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Prognoses for head and neck cancers in Europe diagnosed in 1995–1999: a population-based study

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Background: Head and neck cancers are a heterogeneous group of malignancies, affecting various sites and subsites, with differing prognoses. The aim of this study was to analyse survival for European head and neck cancer patients in populations covered by population-based cancer registries (CRs), in relation to tumour subsite as prognostic factor.

Patients and methods: We analysed 51 912 adult head and neck cancer cases (36 322 mouth–pharynx and 15 590 larynx) diagnosed from 1995 to 1999 and archived by 45 CRs in 20 countries participating in EUROCARE-4. Five-year age-standardised relative survival was estimated for mouth–pharynx and larynx sites by sex and country. Relative survival was modelled to provide estimates of relative excess risks (RERs) of death by country, adjusted for confounding factors.

Results: A large but site-variable proportion of tumours were incompletely specified. Five-year age-standardised relative survival was low in Slovakia and high in The Netherlands. Adjustment for subsite reduced RERs of death for most countries; 5-year relative survival increased from 1990–1994 to 1995–1999 for all subsites, while between-country differences in survival narrowed.

Conclusion: Differences in subsite distribution explain a considerable part of the survival differences for head and neck cancers, however, incomplete/inaccurate subsite reporting complicate interpretation.

Key words: cancer registries, head and neck cancers, relative survival, subsite localisation

introduction

Head and neck cancers are a heterogeneous group of malignancies, affecting various sites and subsites, with a range of histologies and etiological factors. The incidence of cancers of the mouth and pharynx (excluding nasopharynx) in Europe was estimated in 2002 at ~93 500 cases, almost 75% of which were in men. Age-standardised rates were high in men in Western Europe (~21 of 100 000 man-year) followed by Southern and Eastern Europe (14 of 100 000 man-year) and lower in Northern Europe (8 of 100 000 man-year) [1].

Laryngeal cancer, with 45 500 new cases in Europe in 2002, is also more common in men, with a sex ratio of almost 7 : 1. Age-standardised rates for men are among the highest in the world in Southern Europe (10.9 of 100 000 person-year) and Eastern Europe (9.2 of 100 000 person-year), somewhat lower in Western Europe (7.2 of 100 000 person-year) and considerably lower in Northern Europe (4.2 of 100 000 person-year) [1].

This marked geographic variation reflects variation in risk factors for these diseases, which is in turn related to lifestyle [2]. The main risk factors for head and neck cancers are tobacco and alcohol use, but diet is also important [3, 4]. High consumption of fruit and vegetables, and a Mediterranean diet, has been associated with better prognoses for laryngeal cancer [5]. It has also been shown recently that human papillomavirus (HPV) infection is a risk factor for some head and neck cancers including those of the tongue base and tonsil [6]. Patients with HPV-related head and neck cancers are younger and may have prognoses that differ from those of non-HPV-related cancers [7, 8].

Site and subsite are important determinants of prognosis [9]. The complex anatomy of the head and neck region results in complex patterns of local and regional invasion, often making it difficult to establish the exact subsite of origin. Over the last 20 years, surgical and radiotherapy techniques, and also chemotherapy agents, have changed markedly, in attempts to reduce morbidity, preserve organ function and improve

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Table 1. Data quality by country for head and neck cancers diagnosed in 1995–1999 in cancer registries from 17 European countries

Site	Country	National coverage (%)	Number of cases	%HV	%DCO-autopsy	%Alive with f.u.<5 years (1995–1998)	Men : women ratio
Mouth and pharynx	Northern Europe						
	Norway	100	1033	98.7	0.4	0.4	2.1
	Sweden	100	1884	99.8	0.7	0.2	1.8
	UK and Ireland						
	England	100	12 093	98.8	0.0	0.1	1.9
	Northern Ireland	100	431	94.6	0.9	0.0	1.8
	Scotland	100	2161	97.2	0.7	0.0	2.0
	Wales	100	910	n.a.	6.5	0.0	2.2
	Ireland	100	908	94.8	1.7	0.0	2.7
	Central Europe						
	Belgium[a]	58.2	1529	96.8	0.1	0.0	3.8
	France[a]	10.4	3407	99.2[b]	0.0	3.6	7.0
	Germany[a]	1.3	794	98.7	1.0	7.8	4.2
	Switzerland[a]	27.0	821	98.1	0.9	2.8	3.4
	The Netherlands[a]	43.8	1887	99.8	0.1	0.1	1.7
	Southern Europe						
	Italy[a]	9.1	1936	94.6	1.1	1.4	3.3
	Spain[a]	11.4	2149	97.8	0.8	0.6	6.0
	Slovenia	100	1099	98.7	0.9	0.2	7.9
	Eastern Europe						
	Czech Republic[a]	8.3	264	97.7	1.9	6.5	3.6
	Slovakia	100	3016	92.6	6.2	0.3	12.9
	Total		36 322	97.7	1.0	0.8	2.8
Larynx	Northern Europe						
	Denmark	100	1206	98.3	0.2	0.2	4.5
	Iceland	100	38	100.0	0.0	0.0	5.4
	Norway	100	550	98.9	0.5	0.5	5.8
	UK and Ireland						
	England[a]	23.5	1892	91.7	2.9	4.1	4.7
	Northern Ireland	100	315	97.1	0.0	0.0	4.3
	Scotland	100	1368	96.3	0.4	0.0	3.8
	Wales	100	582	n.a.	3.8	0.0	4.3
	Ireland	100	539	95.0	2.0	0.0	5.2
	Central Europe						
	France[a]	9.2	1009	98.6[b]	0.0	5.5	13.4
	Germany[a]	1.3	274	97.8	1.5	9.5	7.1
	Switzerland[a]	27.0	358	97.5	1.1	3.6	5.0
	The Netherlands[a]	43.8	1384	99.7	0.1	0.1	5.3
	Southern Europe						
	Italy[a]	8.4	1819	93.5	0.8	2.1	13.1
	Malta	100	81	97.5	1.2	0.0	9.1
	Spain[a]	12.9	2429	97.4	1.4	0.5	23.8
	Slovenia	100	452	98.5	2.0	0.0	10.6
	Eastern Europe						
	Slovakia	100	1294	92.1	6.8	0.2	18.0
	Total		15 590	96.0	1.6	1.5	7.2

[a]Countries with <100% cancer registration (sometimes because cancer registries were excluded for poor quality data): England: East Anglia, Mersey, South Western; Belgium: Flanders; France: Bas-Rhin, Calvados, Doubs, Haut-Rhin (mouth and pharynx only), Herault, Isere, Manche, Somme, Tarn; Germany: Saarland; Switzerland: Basel, Geneva, St. Gallen, Ticino, Valais; The Netherlands: Amsterdam, Eindhoven, North Netherlands, Twente; Italy: Alto Adige, Biella, Ferrara, Parma (mouth and pharynx only), Ragusa, Reggio Emilia, Romagna, Sassari, Umbria, Varese; Spain: Basque Country, Granada, Murcia, Navarra, Tarragona (larynx only) Czech Republic: West Bohemia.

[b]Not available for cases in the registry of Herault.

f.u., follow-up; n.a, not available; HV, histologically verified.

Table 2. Numbers of head and neck cancer cases diagnosed in 1995–1999 by country and anatomical site of origin

Country	Tongue C01.9–C02.9			Oral Cavity C3.0-C06.9			Oropharynx C09.0–C10.9			Hypopharynx C12.9–C13.9			Larynx C32.0–C32.9		
	n	%Base	%NOS	*n*	%Gum NOS	%Mouth NOS	*n*	%Tonsil	%NOS	*n*	%Pyriform sinus	%NOS	*n*	%Glottis	%NOS
		C01.9	C02.9		C03.9	C06.9		C09	C10.9		C12.9	C13.9		C32.0	C32.9
Northern Europe															
Denmark													1206	50.8	11.6
Iceland													38	65.8	21.1
Norway	293	18.4	26.6	358	2.0	7.0	242	77.7	16.9	132	28.0	65.9	550	60.6	7.6
Sweden	503	19.9	0.6	655	4.7	12.4	453	87.1	7.3	260	12.7	77.3			
UK and Ireland															
England	3667	19.3	46.9	4000	6.3	9.8	2136	76.1	17.1	1564	62.5	14.6	1892	54.5	23.0
Northern Ireland	133	15	36.8	145	6.2	5.5	48	76.1	8.7	64	48.4	12.5	315	47.3	25.1
Scotland	574	23.5	30.3	811	1.2	6.9	335	70.1	17.3	307	58	15.6	1368	44.2	23.0
Wales	297	24.2	29.6	278	6.1	4.7	151	78.4	11.5	123	61	17.9	582	45.7	23.9
Ireland	255	31.8	29	284	3.2	7.8	124	65.9	9.7	176	68.2	9.1	539	58.3	16.3
Central Europe															
Belgium	376	28.7	48.4	537	2.2	11.7	342	72.8	18.3	221	66.1	23.1			
France	658	41.5	19.5	783	3.2	3.6	916	58.0	7.8	879	73.7	9.2	1009	43.6	10.1
Germany	160	32.5	14.4	258	1.9	1.9	185	65.9	20	151	25.8	54.3	274	47.1	16.8
Switzerland	205	42.4	8.3	213	1.4	3.8	251	62.2	14.8	144	59	29.2	358	60.1	5.3
The Netherlands	472	33.3	4.0	718	0.7	1.0	406	63.6	6.4	277	73.7	6.9	1384	65.7	0.4
Southern Europe															
Italy	538	29.7	19.9	544	6.3	10.9	425	59.1	13.7	328	47.3	28.7	1819	56.7	15.2
Malta													81	58.0	14.8
Spain	585	29.6	16.4	655	3.2	7.2	351	53.3	26.5	424	64.6	29.7	2429	39.8	11.0
Slovenia	201	26.4	13.9	258	0.4	1.9	415	37.8	11.3	221	55.2	20.8	452	44.5	8.2
Eastern Europe															
Czech Republic	81	38.3	21.0	85	8.2	8.2	70	75.7	11.4	20	5	60.0			
Slovakia	711	39.5	5.5	757	0.5	2.1	849	43.0	7.3	657	25.6	17.2	1294	36.6	11.0
Total	9709	26.1	31.8	11 339	4.0	7.9	7699	64.9	13.4	5948	55.3	21.6	15 590	49.7	13.8

aesthetic outcomes, while maintaining or improving survival for these cancers.

The aims of the study were to analyse survival for head and neck cancers in the European populations covered by the population-based cancer registries (CRs) participating in EUROCARE-4, in relation to tumour subsite as prognostic factor and to assess the extent to which differences in subsite can account for survival differences between different European populations.

patients and methods

The analysis was confined to adults (age ≥15 years) diagnosed with malignant epithelial head and neck cancers diagnosed in 1995–1999 and followed up until 31 December 2003. We excluded adenocarcinomas and cases occurring after diagnosis of a previous malignancy (except non-melanoma skin cancer) but included 1.5% of cases without histological verification. Most cases (94% of mouth and pharyngeal cancers and 86% of laryngeal cancers) were coded as squamous cell carcinoma (International Classification of Diseases for Oncology-3 8050-8084) [10]. Of the total of 51912 cancers considered, 15590 affected the larynx (C32.0–C32.9) and 36322 affected the mouth–pharynx, comprising base of tongue (C01.9), other and unspecified parts of tongue (C02), gum (C03), floor of mouth (C04), palate (C05), other and unspecified parts of mouth (C06), tonsil (C09), oropharynx (C10), pyriform sinus (C12.9), hypopharynx (C13), and other and ill-defined sites of lip, oral cavity and pharynx (C14).

The cases were contributed by 45 selected (see later) population-based CRs in 20 countries participating in EUROCARE-4. The countries were: Denmark, Iceland, Norway and Sweden (grouped as Northern Europe); the Czech Republic and Slovakia (Eastern Europe); Belgium, France, Germany, The Netherlands and Switzerland (Central Europe); Italy, Malta, Slovenia and Spain (Southern Europe) and England, Ireland, Northern Ireland, Scotland and Wales (UK and Ireland).

For 12 participating countries (Denmark, England, Iceland, Ireland, Malta, Norway, Sweden, Scotland, Wales, Northern Ireland, Slovenia and Slovakia), the entire population is covered by cancer registration; the other countries are represented by regional CRs covering variable proportions of the national population (see footnote of Table 1 for details).

The CR selection criterion was that the proportion of not otherwise specified (NOS) cases should be inferior to 30% of the total: NOS laryngeal (C32.9) and NOS mouth–pharyngeal (02.9, C03.9, C06.9, C10.9, C13.9, C14.0 and C14.8) sites were considered separately as some registries had few NOS cases for mouth–pharynx but not for larynx, while the situation was reversed for other CRs. The choice of 30% was a trade-off between data quality and number of CRs included in the study.

statistical methods

Survival was expressed as relative survival, calculated as the ratio between the observed survival and the expected survival in the population of the same age, sex and country. Relative survival was estimated by the Hakulinen method [11] using estimates of population life tables for each registry area.

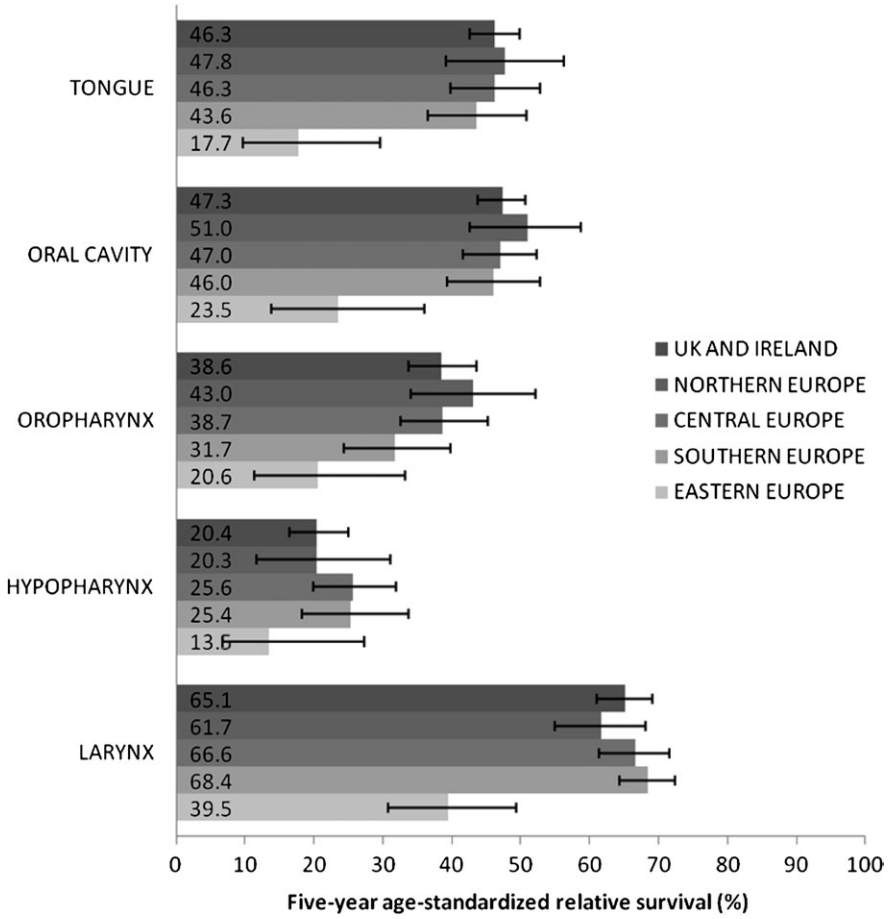

Figure 1. Five-year age-standardised relative survival (%) for head and neck cancers by European area and anatomical site of origin.

To account for differences in the age distribution of the different populations, relative survival was adjusted for age by the direct method using international cancer survival standard age distributions [12].

Relative survival was modelled with a generalised linear model [13], which assumes the hazards are constant within prespecified subintervals, and implies a Poisson distribution of the number of observed deaths in each interval. The models provide estimates of relative excess risks (RER) of death for each country considering age, sex and anatomic subsite as covariates, applied separately to mouth–pharyngeal and laryngeal sites. We also ran models providing estimates of RERs of death for each subsite (mouth–pharyngeal and laryngeal sites considered separately) with age, sex and country as covariates.

To estimate survival time trends, data from EUROCARE-3 (diagnosis period 1990–1994) and EUROCARE-4 (diagnosis period 1995–1999) were compared for CRs that provided data for both periods. Whisker plots was used to represent survival data over the two study periods. Stata software [14] was employed to carry out the analyses.

results

Table 1 shows national coverage by site (mouth–pharynx and larynx), with percentages of cases known by death certificate only (DCO) and discovered at autopsy, percentages of histologically verified cases and percentages of cases alive with follow-up <5 years, as indicators of data quality. DCO/autoptical cases were excluded from the survival analyses. Table 1 also shows men : women ratios.

For most countries, the percentage of histologically verified cases ranged between 97% and 100%. Lower percentages were found for Italy, Ireland and Slovakia for both sites; Northern Ireland for mouth–pharynx only and England and Scotland for larynx only.

The proportion of DCO/autoptical cases was high for Wales (6.5%) and Slovakia (6.2%) for mouth and pharynx; the percentage lost to follow-up was >6% only for the Czech Republic (mouth and pharynx) and Germany (larynx).

The male : female ratio was always >1 and was particularly high for France, Spain, Slovenia and Slovakia (>6 : 1 for mouth and pharynx and >10 : 1 for larynx); for larynx, the ratio was also very high for Italy (13 : 1).

Table 2 shows the number of cases by country with the percentages of cases for the principal anatomical sites and subsites. The percentage of tongue cancers originating from base of tongue (26% overall) was highest in France and Switzerland (>40%) and low in Norway, Sweden, England and Northern Ireland (<20%). Cancers of the tonsil (65% overall) accounted for >70% of all oropharyngeal cases in Northern Europe, the UK, Belgium and the Czech republic, whereas in Southern Europe, France and Slovakia, they accounted for <60%. Pyriform sinus cancers (55% overall) accounted for >70% of all hypopharyngeal cancers in France and The Netherlands but formed a low proportion of the total in several other countries, particularly Norway, Sweden, Germany and

Table 3. Five-year age-standardised relative survival (RS) (%) by country and sex for European patients diagnosed with mouth and pharyngeal and laryngeal cancers in 1995–1999 and archived cancer registries from 17 countries

Country	Mouth and pharynx		Larynx	
	Men	Women	Men	Women
	Five-year age-standardised RS	Five-year age-standardised RS	Five-year age-standardised RS	Five-year age-standardised RS
Northern Europe				
Denmark			61.1 (51.5–70.2)	52.0 (34.3–67.3)
Iceland			59.0 (16.0–100.0)	Value not calculable
Norway	37.4 (28.4–46.9)	47.5 (34.0–60.0)	66.2 (52.6–77.7)	71.1 (39.8–92.5)
Sweden	42.5 (35.4–49.6)	52.8 (43.2–61.3)		
UK and Ireland				
England	38.4 (35.6–41.2)	45.5 (41.7–49.1)	69.7 (62.3–76.5)	61.4 (48.8–72.5)
Northern Ireland	33.4 (20.1–48.2)	33.2 (15.9–52.2)	65.5 (46.2–82.0)	Value not calculable
Scotland	40.1 (32.7–47.7)	46.0 (36.5–55.2)	65.3 (55.3–73.9)	59.8 (46.3–72.4)
Wales	37.3 (27.1–48.2)	42.4 (27.9–56.5)	62.6 (49.0–74.6)	64.4 (42.4–81.8)
Ireland	33.8 (24.6–43.9)	41.0 (26.2–55.6)	62.1 (47.9–73.7)	57.3 (29.0– 80.7)
Central Europe				
Belgium	34.0 (27.0–41.6)	45.1 (31.2–58.7)		
France	30.6 (25.9–35.6)	48.7 (36.8–60.3)	55.2 (45.8–64.4)	56.9 (26.9–81.8)
Germany	44.1 (30.9–58.2)	61.0 (37.1–81.8)	59.4 (39.1–79.4)	59.7 (24.4–91.3)
Switzerland	35.8 (25.5–47.2)	48.5 (29.5–66.3)	62.7 (45.6–77.5)	56.6 (31.6–79.9)
The Netherlands	49.4 (40.7–58.2)	53.6 (43.5–63.3)	78.2 (69.4–85.8)	66.9 (48.8–81.7)
Southern Europe				
Italy	37.4 (30.8–44.3)	48.9 (37.0–60.0)	74.2 (66.9–80.4)	67.5 (43.5–85.5)
Malta			75.0 (37.4–100.0)	Value not calculable
Spain	36.5 (30.1–43.4)	53.1 (39.2–65.7)	64.6 (58.5–70.4)	71.2 (42.1–91.1)
Slovenia	23.8 (16.8–33.7)	56.2 (29.8–79.9)	62.4 (45.6–79.3)	77.7 (28.3–100.0)
Eastern Europe				
Czech	33.4 (11.4–63.4)	48.5 (20.6–77.9)		
Slovakia	17.2 (11.9–23.9)	28.0 (12.3–48.7)	38.9 (29.7–49.1)	53.0 (23.9–84.1)

the Czech Republic, mainly because of the high proportion of hypopharyngeal NOS in these latter countries.

Glottic cancers accounted for 40%–60% of all laryngeal cancers in most countries, the exceptions being Iceland, Norway, Switzerland, The Netherlands (>60%), Spain and Slovakia (<40%).

Five-year age-standardised relative survival with 95% confidence intervals are presented by broad anatomical site and European region in Figure 1. Northern Europe had the highest 5-year relative survival for tongue, oral cavity and oropharynx sites, whereas Southern and Central Europe had highest survival for hypopharynx and larynx sites. For all sites, survival was lower in Eastern Europe, significantly so for larynx, tongue and oral cavity.

Table 3 shows 5-year age-standardised relative survival for the two main sites (mouth–pharynx and larynx) by sex and country. Survival was better for women in all countries except Northern Ireland for mouth–pharynx, whereas for larynx, this was only true for seven countries. Five-year age-standardised relative survival for mouth–pharynx ranged from 17% (Slovakia) to 49% (The Netherlands) for men and from 28% (Slovakia) to 61% (Germany) for women. Survival was better for larynx: rates ranged between 39% (Slovakia) and 78% (The Netherlands) for men and between 52% (Denmark) and 78% (Slovenia) for women. Thus, for both sites, survival was particularly low in Slovakia and high in The Netherlands.

Models estimating RERs of death are shown in Table 4 (mouth–pharynx) and Table 5 (larynx): Model 1 has age at diagnosis and sex as covariates; model 2 has age, sex and anatomical subsite as covariates. For mouth–pharynx (Table 4), by model 1, Sweden and The Netherlands had significantly lower RERs of dying than England (reference), while Northern Ireland, Ireland, France, Slovenia, the Czech Republic and Slovakia had significantly higher RERs of dying than reference. After adjustment for anatomical subsite (model 2), RERs of dying for Italy and Germany became significantly lower than for England, whereas the RER for France was no longer significantly higher.

With regard to subsite, the RER of dying was highest for the postcricoid region (1.70) and lowest for cheek plus vestibule of mouth (0.53) compared with reference (base of tongue plus vallecula plus lingual tonsil).

For larynx (Table 5), RERs of dying in Italy and The Netherlands were significantly lower than England; while Slovakia, France, Denmark, Ireland, Wales and Scotland had significantly higher RERs of dying than England (model 1). After adjustment for anatomical subsite (model 2), RERs remained high only for Slovakia, Ireland, Denmark and France. RERs of dying were higher than reference (glottis) for all anatomical subsites considered.

Analysing men and women separately (data not shown), we found that for most countries RERs were similar to those shown

Table 4. (A) RERs of death by country for all mouth–pharynx sites adjusted by age and sex (model 1) and by age, sex and subsite (model 2) compared with England. (B) RERs of death by subsite relative to base of tongue plus vallecula plus lingual tonsil (reference) with age, sex and country as covariates

(A) Country	Model 1		Model 2	
	RER of death adjusted for age and sex	95% CI	RER of death adjusted for age, sex and subsite	95% CI
Northern Europe				
Norway	0.94	0.86–1.03	0.97	0.88–1.06
Sweden	0.80	0.75–0.86	0.82	0.76–0.88
UK and Ireland				
England	(Reference) 1		(Reference) 1	
Northern Ireland	1.28	1.12–1.45	1.25	1.10–1.42
Scotland	1.01	0.95–1.08	1.01	0.95–1.07
Wales	1.00	0.91–1.10	0.99	0.89–1.09
Ireland	1.19	1.08–1.30	1.12	1.01–1.22
Central Europe				
Belgium	1.06	0.99–1.14	1.03	0.96–1.11
France	1.15	1.09–1.21	1.01	0.96–1.07
Germany	0.90	0.81–1.00	0.83	0.74–0.92
Switzerland	1.00	0.91–1.11	0.94	0.85–1.03
The Netherlands	0.82	0.76–0.88	0.83	0.77–0.89
Southern Europe				
Italy	0.94	0.88–1.00	0.89	0.83–0.95
Spain	1.04	0.97–1.11	0.97	0.91–1.03
Slovenia	1.36	1.26–1.48	1.26	1.16–1.37
Eastern Europe				
Czech Republic	1.52	1.30–1.80	1.47	1.26–1.73
Slovakia	2.40	2.28–2.53	2.16	2.05–2.28
(B) Subsite	**ICD-O-3 code**	**%**		
Base of tongue, vallecula and lingual tonsil	C01.9, C02.4, C02.8, C10.0	9.7	(Reference) 1	
Tongue, other parts	C02.0–C02.3, C02.9	18.4	0.59	0.55–0.62
Gum	C03.0–C03.9	4.9	0.60	0.55–0.66
Floor of mouth	C04.0–C04.9	12.7	0.64	0.6–0.68
Palate	C05.0–C05.9	5.0	0.68	0.63–0.73
Cheek and vestibule of mouth	C06.0–C06.1	3.2	0.53	0.47–0.58
Retromolar area	C06.2	2.7	0.65	0.59–0.72
Mouth, NOS	C06.8–C06.9	2.8	0.79	0.71–0.87
Tonsil	C09.0–C09.9	13.8	0.72	0.67–0.76
Anterior surface of epiglottitis	C10.1	0.5	0.76	0.61–0.94
Lateral wall of oropharynx	C10.2, C10.8	2.4	0.99	0.90–1.09
Posterior wall of oropharynx	C10.3	0.4	1.60	1.33–1.93
Oropharynx and pharynx, NOS	C10.9, C14.0, C14.8	7.1	1.45	1.36–1.54
Pyriform sinus and posterior wall of hypopharynx	C12.9, C13.2	9.7	1.16	1.09–1.23
Aryepiglottic fold	C13.1	0.8	0.87	0.75–1.02
Postcricoid region	C13.0	1.4	1.70	1.52–1.91
Hypopharynx, NOS	C13.8–C13.9	4.5	1.50	1.40–1.61

CI, confidence interval; ICD-O, International Classification of Diseases for Oncology; NOS, not otherwise specified; RERs, relative excess risks.

in Table 4 (mouth–pharynx) for men and women together. However, for women alone, the differences in RERs of death between the Czech Republic, Ireland, Slovenia and England for mouth and pharynx were no longer evident. For larynx, RERs of death for men in Norway and Switzerland were significantly higher than that in England, while for The Netherlands, the RER was similar to reference. For women, RERs of death for larynx were similar to reference (England) for most countries except Italy (significantly lower) and Slovakia (significantly higher).

Country-specific 5-year relative survival was greater in 1995–1999 than in 1990–1994 for larynx and slightly greater also for mouth and pharynx (Figure 2).

Table 5. (A) RERs of death by country for all laryngeal sites adjusted by age and sex (model 1) and by age, sex and subsite (model 2) compared with England. (B) RERs of death by subsite relative to glottis, with age, sex and country as covariates

(A) Country	Model 1		Model 2	
	RER of death adjusted for age and sex	95% CI	RER of death adjusted for age sex and subsite	95% CI
Northern Europe				
Denmark	1.38	1.20–1.59	1.30	1.13–1.50
Iceland	0.95	0.47–1.93	1.00	0.49–2.12
Norway	1.03	0.84–1.25	1.19	0.98–1.44
UK and Ireland				
England	(Reference) 1		(Reference) 1	
Northern Ireland	1.11	0.87–1.41	0.99	0.78–1.25
Scotland	1.21	1.05–1.39	1.06	0.92–1.22
Wales	1.22	1.01–1.46	1.00	0.83–1.21
Ireland	1.33	1.1–1.6	1.43	1.19–1.71
Central Europe				
France	1.54	1.34–1.78	1.3	1.12–1.5
Germany	1.20	0.93–1.54	1.00	0.77–1.29
Switzerland	1.11	0.89–1.39	1.24	0.99–1.55
The Netherlands	0.71	0.6–0.85	0.84	0.71–0.99
Southern Europe				
Italy	0.81	0.7–0.93	0.78	0.68–0.9
Malta	1.00	0.64–1.59	1.06	0.68–1.66
Spain	1.13	1.00–1.29	0.89	0.79–1.01
Slovenia	1.21	0.99–1.49	1.04	0.84–1.28
Eastern Europe				
Slovakia	2.57	2.26–2.92	2.21	1.94–2.52
(B) Subsite	ICD-O-3 code	%		
Glottis	C32.0	50.8	(Reference) 1	
Supraglottis	C32.1	29.5	3.80	3.50–4.12
Subglottis	C32.2	1.5	3.63	2.94–4.48
Overlapping areas of larynx	C32.8	5.6	4.08	3.62–4.61
Larynx, NOS	C32.9	12.6	4.07	3.69–4.49

CI, confidence interval; ICD-O, International Classification of Diseases for Oncology; NOS, not otherwise specified; RERs, relative excess risks.

discussion

Consistent with previous population-based findings [9], the present study found that survival varied markedly with subsite. Thus, among mouth–pharynx sites, hypopharynx, base of tongue, lateral and posterior wall of the oropharynx (Table 4) were characterised by relatively poor survival, while among laryngeal sites, the supraglottic and subglottic subsites had poor survival (Table 5).

Since the distribution of subsites in European countries is not homogeneous, we expected the marked geographic differences in survival that we in fact found (Figure 1). However, important survival differences persisted even after correcting for subsite distribution. In particular, considering mouth–pharynx subsites, age- and sex-adjusted RERs of death were similar in Norway, England, Scotland, Wales, Belgium, Germany, Switzerland, Italy and Spain, but significantly higher in Slovakia and the Czech Republic, and to a lesser extent also in Slovenia, France, Northern Ireland and Ireland (Table 4, model 1). RERs of death continued to be significantly higher in these latter countries, except France, even after correcting for subsite distribution (Table 4, model 2). We may, therefore, provisionally attribute poor survival in these latter countries to poor access to good treatment or late diagnosis.

Adjustment for subsite reduced RERs of death for most countries. Exceptions were the other UK countries, The Netherlands and Northern European countries–all characterised by lower frequencies of poor prognosis subsites (hypopharynx, base of tongue and oropharynx except tonsil). In France, where prognosis was fairly poor, subsite adjustment made the RER of death similar to that of England; in Italy and Germany, subsite adjustment made the prognosis significantly better than England.

Turning now to laryngeal sites, we note that most countries had similar prognoses after subsite adjustment. However, Slovakia, Denmark, Ireland and France continued to have significantly higher RERs of death than reference after subsite adjustment (Table 5, model 2), again suggesting late diagnosis or poor access to good treatment in these countries. Nevertheless, RERs decreased following subsite adjustment in Slovakia and France (as well as in Spain, Germany, Slovenia, Scotland and Wales) also reflecting low frequencies of relatively good prognosis glottic cancers (compared with reference) in these countries (Table 2).

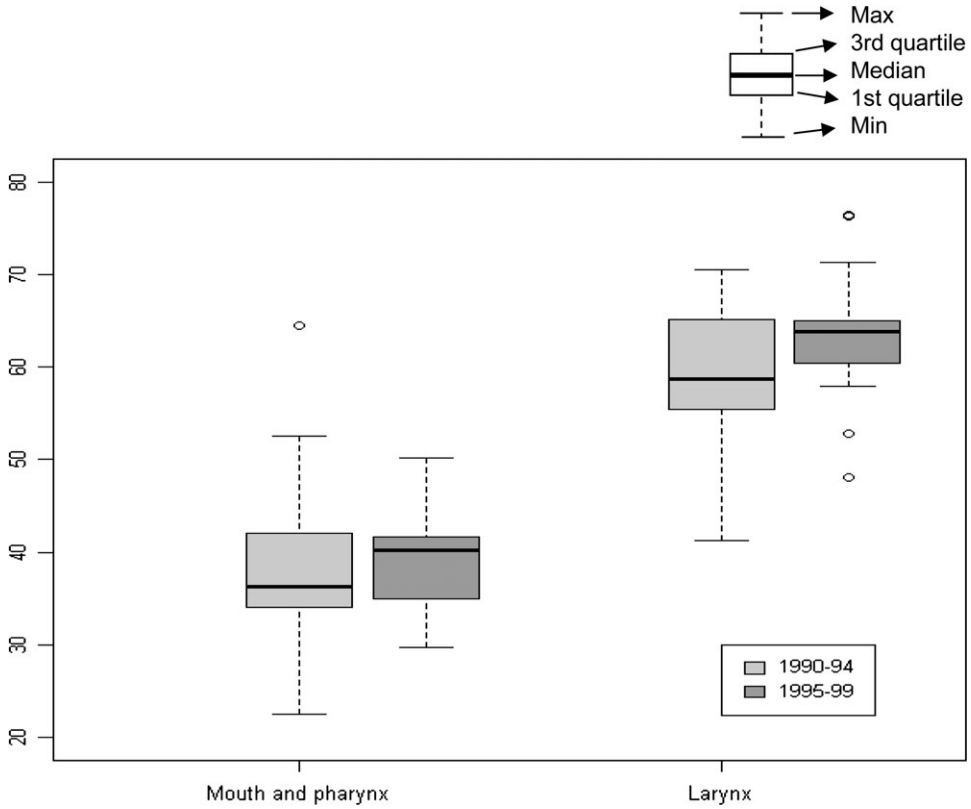

Figure 2. Changes in 5-year country-specific age-standardised relative survival for mouth–pharyngeal and laryngeal sites from 1990–1994 to 1995–1999. Only countries whose registries contributed data for both periods are included.

Another possible reason for between-country differences in survival—even after subsite adjustment—is cancer site misclassification. Thus, possible misclassification of the good prognosis glottic site versus poor prognosis supraglottic, subglottic or NOS sites (Table 5) is suggested by the relatively high proportion of 'overlapping' sites, in turn probably reflecting the difficulty of identifying the primary subsite in the presence of locally advanced disease.

Other factors influencing survival in head and neck cancers are stage [15], comorbidity [16] and patient socioeconomic status at least in the first 12–18 months following diagnosis [17].

As regards stage, it is noteworthy that subsite determines the appearance of symptoms, which in turn influences stage at diagnosis [9]. As regards comorbidity, data suggest that this factor exerts its greatest effects on patients with good prognostic factors (tongue or glottic sites, early-stage disease and young age) [18].

Socioeconomic status exerts its greatest effects on laryngeal cancers, where survival differences between deprived and affluent groups are greater than for any other common cancer [19, 20]. A study on survival trends for laryngeal sites in England and Wales found that the overall increase in 5-year survival between 1986–1990 and 1996–1999 occurred exclusively in the most affluent sector of the population [21].

In the present study, we had no information on stage, comorbidity or socioeconomic status and no means to estimate the effect of confounding by misclassification. It is difficult, therefore, to account for all factors contributing to the survival differences for European head and neck cancer patients revealed by this study. Nevertheless, it is clear that differences in subsite distribution explain a considerable part of the survival differences, from which an important message emerges: survival comparisons require careful adjustment for anatomical subsite, so it is essential that CRs take steps to ensure that subsite information is accurate and complete.

Another important finding of this study is that 5-year relative survival increased from 1990–1994 to 1995–1999 for all types of head and neck cancer. These European results are encouraging because they are not mirrored by similar analysis conducted in the United States in particular for laryngeal cancer [22]. Finally, we note that survival differences between countries decreased from 1990–1994 to 1995–1999, suggesting reductions in inequalities of treatment quality and treatment access across Europe.

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disclosure

None of the authors declare conflicts of interest.

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appendix

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