Original Research Article

Trends and inequalities in laryngeal cancer survival in men and women: England and Wales 1991-2006

Libby Ellis[a], Bernard Rachet[a], Martin Birchall[b], Michel P Coleman[a]

[a] Cancer Research UK Cancer Survival Group, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT
[b] UCL Ear Institute, The Royal National Throat Nose and Ear Hospital, 330 Gray's Inn Road, London WC1X 8DA

Corresponding author:
Libby Ellis
Cancer Research UK Cancer Survival Group,
London School of Hygiene and Tropical Medicine,
Keppel Street,
London WC1E 7HT

Email: libby.ellis@lshtm.ac.uk
Telephone: +44 (0)20 7927 2137

Abstract

Objectives

Laryngeal cancer in men is a relatively common malignancy, with a marked socioeconomic gradient in survival between affluent and deprived patients. Cancer of the larynx in women is rare. Survival tends to lower than for men, and little is known about the association between deprivation and survival in women with laryngeal cancer. This paper explores the trends and socio-economic inequalities in laryngeal cancer survival in women, with comparison to men.

Materials and Methods

We examined relative survival among men and women diagnosed with laryngeal cancer in England and Wales during 1991-2006, followed up to 31 December 2007. We estimated the difference in survival between the most deprived and most affluent groups (the 'deprivation gap') at 1 and 5 years after diagnosis, for each sex, anatomical subsite and calendar period.

Results

Five year survival for all laryngeal cancers combined was up to 8% lower in women than in men. This difference is only partially explained by the differential distribution of anatomical subsites in men and women. Disparities in survival between men and women were also present within specific subsites. In contrast to men, there was little evidence of a consistent deprivation gap in survival for women at any of the anatomical subsites.

Conclusion

The stark socioeconomic inequalities in laryngeal cancer survival in men do not appear to be replicated in women. The origins of the socio-economic inequalities in survival among men, and the disparities in survival between men and women at specific tumour subsites remains unclear.

246 words

Keywords: laryngeal cancer, head and neck cancer, relative survival, socioeconomic inequalities

Introduction

In England and Wales, cancer of the larynx is rare in women, but is a relatively common malignancy in men. Around 80% of the 1,700 new cases diagnosed each year in England occur in men,[1] resulting in one of the largest sex ratios of any common cancer. The difference in laryngeal cancer incidence rates between men and women in other European countries is considerably higher.[2]

As such, most estimates of survival from laryngeal cancer exclude women. Relative survival was approximately 85% at one year and 66% at five years for men diagnosed during 2001-2003 in England (with similar estimates for Wales),[3] and there has been very little improvement since the late 1980s.[4] There is also a marked socioeconomic gradient in survival from laryngeal cancer. Survival is substantially higher in more affluent men than in the more deprived, by 7.7% at one year and 17.2% at five years: one of the steepest socio-economic gradients in survival among the 20 most common cancers.[4]

Survival estimates for women, when reported, tend to be 5-6% lower than for men.[5] Furthermore, little is known about the association between deprivation and survival in women with cancer of the larynx. However, the findings among men cannot be extrapolated to women, because both the anatomical distribution of laryngeal tumours and their risk factors differ widely between the sexes.

The main anatomical subsites of the larynx, as classified in the International Classification of Diseases for Oncology,[6] include the glottis, supraglottis and subglottis. As with other tumours of the head and neck, the precise anatomical origin of tumours within the larynx can be difficult to determine. Cancer of the larynx is caused principally by tobacco smoking and alcohol consumption, and their effects are synergistic.[7-10] Tobacco dominates the risk for cancers of the glottis, which is exposed to mainly inhaled agents. The supraglottis is exposed to both inhaled and ingested agents, and tumours at this subsite have shown the strongest associations with tobacco and alcohol.[7,9-12]

Glottal cancers predominate in men while tumours of the supraglottis tend to be more common in women.[13] In contrast with supraglottal tumours, glottal cancers give rise to early symptoms of hoarseness, are often diagnosed at an early stage, and have a better prognosis than supraglottic tumours. These differences between the sexes in main causal exposure and anatomic distribution of tumours may explain the lower survival from laryngeal cancer among women. The origins of the inequalities in laryngeal cancer survival between affluent and deprived men are still not fully understood. It is likely that both patient and healthcare system factors such as stage at diagnosis, comorbidity, and access to optimal treatment each play an important role[14].

This paper explores the trends and socio-economic inequalities in laryngeal cancer survival in women, with comparison to men. The impact of differences in anatomical tumour distribution on the survival is examined.

Materials and Methods

We examined National Cancer Registry data for all adults (aged 15-99 years at diagnosis) resident in England and Wales who were diagnosed with malignant laryngeal cancer during 1991-2006 and followed up to 2007. Patients who had had a previous cancer of the same organ at any time since 1971 were excluded. Standard criteria were used to determine whether tumour records were eligible for inclusion in the analysis; full details are published elsewhere[3]. Data were analysed for 29,420 patients diagnosed during 1991-2006; 96% of those eligible.

An ecological measure of deprivation was used, based on the administrative characteristics of the Lower Super Output Area (LSOA, population approx 1,500) in which each patient was resident at the time of diagnosis. The income domain scores of the Index of Multiple Deprivation for England (IMD 2004[15]) and Wales (WIMD 2005[16]) were categorised into five groups by quintiles of the 34,378 LSOAs. Cancer patients were assigned to the deprivation category of their LSOA (from one 'most affluent' to five 'most deprived'), using their postcode of residence at diagnosis.

Laryngeal tumours were analysed in two groups defined by subsite: glottis and subglottis (referred to as glottal tumours), and supraglottis and overlapping tumours (referred to as supraglottal tumours). Approximately 30% of patients were recorded as having a tumour of unspecified anatomical location. We estimated relative survival for each of the five deprivation categories, for each subsite group, sex and calendar period of diagnosis (1991-1995, 1996-2000, 2001-2006). Relative survival is the standard approach to estimating population-based cancer survival because it does not rely on the underlying cause of death, which is often not reliable at a population level, especially at older ages.[17,18] Relative survival is interpretable as survival from the cancer after adjustment for the 'background mortality', which corresponds to the age- and sex-specific all-cause mortality of a comparable general population. Background mortality was provided by life tables, defined by region and deprivation category to account for the geographical and socioeconomic differences in all-cause mortality.[19] A maximum likelihood approach of estimating crude and relative survival from individual tumour records was applied [20], using an algorithm in the public domain [21].

We report cumulative probabilities of relative survival at one and five years after diagnosis. All patients were followed up for at least one year, so the cohort approach was used to calculate trends in one-year survival. For five-year survival, the cohort approach was used for the first two calendar periods and a complete approach for the last period. The differences in survival between deprivation categories were fitted with a variance-weighted linear regression. The 'deprivation gap' in survival is quantified as the simple difference between the fitted relative survival values in the most deprived and most affluent groups within each calendar period. A negative value indicates that survival in the most deprived group is lower than survival in the most affluent group. All analyses were carried out in Stata 10.[22]

In an additional analysis, tumour records with an unspecified anatomic location were treated as having missing subsite. A 10-fold multiple imputation approach was applied to the data[23] to account for this incompleteness and to minimise the risk of bias in the relative survival estimates. The mechanism of missingness was assumed to be Missing At Random (MAR). The associations between the variable with missing values (subsite) and other variables enable the imputation model to fill in

the missing values, using records in which subsite is specified. The imputation model, an ordered logistic regression, was iteratively applied to generate 10 'complete' datasets. The parameters of interest and their variance were estimated in each dataset and then pooled using multiple imputation rules.[24] In accordance with guidelines on the reporting of analyses based on multiple imputation, both imputed and un-imputed results are presented.[25]

Results

The analyses comprised of 24,234 (82%) men and 5,186 women diagnosed with laryngeal cancer during the 16-year period 1991-2006. The annual incidence rate in 2006 was 6.7 per 100,000 population for men and 1.4 for women: a sex rate ratio of 4.8. The distribution of tumour subsites within the larynx differed by sex: glottal cancers were more common in men, whereas cancers of the supraglottis were more common in women (Table 1). Women were slightly more deprived than men, with 33% in the most deprived category compared to 29% of men (data not shown).

Trends in survival

One-year survival for all laryngeal cancers combined was some 5-6% lower in women than in men for all three calendar periods (84.7% in men and 78.9% women in 2001-2006). Despite some fluctuation, there has been little improvement in one-year survival since 1991-1995 for either sex. At five years since diagnosis, the survival deficit between men and women was more pronounced; between 6-8% lower in women than in men throughout the period 1991-2006. Five-year survival improved in both sexes by approximately 3% between 1991-1995 and 2001-2006 (Table 2).

Survival from laryngeal cancer depended largely on the anatomical subsite of the tumour. Cancers of the glottis had the highest survival in both sexes, with men benefiting from a consistent survival advantage over women. For patients diagnosed with glottal tumours during 2001-2006, relative survival was 4% higher in men than women, at both one and five years since diagnosis. Supraglottal tumours had considerably poorer survival, and in contrast to glottal cancers, women had consistently higher survival than men. The patterns of survival for tumours with an unspecified location were similar to those for supraglottal tumours, although the deficit in survival between the sexes was reversed in favour of men. The differences in survival between men and women reduced over the three calendar periods examined, for all subsite categories.

Improvements in survival over the study period were restricted to patients diagnosed with glottal tumours. The improvements in survival for women were greater than for men, and this is consistent with the narrowing deficit in survival between the sexes. Five-year survival for women diagnosed with glottal tumours increased by almost 8% over the period 1991-2006 (from 70.1% in 1991-1995 to 77.8% in 2001-2006). In contrast, survival for patients diagnosed with supraglottal or unspecified tumours either did not change, or fell over the period 1991-2006.

The imputation of unspecified subsite resulted in a fall in survival for both glottal and supraglottal tumours compared to the un-imputed results, but the overall pattern of survival in men and women remained the same across the three calendar periods (see Web appendix 1).

Deprivation gap in survival

Due to the small numbers of cases within each stratum of subsite, calendar period and deprivation group, especially for women, the following results are presented for the entire 16-year period 1991-2006.

Figure 2 presents one- and five-year survival by sex and deprivation group for all subsites combined, glottal and suprglottal tumours. Survival patterns for unspecified tumours largely overlapped those

for supraglottal tumours and are therefore not shown. Among women diagnosed with laryngeal cancer (all subsites combined), there was no difference in one-year survival between affluent and deprived patients. At five-years since diagnosis a small deprivation gap in survival was apparent (-4%), although this was not statistically significant. In men, the overall deprivation gap was -7% at one-year since diagnosis and -13% at five-years, both statistically significant at the 5% level.

The magnitude and direction of the deprivation gap in survival again varied according to the anatomical subsite of the tumour. In men, a significant negative deprivation gap was observed for all tumour subsites: -2.5% at one year and -5% at five years for glottal tumours, -5% at one year and -8% at five years for supraglottal tumours, and -9% at one year and -17% at five years for unspecified tumours.

In women, there was no evidence of a deprivation gap in one-year survival for any tumour subsite. At five years since diagnosis, the picture is slightly more complex: a negative deprivation gap was present among women diagnosed with glottal tumours (-7%), and a positive deprivation gap (higher survival in the most deprived than the most affluent) was seem for women diagnosed with supraglottal tumours (3.5%). However, the numbers included in these analyses are small and the unfitted survival estimates fluctuate widely. None of the socioeconomic differences in survival among women were statistically significant at the 5% level.

After imputation of unspecified subsite, the deprivation gap in survival for men diagnosed with supraglottal tumours did not change (see web appendix 2). Conversely, the imputation resulted in an increased deprivation gap in survival for men with glottal tumours, at both one and five years. This suggests that the majority of the unspecified tumours in men were predicted to be glottal tumours (as shown in Table 1), although their survival was somewhat lower. In women, the imputation of unspecified subsite affected the deprivation gap in survival for both glottal and supraglottal tumours, implying that the unspecified tumours in women were mixture of glottal and supraglottal tumours. This is also consistent with the distribution of tumour subsites between the sexes (Table 1).

Discussion

These analyses include approximately 1500 incident cases of laryngeal cancer a year in men and 300 cases a year in women. The sex rate ratio in England and Wales is broadly similar to the US (SEER registries, 4.5), but is considerably smaller than in many other European countries (Germany: 9, Italy: 10, Spain: 21). This is largely due to a higher incidence of laryngeal cancer among women in England and Wales compared to Europe.[2] The differential incidence rates in men and women almost certainly result from different levels of exposure to the main risk factors for laryngeal cancer. As patterns of tobacco smoking and alcohol consumption change over time, say, with a decline in the proportion of male smokers and a rise in female smokers, we might expect to see both the incidence rate ratio, and the distribution of anatomical subsites equalise.

The trends in survival for patients diagnosed with laryngeal cancer over the 16-year period examined were fairly static for both sexes, with only small improvements in one and five year survival between 1991-1995 and 2000-2006 for all laryngeal cancers combined. This was driven by an increase in survival for patients diagnosed with glottal tumours only, particularly between 1991-1995 and 1996-2000. This coincides with significant advances in the diagnosis and treatment of laryngeal tumours over a similar time period, including advances in imaging and the application of postoperative radiotherapy for advanced disease.[26] Conversely, survival for patients diagnosed with supraglottal tumours fell over the period 1991-2006, and this was particularly evident in women. The proportion of tumours with an unspecified anatomic location fell over the same period, suggesting that the classification of tumour subsite improved over time. It is therefore likely that a proportion of these previously unspecified tumours with poor survival are now classified as supraglottal tumours. The resultant fall in survival disproportionately affects women, for whom supraglottal tumours are more common.

The difference in survival between men and women for all laryngeal cancers combined confirms our understanding that the specific anatomical location of tumours is an important predictor of survival. Our findings confirm that in England and Wales, glottal tumours are more common in men and have a better prognosis than supraglottal tumours, which are more common in women. Differences in survival between these two subsites are likely to be influenced by difference in stage at diagnosis and treatment. For example, most glottal tumours are diagnosed at an early stage, as even a small growth on the vocal cords causes a change in voice. Tumours beyond the vocal cords (supraglottal) are associated with much vaguer symptoms, and diagnosis is often made at a later stage. According to the latest report of the National Head and Neck Cancer Audit (2009), 6% of glottal cancers were node positive at diagnosis, compared to 34% of supraglottal tumours.[27] Historically, most early stage laryngeal tumours were treated with radiotherapy, although there is an increasing trend in the use of endoscopic resection techniques.[28] For advanced disease, radical surgery with adjuvant radiotherapy or concomitant chemo-radiation is the curative treatment of choice.[29]

It is however, unclear why women diagnosed with glottal tumours have poorer survival than men with tumours at the same anatomical location, and in contrast, why men diagnosed with supraglottal cancers have lower survival than women with supraglottal tumours. Published estimates of laryngeal cancer survival by anatomic subsite are restricted to men,[30] so insight from other studies is lacking. The difference in overall (all-subsite) survival between the sexes cannot

therefore simply be explained by the fact that women get more supraglottal tumours than men, for which survival is poor. The finding of differences in survival between men and women *within* subsites implies that the reality is more complex. The women included in these analyses were, on average, older than the men, introducing the possibility that factors such as co-morbidity and differences in care management may also influence survival.

The substantial deprivation gap in laryngeal cancer survival in men is well known.[4,31] Our findings suggest that this disparity in survival is primarily driven by tumours with an unspecified anatomical location, and partly by supraglottic tumours. The deprivation gap in survival for men with glottal tumours was comparatively small, although this increased after imputation of the unspecified subsite. The large proportion of unspecified tumours was not unexpected because of the complex anatomy of the larynx. However, the origins of the substantial deprivation gap in survival for unspecified tumours are unclear, although age and stage at diagnosis may play a role. For example, determining the exact anatomic location of tumours that present at an advanced stage is likely to be more challenging than for early stage tumours, and later stage at diagnosis is associated with poorer survival. However, the distribution of unspecified tumours was the same among the deprivation groups. It is therefore more likely that factors such as comorbidity and differential access to healthcare are driving the deprivation gap in survival among men with unspecified tumours. In previous studies, socioeconomic differences in comorbidity made only a small impact on inequalities in survival from colorectal cancer,[32] but access to optimal treatment was shown to have a substantial influence.[33,34] Among women diagnosed with laryngeal cancer, there were no significant differences in survival between affluent and deprived groups. Whilst there was some suggestion that survival among women diagnosed with glottal and supraglottal tumours may differ by deprivation group, the unfitted survival estimates fluctuated widely due to the small number of women included in the analyses. Overall, our findings suggest that the stark socioeconomic inequalities in laryngeal cancer survival in men are not replicated in women.

Whilst laryngeal cancer in women remains relatively rare in England and Wales, the age-standardised incidence rate in the period 1998-2002 was higher than in many other European countries.[2] There is evidence however, that the incidence of laryngeal cancer among women in Europe is increasing. One study in France reported a 67% rise in incidence between 1980 and 2005,[35] while another in Spain predicted that by 2017, incidence would increase by 37%.[36] Whilst this could be due to a combination of factors including an aging population, improved detection of tumours, or improved access to healthcare, the authors relate such trends in women to an increase in exposure to risk factors, specifically smoking. It is therefore possible that, similar to lung cancer, the incidence of laryngeal cancer among women in England and Wales will also rise, although this has not been shown so far.[13] Future research will focus on examining the influence of stage at diagnosis, level of comorbidity, and access to optimal treatment on both the disparities in survival between men and women at specific tumour subsites, and the socio-economic inequalities in survival among men.

Words: 3068

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Conflict of interest statement
None declared

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Table and Figure Legends

Figure 1. Deprivation gap in relative survival (%) by subsite: England and Wales, adults (15-99 years) diagnosed during 1991-2006 followed up to 2007

Table 1. Distribution of tumour subsites by sex, before and after multiple imputation for unspecified subsites

Table 2. Trends in relative survival (%) by subsite and calendar period of diagnosis: England and Wales, adults (15-99 years) diagnosed during 1991-2006 followed up to 2007

Web appendix 1. Trends in relative survival (%) by subsite and calendar period of diagnosis: England and Wales, adults (15-99 years) diagnosed during 1991-2006 followed up to 2007, after multiple imputation of unspecified subsite

Web appendix 2. Deprivation gap in relative survival (%) by subsite: England and Wales, adults (15-99 years) diagnosed during 1991-2006 followed up to 2007, after multiple imputation of unspecified subsite

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Table 1

Distribution of tumour subsites by sex, before and after multiple imputation for unspecified subsites[a]

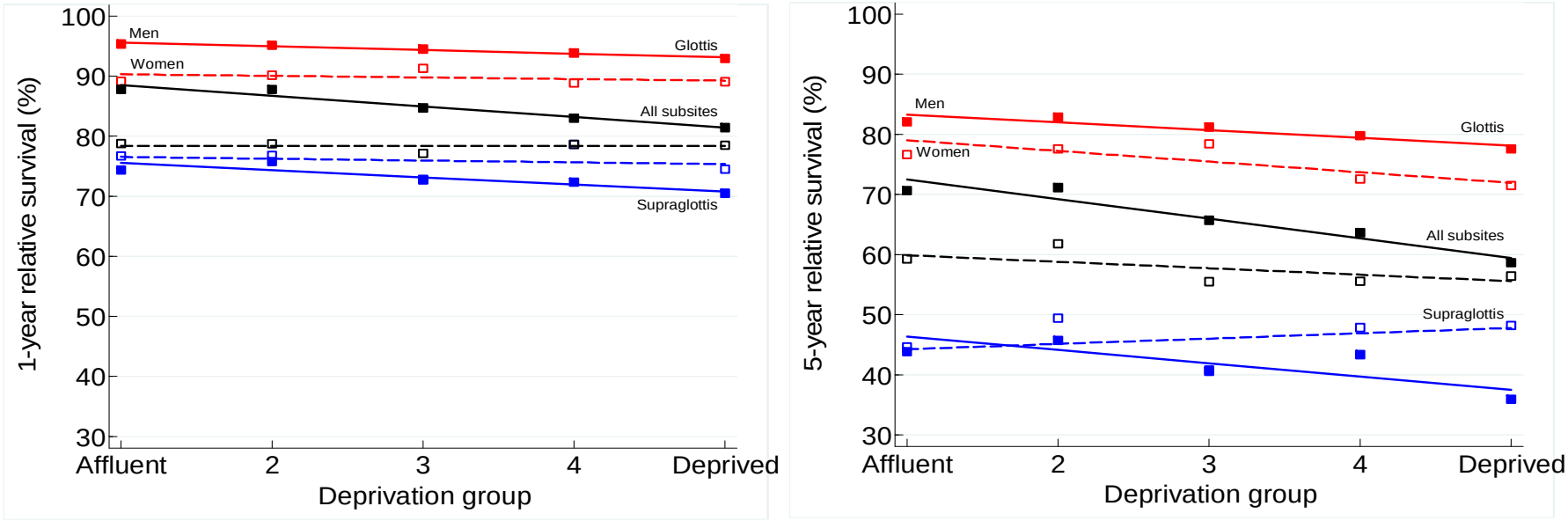
Subsite	men		women		After imputation men		After imputation women	
	N	%	N	%	N	%	N	%
Glottis	12,793	53	1,831	35	17,527	73	2,606	50
Supraglottis	3,882	16	1,521	30	5,940	24	2,304	45
Subglottis	339	1	166	3	509	2	210	4
Overlapping	174	<1	44	<1	258	1	66	1
Unspecified	7,046	29	1,624	31				
Total	24,234		5,186					

[a] Those tumours with an unspecified anatomical location (ICD-10 code C32.9) were treated as 'missing' and the subsite was imputed using multiple imputation techniques.

Table 2.
Trends in relative survival (%) by subsite and calendar period of diagnosis: England and Wales, adults (15-99 years) diagnosed during 1991-2006 followed up to 2007

	One-year relative survival						Five-year relative survival					
	Period 1 1991-1995		Period 2 1996-2000		Period 3 2001-2006		Period 1 1991-1995		Period 2 1996-2000		Period 3 2001-2006	
	Survival (%)	95% CIs	Survival (%)	95% CIs	Survival (%)	95% CIs	Survival (%)	95% CIs	Survival (%)	95% CIs	Survival (%)	95% CIs
Larynx (all subsites)												
Men	**83.7**	82.8 , 84.6	**84.3**	83.4 , 85.3	**84.6**	83.8 , 85.5	**63.2**	61.8 , 64.5	**64.5**	63.2 , 65.9	**66.8**	65.4 , 68.2
Women	**77.2**	75.1 , 79.3	**79.2**	77.0 , 81.3	**78.9**	76.9 , 80.8	**55.2**	52.5 , 58.0	**58.1**	55.3 , 60.9	**58.6**	55.6 , 61.6
Glottis & sub-glottis												
Men	**93.2**	92.2 , 94.2	**94.5**	93.6 , 95.5	**94.6**	93.8 , 95.4	**78.8**	77.1 , 80.6	**80.6**	78.9 , 82.3	**81.7**	80.0 , 83.4
Women	**86.9**	83.9 , 89.8	**90.4**	87.7 , 93.1	**91.2**	88.9 , 93.6	**70.1**	65.7 , 74.6	**76.3**	72.0 , 80.5	**77.8**	73.0 , 82.5
Supraglottis & overlapping												
Men	**73.8**	71.2 , 76.5	**71.8**	69.2 , 74.4	**71.8**	69.4 , 74.2	**41.6**	38.4 , 44.7	**39.1**	36.0 , 42.1	**41.8**	38.4 , 45.2
Women	**77.6**	73.5 , 81.6	**75.8**	71.6 , 79.9	**74.3**	70.6 , 77.9	**48.1**	43.1 , 53.2	**46.4**	41.4 , 51.4	**45.8**	40.7 , 51.0
Unspecified												
Men	**74.2**	72.4 , 76.0	**74.0**	72.1 , 76.0	**69.2**	67.1 , 71.3	**50.9**	48.6 , 53.2	**51.9**	49.5 , 54.3	**48.7**	45.9 , 51.5
Women	**67.8**	63.9 , 71.7	**69.5**	65.3 , 73.8	**65.8**	61.4 , 70.3	**46.8**	42.3 , 51.3	**48.6**	43.6 , 53.5	**46.3**	40.9 , 51.7

Figure 1
Deprivation gap in relative survival (%) by subsite: England and Wales, adults (15-99 years) diagnosed during 1991-2006 followed up to 2007



Web Appendix 1

Trends in relative survival (%) by subsite and calendar period of diagnosis: England and Wales, adults (15-99 years) diagnosed during 1991-2006 followed up to 2007, after multiple imputation of unspecified subsite

	One-year relative survival						Five-year relative survival					
	Period 1 1991-1995		Period 2 1996-2000		Period 3 2001-2006		Period 1 1991-1995		Period 2 1996-2000		Period 3 2001-2006	
	Survival (%)	95% CIs	Survival (%)	95% CIs	Survival (%)	95% CIs	Survival (%)	95% CIs	Survival (%)	95% CIs	Survival (%)	95% CIs
Larynx (all subsites)												
Men	**83.6**	83.4 , 83.9	**84.4**	84.1 , 84.7	**84.7**	84.4 , 84.9	**63.3**	62.8 , 63.7	**64.6**	64.2 , 65.0	**66.9**	66.4 , 67.3
Women	**77.4**	76.8 , 78.1	**79.4**	78.7 , 80.0	**78.9**	78.3 , 79.5	**55.5**	54.7 , 56.4	**58.3**	57.4 , 59.2	**58.5**	57.6 , 59.5
Glottis & sub-glottis												
Men	**89.5**	89.2 , 89.8	**91.0**	90.7 , 91.3	**90.9**	90.7 , 91.2	**72.8**	72.4 , 73.3	**75.3**	74.8 , 75.8	**76.7**	76.2 , 77.2
Women	**84.7**	83.9 , 85.5	**88.3**	87.5 , 89.0	**88.8**	88.1 , 89.5	**67.3**	66.1 , 68.4	**73.0**	71.8 , 74.1	**74.6**	73.3 , 75.9
Supraglottis & overlapping												
Men	**66.9**	66.2 , 67.6	**65.9**	65.2 , 66.6	**65.3**	64.7 , 66.0	**36.4**	35.6 , 37.1	**35.0**	34.2 , 35.7	**36.7**	35.8 , 37.6
Women	**68.6**	67.5 , 69.7	**68.8**	67.7 , 69.9	**67.9**	66.9 , 69.0	**41.5**	40.3 , 42.7	**41.1**	39.9 , 42.4	**41.2**	39.9 , 42.6

Web appendix 2

Deprivation gap in relative survival (%) by subsite: England and Wales, adults (15-99 years) diagnosed during 1991-2006 followed up to 2007, after multiple imputation of unspecified subsite