Trends in the incidence rates of tonsil and base of tongue cancer in England, 1985–2006

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ABSTRACT

INTRODUCTION The aim of this study was to investigate whether incidence rates of tonsil and base of tongue cancer in England are increasing using data from the UK cancer registry.

SUBJECTS AND METHODS Cancer registrations for oral cavity and oropharynx cancer from 1985–2006 in England were obtained from the National Cancer Information Service. Population estimates were obtained from the Office for National Statistics. Age-adjusted incidence rates and age-specific incidence rates were calculated. The sexes were considered separately as incidence rates are known to differ significantly between men and women. Linear regression was performed to establish whether there was a relationship between incidence rates and time.

RESULTS There has been an increase in all oral cavity and oropharyngeal cancer in the study period. Linear regression analysis suggests that approximately 90% of the variance in age-adjusted incidence rates for men and women for tonsil, base of tongue and other oral cavity cancer is explained by the passage of time. For other oropharyngeal cancer, the variance is 62% and 46% in men and women, respectively. The estimated annual percentage change from 1985 to 2006 in age-adjusted incidence rates for tonsil and base of tongue cancer is 5.7% and 6.7% for men, and 4.3% and 6.5% for women, respectively.

CONCLUSIONS This study confirms a wide-spread clinical impression that there has been an increase in age-adjusted incidence rates, between 1985 and 2006, in all oral cavity cancer in England. The age range 40–69 years has seen the biggest increases in age-specific incidence rates for tonsil and base of tongue cancer. This reflects the findings of similar studies in other countries.

KEYWORDS

Tonsillar neoplasms – Tongue neoplasms – Incidence – England – Alpha-papillomavirus

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There is evidence from other western countries that the incidence of tonsil carcinoma is increasing. Davies and Welch.¹ demonstrated a 12% increase in the incidence rate of tonsil cancer in the US between 1975 and 2001. Hammarstedt *et al.*² identified a 2.6% and 1.1% yearly increase in from 1960 to 2003 in Swedish men and women, respectively. The reasons for these trends have yet to be fully established, but many have implicated the role of human papilloma virus (HPV). El-Mofty and Lu³ demonstrated HPV-16 in 91% of specimens with tonsil carcinoma. Ringstrom *et al.*⁴ demonstrated the presence of HPV-16 DNA in 64% of tonsil tumours, 52% of oropharynx tumours and 5% of other oral cavity tumours. Cases with HPV-16 were significantly younger, had a shorter smoking history, lower alcohol consumption and better survival rates.⁴ HPV oncogenes E6 and E7 are known to disrupt the p53 and Rb tumour suppression pathways which are important in the development of head and neck carcinomas.⁵ The aim of this study

was to investigate whether these trends in incidence rates are reflected in the population of England using data from the National Cancer Information Service (NCIS) which is a resource of the United Kingdom Association of Cancer Registries (UKACR). The NCIS has data pertaining to all new cancer registrations in England from all the regional cancer registries.

Subjects and Methods

The NCIS database is coded according to the International Classification of Diseases 10 (ICD-10) from 1985 onwards. At the time of writing, the NCIS database is complete up to 2006, with subsequent years yet to be finalised. The ICD-10 codes for anatomical sites of interest for this study are C09 (tonsil), C01 (base of tongue), C02 (other or unspecified parts of the tongue), C03 (gum), C04 (floor of mouth), C06 (palate) and C10 (oropharynx).

Table 1 Cancer registrations by anatomical site in England, 1985–2006

	Years											Total
	85/86	87/88	89/90	91/92	93/94	95/96	97/98	99/00	01/02	03/04	05/06	
Men												
Tonsil	305	317	364	393	422	429	577	673	698	868	1009	6055
Base of tongue	144	128	141	192	192	196	232	323	410	447	505	2910
Oropharynx	116	127	133	152	183	177	160	185	190	200	251	1874
Oral cavity	1781	1883	1931	2121	2161	2191	2416	2642	2580	2836	2998	25,540
Women												
Tonsil	154	153	165	155	172	172	208	236	259	292	343	2309
Base of tongue	57	49	56	68	79	67	104	112	141	165	163	1061
Oropharynx	50	47	52	42	72	57	74	59	59	76	89	677
Oral cavity	966	1023	1077	1132	1189	1265	1394	1556	1571	1663	1762	14,598

The NCIS database was queried by an information analyst at the South West Public Health Observatory who produced a spreadsheet using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) indicating the number of new registrations of cancers in the anatomical sites of interest in England from 1985 to 2006. The data were presented in 10-year age groupings subdivided by gender. In order to calculate the incidence rates, yearly mid-point population estimates for England only were obtained for 1985 to 2006 from publications produced by the Population Estimates Unit of the Office for National Statistics Centre for Demography.⁵ Calculations for crude and age-adjusted incidence rates were performed using Microsoft Excel 2007. The crude incidence rate was calculated (count/population $\times$ 100,000), and age-adjusted incidence rates (AAIR) were derived using the European Standard Population Distribution. Men and women were considered separately as incidence rates are known to differ significantly between them.

Simple linear regression by the method of least squares was used to describe quantitatively the linear relationship between the dependent variable (y , which was either the age-adjusted incidence rate [AAIR] or the age-specific incidence rate [ASIR]) with the independent variable (x , which was the year in the period of study, 1 to 21, representing each year from 1985 to 2006). Analysis of variance indicated the significance of the regression model. Statistical analysis was performed using SPSS v13.0 (SPSS Inc., Chicago, IL, USA).

Results

New cancer registrations for the tonsil (C09), base of tongue (C01), other oropharynx (C10) and other oral cavity (C02,

C03, C04 and C06) from 1985 to 2006 are shown in Table 1.

Linear regression analysis estimates the equation of a line of best fit between two variables. The basic linear regression model is: $y = a + Bx$. In the first part of the study, we investigated the relationship between time and the AAIR. The components of the equation are as follows: a represents the intercept of the line of best fit on the y -axis; B represents the slope coefficient of the line of best fit; x represents the year in the study period (1 to 21 representing 1985 to 2006); y represents the AAIR. The values of B (the

Table 2 Results of linear regression of age adjusted incidence rates

Anatomical site	B	R ²	P	EAPC
Men				
Tonsil cancer	0.06	0.91	0.00	5.65
Base of tongue cancer	0.03	0.88	0.00	6.72
Other oropharynx cancer	0.01	0.62	0.00	2.53
Other oral cavity cancer	0.08	0.89	0.00	1.71
Women				
Tonsil cancer	0.02	0.86	0.00	4.29
Base of tongue cancer	0.01	0.87	0.00	6.50
Other oropharynx cancer	0.00	0.46	0.00	2.63
Other oral cavity cancer	0.06	0.95	0.00	2.84

B is the slope coefficient in the regression model equation $y = a + Bx$. R^2 indicates the proportion of variance in the AAIR due to time. The analysis of variance P -value indicates the significance of the model. EAPC is the estimated annual percentage change.

Table 3 Results of linear regression of age-specific incidence rates

Ages	Tonsil			Base of tongue			Other oropharynx			Other oral cavity		
	B	R ²	P	B	R ²	P	B	R ²	P	B	R ²	P
Men												
40–49	0.10	0.91	0.00	0.04	0.81	0.00	0.01	0.42	0.00	0.08	0.79	0.00
50–59	0.23	0.90	0.00	0.11	0.87	0.00	0.03	0.60	0.00	0.30	0.94	0.00
60–69	0.15	0.76	0.00	0.11	0.79	0.00	0.02	0.23	0.02	0.24	0.70	0.00
70+	0.00	0.00	0.88	0.10	0.51	0.00	0.02	0.07	0.25	0.00	0.00	0.92
Women												
40–49	0.03	0.80	0.00	0.01	0.40	0.00	0.00	0.16	0.06	0.06	0.64	0.00
50–59	0.06	0.83	0.00	0.04	0.80	0.00	0.01	0.30	0.09	0.15	0.81	0.00
60–69	0.03	0.40	0.00	0.03	0.71	0.00	0.01	0.11	0.13	0.15	0.74	0.00
70+	0.01	0.07	0.24	0.04	0.48	0.00	0.01	0.07	0.25	0.39	0.86	0.00

B is the slope coefficient in the regression model equation $y = a + Bx$. R² indicates the proportion of variance in the ASIR due to time. The analysis of variance *P*-value indicates the significance of the model.

slope coefficient) and the estimated annual percentage change of AAIR are shown in Table 2. The coefficient of determination, denoted by R² in Table 2, indicates the proportion of variance in the AAIR that is due to the passage of time (a model with 100% predictive capability has R² ~1, whereas a model with 0% predictive capability has R² ~0). The analysis of variance *P*-value indicates whether the independent variable (passage of time) has statistically significant predictive capability ($P < 0.01$ at 99% significance level).

In the second part of the study, we investigated the relationship between time and ASIR, (y value in the regression model is the ASIR). The results of linear regression analysis for male and female tonsil, base of tongue, and other oral cavity cancer are shown in Table 3. The coefficient of determination, denoted by R², indicates the proportion of vari-

ance in the ASIR that is due to the passage of time. B slope coefficient and analysis of variance *P*-values are also shown (see above for explanation). Figures 1–4 illustrate the ASIR of age groups 40–70+ years for tonsil and base of tongue cancers in men and women.

Discussion

This study demonstrates an increase in AAIRs from 1985 to 2006 in all oral cavity cancer in England. The age range 40–69 years has seen the biggest increases in ASIR for tonsil and base of tongue cancer (TBOTC). This reflects the findings of other studies. Hammarstedt *et al.*² demonstrated a yearly increase in tonsil cancer of 1.1% in women and 2.6% in men in Sweden from 1960 to 2003 and reported a significant increase in ASIR for the 40–70 year groups after

Figure 1 Age-specific incidence rates of tonsil carcinoma in men. **Figure 2** Age-specific incidence rates of tonsil carcinoma in women.

1990. Shiboski *et al.*⁶ studied the 20–44-year-old population in the US between 1973 to 2001 and identified a significant increase in the incidence rates of TBOTC unlike other sites in the oral cavity which demonstrated a reduction in incidence rates. The similarity in trends of TBOTC suggests they may represent a single disease entity, especially as there is no anatomical distinction between the limits of the palatine and lingual tonsils at the base of the tongue.

The increase in incidence of TBOTC in a younger patient population may be attributed to lower tonsillectomy rates and oral HPV. Freeman *et al.*⁷ demonstrated a 36% reduction in the annual number of tonsillectomies between 1970 to 1977 at private hospitals in the US.

HPV may be involved in an alternative pathway for the development of oropharyngeal squamous cell carcinoma. Syrjanen⁸ reported a HPV prevalence of 8.5% in non-neoplastic tonsils, compared with 51% of neoplastic tonsils based on a review of the literature. A case-control study of 900,000 volunteers in Scandinavia identified 292 patients who subsequently developed head and neck SCC (HNSCC).⁹ Serum sample analysis revealed HPV-16 positivity was twice as high in HNSCC patients compared with controls (12% vs 7%).⁹ There are many studies reporting the presence of HPV-16 in HNSCC specimens ranging from 20–25%.^{4,10} The prevalence is much higher in TBOTC ranging from 64–91%.^{3,4}

Genetic features of HPV-16 positive HNSCC specimens include the expression of E6 and E7 oncogenes, which disrupt the p53 and Rb tumour suppression pathways that are important in the development of head and neck carcinomas.^{3,11} Mutations of p53 are less prevalent in HPV-associated HNSCC specimens.¹⁰ Wiest *et al.*¹² studied 28 HPV-16 positive tumours, demonstrating E6 and E7 oncogene expression and normal p53.

Cigarette smoking and alcohol are the traditional primary risk factors for oropharyngeal carcinoma. The prevalence of

smoking in England is reducing.¹⁵ HPV-16 positive patients had a significantly lower alcohol intake and smoking history⁴ and the odds of oropharyngeal cancer were not increased among heavy users of tobacco and alcohol.¹⁴ There is no evidence of synergy between HPV and tobacco or alcohol use.¹⁴ HPV-16 positive patients are younger (mean age of HPV positive and negative HNSCC patients was 52.7 years and 61.1 years, respectively) and have better overall and disease-specific survival.⁴ This suggests that HPV-associated oropharyngeal cancer has a shorter latent period for the development of malignant clones.⁵

Skin-to-skin sexual contact is the route of transmission of HPV. Most sexually active individuals will acquire HPV at some point in their lives.¹⁵ D'Souza *et al.*¹⁴ conducted a case-control study involving 100 newly diagnosed patients with oropharyngeal cancer. Increasing numbers of vaginal-sex or oral-sex partners was significantly associated with oropharyngeal cancer.¹⁴ Schwartz *et al.*¹⁶ conducted a case-control study comparing sexual history factors between patients with oral SCC with age- and sex-matched controls. Among men, the risk of oral cancer increased with decreasing age at first intercourse, and increasing number of partners.¹⁶ For both sexes, associations with sexual history were strongest for tumours containing HPV-16 DNA.¹⁶

There are several limitations to our study. The ICD-10 code C10 applies to oropharyngeal cancer which may or may not include some tonsil fossa carcinomas, which we considered in the non-tonsil or base of tongue cancer groups. Ethnicity of patients is not given consideration, but may be relevant as different incidence rates between races have previously been reported.^{1,17}

The high association of HPV-16 with TBOTC suggests site specificity and a causative effect, though the exact mechanism of this is yet to be understood. The introduction of a national vaccination programme of HPV-16 and HPV-18

for women in the UK may have implications in the future for the incidence of TBOTC in women. If a direct causative effect for HNSCC with HPV is established, there may be a role for vaccinating men also. The authors suggest that the existing evidence provides a rationale for HPV vaccination in both men and women and that, if a reduction of incidence of oropharyngeal cancer in vaccinated populations is noted, it might be evidence of causality.¹⁴ The findings of this study highlight the need for vigilance regarding tonsil and base of tongue cancer in young patients, even if there is no significant history of smoking or alcohol consumption.

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