Risk factors of head and neck cancer mortality compared with those of all-cause and all-cancer mortalities

Hye Min Cho1), Dae-Woo Lee3), Jeong Jae Park3), Hye Mi Choi4), and Nam-Pyo Cho1)

1) Department of Oral Pathology and Institute of Oral Bioscience, School of Dentistry, Jeonbuk National University, Jeonju, Republic of Korea
2) Department of Pediatric Dentistry and Institute of Oral Bioscience, School of Dentistry, Jeonbuk National University, Jeonju, Republic of Korea
3) Regional Cardiovascular Center, Wonkwang University Hospital, Iksan, Republic of Korea
4) Department of Statistics, Research Institute of Applied Statistics, Jeonbuk National University, Jeonju, Republic of Korea

Abstract: This study aimed to clarify the risk factors of head and neck cancer (HNC) mortality, relative to those of all-cause and all-cancer mortalities, using the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) data set. Data from 238 HNC deaths, 14,769 all-cancer deaths, and 38,086 all-cause deaths were extracted during a median follow-up period of 9.5 years. Baseline characteristics were assessed via chi-square tests, t tests, and multivariable logistic regression. HNC mortality was found to be positively associated with male sex, past and current smoking habits, moderate-to-heavy alcohol consumption, and being underweight. In addition, serum gamma-glutamyltransferase level was found to be significantly elevated in cases of HNC mortality. It was hypothesized that (1) because the NHIS-HEALS serves as a substantial, diverse data resource, some significant HNC mortality factors could be detected, and (2) because the NHIS-HEALS database was constructed via stratified random sampling, main outcomes, such as the effects of smoking and drinking on HNC mortality should be consistent with the results of previous cohort studies.

In the present study, baseline characteristics of HNC (subtypes) mortality cases were assessed relative to those of all-cause or all-cancer mortality to evaluate risk factors of HNC (subtypes) mortality. This study’s objectives were (1) to clarify some significant factors of HNC mortality compared with those of all-cause or all-cancer mortality and (2) to determine differences between HNC subsites using the NHIS-HEALS.

Keywords: diabetes mellitus, drinking, gamma-glutamyltransferase, head and neck cancer mortality, smoking

Introduction

Head and neck cancer (HNC) encompasses a heterogeneous group of malignancies that occur in the lip, oral cavity, pharynx, and larynx. An estimated 686,300 new cases and 375,600 deaths from HNC occurred in 2012 worldwide [1]. Approximately 90% of all HNCs are squamous cell carcinoma, and cigarette smoking (hereafter “smoking”), alcohol consumption (hereafter “drinking”), and human papillomavirus (HPV) are known HNC risk factors [2].

In 2012, the Global Cancer Observatory estimated that the incidence of HNC and its associated mortality rate (per 100,000 people), respectively, were 5.6 and 1.9 in the Republic of Korea (hereafter “Korea”) and 9.1 and 4.9 worldwide [1]. Such a substantial difference could reflect variations in the HNC burden by exposure to risk factors, geographic region, sex, medical care coverage, and so forth. However, not all previous studies have detailed comprehensive demographic and risk factors of HNC mortality.

Recently, the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) data set was released by the NHIS in Korea [3]. The NHIS-HEALS is a cohort of 514,866 examinees who participated in a national health screening program in Korea. The data set includes participants’ sociodemographic information, general health screening data, health care usage records, and death records for the 12-year period from 2002 to 2013.

It was hypothesized that (1) because the NHIS-HEALS serves as a substantial, diverse data resource, some significant HNC mortality factors could be detected, and (2) because the NHIS-HEALS database was constructed via stratified random sampling, main outcomes, such as the effects of smoking and drinking on HNC mortality should be consistent with the results of previous cohort studies.

In the present study, baseline characteristics of HNC (subtypes) mortality cases were assessed relative to those of all-cause or all-cancer mortality to evaluate risk factors of HNC (subtypes) mortality.

This study’s objectives were (1) to clarify some significant factors of HNC mortality compared with those of all-cause or all-cancer mortality and (2) to determine differences between HNC subsites using the NHIS-HEALS.

Materials and Methods

Data sources

The NHIS-HEALS was generated from a random stratified selection (by sex, age, and household income level) of a representative sample of 514,866 examinees, comprising about 10% of all eligible Koreans aged 40-79 years who had health insurance from the NHIS and who had undergone health screenings in 2002 or 2003. The NHIS provides a general health screening to all insurance beneficiaries every two years. Data collected during such checkups include anthropometric measures, sociodemographic factors, basic biochemical data, personal medical histories, oral and general health status records, and death records by the end of 2013. The specific structures and functions of the NHIS-HEALS have been described elsewhere [3]. The Institutional Review Board of Jeonbuk National University approved the study protocol (#JBNU 2016-06-010).

Subjects

The data of 238 HNC deaths, 14,769 all-cancer deaths, and 38,086 all-cause deaths were extracted during a median follow-up period of 9.5 years. The causes of death were classified according to the Korean Standard Classification of Diseases and Causes of Death, a modified version of the International Classification of Diseases 10th Revision (ICD-10), provided by the Korean National Statistical Office.

HNC was reclassified into three subtypes based on the subclassification scheme proposed by Hashibe et al [4]: oral cavity cancer (OCC; ICD codes C02-04, C06, and C14), oro-hypopharyngeal cancer (OHPC; C01, C05, C09-10, and C12-13), and laryngeal cancer (LC; C32).

In line with previous studies [5,6], cancers of the lip (ICD-10: C00), salivary glands (C07-C08), nasopharynx (C11), nasal cavity and middle ear (C30), and accessory sinuses (C31) were excluded from the analysis because of their divergent or unknown etiological pathways. For a competing risk assessment for HNC mortality, all-cause (ICD-10: A00-Z99) and all-cancer (ICD-10: C00-C97) mortalities were used as a comparison group.

In the present study, cohort members with missing information at the baseline were excluded from each mortality category. Therefore, the total number of subjects in each category was not uniform because of differences in missing values for each category.
Definition of variables

Of the 13 variables used in the insurance eligibility database of the NHIS-HEALS cohort, 2002-2013, the following variables were evaluated: (1) demographic and behavioral data: age; sex; smoking (never smoker, ex-smoker, current smoker <10 pack-years [light], 10-19 pack-years [moderate], and ≥20 pack-years [heavy]); drinking (nondrinking, 1-14 g/day [mild], 15-48 g/day [moderate], and ≥49 g/day [heavy]); body mass index (BMI <18.5 [underweight], 18.5-22.9 [normal], 23.0-24.9 [overweight], and ≥25.0 [obese]); socioeconomic level based on household income decile (0-2 [low], 3-8 [middle], and 9-10 [high]); oral status: lost teeth, dental caries, periodontal disease; (3) medical history: hypertension, diabetes mellitus (DM); and (4) biochemical data: total cholesterol, preprandial blood glucose (fasting blood glucose [FBG]), gamma-glutamyltransferase (GGT), aspartate transaminase (AST), and alanine transaminase (ALT) levels.

Sociodemographic characteristics were acquired through self-administered health screening questionnaires and from the NHIS database. Health screening followed a standard procedure and was conducted by medical staff at local hospitals. Oral health status was evaluated by the "presence" or "absence" of missing teeth, dental caries, and periodontal disease. The examinations were carried out by dentists at each local hospital in Korea. A medical history of hypertension and DM was defined from the physicians' diagnoses or based on whether medications were being taken. Serum total cholesterol, FBG, GGT, AST, and ALT levels were obtained after a fast longer than 8 h.

To ensure risk estimates' reliability and international comparability, most confounding variables were classified into categories based on international recommendations, classifications used in previous studies, and standards of the NHIS-HEALS. In contrast, basic biochemical data, such as total cholesterol, FBG, GGT, AST, and ALT levels, were presented as continuous values.

Statistical analysis

The main outcome variables used were HNC-specific mortality, all-cancer mortality, and all-cause mortality for the cohort period. To compare the baseline characteristics of HNC mortality with all-cause or all-cancer mortality, the chi-square test for categorical variables and the t-test for continuous variables were used. Further, the main outcomes against smoking habits alone, drinking habits alone, and smoking and drinking habits combined for the overall HNC and three HNC subsites were assessed. Age and sex were considered predefined confounders. Other variables with P < 0.2 were considered potential confounders for the association between cases and controls. A cutoff value of 0.2 was chosen to avoid collinearity of variables in the regression analysis [7]. The effects of smoking and drinking on the risks of HNC (subtypes) mortality were assessed in terms of odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable logistic regression models adjusted for predefined and potential confounders. Heterogeneity (ψ²) represented multiplicative interactions of baseline smoking and drinking habits with risks of HNC mortality compared with those of all-cause or all-cancer mortality. ψ² > 1 suggested a joint effect that was greater than expected under the multiplicative model.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The participants' baseline characteristics, according to the selected variables, are presented in Table 1. Higher proportions of HNC mortality cases were males, past and current smokers, and moderate and heavy drinkers compared with those of all-cause or all-cancer mortality cases. Regarding BMI values, there was a higher proportion of overweight participants in the HNC mortality group than in the all-cause or all-cancer mortality groups; however, the proportion of obese individuals was inversely associated with HNC mortality. Among HNC subtypes, baseline characteristics of OHPC and LC mortality cases, relative to all-cause or all-cancer mortality, were found to be very similar to those of overall HNC mortality relative to all-cause or all-cancer mortality. However, mortality risks of OCC were not significantly associated with any baseline characteristics.

Health screening characteristics at the baseline for all-cause, all-cancer, and HNC (subtypes) mortalities are shown in Table 2. The most obvious finding of the baseline biochemical analysis was a significant increase in serum GGT level among HNC mortality cases relative to those of all-cause or all-cancer mortality. It was also interesting that a history of DM and serum FBG level were significantly decreased among HNC mortality cases relative to those of all-cause mortality.

The associations between smoking and HNC (subtypes) mortality and all-cause mortality are presented in Table 3. Heavy smoking (OR = 1.63,
Table 2: Health screening characteristics at baseline for all-cause, all-cancer, and head and neck cancer (subtypes) mortalities for the National Health Insurance Service-Health Screening Cohort, 2002-2013

| Characteristics | All-cause mortality | All-cancer mortality | Overall Subtypes | Head and neck cancer mortality |
|----------------|---------------------|----------------------|----------------|------------------------------|
|                | (n = 38,086)        | (n = 14,769)         | OCC*           |          |
|                |                     |                      | OHPC*          | LC*  |
|                |                     |                      | (n = 62)       | (n = 81) |
|                |                     |                      | (n = 95)       |        |
| Oral health status |                   |                      |                |        |
| Missing teeth |                     |                      |                |        |
| Absence (%)   | 8,545 (63.1)        | 3,488 (65.0)         | 52 (65.8)      | 16 (59.3) |
| Presence (%)  | 4,993 (36.9)        | 1,878 (35.0)         | 27 (34.2)      | 11 (40.7) |
| Dental caries |                     |                      |                |        |
| Absence (%)   | 10,565 (78.0)       | 4,240 (79.0)         | 62 (78.5)      | 20 (74.1) |
| Presence (%)  | 2,973 (22.0)        | 1,126 (21.0)         | 17 (21.5)      | 7 (25.9) |
| Periodontal disease |               |                      |                |        |
| Absence (%)   | 6,616 (48.9)        | 2,568 (47.9)         | 39 (48.4)      | 10 (37.0) |
| Presence (%)  | 6,922 (51.1)        | 2,798 (52.1)         | 40 (50.6)      | 17 (63.0) |
| Medical history |                   |                      |                |        |
| History of hypertension |               |                      |                |        |
| Absence (%)   | 32,230 (84.6)       | 12,969 (87.8)        | 208 (87.4)     | 50 (80.7) |
| Presence (%)  | 5,856 (15.4)        | 1,800 (12.2)         | 30 (12.6)      | 12 (19.4) |
| History of diabetes |             |                      |                |        |
| Absence (%)   | 34,376 (90.3)       | 13,711 (92.8)        | 229 (96.2)     | 58 (93.6) |
| Presence (%)  | 3,710 (9.7)         | 1,058 (7.2)          | 9 (3.8)        | 4 (6.5)  |
| Biochemical category |             |                      |                |        |
| Total cholesterol (mg/dL) |       | 196.2 (42.8)         | 193.7 (41.6)   | 191.8 (40.5) |
| FBG (mg/dL) | 108.7 (50.6) | 104.4 (42.9) | 103.4 (39.3) | 106.0 (38.1) |
| GGT (U/L) | 58.1 (104.5) | 58.6 (99.1) | 76.8 (127.3) | 62.2 (96.4) |
| ALT (U/L) | 33.3 (31.9) | 34.1 (32.7) | 35.8 (33.4) | 33.1 (22.4) |

Table 3: Adjusted odds ratios (ORs) for head and neck cancer (subtypes) mortality compared with all-cause mortality associated with baseline smoking in the National Health Insurance Service-Health Screening Cohort, 2002-2013

| Smoking (pack-years) | All-cause mortality | Head and neck cancer mortality |
|---------------------|---------------------|------------------------------|
|                     | (n = 36,135)        | (n = 231)                    |
|                    | OR* (95% CIs)       | (OR* (95% CIs))              |
| Never smoker (0)    | 20,818              | 91                           | 1 (reference) | 32 | 1 (reference) | 30 | 1 (reference) | 29 | 1 (reference) |
| Ex-smoker           | 3,461               | 30                           | 1.33 (0.87, 2.05) | 6 | 0.94 (0.38, 2.35) | 7 | 0.81 (0.35, 1.88) | 17 | 2.22 (1.19, 4.14) |
| Light smoker (1-10) | 4,267               | 26                           | 0.90 (0.57, 1.42) | 10 | 1.16 (0.54, 2.49) | 10 | 0.95 (0.45, 2.00) | 6 | 0.60 (0.25, 1.49) |
| Moderate smoker (10-19) | 2,034             | 15                           | 1.07 (0.59, 1.95) | 1 | 1.07 (0.93, 1.96) | 8 | 0.47 (0.27, 0.65) | 6 | 0.66 (0.44, 0.98) |
| Heavy smoker (≥20)  | 5,555               | 69                           | 1.63 (1.14, 2.33) | 12 | 1.14 (0.54, 2.40) | 25 | 1.34 (0.73, 2.43) | 32 | 2.37 (1.36, 4.15) |

95% CI: 1.14-2.33) was related to an increased overall HNC mortality rate. Among HNC subtypes, past smoking (OR = 2.22, 95% CI: 1.99-4.14) and heavy smoking (OR = 2.37, 95% CI: 1.36-4.15) were independently associated with LC mortality. A significant trend for increasing overall HNC mortality risk (P trend = 0.008) and LC mortality risk (P trend = 0.001) relative to all-cause mortality risk was also found as the number of pack-years for smoking increased.

Associations between alcohol consumption at baseline and HNC (subtypes) mortality relative to all-cause mortality are summarized, with their adjusted ORs and 95% CIs, in Table 4. Compared with nondrinkers, heavy drinkers had a significantly higher risk of overall HNC (OR = 1.62, 95% CI: 1.05-2.49) and OHPC (OR = 1.62, 95% CI: 1.21-4.67) mortality. Moreover, a significant trend for increasing overall HNC mortality risk (P trend = 0.023) and OHPC mortality risk (P trend = 0.017) with increasing alcohol consumption was also noted.

The joint effect of heavy smoking and heavy drinking relative to non-smoking and nondrinking is shown in Table 5. The joint effect was strongly associated with overall HNC mortality (OR = 2.02, 95% CI: 1.09-3.76) and OHPC (OR = 3.69, 95% CI: 1.52-8.97) relative to all-cause mortality. Test for heterogeneity among HNC (subsites) was greater than expected under the multiplicative scale (ψ: 1.41, 95% CI: 1.05-1.90). Although the result was not statistically significant, the joint effect for overall HNC mortality, relative to all-cause mortality, was greater than expected under the multiplicative scale (ψ: 1.19, 95% CI: 0.98-1.44).

Discussion

This study investigated the impact of baseline sociodemographic characteristics, health status, and medical history on mortality risks of HNC using the NHIS-HEALS data set. As Koreans are relatively homogeneous in ethnicity and cultural background [8], this cohort data set can serve as...
a useful tool to study multifactorial disorders such as HNC. Moreover, because the NHIS-HEALS has already been processed for data mining and deidentified from patient data via the NHIS, an enormous wealth of useful health information can be obtained at a minimal cost.

In this study, most of the HNC mortality cases occurred among males (88.2%). Although males presented a higher proportion of all-cause (68.1%) and all-cancer (73.0%) mortalities than females (Table 1), the male to female ratios for overall HNC and subtype mortalities were significantly higher than those of all-cause and all-cancer mortalities. These findings imply that smoking and drinking, well-known HNC risk factors, are responsible for a large proportion of HNC mortality risks, consistent with the results of previous studies [4,9,10]. According to the NHIS-HEALS, 42.3% of men and 96.2% of women studied were nonsmokers, and 35.1% of men and 82.5% of women studied were rare drinkers [3]. Moreover, in these multivariable models, smoking and drinking status at the time of health screening had independent and multiplicative effects on HNC mortality risks relative to all-cause and all-cancer mortalities. Interestingly, the relative risk of cancer mortality associated with smoking in Korea has been reported to be much lower compared with that reported in Western countries but similar to the risk in Japan or China [11]. These results may reflect the differences in the time period of the tobacco epidemic, ages at initiation of smoking, formulation of cigarettes, and differences in genetic susceptibility between Western and Asian populations.

In the present study, when HNC subtype mortalities were compared with all-cause mortality, LC mortality was found to be most strongly associated with past and heavy smoking, and OHPC mortality was most strongly associated with heavy drinking. However, OCC was the least associated with smoking and drinking. These results are generally in line with those of previous studies showing that smoking has a stronger effect on LC than OCC [12-14] and that OHPC is most closely associated with drinking [4,13]. The differential effects of smoking and drinking on the mortality risks of HNC subtypes are likely attributable to differences in exposure according to subsites of the head and neck. However, unlike the present study, Maasland et al. [14] reported a strong association between OCC and alcohol consumption. Hence, the possibility cannot be ruled out that the observed discrepancy in results is partially due to the small sample size.

In the present study, being underweight (BMI < 18.5 kg/m²) was associated with a higher risk of overall HNC and LC mortalities compared with all-cause and all-cancer mortalities, whereas obesity (BMI ≥ 25.0 kg/m²) showed an inverse association. In previous studies [15,16], the impact of BMI on HNC incidence and mortality was found to be controversial, as BMI is intricately related to smoking and drinking habits, nutritional status, and exercise habits. Therefore, additional studies, based on behavioral and nutritional data collected prospectively, are needed to clarify the precise role of BMI in HNC incidence and mortality.

A noteworthy finding derived from the present analysis for biochemical parameters is an inverse association between a history of DM and FBG and risks of overall HNC mortality relative to those of all-cause mortality. Previous studies on the association between DM and HNC (subtypes) incidence and mortality have shown contradictory results [17-21]. Most studies have demonstrated that DM could be correlated with greater risks of HNC mortality [17,19,20], whereas other studies have implied an inverse association between DM and HNC mortality [18,21]. These inconsistencies among various investigations might be attributed to the participants’ genetic backgrounds and to a lack of control for confounding factors, such as age, sex, obesity, smoking habits, and drinking habits during the analysis [22]. Several mechanisms underlying the roles of DM and hyperglycemia in HNC carcinogenesis have been proposed, including hyperinsulinemia contributing to cancer cell metabolism, hyperglycemia contributing to fuel proliferation in neoplasms, and the overproduction of reactive oxygen species [23-25]. By contrast, a few studies have shown that...
metformin, an oral hypoglycemic agent belonging to the biguanide family, can reduce the risks of gastric [26], colorectal [27], lung [28], and head and neck [21] cancers. Unfortunately, the present study could not evaluate the effects of metformin on the risk of HNC because of issues with data availability; thus, large prospective studies assessing the anticarcinogenic effects of DM and antidiabetic drugs must be conducted in the future.

Mounting evidence indicates that liver biomarkers may provide prognostic and predictive information regarding various cancers without hepatic involvement [29-31]. In the present study, baseline serum GGT levels were found to be significantly elevated in cases of overall HNC mortality relative to cases of all-cause or all-cancer mortalities. However, AST and ALT levels were not found to be associated with HNC (subtypes) mortality relative to all-cause or all-cancer mortality, except for a significant decrease in ALT level found for overall HNC mortality relative to all-cause mortality. GGT is a cell surface glycoprotein that can modulate glutathione metabolism [32]. Several studies have suggested that GGT levels are elevated in cancers of various organs and may play a role in the carcinogenesis of various tissues [29,33,34]. Although the underlying mechanisms are uncertain, the current analysis indicates that elevated serum GGT may be significantly associated with increased risks of HNC (subtypes) mortality. Recently, Heikkilä et al. [35] reported a strong association between periodontitis and overall cancer mortality. Moreover, a positive correlation between poor oral hygiene and the risk of oral cancer has also been reported [36,37]. In the present study, oral health status was not significantly related to HNC mortality relative to all-cause or all-cancer mortality. This result might be attributed to the very simple criterion for oral health status based on presence and absence. Furthermore, the lack of association between oral health status and HNC mortality to all-cause or all-cancer mortality may have affected the analysis because oral health status can be correlated with all-cause, all-cancer, and HNC mortalities.

In the present study, other factors, such as socioeconomic status (SES) and a history of hypertension, were not significantly associated with HNC mortality compared with all-cause or all-cancer mortality. Although some studies have shown a negative SES gradient in HNC mortality [38,39], this study’s results suggested a lack of association between SES and HNC mortality. Based on various measurement criteria for SES, such as household income, educational level, work status, and inequality in health care services, this discrepancy may be attributed to differences in categorical standards and universal health care coverage in Korea. Although hypertension itself and antihypertensive drugs may be associated with low cancer-specific mortality and an increased recurrence of head and neck squamous cell carcinoma [40,41], HNC mortality relative to all-cause or all-cancer mortality was not significantly associated with hypertension. This may be related to insufficient information available on the duration and severity of hypertension and the use of antihypertensives.

This study has several strengths. First, the analysis of risk factors for HNC mortality was expanded by using a national health screening data set based on sociodemographic information, general and oral health screening results, clinical laboratory data, and death records. Second, a large data set was obtained at minimal cost, and selection bias was avoided by using the NHIS-HEALS data set established by the NHIS, which covers the health care system available to the entire population of Korea (50 million). Third, as the NHIS-HEALS data set was generated via a random stratified selection of the Korean population, which is relatively homogeneous in ethnicity and cultural background, hidden or unknown factors can be disregarded, and this data set can be used to study multifactorial disorders such as HNC. Fourth, risk factor estimates for HNC mortality used in this study were derived from a comparison with all-cancer and all-cause mortalities, generating more reliable results.

This study also has several limitations. First, the death certificate-based mortality approach taken in the present study is limited because of the underreported cases and miscategorized causes of death. However, previous studies reported the estimated accuracy of cause of death and cancer mortality data of the Korean National Statistical Office to be 92% [42] and 91.6% [3], respectively. Therefore, the results of the present population-based mortality study can be used as a convenient proxy measure of the risk factors of HNC. Second, variables of health behaviors, such as smoking and drinking habits, are limited because such data were obtained from self-reported information only. Accordingly, smoking and drinking habits may be underestimated because heavy drinking and smoking (particularly among females) are considered socially unacceptable in Korea. Such misclassification could have led to information bias, which could have resulted in underestimating risks. However, a previous Korean study, based on a questionnaire on drinking, was found to be highly reliable and valid [43]. Third, as variables analyzed in this study were based on baseline status, changes that occurred during the follow-up period could not be tracked. Fourth, information on other potential confounding variables, such as HPV infection, second-hand smoke exposure, nutritional factors, and treatment efficacy, could not be assessed.

In conclusion, the present study, based on the NHIS-HEALS data set, demonstrates that variables such as a history of DM, BMI, and serum GGT levels, as well as major risk factors of HNC mortality such as smoking and drinking habits, are associated with HNC (subtypes) mortality risks. These results provide substantial evidence showing that big data resources, such as the NHIS-HEALS, will attract much attention for a wide range of health-related studies. In the future, nationwide health information infrastructure and international collaboration will continue to improve and become more capable of supporting health research on new strategies for the prevention, early diagnosis, and treatment of various diseases.

Conflict of interest
None declared.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136, 368-414.
2. Wyss AB, Hushibe M, Lee YA, Chung SC, Muscat J, Chen C et al. (2016) Smokeless tobacco use and the risk of head and neck cancer: pooled analysis of US studies in the INHANCE Consortium. Am J Epidemiol 184, 703-716.
3. Seong SC, Kim YY, Park SK, Kang YH, Kim HC, Park JH et al. (2017) Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open 7, e016640.
4. Hashish M, Brennan P, Chen K, Chung SC, Boccia S, Castleselange X, Chen C et al. (2009) Interac tion between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 18, 541-549.
5. Simard EF, Torre LA, Jemal A (2014) International trends in head and neck cancer inci dence rates: differences by country, sex and anatomic site. Oral Oncol 50, 387-403.
6. Hagedorn P, Vandenhende H, Vanthomme K, Willaert D, Gadeyne S (2016) A cohort study into head and neck cancer mortality in Belgium (2001-11): are individual socioeconomic differences conditional on area deprivation? Oral Oncol 61, 76-82.
7. Sun GW, Shook TL, Kay GL (1996) Inappropriate use of bivariate analysis to screen risk factors for use in multivariable analysis. J Clin Epidemiol 49, 907-916.
8. Lee JH, Lee JS, Choi JK, Kweon HI, Kim YT, Choi SH (2016) National dental policies and socio-demographic factors affecting changes in the incidence of periodontal treatments in Korea: a nationwide population-based retrospective study from 2002-2013. BMC Oral Health 16, 118.
9. La Vecchia C, Tavani A, Franceschi S, Levi F, Corrao G, Negri E (1997) Epidemiology and prevention of oral cancer. Oral Oncol 33, 302-312.
10. Robertson G, Greenlaw N, Steering Group Committee for the Scottish Audit of Head and Neck Cancers, Bray CA, Morrison DS (2010) Explaining the effects of socio-economic deprivation on survival in a national prospective cohort study of 2019 patients with head and neck cancers. Cancer Epidemiol 34, 682-688.
11. Park S, Jee SH, Shin HR, Park EH, Shin A, Jung KW et al. (2014) Attributable fraction of tobacco smoking on cancer using population-based nationwide cancer incidence and mortality data in Korea. BMC Cancer 14, 406.
12. Zeka A, Gore R, Kriebel D (2003) Effects of alcohol and tobacco on aerodigestive cancer risks a meta-regression. Cancer Causes Control 14, 897-906.
13. Lubin JH, Purdue M, Kelsey K, Zhang ZF, Winn D, Wei Q et al. (2009) Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. Am J Epidemiol 170, 937-947.
14. Masseau DH, Brandt PA, Kremer B, Goldbheim A, Schouten LJ (2014) Alcohol consump tion, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study. BMC Cancer 14, 187.
15. Gaudet MM, Olshan AF, Chuang SC, Berthiller J, Zhang ZF, Lisowski J et al. (2010) Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. Int J Epidemiol 39, 1091-1102.
16. Teghizadeh N, Boeren HM, Schouten JP, Schröder CP, Elieshabel de Vries EG, Vink JM (2015) BMI and lifetime changes in BMI and cancer mortality risk. PLoS One 10, e0125261.
17. Jee SH, Ohrr H, Sull JW, Yun J, Jee I, Kim M (2005) Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293, 194-202.
18. Stott-Miller M, Chen C, Schwartz SM (2013) Type I diabetes and metabolic syndrome in relation to head and neck squamous cell carcinoma risk: a SEER-Medicare database study. Cancer Epidemiol 37, 428-433.
19. Tseng KS, Lin C, Lin YS, Weng SF (2014) Risk of head and neck cancer in patients with diabetes mellitus: a retrospective cohort study in Taiwan. JAMA Otolaryngology Head Neck Surg 140, 746-753.
20. Gong Y, Wei B, Wu L, Pan W (2015) Type 2 diabetes mellitus and risk of oral cancer and precancerous lesions: a meta-analysis of observational studies. Oral Oncol 51, 332-340.
21. Figueiredo RA, Weiderpass E, Tajara EH, Ström P, Carvalho AL, de Carvalho MB et al. (2016) Diabetes mellitus, metformin and head and neck cancer. Oral Oncol 61, 47-54.

22. Liu CJ, Chang WJ, Chen CY, Sun FJ, Cheng HW, Chen TY et al. (2015) Differentiation of insulin receptor substrates 1 and 2 by insulin-like growth factor-activated insulin receptors. Mol Cell Biol 27, 3569-3577.

23. Giovannucci E, Harlan DM, Archer MC, Bergensdal RM, Gapturst SM, Habel LA et al. (2010) Diabetes and cancer: a consensus report. Diabetes Care 33, 1674-1685.

24. Denley A, Carroll JM, Brierley GV, Cosgrove L, Wallace J, Forbes B et al. (2007) Differential activation of insulin receptor substrates 1 and 2 by insulin-like growth factor-activated insulin receptors. Proc Natl Acad Sci U S A 67, 1248-1255.

25. Van Hemelrijck M, Jassem W, Walldius G, Fentiman IS, Hammar N, Lambe M et al. (2011) Gamma-glutamyltransferase and risk of cancer in a cohort of 545,460 persons - the Swedish AMORIS study. Eur J Cancer 47, 2033-2041.

26. Mok Y, Son DK, Yun YD, Jee SH, Samet JM (2016) Gamma-glutamyltransferase and cancer risk: the Korean cancer prevention study. Int J Cancer 138, 311-319.

27. Orlowski M, Meister A (1970) The γ-glutamyl cycle a possible transport system for amino acids. Proc Natl Acad Sci U S A 67, 1248-1255.

28. Van Hemelrijck M, Jassem W, Walldius G, Fentiman IS, Hammar N, Lambe M et al. (2011) Gamma-glutamyltransferase and risk of cancer in a cohort of 545,460 persons - the Swedish AMORIS study. Eur J Cancer 47, 2033-2041.

29. Rachet B, Quinn MJ, Cooper N, Coleman MP (2008) Survival from cancer of the larynx in England and Wales up to 2001. Br J Cancer 99 Suppl 1, S35-S37.

30. McDonald JT, Johnson-Obaseki S, Hwang E, Connell C, Corsten M (2014) The relationship between survival and socioeconomic status for head and neck cancer in Canada. J Otolaryngol Head Neck Surg 43, 2.

31. Kim SA, Moon H, Roh JH, Kim SB, Choi SH, Nam SY et al. (2017) Prognostic utility of β-blockers and other antihypertensive drugs and the risk of recurrence and mortality in breast and head and neck cancer patients: an observational study of 10,414 person-years of follow-up. Clin Transl Oncol 19, 826-833.

32. Liang J, Li G, Xu J, Wang T, Jia Y, Zhai Q et al. (2018) Hypertension predicts a poor prognosis in patients with esophageal squamous cell carcinoma. Oncotarget 9, 14068-14076.

33. Won TY, Kang BS, Im TH, Choi HJ (2007) The study of accuracy of death statistics. J Korean Soc Emerg Med 18, 256-262.

34. Park BJ, Kim DS, Koo HW, Bae JM (1998) Reliability and validity study of a life style questionnaire for elderly people. J Prev Med Pub Health 31, 49-58.