Oral Oncology 51 (2015) 332–340

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Type 2 diabetes mellitus and risk of oral cancer and precancerous lesions: A meta-analysis of observational studies

Yuhua Gong, Benjuan Wei, Li Yu, Weijuan Pan *

Department of Stomatology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

ARTICLE INFO

Article history:
Received 8 October 2014
Received in revised form 22 December 2014
Accepted 2 January 2015
Available online 31 January 2015

Keywords:
Type 2 diabetes mellitus
Oral cancer
Meta-analysis
Precancerous lesions

SUMMARY

Objective: Associations between type 2 diabetes mellitus (type 2 DM) and risk of oral cancer and precancerous lesions have been reported with controversial findings. We performed a meta-analysis to explore these associations.

Methods: We identified studies by a literature search of MEDLINE and EMBASE through May 31, 2014, and by searching the reference lists of pertinent articles. Summary relative risk (SRR) with 95% confidence interval (CI) was calculated with a random-effects model. Between- study heterogeneity was assessed using the Cochran's Q and I^2 statistics.

Results: A total of 13 studies (4 case-control and 9 cohort studies) on the association between type 2 DM and oral cancer were included. Overall analysis found that compared with non-diabetic individuals, individuals with type 2 DM had a significantly elevated incidence of oral cancer (SRR = 1.15, 95% CI: 1.02–1.29; $P_{heterogeneity} = 0.277$, $I^2 = 15.4\%$; 10 studies). Subgroup analyses found that duration of follow-up ($\geqslant$11 years) significantly altered this positive association. Type 2 DM was associated with increased oral cancer mortality (SRR = 1.41, 95% CI: 1.16–1.72; 4 studies). Meta-analysis of the four case-control studies showed a positive association between type 2 DM and risk of oral precancerous lesions (SRR = 1.85, 95%CI: 1.23–2.80; $P_{heterogeneity} = 0.038$, $I^2 = 57.5\%$). No significant public bias was found across these studies.

Conclusions: These findings of this meta-analysis indicate that compared with non-diabetic individuals, individuals with type 2 DM have an elevated risk of oral cancer and precancerous lesions development.

Introduction

Oral cancer (OC) represents the eighth most frequent cancer worldwide, which includes cancers of the lip, gums, tongue, soft hard palate, etc. [1]. The geographic area with the highest incidence and mortality from this deadly disease is Melanesia, followed by south central Asia. In China, oral cancer was reported 3.29 per 100,000 as incidence rate and 1.49 per 100,000 as mortality rate in 2008 [2]. Despite the advances in diagnosis and treatment, the 5-year survival rate for patients with OC is still low in many parts of the world [3]. Oral precancerous lesions have been well recognized as the precursors of oral cancer [4], which include oral leukoplakia, erythroplakia, and submucous fibrosis, etc. Recently, progresses have been made through epidemiological studies investigating environmental risk factors for oral cancer and precancerous lesions, and the well documented factors include cigarette smoking, alcohol consumption, betel-quid chewing and some types of viral infections [5–8].

It has been shown that type 2 diabetes (type 2 DM) are risk factors for several malignancies, including cancers of the breast [9], endometrium [10], pancreas [11,12], and liver [13]. The hypothesized biological mechanisms is related to the effect of insulin and insulin-like growth factors (IGFs) axis, which would trigger intracellular signaling cascades with mitogenic and antiapoptotic effects [14]. Additionally, the inflammation-mediated carcinogenesis is also a well-known empirical fact [14].

Is there any correlation between type 2 DM and carcinogenesis of the oral cavity? Inconsistent results have been reported for these associations [15–31]. Campbell and his coauthors prospectively enrolled a cohort of 1,053,831 U.S. adults, and observed a total of 1182 deaths from oral cancers after 28 years of follow-up [29]. Diabetic men had a significant risk of OC mortality than did non-diabetic men (relative risk [RR] = 1.44, 95% confidence interval [CI]:1.07–1.94), while diabetic women had a non-significantly increased risk than non-diabetic women (RR = 1.43, 95%CI:

* Corresponding author at: Department of Stomatology, Ren Ji Hospital, School of medicine, Shanghai Jiao Tong University, 160 Pujian Road, Pudong District, 200127, Shanghai, China. Tel./fax: +86 02168383204.
E-mail address: weijpan@126.com (W. Pan).

http://dx.doi.org/10.1016/j.oraloncology.2015.01.003
1368-8375/

0.94–2.20). Similar results were also observed in the study by Wideroff et al. [17]. However, a non-significantly increased risk association between diabetes and OC was observed in most of the included studies, and even, a significantly inverse association was shown in the study by Hjalgrim et al. [16].

The purpose of the present study was to summarize all available evidence from observational studies to estimate the risk of oral cancer and precancerous lesions in patients with type 2 DM following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [32].

Materials and methods

Data sources and searches

To identify relevant studies, two investigators (G.Y.H. and W.B.J.) independently conducted a systematic literature search of MEDLINE (from January 1, 1966) and EMBASE (from January 1, 1974), through May 31, 2014. In addition, a manual review of references from primary or review articles was performed to identify any additional studies. The relevant studies were searched with the following text word and/or Medical Subject Heading (MeSH) terms: (1) "diabetes"; (2) "oral cancer" OR "oral carcinoma" OR "mouth neoplasm" OR "oral leukoplakia" OR "oral erythroplakia" OR "oral submucous fibrosis"; and (3) "risk" OR "incidence" OR "prevalence" OR "mortality". No language restrictions were imposed.

Study selection

Studies were included in this meta-analysis if: (1) they had original data from case-control or cohort studies; (2) the exposure of interest was type 2 DM (or mainly type 2 DM); (3) the primary outcome was clearly defined as oral cancers or precancerous lesions; and (4) studies should report either adjusted odds ratios, rate ratio, hazard ratio (HR), or standardized incidence/mortality ratios (SIR/SMR) with their 95% CIs (or data to calculate them). Two authors (G.Y.H. and W.B.J.) independently evaluated all of the studies retrieved from the databases; in case of disagreement or uncertainty, a third reviewer (P.W.J.) was consulted. We excluded 2 articles that reported type 1 DM and OC risk [33,34]. If a study appeared in more than one article, data from the most recent publication were used for the statistical analysis [35,36].

Data extraction

The following data were extracted independently by two investigators using a standardized data collection form for each study: the design type (case-control or cohort study), the first author's last name, year of publication, country of origin, sample size and number of cases, age and gender of the subjects, duration of follow-up in cohort studies, assessment of exposure and outcome, covariates adjusted or by matching, and the effect estimates with 95% CIs. From each study, we extracted the risk estimates that reflected the greatest degree of adjustments for potential confounders. Sex-specific risk estimates were extracted whenever available. If studies reported both incidence and mortality rate, we extracted the both [23]. One study reported risk estimations for both young- (age < 30 years) and old-onset (age ⩾ 30 years) DM, and we extracted only the risk estimation for the old-onset DM, because most individuals with young-onset DM are type 1 DM [16].

Quality assessment for individual studies

To assess the study quality, two of us (G.Y.H. and W.B.J.) adopted the Newcastle-Ottawa quality assessment Scale (NOS) [37]. The NOS uses 3 parameters of quality for case-control or cohort studies: selection, comparability, and exposure/outcome assessment. The NOS scale assigns a maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for the exposure/outcome. The total score was 9 stars, and a study with 7 or more stars was defined as a high-quality study. Studies were considered as low quality if they could not be evaluated by the NOS due to insufficient information.

Statistical analysis

We divided epidemiologic studies into three general types according to the measurement of risk estimations: case–control studies (odds ratio), cohort studies using non-diabetic population comparisons (rate ratio and HR) and using external general population comparisons (SIR/SMR). Because the absolute risk of oral cancer is low, all the above measures yield similar estimates of RR [38]. All statistical analyses were performed using STATA, version 11.0 (STATA, College Station, TX, USA). Summary RRs (SRRs) with their corresponding 95% CIs were derived with the method of DerSimonian and Laird using the assumptions of a random effects model, which incorporates between-study variability [39]. A two-tailed $P < 0.05$ was considered statistically significant.

In assessing heterogeneity among studies, we used the Cochran Q and I^2 statistics. The I^2 statistic is the proportion of total variation contributed by between-study variation, which has been suggested that I^2 values of 25%, 50%, and 75% are assigned to low, moderate, and high heterogeneity, respectively [40]. To explore the sources of heterogeneity, subgroup and meta-regression analyses were performed according to sex, geographic locations, publication year, methods of DM ascertainment, study quality score, duration of follow-up, the number of cases, definition of outcome (incidence vs. mortality) and adjustments for confounding factors including smoking, body mass index (BMI), and alcohol use. Sensitivity analyses were performed by excluding one study in the meta-analysis and calculating a pooled estimate for the remainder of the studies to evaluate whether the results were significantly affected by a single study. Publication bias was assessed by using funnel plots and the further Begg's adjusted rank correlation and Egger' regression asymmetry tests [41,42].

Results

Search results, characteristics and quality assessment

The search strategy generated 831 citations of which 29 were considered of potential value and the full text was retrieved for detailed evaluation (Fig. 1). Eighteen of these 29 articles were subsequently excluded: 11 studies did not evaluate this association, 3 studies reported the same population, 3 studies did not report RR and/or 95%CI, and 2 studies reported young-onset DM. Additional 6 articles were included from reference review. Thus, a total of 17 articles provided data to investigate the association between type 2 DM and oral cancer ($n = 13$) or precancerous lesions ($n = 4$; Tables 1 and 2).

Four studies reported the association between type 2 DM and risk or precancerous lesions, all of which had a case-control/cross-sectional design and were published between 2004 and 2010 [19–21,24]. The four studies reported a total of 1407 cases with oral precancerous lesions (1137 cases with oral leukoplakia, 100 cases with oral erythroplakia and 170 cases with oral submucous fibrosis). DM status was ascertained by self-report [19,21] and medical examination [20,24] in two studies, respectively. Diagnosis of precancerous lesions was based on histological or medical examination. Adjustments were made for potential confounders of 1 or more factors in all studies.