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Rare cancers of the head and neck area in Europe

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ABSTRACT

The RARECARE project has proposed a different and more detailed grouping of cancers, based on localisation and histological type, in order to identify rare entities with clinical meaning. RARECARE gathered data on cancer patients diagnosed from 1978 to 2002 and archived in 76 population-based cancer registries, all of which had vital status information available up to at least 31st December 2003. This study provides incidence, prevalence and survival rates for rare head and neck epithelial (H&N) cancers.

Among the rare H&N cancers, those of oral cavity had the highest annual crude incidence rate of 48 per million, followed by oropharynx and 'major salivary glands and salivary gland type tumours' (28 and 13 per million, respectively). Incidence rates of epithelial tumours of nasal cavities, nasopharynx, eye and adnexa and middle ears were all lower than 5 per million. The prevalence for all investigated entities was lower than 35 per 100,000. The 5-year relative survival rates ranged from 40% for epithelial cancer of oropharynx to 85% for epithelial cancer of eye and adnexa. Survival rates were lower for men and for patients aged $\geqslant$65 years. With few exceptions, the lowest and highest survival figures were observed for Eastern Europe and Northern Europe, respectively.

According to the definition for rare tumours by RARECARE (incidence < 6 per 100,000), as well as according to the definition for rare diseases by the European Commission (prevalence < 50 per 100,000) the H&N cancers described in this paper should be considered rare and diagnosis and treatment of these cancers should therefore be centralised.

1. Introduction

Head and Neck (H&N) cancers are a group of tumour entities anatomically close to each other, but different in terms of aetiology, diagnostic and treatment approaches.

The most important risk factors for most H&N cancers (squamous cell carcinomas) are tobacco use[1,2] and alcohol intake.[2,3] In a pooled analysis, the proportion of the incidence due to tobacco and alcohol use was estimated at 72% (95% confidence interval: 61–79%) for H&N cancers (cancer of the oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx, or head and neck cancers unspecified were included, but cancers of the major salivary glands, nasal cavity, ear and paranasal sinuses were excluded), of which 4% was due to alcohol alone, 33% was due to tobacco alone and 35% was due to tobacco and alcohol

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combined.[4] This percentage differed by localisation and was 64% for oral cavity cancer and 72% for pharyngeal cancer.[4] Other risk factors are viral infection (Epstein–Barr Virus (EBV) for nasopharyngeal cancer[5] or Human Papilloma Virus (HPV) for oropharynx cancer),[6] occupational exposure,[7] radiation for major and minor salivary gland cancers,[8] and exposure to sunlight for lip and conjunctival cancers.[7,9]

In the past, due to the very similar diagnostic and therapeutical approaches, H&N cancers were grouped together. At present, stratification by tumour localisation has been implemented in larger studies and tumours of different localisations are managed differently. This should be seen as an indicator of awareness that more sophisticated refinement is needed when dealing with H&N cancers. In Europe, the RARECARE project was initiated with the goals (1) to provide an operational definition of 'rare cancers', and a list of cancers that meet this definition (2) to estimate the burden of rare cancers in Europe (3) to improve the quality of data on rare cancers and (4) to develop strategies and mechanisms for the diffusion of information among all the key players involved in Europe-wide surveillance on and treatment of rare cancers.[10]

Incidence, mortality, prevalence and survival rates are scarce for the specific entities, or often reported in general terms only, such as being rare. In this paper, we aim to give insight in the burden of rare cancers by providing incidence, prevalence and survival rates for the group of rare H&N cancers according to the newly developed definition for rare tumours by RARECARE (incidence < 6 per 100.000) that share the same referral pattern and health care organisation.

2. Materials and methods

Rare cancers of H&N that will be described in this article are epithelial tumours of the nasal cavity and sinuses, the nasopharynx, the major salivary glands and salivary gland type tumours, the oropharynx, the oral cavity and lip, the eye and adnexa and the middle ear.

The list of rare tumours is organised into three layers within RARECARE.[10] The bottom layer (layer 3) corresponds to the World Health Organisation (WHO) list of individual cancer entities and their corresponding ICD-O-3 codes (ICD-O: International Classification of Diseases for Oncology). Bottom layer entities were grouped into categories (layer 2) considered to require similar clinical management and research. Layer 2 entities were grouped into more general categories (top layer) considered to involve the same clinical expertise and patient referral structure. Here we report on the top and middle layer of H&N rare tumours, referred to as layer 1 and layer 2, respectively. As an example, the layer structure for epithelial tumours of the nasopharynx is shown in Table 1, the squamous cell carcinoma with its variants and the papillary adenocarcinoma of the nasopharynx corresponded to cancer entities that require different clinical management and research (layer 2). These second layer entities were grouped into general categories, epithelial tumour of nasopharynx (layer 1), considered to involve the same clinical expertise and patient referral structure. The ICD-O topography and morphology codes of all the entities are reported in detail in Table 2.

Data were gathered on cancer patients archived in 89 population-based cancer registries with vital status information available up to at least 31st December 2003. Included countries were Iceland, Norway and Sweden (region: Northern Europe), France, The Netherlands, Belgium, Switzerland, Germany and Austria (Central Europe), Poland and Slovakia (Eastern Europe), Italy, Slovenia, Spain, Portugal and Malta (Southern Europe) and Ireland, Northern Ireland, Scotland, England and Wales (United Kingdom (UK) and Ireland). For 11 countries, cancer registries covered the entire national population (Austria, Iceland, Ireland, Malta, Norway, Slovakia, Slovenia, Sweden, Northern Ireland, Scotland and Wales); while the other 10 countries were represented by regional cancer registries covering variable proportions of their respective national populations. The mean population period 1995–1999 was about 162,000,000, corresponding to 39% of the population of the countries participating in RARECARE and 32% of the population of the European Union (27 EU members).

Crude, and age specific incidence rates were estimated dividing the number of incident cases (period of diagnosis 1995–2002) for a given entity, by the corresponding person–years lived from the general population calculated during

Table 1 – Illustration of the layer structure.

Layer	Tumour	Topography code	Morphology code
1	Epithelial tumours of nasopharynx	C11	8000–8001, 8004, 8010–8011, 8020-8022, 8032, 8050-8076, 8078, 8082-8084, 8123, 8260, 8560, 8980
2	Squamous cell carcinoma with variants of nasopharynx	C11	8004, 8020–8022, 8032, 8051–8076, 8078, 8082–8084, 8123, 8560, 8980
3	Squamous carcinoma	C11	8070
3	Squamous cell carcinoma non-keratinizing, NOS	C11	8072
3	Squamous cell carcinoma keratinizing, NOS	C11	8071
3	Papillary squamous cell carcinoma	C11	8052
3	Basaloid squamous cell carcinoma	C11	8083
3	Squamous cell carcinoma, adenoid	C11	8075
3	Lymphoepithelial carcinoma	C11	8082
3	Undifferentiated carcinoma	C11	8020–8022
2	Papillary adenocarcinoma of nasopharynx	C11	8050, 8260

Table 2 – Data quality indicators of rare cancers of head and neck, cases diagnosed 1995–2002.

Entity	Number of malignant cancers 1995–2002 (*N*)	Data quality indicators					ICD-O-3 codes[31]	
		Death certificate only (%)	Autopsy (%)	Microscopic verification (%)	Morphology code NOS[a] (%)	Cases 1995–1998 censored before five years (%)	Topography	Morphology
Rare cancers of head and neck	79,537	1.5	0.1	94.1	3.7	1.2		
1. Epithelial tumour of nasalcavity and sinuses	3582	2.5	0.1	89.5	8.3	0.7	C30.0, C31	8000, 8001, 8004, 8010, 8011, 8020–8022, 8032, 8050–8076, 8078, 8082–8084, 8123, 8144[b], 8260[b], 8560, 8980
1. Epithelial tumour of nasopharynx	3574	2.3	0.1	90.7	6.2	1.0	C11	
1. Epithelial tumour of sal glands and sal gland type tumours	10,575	1.4	0.1	93.2	4.9	1.4	C00–C14, C30.0, C31, C32 (major salivary gland tumours: C07 & C08: all other topographies: salivary gland type tumours)	(For C00–C14, C30.0, C31, C32) 8140, 8147, 8200, 8290, 8310, 8430, 8440, 8450, 8480, 8500, 8525, 8550, 8562, 8941, 8982; (Additionally for C07, C08) 8004, 8012, 8020–8022, 8032, 8050–8076, 8082, 8211, 8230, 8255, 8260, 8262, 8290, 8310, 8320, 8323, 8410, 8980
1. Epithelial tumour of oropharynx	22,403	1.7	0.1	94.6	3.0	1.3	C01.9, C02.4, C02.8, C05.1–C05.2, C05.9, C09.0–C10.3, C10.8–10.9, C14.2	8000–8001, 8004, 8010–8011, 8020–8022, 8032, 8050–8076, 8078, 8082–8084, 8123, 8560, 8980
1. Epithelial tumour of oral cavity and lip	38,867	1.3	0.0	94.8	3.0	1.1	C00.0–C00.9 C02.0–C02.3, C02.9, C03.0–C05.0, C06.0–C06.9	

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Table 2 – (continued)

Entity	Number of malignant cancers 1995–2002 (N)	Data quality indicators					ICD-O-3 codes[31]	
		Death certificate only (%)	Autopsy (%)	Microscopic verification (%)	Morphology code NOS[a] (%)	Cases 1995–1998 censored before five years (%)	Topography	Morphology
1. Epithelial tumour of eye and adnexa	292	0.7	0.0	89.7	7.9	2.4	C69.0, C69.5	8000–8001, 8010–8011, 8020, 8050–8084, 8090, 8094, 8120–8121, 8123, 8130, 8140–8141, 8147, 8190, 8200–8201, 8210–8211, 8221, 8230–8231, 8255–8263, 8290, 8310, 8320, 8323, 8333, 8410, 8430–8440, 8480–8490, 8504, 8510, 8512, 8514, 8525, 8542, 8550–8551, 8560–8576
1. Epithelial tumour of middle ear	244	2.5	0.0	83.2	10.2	1.2	C30.1	

SAL = salivary.

See also: http://www.rarecare.eu/rarecancers/rarecancers.asp (Download RARECARE list spreadsheet).

[a] Morphology codes NOS are M8000–8001.

[b] ICD-O morphology code: 8144 (adenocarcinoma, intestinal type) only for nasal cavity; 8260 (papillary adenocarcinoma) only for nasopharynx.

Table 3 – Incident cases (number and rates per million) by sex and age, and estimated number of cases arising in Europe per year.

Entity	Overall			Sex				Age (year)						Estimated number of cases arising in Europe per year[a]
				Male		Female		0–24		25–64		65+		
	Observed cases 1995–2002	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	
Rare cancers of head and neck														
1. Epithelial tumour of nasal cavity and sinuses	3555	4.42	0.07	5.87	0.12	3.04	0.09	0.05	0.01	3.31	0.09	16.77	0.36	2198
2. Squamous cell carcinoma and variants of nasal cavity and sinuses	2498	3.1	0.06	4.17	0.1	2.09	0.07	0.01	0.01	2.35	0.07	11.73	0.3	1545
2. Lymphoepithelial carcinoma of nasal cavity and sinuses	19	0.02	0.01	0.03	0.01	0.01	0.01	0.01	0.01	0.03	0.01	0.05	0.02	12
2. Undifferentiated carcinoma of nasal cavity and sinuses	139	0.17	0.01	0.22	0.02	0.13	0.02	0.00	0.00	0.17	0.02	0.5	0.06	86
2. Intestinal type adenocarcinoma nasal cavity and sinuses	20	0.02	0.01	0.05	0.01	0.00	0.00	0.00	–	0.02	0.01	0.1	0.03	12
1. Epithelial tumour of nasopharynx	3566	4.43	0.07	6.53	0.13	2.43	0.08	0.63	0.05	5.13	0.11	9.52	0.27	2205
2. Squamous cell carcinoma and variants of nasopharynx	2630	3.27	0.06	4.89	0.11	1.72	0.06	0.41	0.04	3.92	0.1	6.7	0.23	1626
2. Papillary adenocarcinoma of nasopharynx	7	0.01	0.00	0.01	0.00	0.01	0.01	0.00	–	0.01	0.01	0.01	0.01	4
1. Epithelial tumour of sal glands and sal gland type	10,514	13.07	0.13	14.74	0.19	11.47	0.17	0.94	0.06	11.23	0.16	43.1	0.58	6501
2. Epithelial tumours of major salivary glands	5861	7.28	0.1	8.3	0.15	6.32	0.12	0.61	0.05	6.13	0.12	24.32	0.44	3624
2. Salivary gland type tumours of head and neck	3451	4.29	0.07	4.79	0.11	3.81	0.10	0.27	0.03	4.21	0.1	12.45	0.31	2134
1. Epithelial tumour of oropharynx	22,104	27.47	0.18	44.51	0.34	11.21	0.17	0.06	0.02	34.31	0.28	58.17	0.68	13,667
2. Squamous cell carcinoma and variants of oropharynx	20,795	25.85	0.18	42.05	0.33	10.37	0.16	0.05	0.01	32.7	0.28	53.31	0.65	12,858
1. Epithelial tumour of oral cavity and lip	38,537	47.9	0.24	68.3	0.42	28.42	0.26	0.28	0.03	42.67	0.32	159.11	1.12	23,828
2. Squamous cell carcinoma and variants of oral cavity	26,422	32.84	0.2	45.27	0.34	20.98	0.23	0.22	0.03	33.81	0.28	93.66	0.86	16,337
2. Squamous cell carcinoma and variants of lip	9854	12.25	0.12	19.51	0.22	5.32	0.11	0.02	0.01	6.89	0.13	54.4	0.66	6093
1. Epithelial tumour of eye and adnexa	287	0.36	0.02	0.44	0.03	0.17	0.02	0.01	0.01	0.24	0.02	1.39	0.10	177
2. Squamous cell carcinoma and variants of eye adnexa	192	0.24	0.01	0.32	0.03	0.08	0.01	0.00	–	0.13	0.02	1.05	0.09	119
2. Adenocarcinoma and variants of eye adnexa	51	0.06	0.01	0.06	0.01	0.04	0.01	0.00	0.00	0.06	0.01	0.18	0.04	32

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Table 3 – (continued)

Entity	Overall			Sex				Age (year)						Estimated number of cases arising in Europe per year[a]
				Male		Female		0–24		25–64		65+		
	Observed cases 1995–2002	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	
1. Epithelial tumour of middle ear	244	0.3	0.02	0.33	0.03	0.27	0.03	0.01	0.01	0.22	0.02	1.17	0.1	151
2. Squamous cell carcinoma and variants middle ear	180	0.22	0.02	0.25	0.03	0.19	0.02	0.00	0.00	0.15	0.02	0.9	0.08	111
2. Adenocarcinoma and variants middle ear	29	0.04	0.01	0.03	0.01	0.04	0.01	0.00	–	0.03	0.01	0.11	0.03	18

SE = standard error of the rate estimate; SAL = salivary.

[a] The expected number of new cases per year in Europe was estimated assuming the same rates in Europe as in the RARECARE sample.

the same period. All newly diagnosed cases were selected, with the inclusion of second primary and 'death certificate only' cases, but excluding cases incidentally discovered at autopsy. In geographical comparisons, age standardised rates were computed to adjust for different age distribution of the compared populations, using the conventional European standard population. The expected number of new cases per year in Europe (EU27) was also estimated assuming the same rates in Europe as in the RARECARE sample. Sixty-four cancer registries (the specialised CRs were not included in the incidence analysis) were included in the incidence analysis.

The number of prevalent cancers and the prevalence per 100,000 were estimated at the index date of 1st January 2003 by applying the counting method based on cancer registries incidence and follow-up data[11] to data from 22 registries covering the whole 15-year period (1988–2002). To obtain the complete prevalence, the estimated number of surviving cases diagnosed with rare cancer prior to 1988 was added.[12] The expected number of new cases per year and of prevalent cases in Europe (EU27) was estimated multiplying the crude incidence and prevalence rates to the 2002 European population (497,455,033) provided by Eurostat (The statistical office of the European Union).

Relative survival of H&N patients refers to the period 2000–2002 and was estimated by the period approach.[13] Relative survival estimates are the ratio of the observed survival of patients to the expected survival of a comparable group (with respect to sex and age) from the general population. Survival data from 46 out of the 76 European cancer registries were included in the analysis.

The main data quality indicators are presented in Table 2. Overall, 1.5% of the cases was Death Certificate Only (DCO) ranging from 0.7% for epithelial tumours of eye and adnexa to 2.5% for epithelial tumours of nasal cavity and middle ear. About 94% of the cases included in the analysis was microscopically verified, although the proportion varied from 83.2% for epithelial tumours of the middle ear to 94.8% for tumours of the oral cavity and lip. On average 1.2% of the cases was censored within 5 years of follow-up.

3. Results

3.1. *Incidence*

Among the selected H&N rare neoplasms, cancer of oral cavity was the most common tumour, with an annual crude incidence rate of 47.9 per million, followed by oropharynx (27.5 per million) and major salivary glands and salivary gland type tumours (13.1 per million) (Table 3). Incidence rates of epithelial tumours of nasal cavities, nasopharynx, eye and adnexa and middle ears were all lower than 4.5 per million.

H&N rare cancers were more common in men than in women (Table 3). The age-standardised male-to-female ratio ranged between 4.0 (oropharynx) and 1.2 (middle ear). Even if exceptional, epithelial cancer of the nasopharynx and salivary gland and salivary gland type tumours appear in children, adolescents and young adults. In adults and in the elderly, epithelial tumours of oropharynx, oral cavity and lip occurred with the highest rates. For all the considered rare

Table 4 – Age standardised incidence rates × million (Adj. rate) and standard errors (SE) by European region for the period of diagnosis 1995–2002.

Entity	European region										EU overall	
	Northern Europe		Central Europe		Eastern Europe		Southern Europe		UK and Ireland			
	Adj. rate	SE	Adj. rate	SE	Adj. rate	SE	Adj. rate	SE	Adj. rate	SE	Adj. rate	SE
Rare cancers of head and neck	72.5	0.8	99.7	0.7	111.7	1.3	101.2	0.8	70.5	0.5	87.1	0.3
1. Epithelial tumour of nasal cavity and sinuses	3.2	0.2	3.7	0.1	3.7	0.2	3.8	0.1	3.6	0.1	3.6	0.1
1. Epithelial tumour of nasopharynx	3.0	0.2	3.4	0.1	4.8	0.3	7.0	0.2	3.2	0.1	4.1	0.1
1. Epithelial tumour of sal glands and sal gland type	12.2	0.3	11.3	0.2	11.0	0.4	11.4	0.3	10.4	0.2	11.1	0.1
1. Epithelial tumour of oropharynx	16.5	0.4	36.9	0.4	39.5	0.8	27.9	0.4	17.7	0.2	25.8	0.2
1. Epithelial tumour of oral cavity and lip	34.9	0.5	43.3	0.5	51.1	0.9	49.4	0.5	34.1	0.3	40.9	0.2
1. Epithelial tumour of eye and adnexa	0.3	0.0	0.2	0.0	0.2	0.1	0.5	0.1	0.2	0.0	0.3	0.0
1. Epithelial tumour of middle ear	0.1	0.0	0.3	0.0	0.4	0.1	0.1	0.0	0.3	0.0	0.3	0.0

SE = standard error of the rate estimate; SAL = salivary.

tumours, incidence was highest in those 65 years and older (Table 3). Overall, each year, 49,000 new cases of H&N rare cancers are estimated to be diagnosed in Europe: ranging from almost 24,000 tumours of oral cavities and lip to about 150 for epithelial tumours of the middle ear (Table 3).

There was a geographical variation in the incidence for cancers of nasopharynx, oropharynx and tumours of the oral cavity and lip (Table 4). Southern Europe experienced the highest incidence rate for the cancer of nasopharynx (7.0 per million) and cancer of eye and adnexa (0.47 per million) and one of the highest for cancer of the oral cavities and lip (49.4 per million). Eastern Europe presented the highest incidence rates for cancer of the oral cavities and lip (51.1 per million) and oropharynx (39.5 per million). The incidence for oropharynx cancer was also high for Central Europe (36.9 per million). The rates for cancer of oral cavities and lip and oropharynx were lower in the Northern Europe and UK and Ireland (Table 4).

3.2. *Prevalence*

More than 330,000 persons were alive in EU at the beginning of the year 2003 with a past diagnosis of the selected rare H&N cancers. Table 5 shows that epithelial tumours of the oral cavity and lip were the most prevalent rare cancers (170,000 cases), followed by those of the salivary glands and salivary gland type (65,000), oropharynx (64,900), nasopharynx (14,600), nasal cavity (14,500), eye (1700) and middle ear (1100). For epithelial tumours of the oral cavity and lip, 20% (34,040 over 169,507) of the prevalent cases was diagnosed within 2 years and 41% (69,929 over 169,507) within 5 years before the prevalence date. The difference (21%) between these two proportions represents the proportion of cases in the 3rd–5th year after diagnosis, presumably undergoing clinical follow-up, while the 2-year prevalence represents the proportion of patients in primary treatment. The remaining fraction represents long-term survivors (59%).

3.3. *Survival*

Relative 1-year survival rates for first layer entities ranged from 71% (tumours of the middle ear and tumours of the oropharynx) to 94% (tumours of the eye and adnexa), while 5-year relative survival rates ranged from 40% for tumours of the oropharynx to 85% for tumours of the eye and adnexa (Fig. 1). The difference between 5-year and 1-year relative survival rates was the largest for tumours of the oropharynx, while this difference was remarkably smaller for tumours of the eye and adnexa, indicating a less steep decline of the survival curve (Fig. 1).

Fig. 1 also shows relative survival rates for second layer entities. A very good prognosis, based on 5-year relative survival rates, was estimated for adenocarcinoma of the middle ear (92%) and for squamous cell carcinoma of the lip (91%). The relative survival for epithelial tumours of the eye and adnexa was higher for squamous cell carcinomas (93%) than adenocarcinomas (76%). A good prognosis was also estimated for epithelial tumours of major salivary gland (66%), while a slightly better 5-year survival rate (71%) was observed for salivary gland type tumours. Intermediate prognosis was reported for squamous cell carcinomas of the oral cavity (48%), oropharynx (40%), nasopharynx (50%), and nasal cavity (51%). Poorer prognosis (<40%) was observed for intestinal type adenocarcinoma of nasal cavities and sinuses and for squamous cell carcinoma of the middle ear. The survival was particularly bad for lymphoepithelial carcinoma of nasal cavities and sinuses (4.5%), but this estimate is based on seven cases only.

Table 5 – Observed prevalence proportion per 100,000 and standard errors (SE) by duration (2, 5, 15-years) and estimated complete prevalence in Europe.

Entity	EU Complete prevalence 1st January 2003			Diagnosed within 2 years before 1st January 2003			Diagnosed within 5 years before 1st January 2003			Diagnosed within 15 years before 1st January 2003		
	N.	Prop.	SE	N.	Prop.	SE	N.	Prop.	SE	N.	Prop.	SE
Rare cancers of head and neck												
1. Epithelial tumour of nasal cavity and sinuses	14,492	2.91	0.08	3082	0.62	0.03	6012	1.21	0.04	11,292	2.27	0.06
2. Squamous cell carcinoma and variants of nasal cavity and sinuses	10,416	2.09	0.07	2482	0.50	0.03	4829	0.97	0.04	8154	1.64	0.05
2. Lymphoepithelial carcinoma of nasal cavity and sinuses	72	0.01	0.01	15	0.00	0.00	15	0.00	0.00	39	0.01	0.00
2. Undifferentiated carcinoma of nasal cavity and sinuses	665	0.13	0.02	163	0.03	0.01	241	0.05	0.01	475	0.10	0.01
2. Intestinal type adenocarcinoma nasal cavity and sinuses	123	0.02	0.01	0	0.00	0.00	23	0.00	0.00	70	0.01	0.00
1. Epithelial tumour of nasopharynx	14,637	2.94	0.09	2445	0.49	0.03	5484	1.10	0.04	10,863	2.18	0.06
2. Squamous cell carcinoma and variants of Nasopharynx	10,966	2.20	0.07	2011	0.40	0.03	4417	0.89	0.04	8531	1.71	0.05
2. Papillary adenocarcinoma of nasopharynx	29	0.01	0.00	8	0.00	0.00	16	0.00	0.00	23	0.00	0.00
1. Epithelial tumour of sal glands and sal gland type	65,063	13.08	0.18	10,237	2.06	0.06	21,958	4.41	0.08	43,292	8.70	0.12
2. Epithelial tumours of major salivary glands	39,290	7.90	0.14	6134	1.23	0.04	13,063	2.63	0.06	25,308	5.09	0.09
2. Salivary gland type tumours of head and neck	22,553	4.53	0.11	3490	0.70	0.03	7688	1.55	0.05	15,424	310	0.07
1. Epithelial tumour of oropharynx	64,877	13.04	0.18	19,905	4.00	0.08	37,241	7.49	0.11	56,970	11.45	0.13
2. Squamous cell carcinoma and variants of oropharynx	62,254	12.51	0.18	19,361	3.89	0.08	36,189	7.27	0.11	54,863	11.03	0.13
1. Epithelial tumour of oral cavity and lip	169,507	34.07	0.35	34,040	6.84	0.10	69,929	14.06	0.15	130,941	26.32	0.20
2. Squamous cell carcinoma and variants of oral cavity	96,196	19.34	0.25	23,694	4.76	0.09	46,221	9.29	0.12	79,015	15.88	0.16
2. Squamous cell carcinoma and variants of lip	63,621	12.79	0.18	9466	1.90	0.05	21,842	4.39	0.08	47,347	9.52	0.12
1. Epithelial tumour of eye and adnexa	1741	0.35	0.04	300	0.06	0.01	587	0.12	0.01	1190	0.24	0.02
2. Squamous cell carcinoma and variants of eye adnexa	895	0.18	0.02	171	0.03	0.01	356	0.07	0.01	726	0.15	0.02

Table 5 – (continued)

Entity	EU Complete prevalence 1st January 2003			Diagnosed within 2 years before 1st January 2003			Diagnosed within 5 years before 1st January 2003			Diagnosed within 15 years before 1st January 2003		
	N.	Prop.	SE	N.	Prop.	SE	N.	Prop.	SE	N.	Prop.	SE
2. Adenocarcinoma and variants of eye adnexa	348	0.07	0.02	83	0.02	0.01	138	0.03	0.01	247	0.05	0.01
1. Epithelial tumour of middle ear	1122	0.23	0.02	155	0.03	0.01	317	0.06	0.01	799	0.16	0.02
2. Squamous cell carcinoma and variants middle ear	709	0.14	0.02	139	0.03	0.01	217	0.04	0.01	504	0.10	0.01
2. Adenocarcinoma and variants middle ear	213	0.04	0.01	8	0.00	0.00	76	0.02	0.00	171	0.03	0.01

N. = number of cases; Prop. = proportion; SE = standard error of the rate estimate.

We additionally investigated the survival by sex, age category and region (Table 6). As expected, low numbers did not always permit calculations and therefore relative survival rates are shown for first layer entities only. For most rare tumours considered, prognosis was lower for men and the lowest for those 65 years of age or older. With few exceptions, the lowest and highest 5-year survival rates were observed for Eastern Europe and Northern Europe, respectively.

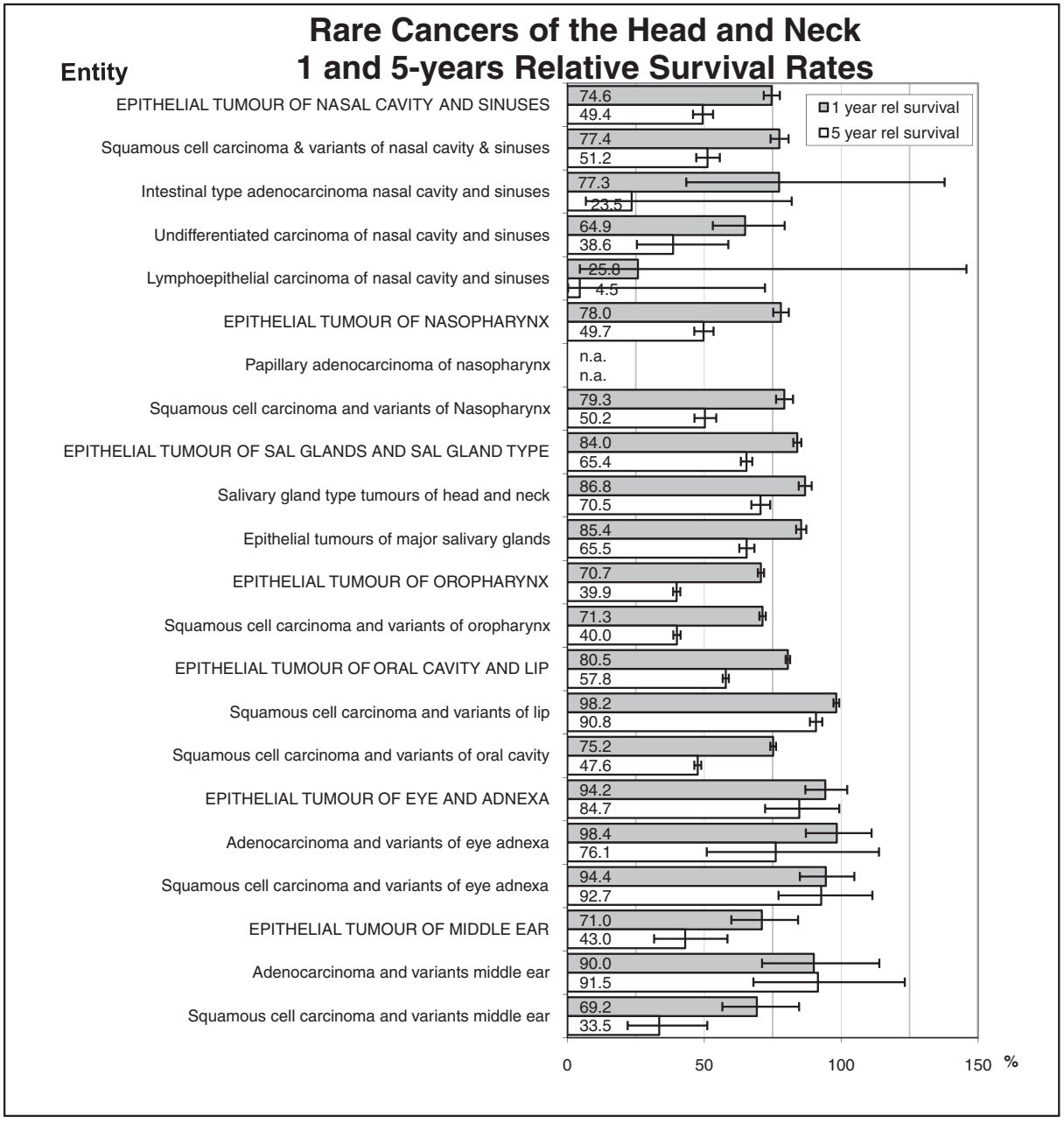
4. Discussion

The epidemiological indicators presented in this paper refer to the specific rare tumour list defined in the framework of the RARECARE project based on localisation and histological type. The underlying principle of this choice is to address cancer entities with specific clinical meaning. In the case of H&N cancers, natural history of different histological types as well as more specific tumour localisations were progressively recognised by physicians dealing with curative loco regional treatments. At present, tumours of different localisations are managed differently. The main therapeutic approaches are surgery, radiotherapy and medical treatment. Depending on site, histotype and tumour extension these approaches are used either alone or in combination. Nasopharyngeal carcinoma, for example, is traditionally treated with radiotherapy as its position, immediately below the base of skull and next to several cranial nerves, precludes curative surgery. To the contrary, surgery is the treatment of choice in salivary gland type tumours, irrespective of their site of origin. Oropharyngeal cancer should be subdivided into HPV-positive and HPV-negative subsets. Unfortunately, we are not able to provide separate estimates according to HPV status, since this information is not usually collected by cancer registries. Tumours of the larynx and hypopharynx must be managed separately from tumours originating from the oropharynx or oral cavity because they can benefit from treatment strategies that are aimed to preserve organ function, such as the combined chemoradiation approach, reserving surgery for salvage treatment. Oral cavity primaries are usually approached surgically, simultaneously implementing sophisticated reconstructive procedures, as they are more easily accessible to clinical evaluation and manual manipulation and are less susceptible to ionising irradiation compared to e.g. oropharyngeal or supraglottic tumours. In this context, epidemiological data reflecting clinically relevant tumour grouping are essential.

The RARECARE grouping is different from commonly used classifications, which are mainly based on topography. Regarding morphology, the rare H&N cancers presented here do not include non-epithelial histotypes, such as melanomas (<10% of all H&N cancers). The results presented in this paper should be compared carefully to previously published figures. For example, within GLOBOCAN[14] the included topography codes for mouth were C01–C08, while we included C00.0–C00.9 C02.0–C02.3, C02.9, C03.0–C05.0, C06.0–C06.9, excluding the base of tongue, parotid gland and salivary glands. Nasopharynx was the only singular entity included in GLOBOCAN, and therefore comparable with regard to topography. However, GLOBOCAN estimates are currently only available for 2008, while the rates presented here cover 1995–2002.

For rare H&N tumours, the specific localisation of the origin of cancer may be difficult to define. To assess the extent of registration bias, cancer registries participating in the RARECARE reviewed the original data (mainly pathology reports) of two localisations across the oral cavity and oropharynx (C02.8 'overlapping lesion of tongue' and C05.9 'Palate NOS') and the generic morphology tumour codes (8000, 8001, 8010, 8011) of oral cavity tumours.[15] Briefly, the great majority of registrations did not change, suggesting that this is mainly a problem of reaching a precise diagnosis, not registration bias.

For all of the investigated entities, incidence was the highest in patients 65 years of age and older. For the oropharynx and nasopharynx, incidence rates were relatively high for those 25–64 years of age as well, which may be related to viral exposure. HPV[6] and EBV,[5] respectively, are well-known risk factors for these tumours. This is supported by the observation that HPV-related cancer appears to be



n.a. Rates could not be calculated.

Fig. 1 – One- and five-year relative survival rates by rare H&N epithelial cancer for cancers diagnosed in 2000–2002.

more common in younger patients.[16] Epithelial tumours of the salivary glands, even if exceptional, already occurred in those 24 years of age and younger. This finding might be explained by exposure to ionising radiation, which was found to be a cause of malignant salivary gland tumours in Japanese survivors of the atomic bomb and in patients who had been receiving irradiation to the head and neck during childhood for benign conditions e.g. to reduce the size of the tonsils and adenoids.[17,18]

There was a geographical variation in incidence for cancers of nasopharynx, oropharynx and oral cavity and lip. Southern Europe experienced the highest incidence rate for cancer of nasopharynx. Eastern Europe presented with the highest incidence rates for cancer of the oral cavities and lip and oropharynx. The rates for cancer of the oral cavities and lip and the oropharynx were lower in the UK and Ireland and Northern Europe. Geographical differences in incidence, as well as differences between men and women, may be explained by differences in risk factors. The highest alcohol consumption was predominantly observed in the Eastern European countries, while the lowest levels were found in Nordic countries.[19] For smoking, the highest prevalence rates in European men were found in the Eastern part (around 47%), and the lowest in Scandinavia and the UK (below 30%), while for Western European countries the prevalence rate was around 34%.[20] For women, smoking prevalence

Table 6 – One- and five-year relative survival rates by sex, age and European region for rare Head and Neck (H&N) cancers for cancers diagnosed in 2000–2002.

Rare cancers of head and neck	1-year relative survival			5-year relative survival		
	N	%	SE	*N*	%	SE
Epithelial tumour of nasal cavity and sinuses	1023	74.60	1.47	1115	49.41	1.83
Sex						
Male	658	75.69	1.82	726	49.37	2.29
Female	365	72.68	2.48	411	49.48	3.04
Age category						
Agecat 0-24	1	0.00	0.00	0	!	!
Agecat 25-64	438	81.31	1.92	492	52.49	2.46
Agecat 65+	584	69.45	2.10	653	46.35	2.63
European region						
Northern Europe	181	76.14	3.40	184	55.41	4.53
Central Europe	245	78.25	2.93	297	52.27	3.74
Eastern Europe	93	64.23	5.17	93	30.67	5.19
Southern Europe	194	77.93	3.21	256	48.84	3.91
United Kingdom (UK) and Ireland	310	71.94	2.73	323	50.62	3.50
Epithelial tumour of nasopharynx	933	77.97	1.42	1057	49.73	1.76
Sex						
Male	658	77.43	1.70	784	47.61	2.06
Female	275	79.27	2.55	283	55.11	3.35
Age category						
Agecat 0-24	46	95.63	3.06	53	85.78	5.06
Agecat 25-64	599	84.55	1.51	648	53.89	2.08
Agecat 65+	288	60.83	3.06	362	32.61	3.09
European region						
Northern Europe	136	78.59	3.66	151	58.84	4.70
Central Europe	202	84.59	2.72	236	55.80	3.96
Eastern Europe	111	72.42	4.37	132	43.49	4.95
Southern Europe	262	80.64	2.55	313	46.88	3.18
UK and Ireland	222	71.51	3.14	256	45.72	3.61
Epithelial tumour of sal glands and sal gland type	3152	83.96	0.73	3499	65.41	1.04
Sex						
Male	1740	81.24	1.03	1951	59.14	1.43
Female	1412	87.29	1.00	1548	72.86	1.49
Age category						
Agecat 0-24	74	100.04	0.00	87	99.05	1.17
Agecat 25-64	1453	89.60	0.83	1621	71.77	1.23
Agecat 65+	1625	77.89	1.18	1793	55.66	1.67
European region						
Northern Europe	592	88.13	1.49	629	73.49	2.35
Central Europe	753	84.29	1.49	936	65.80	2.04
Eastern Europe	314	70.18	2.76	314	43.00	3.39
Southern Europe	567	84.02	1.69	720	66.87	2.33
UK and Ireland	926	85.65	1.32	967	65.84	2.03
Epithelial tumour of oropharynx	6899	70.68	0.57	7171	39.91	0.66
Sex						
Male	5307	69.05	0.67	5586	37.67	0.73
Female	1592	76.06	1.12	1592	47.67	1.44
Age category						
agecat 0-24	6	83.41	15.23	6	55.85	24.98
Agecat 25-64	4689	74.12	0.66	4847	42.56	0.77
Agecat 65+	2204	63.09	1.10	2372	33.33	1.20
European region						
Northern Europe	828	78.78	1.48	828	52.84	2.05
Central Europe	2109	75.48	1.01	2362	42.97	1.20
Eastern Europe	1005	53.61	1.61	1017	20.06	1.34
Southern Europe	1129	71.52	1.39	1458	36.49	1.45
UK and Ireland	1828	70.76	1.11	1828	45.97	1.41
Epithelial tumour of oral cavity and lip	11,148	80.53	0.41	12,331	57.84	0.56
Sex						
Male	7500	79.73	0.51	8480	56.03	0.67
Female	3648	82.18	0.71	3851	61.89	1.02

(continued on next page)

Table 6 – (continued)

Rare cancers of head and neck	1-year relative survival			5-year relative survival		
	N	%	SE	N	%	SE
Age category						
Agecat 0-24	24	83.28	7.66	24	68.49	10.11
Agecat 25-64	5307	81.49	0.55	5935	56.36	0.70
Agecat 65+	5817	79.60	0.61	6377	59.69	0.89
European region						
Northern Europe	1826	82.70	1.00	1870	64.35	1.47
Central Europe	2746	81.04	0.83	3348	58.02	1.08
Eastern Europe	1241	69.55	1.38	1354	41.27	1.57
Southern Europe	1988	81.96	0.94	2768	58.38	1.21
UK and Ireland	3347	82.22	0.74	3347	60.83	1.11
Epithelial tumour of eye and adnexa	70	94.22	0.04	83	84.69	0.07
Sex						
Male	43	90.51	0.06	53	78.76	0.09
Female	27	99.86	0.04	36	93.35	0.10
Age category						
Agecat 0-24	0	!	!	0	!	!
Agecat 25-64	24	96.45	0.04	32	90.09	0.07
Agecat 65+	46	92.91	0.05	51	81.71	0.10
European region						
Northern Europe	14	104.9	0.00	14	89.51	0.25
Central Europe	14	95.26	0.08	20	75.86	0.15
Eastern Europe	7	75.63	0.18	9	62.41	0.30
Southern Europe	15	92.79	0.09	27	81.01	0.13
UK and Ireland	20	93.64	0.07	26	92.43	0.12
Epithelial tumour of middle ear	64	71.04	6.06	89	43.03	6.59
Sex						
Male	36	77.94	7.62	51	44.50	9.35
Female	28	62.51	9.50	41	41.71	9.29
Age category						
Agecat 0-24	0	!	!	0	!	!
Agecat 25-64	25	80.52	8.05	38	52.30	9.46
Agecat 65+	39	64.61	8.34	54	35.48	8.58
European region						
Northern Europe	4	102.40	0.00	0	!	!
Central Europe	17	78.90	11.09	27	74.20	13.66
Eastern Europe	7	72.42	17.31	10	17.56	15.18
Southern Europe	4	54.49	27.24	8	41.79	26.97
UK and Ireland	32	64.71	8.86	40	34.23	8.91

! = not enough cases to produce statistic; SE = standard error of the survival estimate; SAL = salivary.

equals approximately 25% in Western countries and approximately 20% in Eastern countries.[20]

Whether these differences in smoking habits may additionally explain survival differences are unclear. Heavy tobacco smoking[21,22] and heavy alcohol drinking[21] appeared to worsen the prognosis for larynx cancer patients, but also no difference in prognosis for oral tongue squamous cell carcinoma by smoking and alcohol drinking was observed.[23] If alcohol drinking and smoking are prognostic factors, this may explain the difference in survival rates between men and women and between countries. The mostly higher relative survival rates that were observed for women are in accordance with existing literature[24] and might additionally be explained by the detection of cancer at an earlier stage, since women are more involved in health and consult physicians sooner than men,[25] or possibly by hormonal differences, which was suggested by Micheli et al.[24]

Another explanation for the lower survival rates in Eastern Europe may be related to social economic status (as indicated by a lower gross domestic product[26] and lower proportion of persons with tertiary education),[27] since it has been shown that patients living in poorer districts have lower relative survival rates than patients living in wealthier districts in England and Wales.[28] Geographic comparisons of these survival data have to be considered carefully, since our data were not age standardised due to the low number of cases. However, the conclusions will not change since Eastern European populations are generally younger.[29]

The European definition of rare diseases 'Rare diseases, including those of genetic origin, are life-threatening or

chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. As a guide, low prevalence is taken as prevalence of less than 5 per 10,000 in the Community'[30] is different from our definition of rare cancers 'cancer with an incidence rate less than 6 per 100,000'. However, this difference does not affect any of the cancer entities described in this paper, since these are considered rare according to both definitions. Therefore, the diagnosis and treatment for all cancer entities described in this paper should be centralised.

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Conflict of interest statement

None declared.

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REFERENCES

1. IARC. *Tobacco smoke and involuntary smoking*. Lyon, France: IARC Press; 2004. p. 357–62.
2. Lubin JH, Purdue M, Kelsey K, et al. Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2009;**170**:937–47.
3. Rehm J, Baliunas D, Borges GL, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction* 2010;**105**:817–43.
4. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:541–50.

5. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1765–77.
6. Mork J, Lie AK, Glattre E, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2001;**344**:1125–31.
7. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. *Acta Oncol* 2009;**48**:646–790.
8. Guzzo M, Locati LD, Prott FJ, et al. Major and minor salivary gland tumors. *Crit Rev Oncol Hematol* 2010;**74**:134–48.
9. Saornil MA, Becerra E, Mendez MC, et al. Conjunctival tumors. *Arch Soc Esp Oftalmol* 2009;**84**:7–22.
10. Rarecare Working Group. Rationale & questions for consensus. www rarecare eu 2008 December 24 [cited 25th Mar 2011. Available from: <http://www.rarecare.eu/rarecancers/rarecancers.asp>.
11. Capocaccia R, Colonna M, Corazziari I, et al. Measuring cancer prevalence in Europe: the EUROPREVAL project. *Ann Oncol* 2002;**13**:831–9.
12. Capocaccia R, De AR. Estimating the completeness of prevalence based on cancer registry data. *Stat Med* 1997;**16**:425–40.
13. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* 1996;**78**:2004–10.
14. Ferlay J, Shin HR, Bray F, Forman D, Mathers CPD. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide. IARC Cancer Base No. 10 [internet] Lyon, France: International Agency for Research on Cancer 2010 [cited 2010 Jun 22]; Available from: <http://globocan.iarc.fr>.
15. Martinez C, Gatta G, Trama A, Capocaccia R, Sanchez-Perez MJ, Melchor JM. D 15 – Report with quality considerations on the available data on rare cancers. www rarecare eu 2010 [cited 2011 Mar 25]; Available from: <http://www.rarecare.eu/rarecancers/dataquality.asp>.
16. Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. *J Clin Oncol* 2006;**24**:2606–11.
17. Ron E, Saftlas AF. Head and neck radiation carcinogenesis: epidemiologic evidence. *Otolaryngol Head Neck Surg* 1996;**115**:403–8.
18. Schneider AB, Lubin J, Ron E, et al. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose–response relationships. *Radiat Res* 1998;**149**:625–30.
19. Popova S, Rehm J, Patra J, et al. Comparing alcohol consumption in central and Eastern Europe to other European countries. *Alcohol Alcohol* 2007;**42**:465–73.
20. World Health Organization Regional Office for Europe. The European report on tobacco control policy. Review of implementation of the third action plan for a tobacco-free Europe 1997–2001. Copenhagen; 2002. p. 5–12.
21. Dikshit RP, Boffetta P, Bouchardy C, et al. Lifestyle habits as prognostic factors in survival of laryngeal and hypopharyngeal cancer: a multicentric European study. *Int J Cancer* 2005;**117**:992–5.
22. Crosignani P, Russo A, Tagliabue G, et al. Tobacco and diet as determinants of survival in male laryngeal cancer patients. *Int J Cancer* 1996;**65**:308–13.
23. Bachar G, Hod R, Goldstein DP, et al. Outcome of oral tongue squamous cell carcinoma in patients with and without known risk factors. *Oral Oncol* 2011;**47**:45–50.
24. Micheli A, Ciampichini R, Oberaigner W, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. *Eur J Cancer* 2009;**45**:1017–27.
25. Verbrugge LM. Sex differentials in health. *Public Health Rep* 1982;**97**:417–37.
26. Eurostat. GDP per capita in PPS (2005). EUROSTAT 2010 March 18 [cited 2011 Mar 29]; Available from: <http://epp.eurostat.ec.europa.eu/tgm/graph.do?tab=graph&plugin=1&pcode=tsieb010&language=en&toolbox=sort>.
27. Eurostat. Persons with tertiary education attainment by age and sex (%) (2005). Eurostat, the statistical office of the European Union 11 A.D. January 20 [cited 2011 Mar 29]; Available from: <http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do?dvsc=5>.
28. Coleman MP, Babb P, Sloggett A, et al. Socioeconomic inequalities in cancer survival in England and Wales. *Cancer* 2001;**91**:208–16.
29. Eurostat. Proportion of population aged 65 and over (2005). Eurostat, the statistical office of the European Union 2010 January 13 [cited 2011 Mar 23]; Available from: <http://epp.eurostat.ec.europa.eu/tgm/graph.do?tab=graph&plugin=1&pcode=tps00028&language=en&toolbox=data>.
30. Useful information on rare diseases from an EU perspective. European Commission Health & consumer protection directorate-general Directorate C – Public Health and Risk Assessment 2011 [cited 2011 Feb 16]; Available from: <http://ec.europa.eu/health/ph_information/documents/ev20040705_rd05_en.pdf>.
31. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, editors. International Classification of Diseases for Oncology. 3rd ed. Geneva: World Health Organization; 2000. p.45–65,69–104.