Association between oral cavity cancer and metabolic syndrome

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Research Article

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Abstract

Purpose

Few studies have been conducted on the association between oral cavity cancer and metabolic diseases. This study aimed to investigate the relationship between oral cavity cancer and metabolic diseases.

Methods

This cohort study used the database of the Korean National Health Insurance Service, which contains medical data of 97% of the Korean population. Oral cavity cancer occurred in a total of 2,718 patients. Metabolic syndrome was defined according to IDF criteria. The Cox proportional hazard regression model was used.

Results

The HR for oral cavity cancer in patients with metabolic syndrome was 1.113(95% CI, 1.006–1.232), which was significantly higher than that in normal patients, especially in males ($p = 0.0386$). When the number of metabolic syndrome factors was ≥ 3, the HR of oral cavity cancer was 1.191(95% CI, 1.026–1.383), which was significantly higher than that of 0 metabolic syndrome factors, especially in males ($p = 0.0218$). When the number of metabolic syndrome factors was ≥ 3, the HR for oral cavity cancer was 1.439(95% CI, 1.066–1.942), which was significantly higher than that of 0 metabolic syndrome factors, especially in males aged < 50 years ($p = 0.0173$).

Conclusion

Metabolic syndrome increases the risk of oral cavity cancer only in males. In addition, the incidence of oral cavity cancer increased as the number of factors constituting metabolic syndrome increased, only in young males aged < 50 years. Thus, metabolic syndrome is an important risk factor for oral cavity cancer, particularly in young males.

1. Introduction

Oral cavity cancer affects the lining of the lips, mouth, and/or upper throat. In 2017, oral cavity cancer occurred globally in approximately 369,2000 individuals, resulting in 145,328 deaths.(Ghantous & Elnaaj, 2017) In 2015, the rate of oral cavity cancer was 11.6 per 100,000 in the United States. Deaths due to oral cavity cancer were 2.5/100,000. Oral cavity cancer had an overall five-year survival rate of 65% in the United States in 2015.(Institute, 2019) Oral cavity cancer is a disease that is difficult to treat in the head and neck due to poor prognosis and accompanying internal medical diseases or dysfunction of the oral cavity after treatment. Diagnosis and treatment have developed over the past 20 years, but the survival

rate of patients with oral cavity cancer has not improved significantly. Therefore, it is important to identify and prevent oral cancer in advance. Alcohol consumption and smoking are the most common risk factors for oral cavity cancer.[(Gandini et al., 2008; Goldstein, Chang, Hashibe, La Vecchia, & Zhang, 2010)] Those who consume both alcohol and tobacco have an increased risk of oral cancer than those who do not.[(Kabat, Chang, & Wynder, 1994)] Other risk factors include human papillomavirus (HPV) infection and chewing betel nuts. (Goldenberg et al., 2004; Kerawala, Roques, Jeannon, & Bisase, 2016; Kreimer, Clifford, Boyle, & Franceschi, 2005)

Recently, many studies have investigated the association between various cancers and metabolic syndromes. Metabolic syndrome is a term that refers to a combination of diabetes, high blood pressure, and obesity. Diabetes, hypertension (HTN), and obesity are reported to be associated with various cancers as risk factors.(Han et al., 2017; Stocks et al., 2012; Vigneri, Frasca, Sciacca, Pandini, & Vigneri, 2009) Central obesity, a factor of metabolic syndrome, is known to be associated as a risk factor for breast cancer.(Calle & Thun, 2004; Harvie, Hooper, & Howell, 2003) Previous studies have shown a significant association between metabolic syndrome and several cancers and their mortality.(Esposito et al., 2014; Esposito et al., 2013; Hauner & Hauner, 2014; Hsing, Sakoda, & Chua Jr, 2007; Siegel & Zhu, 2009; Xia et al., 2020) However, few studies have been conducted on the association between oral cavity cancer and metabolic diseases. This study aimed to investigate the relationship between oral cavity cancer and metabolic diseases.

2. Materials And Method

2.1 Study population

This cohort study used the database of the Korean National Health Insurance Service (KNHIS), which contains medical data of 97% of the Korean population, such as past medical history, treatment history, and demographics, with official approval from the government. Participants over 40 years of age who had a health checkup recorded in the KNHIS during 2008 were included in this study. Patients previously diagnosed with oral cavity cancer were excluded and continuously followed up to check whether they had oral cavity cancer from 2009 to 2019. Individuals who died, were diagnosed with oral cavity cancer within one year, or were diagnosed with nasal cavity, middle ear, salivary gland, and nasopharynx cancers were excluded. A total of 2718 people were enrolled in this study.

The study was approved by the Institutional Review Board of Kyung Hee University Hospital and was performed in accordance with relevant guidelines and regulations.

2.2 Definition of the risk factors for oral cavity cancer

HTN and diabetes were defined as previously or newly diagnosed according to the KHNIS data. Alcohol consumption and smoking status were confirmed through standardized self-reported questionnaires at the time of enrollment. Alcohol consumption was classified as no drinking, moderate drinking (ethanol 0–30 g/day), and heavy drinking (ethanol > 30 g/day). Smoking status was classified as never smoked, ex-

smoker, or current smoker. Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). People were divided into four weight groups as follows: underweight (BMI < 18.5 kg/m^2), normal (18.5–22.9 kg/m^2), pre-obese (23.0-24.9 kg/m^2), and obese (≥ 25 kg/m^2). For the lipid profile, when the total cholesterol (TC) was ≥ 200 mg/dL, triglycerides (TG) ≥ 150 mg/dL, and low-density lipoprotein (LDL) cholesterol ≥ 100 mg/dL, it was defined as high. High-density lipoprotein (HDL) cholesterol was defined as low when it was < 40 mg/dL for males and 50 mg/dL for females.

Metabolic syndrome was defined according to the International Diabetes Federation (IDF) criteria. According to the IDF, patients must have central obesity (waist circumference ≥ 90 cm for males and ≥ 80 cm for females) to be defined as having metabolic syndrome. Furthermore, patients need to have any two of the following four factors: elevated TG (≥ 150 mg/dL or specific treatment for this lipid abnormality), reduced HDL cholesterol (< 40 mg/dL for males and < 50 mg/dL for females), elevated blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg or treatment of previously diagnosed HTN) and raised fasting plasma glucose (≥ 100 mg/dL or previously diagnosed type 2 diabetes).

2.3 Statistical analysis

Categorical variables, such as sex, alcohol drinking, smoking status, and past medical history, were presented as a frequency and percentage. The values of BMI, central obesity, TC, TG, LDL cholesterol, and HDL cholesterol are presented as the mean ± SD. The differences between the oral cavity cancer group and the control group were analyzed using the chi-square test and t-test. The Cox proportional hazard regression model was used to determine the relationship between metabolic syndrome and oral cavity cancer. The hazard ratios and 95% confidence intervals (CI) are presented. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used, and the significance of the statistical tests was determined using the 0.05 level.

3. Results

3.1 Participant characteristics

The demographic characteristics are presented in Table 1. A total of 4,575,818 patients were analyzed, and 2,718 were newly diagnosed with oral cavity cancer during the follow-up period. In the oral cavity cancer group, 67.26% were males, and 54.07% were males in the control group, showing a significant difference between the two groups ($p < 0.0001$). The mean age was 58.52 years in the oral cavity cancer group and 53.96 years in the control group, showing a higher age in the oral cavity cancer group and significant differences between the two groups ($p < 0.0001$). The mean BMI was 24.04 kg/m^2 in the oral cavity cancer group and 23.98 kg/m^2 in the control group, with significant differences between the two groups ($p = 0.001$). The mean waist circumference was 83.24 cm in the oral cavity cancer group and 81.68 cm in the control group, showing a significant difference between the two groups ($p < 0.0001$). The mean TC, TG, LDL, and HDL values were 195.26 and 197.45 md/dL; 145.02 and 139.80 md/dL; 55.03 and 55.55 md/dL; and 117.89 and 119.64 md/dL in the oral cavity and control groups, respectively. The

prevalence of HTN in the oral cavity cancer group was 57.17%, and the prevalence of HTN in the control group was 48.98%, with a higher proportion of HTN in the oral cavity cancer group and a significant difference between the two groups ($p < 0.0001$). The prevalence of diabetes mellitus was 15.71% in the oral cavity cancer group and 11.77% in the control group, showing a significant difference between the two groups ($p < 0.0001$). The prevalence of dyslipidemia in the oral cavity cancer group was 38.96%, and 37.35% in the control group. The prevalence of metabolic syndrome in the oral cavity cancer group was 30.94%, and that in the control group was 26.16%, showing a higher proportion of metabolic syndrome between the two groups ($p < 0.0001$). The drinking history of the oral cavity cancer group was higher than that of the control group (54.08% for no drinking, 41.50% for moderate drinking, 4.42% for heavy drinking; $p = 0.0002$), and the smoking history of the oral cavity cancer group was higher than that of the control group (62.73% had never smoked, 12.18% were ex-smokers, and 25.09% were current smokers; $p < 0.0001$).

Table 1
Analysis of the factors potentially associated with oral cavity cancer. Values are the mean ± SD or n (%). *Significant at $p < 0.05$.

Parameter	Oral cavity cancer (n = 2718)	Non-oral cavity cancer (n = 4,567,069)	p-value
Sex, n (%)			< .0001
Male	1,828 (67.26)	2,469,600 (54.07)	
Female	890 (32.74)	2,097,469 (45.93)	
Age, yr	58.52 ± 10.10	53.96 ± 9.32	< .0001
Body mass index, kg/m^2	24.04 ± 3.06	23.98 ± 3.32	0.001
Waist circumference, cm	83.24 ± 8.47	81.68 ± 8.45	< .0001
Total cholesterol, mg/dL	195.26 ± 38.31	197.45 ± 36.95	0.002
Triglyceride, mg/dL	145.02 ± 96.08	139.80 ± 108.34	0.0119
LDL, mg/dL	55.03 ± 35.49	55.55 ± 31.89	0.3955
HDL, mg/dL	117.89 ± 196.98	119.64 ± 79.48	0.254
Hypertension, n (%)			< .0001
No	1,164 (42.83)	2,330,154 (51.02)	
Yes	1,554 (57.17)	2,236,915 (48.98)	
Diabetes, n (%)			< .0001
No	2,291 (84.29)	4,029,420 (88.23)	
Yes	427 (15.71)	537,649 (11.77)	
Dyslipidemia, n (%)			0.0825
No	1,659 (61.04)	2,861,219 (62.65)	
Yes	1,059 (38.96)	1,705,850 (37.35)	
Metabolic syndrome, n (%)			
No	1,877 (69.06)	3,372,434 (73.84)	< .0001
Yes	841 (30.94)	1,194,635 (26.16)	
Alcohol drinking, n (%)			0.0002
No	1,470 (54.08)	2,564,134 (56.14)	
Moderate	1,128 (41.50)	1,860,466 (40.74)	

Parameter	Oral cavity cancer (n = 2718)	Non-oral cavity cancer (n = 4,567,069)	p-value
Heavy	120 (4.42)	142,469 (3.12)	
Smoking status, n (%)			< .0001
Never smoked	1,705 (62.73)	3,167,225 (69.35)	
Ex-smoker	331 (12.18)	472,603 (10.35)	
Current smoker	682 (25.09)	927,241 (20.30)	

3.2 Oral cavity cancer risk factor according to each factor

To identify the risk factors for oral cavity cancer, each parameter was analyzed using multivariable regression analysis adjusted for age, sex, drinking, and smoking in Table 2. The hazard ratio (HR) of oral cavity cancer was 1.503(95% CI, 1.187–1.903) in the low BMI group (< 18.5), which was significantly higher than that of the normal BMI group (18.5–22.9) and showed a significant difference (p = 0.0007). Thus, obesity, represented by BMI, lowers the risk of oral cavity cancer. When TC was high, the HR for oral cavity cancer was 0.903(95% CI, 0.836–0.975), which was lower than the normal group and showed a significant difference (p = 0.0088). When the LDL cholesterol level was high, the HR for oral cavity cancer was 0.846(95% CI, 0.781–0.915), which was significantly lower than that in the normal group (p < 0.0001). Central obesity and TG and HDL levels did not affect the risk of oral cavity cancer. HTN did not affect the risk of oral cancer. The HR of patients with diabetes mellitus was 1.172(95% CI, 1.056–1.301), which was significantly higher than that in the normal group (p = 0.0028). HTN and dyslipidemia did not significantly affect the risk of oral cavity cancer. Metabolic syndrome did not have a significant effect on the risk of oral cavity cancer when adjusted for age, sex, alcohol consumption, and smoking.

Table 2
Hazard ratios for the incidence of oral cavity cancer according to each factor adjusted for age, sex, smoking, and drinking.

		Oral cavity cancer (Adjusted for age, sex, smoking, drinking)	
Parameter	**n**	**p-value**	**HR (95% CI)**
BMI, kg/m^2			
< 18.5	75	0.0007	1.503 (1.187–1.903)
18.5–22.9	906		1 (Reference)
23-24.9	748	0.9891	0.999 (0.907–1.101)
≥ 25	989	0.5408	1.029 (0.94–1.126)
Central obesity			
No	2,104		1 (Reference)
Yes	614	0.3326	1.046 (0.955–1.147)
Total cholesterol			
Low	1,573		1 (Reference)
High	1,145	0.0088	0.903 (0.836–0.975)
TG			
Low	1,758		1 (Reference)
High	960	0.3308	1.04 (0.961–1.126)
LDL cholesterol			
Low	961		1 (Reference)
High	1,757	< .0001	0.846 (0.781–0.915)
HDL cholesterol			
Low	2,144	0.9165	1.005 (0.914–1.105)
High	574		1 (Reference)
Hypertension			
No	1,164		1 (Reference)
Yes	1,554	0.0808	1.072 (0.991–1.16)
Diabetes			

		Oral cavity cancer (Adjusted for age, sex, smoking, drinking)	
No	2291		1 (Reference)
Yes	427	0.0028	1.172 (1.056–1.301)
Dyslipidemia			
No	1659		1 (Reference)
Yes	1059	0.7836	0.989 (0.916–1.069)
Metabolic syndrome			
No	1877		1 (Reference)
Yes	841	0.0674	1.08 (0.994–1.173)

Hazard ratios for the incidence of oral cavity cancer according to alcohol and smoking are presented in Table 3. When drinking history was divided into three stages (no drinking, moderate drinking, and heavy drinking), the HR of oral cavity cancer in heavy drinking patients was 1.274(95% CI, 1.052–1.545), which was significantly higher than that in non-drinking patients ($p = 0.034$). When smoking history was divided into three stages (never smoked, ex-smoker, and current smoker), the HR of oral cavity cancer in current smokers was 1.243(95% CI, 1.124–1.374), which was significantly higher than that in non-smokers ($p < 0.0001$). This shows that drinking and smoking history have a significant effect on the risk of oral cavity cancer when adjusted for age and sex.

Table 3
Hazard ratios for the incidence of oral cavity cancer according to alcohol and smoking adjusted for age and sex

		Oral cavity cancer (adjusted for age and sex)	
Parameter	**n**	**p-value**	**HR (95% CI)**
Alcohol drinking, n			
No	1,470		1 (Reference)
Moderate	1,128	0.9919	1.000 (0.918–1.091)
Heavy	120	0.0134	1.274 (1.052–1.545)
Smoking status, n			
Never smoked	1,705		1 (Reference)
Ex-smoker	331	0.3963	1.056 (0.931–1.198)
Current smoker	682	< .0001	1.243 (1.124–1.374)

3.3 Sex differences in oral cavity cancer risk factors

The difference in the HR of oral cavity cancer according to HTN, diabetes mellitus, and metabolic syndrome was analyzed by dividing the patients by sex in Table 4. The HR for oral cavity cancer in patients with HTN was 1.13(95% CI, 1.027–1.243), which was significantly higher than that in normal patients, especially in males (p = 0.0123). HTN was a risk factor for the occurrence of oral cavity cancer only in males. The HRs of oral cavity cancer in males and females with diabetes mellitus were 1.141(95% CI, 1.04–1.253) and 1.201(95% CI, 1.045–1.381), respectively, which were significantly higher than those of healthy patients in both sexes (p = 0.0053, p = 0.01). The HR for oral cavity cancer in patients with metabolic syndrome was 1.113(95% CI, 1.006–1.232), which was significantly higher than that in normal patients, especially in males (p = 0.0386). Thus, metabolic syndrome was a risk factor for oral cavity cancer, especially in males, when adjusted for age, alcohol consumption, and smoking.

Table 4
Hazard ratios for the incidence of oral cavity cancer according to diabetes mellitus, hypertension, and metabolic syndrome adjusted for age, alcohol, and smoking

	Males (n = 1,828)			Females (n = 890)		
Parameter	**n**	**p-value**	**HR (95% CI)**	**n**	**p-value**	**HR (95% CI)**
Hypertension						
No	536		1 (Reference)	428		1 (Reference)
Yes	1,292	0.0123	1.13 (1.027–1.243)	462	0.656	0.969 (0.842–1.115)
Diabetes						
No	1,514		1 (Reference)	777		1 (Reference)
Yes	314	0.0053	1.141(1.04–1.253)	113	0.01	1.201 (1.045–1.381)
Metabolic syndrome						
No	261		1 (Reference)	141		1 (Reference)
Yes	1,567	0.0386	1.113 (1.006–1.232)	749	0.6877	1.03 (0.892–1.19)

3.4 Association between the number of factors constituting metabolic syndrome and oral cavity cancer according to age and sex

The HR of oral cavity cancer was analyzed according to sex and the number of factors constituting metabolic syndrome in Table 5. When the number of metabolic syndrome factors was ≥ 3, the HR of oral cavity cancer was 1.191(95% CI, 1.026–1.383), which was significantly higher than that of zero metabolic syndrome factors, especially in males (p = 0.0218). Thus, it was confirmed that metabolic syndrome acts as a risk factor for oral cavity cancer only in males, and the incidence of oral cavity cancer increases as the number of factors constituting metabolic syndrome increases when adjusted for age, alcohol consumption, and smoking.

Table 5
Hazard ratios for the incidence of oral cavity cancer according to the number of factors constituting metabolic syndrome and adjusted for age, alcohol, and smoking

	Male (n = 1,828)			Female (n = 890)		
Parameter	**n**	**p-value**	**HR (95% CI)**	**n**	**p-value**	**HR (95% CI)**
Metabolic syndrome, n						
0	261		1 (Reference)	141		1 (Reference)
1–2	1,038	0.2218	1.089 (0.95–1.248)	437	0.9685	1.004 (0.826–1.221)
≥ 3	529	0.0218	1.191 (1.026–1.383)	312	0.764	1.033 (0.834–1.28)

The HR for oral cavity cancer was divided and analyzed according to sex, age, and the number of factors constituting metabolic syndrome in Table 6. When the number of metabolic syndrome factors was ≥ 3, the HR for oral cavity cancer was 1.439(95% CI, 1.066–1.942), which was significantly higher than that of zero metabolic syndrome factors, especially in males aged < 50 years (p = 0.0173). Thus, it was confirmed that metabolic syndrome acts as a risk factor for oral cavity cancer only in young males under the age of 50 years and that the incidence of oral cavity cancer increases as the number of factors constituting metabolic syndrome increases when adjusted for alcohol and smoking.

Table 6
Hazard ratios for the incidence of oral cavity cancer according to the number of factors constituting metabolic syndrome and adjusted for alcohol, and smoking

	Males (n = 1,828)			Females (n = 890)		
Parameter	**n**	**p-value**	**HR (95% CI)**	**n**	**p-value**	**HR (95% CI)**
Age < 50						
Metabolic syndrome, n						
0	73		1 (Reference)	60		1 (Reference)
1–2	228	0.2028	1.187 (0.912–1.546)	92	0.6794	1.071 (0.773–1.483)
≥ 3	106	0.0173	1.439 (1.066–1.942)	23	0.753	1.08 (0.667–1.749)
Age > = 50						
Metabolic syndrome, n						
0	188		1 (Reference)	81		1 (Reference)
1–2	810	0.2908	1.089 (0.929–1.277)	345	0.5003	1.087 (0.853–1.385)
≥ 3	423	0.0722	1.171 (0.986–1.391)	289	0.0959	1.234 (0.963–1.58)

4. Discussion

Using data from the KNHIS, we investigated how metabolic diseases, such as high blood pressure, diabetes, dyslipidemia, and obesity, affect the incidence of oral cavity cancer. The risk of oral cavity cancer increases in patients with a low BMI. In addition, high TC and LDL levels showed a protective effect against oral cavity cancer. In the case of diabetes mellitus, the risk of oral cavity cancer increased in both males and females, whereas HTN increased the risk of oral cavity cancer only in males.

Metabolic syndrome is a risk factor for oral cancer in males. When analyzed by sex and age, metabolic syndrome was a risk factor for oral cavity cancer only in young males aged < 50 years, and the risk of oral cavity cancer increased as the number of factors constituting metabolic syndrome increased.

Alcohol and smoking are the most common causes of cancer.(Gandini et al., 2008; Goldstein et al., 2010) Betel nut chewing, HPV infection, exposure to sunlight, mechanical stimulation due to dentures or teeth, damage by heat, chemical stimulation, Plumer-Vinson syndrome, poor oral defiance, syphilis, lichen planus, and submucous fibrosis are known to be associated with oral cavity cancer.(Goldenberg et al., 2004; Kerawala et al., 2016; Kreimer et al., 2005) Metabolic syndrome has an increasing incidence worldwide as the prevalence of diabetes and obesity increases, affecting various diseases. Recently, it has been reported that metabolic syndrome increases the risk of various cancers. However, the relationship between metabolic syndrome and oral cancer is unclear.

Several studies have investigated the association between metabolic syndrome and cancer. According to one study, middle-aged males with metabolic syndrome are more likely to develop prostate cancer. The association between metabolic syndrome and the risk of prostate cancer was stronger among overweight males than in lighter males.(Laukkanen et al., 2004) According to another study, inflammatory and angiogenic changes because of underlying insulin resistance and fatty liver disease will likely increase the incidence of hepatocellular carcinoma.(Siegel & Zhu, 2009) In one study, metabolic syndrome, obesity, and a large waist circumference were found to be associated with an increased risk of endometrial cancer.(Esposito et al., 2014) In a cohort study from the United Kingdom, metabolic syndrome, central obesity, and hyperglycemia were associated with an increased risk of pancreatic cancer.(Xia et al., 2020) In several studies, metabolic syndrome was associated with an increased risk of colorectal cancer incidence and mortality.(Esposito et al., 2013; Esposito, Chiodini, Colao, Lenzi, & Giugliano, 2012; Stocks et al., 2008) However, few studies have been conducted on the relationship between oral cavity cancer and metabolic syndrome. Unlike in other studies, there was no association between metabolic syndrome and oral cavity cancer in the current study when sex was not considered. When considered separately by sex, it was confirmed that metabolic syndrome only increases the risk of oral cavity cancer in males. In particular, metabolic syndrome increased the risk of oral cavity cancer by 1.43 times only in males aged < 50 years. In contrast to other studies on cancer and metabolic syndrome, the risk of oral cavity cancer was found to depend on the number of components of metabolic syndrome. In males with one to two metabolic syndrome components, the risk of oral cavity cancer increases 1.089 times. In contrast, when the number of metabolic syndrome components is three or more, the risk of oral cavity cancer is

increased by 1.187 times. In young males with one to two metabolic syndrome components, metabolic syndrome increases the risk of oral cavity cancer by 1.187 times. When the number of metabolic syndrome components is three or more, metabolic syndrome increases the risk of oral cavity cancer 1.439 times. The risk of oral cavity cancer in young males was related to insulin resistance, high blood pressure, high blood glucose levels, and abnormal lipid levels, and an increase in the components of metabolic syndrome significantly affected the risk of oral cavity cancer.

In other cancers, obesity increases the risk of cancer occurrence. However, lean patients tend to have an increased risk of oral cavity cancer. One study explained that obesity upsets the balance of hormones and causes metabolic disorders, which increases the risk of cancer.(Calle & Kaaks, 2004) The association between oral cavity cancer and obesity remains unclear, with conflicting results between the risk of head and neck cancer (HNC) and obesity. Several studies have reported that HNC and obesity are not related. (Gaudet et al., 2012; Hashibe et al., 2013) Other studies have reported that a high BMI and central obesity lower the incidence of HNC.(Chen et al., 2019; Etemadi et al., 2014)[,39,40,41] In addition, there are reports that prognosis is better in obese patients because obesity plays a defensive role in malnourishment, immune disability, and cachexia induced by dysphagia or poor appetite after HNC surgery. Cigarettes, the main cause of oral cavity cancer, are known to secrete many carcinogens, causing intraoral DNA damage. (Etemadi et al., 2013) According to one study, DNA damage caused by cigarettes in lean people is worse than in normal patients.(Mizoue, Kasai, Kubo, & Tokunaga, 2006) Therefore, we can assume that thin patients have a higher risk of oral cavity cancer than normal patients. Conversely, the risk of oral cavity cancer seems to be increased in lean patients due to its unique characteristics. Due to the nature of oral cavity cancer, cancer lesions are located in the oral cavity. Therefore, unlike with other cancers, there is a high probability of developing dysphagia or loss of appetite. Therefore, it can be assumed that weight loss occurred before diagnosis, and the incidence of oral cavity cancer seems to be higher in lean patients.(Alberti, Zimmet, & Shaw, 2005)

Metabolic syndrome is characterized by central obesity, dyslipidemia, hyperglycemia, insulin resistance, and HTN, which lead to various diseases, such as cardiovascular disease and cancers. First, insulin resistance, a core abnormality of metabolic syndrome, increases the risk of cancer. Insulin resistance increases insulin secretion, which results in hyperinsulinemia. Hyperinsulinemia may activate the IGF-1 and insulin receptors or disrupt IGF-binding protein to increase IGF-1 bioavailability to the IGF-1 receptors. The IGF-1 axis might result in tumorigenesis of cancers such as breast, prostate, or endometrium.(Hsing, Gao, Chua Jr, Deng, & Stanczyk, 2003; Lukanova et al., 2004; Muti et al., 2002) In addition, the hyperglycemic state increases protein glycosylation and lipid peroxidation, resulting in toxic products. When an individual has metabolic syndrome with more than three criteria as a risk factor, there is a higher probability of insulin resistance facilitating colorectal cancer.(Laukkanen et al., 2004) Metabolic syndrome is a systemic disease that can affect the oral cavity mucosa. *In vitro* studies are needed to examine whether oral cavity mucosa overexpressing IFG-1 receptors and IGF-1 can induce malignant lesions and cancer. Metabolic syndrome affects insulin resistance and chronic inflammation. In these states, IL-6 is involved in the regulation of immune and inflammatory responses and increases insulin

resistance. The role of IL-6 in carcinogenesis is mediated by autocrine and paracrine mechanisms that stimulate angiogenesis and cell growth and inhibit apoptosis.(Pais, Silaghi, Silaghi, Rusu, & Dumitrascu, 2009; Sonnenberg & Müller, 1993) In our study, metabolic syndrome only increased the risk of oral cavity cancer in males. The HR for oral cavity cancer increased as the number of factors constituting metabolic syndrome increased only in young males aged < 50 years. A possible mechanism to explain this sex difference is the free IGF-1 and adipose tissue levels. Males have a higher circulating concentration of IGF-1, which may be associated with cancer occurrence.(Juul et al., 1994) Adiponectin, a hormone secreted by adipose tissue, has a protective effect on cancer occurrence by decreasing insulin sensitivity.(Esposito et al., 2012) Adiponectin serum levels are higher in females than in males.(Renehan, Tyson, Egger, Heller, & Zwahlen, 2008) Metabolic syndrome affects the metabolism of IGF-1, sex hormones, and sex hormone-binding globulin,(Brand, Van Der Tweel, Grobbee, Emmelot-Vonk, & Van Der Schouw, 2011; Pugeat et al., 2010; Wang, Yu, Tang, Tang, & Liang, 2019) which may cause sex differences in oral cavity cancer. The fact that metabolic syndrome increases the HR for oral cavity cancer only in young males is unexpected. To explain this result, other causes of oral cavity cancer should be considered. Alcohol consumption and smoking are the main causes of oral cancer. Older males (aged > 50 years) had a longer smoking and alcohol history than young males. Therefore, it can be assumed that longer smoking and alcohol history obscure the effect of metabolic syndrome on oral cavity cancer because of the stronger effect of smoking and alcohol consumption. In addition, the association between metabolic syndrome and oral cavity cancer in young males might be the result of genetic issues in oral cavity cancer, which is affected by metabolic syndrome. Further research is needed to evaluate how metabolic diseases affect oral cavity cancers.

The strength of our study is that it is the first cohort study of the association between metabolic syndrome and oral cavity cancer using nationwide data from Korea. Multiple variables such as age, sex, alcohol consumption, and smoking were considered to determine the effects of metabolic syndrome on oral cavity cancer.

5. Conclusion

Metabolic syndrome increases the risk of oral cavity cancer only in males. In addition, the incidence of oral cavity cancer increased as the number of factors constituting metabolic syndrome increased, only in young males aged < 50 years. Thus, metabolic syndrome is an important risk factor for oral cavity cancer, particularly in young males. Further research is needed to determine how metabolic syndrome affects oral cavity cancer, especially in young males.

Declarations

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Competing interests

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Author Contributions

Gang Won Choi: study design, writing, data collection and analysis, revising the article, final approval of the version; Hyeon-Kyoung Cheong: study design, writing, data collection and analysis, revising the article, final approval of the version; Soo Young Choi: data collection and analysis, revising the article; Young Chan Lee: study design, revising the article; In-Hwan Oh: study design, data collection and analysis, revising the article, final approval of the version, supervising this study; Young-Gyu Eun: study design, data collection and analysis, revising the article, final approval of the version, supervising this study.

Data Availability

Datasets generated during the current study are available in the database of the Korean National Health Insurance Service (KNHIS)

Ethics approval

Approval was obtained from IRB board of our institute(299-11-002-002). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate

No need to obtain informed consent

Consent to publish

No need to obtain consent to submission

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