

## A BRIEF ORIGINAL CONTRIBUTION

# Cigarette Smoking and Warthin's Tumor

John A. Pinkston<sup>1</sup> and Philip Cole<sup>2</sup>

The etiology of Warthin's tumor, a benign parotid gland tumor, is unknown. Recent evidence suggests a possible relation with cigarette smoking as well as increasing incidence. We reviewed the medical record of subjects with a major salivary gland tumor newly diagnosed in Jefferson County, Alabama, from 1968 to 1989, and identified 149 Warthin's tumors. The 533 cases with other major salivary gland tumors were used as controls. The analysis showed that 96% of Warthin's tumors occurred in whites. The relative incidence of Warthin's tumor among smokers versus nonsmokers was 7.6 for men (95 percent confidence interval 3.2–18.3;  $p < 0.001$ ) and 17.4 for women (95 percent confidence interval 6.5–54.7;  $p < 0.001$ ). Smokers of both sexes with Warthin's tumor smoked more heavily than did those with other salivary gland tumors ( $p < 0.001$ ). From 1968 through 1988, Warthin's tumors steadily increased in number and as a proportion of salivary gland tumors (males,  $p = 0.003$ ; females,  $p = 0.008$ ). We also observed a significant increase in the incidence rate for Warthin's tumor ( $p = 0.041$ ) but not for other salivary gland tumors. We conclude that Warthin's tumor is strongly associated with cigarette smoking and that the incidence rate is increasing. The disease is rare in blacks. *Am J Epidemiol* 1996;144:183–7.

adenolymphoma; salivary gland neoplasms

Warthin's tumor (papillary cystadenoma lymphomatosum or adenolymphoma) is a benign tumor that occurs almost exclusively in the parotid gland. It has been reported predominantly in whites, less frequently in Orientals, and rarely in blacks. The incidence rate is higher than that of salivary gland cancer but is lower than that of benign mixed tumors (pleomorphic adenoma). Malignant transformation is rare (1, 2).

Little is known of the etiology of Warthin's tumor. The male:female ratio has decreased since Warthin's description in 1929 (3). In addition, in some studies an excess of smokers (4–9) and an increasing number of cases over time (4–6, 8) have been observed. This study evaluates the relation between cigarette smoking and Warthin's tumor.

## MATERIALS AND METHODS

We intended to review the medical record of all cases of histologically confirmed epithelial tumors of a major (parotid, submaxillary, or sublingual) salivary gland newly diagnosed in Jefferson County, Alabama,

hospitals for the 22 years from 1968 through 1989. All 14 hospitals serving the county participated. The medical record was obtained for all persons with a discharge diagnosis of salivary gland tumor (*International Classification of Diseases*, Ninth Revision, diagnosis code 142.0–142.9, 210.2, 230.0, or 235.0). A pathology report confirming the histologic diagnosis was required for inclusion in the study. We focused on tumors of epithelial origin and excluded other tumor types. Effort was made to exclude tumors metastatic to the salivary glands, particularly squamous carcinomas originating in the skin or other head and neck sites.

The entire medical record for each case was reviewed, including archives and previous admissions at other area hospitals. Data on numerous factors of possible relevance to tumor occurrence were gathered, including medical history, demographic information, family history, and lifestyle factors such as tobacco and alcohol use.

## Incidence series

A subset of the total case series, the "incidence series," was used to estimate incidence rates. The incidence series was restricted to residents of Jefferson County with tumors first diagnosed during 1979–1980, 1983–1984, or 1987–1988. The population of Jefferson County is 64.2 percent white, 35.1 percent

Received for publication March 30, 1995, and accepted for publication January 22, 1996.

<sup>1</sup> Gordon L. Ross Cancer Center, Princeton Baptist Medical Center, Birmingham, AL.

<sup>2</sup> Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL.

black, and 0.7 percent other groups (1990 US Census), providing an opportunity to explore possible differences between blacks and whites. The size of the population at risk was estimated by averaging the numbers from the 1980 and 1990 US censuses for each stratum of sex, race (black and white), and age (ages 0–14, 10-year groups to age 74, and over age 74). The average (white and black) population of Jefferson County numbered 657,459 and decreased by 3.2 percent from 1980 to 1990.

We attempted to ascertain all cases for the incidence series by expanding case finding to include all outpatient offices, clinics, and other facilities where a diagnosis of salivary gland tumor might be made. All pathology reports issued in the hospitals and outpatient surgical pathology laboratories in Jefferson County for the incidence years were reviewed. We also reviewed all death certificates coded with salivary gland cancer as the cause of death among Jefferson County residents during 1979 through 1988. Hospitals in surrounding counties were also surveyed to rule out the possibility that some residents of Jefferson County with these tumors were diagnosed or treated at out-of-county facilities. Thus, we believe the incidence series of histologically confirmed cases to be complete.

### Statistical analysis

The relative incidence of Warthin's tumor among smokers compared with nonsmokers was estimated using other salivary gland tumors as the control group.

Statistical analysis was performed using *t* tests, the Wilcoxon rank sum test, Mantel-Haenszel techniques, and tests for trend in proportions. For analysis of trends in incidence rates, Poisson regression models were fit using eight strata of age (0–14, 10-year groups to age 74, and over age 74), sex, race, and year of diagnosis as covariates. All *p* values are two sided.

### RESULTS

We identified 682 cases of salivary gland tumors, of which 149 were Warthin's tumors. A total of 143 (96 percent) of the Warthin's tumors occurred in whites, and six (4 percent) occurred in blacks. The mean age of the subjects with Warthin's tumor was 59.2 years (standard deviation, 11.4; range, 25–84), which was significantly greater than the 52.3 years (standard deviation, 18.6; range, 8–103) observed for other tumors ( $p = 0.0001$ ). Information on cigarette use was obtained for 83.9 percent of cases. The smoking frequency by sex for Warthin's and other salivary gland tumors is shown in table 1. For both sexes, cigarette use among subjects with Warthin's tumor was significantly greater ( $p < 0.001$ ) than among subjects with other salivary gland tumors. The relative incidence of Warthin's tumor among smokers compared with nonsmokers was 7.6 for males (95 percent confidence interval 3.2–18.3;  $p < 0.001$ ) and 17.4 for females (95 percent confidence interval 6.5–54.7;  $p < 0.001$ ). For smokers of both sexes, cigarette use among subjects

TABLE 1. Relative incidence\* of Warthin's tumor according to cigarette smoking status for males and females, Jefferson County, Alabama, 1968–1989

Smoking status	Males			Females		
	Warthin's tumor (%)†	Other tumors (%)‡	RI§	Warthin's tumor (%)	Other tumors (%)¶	RI
Nonsmokers	7.7	37.4	1.0	13.3	56.4	1.0
Smokers, amount smoked (packs/day)						
<1	10.6	11.3	4.2	20.0	6.4	15.6
1–2	37.4	14.9	11.5	40.1	9.7	20.5
≥2	22.1	9.4	9.9	13.3	3.3	19.8
Unknown	13.5	10.3		11.1	4.2	
All smokers	83.6	45.9	7.6 (3.2–18.3)#,**	84.5	23.6	17.4 (6.5–54.7)**
Unknown	8.7	16.7		2.2	20.0	
Total	100.0	100.0		100.0	100.0	

\* Adjusted over four strata of age: 0–29, 30–49, 50–69, and ≥70 years.

†  $n = 104$ .

‡  $n = 203$ .

§ RI, relative incidence.

||  $n = 45$ .

¶  $n = 330$ .

# Numbers in parentheses, 95% confidence interval.

\*\* *p* value for trend < 0.001 for males and females.

with Warthin's tumor was heavier than with other salivary gland tumors ( $p$  for trend  $< 0.001$ ).

To explore a possible increasing incidence rate of Warthin's tumor over time, we aggregated cases into five groups consisting of those diagnosed before 1977 and four 3-year groups for those diagnosed during the 12 years from 1977 through 1988. For both sexes, Warthin's tumors consistently increased in number and as a proportion of all cases in each succeeding time period. A test for linear trend in proportions was highly significant (males,  $p = 0.003$ ; females,  $p = 0.008$ ). No evidence of increasing frequency was observed for any other salivary gland tumor. Poisson regression analysis of cases in the incidence series revealed that the incidence rate of Warthin's tumor significantly increased from 1979 through 1988 ( $p = 0.041$ ), while no change was evident for other salivary gland tumors. Among whites the incidence rate was 1.85 per 100,000 person-years in 1979–1980. It rose to 3.01 per 100,000 person-years by 1987–1988.

## DISCUSSION

The results of this study provide evidence that the incidence of Warthin's tumor is increasing and that the increase is associated with cigarette smoking. The association with smoking is strong and consistent for all categories of age and sex. For the 93.3 percent of Warthin's cases where smoking status was known, 90 percent were smokers. We also observed that smokers with Warthin's tumor smoked more heavily than did smokers with other salivary gland tumors. In addition, we found a significant increase in the incidence rate for Warthin's tumors among residents of Jefferson County over the 10 years from 1979 to 1988. No change in incidence rate was observed for other histologic types. The proportion of Warthin's tumors among all cases consistently and significantly increased for both sexes during the 21 years from 1968 through 1988.

Our study was based on histologically verified cases; thus, true incidence rates may be underestimated. Some subjects described a mass that had been present, often for years, for which medical attention was sought only when enlargement or other changes occurred. The proportion of salivary gland tumors that remain asymptomatic or otherwise go undiagnosed is unknown but is probably higher for benign than for malignant tumors.

We used other salivary gland tumors as the control group for estimating the strength of the association between smoking and Warthin's tumors. Previous studies have found no association between cigarette smoking and salivary gland cancer (10–12) or other benign salivary gland tumors (10, 12). The percentage

of nonsmokers (males, 37.4 percent; females, 56.4 percent) (see table 1) in the control group is similar to that in the general population (males, 34.7 percent; females, 54.4 percent) (see ref. 13) and suggests that our relative incidence estimates for both men (relative incidence = 7.6) and women (relative incidence = 17.4) using other salivary gland tumors as the control group are valid.

Information on smoking status was obtained from medical records and came from several sources, including physician's office and hospital admission histories, anesthesia presurgical histories, and hospital admission histories by nurses. More than one source was available for most subjects. We consider the data to be mostly reliable, but the smoking status for some subjects may be misclassified. Any misclassification, however, is likely to be random, and any resultant bias was toward the null hypothesis of no association between smoking and Warthin's tumor.

A possible smoking-related increase in the frequency of Warthin's tumor has been observed previously. Ebbs and Webb (6) reported 57 cases seen between 1951 and 1984 at the Bristol Royal Infirmary, United Kingdom. Of 48 cases with known smoking status, 94 percent were smokers. They also noted a decrease in the male:female ratio and an increase in the number of cases diagnosed over time. Lamelas et al. (5) reported 122 cases of Warthin's tumor that underwent parotidectomy in two New York hospitals from 1957 through 1986. Of 84 cases with the smoking history recorded, 89 percent were smokers. An increase in the number of females over time and a decrease in the male:female ratio were also observed. In a report by Monk and Church (7) of 42 cases with Warthin's tumor, among those whose smoking status was known, 85 percent were smokers. Others report similar results (4, 8, 9). Our observations are consistent with these earlier findings.

Other evidence also suggests that the incidence of Warthin's tumor is increasing. Among several hundred parotid tumors examined over a 34-year period prior to 1929, Warthin (14) identified only two with this histology. Subsequent studies have revealed that over time Warthin's tumor has constituted an increasing proportion of parotid tumors (15) and shown a decreasing male:female ratio (3). In 1954, Frazell (16) reported 6.5 percent of 766 parotid tumors diagnosed from 1930 to 1949 at Memorial Hospital in New York to be of Warthin's histology, with a 15.7:1 male:female ratio. In our study, 24.2 percent of parotid tumors had Warthin's histology, with a 2.2:1 male:female ratio.

The paucity of Warthin's tumor in blacks (and possibly in other nonwhite populations) is noteworthy (5,

17). No racial disparity this great has been observed for other smoking-related conditions, including neoplasms. The difference is difficult to explain by variation in lifestyle or other environmental influence, and it suggests that genetic factors may be of importance. Our data also confirm previous observations that Warthin's tumor occurs predominantly in males and at an older age than do other salivary gland tumors (3-6, 8, 17). This is consistent with a smoking-related induction period for this tumor not present with other salivary gland tumors. Of 149 Warthin's tumors, only two (1.3 percent) occurred under the age of 35 years, compared with 113 of the 533 other tumors (21.2 percent). In addition, the observation that the relative incidence of Warthin's tumor among smokers versus nonsmokers for females is twice that for males (relative incidence = 7.6 for males, 17.4 for females) suggests that factors other than smoking may be involved in the etiology of these tumors.

Malignant transformation of Warthin's tumor is considered rare but is being reported with increasing frequency (2). In 1982, McClatchey et al. (18), in a review of American literature, noted that only six cases had been reported. Other cases have since been described, and these may occur as lymphomas associated with the lymphoid stroma (19, 20) or carcinomas originating from epithelial elements (2, 18, 21, 22). With the increased occurrence of Warthin's tumor, the number of malignancies originating from these tumors may also increase.

Benign tumors have only rarely been associated with cigarette smoking, which focuses attention on the nature of the underlying neoplastic process and how it may differ from other benign tumors. Although generally believed to be an adenoma, Warthin's tumor, as suggested by Allegra (23), may be a delayed hypersensitivity reaction, and he proposed mechanisms for the development of its characteristic histologic appearance. The observed strong association with smoking should stimulate research that may further clarify the pathogenesis of Warthin's tumor.

#### ACKNOWLEDGMENTS

Supported by a grant from the National Cancer Institute (NIH/NCI 2P30CA13148-21) and a Departmental Grant from the Shell Oil Company Foundation.

The authors are indebted to the following Jefferson County, Alabama, hospitals for their assistance: Princeton Baptist Medical Center, Montclair Baptist Medical Center, Children's Hospital of Alabama, University of Alabama Hospital, AMI Brookwood Medical Center, Saint Vincent's Hospital, Carraway Methodist Medical Center, Bessemer Carraway Medical Center, Medical Center East, Health

South Medical Center, Cooper Green Hospital, Longview General Hospital, Lloyd Noland Hospital, and the Veterans Administration Hospital; to Pathology Associates, BMC Pathology Group, Cunningham Pathology Associates, and Dermatopathology Associates for their cooperation; to Tammy Weaver for assistance with data collection and management; and to Shirley Jones for manuscript preparation.

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