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Epidemiology of rare cancers and inequalities in oncologic outcomes

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ABSTRACT

Rare cancers epidemiology is better known compared to the other rare diseases. Thanks to the long history of the European population-based cancer registries and to the EUROCARE huge database, the burden of rare cancers has been estimated the European (EU28) population. A considerable fraction of all cancers is represented by rare cancers (24%). They are a heterogeneous group of diseases, but they share similar problems: uncertainty of diagnosis, lack of therapies, poor research opportunities, difficulties in clinical trials, lack of expertise and of centres of reference. This paper analyses the major epidemiological indicators of frequency (incidence and prevalence) and outcome (5-year survival) of all rare cancers combined and of selected rare cancers that will be in depth treated in this monographic issue. Source of the results is the RARECARENet search tool, a database publicly available. Disparities both in incidence and survival, and consequently in prevalence of rare cancers were reported across European countries. Major differences were shown in outcome: 5-year relative survival for all rare cancers together, adjusted by age and case-mix, varied from 55% or more (Italy, Germany, Belgium and Iceland) and less than 40% (Bulgaria, Lithuania and Slovakia). Similarly, for all the analyzed rare cancers, a large survival gap was observed between the Eastern and the Nordic and Central European regions. Dramatic geographical variations were assessed for curable cancers like testicular and non epithelial ovarian cancers. Geographical difference in the annual age-adjusted incidence rates for all rare cancers together varied between >140 per 100,000 (Italy, Scotland, France, Germany, and Switzerland) and <100 (Finland, Portugal, Malta, and Poland). Prevalence, the major indicator of public health resources needs, was about 7–8 times larger than incidence. Most of rare cancers require complex surgical treatment, thus a multidisciplinary approach is essential and treatment should be provided in centres of expertise and/or in networks including expert centres. Networking is the most appropriate answer to the issues pertaining to rare cancers. Actually, in Europe, an opportunity to improve outcome and reduce disparities is provided by the creation of the European Reference Networks for rare diseases (ERNs). The Joint Action of rare cancers (JARC) is a major European initiative aimed to support the mission of the ERNs. The role of population based cancer registries still remains crucial to describe rare cancers management and outcome in the real word and to evaluate progresses made at the country and at the European level.

Introduction

In Europe, about 1 out of 4 new cancer patients has a diagnosis of rare cancer. For these patients 5-year survival is 49% and no major improvements in outcome were observed until the beginning of 2000's [1]. Rare cancers include a heterogeneous group of tumours difficult to treat because of the difficulties in performing clinical trials which lead to limited evidence to develop clinical guidelines and therefore to treat patients in a standardised and evidence-based way. In addition, because of the rarity of these tumours, it is difficult for professionals to develop the expertise to treat them especially in small size countries. The timely and correct diagnosis is not always easy to reach and treatment, even if most of rare cancers are surgically treated [2], may be complex. Thus, a multidisciplinary approach is essential as well as the treatment of these cancers in centres of expertise and/or in networks including expert centres. It is well known that survival for common cancers is better in young than in old patients, in females than in males, and that survival disparities exists across European countries [3]. One

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might expect the same for rare cancers. An analysis of the burden of rare cancers in Europe was provided by the RARECARE and RARECAREnet projects [1,4]. A country-based analysis of the burden of rare cancers including survival differences across EU countries is needed to suggest the best health care organisation for rare cancers. The point is crucial, because an effective organisation of the health care system could avoid unnecessary inequalities in quality of care and survival.

This paper has 2 main aims:

1) to analyse possible variations and inequalities in incidence, survival and prevalence across European countries for all rare cancers combined and,
2) to analyse the rare cancers addressed in this monographic issue to report on their incidence, survival and possible differences by age, sex and geographic regions.

The rare cancers addressed are: the epithelial tumours of head and neck (H&N), the gastroenteropancreatic (GEP) neuroendocrine tumours, the urogenital and ovarian rare cancers, soft tissue sarcomas, malignant thymoma and mesothelioma. They are relevant for different specific issues: availability of new treatments, complex treatment management, multidisciplinary approach, low outcome because none therapeutic novelties in use.

Material and methods

All the data presented in this paper come from the online analysis tool [5] developed by the 'Information Network of Rare Cancers - RARECAREnet' project. This database contains aggregated data and is publicly available. Data source and methods are described in detail in the RARECAREnet web site. Briefly, the RARECAREnet database is a subset of EUROCARE-5, the wider collaborative study on cancer patients' survival in Europe (www.eurocare.it). Ninety-four European population-based cancer registries (CRs) adhered to the RARECAREnet project. They provided information on cancer patients diagnosed up to 2007 and followed-up for vital status ascertainment to the end of 2008 or later. Data on incidence, survival and prevalence were produced for 198 rare cancers. They were defined combining topography and morphology codes of the International Classification of Diseases for Oncology, 3rd edition (ICD-*O*-3) [6]. Rare entities are grouped according to clinical management and research point of views. In this monograph we consider 41 rare cancers grouped into 7 families:

- 8 epithelial cancers of the H&N (epithelial tumours of nasal cavity and sinuses, nasopharynx and, oropharynx, tumours of major salivary glands and salivary gland type tumours, squamous cell carcinoma of hypopharynx, larynx and, oral cavity;
- 2 tumours of the thoracic tract (epithelial tumours of thymus and mesothelioma of pleura and pericardium),
- 4 ovarian cancers (rare adenocarcinomas and non epithelial tumours),
- 2 male genital tumours (epithelial tumour of penis, testicular and paratesticular tumours)
- 18 soft tissue sarcomas (STS) (head and neck, limbs, superficial trunk, mediastinum, hearth, breast, uterus, genitourinary tract, viscera, paratestis, retroperitoneum and peritoneum, pelvis, skin, periorbit, brain, embryonal rhabdomiosarcoma, alveolar rhabdomiosarcoma and Ewin's sarcoma),
- 4 GEP neuroendocrine tumours (well differentiated not functioning endocrine carcinoma, well differentiated functioning

Table 1
Crude incidence rate with 95% confidence intervals (95%CI), estimated number of new diagnoses per year and prevalence (estimated number) for all rare cancers, by European countries.

All rare cancers			
Country	*incidence*		*prevalence*
	crude rate (95%CI)	No. of expected new cases 2013	No. of expected prevalent cases at 2008
Austria	102.280 (101.505–103.059)	10,576	84,302
Belgium	132.780 (131.754–133.812)	13,696	108,654
Bulgaria	84.363 (83.645–85.085)	9496	79,676
Croatia	95.545 (94.530–96.568)	5394	44,542
Czech Republic	110.483 (109.764–111.205)	12,708	101,917
Estonia	115.560 (113.544–117.603)	1608	13,469
Finland	88.876 (87.974–89.784)	6941	54,642
France	125.333 (124.224–126.450)	80,009	635,085
Germany	130.240 (129.645–130.837)	112,617	899,961
Iceland	104.677 (100.579–108.900)	327	2635
Ireland	91.026 (89.991–92.070)	4564	35,652
Italy	142.048 (141.370–142.728)	81,617	648,661
Latvia	83.440 (82.128–84.768)	2523	22,056
Lithuania	97.684 (96.441–98.938)	3664	31,713
Malta	86.090 (82.897–89.375)	509	3949
Norway	113.766 (112.678–114.863)	5746	45,097
Poland	76.161 (75.305–77.025)	43,773	351,229
Portugal	87.983 (87.173–88.799)	13,604	108,447
Slovakia	109.182 (108.130–110.243)	5855	47,492
Slovenia	122.627 (120.916–124.356)	2567	20,337
Spain	118.766 (117.602–119.938)	57,601	453,534
Switzerland	134.887 (133.185–136.606)	9896	77,205
The Netherlands	122.006 (121.406–122.609)	20,349	159,546
United Kingdom	117.162 (116.856–117.469)	76,601	601,597
UK England	116.163 (115.830–116.497)	64,063	503,160
UK Northern Ireland	88.079 (86.515–89.664)	2024	16,113
UK Scotland	134.286 (133.162–135.417)	6577	51,738
UK Wales	121.553 (120.149–122.970)	3937	30,586
EU28	114.47 (114.31–114.64)	636,753	5,085,137

Data from www.rarecarenet.eu.

endocrine carcinoma, poorly differentiated endocrine carcinoma, mixed endocrine-exocrine carcinoma).

Rare cancers are those with an incidence rate <6 per 100,000 per year in the European population [4], thus all the selected cancer have an incidence rate <6. This paper also presents incidence, prevalence and survival for all rare cancer together, which have an interest for the public health point of view. Rational and list of all rare cancers are at http://www.rarecarenet.eu/rarecarenet/index.php/cancerlist.

Data are presented according to age, sex, country and 5 European regions: Northern Europe (Finland, Iceland, Norway); United Kingdom and Ireland (England, Northern Ireland, Republic of Ireland, Scotland, Wales); Central Europe (Austria, Belgium, France, Germany, Switzerland, the Netherlands); Eastern Europe (Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Poland, Slovakia) and Southern Europe (Croatia, Italy, Malta, Portugal, Slovenia, Spain).

Countries were covered by 94 CRs: 19 countries were covered by national CRs (Austria, Bulgaria, Czech Republic, Croatia, Estonia, England, Finland, Iceland, Northern Ireland, Latvia, Lithuania, Malta, Norway, Republic of Ireland, Slovakia, Slovenia, Scotland, the Netherlands, Wales); 8 countries were covered by regional CRs partially representing the population of their country (Belgium, France, Germany, Switzerland, Italy, Portugal, Poland, Spain).

The mean European population covered, over the period 2000–2007, was about 207,942,000, corresponding to 48% of the population of countries participating in RARECAREnet and 46% of the European Union population (excluding Norway, Switzerland, and Iceland, which are not EU members).

We analyzed incidence and survival for rare cancers for the period 2000–2007. Crude and age-adjusted incidence rates were calculated from 83 CRs data, excluding 11 CRs collecting data only for specific cancer sites. The estimated numbers of new diagnoses in 2013 was calculated applying 2000–2007 incidence rates to the 2013 population. Relative survival estimates were obtained by the cohort approach considering patients diagnosed with a rare cancer in the period 2000–2007 and followed-up to 31st December 2008. Since all patients were included (not only those followed up for 5 years) this method is also called 'complete' cohort analysis. All the 94 CRs contributed data to survival analysis. More details of the calculation of incidence and survival are reported in the RARECAREnet website (http://app.rarecarenet.eu/index.php).

For the category of all rare cancers together the distribution of patients by age and rare cancers type may differ by country. Adjusted country-specific 5-year survival was then estimated by a multivariable survival model including country, age class and cancer entity as covariates.

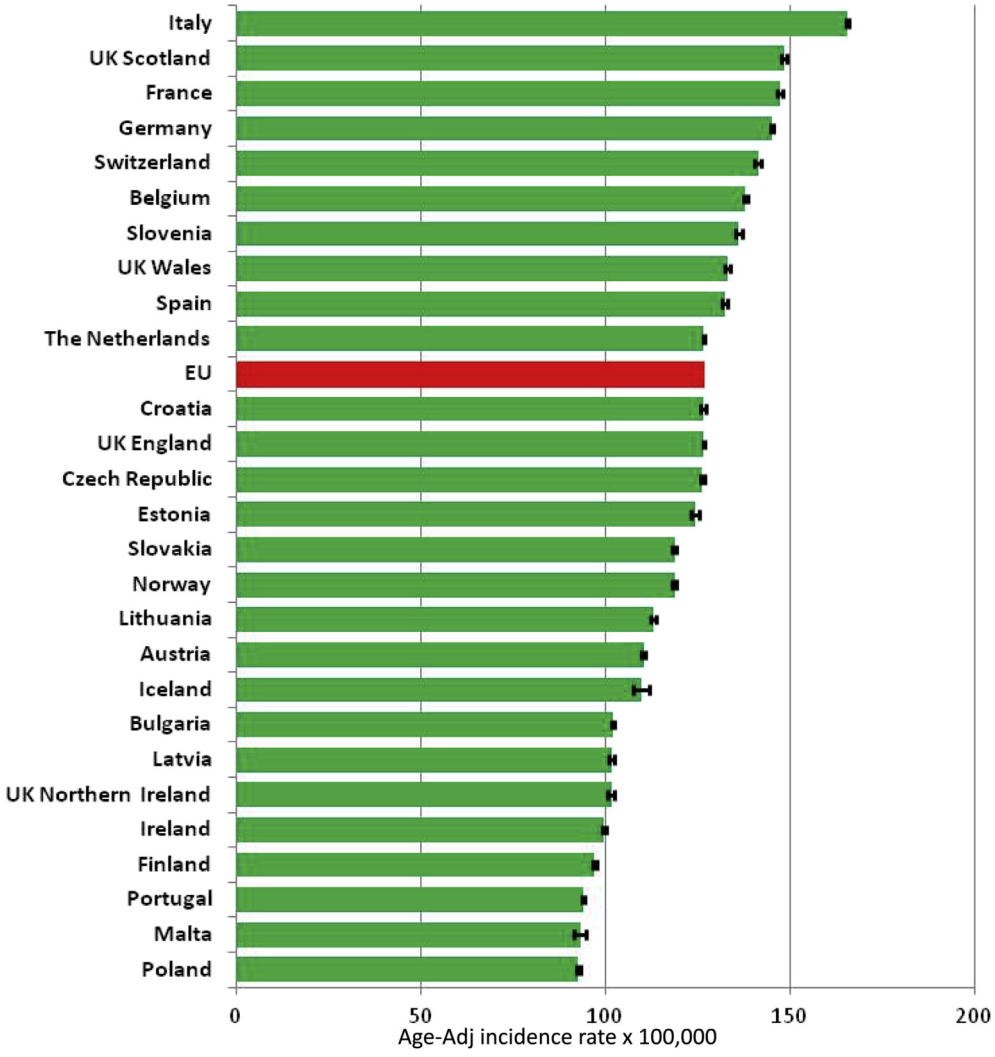

Fig. 1. Age-adjusted annual incidence rate (per 100,000) for all rare cancers by European country and Europe (EU). Error bars are 95% Confidence Intervals.

Results

All rare cancers together

Table 1 shows for all rare cancers combined, the crude incidence rate, the expected number of new cases/year and the number of prevalent cases, by country. According to the population size of a country, the estimated new diagnoses per year ranged from 500 or less (Malta and Iceland) to more than 80,000 (France, Italy and Germany). The annual incidence rates (per 100.000 people) depend on the prevalence of risk factors across European countries. Among risk factors, age is the most important, therefore country variation are better compared when rates are age-adjusted (Fig. 1). The age-adjusted rates varied from less than 90 (Bulgaria, Malta, Finland, Northern Ireland) to more than 130 (Germany, Belgium, Switzerland, Scotland). For incidence, all adjusted rates were higher than the crude rates (Table 1), especially in countries with young population. However, rare cancers incidence ranking of countries did not change after age adjustment. The estimated number of prevalent cases were about 8 times higher than the number of new cases per year (Table 1). Prevalent cases were more than 500,000 in Germany, France, Italy and England and less than 4000 in Iceland and Malta. Five-year survival adjusted by age and case mix, for all rare cancer together, showed figures <40% in Bulgaria, Lithuania and Slovakia and >50% in the Northern countries, Germany, Switzerland, Italy, Belgium, Austria, France and, Spain (Fig. 2).

Incidence of selected rare cancers

The majority of the rare cancers studied had an annual incidence rates lower than 1 per 100,000 people, with an estimated annual number of cases in EU28 up to about 5500 (epithelial tumour of major salivary glands) (Table 2). Less rare tumours, with incidence rate >3, had an estimated number of new diagnoses ranging between 16,000 and 26,000 in EU28 (epithelial tumours of larynx, epithelial tumours of oropharynx and, testicular cancers).

Survival of selected rare cancers

Five-year relative survival was very good (>80%) for testicular cancers, STS of paratestis and skin, and non-epithelial tumours of ovary (Table 3). They accounted for only 12% of the all rare cancers here considered. The majority of these had a 5-year survival lower than 50%. Very poor outcome (≤25%) characterised several rare cancers like the epithelial tumour of hypopharynx, STS of

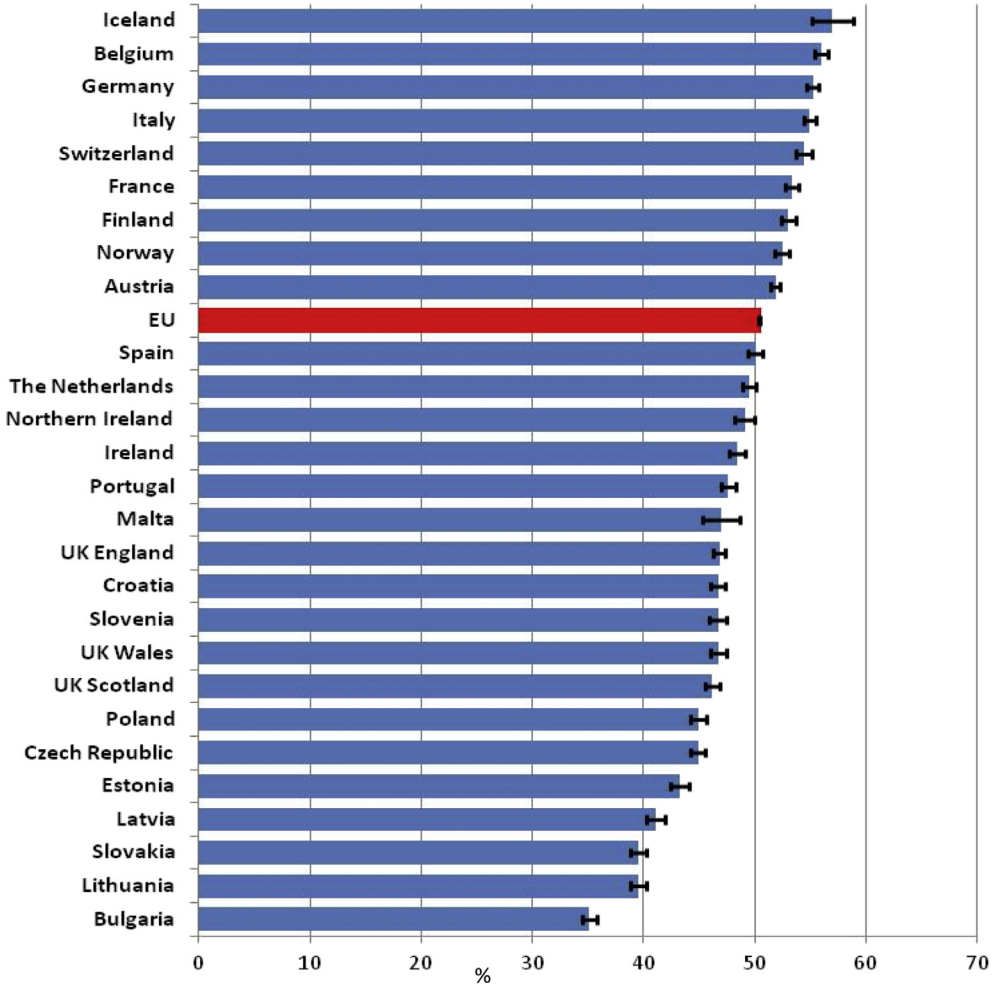

Fig. 2. Five-year relative survival (%) for all rare cancers by European country and in Europe (EU). Error bars are 95% Confidence Intervals.

Table 2
No. of observed cases (obs.), crude rate with (95% CI) and number of estimated new cases EU28 in 2013 (est.) by selected rare cancers.

Family	*Rare cancer entity*	*obs.*	*crude rate*	*est.*
head and neck rare cancers	Epithelial tumours of nasal cavity and sinuses	7046	0.450 (0.439–0.460)	2564
	Epithelial tumours of nasopharynx	7439	0.475 (0.464–0.486)	2580
	Epithelial tumours of major salivary glands	15,053	0.961 (0.946–0.976)	5454
	Salivary gland type tumours of head and neck	6741	0.430 (0.420–0.441)	2384
	Squamous cell carcinoma of hypopharynx	19,828	1.266 (1.248–1.283)	7074
	Squamous cell carcinoma of larynx	72,210	4.609 (4.576–4.643)	26,153
	Epithelial tumours of oropharynx	52,016	3.320 (3.292–3.349)	18,437
	Squamous cell carcinoma of oral cavity	54,930	3.506 (3.477–3.536)	19,670
rare thoracic cancers	Epithelial tumours of thymus	2795	0.178 (0.172–0.185)	975
	Mesothelioma of pleura and pericardium	28,676	1.830 (1.809–1.852)	10,703
rare epithelial and not epithelial ovarian cancers	Mucinous adenocarcinoma of ovary	12,066	0.770 (0.757–0.784)	4144
	Clear cell adenocarcinoma of ovary	4753	0.303 (0.295–0.312)	1648
	Mullerian mixed tumour of ovary	2255	0.144 (0.138–0.150)	798
	Non epithelial tumours of ovary	3977	0.254 (0.246–0.262)	1288
rare male genital cancers	Testicular and paratesticular cancers	51,605	3.294 (3.266–3.323)	16,061
	Epithelial tumours of penis	10,368	0.662 (0.649–0.675)	3887
soft tissue sarcomas	Soft tissue sarcoma	73,795	4.711 (4.677–4.745)	25,851
	Soft tissue sarcoma of head and neck	4087	0.261 (0.253–0.269)	1488
	Soft tissue sarcoma of limbs	17,177	1.096 (1.080–1.113)	6047
	Soft tissue sarcoma of superficial trunk	7813	0.499 (0.488–0.510)	2763
	Soft tissue sarcoma of mediastinum	465	0.030 (0.027–0.033)	160
	Soft tissue sarcoma of heart	216	0.014 (0.012–0.016)	72
	Soft tissue sarcoma of breast	2865	0.183 (0.176–0.190)	987
	Soft tissue sarcoma of uterus	8657	0.553 (0.541–0.564)	2984
	Other soft tissue sarcomas of genitourinary tract	3160	0.202 (0.195–0.209)	1114
	Soft tissue sarcoma of viscera	6004	0.383 (0.374–0.393)	2145
	Soft tissue sarcoma of paratestis	510	0.033 (0.030–0.036)	185
	Soft tissue sarcoma of retroperitoneum and peritoneum	4911	0.313 (0.305–0.322)	1740
	Soft tissue sarcoma of pelvis	3090	0.197 (0.190–0.204)	1088
	Soft tissue sarcoma of skin	4737	0.302 (0.294–0.311)	1642
	Soft tissue sarcoma of paraorbit	117	0.007 (0.006–0.009)	40
	Soft tissue sarcoma of brain and other parts of nervous system	2723	0.174 (0.167–0.180)	921
	Embryonal rhabdomyosarcoma of soft tissue	836	0.053 (0.050–0.057)	257
	Alveolar rhabdomyosarcoma of soft tissue	519	0.033 (0.030–0.036)	160
	Ewin's sarcoma of soft tissue	998	0.064 (0.060–0.068)	315
gastroenteropancreatic (GEP) neuroendocrine tumours	GEP - well differentiated not functing endocrine carcinoma	15,852	1.012 (0.996–1.028)	5599
	GEP - well differentiated functing endocrine carcinoma	411	0.026 (0.024–0.029)	142
	GEP - poorly differentiated endocrine carcinoma	10,421	0.665 (0.652–0.678)	3742
	GEP - mixed endocrine-exocrine carcinoma	147	0.009 (0.008–0.011)	51

Data from www.rarecarenet.eu.

mediastinum and hearth, undifferentiated carcinoma of thymus, and thoracic mesothelioma.

Survival by age. Five-year survival reduced with increasing age (Table 4). The decrease was marked for patients with epithelial tumours of nasopharynx, testicular cancers, visceral STS and embrional rhabdomiosarcoma of soft tissue.

Survival by sex. For the majority of epithelial rare cancers, outcome was better in women than men (Table 5), with the exception of epithelial tumours of renal pelvis and ureter and rare epithelial tumours of bladder. For STS, outcome was similar between sexes. However, women experienced a worse survival than men for STS of head and neck, breast and heart.

Geographical variation of survival. With some exception, and similarly to what shown in Figure 2, 5-years survival figures for the considered rare tumours were lower in the East Europe and highest in North and Central Europe (Table 6). Dramatic variation was observed for testicular cancer, a highly curable tumour, in which all region presented 5-year survival higher than 95% whereas in the Eastern region survival was 88%. Similar variability emerged for non-epithelial tumour of ovary with a wide 5-year survival range between 86% (UK and Ireland) and 77% (East Europe).

Discussion

With this analysis, based on about 2 million rare cancer patients from 27 European countries, we outlined large disparities in the frequency of and outcome for rare cancers. Age-adjusted incidence rates (per 100,000 people) of all rare cancers combined ranged from less than 100 (Iceland, Finland, Poland, Malta, Portugal) to more than 150 in Italy. The latter high figure is due to a high incidence of thyroid, larynx and liver cancers [7], with an incidence in Italy higher than the conventional threshold of 6 × 100,000 [4]. Different prevalence in the exposure to risk factors, mainly explains geographical incidence variation. However, differences in pathological diagnosis skill (neuroendocrine tumours), or in overdiagnosis (thyroid) cannot be excluded. Finally, we should consider that part of the incidence geographical variability is likely due to problems in rare cancer registration [1,4] which in turn may depend of difficulties in reaching a correct diagnosis from the pathologists [1,8]. We have estimated that a not negligible burden of new diagnoses is due to rare cancers, an important fraction among all cancers requiring specific investment from the public health organisation. Prevalence is another important indicator of the burden of rare cancers for public health, representing how many people with a diagnosis of rare cancers are alive in the country population. Some of prevalent cases are in their major treating phase, others in treatment for their recurrences. Part of prevalent people can be considered cured and part of them are suffering for late effect of treatment. Prevalence indicates a heterogeneous population group who deserves different needs. Furthermore, prevalence is strongly influenced by incidence [9], which in turn means by prevalence of risk factors in the populations. In order to

Table 3
Number of cases (No.) and 5-year Relative Survival (RS%) with (95% CI) by selected rare cancers.

Family	Rare cancer entity	No.	5-year RS %
head and neck rare cancers	Epithelial tumours of nasal cavity and sinuses	6867	47 (46–49)
	Epithelial tumours of nasopharynx	7276	49 (48–50)
	Epithelial tumours of major salivary glands	14,703	61 (60–62)
	Salivary gland type tumours of head and neck	6683	67 (66–69)
	Squamous cell carcinomaof hypopharynx	19,878	25 (24–26)
	Squamous cell carcinoma of larynx	71,928	61 (60–61)
	Epithelial tumours of oropharynx	50,843	41 (40–41)
	Squamous cell carcinoma of oral cavity	54,229	48 (48–49)
rare thoracic cancers	Epithelial tumours of thymus	2729	64 (62–67)
	Mesothelioma of pleura and pericardium	27,893	5 (4–5)
rare epithelial and not epithelial ovarian cancers	Mucinous adenocarcinoma of ovary	12,010	60 (59–61)
	Clear cell adenocarcinoma of ovary	4761	56 (54–57)
	Mullerian mixed tumour of ovary	2242	21 (20–24)
	Non epithelial tumours of ovary	3970	82 (81–84)
rare male genital cancers	Testicular and paratesticular cancers	51,011	95 (95–95)
	Epithelial tumours of penis	10,210	68 (66–69)
soft tissue sarcomas	Soft tissue sarcoma (STS)	72,696	57 (56–57)
	STS of head and neck	4062	60 (58–62)
	STS of limbs	17,094	68 (67–69)
	STS of superficial trunk	7723	48 (47–50)
	STS of mediastinum	457	23 (19–28)
	STS of heart	203	14 (10–21)
	STS of breast	2864	75 (73–77)
	STS of uterus	8568	52 (51–53)
	Other STSs of genitourinary tract	3107	50 (48–53)
	STS of viscera	5915	42 (41–44)
	STS of paratestis	510	87 (82–92)
	STS of retroperitoneum and peritoneum	4854	39 (37–41)
	STS of pelvis	3064	47 (45–50)
	STS of skin	4728	90 (89–92)
	STS of paraorbit	115	63 (53–76)
	STS of brain and other nervous system	2695	55 (52–57)
	Embryonal rhabdomyosarcoma of soft tissue	825	66 (63–70)
	Alveolar rhabdomyosarcoma of soft tissue	515	36 (32–41)
	Ewin's sarcoma of soft tissue	992	45 (42–49)
gastroenteropancreatic (GEP) neuroendocrine tumours	GEP - well differentiated not functing endocrine carcinoma	15,656	72 (71–73)
	GEP - well differentiated functing endocrine carcinoma	407	61 (56–67)
	GEP - poorly differentiated endocrine carcinoma	10,456	35 (34–36)
	GEP - mixed endocrine-exocrine carcinoma	141	26 (18–37)

Data from www.rarecarenet.eu.

reduce rare cancers prevalence, investment in preventive public health programs have to be implemented.

Variation in survival for all rare cancers together appears relevant. Five-year adjusted survival of all cancers published by EUROCARE-5 [3], showed a similar geographical pattern of Fig. 2, for the overall rare cancers. Interestingly, the paper by Baili et al. [3] shows that adjusted survival correlated with macro-economic variables like the GDP and the TNEH. Since, in our study, survival discrepancy was only partially explained by different rare cancer incidence by country (case mix) or by different age distributions of various populations, we can speculate that investment in health care system may explain part of survival variation. Actually, five years relative survival adjusted for age distribution and case mix, is one of the most succinct indicator of cancer control performance.

International collaboration in research on and cure of rare cancers is crucial. Since most rare cancers are particularly rare [1], trial are impossible at national level and the expertise is low because of the low number of the disease in small populations. Reference centres should be strictly connected between them: patients movement between one centre to another are not so unusual in small countries or in countries without facilities for complex treatments. Strong collaboration is also relevant for experience exchanging and training as for twinning programs.

Most countries do not consider specifically rare cancers in their cancer plans. In Europe, a brilliant experience comes from the French second National Plan for Cancers, which included specific actions dedicated to the development of a network of regional centres for rare cancers patients, labelled 'reference centre for rare cancers', linked to national reference centres [10].

Survival disparities across countries were important for specific rare cancers considered by this monograph. Examples are H&N and penis cancers. For H&N and penis cancers treatments are available, even if complex, an early diagnosis is crucial. Recognising borderline lesions, especially in the high risk population, is relatively simple, and greater awareness should be diffused among GPs, health care providers and general public. Actually, low-income and disadvantaged groups are generally more exposed to avoidable risk factors such as environmental carcinogens, alcohol, tobacco use, diet and infectious agents. These groups have less access to the health services and health education programme that would empower them to make decisions to protect and improve their own health [11].

Age affects survival and about 50% of all rare cancers occurs in the elderly (65+) [5]. This was relevant for some rare cancers chosen to be described by this monograph. Actually, 50% or more cases occurred in the elderly for the epithelial tumours of nasal cavities, STS of H&N, viscera and paratestis. This point makes difficult to plan clinical trials, in which elderly are not usually included, and finally the question of disparities in accessing to proper treatment remains quite unsolved in the elderly.

Table 4
Number of cases (No.) and 5-year Relative Survival (RS%) with (95% CI) for selected rare cancers by age.

Family	Rare cancer entity	age class							
		0–14		15–24		25–64		65+	
		No.	5-year RS	No.	5-year RS	No.	5-year RS	No.	5-year RS
head and neck rare cancers	Epithelial tumours of nasal cavity and sinuses	8	100 (NE)	27	63 (45–88)	3055	53 (51–55)	3777	42 (40–45)
	Epithelial tumours of nasopharynx	69	84 (75–93)	259	73 (67–79)	4791	55 (53–56)	2157	31 (29–34)
	Epithelial tumours of major salivary glands	97	97 (94–100)	278	95 (92–98)	6703	70 (69–71)	7625	50 (49–52)
	Salivary gland type tumours of head and neck	16	94 (83–100)	101	93 (87–98)	3574	71 (70–73)	2992	60 (58–63)
	Squamous cell carcinoma of hypopharynx	1	0 (NE)	2	100 (NE)	13,136	27 (26–27)	6739	22 (21–24)
	Squamous cell carcinoma of larynx	3	(NE)	24	96 (87–100)	38,749	62 (61–62)	33,155	59 (58–60)
	Epithelial tumours of oropharynx	3	100 (NE)	37	67 (53–84)	35,409	44 (43–44)	15,411	34 (33–35)
	Squamous cell carcinoma of oral cavity	11	79 (57–100)	106	64 (55–75)	31,440	50 (49–50)	22,688	46 (45–47)
rare thoracic cancers	Epithelial tumours of thymus	5	60 (30–100)	54	65 (53–80)	1596	70 (67–73)	1074	55 (52–60)
	Mesothelioma of pleura&pericardium	1	(NE)	5	(NE)	8936	6 (6–7)	18,951	4 (3–4)
rare epithelial and not epithelial ovarian cancers	Mucinous adenocarcinoma of ovary	2	50 (13–100)	227	88 (84–93)	7114	68 (67–69)	4667	46 (44–48)
	Clear cell adenocarcinoma of ovary	0	(NE)	8	74 (49–100)	3150	58 (56–60)	1603	51 (48–54)
	Mullerian mixed tumour of ovary	0	(NE)	3	67 (30–100)	904	27 (24–31)	1335	17 (15–20)
	Non epithelial tumours of ovary	302	95 (92–98)	675	92 (89–94)	2231	84 (82–85)	762	63 (59–68)
rare male genital cancers	Testicular and paratesticular cancers	206	97 (94–100)	7406	94 (94–95)	42,103	96 (96–96)	1308	73 (69–77)
	Epithelial tumours of penis	0	(NE)	6	84 (59–100)	4400	73 (71–74)	5805	63 (61–65)
soft tissue sarcomas	Soft tissue sarcoma (STS)	2222	68 (66–71)	2631	64 (62–66)	37,226	64 (63–64)	30,625	46 (45–47)
	STS of head and neck	174	71 (65–79)	128	64 (55–74)	1553	67 (64–70)	2207	53 (50–56)
	STS of limbs	257	87 (83–92)	651	78 (74–81)	8541	74 (73–75)	7645	58 (57–60)
	STS of superficial trunk	145	59 (51–68)	234	59 (53–66)	3775	57 (55–59)	3569	37 (35–39)
	STS of mediastinum	11	63 (40–100)	20	23 (8–63)	262	27 (22–33)	164	15 (9–23)
	STS of heart	5	40 (14–100)	14	(NE)	143	15 (10–24)	41	6 (2–23)
	STS of breast	2	50 (13–100)	60	85 (76–96)	1794	81 (79–83)	1008	61 (57–66)
	STS of uterus	1	100 (NE)	38	78 (66–93)	5829	59 (58–60)	2700	36 (34–38)
	Other STSs of genitourinary tract	132	60 (52–70)	97	71 (62–81)	1447	60 (57–63)	1431	38 (34–41)
	STS of viscera	65	66 (55–79)	69	53 (42–67)	2587	45 (43–47)	3194	39 (37–41)
	STS of paratestis	5	100 (NE)	15	52 (30–91)	222	92 (87–97)	268	85 (77–94)
	STS of retroperitoneum and peritoneum	11	73 (51–100)	48	42 (28–61)	2444	46 (44–48)	2351	31 (28–33)
	STS of pelvis	63	62 (50–76)	93	53 (44–65)	1569	55 (53–58)	1339	36 (33–40)
	STS of skin	67	98 (94–100)	258	99 (97–100)	2731	96 (95–97)	1672	77 (73–81)
	STS of paraorbit	34	74 (59–92)	11	46 (22–96)	32	65 (49–88)	38	57 (37–88)
	STS of brain and other nervous system	147	49 (40–58)	209	59 (52–66)	1573	59 (56–62)	766	44 (40–49)
	Embryonal rhabdomyosarcoma of soft tissue	584	76 (72–79)	148	48 (40–58)	80	40 (29–53)	13	11 (2–75)
	Alveolar rhabdomyosarcoma of soft tissue	238	49 (43–57)	128	24 (17–34)	117	24 (17–34)	32	29 (14–61)
	Ewin's sarcoma of soft tissue	167	67 (60–76)	270	51 (45–58)	423	40 (35–45)	132	21 (14–31)
gastroenteropancreatic (GEP) neuroendocrine tumours	GEP - well differentiated not functing endocrine carcinoma	112	98 (96–100)	447	97 (95–99)	7798	81 (79–82)	7299	60 (59–62)
	GEP - well differentiated functing endocrine carcinoma	2	100 (NE)	4	100 (NE)	278	68 (61–74)	123	44 (34–57)
	GEP - poorly differentiated endocrine carcinoma	15	79 (60–100)	83	71 (61–83)	4627	45 (43–46)	5731	26 (25–28)
	GEP - mixed endocrine-exocrine carcinoma	0	(NE)	2	100 (NE)	68	25 (15–41)	71	27 (17–44)

Data from www.rarecarenet.eu.
NE: not estimable.

There is general agreement that treatment of rare cancers should be concentrated in specialised multidisciplinary centres. However, there is scarce knowledge about the extent of centralisation of rare cancers treatment at the population level. In a recent publication [1], the extent of hospital centralisation for rare cancers, at the beginning of 2000, has been described for 7 European countries and the data showed that, overall, centralisation of rare cancer treatment was generally low and varied widely between countries. Treatment of patients with epithelial tumours of the ovary, urinary tract, penis, STS, GEP neuroendocrine tumours were spread among a large number of hospitals. Slovenia and the Netherlands had, among the considered countries, the highest centralisation patterns.

To conclude, even if rare cancers account for 24% of all cancer diagnoses [1], their management do not reach optimal standards in most EU countries, and the overall survival could highly improve if all the countries could offer the best available treatments. Provision of inadequate treatments is more likely when healthcare is delivered by institutions with limited expertise, suboptimal multidisciplinary organisation of cancer care and/or low case volumes. However, since survival appears to correlate with macro-economic determinants [3], investments in the health care system may explain part of the difference in outcome and decision in the allocation of resources at national level could be facilitated with the European positive scenario. Actually, in Europe, an opportunity to reduce disparities is provided by the creation of the European Reference Networks for rare diseases (ERNs). Networking is the most appropriate answer to the issues pertaining to rare cancers. The Joint Action of rare cancers (JARC) is another major European initiative that will help the mission of the ERNs. The JARC objectives are to prioritise rare cancers in the agendas of the European Member States and to optimise the functioning of the ERNs, providing operational solutions and professional guidance in quality of care, epidemiology, research, education and state of the art definition on prevention, diagnosis and treatment of rare cancers. All of these objectives should contribute to reduce the survival gap across countries. The role of population based CRs still remain crucial to describe the real word and to evaluate progresses made at country and European level.

Table 5
Number of cases (No.) and 5-year Relative Survival (RS%) with (95% CI) for selected rare cancers, by sex.

Family	Rare cancer entity	sex			
		Male		Female	
		No.	5-year RS	No.	5-year RS
head and neck rare cancers	Epithelial tumours of nasal cavity and sinuses	4430	46 (44–48)	2437	50 (48–53)
	Epithelial tumours of nasopharynx	5205	47 (45–49)	2071	54 (51–56)
	Epithelial tumours of major salivary glands	8249	54 (52–55)	6454	70 (68–71)
	Salivary gland type tumours of head and neck	3701	58 (56–61)	2982	78 (76–80)
	Squamous cell carcinoma of hypopharynx	17,272	25 (24–25)	2606	29 (27–31)
	Squamous cell carcinoma of larynx	63,906	60 (60–61)	8022	62 (60–63)
	Epithelial tumours of oropharynx	40,212	38 (38–39)	10,631	51 (50–52)
	Squamous cell carcinoma of oral cavity	36,623	44 (44–45)	17,606	56 (55–57)
rare thoracic cancers	Epithelial tumours of thymus	1482	62 (59–65)	1247	67 (64–71)
	Mesothelioma of pleura and pericardium	22,915	4 (4–5)	4978	6 (5–7)
soft tissue sarcomas	Soft tissue sarcoma (STS)	32,964	57 (56–57)	39,732	57 (56–57)
	STS of head and neck	2659	62 (60–65)	1403	55 (52–58)
	STS of limbs	9029	67 (66–69)	8065	68 (67–69)
	STS of superficial trunk	4236	48 (47–50)	3487	48 (46–50)
	STS of mediastinum	285	21 (16–27)	172	27 (21–36)
	STS of heart	105	17 (11–26)	98	12 (7–23)
	STS of breast	35	79 (61–100)	2829	75 (73–77)
	STS of uterus	–	-	8568	52 (51–53)
	Other STSs of genitourinary tract	1316	53 (50–57)	1791	48 (46–51)
	STS of viscera	3.2	38 (36–40)	2715	47 (45–50)
	STS of paratestis	510	87 (82–92)	–	-
	STS of retroperitoneum and peritoneum	2311	34 (32–37)	2543	43 (41–45)
	STS of pelvis	1562	48 (45–51)	1502	47 (44–50)
	STS of skin	2595	91 (89–93)	2133	90 (88–92)
	STS of paraorbit	62	58 (44–77)	53	69 (54–87)
	STS of brain and other nervous system	1399	54 (51–57)	1296	55 (52–58)
	Embryonal rhabdomyosarcoma of soft tissue	507	67 (63–72)	318	65 (59–71)
	Alveolar rhabdomyosarcoma of soft tissue	291	34 (29–41)	224	38 (32–46)
	Ewin's sarcoma of soft tissue	551	45 (40–50)	441	45 (40–51)
gastroenteropancreatic (GEP) neuroendocrine tumours	GEP - well differentiated not functing endocrine carcinoma	7888	70 (68–71)	7768	75 (73–76)
	GEP - well differentiated functing endocrine carcinoma	195	57 (50–66)	212	65 (58–73)
	GEP - poorly differentiated endocrine carcinoma	5719	33 (31–34)	4737	38 (36–40)
	GEP - mixed endocrine-exocrine carcinoma	77	23 (14–37)	64	28 (15–49)

Data from www.rarecarenet.eu.

Table 6
Five-year relative survival (RS%) with (95% CI) for selected rare cancers by European region.

Family	Cancer entity		North	UK and Ireland	Centre	South	East
Head and neck rare cancers	Epithelial tumours of nasal cavity and sinuses	No.	382	2.009	2.007	1.243	1.226
		RS (95%CI)	49 (43–56)	48 (45–51)	54 (52–57)	47 (43–50)	35 (32–39)
	Epithelial tumours of nasopharynx	No.	218	1.793	1.764	2,030	1.471
		RS (95%CI)	55 (47–63)	51 (48–54)	55 (52–58)	51 (48–53)	36 (33–39)
	Epithelial tumours of major salivary glands	No.	789	4.503	3.884	2.749	2.778
		RS (95%CI)	70 (66–75)	63 (61–65)	64 (62–66)	61 (59–63)	51 (48–53)
	Salivary gland type tumours of the head and neck	No.	343	2.088	2.154	1.216	882
		RS (95%CI)	84 (79–90)	70 (68–73)	68 (65–70)	65 (62–69)	55 (51–60)
	Squamous cell carcinoma of hypopharynx	No.	402	3.749	8.371	3.949	3.407
		RS (95%CI)	21 (17–26)	26 (24–28)	29 (28–30)	26 (24–27)	15 (14–17)
	Squamous cell carcinoma of larynx	No.	1.813	17,660	19,070	18.216	15.169
		RS (95%CI)	65 (62–68)	64 (63–65)	63 (62–64)	63 (62–64)	51 (50–52)
	Epithelial tumours of oropharynx	No.	1.335	12.697	19,330	8.192	9.289
		RS (95%CI)	55 (52–58)	50 (49–51)	43 (42–44)	35 (34–37)	28 (27–29)
	Squamous cell carcinoma oral cavity	No.	2.558	16.685	17.794	9.993	7.199
		RS (95%CI)	56 (54–59)	53 (52–54)	51 (50–52)	47 (46–48)	28 (27–29)
Rare thoracic cancers	Epithelial tumours of thymus	No.	93	778	935	595	328
		RS (95%CI)	50 (39–64)	63 (59–68)	67 (63–71)	65 (61–70)	62 (55–68)
	Thoracic mesothelioma	No.	1.113	14,570	7.685	3.590	935
		RS (95%CI)	6 (4–8)	3 (3–4)	5 (5–6)	7 (6–8)	7 (5–9)
Gastroenteropancreatic (GEP) neuroendocrine tumours	GEP – well diff not funct endocrine tumours	No.	1.984	4.937	5.306	1.789	1.640
		RS (95%CI)	78 (76–81)	67 (65–68)	76 (74–77)	75 (72–77)	65 (62–68)
	GEP – well diff funct endocrine tumours	No.	51	103	139	57	57
		RS (95%CI)	40 (27–60)	61 (51–74)	71 (62–81)	67 (55–82)	50 (36–69)
	GEP – poorly diff endocrine tumours	No.	589	3.422	4.282	1.446	717
		RS (95%CI)	35 (30–40)	24 (22–26)	44 (42–45)	39 (37–42)	26 (22–30)
	GEP – mixed endocrine-exocrine tumours	No.	0	6	40	32	63
		RS (95%CI)	(–)	70 (40–100)	34 (20–59)	20 (8–49)	19 (10–38)

Table 6 (*continued*)

Family	Cancer entity		North	UK and Ireland	Centre	South	East
Rare male genital cancers	Testicular and paratesticular tumours	No.	2.937	16.899	16.864	6.589	7.722
		RS (95%CI)	97 (97–98)	97 (96–97)	96 (96–96)	95 (94–95)	88 (88–89)
	Epithelial tumours penis	No.	477	3.655	2.723	1.727	1.628
		RS (95%CI)	77 (71–83)	69 (67–72)	68 (66–71)	67 (64–70)	60 (57–64)
Soft tissue sarcomas	Soft tissue sarcoma	No.	3.561	23.273	21.435	13.053	11.374
		RS (95%CI)	55 (53–57)	55 (55–56)	58 (57–59)	60 (59–61)	53 (52–54)
Rare epithelial and not epithelial ovarian cancers	Epithelial tumours ovary & falloppian tube	No.	6.767	38.943	32.858	15.685	21.411
		RS (95%CI)	47 (46–49)	36 (36–37)	43 (43–44)	46 (45–47)	44 (43–44)
	Non epithelial tumours ovary	No.	179	1.069	1.038	487	1.197
		RS (95%CI)	85 (79–92)	86 (83–88)	82 (80–85)	85 (81–88)	77 (74–80)

Data from www.rarecarenet.eu.

Conflict of interest

The authors of the present study have no conflict of interest to declare.

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