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Title: The changing aetiology of head and neck squamous cell cancer: a tale of three cancers?

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Standfirst: The incidence and survival in people with head and neck cancer are changing, we argue that known risk factors may not fully explain these changes.

What do we know about the aetiology of head and neck cancer?

Head and neck cancers are the sixth most common cancers worldwide and an important cause of ill health.(1) Each year about 9000 cases are reported in the UK.(2) Survival is poor and despite advances in treatment, has not improved until recently.(3) The majority of head and neck cancers are squamous cell carcinomas, affecting the larynx, oropharynx and oral cavity. The aetiology is changing and this has implications for prevention and treatment. Twenty years ago, tobacco and alcohol consumption were considered to be the established risk factors and it was estimated that these risk factors accounted for about 75% of cases.(4) More recently human papillomavirus (HPV) has emerged as a likely cause of oropharyngeal cancer.(4) Here we argue that each cancer site is predicted differently by smoking, alcohol and sexual behaviour. We also suggest that these risk factors do not fully explain the changing pattern of disease observed in the UK.

Trends in UK incidence and risk factor profiles in a large contemporary cohort could offer clues to the changing aetiology?

We present recent data on trends in disease incidence and risk factors in the United Kingdom (UK) using the rolling 3-year age standardised rate per 100,000, obtained from Cancer Research UK (2) in September 2016, UK trends in smoking,(5) sexual behaviours,(6) and alcohol (7–9) and the risk

factor profiles of incident cases from a large NIHR funded UK-based clinical cohort study of head and neck cancer called Head and Neck 5000 (H&N5000). The cohort is described in detail elsewhere.(10) Briefly, we recruited people with a new diagnosis of head and neck cancer and obtained wide ranging consent including agreement to collect clinical and longitudinal data, to store and analyse biological samples and for ongoing record linkage. Prior to treatment, participants completed questionnaires on health and lifestyle, quality of life and sexual history. The key variables used in this analysis were anatomical site (grouped according to ICD-10 code), age, gender and participant reported current smoking status, current drinking (units per week alcohol consumed) and history of giving oral sex. Alcohol consumption was categorized using the revised UK Department of Health guidelines (11) and higher thresholds defined by the 'Institute of Alcohol Studies' (12) resulting in four categories: 'Non-drinkers' (0 units/week), 'Moderate' (>0 and ≤14 units/week), 'Hazardous' (Females >14 and ≤35, Males >14 and ≤50 units/week) and 'Harmful' (Females >35, Males >50 units/week). The data were collected in 76 centres throughout the UK. Forty nine percent of all people with a cancer, attending the Head and Neck Cancer MDT (Multi Disciplinary Team Clinic), were recruited. Skin cancers and lymphomas affecting the head and neck were excluded. The results for 2,615 people diagnosed with cancer of the oral cavity, oropharynx or larynx from April 2011 to December 2014 and with complete data are presented (Figure 1).

Laryngeal cancer – less of the same?

In the UK the incidence of laryngeal cancer declined by nearly 20% between 1990 and 2013, but this decline has levelled off since 2002.(2) People enrolled in H&N5000 who have laryngeal cancer are predominantly older, male smokers. Half of these people consume hazardous amounts of alcohol and a quarter report that they have never given oral sex. The established risk factors of smoking (90% had smoked) and alcohol (74% currently drank alcohol) are common behaviours amongst this recently diagnosed cohort of people with laryngeal cancer (see Figure 1).

This pattern of behaviours is consistent with the risk factors reported in a large international consortium of case-control studies.(13) The consortium estimated that the joint effects of tobacco and alcohol use accounted for 89% of laryngeal cancers.(13) There was a substantial decline in the prevalence of smoking in most parts of the world between 1980 and 2012.(14) In the UK in 1980, 42% of men and 36% of women reported smoking compared with 20% of men and 19% of women in 2010.(5) Longer-term trends in alcohol consumption are more difficult to interpret as UK Office of National Statistics data was irregular until 2005. The British Beer and Pub Association data from 1990 to 2013 show no marked change in litres of alcohol consumed per person per year in the UK.(8) The falling incidence of laryngeal cancer in the UK may be linked to the reduction in smoking rates but the role of alcohol is less clear.

Oropharyngeal cancer – just a consequence of the sexual revolution?

In the last twenty years the incidence of oropharyngeal cancer in the UK has more than trebled. This increase is most marked in younger people. People with oropharyngeal cancer in the H&N5000 study are younger, less likely to smoke and more likely to have given oral sex than those with laryngeal cancer. Ninety three percent of people with oropharyngeal cancer had given oral sex (93% of men and 90% of women). Men were more likely than women to have had more than five oral sex partners (44% of men and 13% of women). The established risk factors of smoking and alcohol consumption are common (72% had smoked and 74% currently drink alcohol) but smoking is not as common as in those with laryngeal cancer.

While transmission of HPV to the upper aerodigestive tract is thought to be through oral sexual contact the epidemiologic evidence of the role of sexual behaviour in head and neck cancer aetiology is inconsistent. A recent meta-analysis examining the association between sexual behaviour and head and neck cancer reported no association with oral sex practices (but 12 of 17 studies combined oral cavity and oropharynx cancers).(15) A case control study that just included people with oropharyngeal cancer showed that they were more likely than controls to have ever had oral sex and to have had multiple oral sex partners.(16)

The profile of sexual behaviour for people with oropharyngeal tumours is

markedly different from that for people with laryngeal cancer. It suggests a sexually transmitted aetiology but there are inconsistencies that make this association more complicated. The reported prevalence of oral sex with a partner of the opposite gender increased between the first UK National Survey of Sexual Attitudes and Lifestyles (6) Survey-1 (1990-91) and Survey -2 (1999-2001) but plateaued in Survey-3 (2010-2012). Furthermore men reported little change in number of female oral sexual partners over the lifetime or the number of female oral sexual partners in the past year between Surveys-2 and -3 (1999 -2012).(6) Thus recent changes in sexual behaviour do not mirror the continued rise in the incidence of oropharyngeal cancer.

Sexual behaviour may explain some of the increase in incidence of oropharyngeal cancer in the UK, it does not seem to account for all of this change. A recent study in the UK found there was no change in the proportion of HPV-attributable cases over time (2002-2011) however, during the same period, the incidence of oropharyngeal cancer doubled and similar findings have been made elsewhere in Europe.(17) HPV has an important role in the continuing increase in incidence of oropharyngeal cancer, but this may not be explained by changes in sexual behaviour and HPV infection alone.

Oral cavity cancer – different again?

In the UK the incidence of oral cavity cancer has risen by 50% since 1990 (Figure 1). In Figure 1 we show that people with oral cavity cancer in the

H&N5000 study differed from those with laryngeal and oropharyngeal cancer. They were younger, more likely to be female and less likely to smoke than people with laryngeal cancer, but no more likely to have given oral sex. The prevalence of the established risk factors of smoking and alcohol was similar to that observed in people with oropharyngeal cancer but again less for giving oral sex. Oral cavity cancer is not typically associated with HPV infection (15) and the risk factor profile for people with oral cavity cancer does not suggest aetiology related to sexual behaviour.

Previous studies suggest that smoking and alcohol have a multiplicative interaction and that the joint behaviours account for the majority of cases of oral cavity cancer (64%).(18) The decline in the prevalence of smoking in the UK should have resulted in a decline in the incidence of oral cavity cancer (as observed in laryngeal cancer).

Though between 2005 and 2013 there has been little change in drinking behaviour in people aged over 64 in the UK (8) data from the beer and pub association (8) suggest that alcohol consumption doubled from 1950 to 1990. This trend is consistent with data from 1979 to 2005 that show hospital admissions and mortality from alcohol-induced liver disease in England have increased. (9) Furthermore, lifetime consumption appears to be important as the greater the number of years drinking varies by site, the risk of oral and pharyngeal cancer being higher than that for laryngeal cancer.(19) So longer term trends in alcohol consumption could explain some of the observed increase in incidence of oral cancer.

Interestingly, we observed a high proportion of women in H&N5000 with oral cavity cancer and a third of these women have never smoked and a third did not currently consume alcohol and 42% had never given oral sex (supplementary table). These data suggest that this increase in the incidence in oral cancer may (in part) represent an emerging and distinct clinical entity of unknown aetiology.

Head and neck cancer – a tale of three cancers?

We used three sources to explain recent trends in the incidence of head and neck squamous cell cancers in the UK, past risk factors, recent changes in the risk factors and current exposure in a large UK cohort. The data we have are imperfect but they represent the most contemporary UK data for these cancers. Changes in smoking, alcohol and HPV infection related to sexual behaviour explain some of the observed changes in incidence of head and neck cancer. The reduction in laryngeal cancer incidence parallels the decline in smoking, but oral cancer and oropharyngeal cancer have not declined. Oropharyngeal cancer is associated with sexual behaviour and HPV but recent data suggest this is not the complete explanation. Oral cancer incidence has increased as has long term trends in alcohol consumption and alcohol-related mortality but this may not explain all of the change in incidence. The divergent trends in incidence and striking differences in the risk profile for people with squamous cell cancers at each of the three sites

suggest important differences in the main aetiological drivers for each cancer.

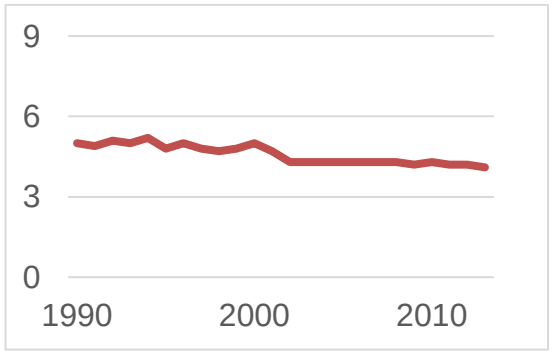
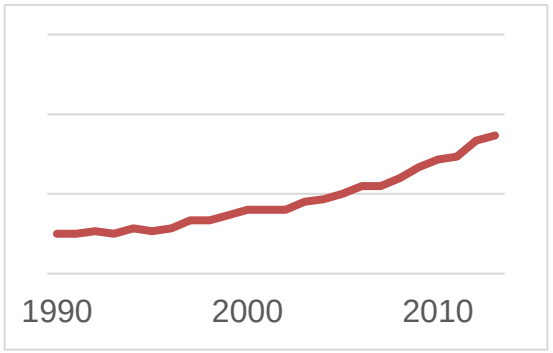
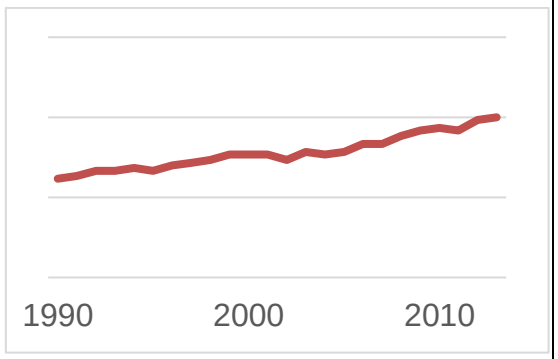
This is important because aetiology may predict treatment response and prognosis. People with HPV positive oropharyngeal cancers have better survival than those with HPV negative cancers and trials are underway to assess the impact of modifying treatment according to HPV status. Improved understanding of the changing aetiology of head and neck cancer may therefore allow refinements to treatment modality and intensity and better targeted preventive efforts.

Combined analysis of head and neck cancers from different sites may be unhelpful when trying to tease out the aetiology and prognosis of these heterogeneous cancers. H&N5000 has recently contributed to a genome wide association study of head and neck cancers which points to aetiological differences between head and neck cancers. The study identified seven new genetic loci - one was linked to oropharyngeal cancer and six with oral cavity cancer.(20) Future studies are needed to characterise tumours epidemiologically, genetically and epigenetically. This will help to confirm the role of risk factors and identify tumours with different prognoses that may respond differently to treatment. Large bio-collections set up to study prognosis (such as H&N5000) will be required to do this.

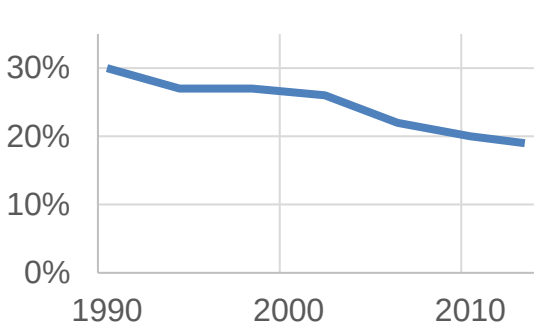
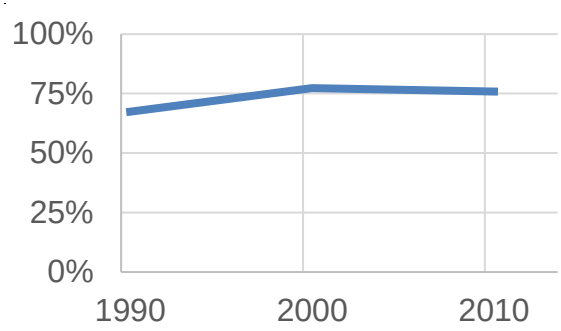
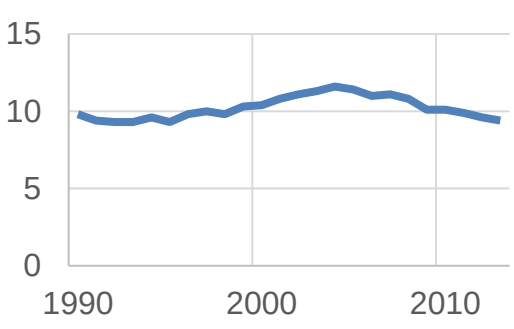
Key messages

- The incidence of laryngeal cancer is falling in the UK and is consistent with the decline in tobacco consumption
- The incidence of oropharyngeal cancer is rising rapidly in the UK and is associated with sexual behaviour and Human Papilloma Virus
- Patients with oropharynx cancer report increased numbers of lifetime sexual partners and oro-genital sexual contact compared with [patients who have larynx and oral cavity cancer
- Whether HPV OPSCC is a sexually transmitted disease has not been firmly established
- The incidence of oral cavity cancer is increasing in the UK and may reflect long term trends in alcohol consumption

Figure 1: Change in incidence of Larynx, Oropharynx and Oral Cavity cancers, key risk factors and descriptives for H&N5000 Cohort

Change in cancer incidence			
Cancer incidence: 1990-2013[1]	Larynx 	Oropharynx 	Oral Cavity 
Head and Neck 5000			
	Larynx	**Oropharynx**	**Oral Cavity**

	(n=627)	(n=1,175)	(n=813)
Female	15%	21%	38%
Age<60	29%	57%	43%
Never smoked	9%	28%	25%
Alcohol non-drinker	25%	26%	27%
Never performed oral sex	27%	7%	31%
Change in health behaviours			
	Smoking[2]	Oral sex[3]	Alcohol[4]

Health behaviours: 1990-2013			

1 – Rolling 3-year age standardised rate/100,000, source: Calculated by the Statistical Information Team at Cancer Research UK upon request, September 2016 (2).

2 – Proportion of adults smoking, sources: Action on Smoking and health (February 2016), Opinions and Lifestyle Survey, and the General Household/General Lifestyle Surveys (10)

3 – Proportion given or received oral sex in past year (data collected 1990, 2000, 2010), sources: The National Survey of Sexual Attitudes and Lifestyles (NATSAL) 1, 2 & 3 (15)

4 – Litres of alcohol consumed per person per year, sources: Health & Social Care Information Centre, HM Revenue and Customs and Excise (11)

Supplementary Table 1: Variation in deprivation, behaviour and age by gender and tumour site

	Larynx		Oropharynx		Oral cavity	
	Males N=535	**Females N=92**	**Males N=924**	**Females N=251**	**Males No. 502**	**Females No. 311**
Quintile of 2010 IMD						
Least deprived	94 (17.6%)	14 (15.2%)	176 (19.1%)	54 (21.5%)	111 (22.1%)	71 (22.8%)
Less	106 (19.8%)	15 (16.3%)	216 (23.4%)	39 (15.5%)	96 (19.1%)	63 (20.3%)
Middle	114 (21.3%)	15 (16.3%)	217 (23.5%)	60 (23.9%)	105 (20.9%)	72 (23.2%)
More	108 (20.2%)	18 (19.6%)	178 (19.3%)	59 (23.5%)	74 (14.7%)	51 (16.4%)
Most deprived	113 (21.1%)	30 (32.6%)	137 (14.8%)	39 (15.5%)	116 (23.1%)	54 (17.4%)
Alcohol consumption						
Non drinker	117 (21.9%)	42 (45.7%)	203 (22.0%)	97 (38.7%)	110 (21.9%)	114 (36.7%)
Moderate	120 (22.4%)	22 (23.9%)	203 (22.0%)	72 (28.7%)	92 (18.3%)	92 (29.6%)
Hazardous	227 (42.4%)	18 (19.6%)	386 (41.8%)	54 (21.5%)	213 (42.4%)	60 (19.3%)
Harmful	71 (13.3%)	10 (10.9%)	132 (14.3%)	28 (11.2%)	87 (17.3%)	45 (14.5%)
Smoking status						
Never	47 (8.8%)	12 (13.0%)	257 (27.8%)	74 (29.5%)	107 (21.3%)	100 (32.2%)
Former	380 (71.0%)	62 (67.4%)	518 (56.1%)	136 (54.2%)	270 (53.8%)	142 (45.7%)
Current user	108 (20.2%)	18 (19.6%)	149 (16.1%)	41 (16.3%)	125 (24.9%)	69 (22.2%)
Age at consent						
<50 years old	28 (5.2%)	9 (9.8%)	154 (16.7%)	45 (17.9%)	91 (18.1%)	48 (15.4%)
50-60	117 (21.9%)	28 (30.4%)	364 (39.4%)	108 (43.0%)	130 (25.9%)	78 (25.1%)
60-70	211 (39.4%)	34 (37.0%)	295 (31.9%)	68 (27.1%)	166 (33.1%)	97 (31.2%)
70+	179 (33.5%)	21 (22.8%)	111 (12.0%)	30 (12.0%)	115 (22.9%)	88 (28.3%)

Ever performed oral sex*						
Never	90 (23.9%)	27 (41.5%)	46 (6.6%)	20 (10.5%)	80 (23.4%)	96 (41.6%)
1-5 people	206 (54.8%)	33 (50.8%)	348 (49.6%)	147 (77.0%)	185 (54.1%)	117 (50.7%)
>5 people	80 (21.3%)	5 (7.7%)	308 (43.9%)	24 (12.6%)	77 (22.5%)	18 (7.8%)
Missing	159	27	222	60	160	80

*- People who did not report their oral sex behaviour were excluded from the calculated proportions

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Contributors and Sources

Contributors and Sources: ST, CP and AN were involved in the initial conception and design of the study. ST, CP and AN were involved in the data analysis. ST and AN were involved in the interpretation and discussion of results. ST developed the first draft of the manuscript and all authors critically revised it and approved the final version including AW. ST is guarantor of the article. We have used data from the following sources: Head and Neck 5000 clinical cohort, HSCIC, British Beer and Pub Association (c/o OECD), NATSAL, Cancer Research UK. Head and Neck 5000 was funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research scheme (RP-PG-0707-10034). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no competing interests.

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