Risk of Head and Neck Cancer in Patients With Diabetes Mellitus
A Retrospective Cohort Study in Taiwan

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An increasing body of evidence suggests that certain types of cancers are more common in people with diabetes mellitus (DM). However, the risk of head and neck cancer (HNC) in patients with DM has seldom been explored.

OBJECTIVE To examine the risk of HNC in patients with DM.

DESIGN, SETTING, AND PARTICIPANTS In this retrospective cohort study using Taiwan’s Longitudinal Health Insurance Research Database, we compared 89,089 patients newly diagnosed as having DM and controls without DM-related medical claims matched for comorbidities (obesity, coronary artery disease, hyperlipidemia, and hypertension), sex, and age. Patients were assessed from the index date until the end of follow-up on December 31, 2011, or until the patient was censored because of death.

MAIN OUTCOMES AND MEASURES The incidence of HNC at the end of 2011.

RESULTS The incidence of HNC was 1.47 times higher in patients newly diagnosed as having DM than was the risk of a first malignant tumor in the control group (adjusted hazard ratio [AHR], 1.48; 95% CI, 1.31-1.67). The risks of oral cancer (AHR, 1.74; 95% CI, 1.47-2.06), oropharyngeal cancer (AHR, 1.53; 95% CI, 1.01-2.31), and nasopharyngeal carcinoma (AHR, 1.40; 95% CI, 1.03-1.89) were significantly higher in patients with DM than in controls.

CONCLUSIONS AND RELEVANCE Diabetes is associated with an increased risk of developing HNC. The risks of developing oral cavity cancer, oropharyngeal cancer, and nasopharyngeal carcinoma were significantly higher in patients with DM.

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Head and Neck Cancer in Patients With Diabetes

Original Investigation Research

A retrospective cohort study was conducted with 2 study groups: a DM cohort and a matched non-DM control cohort. The DM cohort consisted of patients with a first-time diagnosis of DM (ICD-9-CM code 250) in 2002. Information that identified patients with DM was based on a minimum of 2 visits or a corresponding diagnosis provided by referral teaching hospitals and tertiary referral medical centers. We identified 89,530 patients with DM-related medical claims, matched (1 to 1 case-control matching) for sex, age, geographic distribution, monthly income, and the comorbidities of obesity, coronary artery disease, hypertension, hyperlipidemia, and chronic kidney disease, chronic obstructive pulmonary disease, and chronic obstructive pulmonary disease (ICD-9-CM code 490-496, a surrogate for smoking) were selected as the comparison cohort. The index date for the patients in the DM cohort was the date of their first diagnosis of DM. The index date for the patients in the non-DM cohort was created by matching the year of the index date of patients in the DM cohort. Head and neck cancers (ICD-9-CM codes 140-149, excluding code 142, and 160-161) presented after the index date were classified as follows: oral cavity (ICD-9-CM codes 140, 141.1-141.4, 143-145, and 149), oropharynx (ICD-9-CM codes 140.1 and 146), hypopharynx (ICD-9-CM code 148), rhinosinusitis (ICD-9-CM code 160), nasopharynx (ICD-9-CM code 147), and larynx (ICD-9-CM code 161). The patients were linked to the registry of Taiwan’s Catastrophic Illness Patient Database to identify those whose diagnosis of cancer had been histologically confirmed. A routine peer review is conducted within the Taiwan Health Insurance Bureau to maintain consistency in the diagnoses in every referral teaching hospital and tertiary referral medical center. This study is retrospective because all the data had been collected before the study was designed; however, the data were analyzed to project possible future outcomes. To determine the incidence of HNC, each patient was assessed from the index date until the end of follow-up on December 31, 2011, or until the patient was censored because of death.

Statistical Analysis

Descriptive statistical analyses using Pearson χ² tests were performed to compare differences in sociodemographic characteristics and comorbidities between the DM and non-DM cohorts. The incidence rate was calculated as the number of HNC incidents identified during patient follow-up, divided by the total person-years for each cohort by sex, age, and the number of follow-up years. The risk of developing HNC in each cohort was compared by estimating the incidence rate ratio (IRR) using Poisson distribution regression analysis. The risk of developing HNC at various anatomical sites in the DM cohort was estimated using Cox proportional hazards models, the cumulative incidence rates of HNC in the 2 cohorts were calculated using Cox proportional hazards regression analyses and Kaplan-Meier analyses, and differences between the survival curves of the 2 cohorts were analyzed using a log-rank test. To meet the proportional hazards assumption, each dichotomous variable in the model was tested for proportionality using investigatory diagnostic log-log survival plots. A Cox proportional hazards regression analysis with propensity score matching was used to estimate the hazard ratio between the DM and non-DM cohorts. Propensity score matching, which can bundle many confounding covariates that may be present in an observational study with a large number of variables, was used to reduce any selection bias in our hypothesis. Score matching identified the predicted probability of obtaining one patient with DM vs one without DM from the logistic regression model using the baseline covariates of age, sex, and the comorbidities of obesity, coronary artery disease, hyperlipidemia, and hypertension. SAS statistical software, version 9.2 (SAS Institute Inc), was used for all analyses. Significance was set at P < .05 (2-tailed).

Results

Correlation of HNC Incidence With Patient Characteristics

No significant differences were found in the distribution of sex, age, geographic distribution, monthly income, or comorbidities.
ties (P > .99 for all) (Table 1). We compared the differences in the estimated risk of HNC between the DM and non-DM cohorts by sex, age, and number of follow-up years. By the end of the follow-up period, the incidence of HNC was 1.47 times higher in the DM cohort than in the non-DM cohort (P < .001) (Figure 1). No significant difference was found in the mean interval between the index date and the occurrence of HNC in the DM and non-DM cohorts (P = .39). The mean (SD) age in the DM cohort at the diagnosis of HNC was 55.52 (15.13) years. The incidence of HNC was significantly higher in DM cohort patients aged 40 to 65 years than in non-DM cohort patients aged 40 to 65 years (IRR = 1.57, P < .001) (Table 2). The HNC incidence rate was also significantly different based on sex (IRR, 1.48; 95% CI, 1.31-1.69; P < .001 for men) (Table 2).

Adjusted Hazard Ratios of HNC for Different Anatomical Sites in the DM Cohort

A multivariate Cox proportional hazards regression analysis, adjusted for sex, age, comorbidities (obesity, hypertension, hyperlipidemia, coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease), geographic distribution, and monthly income, revealed an adjusted hazard ratio (AHR) of 1.48 (95% CI, 1.31-1.67) for HNC between the DM and non-DM cohorts (Table 3). The incidence of HNC in the oral cavity was the highest (0.41%) in the DM cohort; the AHR (1.74; 95% CI, 1.47-2.06) for HNC in the oral cavity was also the highest. The incidence of HNC in the oropharynx in the DM cohort was 0.06% (AHR, 1.53; 95% CI, 1.01-
The incidence of HNC in the nasopharynx in the DM cohort was 0.11% (AHR, 1.40; 95% CI, 1.03-1.89).

### Association of HNC With Comorbidities

To examine the effects of the comorbidities, the IRR for each comorbidity was calculated in the DM and the non-DM cohorts (Table 2). The IRRs between the comorbidity subcohorts of hypertension (P = .59), hyperlipidemia (P = .80), coronary artery disease (P = .46), chronic kidney disease (P = .85), and chronic obstructive pulmonary disease (P = .45) were not significantly different.

### Effect of DM on the Overall Survival of Patients With HNC

The overall survival for patients without HNC was significantly higher in the non-DM cohort than in the DM cohort (P = 0.001). However, there was no significant difference in overall survival between patients in the DM and non-DM cohorts who subsequently developed HNC (P = .22) (Figure 2).

Patterns of the effect of DM on the overall survival of patients were similar across different anatomical sites with HNC. Without oral cavity cancer, oropharyngeal cancer, and nasopharyngeal carcinoma (NPC), the overall survival for patients was significantly higher in the DM cohort than for those in the non-DM cohort (P < .001 for all) (Figures 3, 4, and 5). No significant difference was found in overall survival between patients in the DM and non-DM cohorts who subsequently developed oral cavity cancer (P = .36), oropharyngeal cancer (P = .22), and NPC (P = .07).
Discussion

Risk of HNC in Patients With DM
We found that patients with newly diagnosed DM had an overall incidence of HNC 1.47 times higher than did controls without DM matched for age, sex, geographic distribution, monthly income, and comorbidities. The female to male ratio in this cohort was 0.89:1, which was consistent with other studies in most populations. Generally, the IRR for HNC was substantially higher for patients aged 40 to 65 years than for any other age group. Although a positive link between DM and many types of cancers has been suggested, evidence of a link between DM and HNC has been limited and inconsistent. For example, a Danish population-based study reported a higher risk of oral and pharyngeal cancer but not laryngeal cancer in patients younger than 50 years with DM. Two studies reported a weak association between DM and HNC; however, 2 different studies found no significant association, or even inverse associations, between DM and HNC. These studies, however, did not control for the confounding factor of comorbidities. Because we adequately controlled for the confounding factors, our findings disclose a higher incidence of HNC in patients with DM (P < .001) and highlight the importance of monitoring patients with DM for HNC.

Effect of Newly Diagnosed DM on the Specific Site of HNC
The first prevalent site of HNC in patients with DM was the oral cavity (57.1%). Other studies have reported a higher risk of oral cavity precancerous lesions and oral and pharyngeal cancer in patients with DM. In contrast, however, a case-control study found no association between DM and oral cavity cancer, but the cases and controls were not age and sex matched. In addition, confounding factors, such as overweight or obesity, might not have been adequately controlled for, which would have biased their results. A retrospective cohort design made it possible for the present study to highlight the links between DM and oral cavity cancer and between DM and oropharyngeal cancer.

The second prevalent site of HNC in patients with DM was the nasopharynx (15.3%). Patients with newly diagnosed DM were associated with an increased risk of NPC. It is well known that NPC is a highly prevalent Epstein-Barr virus–associated cancer in Taiwan. Further study is needed to explore whether DM contributes to long-term Epstein-Barr virus infection and subsequent virus-associated cancer.

Other than oral cavity cancer and NPC, no significant increase was found in the risk of HNC in patients with DM. For example, in agreement with other studies, we found no significant difference in the prevalence of laryngeal cancer between patients in the DM and non-DM cohorts (AHR, 1.03; 95% CI, 0.68-1.56).
Cumulative survival probability of patients with DM who subsequently developed oropharyngeal cancer (group A), patients with DM who did not subsequently develop oropharyngeal cancer (group B), patients without DM who subsequently developed oropharyngeal cancer (group C), and patients without DM who did not subsequently develop oropharyngeal cancer (group D). For the survival probability of patients who subsequently developed oropharyngeal cancer, there was no significant difference ($P = .22$) in survival probabilities between the DM and non-DM cohorts. $P < .001$ for all other comparisons (group A vs B, group B vs D, and group C vs D). Each patient was assessed from the index date to the end of follow-up on December 31, 2011, or until the patient was censored because of death.

We also found that DM had no significant effect on the overall survival of patients who subsequently developed HNC. The follow-up periods for patients with or without DM are limited because of the decreased overall survival of patients with HNC. Therefore, we might not be able to access the effect of DM on the overall survival of patients with HNC.

Pathogenesis of HNC in Patients With Newly Diagnosed DM

Diabetes mellitus and cancer are multifactorial diseases; several potential pathophysiological pathways can contribute to their interdependence. However, most mechanisms underlying the association between DM and the subsequent development of HNC remain unclear. A potential cause of the increased risk of HNC in patients with newly diagnosed DM might be shared genetic risk factors, DM-related metabolic morbidities (eg, hypertension and dyslipidemia), obesity, aging, and sex as the link between DM and other cancers.21,22

Epigenetic modifications of the inherited or acquired genetic mutations in cancer might provide another possible mechanism linking the causes of cancer and DM.23-24 For example, RRA D (OMIM 179503), a member of the Ras-related GTPase superfamily, is frequently methylated in multiple human malignant tumors.25 In human cancers, RRAD may play opposite roles as an oncogene or a tumor suppressor, depending on the cancer and cell type.26 RRAD has been suggested to be a tumor suppressor gene in several human malignant tumors, including malignant mesothelioma, lung cancer, breast cancer, cervical cancer, prostate cancer, and NPC.26-30 RRAD is epigenetically inactivated in NPC. Epigenetic down-regulation of RRAD might disrupt the pathways downstream of the tumor suppressor p53 and lead to a malignant and invasive phenotype.36 In contrast, RRAD translocates Grap2 and GCIP from the nucleus to the cytoplasm, thereby inhibiting the tumor suppressor activity of GCIP, which occurs in the nucleus.36 Consequently, RRAD may promote carcinogenesis at least in part by inhibiting GCIP-mediated tumor suppression.

One possible mechanism that links DM to the development of HNC is long-term exposure to hyperinsulinemia, which leads to breast cancer.32-33 Insulin is a potent growth factor that promotes proliferation and carcinogenesis in various ways, directly and through IGF.34-36 Another reasonable explanation is hyperglycemia, which may directly promote tumors: cancer cells rely on increased glucose consumption.37 The literature also reports that hyperglycemia induces DNA damage,38 down-regulates the expression of antioxidants,39 and increases the generation of reactive oxygen species.40

Apart from the direct actions of insulin and high glucose, various metabolic dysfunctions, parallel to DM, can contribute to the development of a tumor.37-39 Because of this, the frequencies of hypertension, dyslipidemia, and obesity were matched in the present study.
Patients aged 40 to 65 years with DM (9.78 per 10,000 person-years) had a higher risk of HNC than did patients younger than 40 years (4.34 per 10,000 person-years). It is well known that the incidence of most types of HNC increases with age. Although this finding suggests that in patients with DM, age may be a confounding risk of developing HNC, we did not find this to be the case for our age-matched participants.

Head and neck cancer is more common in male patients with DM, according to this and other studies. Therefore, sex was matched as another confounder. Consequently, the increased risk of HNC in male patients with DM cannot be attributed to the confounder of sex in the present study. Further exploration of the underlying mechanisms is needed but beyond the scope of our study.

Strengths and Limitations

The major strengths of the present study are that the sample size is large and that patients in both cohorts were carefully matched by age, sex, and confounding factors, such as DM-related metabolic dysfunctions and obesity, which was not done in earlier studies. The large, population-based data set from Taiwan's NHIRD allowed us to examine, with a low chance of selection bias, the risk factors for developing HNC. The large sample size increased the statistical power and the precision of the risk appraisals in our analyses.

However, this study has some limitations. First, several suspected risk factors for HNC were not available from the insurance claims data (eg, patient histories of smoking, alcohol abuse, and physical activity). Therefore, we used chronic obstructive pulmonary disease as a surrogate for smoking to reduce the possible confounder. However, the lack of access to other factors, such as alcohol abuse, might have resulted in some degree of bias. Second, a certain proportion of DM remains undiagnosed; some members of the non-DM cohort may have had undiagnosed DM. Such a misclassification would create a conservative bias toward the null. Third, regular medical visits might have increased the chances of an early diagnosis of HNC in patients with DM.

Conclusions

The present study indicated that the incidence of developing HNC in patients with newly diagnosed DM was 1.47 times higher than in a comparison cohort without DM matched by age, sex, and comorbidities. For patients with DM aged 40 to 65 years, the risk of developing HNC was significantly higher than in younger patients. The risks of developing oral cavity cancer, oropharyngeal cancer, and NPC were significantly higher in patients with DM.