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Original Article

Association of Body Mass Index with Oral Cancer Risk

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Abstract

Purpose: Although obesity is a well-established risk factor for many cancers, the effect of body mass index (BMI) on oral cancer risk remains controversial. We therefore investigated the effect of BMI on oral cancer risk in a case-control study in Korea.

Methods: Overall, 364 patients with oral cancer and 439 community controls were enrolled. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression models, adjusted for age, smoking status and alcohol consumption.

Results: We found no overall significant evidence of an association between oral cancer risk and BMI in either gender. However, when the relationship between BMI and oral cancer risk was examined according to female age groups (<50 and ≥50 years), there was a significant association between oral cancer risk and high BMI in female subjects younger than 50 years of age (OR=3.92, 95% CI 1.03~14.9, *P* for trend=0.04), but not in older (≥50 years) female subjects (OR=1.11, 95% CI 0.55~2.24, *P* for trend=0.76). There was no significant relationship between BMI and oral cancer risk in any of the male age subgroups.

Conclusion: Our study provides the first epidemiological evidence supporting an association between obesity and an increased risk of oral cancer.

Key words: Oral cancer, Obesity, Body mass index

Introduction

Obesity has become one of the major risk factors for cancerand one of the leading causes of death in Western and Asian countries[1-4].

World Cancer Research Fund (WCRF) and the International Agency for Research on Cancer provided evidence that obesity is causally linked to cancer of the colorectum, breast, pancreas, endometrium, kidney, and esophagus[5,6].

However, little evidence regarding the relationship between obesity and oral cancer (including precancerous lesions) is available, and the study results have thus far been inconsistent. Although some populations exhibit inverse relationships between body mass index (BMI) and oral cancer risk as well as the premalignancy of oral cancer, other populations do not showed correlation betwewn BMI and oral cancer risk because the prevalence and degree

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of obesity among populations differs and the association between obesity and oral cancer risk may differ between gender[7-12]. There is sufficient evidence to indicate that the use and abuse of tobacco is a major cause of oral cancer on a global scale[13-18].

Currently, incidence of oral cancer is increasing in non-smoker group including young age woman. Nevertheless, risk factors for oral cancer among non-smokers and non-drinkers, primarily among women, have not been well established. The etiologic factors of oral cancer in women may be different from men because the majority of female oral cancer patients are non-smokers[19-24]. Although Human papillomatous virus (HPV) plays an important role in oropharyngela cancer, HPV is not main etiologic factor for nonsmoker groups in oral cancer patients. Above mentioned, it has been reported that excess body weight may be a major risk factor for cancers. Unfortunately, the percentage of obese adults has greatly increased worldwide. Taken together, the percentage of adults with overweights was also increasing in Korea.

We hypothesized that overweight is a risk factor for oral cancer among the non-smokers. In our study, a case-control study was conducted to assess the relationship between BMI and oral cancer risk in the Korean population.

Materials and Methods

1. Study subjects

Patients with oral cavity and oropharyngeal cancers (Codes C00～C06 of the International Classification of Disease, Tenth Revision), henceforth referred to as oral cancer, were recruited at the National Cancer Center (NCC) and the Seoul National University Dental Hospital (SNUDH) in Korea between 2004 and 2006. Three hundred sixty-four cases (242 men, 122 women) with an initial histopathologic diagnosis of oral squamous cell carcinoma were selected. Subjects ranged in age from 20- to 80-years-old. Community-based cancer-free control subjects were randomly selected during the same study period, and were frequency matched to case distributions according to gender, age (±5 years), and residential region. Thus, a total of 364 cases and 439 community control participants were included in this study. Informed consent was obtained from all subjects after a full explanation of the study, which was approved by the institutional review boards of the Korea National Cancer Center.

2. Exposure assessment

All subjects were interviewed by individuals trained to adhere to institutional guidelines for studies including human subjects. Information was collected using a structured questionnaire on socio-demographic characteristics, smoking, and drinking history. Self-reported height and weight were collected at diagnosis. Subjects were measured only if they did not know their height and weight. Self-reported height and weight were also categorized into tertiles for analyses based on the distribution of each value among control subjects using the highest tertile as the reference category. BMI (kg/m^2), computed as weight in kilograms divided by the square of the height in meters, was categorized using the World Health Organization definition of obesity for Asians (underweight: <18.5 kg/m^2, normal weight: 18.5 to 23 kg/m^2, overweight: 23 to 25 kg/m^2, obesity: >25 kg/m^2)[25]. Because the number of underweight subjects was small in this study, we merged underweight (<18.5 kg/m^2) and normal weight (18.5 to 23 kg/m^2) categories into one normal weight group. Habitual cigarette smoking was defined as having smoked at least once a week for more than 1 year. Similarly, habitual alcohol drinking was defined as consuming any alcoholic beverage at least once a week for more than 1 year. Details on the duration and amount of smoking and alcohol consumption were obtained.

3. Statistical analysis

The mean values and standard deviations were calculated for continuous demographic variables, and the mean differences were tested by t-test or ANCOVA (age-adjusted). Distributions in cigarette smoking and alcohol drinking status among cases and control groups were evaluated using the χ^2 test. Unconditional logistic regression models were used to estimate crude and multivariate odds ratios (ORs) and corresponding 95% confidence intervals (CIs)[26]. Risk estimates were computed with multivariate adjustments for age, smoking habits (ever versus never), and alcohol consumption (ever versus never). Tests for linear trends were calculated by treating the categories as

ordinal variables. All analyses were performed using SAS 9.1 software (SAS Institute, Inc., Cary, NC, USA). The average ages of cases and controls ranged from 43.3 to 55.5 years old and we divided two groups using median value of 43.3 and 55.5 years. So, we conducted subgroup analyses according to age group (<50 and ≥50 years) and smoking behavior and alcohol consumption. All analyses were performed separately according to gender.

Results

1. Characteristics of cases and controls

The selected characteristics of the cases and controls according to gender are provided in Table 1. Cases with oral cancer were older than the controls (mean 54.9 years (cases) and 43.3 years (controls) for males, 55.5 years (cases) and 51 years (controls) for females). Overall, cases were shorter than controls, but mean BMI did not differ between case and control in either gender. There was a higher percentage of current smokers among oral cancer cases in males compared to the control, while the percentage of current drinkers among oral cancer cases was much lower compared to the control for both genders ($P<0.0001$).

2. Weight, height, BMI, and oral cancer risk

Table 2 presents the ORs (95% CI) of oral cancer classi-

Table 1. Distribution of potential risk factors in cases and controls by gender[a]

	Female		*P* value[b]	Male		*P* value[b]
	Case (n=122)	Control (n=244)		Case (n=242)	Control (n=195)	
Age (year)	55.5±15.7	51.0±12.7	0.0061	54.9±13.7	43.3±15.5	<.0001
BMI[c] (kg/m^2)	24.1±3.82	23.4±2.94	0.0902	23.5±2.88	23.8±2.69	0.34
Height (cm)	154±6.81	158±5.10	<.0001	167±6.36	171±5.42	<.0001
Weight (kg)	57.3±9.78	58.0±7.42	0.47	66.0±9.76	69.8±9.01	<.0001
Smoking status						
Non-smoker	116 (95.1)	233 (95.5)	0.86	111 (45.9)	119 (61.0)	0.001
Smoker	6 (4.9)	11 (4.5)		131 (54.1)	76 (39.0)	
Duration of smoking (year)						
Non-smoker	116 (95.1)	233 (97.1)		108 (44.8)	119 (61.3)	
0~10	2 (1.6)	3 (1.3)		12 (4.98)	23 (11.9)	
11~20	2 (1.6)	0 (0)	0.39	28 (11.6)	17 (8.8)	<.0001
21~30	1 (0.8)	2 (0.8)		44 (18.3)	23 (11.9)	
>30	1 (0.8)	2 (0.8)		49 (20.3)	12 (6.2)	
Pack-year						
Non-smoker	116 (95.1)	233 (96.7)		108 (44.6)	119 (61.0)	
0~10	3 (2.5)	6 (2.5)	0.3	12 (5.0)	28 (14.4)	<.0001
11~20	0 (0)	1 (0.4)		44 (18.2)	41 (21.0)	
>20	3 (2.5)	1 (0.4)		78 (32.2)	7 (3.6)	
Alcohol consumption						
Non-drinker	113 (92.6)	130 (53.3)	<.0001	123 (50.8)	43 (22.1)	<.0001
Drinker	9 (7.4)	114 (46.7)		119 (49.2)	152 (77.9)	
Duration of drinking (year)						
Non-drinker	113 (94.2)	130 (54.6)		126 (60.0)	43 (22.6)	
1~10	3 (2.5)	46 (19.3)		10 (4.8)	50 (26.3)	
11~20	3 (2.5)	40 (16.8)	<.0001	26 (12.4)	43 (22.6)	<.0001
21~30	0 (0)	15 (6.3)		30 (14.3)	31 (16.3)	
>30	1 (0.8)	7 (2.9)		18 (8.6)	23 (12.1)	
Mean frequency of alcohol drinking (times per week)						
Non-drinker	113 (93.4)	130 (53.5)		123 (54.7)	43 (22.2)	
<1	4 (3.3)	97 (39.9)		14 (6.2)	63 (32.5)	
1~2	2 (1.6)	14 (5.80)	<.0001	21 (9.3)	51 (26.3)	<.0001
3~4	1 (0.8)	1 (0.4)		31 (13.8)	25 (12.9)	
≥5	1 (0.8)	1 (0.4)		36 (16.0)	12 (6.2)	

[a]Some strata do not add up to the total because of a few missing data.
[b]*P* values are from t-test for continuous variable and from χ^2-test for categorical variables.
[c]BMI, body mass index (kg/m^2).

Table 2. Multivariate odds ratios (ORs) and their 95% confidence intervals (CIs) of oral cancer in relation to weight, height, and body mass index

	Female		Male	
	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)
Weight (kg)[a]				
T1	44/78	1 (ref.)[d]	53/61	1 (ref.)[d]
T2	40/86	0.74 (0.41~1.33)	76/66	0.98 (0.59~1.64)
T3	38/80	0.67 (0.37~1.20)	113/68	0.75 (0.44~1.28)
P for linear trend		0.1803		0.3101
Height (cm)[b]				
T1	70/86	1 (ref.)[d]	41/62	1 (ref.)[d]
T2	22/74	0.39 (0.21~0.73)	55/70	0.47 (0.28~0.79)
T3	30/84	0.45 (0.23~0.86)	146/63	0.58 (0.32~1.03)
P for linear trend		0.007		0.0254
Body mass index (kg/m^2)[c]				
<23	49/115	1 (ref.)[d]	105/80	1 (ref.)[d]
23~24.9	27/59	0.88 (0.47~1.63)	58/56	0.78 (0.45~1.33)
≥25	46/70	1.23 (0.70~2.15)	79/59	1.08 (0.65~1.79)
P for linear trend		0.4998		0.8119
Age <50 y				
Body mass index (kg/m^2)[c]				
<23	22/59	1 (ref.)[d]	33/53	1 (ref.)[d]
23~24.9	7/16	1.49 (0.39~5.64)	23/32	0.93 (0.43~2.02)
≥ 25	13/9	3.92 (1.03~14.9)	27/40	0.76 (0.37~1.58)
P for linear trend		0.045		0.4669
Age ≥50 y				
Body mass index (kg/m^2)[c]				
<23	27/56	1 (ref.)[d]	72/27	1 (ref.)[d]
23~24.9	20/43	0.94 (0.44~2.06)	35/24	0.69 (0.32~1.47)
≥25	33/61	1.11 (0.55~2.24)	52/19	1.71 (0.78~3.74)
P for linear trend		0.7666		0.2213

[a]Tertile 1: ≤53 kg, tertile 2: 53.1~61 kg and tertile 3: >61 kg for female, tertile 1: ≤65 kg, tertile 2: 65.1~73 kg and tertile 3: >73 kg for male.
[b]Tertile 1: ≤155 cm, tertile 2: 155.1~159 cm and tertile 3: >159 for female, tertile 1: ≤169 cm, tertile 2: 169.1~173 cm and tertile 3: >173 for male.
[c]All variables are adjusted for age, smoking status, alcohol consumption.
[d]Reference category.

fied according to height, weight, and BMI by gender. The mean body weight for the male cases was less than the control, but no significant relationship to body weight was determined in either gender. As for BMI, we found no overall significant evidence of association between oral cancer risk and BMI in either gender. However, when the relationship between BMI and oral cancer risk was examined according to female age groups (<50 and ≥50 years), there was a significant association between oral cancer risk and high BMI in female subjects younger than 50 years old (OR=3.92, 95% CI 1.03~14.9, *P* for trend=0.04), but not in older (≥50 years) female subjects (OR=1.11, 95% CI 0.55~2.24, *P* for trend=0.76). There was no significant relationship between BMI and oral cancer risk in any of the male age subgroups. A significant inverse association was found to exist between height and oral cancer risk. Compared with the lowest tertile of height, oral cancer risks were elevated among the highest tertile for both genders (OR=0.45, 95% CI 0.23~0.86, *P* for trend=0.007 in females and OR=0.58, 95% CI 0.32~1.03, *P* for trend=0.02 in males).

We further examined the different effects of BMI on oral cancer risk in a separate category for cigarette smoking and alcohol consumption among female and male subjects (Table 3). The number of female smokers in the Korean population was not enough to allow us to fully examine the effect of BMI on cancer risk. The results among non-smokers were nearly the same as those of all female subjects. Among male smokers, the effect of BMI on oral cancer risk was not the same as in females. Although the results of male non-smokers were not statistically significant, the risk for oral cancer was slightly elevated

Table 3. Multivariate odds ratios (ORs) and their 95% confidence intervals (CIs) of oral cancer in relation to BMI by smoking and alcohol drinking

	Female		Male	
	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)
Smoking status[a]				
Non-smoker				
<23	44/111	1 (ref.)	45/53	1 (ref.)
23~24.9	27/54	1.03 (0.54~1.94)	24/34	0.84 (0.38~1.85)
≥25	45/68	1.35 (0.76~2.40)	42/32	1.79 (0.86~3.72)
		0.3179		0.1294
Smoker				
<23	5/4	1 (ref.)	60/27	1 (ref.)
23~24.9	0/5	-	34/22	0.93 (0.42~2.09)
≥25	1/2	0.38 (0.02~6.66)	37/27	0.87 (0.40~1.87)
		0.2202		0.7123
Alcohol consumption[b]				
Non-drinker				
<23	44/54	1 (ref.)	54/20	1 (ref.)
23~24.9	26/33	0.95 (0.49~1.84)	29/9	1.19 (0.47~3.02)
≥25	43/43	1.20 (0.66~2.18)	40/14	1.20 (0.53~2.73)
		0.5484		0.6475
Drinker				
<23	5/61	1 (ref.)	51/60	1 (ref.)
23~24.9	1/26	0.29 (0.03~3.07)	29/47	0.64 (0.32~1.28)
≥25	3/27	1.99 (0.34~11.6)	39/45	1.06 (0.55~2.06)
		0.6358		0.9153

[a]Adjusted for age, alcohol consumption.
[b]Adjusted for age, smoking status.

(OR=1.79, 95% CI 0.86~3.72) in the highest BMI category (≥25) compared with males in the lowest BMI category (<23). In contrast, oral cancer risk was not elevated among male smokers (OR=0.87, 95% CI 0.40~1.87) in the highest BMI category (≥25). Relationships between BMI and the risk of oral cancer did not differ substantially based on the alcohol consumption habits of each gender.

Discussion

Our case-control study found a statistically significant relationship between BMI and increased risk of oral cancer among young (aged <50), mostly non-smoking Korean females with relatively low BMI levels as compared to Western countries. However, no significant association between BMI and oral cancer was found among males, though tobacco smoking was strongly linked to an increased risk of oral cancer among male subjects. Etiologic factors for oral cancer may differ between males and females, especially in Korea. Most Korean women do not smoke (prevalence rate of 5.8% for females ≥20 years in age), nevertheless the yearly trends for oral cancer incidence have been increasing among both males and females[27,28]. This implies that risk factors other than cigarette smoking may present an oral cancer risk for females. For now, the other risk factors in the non-smoking and/or non-drinking group remain unknown. We attempted to determine the effect of other etiologic factors in female patients, particularly non-smokers, on the risk for oral cancer. Our study found that obesity increases the risk of oral cancer in women. This is the first study to show that obesity is an independent risk factor for female-specific oral cancer in non-smokers from a relatively lean population.

Obesity is an epidemic in Korea and other Asian countries which has drastically increased in recent decades, and the prevalence of cigarette smoking has recently declined[27,29,30]. In addition, obesity-related cancers are reported to be rapidly increasing with the quick-rising obesity epidemic in Korea[30]. Excess body weight has been markedly linked to increased mortality rates, not only from all causes but also from cancer and cardiovascular disease in Western populations[1,2,31]. However, the relationship between body weight and mortality has not been com-

pletely consistent in the Asian population. U-shape, J-shape relationships between BMI and all-cause mortality were observed in the Asian population[3,4]. The risk of death from cancer, however, was higher only in overweight and obese subjects, not in underweight subjects. Much like the Koreans, a higher BMI was linked to an increased risk of cancer among females and non-smoking males in Japan[29]. Unlike other Asian countries, a direct inverse relationship was observed in India[32]. A recent prospective study conducted in India where the mean BMI level is much lower than in Western populations reported that extremely lean (BMI of <16 kg/m^2) or mild-to-moderate lean (BMI of 16~18.4 kg/m^2) individuals exhibited increased all-cause mortality when compared with normal weight individuals (BMI of 18.5 to 23 kg/m^2), while overweight individuals did not experience these trends[32]. However, BMI was not linked to death from cancer.

Several case-control studies have investigated the relationship between BMI, oral cancer risk, and oral premalignant lesions in India with extremely lean populations (very low BMIs) and other populations (Italy, Spain, China, and USA)[7-11,24,32-35]. Although the results of these studies are conflicting, the majority of previous studies reported a negative relationship between BMI and oral cancer risk, and only one study reported no association between BMI and oral cancer risk[7,8,11,22,24,35].

In a study on the Indian population, an inverse relationship was determined between BMI and the risk of oral cancer and leukoplakia[8,9]. The authors concluded that BMI was inversely related to an increased risk of leukoplakia. However, these results should be interpreted with care. The BMI of the referent group (the lowest tetile) was extremely low with a BMI ceiling of 18.3 kg/m^2. And even the BMI cut-point of the highest tertile group was 21.8 kg/m^2 in the study, which corresponds to the lowest BMI category in other populations in a comparison of BMI levels between Western and other Asian populations. Within the Indian population, an increased BMI does not necessarily refer to obesity. Increased body weight for a BMI of 22~23 kg/m^2 may indicate an optimal body weight for this population.

It has been suggested that low BMI is an indicator of low socio-economic status (SES) and poor nutrition and that it exhibits a close relationship with smoking[22,36]. Therefore, several potential explanations for the discrepancy between prior results and our present findings can be investigated. Cigarette smoking and SES are major factors that need to considered when investigating the relationship between BMI and oral cancer risk. Numerous cross-sectional epidemiological studies indicate that body weight, or BMI, is lower in cigarette smokers than in nonsmokers[37,38]. The relationship between oral cancer risk and BMI varies according to individual smoking habits. It is reported that an inverse relationship between BMI and oral cancer risk was restricted to smokers and moderate/heavy drinkers in Italy and Switzerland[7]. Low BMI was strongly linked to an increased risk of oral cancer among current smokers, but not among nonsmokers. These findings suggested that low BMI could be the result of heavy smoking. Although smoking habits were adjusted for in statistical analysis, the confounding effect of smoking cannot be entirely controlled.

Secondly, low BMI is closely related to SES, and this is particularly true for the Indian study[32]. Low SES was prevalent in severely lean subjects (low SES=65%, high SES=1%), whereas high SES was prevalent in obese subjects (low SES=19%, high SES=16%). When the relationship between BMI and total mortality according to SES was taken into account, leanness was not linked to the risk of death in the high SES category. In addition, BMI was not linked to death from cancer. Therefore, it can be concluded that normal weight subjects have a reduced risk for oral cancer compared to extremely lean people (BMI less than 18 kg/m^2). The potential for reverse causality, however, cannot be excluded; Franceschi et al.[7] found that cancers of the oral cavity, pharynx, and larynx cause significant weight loss during preclinical stages.

As with most case-control studies, our case-control study may be influenced by biases. One limitation was the potential measurement errors for the self-reported weight and height, which were collected for the study. However, the reported correlation coefficient between measured and reported BMI was approximately 0.9, making it unlikely that such information bias would have impacted BMI estimates[39]. Although self-reported height tends to be overestimated and weight underestimated, such misinformation is unlikely to differ between case and control groups[40]. Another potential limitation was weight loss due to pre-

clinical disease. Even though we may have underestimated the weight of the case group, we still found a positive association between BMI and oral cancer risk. Third, there remains the possibility that potential confounding factors such as nutrition and diet habit may have been missed.

In conclusion, our results showed that there was no correlation between obesity and oral cancer risk. But, in subgroup analysis, our study demonstrated a significant positive relationship between obesity and oral cancer risk in females younger than 50 years of age. Our data suggest that obesity may be another risk factor for oral cancer, especially nonsmoker female with oral cancer. However, to further clarify whether overweight is a risk factor for oral cancer, prospective multicenter study is need.

Conclusions

Until now, it has been not clear that obesity is another risk factor in oral cancer. But out study showed that obesity might be possible risk factor for nonsmoker women group in oral cancer.

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