Research Article

Warthin Tumour: A Potential Benign Mass for Assessing Smoking Index and Predicting Synchronous Neoplastic Tumours in Smokers

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Abstract

Background: Warthin Tumour (WT), common in smokers, is the second most prevalent benign mass with epithelia-glandular and lymphoid characteristics. This study determined the prevalence of WT in some countries and the prevalence of subgroups of Synchronous Salivary Gland Tumours (SSGT) in patients with WT. It also assessed the relationship between WT and cigarette consumption.

Methods: Peer-reviewed articles published between 1999 and 2019, and found on Google scholar, African Journal Online and PubMed were reviewed.

Results: The prevalence of WT is higher in developed countries (41.3% to 12.2%) than in developing countries (8.6% to 0.0%; p= 0.0002) with a male to female ratio of 18:1 to 1.2:1. There was a significant relationship between WT and intensity/prevalence of smoking (p=0.002). In documented cases of SSGT (n= 142), the mean age of males (n= 179 years; 63.51 years ± 2.42 years) was significantly higher than that of their females counterparts (n= 27 years; 47.11 years ± 6.17 years; p= 0.0062). The ratio of males to females with SSGT was 6.6:1. The SSGTs subgroups are: Head and neck (55.4%), lymphoma (19.2%), lungs (13.0%), breast (3.4%), thyroid and urinary tract (2.7% each), prostate (2.1%), liver and cervix (0.7%). The frequency of squamous cell carcinoma (28.8%) was higher than other histologically classified tumours.

Conclusion: This study revealed that the prevalence of WT could be used to assess the extent and effect of cigarette consumption in countries. Screening heavy smokers may not only detect WT early but also help in identifying those at higher risk of developing SSGTs.

Keywords: Warthin tumour; Smokers; Age; Malignant tumours; Synchronous tumours

Introduction

The salivary glands, which majorly include parotid, submandibular and sublingual regions, control saliva-associated functions including maintaining buccal integrity. They are affected by a variety of lesions ranging from inflammation (24.4%) to neoplasia (73.1%). Salivary gland neoplasia accounts for 5% of all head and neck neoplasms and 0.5%-2% of all tumours worldwide [1-3]. They also account for 2%-6.5% and 2.8%-10% of all the head and neck tumours in developed and developing countries, respectively. In Nigeria, Salivary Gland Tumours (SGTs) are very rare, accounting for 0.32% of histological specimens and 5.1% of all head and neck tumours. The male to female ratio is 1:1.3-1.8, and the ratio of benign to malignant tumors is 1:1. Salivary gland benign neoplasia include pleomorphic adenoma, Warthin's Tumour (WT), oncocytoma among others while malignant tumours include squamous cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma and others. Warthin's tumour, also known as adenolymphoma or papillary lymphomatous cystadenoma, is a slow growing mass with epithelial, glandular and lymphoid histological characteristics. It is exclusively localized in parotid gland cauda and rarely in peri-parotid lymph nodes (8%). It is the second most common benign neoplasm of the parotid gland, comprising 2%-15% of the parotid epithelial tumors and approximately 5%-6% of epithelial salivary gland neoplasms. It majorly occurs in individuals between the ages of 40 years to 71 years in smokers and ex-smokers [4-6]. About 72% of patients with WT express some inclusions in the parotid lymph node A lot have been written at the WT, however there is no comprehensive review on the prevalence of SSGTs associated with WT. This review provides an update on the prevalence of WT in countries and continents in relation to cigarette consumption. It also revealed the age of SSGT occurrence [7-9].

Materials and Methods

Peer-reviewed articles (n=123) published between 1999 and 2019 and found on databases such as African journal online, Google scholar and PubMed/PubMed central were reviewed. Journals on Oral and maxillofacial pathologies and surgery were also reviewed in order to identify cases of synchronous and metachronous tumours. Only articles with accessible full text were reviewed [10-12]. The data generated were analyzed and presented as descriptive statistics. T-test and Analysis of Variance (ANOVA) were used to determine the mean ages of males and females with synchronous tumours, and to determine the prevalence of WT in Africa, Asia, Australia, Europe, North and South America continents, respectively [13-15].

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Intensity and prevalence of smoking in countries (lower and upper limits) were graded on a scale of 1 to 6: Low consumption of cigarette by smoker/day (1 and 2), medium consumption (3 and 4) and high consumption of cigarette by smoker/day (5 and 6).

Results

The mean age of patients with WT was 60.83 ± 1.029 (range 9 years to 86 years). The tumour is preponderant in males than in female with a ratio of 18:1 to 1.2:1 across the world [16-18]. Result showed that the mean age of males with SSGT (n=179; 63.51 years ± 2.42 years) was significantly higher than that of their females counterparts (n=27; 47.11 years ± 6.17 years) at p=0.0062. The median ages of occurrence for males and females is 64 years and 48 years, respectively [19,20]. The maximum ages of SSGT occurrence in males and females were 102 years and 68 years, respectively while the minimum ages of occurrence were 30 years and 16 years, respectively. The ratio of males to females with SSGT is 6.6:1 while the median age is 64 years. The prevalence of synchronously and metachronously neoplastic tumours associated with WT ranges from 19.2% to 37% and 7.7% to 14.8%, respectively [21-23]. Such neoplastic tumours include: Head and neck (55.4%), lymphoma (19.2%), lungs (13.0%), breast (3.4%), thyroid and urinary tract (2.7% each), prostate (2.1%), liver and cervix (0.7%). The frequency of squamous cell carcinoma (28.8%) was higher than other histologically classified tumours [24-26]. Result showed Europe had the highest prevalence of WT and that Africa had significantly lower prevalence of WT when compared with Asia, Australia, Europe, and North America (Figure 2; p=0.0002). Based on the study carried out on cigarette smoking, higher consumption of cigarette was observed in Europe followed by Australia while the lowest consumption was observed in Africa (p=1212). About 68% to 97% of patients with WT are smokers [27-29]. There was a significant relationship between the frequency of WT in Benign SGT (BSGT) and intensity and prevalence of smoking in different countries (p=0.002) (Figure 1).

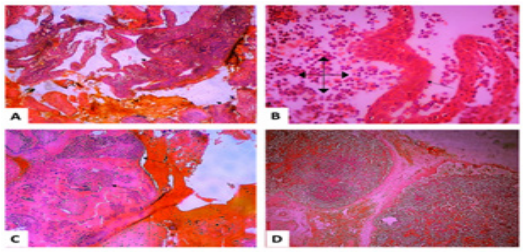

Figure 1: Photomicrograph of parotid gland section with Warthin Tumour.

Discussion

Prevalence of Warthin tumour

Except for the US, Ghana, Malaysia, Western Australia and Libya, the prevalence of benign SGT tumour is greater than malignant tumours. Developed countries such as Germany, Italy, US, Turkey and Japan have higher prevalence of WT than African countries [30-32]. Women with WT are significantly older (60.93 years ± 11.1 years) than their men counterparts (57.95 years ± 10.41 years) while males who are positive for WT and other SSGT were significantly older than their female counterparts (Figure 2).

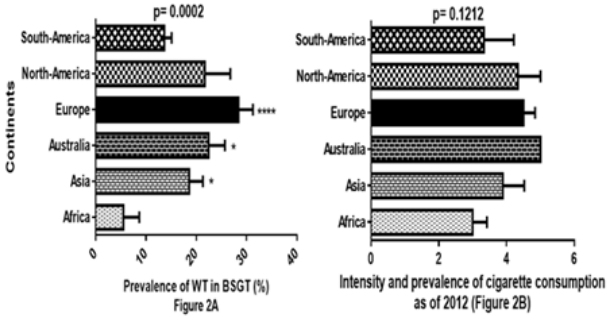

Figure 2: Mean (±SEM) comparison of continent-based prevalence of WT in benign SGT (2A; current study), and intensity and prevalence of cigarette consumption.

Despite the consistent decrease in cigarette smoking in countries with stable and strong economies such as Germany, Poland, US, Brazil and Japan the prevalence of WT is consistently increasing. In Germany, reported lower percentage of WT in 1990 (24%) than in 2014 (48%). In the same country, another study shows a decade-wise increase in the incidence of WT from 20.6% (in 1975) to 44.9%. In Poland, the percentage of the tumour increased from 23% in 1995-2000 to 35% in 2001-2006. Also observed percentage increase in WT from 1960 (9.1%) to 2000s (50%) in Austria. Interestingly, the prevalence of WT is higher in whites (29.6%) than in blacks (4.08%) with a white to black ratio of 30:1. Regression analysis show that the occurrence of WT is 13 times higher in whites than in blacks. Despite the low prevalence of WT in blacks, decade-wise increasing prevalence of the tumour (0%-16%) have also been documented in them over four decades. Studies have linked the increasing prevalence of WT to environmental, metabolic syndrome, nutritional deficiencies, genetic and lifestyle factors, especially cigarette smoking [33-35].

Smoking and Warthin tumour

Evidence suggests that smokers are 8 times at risk of developing WT than non-smokers. The prevalence of cigarette smokers among patients with WT ranges from 68% in China to 97% in the Netherlands. However, other factors may play critical roles in the development of WT [36-38]. Such factors include high body mass index and triglyceride, and exposure to electrical, electronical, welding, plastic and painting materials have also been implicated in WT tumorigenesis (Table 1).

Table 1: Country-based prevalence of smokers among patients with Warthin tumour

Country	Smokers (%) with WT	References
Netherlands	97.5	De Ru et al., 2005[26]
US (New York)	96.8	Zaccarini and Khurana, 2019[23]

US (Baltimore)	87.9	Yoo et al., 1994[22]
Spain	93.8	Bothe et al., 2015[27]
Canada	92.5	Cope et al., 2014[11]
UK (Swansea)	92.3	Lewis et al., 2000[28]
Germany (Neuruppin)	92	Franzen et al., 2018[18]
Germany (Cologne)	89	Klussmann et al., 2006[29]
Germany (Marburg)	74.1	Teymoortash et al., 2005[9]
Brazil	83	Chulam et al., 2013[30]
South Korea	83.1	Lee et al., 2019[31]
Romania	71	Daguci et al., 2009[13]
New Zealand	70	Patel and Morton, 2015[32]
Austria	69	Kadletz et al., 2019[20]
China	68.4	Tian et al., 2010[33]

Revealed variation in smoking index (SI; prevalence and intensity) between counties and regions in the world [39,40]. Their study show that Africa has the highest number of countries (29.6% including Uganda) with low consumption of cigarette (<10) against the 6.4% of the rest of the world. Medium consumption of cigarette (≥ 10 to <20) is seen in Europe, Australia and America while high consumption is observed in Asia. On the average, smokers in Nigeria, Cameroon, Ghana, Kenya, Egypt, and South Africa consume 10 to 15 cigarette/day (medium consumption of cigarette) while smokers in Libya, Somalia, and countries in Western Asia (Saudi Arabia, Iraq and Iran) consume more than 20 cigarette/day but less than smokers in Asia [41-43]. The low prevalence of smoking could be associated with the low prevalence of WT in most African countries while the medium to high prevalence of WT observed in developed countries could be adduced to the medium to high prevalence of smoking in Europe, America, Australia and Asia. However, this position is beginning to change as higher prevalence of smoking is being observed in African countries, Nigeria for one [44-46]. Thus, the reason for the increasing percentage of WT could be linked to increasing intensity or steady consumption of cigarette in some countries. The extent and duration of smoking determine the age at which WT will develop in an individual [47]. Evidence show that WT is more prevalent in individuals who smoke more than 10 cigarette/day and have been smoking for over 20 years. The moderate prevalence of WT observed in Japan when compared with the other developed countries may be due to reduction in cigarette consumption from 2003 upwards. This is underscored by studies which show that only 6.5% to 12.3% of WT-positive patients were former smokers [48-50]. Although the prevalence of WT in China is moderate, the prevalence is expected to increase in geometric progression since it consumed cigarette 7 to 13 times higher than other developed countries in 2013.

In Nigeria, 32.2% of adolescent have smoked cigarette at one point in their lives while 20.8% are current smokers. The prevalence of smoking among young Nigerian females is 2.2% to 10% while that of males is ranges from 1% to 32.5%. In Ibadan, another group of researcher stated that the prevalence of outdoor smoking by adults is 63.8%. The prevalence of smoking in Lagos ranges from 3% (2011) to 32.5 (2016) while the prevalence ranges from 16% to 19.1% in Borno (2009), 11.3% (2009), 1 to 6.2% (2010) in Kano, 13.7% (2012) to 14.6% (2013) The decade-wise increase in WT percentage may be due to increasing cigarette smoking or tobacco use [51-53]. Interestingly, no study have been carried out to assess the prevalence of WT in smokers and non-smokers in Africa. Apart from Egypt and South-Africa, other countries in Africa have low prevalence of WT. The low prevalence of WT in some African countries despite the increasing prevalence of smoking may be due to low income. Ailing smokers with low income are less likely to seek medical attention. Again, some ailing individuals in Africa often prefer herbal remedies to hospital based therapy. Hence, the low prevalence of WT in African hospitals [54-56].

Adjunct technique for diagnosing Warthin tumour

Despite the increasing reports of WT in literature and the consumption of greater than 10 cigarette/day in some African countries, only a few cases of WT have been reported in Africa. Again, none of the reviewed study in Africa employed advance adjunct diagnostic techniques in making diagnosis [57,58]. Such adjunct techniques include magnetic resonance imaging, Positron Emission Tomography (PET), PET-Computer Tomography (PET-CT), Computer tomography and Sonography. These technique can identify symptomless tumours. Thus, the low prevalence of WT in Nigeria and other African countries could be due to under-diagnosis accrued to limited availability of such techniques for differentiating between WT and other benign tumours or malignant tumours. With sonography, the internal texture of WT appear homogenous, its margin are well defined [59,60]. Additionally, absence of inflammatory reaction, squamous like cells and vacuolized cytoplasm, and non-adherence to recent guidelines for classifying SGT could lead to some diagnostic dilemma and misdiagnosis eventually. More so, over reliance on cytology for the diagnosis of salivary gland tumours without advance techniques could lead to false positive diagnosis of oncocytoma, acinic cell carcinoma, or mucoepidermoid carcinoma, among others instead of WT especially when the Milan System for Reporting Salivary Gland Cytopathology. Immune Cyto Chemistry (ICC) and Fluorescence In Situ Hybridisation (FISH) are not employed. The percentage of misdiagnosis of WT is 4.2%. The low benign to malignant ratio and non-availability of adjunct diagnostic techniques in some African literatures question the diagnostic accuracy of their investigations. A recent study show that multi-phasic CT examination with 8 minutes delayed acquisition is effective in differentiating between WT and other tumours, particularly pleomorphic tumour. On the other hand, genomic-geographical variation may account for the low prevalence in Africa.

Males to female prevalence of Warthin tumour

Although smoking has been associated with the development of WT, studies have shown a significant association between male factor and WT. Country-based evidence also show that there is a high preponderance of WT in males than in females. However, there seem to be a decline in the male to female ratio over the years. First reported that the male to female ratio of WT is beginning to change. This is evident in a recent study which shows a change in the male to female ratio of WT from 5.3:1 to 1:2.1. over three decades. The dynamic shift in incidence between males and females is associated with increasing female smokers. Interestingly, in South Africa, the number of females with the tumour is twice that of males. Recent findings show that WT-associated malignancy is slightly higher in males than in females (1.1:1) while WT without any malignancies is higher in females than in males (10.5:1) (Tables 2 and 3).

Table 2: Country-based prevalence of Warthin tumour in Salivary gland tumours (Extra-Africa)

Country	Salivary Gland Tumour (SGT)			WT/ BSGT	WT/ SGT	Reference
	Benign(B)	Malignant (M)	B/M ratio	(%)	(%)	
Austria	919	--	--	41.3	--	Kadletz et al., 2019[20]
France	145	37	3.9:1	37.9	30.2	Dubucs et al., 2019[44]
Germany	2817	--	--	34.5	--	
Germany (Neuruppin)	629	177	3.6:1	42.1	32.9	Franzen et al., 2018[18]
Germany (Cologne)	2188	--	--	32.3	--	Luers et al., 2016[16]
Italy (n= 398)	308	90	3.4:1	34.1	26.4	
Italy (Roma)	69	25	2.8:1	26.1	19.1	Tartaglione et al., 2015[48]
Italy (Rome)	239	65	3.7:1	36.4	28.6	Catania et al., 2003[49]
Finland	1606	282	5.7:1	31.3	14.4	Bello et al., 2012[50]
Poland	586	82	7.1:1	30.9	27.1	Wierzbicka et al., 2010[19]
Turkey (n= 511)	403	108	3.7:1	30.8	24.3	
Turkey (Istanbul)	304	65	4.7:1	30.6	25.2	Comoglu et al., 2017[51]
Turkey(Ataturk)	99	43	2.3:1	31.3	21.8	Etit et a., 2012[52]
US	209	248	0.000708	29.2	24.6	Pinkston and Cole, 1999
Cuba	113	46	2.5:1	29.1	20.7	Cornejo
Japan	3998	1017	3.9:1	26	21	Sentani
Malaysia (n= 243)	96	147	1.5:1	26	10.3	
Malaysia (Kubang Kerian)	45	142	0.000731	13.3	3.2	Rahman
Malaysia (Sembilan)	51	5	10.2:1	37.3	33.9	Ambu
United Arab Emirates	231	83	2.8:1	24.8	6.7	Sarraj et al., 2015[57]
New Zealand	170	-	-	24.1	-	Patel and Morton
China (n= 9490)	6677	2813	2.4:1	21.4	15.1	
China (Shenyang)	1934	574	3.4:1	24.4	18.8	Wang
China (Shanghai)	4743	2239	2.1:1	20.3	14.2	Tian
Romania	116	46	2.5:1	21	14.8	Ungureanu
Trinidad and Tobago	53	7	7.6:1	20.8	18.3	Noel

Israel	220	110	2.0:1	20	8	Bello
Mexico (n=439)	338	101	3.3:1	7.7	5.9	
Mexico (Veracruz)	61	18	3.4:1	9.8	7.6	Sotelo-Gavito
Mexico (Mexico City)	277	83	3.3:1	7.2	5.6	Mejía-Velázquez
Portugal	92	15	6.1:1	18.5	15.9	Ferriera
Croatia	500	279	1.8:1	17.4	11.2	Luksic
Australia (Queensland)	68	16	4.3:1	27.9	22.6	Coombe
Australia (Western Australia)	322	364	0.000707	24.8	11.7	Davidos
Australia (Victoria)	69	8	8.6:1	13	11.7	Burgess and Serpell
UK (n=1806)	1399	407	3.4:1	16.9	13.1	
UK (Nottingham)	918	147	6.2:1	22.1	19.1	Bradley and McGurk
UK (Sheffield)	481	260	1.9:1	7.1	4.6	Jones
Brazil (n=816)	641	175	3.7:1	15.1	11.9	
Brazil (São Paulo)	306	14	21.9:1	18	17.2	Castro
Brazil (Parana)	335	161	2.1:1	12.5	8.5	Ito
Kingdom of Saudi Arabia	46	16	2.9:1	13	9.8	Fatima
Chile	188	91	2.1:1	12.2	8.2	Araya
Iran	267	125	2.1:1	8.6	8.6	Shishegar
Sri Lanka	356	357	0.042361	8.1	4.1	Tilakaratne
India (n=801) India	490	311	1.6:1	7.1	4.4	
(Kashmir) India	68	49	1.4:1	20.6	17.5	Atri
(Pondicherry)	422	262	1.6:1	5	3.1	Subhashraj

Table 3: Africa-based prevalence of Warthin tumour in Salivary gland neoplasia

Country	Salivary Gland Tumour (SGT)			WT/ BSGT	WT/ SGT	Reference
	Benign (B)	Malignant (M)	B/M ratio	(%)	(%)	
Egypt	96	44	2.2:1	31.3	21.4	Nakhala et al., 2013[77]
South Africa	119	53	2.2:1	13.4	9.3	Lierop and Fagan, 2007[47]
Ghana (n= 492)	223	269	0.000708	5.8	2.6	
Kumasi, Ghana	167	204	0.000708	5.4	3.3	Titiloye et al., 2017[78]
Kumasi, Ghana	56	65	0.000708	7.1	3.3	Oti et al., 2013[79]
Somalia	72	44	1.6:1	1.4	0.9	Baş, 2018[80]
Nigeria (n= 1048)	531	516	0.042361	1.3	0.7	
Ekiti, Nigeria	37	28	1.3:1	8.1	4.6	Obimakinde et al., 2019[81]
Lagos, Nigeria	19	17	1.1:1	5.3	2.8	Adeyemo et al., 2009[7]
Maiduguri, Nigeria	44	35	1.3:1	4.5	2.5	Otoh et al., 2005
Lagos, Nigeria	189	308	0.000713	0.5	0.2	Omitola et al., 2018

Lagos, Nigeria	77	45	1.7:1	0	0	Ladeji et al., 2018[6]
Imo, Nigeria	41	7	5.9:1	0	0	Onotai and Opara, 2015[23]
Benin, Nigeria	81	42	1.9:1	0	0	Jude et al., 2019[8]
Kano, Nigeria	44	34	1.3:1	0	0	Ochicha et al., 2009[40]
Kenya	92	43	2.1:1	1.1	0.7	Hill, 2002[34]
Cameroon	217	58	3.7:1	0.9	0.7	Sando et al., 2016[8]
Uganda	145	123	1.2:1	0	0	Vuhahula, 2004[87]
Tanzania	1315	1120	1.2:1	0	0	Masanja et al., 2003[20]
Libya	29	46	0.000713	0	0	Jaber et al., 2006[8]

Synchronous and metachronous Warthin tumour

Despite the benign nature of WT and its low prevalence, patients with WT are at a higher chance of harboring or developing other primary neoplasia, especially malignant tumours than individuals without WT. Malignant transformation of WT is rare (1%) and in such cases mucoepidermoid carcinoma is usually seen. The latter tumour has also been known to arise from WT. This feature has led to some misdiagnosis in the past. Hence, the need for adjunct diagnostic techniques. Studies have shown that WT can synchronously develop (19.2% to 37%) while malignant tumours can metachronously exist with Warthin tumour tumours (7.7% to 14.8%), especially squamous cell carcinoma and lymphoma. Additionally, Zaccarini and Khurana stated that 70.4% of WT diagnosed with malignant tumours developed metachronously. About 5%-10% of this tumour reoccur after resection. This suggests that WT can develop before, simultaneously with or after malignant tumourigenesis. Thus, screening for WT may facilitate early diagnosis of malignant tumours in smokers, especially head and neck tumours. More so, literature show that individuals with co-existing WT and pleomorphic adenoma are a decade older than individuals with pleomorphic adenoma. This suggests that WT may developed ten years before pleomorphic adenoma in synchronous cases. Thus, a diagnosis of pleomorphic adenoma could trigger more investigation for WT. Warthin tumour is usually positive for CD9 but immunohistochemical staining for cytokeratin, epithelial membrane antigen and Ki67 is suggestive of synchronous existence of WT and a malignant tumour. Furthermore, since WT has be known to have inflammatory origin, smokers with sialadenitis should be closely monitored for evidence of neoplastic transformation.

Limitation

Some of the limitations in this study are unavailable data, language used in articles, incomplete information and closed access of some journal articles.

Conclusion

This study revealed that WT was higher in countries with higher cigarette consumption. It also reveals that age at which WT-positive present with SSGT is Gender dependent and that SSGTs are preponderant in males. It suggests that the prevalence of WT could be used to assess the paradigm shifts in smoking index in and between countries. Screening individuals who smoke greater than 10 cigarette/day over a period of 20 years may not only detect WT early but also identify those at risk of developing SSGTs.

Competing Interest

The authors declare that they have no competing interests.

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