Attribution of oral cancer in the Sudan to Toombak dipping

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Abstract

Background: Toombak dipping—a form of smokeless tobacco—is highly prevalent in the Sudan.

Materials and methods: For a case–control study, we selected oral cancer cases (n = 98) and controls (n = 98) at the Khartoum Teaching Dental Hospital. They were directly interviewed using a validated and a reliable instrument. For descriptive statistics, χ² test was used for determining the odds ratio (OR) measuring the association between exposed and non-exposed. The effects of the confounding factors were tested by multivariate logistic regression analyses. The attributable risk of this agent in oral carcinogenesis was evaluated.

Results: Significant risks for Toombak dipping (OR 3.8, 95% CI 1.7–8.6) and cigarette smoking (OR 2.7, 95% CI: 1.2–6.2) were found. The site of Toombak dipping and the tumor location showed positive correlation. The attribute risk for exclusive dippers was found to be 93% and 67% in females and males, respectively, whereas the adjusted attributable risk was 70.1%. The remaining 20–30% risks were attributed to other risk factors.

Conclusion: In the Sudan, Toombak dipping is a major risk factor for oral squamous cell carcinoma. We were able to demonstrate a high attributable risk to this agent in oral carcinogenesis.

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Introduction

The occurrence of oral cancer in the Sudan is reported to be high. The age standardized rate (ASR) of oral cancer in males in the Sudan is the second highest in the Middle East and North African region.¹ The number of registered cases at the national hospital which treats all cancers in the Sudan is at a rate of 920 per year, comprising 9% of the cancers reported annually. The consumption of local type of snuff known as Toombak, a very popular substance used by the Sudanese community, has previously been reported as causative.²–⁵

The prevalence of Toombak use is around 45% among men aged 40 years and older and 10% among women aged 60 years and older.⁶ The most abundant potent carcinogens in smokeless tobacco are tobacco-specific nitrosamines (TSNA), N-nitrosornornicotine, and 4′-(nitrosomethylamino)-1-(3-pyridyl)-1-butane. Inordinately, high level of these carcinogens has been reported in Toombak.⁷

A case–control study to establish the association between oral squamous cell carcinoma (OSCC) and Toombak dipping was conducted by Idris et al.⁸ However, the limitation of this study was due to the fact that cases and controls were recruited retrospectively from hospital records.⁸

We therefore set out to strengthen the causal relationship of Toombak and oral cancer eliminating the limitations of the previous epidemiologic study⁴ by conducting direct interviews with cases and controls. The objective was to establish any causal association and to estimate the exact attributable risk for both exclusive Toombak dippers and those who also smoke.

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Material and methods

The study used a similar questionnaire and a consent form earlier developed by the same authors for our previous studies on Toombak in the Sudan and on Shammah use in Saudi Arabia with minor modifications. The study design and the questionnaires were approved by the ethical committee of the institution where the research was conducted (Khartoum Teaching Dental Hospital (KTDH)).

KTDH is the main referral hospital for cases from all parts of the country suspected to have oral cancer. All patients reporting to KTDH during the period from July to October 2014 were directly interviewed. All cases were pathology confirmed. Controls were selected from patients reporting to the same hospital but for noncancer ailments and from nonsurgical departments. The cases and controls were matched for age ± 5 years, sex and tribe, and geographic place of residents.

Data were entered into the computer and analyzed using SPSS software version 16 (Statistical Product and Service Solution, SPSS Inc., Chicago, Illinois, USA, 2007). Descriptive statistics for demographic characteristics were inferred. Data of cases and controls were cross-tabulated according to Toombak usage. The χ² test was conducted and odds ratio (OR) was used to measure the association between Toombak dipping and other possible risk factors that may contribute to the development of oral squamous cell carcinoma. All variables, age, sex, and cigarette smoking that are likely to be confounding factors for Toombak dipping were further analyzed by logistic regressions for estimation of adjusted ORs. The attributable risk due to Toombak use was estimated by the following formula: (risk in exposed group − risk in unexposed group)/risk in exposed group.

Results

During the study period, 98 cases and 98 controls were directly interviewed. Distribution of their demographic characteristics is shown in Table 1. Their mean ages were closely similar, 64 and 61 years for the cases and controls, respectively, and this difference was not significant (p > 0.05). The geographic location of residence and tribe among cases and controls also showed no significant differences. The relative frequency of the clinical sites for occurrence of the carcinomas is shown in Figure 1 and the clinical presentations are shown in Figures 2 to 3.

Toombak use was significantly high among cases in comparison with controls (OR 3.35, 95% CI: 1.82–6.14). Using logistic regressions, we adjusted for cigarette smoking and alcohol consumption, and exclusive Toombak dipping was significantly associated with OSCC (OR 3.8, 95% CI 1.7–8.6). Furthermore, when adjusting for Toombak use, cigarette smoking and alcohol consumption and cigarette smoking was found to be significantly associated with development of OSCC compared to non-smokers (OR 2.7, 95% CI: 1.2–6.2). When adjusted for cigarette smoking and Toombak use, alcohol consumption did not attain any significant association (OR 0.7, 95% CI: 0.3–1.7).

Among both males and females, Toombak use was found significantly associated with the development of OSCC (OR 3.0, 95% CI: 1.35–6.7) and (OR 15.2, 95% CI: 1.8–6.1), respectively. The attribute risk for Toombak use was 66.9% for males and 93.4% for females and 70.1% overall. The site of quid placement that was in contact with oral mucosa and development of the carcinoma showed a clinical association (Figures 1

Table 1. Description of the demographic characteristics of cases and controls.

| Variable         | Cases (n = 98) | Controls (n = 98) | Chi-square test, p-value |
|------------------|---------------|------------------|--------------------------|
| Sex              |               |                  |                          |
| Males            | 57 (58.2)     | 50 (51.0)        | 0.3153                   |
| Females          | 41 (41.8)     | 48 (49.0)        |                          |
| Age group        |               |                  |                          |
| <54              | 21 (21.4)     | 27 (27.6)        | 0.3717                   |
| 55–69            | 36 (36.7)     | 39 (39.8)        |                          |
| ≥70              | 41 (41.8)     | 32 (32.7)        |                          |
| Residence        |               |                  |                          |
| Khartoum state   | 11 (11.2)     | 8 (8.2)          | 0.7679                   |
| Northern state   | 23 (23.5)     | 24 (24.5)        |                          |
| Central state    | 27 (27.6)     | 34 (34.7)        |                          |
| East and blue Nile state | 18 (18.4) | 14 (14.3) |                          |
| Western state    | 19 (19.4)     | 18 (18.4)        |                          |
| Tribe            |               |                  |                          |
| Nubian           | 11 (11.2)     | 13 (13.3)        | 0.6707                   |
| Arabonubia       | 25 (25.5)     | 31 (31.6)        |                          |
| Johina           | 41 (41.8)     | 36 (36.7)        |                          |
| Sudanic          | 21 (21.4)     | 17 (17.3)        |                          |
| Occupation       |               |                  |                          |
| Agricultures sector | 30 (30.6) | 17 (17.3) | 0.0383                   |
| Governmental and labor | 30 (30.6) | 38 (38.8) |                          |
| Housewife        | 30 (30.6)     | 43 (43.9)        |                          |
and 2). Furthermore, sleeping with the quid (reference group: non users) was found to be significantly associated with the development of OSCC (OR 3.06, 95% CI: 1.12–8.36; Table 2).

Discussion

This study directly interviewed cases and controls, thus removing the limitation of the previous study that used hospital records. The OR and attributable risk estimated in the present study suggest a causal relationship. These findings are in agreement with previous studies, such as the studies by Elbeshir et al. and Idris et al. The IARC Monograph evaluation used earlier reported data for their conclusions in 2007, highlighting the carcinogenicity of Toombak to humans.

To establish any causal association by epidemiologic methods, IARC reviewed and considered studies that only used quantitative methods, such as cohort and case–control studies. Among the studies conducted in the Sudan by Elbeshir et al. and Idris et al. on Toombak use, one was descriptive and the other was quantitative: Both studies found that more than 80% of patients with oral cancer were Toombak users and developed the neoplasm at the site of Toombak dipping strongly implicating its causal role. The case–control study by Idris et al. was reviewed by IARC, and they noted methodological limitations that the study used hospital records, for selection of the subjects. Furthermore, despite the use of two control groups (300 volunteers), neither group was perfect: one of the control groups was selected from the general population survey, and in the other, there were no matching for personal data. Therefore, the present study addresses and overcomes these previous study limitations.

The risk among exclusive Toombak users was higher among females than males. That is explained by the fact that females dip Toombak at the buccal mucosa and tend to keep the smokeless tobacco quid at the site of dipping for longer periods compared to males. This allows exposure of the tissues for longer periods to carcinogens found in Toombak. Furthermore, females indulge in the habit at an older age than males, usually after menopause. At that age, the female Sudanese probably may also have micronutrients deficiencies. Sleeping with the quid was a significant risk factor in this study, which suggests keeping the quid in contact with the mucosa for longer periods increases the risk. The lower OR reported for sleeping with the quid (compared with the total quid users) may arise from misclassification. The site of dipping further showed a strong correlation with lip and buccal cancers.

This and previous studies showed that the risk attributed to exclusive Toombak use ranges from 70% to 80%. For the remaining 20–30%, it is highly likely that other risk factors such as cigarette smoking and alcohol consumption (Warnakulasuriya et al.) are attributable factors. We adjusted for confounders, for example, cigarette smoking and Toombak remained a significant risk. Alcohol consumption, however, is under reported in this study, as it is considered as a violation of Islamic law in the Sudan.

Other potential risk factors are oncogenic viruses and genetic predisposition leading to susceptibility. In the Sudan, particularly, HPV subtypes 16 and 18 play a role in the etiology of oral cancer.

The findings of this study of high attributable risk for cancer among Toombak users, demand questions for plausible mechanism for the carcinogenesis caused by this substance. The previous laboratory studies by Idris et al. showed Toombak contains high levels of potent carcinogenic compounds such as TSNA.

Control and management of this malignancy require detection of its earliest phases. As reported in the natural history oral precancer precedes the development of oral cancer. Low frequency of cellular atypia and epithelial dysplasia in the precancerous lesions of Toombak dippers makes the detection of the early stages by cytological or histological methods challenging. As shown in this study, Toombak dippers are at high risk, or OSCC, consequently, detection of the early stages of this malignancy is vital. The problem remains as how to identify among Toombak dippers those at risk. Tobacco metabolites in urine may be used to assess cancer risk arising from

Figure 2. Cancer of the gum and alveolus.

Figure 3. Cancer of lower buccal sulcus where toombak is held.
tobacco use. Sudanese Toombak users were reported to excrete urinary metabolites of tobacco-specific carcinogens, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and NNAL-Gluc. Murphy et al. reported the detection of these molecules as urinary biomarkers for identification of those at risk for carcinogenesis resulting from consumption of this type of tobacco product. The detection of DNA adducts in oral tissues at the site of dipping may also serve to identify individuals at high risk. We, therefore, propose a further study of urinary metabolites of TSNAs in chronic Toombak users.

Tobacco use cessation can reduce the cancer risk in ex-tobacco users. At a population level, efforts are needed to promote appropriate tobacco cessation messages for the Sudanese Toombak users.

Conclusion
Toombak use is a significant risk for the development of high proportion of OSCC among the Sudanese people. Sleeping with quid was shown to have an association. Site of dipping was significantly correlated with the site of the lesion, suggesting chronic contact with the carcinogens was important in the evolution of OSCC. Cigarette smoking was shown to be further risk factor for OSCC, but the study failed to ascertain any synergism between Toombak use and cigarette smoking or with alcohol consumption.

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Table 2. Risk estimation (OR) for Toombak dipping, cigarette smoking, and alcohol consumption.

| Description                              | Cases (n = 98) | Controls (n = 98) |
|------------------------------------------|---------------|-------------------|
|                                          | Yes (n (%)    | No (n (%)        | Crude OR | 95% CI       | Adjusted OR | 95% CI       |
|                                          |               |                  |          |              |             |              |
| Exclusive Toombak dipper                 | 51 (52)       | 47 (48)         | 24 (24.5)| 74 (75.5)     | 3.346        | 1.822–6.142  | 3.804        | 1.704–8.591  |
| Combined user Toombak + smoking         | 15 (15.3)     | 83 (84.7)       | 15 (15.3)| 88 (89.8)     | 1.060        | 0.488–2.304  | 0.448        | 0.107–1.880  |
| Combined user Toombak + alcohol         | 26 (26.5)     | 72 (73.5)       | 8 (8.2) | 90 (91.8)     | 4.063        | 1.735–9.513  | 5.271        | 0.488–56.962 |
| Exclusive cigarette smoker              | 19 (19.4)     | 79 (80.6)       | 24 (24.5)| 74 (75.5)     | 0.742        | 0.376–1.464  | 2.715        | 1.188–6.200  |
| Exclusive alcohol consumption           | 26 (26.5)     | 72 (73.5)       | 12 (12.2)| 86 (87.8)     | 2.588        | 1.220–5.491  | 0.675        | 0.262–1.742  |
| Site of dipping                          |               |                  |          |              |             |              |             |              |
| Labial mucosa                            | 31 (60.8)     | 20 (39.2)       |          |              |             |              |             |              |
| Buccal mucosa                            | 20 (39.2)     | 4 (16.7)        |          |              |             |              |             |              |
| Sleeping with quid                       |               |                  |          |              |             |              |             |              |
| Yes                                      | 35 (68.6)     | 10 (41.7)       |          |              | 3.06         | 1.12–8.36    |             |              |
| No                                       | 16 (32.4)     | 14 (58.3)       |          |              |             |              |             |              |

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**Translational value**

This publication adds further support that Toombak is carcinogenic to humans and to deter investigators that suggested the use of smokeless tobacco products for risk modification. Smokeless tobacco should not be used for quitting cigarette smoking. In the Sudan, it is important to increase the level of education and awareness of harms related specifically to Toombak use and inform the dangers of sleeping with quid and other forms of tobacco use. We recommend the establishment and implementation of a Toombak Control Program with evidence-based treatments that have been scientifically documented to help people to quit Toombak use.