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Diabetes mellitus, metformin and head and neck cancer

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SUMMARY

Introduction: Diabetes mellitus (DM (Diabetes Mellitus)) is directly associated with some cancers. However, studies on the association between diabetes mellitus and head and neck cancer (HNC (Head and Neck Cancer)) have rendered controversial results. The objective of this study was to evaluate the association between DM and HNC, as well as the impact of metformin use on the risk of HNC.

Material and methods: This case-control study was conducted within the framework of the Brazilian Head and Neck Genome Project in 2011–2014. The study included 1021 HNC cases with histologically confirmed squamous cell carcinoma of the head and neck admitted to five large hospitals in São Paulo state. A total of 1063 controls were selected in the same hospitals. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression.

Results: Diabetic participants had a decreased risk of HNC (OR = 0.68; 95% CI: 0.49–0.95) than non-diabetic participants, and this risk was further decreased among diabetic metformin users (OR = 0.54; 95% CI: 0.29–0.99). Diabetic metformin users that were current smokers (OR = 0.13; 95% CI: 0.04–0.44) or had an alcohol consumption of >40 g/day (OR = 0.31; 95% CI: 0.11–0.88) had lower risk of HNC than equivalent non-diabetic participants.

Conclusion: The risk of HNC was decreased among diabetic participants; metformin use may at least partially explain this inverse association.

Introduction

Head and neck cancer (HNC) includes tumours of the oral cavity, oropharynx, hypopharynx, and larynx. Nasopharyngeal cancer is also a HNC sub-site but is usually considered a separate disease with a distinct aetiology and particular characteristics [1]. Approximately 600,000 cases of HNC are diagnosed each year, and HNC accounts for 4% of cancer mortality worldwide [2]. More than 90% of HNC are squamous cell carcinoma [3]. The main risk factors associated with HNC are smoking and alcohol consumption, and the interaction between these factors can increase the risk of HNC [4]. Other risk factors include poor oral health, diet, genetic factors, low body mass index (BMI), and occupational factors [5–8].

The association between diabetes mellitus (DM) and the increased risk of certain cancers, such as liver, pancreatic, colon, kidney, bladder, endometrial, and breast cancer, is well established [9–11], while the risk of prostate cancer is decreased among diabetic patients [11,12]. Although some studies with DM has also

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Table 1
Description of excluded and included cases and controls.

Description	Subjects
Cases included	1021
Cases excluded	270
Missing anatomical location of tumor	126
Missing morphology information	50
Cancer diagnosis not confirmed	34
Cancer at other sites (not HNC)	21
Others histology (not SCC)	12
Cancer in situ	9
Synchronous cancers	7
Previous cancer treatment	4
Cancers with previous HNC treatment	3
Repeat cases	3
Missing information on diabetes mellitus	1
Total cases	1291
Controls included	1063
Controls excluded	52
Did not meet inclusion criteria	36
With cancer diagnosis	13
Repeated controls	3
Total controls	1115

HNC: head and neck cancer; SCC: squamous cell carcinoma.

been associated with HNC, these results are still controversial. In some studies, diabetic patients had an increased risk of cancer at some HNC sub-sites [10,13–15], while in other studies this risk was decreased [9,16].

One possible explanation for inverse association between DM and some kinds of cancers is metformin use among diabetic patients. Metformin is a medication used to control Type 2 DM and can inhibit cell proliferation, which has been inversely associated with cancer risk [11,17]. It has been shown that metformin users have a reduced risk of colorectal, liver, lung, and prostate cancer [18–20]. Studies on the association between DM and the risk of HNC that take into account metformin use have also reported conflicting results. A Taiwanese study reported a decreased risk of HNC among metformin users (adjusted hazard ratio = 0.66; 95% confidence interval [CI] 0.55–0.79) [21], while another study in the United Kingdom reported no association [22].

The objective of this study was to evaluate the association between DM and HNC, as well as the impact of metformin use on the risk of HNC.

Material and methods

This case-control study was conducted within the framework of the Brazilian Head and Neck Genome Project (GENCAPO) from December 2011 to November 2014. The study recruited 1291 HNC cases admitted to three general hospitals and two cancer hospitals in Sao Paulo state, Brazil. All HNC cases had histologically confirmed squamous cell carcinoma of the head and neck, and the International Classification of Diseases, 10th Revision [23] was used to classify these cancers into five sub-sites [24]: oral cavity, oropharynx, hypopharynx, larynx, and oral-oropharynx-hypopharynx not specified.

A total of 1115 controls were selected from the same hospitals as the HNC cases: in the general hospitals we recruited hospital controls who were individuals admitted with diseases other than cancer (for example, diseases related to skin, eyes, ears, genitourinary tract, circulatory disorders, nervous system disorders and others); visitor controls were recruited in the cancer hospitals, excluding visitors of HNC patients, since they could have similar habits to the HNC patients.

After exclusions, the final study sample comprised 1021 cases and 1063 controls (Table 1). Controls were frequency-matched to HNC cases by sex and age (in 5-year groups). This study was approved by the institutional ethical review boards of all hospitals, and all participants gave written informed consent.

Data collection

Participants were interviewed using a standardised questionnaire to collect information on socio-demographic, socio-economic, and lifestyle factors, as well as family history of cancer. Authors extracted information on age, sex, education, BMI (based on height and weight 2 years before the interview), DM, tobacco consumption, and alcohol consumption from the questionnaire.

Blood samples were also collected from cases and controls, stored in tubes containing EDTA at −70 °C, and used for glycated haemoglobin tests (A1C). A1C provides an average assessment of glucose control for the previous 60–90 days without the need for fasting. A1C was performed using 1 ml of blood at a laboratory certified by the National Glycohemoglobin Standardization Program and was considered positive for diabetes when values were above 6.5% [25].

The final DM variable was constructed by combining information from three sources in order to ensure a better characterisation of the main explanatory variable and avoid underestimating the prevalence of DM. Thus, participants who reported they were diabetic at interview, or had a diagnosis of DM in medical records, or had a positive A1C result were categorised as diabetic (Table 2). Patients with self-reported DM were categorised as diabetic even if A1C values were below 6.5% (controlled DM). Diabetic participants were then further categorised as metformin users and non-users. Information about metformin use was taken from medical records.

Tobacco consumption was assessed in pack-years, calculated by multiplying the average number of packs of cigarettes smoked in 1 day by the number of years the participant smoked. One cigarette, one pipe and one cigar are equivalent to 1 g, 3.5 g and 4 g of tobacco, respectively. Analyses were performed for both smoking status and pack-years of tobacco consumption.

Alcohol consumption was assessed in g/day. One litter of different alcoholic beverages was converted to 5%, 12%, and 40% of alcohol for beer, wine, and spirits, respectively. Consumption was then converted to grams of alcohol (one litter is equivalent to 798 g of alcohol) and the daily average alcohol intake during the consumption period was calculated. Analyses were performed for both drinking status and g/day of alcohol consumption.

Statistical analysis

Odds ratios (OR) and 95% CI were estimated using unconditional logistic regression. Analyses comparing participants with and without DM were adjusted for sex, age, education, BMI (in kg/m^2), tobacco consumption, and alcohol consumption. The models were also adjusted for hospital of recruitment (centre), since heterogeneity was detected by the likelihood ratio-test.

In metformin analyses, diabetic metformin users and non-users were compared with those without DM. However, these analyses did not include controls who were visitors in cancer hospitals. Indeed, as they were not patients they did not have medical records available in which to verify metformin use. Consequently, metformin analyses were not adjusted for centre.

Analyses were stratified by sex, HNC sub-site, smoking status, drinking status, tobacco consumption (non-smokers, >0–40, >40 pack-years) and alcohol consumption (non-drinkers, >0–40, >40 g/day).

Missing data were found for the following variables: education (18 cases and two controls), BMI (86 cases and five controls), alcohol consumption (50 cases and 20 controls), and tobacco consump-