, chronic kidney disease, HDL level, LDL level, and triglyceride level. All variables that could affect the incidence of HNC were adjusted. Statistical analyses were performed using SAS ver. 9.4 (SAS Institute, Cary, NC, USA). A *P*-value <0.05 was considered significant.

Table 1. General characteristics of the participants according to smoking status

Parameter	Non-smoker (N=5772362)	Ex-smoker (N=1325452)	Current smoker (N=2500271)	*P* value
Age (group)				<.0001
<40	1560740 (27.04%)	339396 (25.61%)	1130062 (45.2%)	
40-64	3314168 (57.41%)	815479 (61.52%)	1213421(48.53%)	
≥65	897454 (15.55%)	170577 (12.87%)	156788 (6.27%)	
Age (years)	48.47±14.52	48.74±12.9	42.7±12.39	<.0001
Sex				<.0001
Male	1612028 (27.93%)	1256220 (94.78%)	2352553 (94.09%)	
Female	4160334 (72.07%)	69232 (5.22%)	147718 (5.91%)	
Alcohol				<.0001
Non	3971909 (68.81%)	387874 (29.26%)	579528 (23.18%)	
Mild	1659414 (28.75%)	759507 (57.3%)	1473652 (58.94%)	
Heavy	141039 (2.44%)	178071 (13.43%)	447091 (17.88%)	
Regular exercise	969922 (16.8%)	332694 (25.1%)	405796 (16.23%)	<.0001
Low income	1284888 (22.26%)	181487 (13.69%)	411541 (16.46%)	<.0001
Body mass index (kg/m^2)				<.0001
<18.5	254354 (4.41%)	22405 (1.69%)	80711 (3.23%)	
<23	2427070 (42.05%)	397607 (30%)	925389 (37.01%)	
<25	1359999 (23.56%)	377572 (28.49%)	621391 (24.85%)	
<30	1533879 (26.575)	483365 (36.47%)	771930 (30.87%)	
≥30	197060 (3.41%)	44503 (3.36%)	100850 (4.03%)	
Body mass index (kg/m^2)	23.47±3.42	24.34±2.92	23.9±3.75	<.0001
Diabetes mellitus	466341 (8.08%)	147086 (11.1%)	217212 (8.69%)	<.0001
Hypertension	1500895 (26%)	419576 (31.66%)	546373 (21.85%)	<.0001
Hyperlipidemia	1085385 (18.8%)	264361 (19.94%)	386620 (15.46%)	<.0001
Chronic kidney disease	436440 (7.56%)	98814 (7.46%)	123296 (4.93%)	<.0001
Height (cm)	159.98±8.55	169.09±6.66	169.96±7.03	<.0001
Weight (kg)	60.21±10.55	69.73±10.2	69.23±11.43	<.0001
Waist circumference (cm)	78.26±9.55	84.05±8.28	82.66±8.71	<.0001
Systolic blood pressure (mmHg)	121.33±15.53	125.15±14.3	123.52±14.09	<.0001
Diastolic blood pressure (mmHg)	75.35±10.13	78.27±9.81	77.5±9.8	<.0001
Glucose level (mM)	96.14±22.27	100.32±25.1	98.13±26.39	<.0001
HDL level (mM)	58.37±34.65	54.03±29.91	53.46±29.21	<.0001
Cholesterol level (mM)	195.27±41.66	196.48±40.93	194.91±41.29	<.0001
LDL level (mM)	122.08±206.17	119.97±191.54	116.71±196.97	<.0001
Triglyceride level (mM)	101.48 (101.44-101.53)	126.15 (126.02-126.27)	135.12 (135.02-135.22)	<.0001

Results

General characteristics

The general characteristics of the participants according to smoking status are presented in **Table 1**. A total of 9,598,085 participants were eligible for this study from 2009 to 2019. Among them, 10,732 participants were newly diagnosed with HNC: 2,972 with laryngeal cancer, 2,225 with oral cavity cancer, 1,814 with oropharyngeal cancer, 929 with hypopharyngeal cancer, 1,101 with nasopharyngeal cancer, 539 with sinus cancer, and 1,273 with salivary gland cancer. There were 2,500,271 (26.0%) current smokers, 1,325,452 (13.8%) ex-smokers, and 5,772,362 (60.2%) never smokers. Among current smokers, 94.1% were male; among ex-smokers, 94.8% were male; and among never smokers, 72.1% were female, showing an overwhelmingly male smoking history. Comparing drinking and smoking status, 17.8% of current smokers and 13.4% of ex-smokers were heavy drinkers, whereas only 2.4% of non-smokers were heavy drinkers, and 68.8% of never smokers were non-drinkers.

Table 2. Hazard ratios of head and neck cancer and its subtypes according smoking status

subsites	Smoking status	N	Event	Incidence Rate	Model 1	*P* value	Model 2	*P* value
Head and neck cancer								
	Never smoker	5772362	4273	0.08969	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	1325452	2239	0.2061	1.245 (1.174, 1.319)		1.242 (1.172, 1.317)	
	Current smoker	2500271	4220	0.20626	1.832 (1.739, 1.930)		1.822 (1.729, 1.92)	
Larynx								
	Never smoker	5772362	682	0.01431	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	1325452	719	0.06616	1.669 (1.494, 1.866)		1.658 (1.483, 1.853)	
	Current smoker	2500271	1571	0.07676	3.294 (2.980, 3.641)		3.256 (2.945, 3.599)	
Sinonasal cavity								
	Never smoker	5772362	280	0.00588	1 (Ref.)	0.0755	1 (Ref.)	0.0766
	Ex-smoker	1325452	94	0.00865	0.981 (0.748, 1.286)		0.982 (0.749, 1.288)	
	Current smoker	2500271	165	0.00806	1.263 (0.993, 1.606)		1.264 (0.993, 1.610)	
Hypopharynx								
	Never smoker	5772362	271	0.00569	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	1325452	193	0.01776	1.150 (0.946, 1.398)		1.15 (0.946, 1.398)	
	Current smoker	2500271	465	0.02272	2.252 (1.903, 2.664)		2.229 (1.883, 2.638)	
Oropharynx								
	Never smoker	5772362	685	0.01438	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	1325452	418	0.03846	1.182 (1.033, 1.353)		1.178 (1.030, 1.348)	
	Current smoker	2500271	711	0.03473	1.564 (1.383, 1.769)		1.555 (1.374, 1.759)	
Oral cavity								
	Never smoker	5772362	1172	0.0246	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	1325452	383	0.03524	1.085 (0.947, 1.243)		1.081 (0.944, 1.239)	
	Current smoker	2500271	670	0.03273	1.415 (1.254, 1.597)		1.399 (1.239, 1.580)	
Nasopharynx								
	Never smoker	5772362	492	0.01033	1 (Ref.)	0.0276*	1 (Ref.)	0.0269*
	Ex-smoker	1325452	237	0.0218	1.175 (0.984, 1.404)		1.177 (0.985, 1.405)	
	Current smoker	2500271	372	0.01817	1.245 (1.058, 1.466)		1.247 (1.059, 1.469)	
Salivary gland								
	Never smoker	5772362	733	0.01538	1 (Ref.)	0.0537	1 (Ref.)	0.0485
	Ex-smoker	1325452	220	0.02024	1.213 (1.011, 1.456)		1.214 (1.011, 1.457)	
	Current smoker	2500271	320	0.01563	1.201 (1.015, 1.421)		1.208 (1.020, 1.431)	

Incidence rate per 1,000 person-years. Model 1: Age, sex, income, BMI, alcohol consumption, regular exercise, diabetes, and hypertension. Model 2: Age, sex, income, BMI, waist circumference, alcohol consumption, regular exercise, diabetes, hypertension, hyperlipidemia, chronic kidney disease, HDL level, LDL level, and triglyceride level. *Significant at $p<0.05$.

Relationship between smoking status and HNC

The incidence of HNC according to smoking status is shown in **Table 2**. The overall incidence of HNC was highest in current smokers (HR: 1.822, 95% CI: 1.729-1.920), followed by ex-smokers (HR: 1.242, 95% CI: 1.172-1.317). Analysis by subtype showed similar results, with increasing incidence rates from ex-smokers to current smokers. This trend was very strong in laryngeal cancer and hypopharynx cancer, and was clearly shown in oropharynx cancer and oral cavity cancer. However, this trend was not statistically significant in sinonasal cancer or nasopharynx cancer.

Relationship between smoking duration and HNC

The incidence of HNC according to smoking duration is shown in **Table 3**. The overall incidence of HNC increased in proportion to smoking duration in both ex-smokers and current smokers. However, in both groups, the HR did not increase when the duration was less than 10 years (HR: 0.873, 95% CI: 0.758-1.006 for ex-smokers; HR: 0.932, 95% CI: 0.785-1.107 for current smokers).

All subtypes except sinonasal cancer showed a similar trend to HNC overall. HRs increased in proportion to duration, but did not increase

Table 3. Hazard ratios of head and neck cancer and its subtypes according to smoking duration

subsites	Smoking status	Year	N	Event	Incidence Rate	Model 1	*P* value	Model 2	*P* value
Head and neck cancer									
	Never smoker		5772362	4273	0.08969	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	313103	210	0.08103	0.872 (0.757, 1.004)		0.873 (0.758, 1.006)	
		<20	471205	540	0.1387	1.126 (1.024, 1.237)		1.125 (1.024, 1.237)	
		≥20	541144	1489	0.34005	1.388 (1.300, 1.483)		1.384 (1.296, 1.479)	
	Current smoker	<10	361298	142	0.0475	0.931 (0.785, 1.106)		0.932 (0.785, 1.107)	
		<20	937530	503	0.06488	1.071 (0.968, 1.185)		1.069 (0.966, 1.182)	
		≥20	1201443	3575	0.36788	2.061 (1.954, 2.175)		2.050 (1.943, 2.163)	
Larynx									
	Never smoker		5772362	682	0.01431	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	313103	42	0.0162	0.878 (0.641, 1.203)		0.881 (0.643, 1.206)	
		<20	471205	120	0.03081	1.193 (0.978, 1.455)		1.191 (0.976, 1.453)	
		≥20	541144	557	0.12713	1.951 (1.733, 2.196)		1.933 (1.717, 2.176)	
	Current smoker	<10	361298	32	0.0107	1.449 (1.101, 2.078)		1.451 (1.012, 2.082)	
		<20	937530	105	0.01354	1.561 (1.253, 1.945)		1.556 (1.249, 1.939)	
		≥20	1201443	1434	0.14747	3.532 (3.194, 3.906)		3.492 (3.157, 3.863)	
Sinonasal cavity									
	Never smoker		5772362	280	0.005876	1 (Ref.)	0.0593	1 (Ref.)	0.0641
	Ex-smoker	<10	313103	13	0.005015	0.949 (0.535, 1.682)		0.954 (0.538, 1.692)	
		<20	471205	23	0.005905	0.861 (0.549, 1.349)		0.865 (0.552, 1.356)	
		≥20	541144	58	0.013232	1.054 (0.768, 1.447)		1.052 (0.766, 1.445)	
	Current smoker	<10	361298	8	0.002676	0.830 (0.402, 1.711)		0.831 (0.403, 1.714)	
		<20	937530	26	0.003353	0.879 (0.565, 1.368)		0.885 (0.568, 1.378)	
		≥20	1201443	131	0.013466	1.409 (1.094, 1.814)		1.409 (1.093, 1.816)	
Hypopharynx									
	Never smoker		5772362	271	0.005687	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	313103	8	0.003086	0.441 (0.217, 0.894)		0.444 (0.219, 0.901)	
		<20	471205	31	0.007959	0.826 (0.565, 1.206)		0.831 (0.568, 1.213)	
		≥20	541144	154	0.035136	1.356 (1.102, 1.670)		1.354 (1.099, 1.667)	
	Current smoker	<10	361298	6	0.002007	0.680 (0.3, 1.542)		0.681 (0.3, 1.542)	
		<20	937530	13	0.001677	0.5 (0.282, 0.887)		0.499 (0.281, 0.886)	
		≥20	1201443	446	0.045849	2.471 (2.089, 2.924)		2.447 (2.067, 2.897)	
Oropharynx									
	Never smoker		5772362	685	0.014375	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	313103	38	0.01466	0.783 (0.562, 1.092)		0.784 (0.562, 1.093)	
		<20	471205	121	0.031068	1.248 (1.019, 1.530)		1.247 (1.017, 1.528)	
		≥20	541144	259	0.059098	1.247 (1.067, 1.456)		1.241 (1.062, 1.449)	
	Current smoker	<10	361298	27	0.009031	0.861 (0.580, 1.278)		0.86 (0.58, 1.277)	
		<20	937530	93	0.011994	0.949 (0.749, 1.201)		0.946 (0.747, 1.198)	
		≥20	1201443	591	0.06076	1.757 (1.548, 1.993)		1.748 (1.539, 1.984)	
Oral cavity									
	Never smoker		5772362	1172	0.024596	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	313103	47	0.018133	0.916 (0.678, 1.236)		0.918 (0.680, 1.239)	
		<20	471205	110	0.028244	1.121 (0.909, 1.382)		1.118 (0.907, 1.379)	
		≥20	541144	226	0.051565	1.124 (0.956, 1.320)		1.117 (0.951, 1.313)	
	Current smoker	<10	361298	28	0.009366	0.785 (0.535, 1.153)		0.784 (0.534, 1.151)	
		<20	937530	126	0.016251	1.181 (0.961, 1.451)		1.171 (0.953, 1.439)	
		≥20	1201443	516	0.053048	1.548 (1.362, 1.759)		1.529 (1.345, 1.739)	
Nasopharynx									
	Never smoker		5772362	492	0.010325	1 (Ref.)	0.0015*	1 (Ref.)	0.0015*
	Ex-smoker	<10	313103	31	0.01196	0.913 (0.629, 1.327)		0.914 (0.629, 1.329)	
		<20	471205	71	0.018229	1.133 (0.87, 1.477)		1.134 (0.87, 1.478)	
		≥20	541144	135	0.030801	1.3 (1.052, 1.607)		1.302 (1.053, 1.610)	

	Current smoker	<10	361298	24	0.008028	0.853 (0.557, 1.305)		0.855 (0.559, 1.309)	
		<20	937530	83	0.010705	0.966 (0.745, 1.253)		0.968 (0.746, 1.257)	
		≥20	1201443	265	0.027242	1.401 (1.177, 1.669)		1.404 (1.178, 1.673)	
Salivary gland									
	Never smoker		5772362	733	0.015383	1 (Ref.)	0.0013*	1 (Ref.)	0.0011*
	Ex-smoker	<10	313103	31	0.01196	1.019 (0.702, 1.479)		1.017 (0.701, 1.477)	
		<20	471205	70	0.017973	1.284 (0.983, 1.678)		1.285 (0.983, 1.679)	
		≥20	541144	119	0.02715	1.260 (1.008, 1.575)		1.262 (1.009, 1.577)	
	Current smoker	<10	361298	20	0.00669	0.790 (0.499, 1.249)		0.791 (0.5, 1.251)	
		<20	937530	63	0.008125	0.868 (0.653, 1.155)		0.873 (0.656, 1.162)	
		≥20	1201443	237	0.024363	1.396 (1.164, 1.675)		1.407 (1.172, 1.688)	

Incidence rate per 1,000 person-years. Model 1: Age, sex, income, BMI, alcohol consumption, regular exercise, diabetes, and hypertension. Model 2: Age, sex, income, BMI, waist circumference, alcohol consumption, regular exercise, diabetes, hypertension, hyperlipidemia, chronic kidney disease, HDL level, LDL level, and triglyceride level. *Significant at $p<0.05$.

when smoking duration was less than 10 years in both ex- and current smokers. However, in the case of larynx cancer, the HR increased in the case of current smokers even if the duration was less than 10 years (HR: 1.451, 95% CI: 1.012-2.082). Larynx cancer (HR: 3.492, 95% CI: 3.157-3.863) and hypopharynx (HR: 2.447, 95% CI: 2.067-2.897) cancer showed very high HRs in current smokers with a smoking duration over 20 years.

Relationship between smoking amount and HNC

The incidence of HNC according to smoking amount is shown in **Table 4**. Like smoking duration, the overall incidence of HNC increased in proportion to smoking amount in both ex-smokers and current smokers; for the same smoking amount, current smokers had a higher HR than ex-smokers. As seen for smoking duration, when the smoking amount was 10 PYs or less in ex-smokers, the HR was not increased (HR: 1.068, 95% CI: 0.933-1.223).

HR significantly increased according to smoking amount in all subtypes except sinonasal and salivary cancers. In particular, larynx (HR: 4.64, 95% CI: 3.642-4.535) and hypopharynx (HR: 2.820, 95% CI: 2.340-3.400) cancer showed very high HRs in current smokers with over 20 PYs.

Discussion

Cigarette smoke is a potent carcinogen that is strongly associated with many cancers. HNC is one of many cancers that are closely related to tobacco use. According to Hashibe et al. who identified independent associations of tobacco and alcohol with HSC, cigarette smoking was associated with an increased risk of HNC (HR: 2.13, 95% CI: 1.52-2.98) [11]. The recent understanding of the harmful effects of smoking has created a pathway towards education and regulatory efforts aimed at reducing tobacco use [12, 13]. As a result of this effort, the smoking ratio has been gradually decreasing. In addition, recently, as the incidence of cancer caused by HPV has gradually increased, the influence of traditional risk factors such as smoking and alcohol on cancer development has gradually decreased. However, while HPV-induced HNC is rising in incidence, a 2013 analysis of over 100,000 subjects showed that 66% of HNC diagnoses were tobacco- and alcohol-related [5]. Thus, tobacco remains a prominent cause of HNC.

Although many studies have already explored HNC and smoking, we looked into the association in more detail using big data, and examined the association by subtype and by smoking status, duration and amount. The strengths of our study are that the results were from cohort data including more than 9.5 million participants over 10 years. Therefore, we investigated the association between smoking and HNC subtype with sufficient power.

As mentioned earlier, the HR of developing HNC in current smokers compared to never smokers was approximately 2.13 [11]. Our data showed similar results. The HR of current smokers was 1.822 (95% CI: 1.729-1.920, $P<0.0001$). Smoking cessation, however, lowers the likelihood of occurrence of HNC to some extent. Because the period after cessation was not analyzed separately in this study, it is not known how long after cessation can be free from HNC. According to previous studies, while cessation does certainly lower risk, it is unclear

Table 4. Hazard ratios of head and neck cancer and its subtypes according to smoking amount

subsites	Smoking status	Pack-year	N	Event	Incidence Rate	Model 1	*P* value	Model 2	*P* value
Head and neck cancer									
	Never smoker		5772362	4273	0.08969	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	192061	229	0.1451	1.066 (0.931, 1.221)		1.068 (0.933, 1.223)	
		<20	527968	704	0.16201	1.098 (1.008, 1.195)		1.098 (1.008, 1.195)	
		≥20	605423	1306	0.26438	1.405 (1.312, 1.504)		1.4 (1.307, 1.499)	
	Current smoker	<10	274587	360	0.16111	1.410 (1.262, 1.574)		1.408 (1.261, 1.573)	
		<20	1065782	1392	0.15911	1.607 (1.502, 1.720)		1.603 (1.497, 1.715)	
		≥20	1159902	2468	0.26043	2.129 (2.007, 2.259)		2.115 (1.993, 2.244)	
Larynx									
	Never smoker		5772362	682	0.01431	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	192061	54	0.0342	1.066 (0.806, 1.409)		1.066 (0.806, 1.41)	
		<20	527968	201	0.04624	1.352 (1.150, 1.590)		1.347 (1.145, 1.584)	
		≥20	605423	464	0.09388	2.032 (1.795, 2.300)		2.013 (1.778, 2.279)	
	Current smoker	<10	274587	125	0.05593	2.138 (1.761, 2.596)		2.129 (1.753, 2.585)	
		<20	1065782	474	0.05416	2.712 (2.393, 3.075)		2.693 (2.375, 3.053)	
		≥20	1159902	972	0.10252	4.121 (3.694, 4.597)		4.064 (3.642, 4.535)	
Sinonasal cavity									
	Never smoker		5772362	280	0.005876	1 (Ref.)	0.1104	1 (Ref.)	0.1104
	Ex-smoker	<10	192061	8	0.005066	0.698 (0.342, 1.425)		0.701 (0.344, 1.432)	
		<20	527968	27	0.00621	0.788 (0.518, 1.198)		0.791 (0.52, 1.203)	
		≥20	605423	59	0.011934	1.194 (0.872, 1.636)		1.192 (0.87, 1.634)	
	Current smoker	<10	274587	15	0.00671	1.065 (0.625, 1.814)		1.067 (0.626, 1.818)	
		<20	1065782	59	0.006741	1.199 (0.874, 1.646)		1.203 (0.876, 1.652)	
		≥20	1159902	91	0.009595	1.371 (1.034, 1.819)		1.372 (1.033, 1.822)	
Hypopharynx									
	Never smoker		5772362	271	0.005687	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	192061	14	0.008866	0.699 (0.407, 1.2)		0.704 (0.410, 1.208)	
		<20	527968	46	0.010581	0.799 (0.581, 1.1)		0.803 (0.583, 1.105)	
		≥20	605423	133	0.026904	1.493 (1.201, 1.855)		1.488 (1.197, 1.85)	
	Current smoker	<10	274587	46	0.020578	1.776 (1.291, 2.443)		1.768 (1.285, 2.432)	
		<20	1065782	127	0.01451	1.693 (1.353, 2.118)		1.682 (1.344, 2.106)	
		≥20	1159902	292	0.030791	2.855 (2.370, 3.439)		2.82 (2.34, 3.4)	
Oropharynx									
	Never smoker		5772362	685	0.014375	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	192061	45	0.028501	1.076 (0.792, 1.462)		1.077 (0.792, 1.463)	
		<20	527968	142	0.032665	1.111 (0.919, 1.344)		1.109 (0.917, 1.342)	
		≥20	605423	231	0.046731	1.263 (1.076, 1.483)		1.256 (1.07, 1.475)	
	Current smoker	<10	274587	60	0.026842	1.239 (0.946, 1.622)		1.237 (0.945, 1.62)	
		<20	1065782	263	0.030051	1.516 (1.297, 1.773)		1.511 (1.292, 1.768)	
		≥20	1159902	388	0.040916	1.681 (1.459, 1.938)		1.669 (1.448, 1.924)	
Oral cavity									
	Never smoker		5772362	1172	0.024596	1 (Ref.)	<.0001*	1 (Ref.)	<.0001*
	Ex-smoker	<10	192061	49	0.031035	1.121 (0.836, 1.503)		1.123 (0.838, 1.506)	
		<20	527968	143	0.032895	1.117 (0.925, 1.349)		1.116 (0.924, 1.348)	
		≥20	605423	191	0.038638	1.067 (0.9, 1.265)		1.06 (0.894, 1.257)	
	Current smoker	<10	274587	61	0.027289	1.143 (0.878, 1.489)		1.138 (0.874, 1.482)	
		<20	1065782	234	0.026737	1.288 (1.099, 1.511)		1.278 (1.089, 1.499)	
		≥20	1159902	375	0.039545	1.598 (1.387, 1.84)		1.575 (1.367, 1.85)	
Nasopharynx									
	Never smoker		5772362	492	0.010325	1 (Ref.)	0.0449*	1 (Ref.)	0.0449*
	Ex-smoker	<10	192061	30	0.019	1.216 (0.834, 1.773)		1.221 (0.837, 1.779)	
		<20	527968	81	0.018632	1.065 (0.829, 1.369)		1.069 (0.832, 1.374)	
		≥20	605423	126	0.025488	1.255 (1.012, 1.556)		1.254 (1.011, 1.556)	

	Current smoker	<10	274587	33	0.014763	1.094 (0.763, 1.569)		1.098 (0.765, 1.575)	
		<20	1065782	134	0.01531	1.124 (0.908, 1.390)		1.128 (0.912, 1.396)	
		≥20	1159902	205	0.021617	1.380 (1.142, 1.667)		1.38 (1.141, 1.668)	
Salivary gland									
	Never smoker		5772362	733	0.015383	1 (Ref.)	0.0701	1 (Ref.)	0.0701
	Ex-smoker	<10	192061	31	0.019634	1.336 (0.923, 1.935)		1.337 (0.923, 1.936)	
		<20	527968	72	0.016562	1.077 (0.827, 1.402)		1.079 (0.829, 1.405)	
		≥20	605423	117	0.023668	1.3 (1.04, 1.625)		1.3 (1.04, 1.626)	
	Current smoker	<10	274587	27	0.012078	0.916 (0.619, 1.357)		0.921 (0.622, 1.364)	
		<20	1065782	120	0.013711	1.152 (0.924, 1.437)		1.16 (0.93, 1.447)	
		≥20	1159902	173	0.018242	1.323 (1.082, 1.617)		1.331 (1.088, 1.629)	

Incidence rate per 1,000 person-years. Model 1: Age, sex, income, BMI, alcohol consumption, regular exercise, diabetes, and hypertension. Model 2: Age, sex, income, BMI, waist circumference, alcohol consumption, regular exercise, diabetes, hypertension, hyperlipidemia, chronic kidney disease, HDL level, LDL level, and triglyceride level. *Significant at $p<0.05$.

whether risk returns to that of a never smoker [14, 15]. Some data suggest that the risk returns to that of a never smoker after about 20 years of cessation [16]. When the correlation between smoking and cancer incidence was divided by subtype, larynx cancer, hypopharynx cancer, oropharynx cancer, oral cavity cancer, and nasopharynx cancer showed a significant association with smoking status, but sinonasal cancer and salivary gland cancer did not. In particular, larynx cancer and hypopharynx cancer had a very high HR in current smokers compared to other subtypes. The mucosal lining of the upper aerodigestive tract receives considerable exposure to tobacco smoke as it is transmitted from the lips to the lungs. Because of this direct contact with the smoke, a strong association with smoking was expected. Sinonasal cavities and salivary glands not in direct contact with smoke did not show a significant association with smoking status. Nasopharynx cancer and oropharynx cancer showed a relatively low association compared to the larynx and hypopharynx. This is probably because, unlike other subtypes, virus-related cancers account for a higher proportion of disease (Epstein-Barr virus for nasopharynx cancer and HPV for oropharynx cancer).

Smoking duration and amount showed a dose-dependent relationship with the occurrence of HNC [17-20]. However, the incidence of HNC did not increase significantly when the smoking duration was less than 10 years, or when the smoking amount was less than 10 PYs in ex-smokers. In the case of current smokers, the incidence of HNC was slightly increased when the smoking amount was 10 PYs. This is an important implication, and can be the basis for strongly recommending quitting smoking to smokers who have not smoked for a long time, as much as abstaining from smoking altogether to prevent HNC. Similarly, cancer incidence rate according to subtype did not increase significantly when the smoking duration was less than 10 years, and when the smoking amount was less than 10 PYs in ex-smokers. Unlike other subtypes, in the case of larynx cancer, even if smoking duration was less than 10 years, the cancer incidence rate was significantly higher for current smokers; thus, smoking cessation is recommended for the prevention of larynx cancer.

This study has several limitations. First, most of the participants were Korean, so the results may not be generalizable to other Asians. Another limitation is that we used the PY method when expressing smoking amount. The use of PYs to summarize smoking history has been criticized as inconsistent with epidemiologic and molecular models of cancer [21]. PYs or drink-years (the multiplication of a frequency times a duration measure) cannot distinguish between low frequency use for a long time period and high-frequency use for a short period. Second, the effects of HPV on oropharyngeal cancer were not included. Because the diagnosis in the Korea NHIS is based on the International Classification of Diseases, we cannot distinguish between oropharynx cancer related to HPV status. Another limitation is that the effects of alcohol could not be excluded. Smoking and alcohol have a synergistic effect in cancer development, so in order to see the pure effect of smoking, the effects of alcohol should be excluded, which was not done in this study.

In conclusion, despite these limitations, this study is meaningful because it analyzed the

effects of smoking on the occurrence of HNC in depth using big data, and separately for each subtype. In addition, this study provided a basis for recommending smoking cessation in patients who have already started smoking by revealing that smoking cessation within 10 years and before reaching 10 PYs could help mitigate the risk of HNC.

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None.

Abbreviations

CI, Confidence interval; HNC, Head and neck cancer; HPV, Human papillomavirus; HR, Hazard ratio; KNHIS, Korean National Health Insurance Service; PYs, Pack-years.

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