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Moayad Aziz Alabdaly

Alnoor University, Iraq, Mosul City, Alshallalat Road, moayad.aziz@alnoor.edu.iq

Shahbaa Al Bayati

College of Medicine, University of Nineveh, Iraq

Taha Hassan Taha

College of Medicine, University of Nineveh, Iraq

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ORIGINAL STUDY

The Effect of Smoking on Occurrence of Parotid Gland Tumors in Nineveh: Case-Control Study

Moayad Aziz Alabdaly^{a,*}, Shahbaa Al Bayati^b, Taha Hassan Taha^b^a Alnoor University, Iraq, Mosul City, Alshallalat Road^b College of Medicine, University of Nineveh, Iraq**ABSTRACT**

Background: The parotid gland is the most common site of salivary gland tumors, the majority of these tumors are not malignant, Warthin tumors are the second most common type of cancer after pleomorphic adenomas. At present, tobacco is not classified as carcinogenic for the salivary gland due to inadequate research on the association between smoking and salivary gland tumors. The purpose of this study was to evaluate the connection between smoking and parotid gland tumors (PTG) in a state-scale study.

Materials and Methods: A group of (438) population-based controls that are individually matched and 200 incident PGT patients who were diagnosed between 2007 and 2020 were included in the sample. An analysis was conducted to evaluate the danger of PGT correlated with different smoking factors by using odds ratios (ORs) and accompanying 95% confidence intervals (95% CI) around rates, and the statistical significance was determined by a P value of ≤ 0.05 .

Results: Cigarette smoking was found to be associated with a PGT development with an odds ratio (OR) of (1.5) (95% CI), (1.0156–2.3003). The risk was higher when there was an increase in smoking intensity, in which (OR) 2,2 and [95% CI] (1.1012–4.3952), p value = 0.0255. Whereas smoking duration (OR) 2,1 and 95% confidence intervals (1.0379–4.1819). Histological type analysis revealed remarkably high risks for pleomorphic adenomas (Chi-squared: Significance level: P < 0.0001).

Conclusions: The current study indicates that smoking is associated with the risk of PGT and has multiple causal relationships: extremely high ORs; the intensity and duration of tobacco use were found to have significant dose-response relationships.

Keywords: Parotid gland tumors, Pleomorphic adenoma, Warthin tumors, Malignant

1. Introduction

Salivary gland tumors are most frequently found in the parotid gland, which is responsible for 70% to 85% of the cases. Most of them are benign, with pleomorphic adenomas and warthin tumors are the most common types of cancer (Johns, 2016; Zhao et al., 2020; Chang et al., 2021). The cause of tumors in salivary glands remains unclear, but exposure to ionization radiation is the only positive factor (Pan, de Groh and Morrison, 2017; Guzzo et al., 2010; Saku et al., 1997). It has been determined that tobacco use is a potent agent that causes cancers (Dhhs,

2004). Due to sparse and inadequate data, a recent researches on cancer article on smoking was unable to categorize tobacco as a carcinogen of the salivary gland (Yach, 2005). Of the few studies available, some have assessed the risk of malignancies only (Pan, de Groh and Morrison, 2017; Guzzo et al., 2010; Tomasi, Facchini and Maia, 2004; Taha, Alabdaly and Ali, 2012; Radoi et al., 2018; Bunnell et al., 2010), few studies evaluate the risk of malignant and benign tumors (Pan, de Groh and Morrison, 2017; Kim et al., 2019) and other studies only assessed the risk of benign warthin tumors (Del Signore and Megwalu, 2017; Freedman, Oberman and Sadetzki, 2009;

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* Corresponding author.
E-mail address: moayad.aziz@alnoor.edu.iq (M. A. Alabdaly).

Franzen et al., 2018; Chedid et al., 2011; Chulam et al., 2013; Vories and Ramirez, 1997; De Ru et al., 2005; Chung et al., 1999).

As far as we know, only a few studies on tobacco use and malignant tumors of the salivary glands have shown a positive association (Pan, de Groh and Morrison, 2017; Radoi et al., 2018; Bunnell et al., 2010). Studies that focused on benign Warthin tumors revealed that 78%–98% of these patients smoked compared to other salivary gland tumors (Del Signore and Megwalu, 2017; Freedman, Oberman and Sadetzki, 2009; Chedid et al., 2011; Vories and Ramirez, 1997; De Ru et al., 2005; Chung et al., 1999). Small sample sizes were a common characteristic of the study of patients with Warthin tumor and the statistical analysis is limited. No association was observed in other studies that evaluated the risk of developing a salivary gland tumor (apart from Warthin tumors) due to smoking (Guzzo et al., 2010; Tomasi, Facchini and Maia, 2004; Taha, Alabdaly and Ali, 2012; Pan, de Groh and Morrison, 2017; Kim et al., 2019).

1.1. Aim of the study

This study aimed to evaluate the epidemiology of PGT in Nineveh and smoking as a risk factor.

1.2. Objectives

1. To describe the baseline characteristics of cases and controls.
2. Determine the relationship between tobacco use and the development of parotid tumors.

2. Materials and methods

Nineveh study cases included all individuals over the age of 15 with benign or malignant PGT confirmed by histology or cytology, diagnosed between January 2007 and December 2020. Two hundred eligible patients were identified during the study period, 16 of whom had malignant tumors and 184 benign tumors. Randomly selected controls for the entire Nineveh cases were matched to a patient (case) with PGT. Individually, up to 2.2 controls were assigned to each case, corresponding to gender, age, and interview date. In total, 438 controls were interviewed. A questionnaire that was developed for the interview study was used to obtain data during a personal interview. The questionnaire included information on demographic factors and a comprehensive history of smoking. The histological types of the tumor were determined using medical records. Whether

(Pleomorphic adenomas; PA, Warthin tumors; WT, lymphoma, monomorphic adenomas; MA or Malignant tumor).

People who smoked regularly (as a minimum once per day for at least 6 months) were included in this study for smoking variables. Those who have reported smoking any ingredient (cigarette, pipe, nargila, cigar, or marijuana) are referred to as the “Ever smoking total”. Other events of smoking exposure involved “age at the start”, which was categorized into 2 age groups (<20 and \geq 20 years age); Two groups are used to analyze (Intensity); This determines how many cigarettes are smoked per day (<20 or \geq 20 cigarettes for each day) and (duration); indicating the number of years and stratified into 2 groups (<20 and \geq 20 years).

2.1. Statistical analysis

We calculated odds ratios (ORs) and accompanying 95% confidence intervals (95% CI) around rates, for the association of PGT with smoking variables as risk factors (Celentano and Mhs, 2018). A One-way Chi-squared test was used to study if there were significant differences between the types of PGT and smoking (Bohning, Peter and Heijden, 2017). The statistical significance level has been determined at $P < .05$. The data was statistically analyzed using Spss version 26.

3. Results and discussion

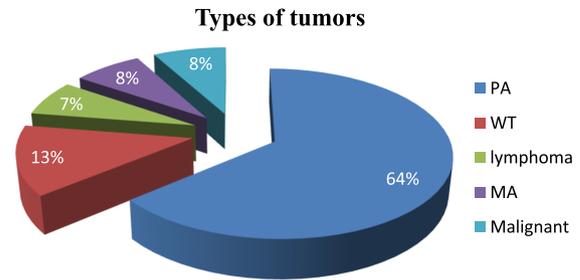
Table 1 shows that the ratio of males to females was 1.1 and the average age was approximately 52 ages at the time of diagnosis. About 70% of the cases were from urban areas, 31% were illiterate (had no level of education), 78% of them were married and 33% had a University/ high-level technical school educational level.

The association of smoking habits with the occurrence of PGTs for the histologic types presented in Table 2. Twenty-four per cent of cases said they had ever smoked. Smoking patterns analysis is limited to cigarette smoking only. About 6% of the controls and 4.5% of the cases reported smoking at some time. Current cigarette smokers identified by 8% and 12% of cases and controls, congruently. In 62% of cases, smoking was initiated before the age of 20, and 38.5% of controls. The age at the start was analyzed and showed a positive association, with a risk of having PGT is 3.33 times among those with age at start <20 years compared with those \geq 20 years of age at the start: the 95% CI (1.5647–7.1012) (P -value < .05). Smoking intensity had a significant dose-response

Table 1. Demographic characteristics distributed among the study groups.

Characteristic	Cases (n = 200)		Controls (n = 438)	
	No.	%	No.	%
Sex				
Male	105	52.5	273	62.3
Female	95	47.5	165	37.7
(Age) y				
<20	23	12	58	13
20-<30	35	18	120	27
30-39	31	16	79	18
40-49	20	10	71	16
50-59	35	18	55	13
60-69	38	19	34	8
≥70	18	9	21	5
Origin				
Urbane	141	70.5	335	76.5
Rural	59	29.5	103	23.5
Marital status				
Married	156	78	284	64.8
Single	34	17	14	3.2
Divorced	3	1.5	130	29.7
Widowed	7	3.5	10	2.3
Education				
Illiterate	62	31	35	8
Primary school	9	4.5	69	15.8
Middle school	16	8	67	15.3
Secondary school	47	23.5	86	19.6
University/high-level technical school	66	33	181	41.3

association, Smoking more than 20 cigarettes a day caused more than twice the risk of those who smoked less than 20 cigarettes a day (2.1 OR) with 95% CI(1.0053-4.3869). The duration of smoking also showed a positive association, those who have been smoking for 20 years have a higher risk; OR 2.12, 95% CI (1.0109-4.4512) and significant p-value (0.047).

**Fig. 1.** Histological type of tumors of the parotid gland.

The results showed that sex did not have any significant differences in the smoking measures.

The histological type of tumors of the parotid gland as shown in Fig. 1

According to histological analysis of PGT, smoking history was reported by 13% and 53% of individuals with pleomorphic adenomas and malignant PGTs, respectively, and nearly forty-eight percent of patients with Warthin's tumor have ever smoked cigarettes. There is a significant difference between the frequencies of pleomorphic adenomas among those who never smoke and ever smoke $P < 0.0001$ using the One-way Chi-squared test (Table 3).

The outcomes of this study specify a solid and perhaps fundamental suggestion among tobacco use and the occurrence of PGT. PA tumors, which have established 64% of all cases in our sample, seem to be the cause of this suggestion. This result is reinforced by a dose-response association and coherence between all variables of tobacco use studied. There is a significant association between smoking and the development of pleomorphic adenomas, similar to that observed (Chi-squared: Significance level: $P < 0.0001$). The point estimates of most Chi squared results were not significant for other types of PGTs; these outcomes are

Table 2. Study groups' smoking habits and the risk of parotid gland tumors

Variable	Cases (n = 200)		Controls (n = 438)		OR	95% CI	P value
	No.	%	No.	%			
Smoking							
Never	152	76	330	75	1.53	1.0156-2.3003	0.042*
Ever	48	24	108	25			
Age at start (smoking), y							
<20	7	3.5	18	4	0.85	0.3308-2.2028	0.744
≥20	41	20.5	90	21			
Intensity (cigarettes per day)							
≥20	28	14	42	10	2.2	1.1012-4.3952	0.026*
<20	20	10	66	15			
Duration (smoking cigarettes) y							
≥20	30	15	48	11.0	2.08	1.0379-4.1819	0.039*
<20	18	9	60	13.7			

*Statistically significant.

Table 3. Analysis by histological type of PGT.

Types of tumors	Smoking	No.	Chi-squared: Significance level
PA	Never	112	P < 0.0001*
	Ever	16 (13%)	
WT	Never	14	P = 0.8474
	Ever	13 (48%)	
lymphoma	Never	8	P = 0.5930
	Ever	6	
MA	Never	7	P = 0.7963
	Ever	8 (53%)	
Malignant	Never	10 (48%)	P = 0.3173
	Ever	6	

*Statistically significant.

derived from a small number of cases. Thus, it seems equitable to accept that our results reveal the real disconnect between these types of PGTs and smoking. The study confirms that benign tumors occur in 92% of the cases studied, in which pleomorphic adenoma form 64% of cases, while Warthin tumors presented in 13%, according to other studies, pleomorphic adenoma is the most common diagnosis of parotid tumors, and these findings are close to that (Shashinder et al., 2009; Sungur et al., 2002; Lin et al., 2008), followed by Warthin tumors (Freedman, Oberman and Sadetzki, 2009; Chedid et al., 2011; Vories and Ramirez, 1997; De Ru et al., 2005; Chung et al., 1999). Despite the high percentage of regular smokers observed in cases of Warthin's tumor (48%), it was described as having no significant association (P = 0.8474), this was also noted by Pinkston JA (Freedman, Oberman and Sadetzki, 2009), while Sadetzki et al showed association with cigarette smoking for warthin tumors only (Sadetzki et al., 2008; Espinoza et al., 2016).

For tumors that are malignant, in contrast, the opposite may be true. There were 16 cases (8%) in the group and did not indicate risk associated with smoking, where smoking status was identified in 38 percent of cases. Other studies also found an equivalent percentage of malignant tumors (Sungur et al., 2002; Lin et al., 2008). One of the two hospital-based studies on malignant salivary gland tumors was conducted by Spitz et al. and the other made by Muscat and Wynder, did not check any relationship between smoking and the development of such malignancies (Guzzo et al., 2010; Tomasi, Facchini and Maia, 2004; Taha, Alabdaly and Ali, 2012). Sungur discovered that there were a different percentage of malignant tumors in 2002, which was 17% (Sungur et al., 2002; Maahs et al., 2015; Stryjewska-Makuch et al., 2017). Based on these findings, we believe that certain malignancies should be considered for suspected malignancies of the tumor.

The intensity and duration of smoking were the main factors that led to a significant increase in ORs observed in this study (OR 2,2 with 95% CI = 1.1012 to 4.3952 and OR 2.1 with 95% CI = 1.0379 to 4.1819) respectively. While lacking many indications of a dose-response association (Pan, de Groh and Morrison, 2017). Another study of 84 cancers of the salivary glands showed a significant increase in PGT occurrence, only in patients who reported an increase in smoking intensity (OR, 1.8) (Bunnell et al., 2010).

The population-based state nature of our study has prevented it from being subject to biases that may be present in other case-control studies. The frequency of smoking among our controls (25.1%), the same as the smoking frequency among Israeli adults, as part of a national survey for 2004 and 2005 (Kopel et al., 2013), also that was found by Erovcic BM, et al. (Erovcic et al., 2015), it is apparent from this that our control group is a representative of the Nineveh population for smoking. However, the dissimilar risks detected by histologic category, say compared to the probability that current outcomes can be attributed to recall bias.

This study may not be representative of all men and women who are diagnosed with this disease. Furthermore, themes may not remember exposure facts precisely because of their illness. Although matching, such as age and gender, lessens the possibility of confounding between the two study groups, the independent effects of marital status and education on the risk of PGT cannot be tested. Similarly, in all case-control studies, recall bias cannot be excluded when exposure data are collected retrospectively and based on self-declaration.

4. Conclusion

The association between smoking and the danger of PGT is demonstrated in this study through multiple causal relationships: extremely elevated ORs;

Smoking intensity and duration have significant dose-response relationships, but there is an inverse association between age at smoking initiation and risk of PGT. It is necessary to conduct additional research on the link between smoking and malignant PGTs in a larger sample size.

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All participants put in the effort in collecting data.

Conflicts of interest

No conflict of interest

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