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RARECARENet

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REPORT ON THE HEALTH CARE PATHWAY STUDY AND ON THE UPDATED EPIDEMIOLOGICAL INDICATORS

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TASK 1 Updating the epidemiological indicators for the RARECARENet list of cancers

INTRODUCTION

The RARECARENet project gathered European population based cancer registries (CRs) data on patients diagnosed from 1978 up to 2007, with vital status information available up to 31st December 2008 or later from the EUROCARE-5 [1] database.

This report provides updated estimates of epidemiological indicators of rare tumours in Europe with the methods already used in the previous project RARECARE. Therefore, incidence and survival estimates of rare cancer cases diagnosed in 2000-2007 together with trends in incidence (1995-2007) and survival (2001, 2004, 2007 period estimates) rates are reported. In addition, observed prevalence at 1st January 2008 is also described. The analyses to estimate the complete prevalence are on-going.

MATERIALS

Selection of CRs and population coverage

115 CRs contributing to the EUROCARE-5 project accepted to participate to the RARECARENet project.

Twenty-one out of the 115 participating CRs were excluded from the analyses according to the following criteria:

- The CR of Denmark was excluded from the systematic analyses carried out for the estimation of burden indicators because morphology data are not available, so making it impossible to attribute most diagnoses to a specific cancer entity;
- Ten childhood CRs: 2 of France (National, Haematolgical and Solid Tumors) and those of Germany, Hungary, Marche, Piemonte, Girona, Barcelona, Comunitat Valenciana, England & Wales were excluded because they collect childhood cancers only while our focus is on the entities that are rare over the entire population;
- Three other CRs (Tyrol, Liguria mesothelioma, Palermo breast) were excluded to avoid geographical overlaps with the CR of Austria national, Genova (Genova is in Liguria) and of Palermo;
- The CR of Cluji was excluded because the period of incidence and follow up (from 2007 on) is too short and recent;
- The CRs of Bavaria, Berlin, Niedersachsen, Saxony-Anhalt, Schleswig-Holstein, Thuringen were excluded because the proportion of DCO exceeded 13% (and this is not accetable for appropriate survival estimates).

Table 1 lists the remaining 94 CRs from 24 European countries which were included in the RARECARENet database, that was imported into the SEER*Stat [2] software (version 8.1.5). Of these, 4 specialized CRs collect data only for specific cancer sites, and 8 CRs contributed data for a subset of cancers, for which follow-up status was complete.

Seventeen European countries have national cancer registration: Austria, Bulgaria, Czech Republic, Croatia, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Malta, Norway, Slovakia, Slovenia, Sweden, England, Northern Ireland. The remaining countries have cancer registration covering between 13% and 71% of their population. The mean population covered over the period 2000–20007 was about 207,942,000, corresponding to 48% of the population of the countries

participating in RARECARENet and 46% of the population of the European Union (excluding Norway, Switzerland and Iceland which are not EU members).

Table 1. Countries and cancer registries partecipating to RARECARENet with mean population size covered by registration in 2000-2007 and proportion (%) of national population covered. Countries nation-wide are in bold.

Country	European region	Registry	Population	% Coverage
Finland	North	Finland	5,225,553	100
Norway	North	Norway	4,586,593	100
Iceland	North	Iceland	293,403	100
Austria	Center	Austria	8,150,455	100
Belgium	Center		10,388,282	58
	Center	Flanders	6,032,735	
France	Center		62,094,034	19
	Center	Bas Rhin	791,854	
	Center	Basse Normandie, HM	542,676	
	Center	Burgundy, dig.	1,059,101	
	Center	Calvados, noHM2004	577,887	
	Center	Calvados, dig.	577,887	
	Center	Cote dOr, gyn.	383,531	
	Center	Cote dOr, HM	512,767	
	Center	Doubs	381,409	
	Center	Finistere, dig.	650,405	
	Center	Gironde, HM	679,851	
	Center	Gironde, SNC	1,008,400	
	Center	Herault	714,243	
	Center	Isere	853,134	
	Center	Loire Atlantique, CB1997_gen	1,193,546	
	Center	Manche, noHM2004	364,808	
	Center	Marne-Ardennes, thyroid	852,664	
	Center	Somme	418,553	
	Center	Tarn	266,783	
Germany	Center		82,398,178	21
	Center	Brandeburg	2,573,201	
	Center	Bremen	662,278	
	Center	Hamburg	1,734,369	
	Center	Mecklenburg-Vorpommern	1,733,265	
	Center	Munich	2,902,512	
	Center	Northrhine Westfalia	2,620,248	
	Center	Saarland	1,058,000	
	Center	Saxony	4,329,470	
Switerland	Center		7,335,640	30
	Center	Basel	436,288	
	Center	Geneva	431,029	

	Center	Grisons	225,361	
	Center	St. Gallen	524,546	
	Center	Ticino	317,625	
	Center	Valais	285,339	
The Netherlands	Center	The Netherlands	16,209,421	100
Bulgaria	East	Bulgaria	7,831,973	100
Croatia	East	Croatia	4,430,233	100
Czech Republic	East	Czech Republic	10,241,184	100
Estonia	East	Estonia	1,353,303	100
Latvia	East	Latvia	2,309,150	100
Lithuania	East	Lithuania	3,442,030	100
Slovakia Republic	East	Slovakia	5,385,162	100
Slovenia	East	Slovenia	1,998,138	100
Poland	East		38,251,902	13
	East	Cracow	751,898	
	East	Kielce	1,306,236	
	East	Silesia	2,902,054	
Italy	South		57,804,081	28
	South	Alto Adige	412,013	
	South	Biella	188,077	
	South	Catanzaro	133,963	
	South	Ferrara	349,478	
	South	Firenze-Prato	1,031,947	
	South	Friuli Venezia Giulia	1,202,596	
	South	Genova	659,601	
	South	Latina	510,002	
	South	Mantova	287,058	
	South	Milano	1,278,884	
	South	Modena	651,890	
	South	Napoli	546,790	
	South	Nuoro	126,409	
	South	Palermo	774,872	
	South	Parma	409,530	
	South	Ragusa	302,443	
	South	Reggio Emilia	478,432	
	South	Romagna	1,081,380	
	South	Salerno	946,357	
	South	Sassari	461,599	
	South	Siracusa	397,844	
	South	Sondrio	178,503	
	South	Trapani	214,644	
	South	Trentino	491,185	
	South	Umbria	851,038	
	South	Varese	619,386	
	South	Veneto	1,825,434	
Malta	South	Malta	397,984	100
Portugal	South		10,420,138	71

	South	Açores	170,536	
	South	Northern Portugal	3,252,304	
	South	Southern Portugal	3,976,166	
Spain	South		42,096,329	13
	South	Albacete, CLBP	276,873	
	South	Basque Country	1,572,062	
	South	Castellón-Valencia, breast	457,378	
	South	Cuenca	151,754	
	South	Girona	605,006	
	South	Granada	734,476	
	South	Murcia	778,777	
	South	Navarra	509,442	
	South	Tarragona	567,874	
Ireland	UK-IRE	Ireland	4,055,564	100
United Kingdom	UK-IRE		59,670,455	100
	UK-IRE	England	50,172,734	
	UK-IRE	Northern Ireland	1,713,379	
	UK-IRE	Scotland	5,084,205	
	UK-IRE	Wales	2,941,925	
European Union			434,149,268	48
		94 EU registries	207,942,338	

RARECARENet list of cancers and related SEER*Stat variable

The rare cancer entities included in the RARECARE list were revised by the RARECARENet group of experts in a consensus process under the supervision of the project coordinator.

The revised RARECARENet list includes 261 cancers, of which 46 Tier1 cancers and 215 Tier2 cancers, defined using both ICD-O-3 [3] topography and morphology codes:

- Tier1 cancers are families of tumours identified as having a common referral pattern
- Tier2 cancers are the tumours, pertaining to a specific Tier1 cancer family, defined as clinically distinct (perceived by clinicians as single diseases).

Unspecified morphologies, such as cancer Not Otherwise Specified (NOS: morphology code 8000), cancer cells NOS (8001), malignant lymphoma NOS (9590) were excluded from the definition of any Tier2 cancer entity in the tumour list.
The updated list of cancer entities with the corresponding coding system, based on ICD-O-3 Topography and Morphology, is available on the project web-site. The major changes per site are reported in Table 2.

Table 2. Changes in the list of rare cancers

	Old list	**New list**	**Changes**	
	No rare cancers	No rare cancer	tumour entities added	tumour entities deleted
head and neck tumours	13	13	**no changes**	
gastro-intestinal tract tumors	30	32	**3 new entities** Fibromixoma and low grade mucinous adenocarcinoma of the appendix Hepatocellular carcinoma, fibrolamellar of liver and IBT Adenocarcinoma of EBT separted from gallbladder	
lower respiratory tract tumors				
thymus and trachea	8	8	**no changes**	
lung	6	4	Adenosquamous carcinoma of lung (new tumor, before was with squamous cell tumours)	Bronchiolo-alveolar carcinoma of lung (with adk), Undifferentiated carcinoma of lung (with tier 1); Well differentiaded endocrine carcinoma of lung (moved with the NET)
female genital tract tumours				
uterus and ovary	15	18	Clear cell adenocarcinoma, NOS of corpus uteri; Serous (papillary) carcinoma of corpus uteri; Mullerian mixed tumour of corpus uteri; Mullerian mixed tumour of cervix uteri; Primary peritoneal serous/papillary carcinoma of ovary	Transitional cell carcinoma of corpus uteri; Mixed epithelial and mesenchymal tumours of uterus
vulva + vagina	4	4	no changes	
placenta	1	1	no changes	
breast	5	5	no changes	
urogenital tumours				
prostate, testicular, penis, kidney bladder	17	17	no changes	
pelvis and urethra	4	6	Pelvis separated from the urethra thus 3 new entities for urethra alone: Transitional cell carcinoma, squamous cell and adk	Salivary gland-type tumours of pelvis, ureter and urethra

	Old list	New list	Changes	
neuroendocrine tumors	8	10	grouped by site. Added Pheochromocytoma, malignant, paraganglioma and NET of other iste	
central nervous system tumours	10	7	grouped together glial and non glial tumours	
extragondal germ cell	2	3	grouping changed completly	
Lymphoma	7	11	Hodgkin lymphoma nodular lymphocyte predominance; Mantle cell lymphoma; Prolymphocytic leukaemia, B cell; Diffuse B lymphoma; Follicular B lymphoma; Lymph node accessory cell tumors	Diffuse and follicular B lymphoma
Haematological tumours				
Hitiocytic and dendritic cell neoplasm	1	2	Histiocytic malignancies and Lymph node accessory cell tumors	Histiocytic and dendritic cell neoplasms
acute myeloid leukemia, myeloproliferativ, myelodisplastic syndromes	9	9	no changes	
endocrine tumors	4	4	no changes	
sarcomas	27	27	no changes	
adnexal ca skin	1	1	no changes	
melanoma uvea	1	1	no changes	
melanoma of mucosae	1	1	no changes	
mesothelioma	2	2	no changes	
eye and middle hear	4	4	no changes	
embryonal tumours	6	6	no changes	
olfactory neuroblastoma and odontogenic tumors		**2**	NEW	
		186	198	

The combination of ICDO-3 topography and morphology codes defining the RARECARENet cancer entities, were inserted in the SEER*Stat software to build-up the variable necessary to perform the statistical analyses. The following checks were done to identify possible mistakes in the cancer definition and/or in the variable building:

- Tier1 entities should include all the patients attributed to the set of pertaining Tier2 cancers;
- the opposite does not necessarily hold, but the list of cases included in any Tier1 and not in the pertaining Tier2 entities was scrutinized in order to identify potentially relevant codes that were missed in the rare cancer entities list.

Identification of the rare cancers of the RARECARENet list

Crude incidence rates of all the entities defined in the RARECARENet list were estimated from the pool of eligible CRs for the period 2000-2007 to identify the rare cancers, i.e. those with incidence lower than 6/100,000 per year. A total of 198 cancers were defined as rare according to the above reported frequency criterion.

Finally, incidence estimates were checked for consistency, whenever possible, with the previous RARECARE estimates by comparing the results obtained using:

a. the RARECARENet list of cancers and both the RARECARE (64 CRs, cases registered between 1995 and 2002) and the RARECARENet (83 CRs, cases registered between 2000 and 2007) database;
b. the RARECARE list of cancers (www.rarecare.eu) and both the RARECARE (64 CRs, cases registered between 1995 and 2002) and the RARECARENet (83 CRs, cases registered between 2000 and 2007) database.

Data quality controls

All the individual incidence and follow-up data used for the RARECARENet analyses were extracted from the EUROCARE-5 database, and had therefore previously undergone the standard EUROCARE checks for the validity of each data field and combinations of fields in each case record. Topographies and morphologies were checked against ICD-O-3 lists, and records with invalid codes were excluded [4]. Other checks were carried out on combinations of data fields. They concerned consistency between dates of birth, diagnosis and follow-up, of site–morphology combinations, of age–site, age–morphology, sex–site and sex–morphology combinations, and of morphology–behaviour combinations. Combinations not listed in ICD-O-3 classification were flagged as unlikely, but the corresponding records were used in the analysis.
More detailed description of the procedure of the data quality check is available in the paper by De Angelis et al [5].

Data quality analysis by CRs

The following data quality indicators, usually considered in international population-based survival studies like EUROCARE, were calculated for patients diagnosed in 2000-2007 and followed up to the end of 2008:

- Proportions of major errors (errors/inconsistencies in core variables);
- Proportion of cases known by death certificate only (DCO);
- Proportion of cases diagnosed incidentally at Autopsy;
- Proportion of microscopically verified tumours;
- Proportion of survivors with survival time equal 0 (date of diagnosis coincident with date of life status ascertainment);
- Proportion of patients with a potential follow up of more than five years (cases diagnosed in 2000-2003) who are lost to follow up or censored before 5 years.

Estimation of incidence rates can be biased by the inclusion of registries with insufficient quality of morphological information at diagnosis. In these registries, specific tumours may not be precisely

recognized and a certain number of patients may have their cancer classified within a NOS category (8000,8001,9590). For each CR, the proportion of cases with NOS morphology, together with other standard quality indicators (proportion of microscopically verified cases, of death certificates/autopsies only cases, of patients lost to follow-up) were calculated. The results are shown in Table 3. A total of 8,401,385 of cancer cases were then analyzed. None of the registries show clearly outlier values of NOS. Fixing an (arbitrary) maximum proportion of NOS at 20%, 5 CRs (Bulgaria, Croatia, Palermo, Latvia, Silesia) were identified to be potentially removed from the analysis for having a higher proportion of unspecified morphology cases.

By definition, crude incidence calculated for all Tier 1 entities combined should be higher than crude incidence calculated for all Tier 2 entities combined, and the difference between the two estimates can be taken as an indicator of the proportion of poorly specified morphology codes (8000, 8001, 9590, etc.). This analysis is reported in Table 4. Using a cut point of 20 percent difference, 15 additional registries to be potentially removed from the analysis were identified. When all the above 20 CRs were removed from the incidence analysis, the estimate of the European crude incidence for Tier 1 cancers did not change substantially (percentage difference of 3.5%).

A sensitivity analysis was performed on the European crude incidence: the proportional difference in incidence obtained by the removal of each single registry from the data in analysis was calculated (Table 4). Positive values may be due to lower data quality, indicating that the registry data tends to lower the European pooled incidence estimate. These data are quite reassuring: only two registries have a value greater that 1.0%, and six a value greater that 0.5%.

Table 3. Number of malignant cases diagnosed between 2000 and 2007 and quality indicators by CRs (in alphabetical order). 94 CRs participating to the RARECARENet project

Country	Registry	malignant cases diagnosed between 2000 and 2007	col A		col B		col C		included malignant cases (excluded colums A+B+C)		Quality indicators					
			major errors		cases known by death certificate only (DCO)		diagnosed incidentally at autopsy				microscopically verified		lost to follow-up*		NOS (8000,8001, 9590**)	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
Austria	Austria National	299,572	2,100	0.7	21,864	7.3	0	0.0	275,608	92.0	269,588	97.8	0	0.0	6,337	2.3
Belgium	Flanders	278,289	1	0.0	0	0.0	39	0.0	278,249	100.0	263,314	94.6	0	0.0	6,788	2.4
Bulgaria	Bulgaria National	249,866	69	0.0	21,352	8.5	0	0.0	228,445	91.4	192,126	84.1	328	0.1	51,491	22.5
Croatia	Croatia National	164,255	401	0.2	8,917	5.4	0	0.0	154,937	94.3	127,752	82.5	0	0.0	30,896	19.9
Czech Republic	Czech Republic National	399,465	877	0.2	14,543	3.6	19,407	4.9	364,638	91.3	325,624	89.3	455	0.1	49,823	13.7
Estonia	Estonia National	44,456	33	0.1	61	0.1	617	1.4	43,745	98.4	39,378	90.0	29	0.1	4,918	11.2
Finland	Finland National	191,206	52	0.0	1,814	0.9	3,773	2.0	185,567	97.1	173,513	93.5	70	0.0	16,386	8.8
France	Bas Rhin	26,077	74	0.3	0	0.0	0	0.0	26,003	99.7	24,505	94.2	364	1.4	955	3.7
	Basse Normandie, HM	1,461	0	0.0	0	0.0	0	0.0	1,461	100.0	1,395	95.5	0	0.0	0	0.0
	Burgundy, dig.	14,191	11	0.1	0	0.0	0	0.0	14,180	99.9	13,601	95.9	454	3.2	1,678	11.8
	Calvados, noHM2004	4,316	10	0.2	0	0.0	0	0.0	4,306	99.8	3,380	78.5	195	4.5	521	12.1
	Calvados, dig.	10,616	0	0.0	0	0.0	0	0.0	10,616	100.0	8,928	84.1	451	4.2	819	7.7
	Cote D'Or, gyn.	2,018	4	0.2	0	0.0	0	0.0	2,014	99.8	1,908	94.7	24	1.2	5	0.2
	Cote D'Or, HM	2,338	0	0.0	0	0.0	0	0.0	2,338	100.0	2,333	99.8	15	0.6	0	0.0
	Doubs	11,768	0	0.0	0	0.0	0	0.0	11,768	100.0	11,302	96.0	104	0.9	222	1.9
	Finistere, dig.	5,337	18	0.3	0	0.0	0	0.0	5,319	99.7	4,733	89.0	118	2.2	192	3.6
	Gironde, HM	2,081	1	0.0	0	0.0	0	0.0	2,080	100.0	2,058	98.9	54	2.6	0	0.0
	Gironde, SNC	521	6	1.2	0	0.0	0	0.0	515	98.8	423	82.1	18	3.5	19	3.7
	Herault	24,832	0	0.0	0	0.0	0	0.0	24,832	100.0	23,254	93.6	688	2.8	685	2.8
	Isere	25,911	12	0.0	0	0.0	0	0.0	25,899	100.0	23,934	92.4	367	1.4	989	3.8
	Loire Atlantique, CB1997_gen	42,250	0	0.0	0	0.0	0	0.0	42,250	100.0	39,680	93.9	248	0.6	1,148	2.7
	Manche, no HM2004	11,718	14	0.1	0	0.0	0	0.0	11,704	99.9	11,262	96.2	674	5.8	320	2.7
	Marne & Ardennes, thyroid	672	0	0.0	0	0.0	0	0.0	672	100.0	671	99.9	29	4.3	0	0.0
	Somme	13,976	0	0.0	0	0.0	0	0.0	13,976	100.0	12,746	91.2	617	4.4	584	4.2
	Tarn	10,369	12	0.1	0	0.0	0	0.0	10,357	99.9	9,682	93.5	103	1.0	532	5.1

Germany	Brandeburg	125,998	55	0.0	14,813	11.8	21	0.0	111,109	88.2	108,457	97.6	0	0.0	13,654	12.3
	Bremen	32,223	99	0.3	2,867	8.9	17	0.1	29,240	90.7	27,981	95.7	404	1.4	470	1.6
	Hamburg	71,471	0	0.0	4,736	6.6	0	0.0	66,735	93.4	62,215	93.2	524	0.8	1,130	1.7
	Mecklenburg-Vorpommern	86,136	49	0.1	8,259	9.6	29	0.0	77,799	90.3	75,602	97.2	0	0.0	8,286	10.7
	Munich	122,804	0	0.0	14,993	12.2	0	0.0	107,811	87.8	103,547	96.0	1,469	1.4	13,995	13.0
	Northrhine Westfalia	129,917	3	0.0	6,981	5.4	130	0.1	122,803	94.5	115,545	94.1	0	0.0	1,182	1.0
	Saarland	50,625	0	0.0	2,854	5.6	0	0.0	47,771	94.4	46,378	97.1	0	0.0	4,870	10.2
	Saxony	223,176	81	0.0	24,980	11.2	178	0.1	197,937	88.7	191,672	96.8	0	0.0	25,104	12.7
Iceland	Iceland National	10,252	18	0.2	15	0.1	120	1.2	10,099	98.5	9,728	96.3	0	0.0	352	3.5
Ireland	Ireland National	175,305	1,254	0.7	1,593	0.9	592	0.3	171,866	98.0	157,037	91.4	0	0.0	12,560	7.3
Italy	Alto Adige	15,386	0	0.0	160	1.0	2	0.0	15,224	98.9	14,017	92.1	52	0.3	1,158	7.6
	Biella	10,178	0	0.0	130	1.3	0	0.0	10,048	98.7	8,850	88.1	8	0.1	1,063	10.6
	Catanzaro	3,591	0	0.0	38	1.1	0	0.0	3,553	98.9	3,051	85.9	1	0.0	418	11.8
	Ferrara	27,615	0	0.0	220	0.8	35	0.1	27,360	99.1	24,389	89.1	114	0.4	2,636	9.6
	Firenze-Prato	54,275	367	0.7	342	0.6	3	0.0	53,563	98.7	44,732	83.5	278	0.5	6,624	12.4
	Friuli Venezia Giulia	83,268	9	0.0	244	0.3	1,252	1.5	81,763	98.2	75,015	91.7	167	0.2	6,170	7.5
	Genova	40,187	5	0.0	568	1.4	34	0.1	39,580	98.5	34,897	88.2	3	0.0	4,422	11.2
	Latina	16,686	0	0.0	260	1.6	0	0.0	16,426	98.4	12,928	78.7	152	0.9	2,893	17.6
	Mantova	12,142	0	0.0	212	1.7	0	0.0	11,930	98.3	9,927	83.2	23	0.2	2,295	19.2
	Milano	71,481	4	0.0	1,271	1.8	0	0.0	70,206	98.2	58,942	84.0	1,611	2.3	7,833	11.2
	Modena	41,380	4	0.0	104	0.3	3	0.0	41,269	99.7	37,673	91.3	69	0.2	3,165	7.7
	Napoli	17,296	16	0.1	246	1.4	0	0.0	17,034	98.5	13,972	82.0	53	0.3	2,068	12.1
	Nuoro	4,198	0	0.0	88	2.1	0	0.0	4,110	97.9	3,535	86.0	0	0.0	581	14.1
	Palermo	20,962	26	0.1	506	2.4	0	0.0	20,430	97.5	16,172	79.2	6	0.0	4,133	20.2
	Parma	25,445	0	0.0	93	0.4	15	0.1	25,337	99.6	22,366	88.3	126	0.5	2,648	10.5
	Ragusa	11,307	2	0.0	110	1.0	0	0.0	11,195	99.0	9,513	85.0	25	0.2	2,059	18.4
	Reggio Emilia	28,390	0	0.0	63	0.2	4	0.0	28,323	99.8	25,063	88.5	104	0.4	3,538	12.5
	Romagna	72,734	0	0.0	827	1.1	64	0.1	71,843	98.8	64,371	89.6	21	0.0	7,153	10.0
	Salerno	29,774	0	0.0	698	2.3	0	0.0	29,076	97.7	24,170	83.1	122	0.4	5,200	17.9
	Sassari	18,465	18	0.1	510	2.8	0	0.0	17,937	97.1	15,891	88.6	0	0.0	2,536	14.1
	Siracusa	13,470	0	0.0	310	2.3	0	0.0	13,160	97.7	11,421	86.8	0	0.0	1,736	13.2
	Sondrio	10,530	0	0.0	39	0.4	0	0.0	10,491	99.6	9,295	88.6	4	0.0	1,182	11.3
	Trapani	6,187	1	0.0	37	0.6	0	0.0	6,149	99.4	5,208	84.7	1	0.0	1,178	19.2
	Trentino	21,231	0	0.0	218	1.0	4	0.0	21,009	99.0	19,037	90.6	83	0.4	2,221	10.6
	Umbria	49,564	0	0.0	99	0.2	0	0.0	49,465	99.8	48,089	97.2	64	0.1	3,744	7.6

	Varese	29,250	56	0.2	112	0.4	42	0.1	29,040	99.3	25,746	88.7	241	0.8	2,770	9.5
	Veneto	95,340	0	0.0	923	1.0	231	0.2	94,186	98.8	84,492	89.7	115	0.1	9,981	10.6
Latvia	Latvia National	69,841	671	1.0	4,026	5.8	1,375	2.0	63,769	91.3	51,924	81.4	0	0.0	18,111	28.4
Lithuania	Lithuania National	109,446	174	0.2	3,536	3.2	0	0.0	105,736	96.6	92,985	87.9	460	0.4	18,180	17.2
Malta	Malta National	11,105	113	1.0	483	4.3	20	0.2	10,489	94.5	9,314	88.8	0	0.0	1,029	9.8
Norway	Norway National	179,035	1,344	0.8	1,727	1.0	857	0.5	175,107	97.8	164,878	94.2	159	0.1	9,371	5.4
Poland	Cracow	25,391	5,469	21.5	110	0.4	51	0.2	19,761	77.8	18,739	94.8	155	0.8	799	4.0
	Kielce	39,517	36	0.1	996	2.5	32	0.1	38,453	97.3	33,103	86.1	0	0.0	5,685	14.8
	Silesia	84,959	609	0.7	322	0.4	65	0.1	83,963	98.8	59,628	71.0	662	0.8	19,551	23.3
Portugal	Açores	4,820	5	0.1	186	3.9	1	0.0	4,628	96.0	4,057	87.7	175	3.8	562	12.1
	Northern Portugal	75,864	998	1.3	0	0.0	0	0.0	74,866	98.7	71,074	94.9	185	0.2	1,381	1.8
	Southern Portugal	105,434	2,400	2.3	8	0.0	0	0.0	103,026	97.7	96,820	94.0	332	0.3	5,954	5.8
Slovakia	Slovakia National	165,302	5	0.0	14,306	8.7	2,068	1.3	148,923	90.1	135,228	90.8	1	0.0	13,087	8.8
Slovenia	Slovenia National	83,710	0	0.0	881	1.1	828	1.0	82,001	98.0	76,832	93.7	0	0.0	5,720	7.0
Spain	Albacete, CLBP	3,433	1	0.0	106	3.1	4	0.1	3,322	96.8	3,028	91.1	51	1.5	392	11.8
	Basque Country	54,137	3	0.0	1,496	2.8	167	0.3	52,471	96.9	47,224	90.0	458	0.9	5,132	9.8
	Castellón-Valencia, breast	1,344	0	0.0	49	3.6	0	0.0	1,295	96.4	1,287	99.4	9	0.7	62	4.8
	Cuenca	4,729	0	0.0	333	7.0	0	0.0	4,396	93.0	3,752	85.4	140	3.2	795	18.1
	Girona	23,679	134	0.6	877	3.7	12	0.1	22,656	95.7	20,342	89.8	0	0.0	2,475	10.9
	Granada	18,167	0	0.0	122	0.7	12	0.1	18,033	99.3	15,866	88.0	27	0.1	1,825	10.1
	Murcia	17,395	0	0.0	497	2.9	7	0.0	16,891	97.1	15,042	89.1	88	0.5	1,511	8.9
	Navarra	16,318	0	0.0	252	1.5	77	0.5	15,989	98.0	14,459	90.4	6	0.0	1,168	7.3
	Tarragona	18,653	44	0.2	808	4.3	45	0.2	17,756	95.2	16,367	92.2	0	0.0	1,797	10.1
Switzerland	Basel	17,464	0	0.0	447	2.6	570	3.3	16,447	94.2	15,855	96.4	782	4.8	13	0.1
	Geneva	17,623	96	0.5	110	0.6	134	0.8	17,283	98.1	16,199	93.7	335	1.9	1,037	6.0
	Grisons	8,776	26	0.3	27	0.3	38	0.4	8,685	99.0	8,090	93.1	58	0.7	515	5.9
	St. Gallen	17,896	1	0.0	68	0.4	168	0.9	17,659	98.7	16,773	95.0	60	0.3	737	4.2
	Ticino	14,193	33	0.2	323	2.3	25	0.2	13,812	97.3	12,926	93.6	132	1.0	515	3.7
	Valais	11,049	0	0.0	106	1.0	25	0.2	10,918	98.8	10,036	91.9	89	0.8	764	7.0
The Netherlands	The Netherlands National	641,037	0	0.0	0	0.0	1,908	0.3	639,129	99.7	612,667	95.9	1,004	0.2	22,094	3.5
England	England National	2,440,707	7,986	0.3	66,798	2.7	0	0.0	2,365,923	96.9	2,114,344	89.4	1,869	0.1	88,996	3.8
Northern Ireland	Northern Ireland National	75,502	469	0.6	713	0.9	107	0.1	74,213	98.3	64,822	87.3	0	0.0	711	1.0
Scotland	Scotland National	217,639	585	0.3	1,381	0.6	325	0.1	215,348	98.9	183,706	85.3	16	0.0	9,395	4.4
Wales	Wales National	131,420	167	0.1	4,927	3.7	0	0.0	126,326	96.1	97,425	77.1	0	0.0	16,056	12.7

European pool	European pool	8,401,385	27,131	0.3	265,091	3.2	35,533	0.4	8,073,630	96.1	7,312,806	90.6	18,498	0.2	26,674	0.3

*Proportion of patients diagnosed while alive in 2000–03, censored with less than 5 years of follow-up. For the French registries this quality indicator was calculated for cases diagnosed in 2000–02.

** 8000, neoplasm malignant; 8001, tumor cell malignant; 9590,malignant lymphoma, NOS.

Table 4. Crude incidence for Tier1 and Tier2 cancers by CRs (in alphabetical order), differences (%) due to poorly specified morpholgies and sensitivity analysis of European crude incidence for Tier1 cancers. Cases diagnosed between 2000 and 2007. 83 CRs included in the incidence analyses

Country	Registry	Tier1 cancers				Tier2 cancers			differences (%) between col. A and col. B (poorly specified morphologies)	differences (%) in crude incidence for Tier1 cancers obtained removing a single CR
		col. A				col. B				
		population	cases	crude rate per 100,000	SE	cases	crude rate per 100,000	SE		
Austria	Austria National	65,203,639	271,465	416.3	0.8	221,396	339.5	0.7	18.4	0.80
Belgium	Flanders	48,261,879	271,323	562.2	1.1	243,582	504.7	1.0	10.2	-0.32
Bulgaria	Bulgaria National	62,655,783	237,186	378.6	0.8	174,252	278.1	0.7	26.5	1.08
Croatia	Croatia National	35,441,864	155,860	439.8	1.1	102,954	290.5	0.9	33.9	0.32
Czech Republic	Czech Republic National	81,929,470	381,811	466.0	0.8	300,588	366.9	0.7	21.3	0.48
Estonia	Estonia National	10,826,420	43,204	399.1	1.9	35,211	325.2	1.7	18.5	0.15
Finland	Finland National	41,804,424	184,718	441.9	1.0	149,497	357.6	0.9	19.1	0.37
France	Bas Rhin	5,260,654	25,187	478.8	3.0	22,343	424.7	2.8	11.3	0.02
	Calvados, noHM2004	3,954,334	13,759	347.9	3.0	12,047	304.7	2.8	12.4	0.08
	Calvados, dig.	3,954,334	4,233	96.2	0.9	3,349	84.7	1.5	11.9	0.20
	Doubs	2,536,672	11,535	365.1	2.1	10,490	413.5	4.0	-13.3	0.02
	Herault	4,724,384	24,247	419.9	2.0	21,989	465.4	3.1	-10.9	0.00
	Isere	5,660,084	25,222	361.5	1.4	22,131	391.0	2.6	-8.2	0.05
	Loire Atlantique, CB1997_gen	8,313,911	40,902	492.0	2.4	36,611	440.4	2.3	10.5	0.02
	Somme	2,790,099	13,443	382.1	2.0	11,875	425.6	3.9	-11.4	0.01
	Tarn	1,771,202	9,978	456.1	2.8	8,795	496.6	5.3	-8.9	-0.01
Germany	Brandeburg	20,585,604	122,470	594.9	1.7	101,695	494.0	1.5	17.0	-0.22
	Bremen	5,298,222	31,263	590.1	3.3	26,473	499.7	3.1	15.3	-0.05
	Hamburg	13,874,954	69,061	497.7	1.9	52,925	381.4	1.7	23.4	0.02
	Mecklenburg-Vorpommern	13,866,116	83,387	601.4	2.1	69,502	501.2	1.9	16.7	-0.16
	Munich	23,220,093	118,617	510.8	1.5	94,156	405.5	1.3	20.6	0.00
	Northrhine Westfalia	20,961,981	125,834	600.3	1.7	106,038	505.9	1.6	15.7	-0.24
	Saarland	8,463,999	49,081	579.9	2.6	39,596	467.8	2.4	19.3	-0.07
	Saxony	34,635,761	215,735	622.9	1.3	175,503	506.7	1.2	18.6	-0.50
Iceland	Iceland National	2,347,220	10,021	426.9	4.3	8,682	369.9	4.0	13.4	0.02
Ireland	Ireland National	32,444,512	168,181	518.4	1.3	143,170	441.3	1.2	14.9	-0.03
Italy	Alto Adige	2,810,941	14,957	471.0	2.9	12,563	446.9	4.0	5.1	-0.01
	Biella	1,317,417	9,886	689.7	5.3	8,260	627.0	6.9	9.1	-0.04
	Catanzaro	704,083	3,424	486.3	8.3	2,735	388.4	7.4	20.1	0.00
	Ferrara	2,795,820	26,875	961.3	5.9	22,160	792.6	5.3	17.5	-0.16
	Firenze-Prato	7,048,510	51,950	594.7	1.5	40,573	575.6	2.9	3.2	-0.20
	Friuli Venezia Giulia	9,620,766	80,224	833.9	2.9	67,004	696.5	2.7	16.5	-0.39
	Genova	4,393,506	38,789	700.4	2.1	30,841	702.0	4.0	-0.2	-0.20

	Latina	3,547,078	16,080	397.4	2.6	11,146	314.2	3.0	20.9	0.03
	Mantova	1,904,126	11,768	519.5	4.4	8,648	454.2	4.9	12.6	-0.03
	Milano	8,929,539	66,073	655.3	2.4	52,602	589.1	2.6	10.1	-0.26
	Modena	5,215,118	40,510	776.8	3.9	31,865	611.0	3.4	21.3	-0.17
	Napoli	4,374,323	16,467	376.4	2.9	12,810	292.8	2.6	22.2	0.07
	Nuoro	791,089	4,104	405.8	6.3	3,239	409.4	7.2	-0.9	0.00
	Palermo	4,956,666	20,068	404.9	2.9	13,970	281.8	2.4	30.4	0.07
	Parma	3,276,242	24,780	756.4	4.8	19,622	598.9	4.3	20.8	-0.10
	Ragusa	2,109,022	10,899	371.1	2.2	8,004	379.5	4.2	-2.3	0.00
	Reggio Emilia	3,827,459	27,670	722.9	4.3	21,969	574.0	3.9	20.6	-0.10
	Romagna	8,651,036	70,716	817.4	3.1	57,993	670.4	2.8	18.0	-0.33
	Salerno	6,480,516	28,710	388.7	1.8	21,067	325.1	2.2	16.4	0.06
	Sassari	3,222,923	17,852	458.4	2.5	13,914	431.7	3.7	5.8	-0.02
	Siracusa	2,782,890	13,177	413.8	3.4	10,379	373.0	3.7	9.9	0.01
	Sondrio	1,428,024	10,241	717.1	7.1	8,460	592.4	6.4	17.4	-0.04
	Trapani	1,283,455	6,002	467.6	6.0	4,305	335.4	5.1	28.3	0.01
	Trentino	3,419,286	19,223	515.9	2.9	15,813	462.5	3.7	10.4	-0.02
	Umbria	6,808,301	48,581	713.6	3.2	39,698	583.1	2.9	18.3	-0.17
	Varese	4,111,840	28,394	512.2	1.5	23,594	573.8	3.7	-12.0	-0.09
	Veneto	12,595,433	92,326	625.1	1.3	75,751	601.4	2.2	3.8	-0.35
Latvia	Latvia National	18,473,199	66,823	361.7	1.4	43,111	233.4	1.1	35.5	0.35
Lithuania	Lithuania National	24,160,618	105,195	359.3	0.8	77,606	321.2	1.2	10.6	0.23
Malta	Malta National	3,183,875	10,325	324.3	3.2	8,220	258.2	2.8	20.4	0.07
Norway	Norway National	36,692,746	172,176	469.2	1.1	144,940	395.0	1.0	15.8	0.19
Poland	Cracow	6,015,180	19,616	326.1	2.3	16,371	272.2	2.1	16.5	0.14
	Kielce	10,449,885	37,109	355.1	1.8	26,837	256.8	1.6	27.7	0.20
	Silesia	23,216,435	78,756	339.2	1.2	50,139	216.0	1.0	36.3	0.51
Portugal	Açores	1,364,291	4,635	339.7	5.0	3,465	254.0	4.3	25.2	0.03
	Northern Portugal	22,725,329	74,255	285.4	1.0	64,000	281.6	1.1	1.3	0.53
	Southern Portugal	27,172,292	99,629	320.3	0.9	82,759	304.6	1.1	4.9	0.50
Slovakia	Slovakia National	37,684,618	160,700	335.4	0.5	137,719	365.5	1.0	-9.0	0.41
Slovenia	Slovenia National	15,985,101	81,662	510.9	1.8	68,075	425.9	1.6	16.6	0.00
Spain	Basque Country	10,461,201	51,627	366.7	0.9	43,090	411.9	2.0	-12.3	0.02
	Cuenca	1,007,443	4,542	374.1	5.6	3,499	347.3	5.9	7.2	0.01
	Girona	4,840,050	22,474	464.3	3.1	18,700	386.4	2.8	16.8	0.03
	Granada	5,001,446	17,366	298.4	1.7	14,189	283.7	2.4	4.9	0.10
	Murcia	4,914,972	16,739	340.6	2.6	13,835	281.5	2.4	17.3	0.10
	Navarra	3,471,661	15,737	347.3	1.5	13,403	386.1	3.3	-11.2	0.02
	Tarragona	3,820,452	17,871	366.9	1.7	14,621	382.7	3.2	-4.3	0.02
Switzerland	Basel	3,490,307	16,992	486.8	3.7	15,291	438.1	3.5	10.0	0.01
	Geneva	3,448,231	17,162	497.7	3.8	14,062	407.8	3.4	18.1	0.01
	Grisons	1,802,890	8,556	474.6	5.1	7,286	404.1	4.7	14.8	0.01
	St. Gallen	4,196,367	17,447	415.8	3.1	14,859	354.1	2.9	14.8	0.05
	Ticino	2,540,996	13,695	539.0	4.6	11,756	462.7	4.3	14.2	-0.01

	Valais	2,282,709	10,764	471.5	4.5	8,804	385.7	4.1	18.2	0.01
The Netherlands	The Netherlands National	129,675,371	618,761	477.2	0.6	542,399	418.3	0.6	12.3	0.59
England	England National	401,381,873	2,325,656	579.4	0.4	1,908,326	475.4	0.3	17.9	-4.64
Northern Ireland	Northern Ireland National	13,707,029	71,822	524.0	2.0	57,559	419.9	1.8	19.9	-0.02
Scotland	Scotland National	40,673,640	209,981	516.3	1.1	165,046	405.8	1.0	21.4	-0.03
Wales	Wales National	23,535,397	124,719	529.9	1.5	96,306	409.2	1.3	22.8	-0.06
European pool		1,566,568,628	8,000,261	510.687	0.2	6,520,108	416.203	0.2	18.5	0.01

An analysis of the possible association between the proportion of NOS in the Tier1 cancers and the crude/adjusted incidence for rare Tier2 cancers was also performed. Figure 1 shows the negative relationship between the proportion of NOS and the incidence for rare cancers (incidence decreases as proportion of NOS inceases). Table 5 shows the proportion of NOS in Tier1 cancers and the crude/adjusted incidence for rare Tier2 cancers by CRs. Removing the 5 CRs (Bulgaria, Croatia, Latvia, Palermo, Silesia) with a proportion of NOS higher than 20% the crude and adjusted European incidence did not change substantially (2.6% and 2.3%, respectively).

Therefore, none of the 83 RARECARENet CRs considered for the incidence analyses was finally excluded from the study.

Figure 1. Crude and adjusted incidence of rare tier 2 cancers and proportion of NOS in Tier1 cancer by CR

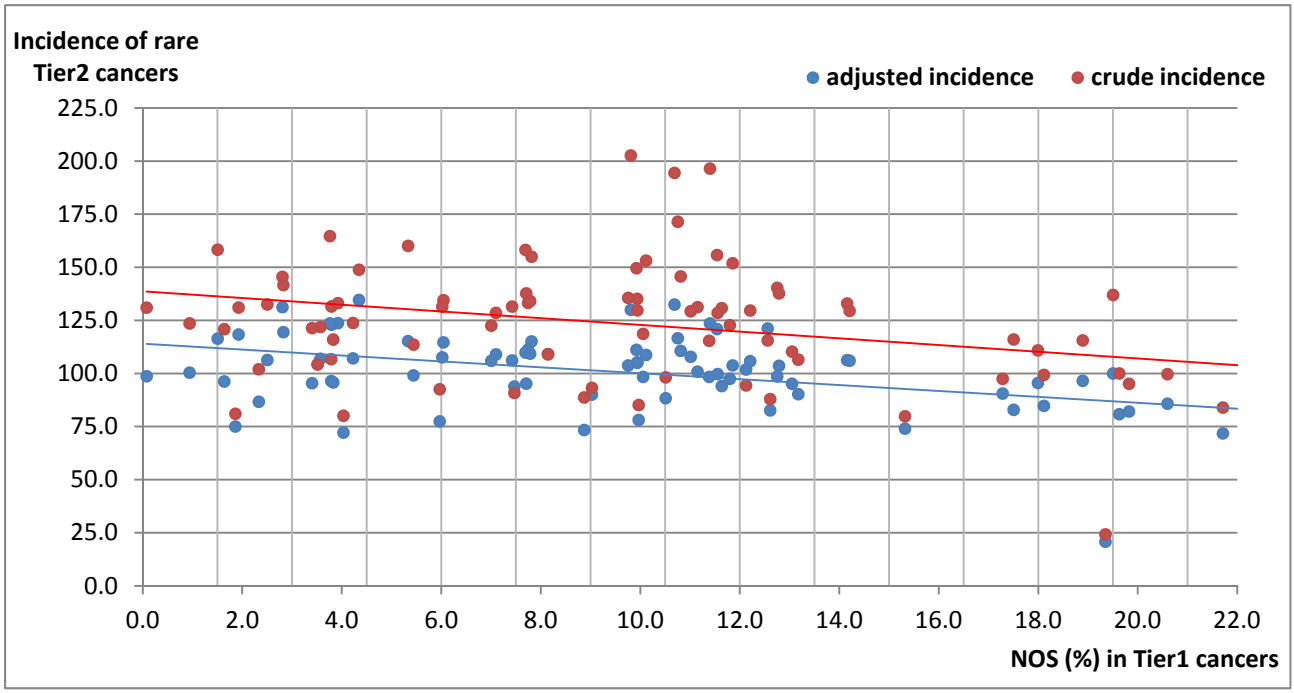


Table 5. Proportion of NOS in tier1 cancers, crude and adjusted incidence for rare tier2 cancers by CRs (in alphabetical order). Cases diagnosed between 2000 and 2007. 83 CRs included in the incidence analyses

Country	Registry	Tier1 cancers			rare Tier2 cancers			
		cases	NOS (8000,8001, 9590)		crude incidence	SE	adjusted incidence	SE
			N	%				
Austria	Austria National	271,465	6,328	2.3	102.0	0.4	86.7	0.3
Belgium	Flanders	271,323	6,788	2.5	132.5	0.5	106.4	0.4
Bulgaria	Bulgaria National	237,186	51,491	21.7	84.0	0.4	71.8	0.3
Croatia	Croatia National	155,860	30,896	19.8	95.2	0.5	82.1	0.5
Czech Republic	Czech Republic National	381,811	49,822	13.0	110.3	0.4	95.2	0.3
Estonia	Estonia National	43,204	4,918	11.4	115.4	1.0	98.4	0.9
Finland	Finland National	184,718	16,386	8.9	88.7	0.5	73.4	0.4
France	Bas Rhin	25,187	955	3.8	131.6	1.6	123.0	1.5
	Calvados, noHM2004	13,759	521	3.8	106.8	1.6	96.5	1.5
	Calvados, dig.	4,233	819	19.3	24.3	0.8	20.8	0.7
	Doubs	11,535	222	1.9	131.1	2.3	118.4	2.1
	Herault	24,247	685	2.8	141.7	1.7	119.5	1.5
	Isere	25,222	989	3.9	133.1	1.5	123.7	1.5
	Loire Atlantique, CB1997_gen	40,902	1,148	2.8	145.6	1.3	131.3	1.2
	Somme	13,443	584	4.3	148.9	2.3	134.7	2.2
	Tarn	9,978	532	5.3	160.1	3.0	115.3	2.3
Germany	Brandeburg	122,470	13,654	11.1	131.3	0.8	100.9	0.6
	Bremen	31,263	470	1.5	158.3	1.7	116.4	1.3
	Hamburg	69,061	1,130	1.6	120.9	0.9	96.3	0.8
	Mecklenburg-Vorpommern	83,387	8,286	9.9	135.2	1.0	105.1	0.8
	Munich	118,617	13,995	11.8	122.8	0.7	97.5	0.6
	Northrhine Westfalia	125,834	1,182	0.9	123.6	0.8	100.4	0.6
	Saarland	49,081	4,870	9.9	149.6	1.3	111.2	1.0
	Saxony	215,735	25,104	11.6	130.8	0.6	94.1	0.5
Iceland	Iceland National	10,021	352	3.5	104.3	2.1	104.4	2.2
Ireland	Ireland National	168,181	12,560	7.5	90.9	0.5	93.9	0.6
Italy	Alto Adige	14,957	1,158	7.7	133.3	2.2	111.3	1.9
	Biella	9,886	1,063	10.8	171.5	3.6	116.6	2.7
	Catanzaro	3,424	418	12.2	129.7	4.3	105.8	3.7
	Ferrara	26,875	2,636	9.8	202.7	2.7	130.0	1.9
	Firenze-Prato	51,950	6,624	12.8	140.4	1.4	98.7	1.1
	Friuli Venezia Giulia	80,224	6,170	7.7	158.2	1.3	109.9	1.0
	Genova	38,789	4,422	11.4	196.5	2.1	123.6	1.5
	Latina	16,080	2,893	18.0	110.9	1.8	95.6	1.6
	Mantova	11,768	2,295	19.5	137.0	2.7	100.0	2.1
	Milano	66,073	7,833	11.9	151.9	1.3	103.8	1.0
	Modena	40,510	3,165	7.8	155.0	1.7	115.1	1.4

	Napoli	16,467	2,068	12.6	115.6	1.6	121.2	1.7
	Nuoro	4,104	581	14.2	133.0	4.1	106.3	3.4
	Palermo	20,068	4,133	20.6	99.7	1.4	85.8	1.3
	Parma	24,780	2,648	10.7	194.5	2.4	132.5	1.8
	Ragusa	10,899	2,059	18.9	115.6	2.3	96.6	2.0
	Reggio Emilia	27,670	3,538	12.8	137.8	1.9	103.7	1.5
	Romagna	70,716	7,153	10.1	153.2	1.3	108.8	1.0
	Salerno	28,710	5,200	18.1	99.4	1.2	84.8	1.1
	Sassari	17,852	2,536	14.2	129.5	2.0	106.0	1.7
	Siracusa	13,177	1,736	13.2	106.5	2.0	90.3	1.7
	Sondrio	10,241	1,182	11.5	155.8	3.3	120.9	2.7
	Trapani	6,002	1,178	19.6	100.0	2.8	80.9	2.4
	Trentino	19,223	2,221	11.6	128.6	1.9	99.8	1.6
	Umbria	48,581	3,744	7.7	137.7	1.4	95.3	1.1
	Varese	28,394	2,770	9.8	135.6	1.8	103.8	1.5
	Veneto	92,326	9,981	10.8	145.7	1.1	110.7	0.9
Latvia	Latvia National	66,823	18,108	27.1	83.4	0.7	72.5	0.6
Lithuania	Lithuania National	105,195	18,180	17.3	97.5	0.6	90.6	0.6
Malta	Malta National	10,325	1,029	10.0	85.2	1.6	78.2	1.5
Norway	Norway National	172,176	9,367	5.4	113.6	0.6	99.1	0.5
Poland	Cracow	19,616	791	4.0	80.1	1.2	72.2	1.1
	Kielce	37,109	5,685	15.3	79.9	0.9	74.1	0.8
	Silesia	78,756	19,547	24.8	72.9	0.6	68.3	0.5
Portugal	Açores	4,635	562	12.1	94.4	2.6	101.9	2.9
	Northern Portugal	74,255	1,381	1.9	81.1	0.6	75.1	0.6
	Southern Portugal	99,629	5,945	6.0	92.6	0.6	77.5	0.5
Slovakia	Slovakia National	160,700	13,087	8.1	109.0	0.5	109.2	0.5
Slovenia	Slovenia National	81,662	5,720	7.0	122.6	0.9	106.0	0.8
Spain	Basque Country	51,627	5,132	9.9	129.7	1.1	105.3	0.9
	Cuenca	4,542	795	17.5	116.0	3.4	82.9	2.8
	Girona	22,474	2,475	11.0	129.3	1.6	107.9	1.4
	Granada	17,366	1,825	10.5	98.2	1.4	88.4	1.3
	Murcia	16,739	1,511	9.0	93.3	1.4	90.1	1.4
	Navarra	15,737	1,168	7.4	131.6	1.9	106.2	1.7
	Tarragona	17,871	1,797	10.1	118.7	1.8	98.4	1.5
Switzerland	Basel	16,992	13	0.1	131.0	1.9	98.7	1.5
	Geneva	17,162	1,037	6.0	134.5	2.0	114.7	1.7
	Grisons	8,556	515	6.0	131.5	2.7	107.6	2.3
	St. Gallen	17,447	737	4.2	123.8	1.7	107.2	1.5
	Ticino	13,695	515	3.8	164.7	2.5	123.6	2.0
	Valais	10,764	764	7.1	128.6	2.4	109.0	2.1
The Netherlands	The Netherlands National	618,761	22,094	3.6	121.9	0.3	107.0	0.3
England	England National	2,325,656	88,995	3.8	116.0	0.2	95.8	0.1
Northern Ireland	Northern Ireland National	71,822	9,057	12.6	88.0	0.8	82.7	0.8
Scotland	Scotland National	209,981	16,348	7.8	134.1	0.6	109.4	0.5

Wales	Wales National	124,719	4,242	3.4	121.4	0.7	95.5	0.6
European pool		8,000,261	604,514	7.6	114.3	0.1	95.8	0.1

METHODS

The SEER*Stat variable defining the RARECARENet list of cancer entities was finally used in specific incidence, survival and prevalence SEER*Stat sessions to update the epidemiological indicators for all the 261 cancers.
We obtained point estimates of incidence and relative survival for the period of diagnosis 2000-2007 and their time trends during the period of diagnosis 1995-2007. All the analyses of cancer burden indicators in RARECARENet were performed using the SEER*Stat software released by the National Cancer Institute (US) (version 8.1.5).

Incidence

Eighty-three CRs with incidence data on patients registered between 2000 and 2007, were included in the incidence analysis. Twelve CRs out of the 94 eligible RARECARENet CRs have information available only for some anatomical sites, and thus were excluded from the incidence analysis.
Crude incidence of rare cancers was obtained using the pool of the eligible 83 RARECARENet CRs data in Europe, overall, by sex, by age class (0-14, 15-24, 25-64, 65+), by country, and by five European regions: Northern Europe, Central Europe, Eastern Europe, Southern Europe, United Kingdom-Ireland. The number of new incident cases in 2008 and 2014 in Europe was calculated applying the estimated European crude incidence (2000-2007) to the EU28 population in 2008 and 2014 (EUROSTAT).
Age-adjusted incidence rates with the European standard population were also estimated using the same data and with the same sex and geographical stratification.
Analysis of temporal incidence trends (crude and age-adjusted) was performed, for the whole Europe and by European region, according to three time intervals (1995-1998; 1999-2003; 2003-2007) and using the pool of 42 CRs with available incidence data between 1995 and 2007. In addition, a linear trend analysis was carried out for each rare tumours by fitting a regression model to age-adjusted incidence rates by single years of diagnosis. The incidence annual percent changes and the corresponding standard errors were then estimated from the regression statistics.

Survival

All the participating 94 RARECARENet CRs were included in the survival analysis.
Relative survival estimates were obtained using the 'complete' approach considering cases diagnosed between 2000 and 2007, and followed up to 31st December 2008. The Ederer II estimator was used.
The 1-, 3-, and 5-year observed and relative survival (RS) were estimated in Europe overall, and by sex, by age class (0-14, 15-24, 25-64, 65+), and by the five European regions.
Temporal trends in RS in Europe (overall) and in each European region, were also estimated using the period approach [6] for the periods of follow-up 2000-2002, 2003-2005, 2006-2008.

Prevalence

Twenty-five CRs out of the 94 RARECARENet CRs, which provided incidence and follow-up data for the period 1993-2007 were included in the prevalence analysis, with prevalence index date of 1st January 2008.
Observed prevalence disentangled by time since diagnosis (2, 5, 15 years) was estimated by sex and age class using the counting method [7,8]. The life status of cases lost to follow-up or censored before the

index date was estimated from the survival probability between the censoring and the index dates, derived from a subset of cancer patients matched by age and cancer grouping.
The number of prevalent cases in 2008 and 2014 in Europe was calculated applying the obtained European 15-year prevalence proportion at 1st January 2008 to the EU28 population at 2008 and 2014 (EUROSTAT).

We are running all the necessary procedures that will enable to provide the complete prevalence for the rare cancer entities (by the end of 2014). The complete prevalence (counts and proportions) will be estimated overall in Europe using the completeness index method. Completeness indices are the ones obtained from the RARECARE project apart from the new cancer entities and from those whose definition changed during the revision of the RARECARE list [9]. For these entities, completeness index will be calculated.

RESULTS

Incidence

The European crude and adjusted incidence rates per 100,000 in the period 2000-2007 for all the entities defined in the RARECARENet list are reported in the incidence file available on the project web-site. The half of all the rare Tier 2 entities have an incidence rate less than 0.1, one third (about other 60) have incidence ranging between 0.1 and 1, and only 33 of them have values beween than 1 and 6, the latter being the cutpoint used for separating rare from common tumours. **All together, the rare Tier 2 entities have an incidence rate of 115/100,000 per year, corresponding to about 585,000 new diagnoses each year, 22% of the global incidence of cancer in Europe.**

Age-adjusted rare cancers incidence varied by region from 86.5/100,000 in Eastern Europe to 102.8/100,000 in Central Europe, differently from common cancer incidence, that is also the lowest in the East, but takes the highest values in UK and Ireland region. Please note that rare entities are defined as such on the basis of the crude European incidence rates. Therefore in some regions, rare tumours incidence could locally be higher than the conventional threshold of 6 per 100,000. This happens for instance for the adenocarcinoma with variants of ovary in UK-Ireland, Northern, and Eastern Europe; for adenocarcinoma of oesophagus in UK-Ireland; for large cell carcinoma of lung in Central Europe; for squamous cell carcinoma of larynx and thyroid carcinoma in Southern Europe; and for squamous cell carcinoma of cervix uteri in Eastern Europe.

For the great majority of rare cancers, incidence was higher in male than female. Excluding sex-specific cancers, men had a 50% higher risk to have a rare cancers than women (incidence of non sex-specific rare cancers: 109.1 vs. 72.5). The most relevant exception is thyroid cancers, for which incidence is more than three times higher in women than in men. Several rare malignancies are now wellknown to be caused by occupational factors, the most relevant of which are pleural mesothelioma in asbestos workers, nasal cavities carcinoma in wood workers [10] and liver angiosarcoma in vinylchloride workers. One of the reason of sex differences may be the professional exposure of men. Actually the highest male female ratio (>2) were for the mesothelioma, quite all the head and nech cancers, cancer of the pelvis, urether and urethra, Kaposi's sarcoma, epithelial tumour of trachea, epithelial tumour of eye and adnexa. For the majority of them an association with occupational exposure was supported by IARC monographs and/or consistent evidence from epidemiology studies [10]. Tobacco and alchol are also habits whose prevalence is higher in men than women.

Incidence time trends

Crude incidence of rare tumours increased overall by about 20%, from 97.9 in 1995-99 to 117.1 in 2003-07. Adjusting by age, the overall increase was lower, from 87.9 to 89.3, respectively. The incidence trends for all the rare cancers are provided in the incidence trends file available on the project web-site. A global representation of age-adjusted trends for all the single rare tumours is provided by the funnel plot (Figure 2), where the y-axis reports the estimated Annual Percent Change (APC) of incidence, the x-axis is a measure of the precision of estimates, and precisely the inverse of its standard error, and each dot represents a rare tumor entity. Dots over the horizontal line y=0 correspond to tumours with increasing trend, while those under the line correspond to entites with decreasing incidence. The two broken lines represent the lower and upper 99% confidence bounds, thus cancers represented by dots laying outside the region between the two lines indicate a statistically significant variation in incidence. The graph clearly shows that the majority of the cancers had an increasing trend. For 64 entities, the rise was estimated as statistically significant, while only 20 cancers presented a significantly decreasing trend. Table 12 reports the estimated trends for the entities with significant incidence variation greater than 5% or lower than -5% per year. For many of the rare entities included in Table 12 the increment may be artificial, because due to the new ICD-O codes of the third version, like several haematological tumours, the GIST, several pancreatic type of cancers and also serous (papillary) carcinoma of corpus uteri. The intestinal type adenocarcinoma of nasal cavities should be due to the improved awareness of pathologists versus a typical professional disease. A deeper analysis is necessary to understand for which rare cancers incidence and therefore the risk is increasing. Also for some neuroendocrine tumours (skin and the poorly differentiated) is important to discuss the phenomenon with clinicians and pathologists. As all the gastric carcinoma, also undifferentiated carcinoma, reduced their incidence.

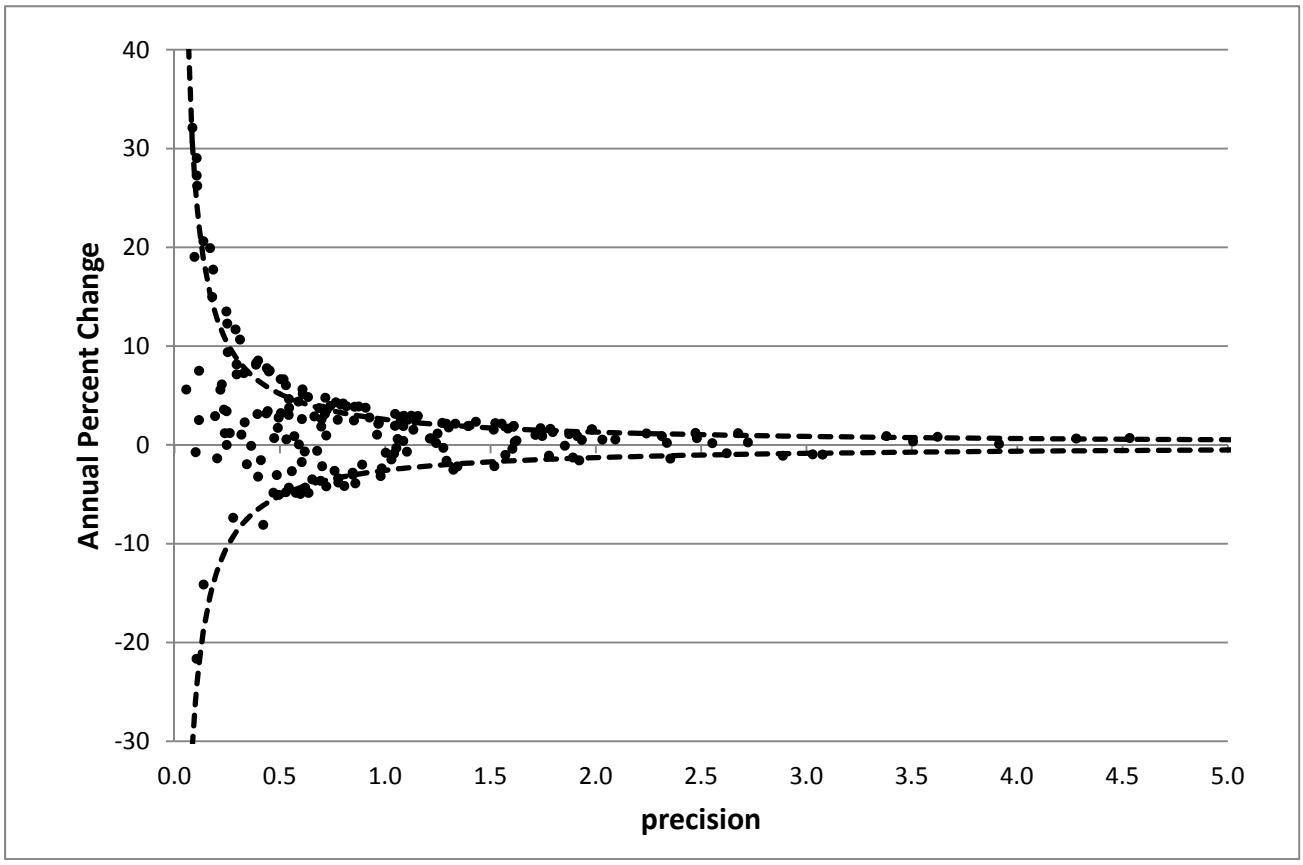
Table 12. List of rare cancers with significant increase or decrease of incidence

Entity	APC	No of cases	Incidence rate
Carcinoma with osteoclast-like giant cells of pancreas	32.1	19	0.00121
Myelodysplastic syndrome with 5q syndrome	27.3	156	0.01
Intraductal papillary mucinous carcinoma invasive of pancreas	29.0	173	0.01
Solid pseudopapillary carcinoma of pancreas	26.2	44	0.00281
Intestinal type adenocarcinoma of nasal cavity and sinuses	20.6	42	0.00268
Gastrointestinal Stromal Sarcoma	19.9	4706	0.30
Neuronal and mixed neuronal-glial tumors	15.0	174	0.00472
Atypical chronic myeloid leukemia BCR/ABL negative	17.8	239	0.02
Serous (papillary) carcinoma of corpus uteri	13.5	1227	0.08
Mast cell tumour	12.3	461	0.03
GEP, poorly differentiated endocrine carcinoma	11.7	10421	0.67
Primary peritoneal serous/papillary carcinoma of ovary	10.7	1280	0.08
Fibromixoma and low grade mucinous adenocarcinoma of the appendix	8.1	1674	0.11
Metaplastic carcinoma of breast	8.3	1576	0.10
Hodgkin lymphoma nodular lymphocyte predominance	8.6	1483	0.09
Other T cell lymphomas and NK cell neoplasms	7.8	9656	0.62
Other myelodysplastic syndrome	7.4	33542	2.14
Mantle cell lymphoma	7.5	8748	0.56

Neuroendocrine carcinoma of skin	6.7	3024	0.19
Diffuse B lymphoma	6.7	67645	4.32
Other myeloproliferative neoplasms	6.1	33954	2.17
Follicular B lymphoma	5.6	34346	2.19
Acute promyelocytic leukemia (AML with t(15;17) with variants	5.2	1876	0.12
Undifferentiated carcinoma of stomach	-8.1	3300	0.21

APC= annual percent change

Figure 2. Funnel plot of the incidence rate change in rare cancer (period of study, 1995-2007)



Survival

Five-year relative survival of all the 198 Tier2 rare entities combined was 48.4% overall (based on 1,755,569 patients diagnosed in 2000-2007). The corresponding absolute survival was 43.6%. These figures contrast with the higher relative and absolute survival level of common Tier2 cancers, estimated as 69.1% and 58.2%, respectively. Overall survival was therefore poorer for rare than for common cancer patients. This difference may be affected by case mix. Actually, the most common cancers like breast, colorectum, prostate and skin (melanoma and epithelial) had 5-year survival higher than 50%. All of them were half of all the malignant neoplasm. By contrast, rare cancers, except sarcomas, testis, thyroid, larynx, cervix tumours and some haematological entities, had poor outcome (1-, 3-, 5-year relative survival file available on the project web-site). Poor prognosis (survival<20%) was shown for 14% of the rare cancers. Among these: the astrocytic tumours of CNS (15%), the acute myeloid leukemia (17%), mesothelioma of pleura

and pericardium (4.6%). The higher survival (>90%) was estimated for 8 out of the 198 rare cancers: several type of tumours of testis and of breast, retinoblastoma and Hodgkin lymphoma nodular lymphocyte predominance. Age at diagnosis is another prognostic factor that can affect the differences in outcome between common and rare cancers. Infact, the age-adjustment of survival increases the gap between common and rare cancers.

Survival time trends

Relative survival at 5 years since diagnosis of all rare cancers combined increased very little: only 3 percent points, from 45.8% in the period 1999-2001 to 48.8% in 2005-2007. During the same period, survival of common Tier2 cancer entities rised by 5.6 percent points, from 65.1% to 70.7%. This overall picture doesn't change when adjusting by age, with estimated increases from 40.4% to 43.9% for rare cancers and from 65.4% to 71% for common cancers. It can be observed that most of the attained survival improvement was already evident at the end of the first year after diagnosis.

Table 14. Time variations of 1-year, 3-year, and 5-year relative survival of rare and common cancers. Standard patients population 1 (for all cancres combined) from [Corazziari et al].

Rare cancers

	1 yr	1 yr	1 yr	3 yr	3 yr	3 yr	5 yr	5 yr	5 yr
	Crude Relative	Age St Relative	SE	Crude Relative	Age St Relative	SE	Crude Relative	Age St Relative	SE
1999-2001	0.679	0.641	0.001	0.515	0.466	0.001	0.458	0.404	0.001
2002-2004	0.690	0.655	0.001	0.527	0.480	0.001	0.470	0.417	0.001
2005-2007	0.703	0.672	0.001	0.544	0.501	0.001	0.488	0.439	0.001
Difference	**0.024**	**0.032**		**0.029**	**0.035**		**0.029**	**0.035**	

Common cancers

	1 yr	1 yr	1 yr	3 yr	3 yr	3 yr	5 yr	5 yr	5 yr
	Crude Relative	Age St Relative	SE	Crude Relative	Age St Relative	SE	Crude Relative	Age St Relative	SE
1999-2001	0.815	0.818	0.000	0.703	0.707	0.000	0.651	0.654	0.001
2002-2004	0.832	0.835	0.000	0.728	0.732	0.000	0.681	0.684	0.001
2005-2007	0.845	0.849	0.000	0.750	0.754	0.000	0.707	0.710	0.001
Difference	**0.030**	**0.031**		**0.046**	**0.047**		**0.056**	**0.057**	

Survival trends by single rare entities were analysed across the same periods of follow-up, but only considering crude survival, to avoid a large number of missing estimates for insufficient number of patients in some age class (survival trends file available on the project web-site). The differences between 5-year relative survival in the first and last triennial periods are represented by a funnel plot (Figure 3). As expected, the dots laying over the horizontal axis y=0, representing cancers with survival increases, are more than those indicating a decrease. In addition, for 33 cancers the increase was statistically significant ($p<0.01$), and only for a single rare cancer (Other myelodysplastic syndrome) a significant decrease was estimated. Table 18 presents a list of rare entities with significant changes greater than 5 percent points.

Figure 3. Funnel plot of 5-year survival change for rare cancers during the period 1999-2007

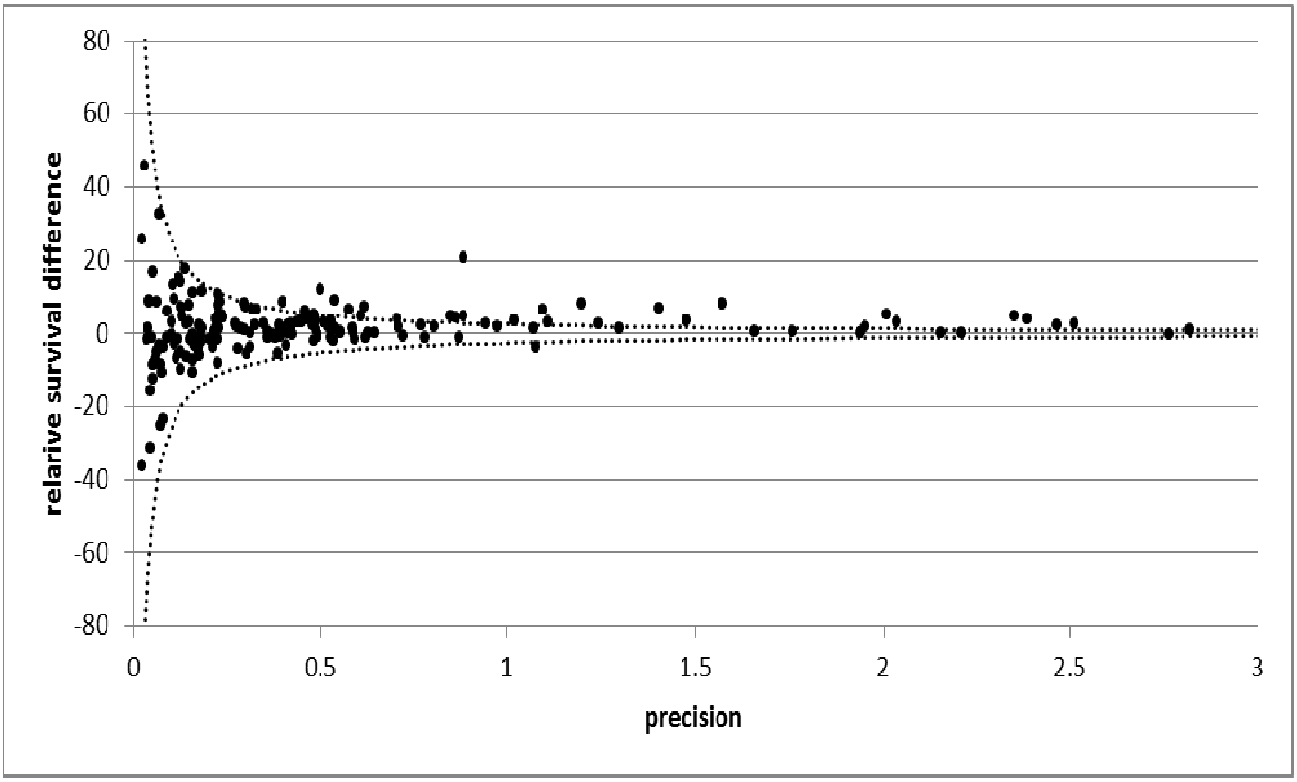


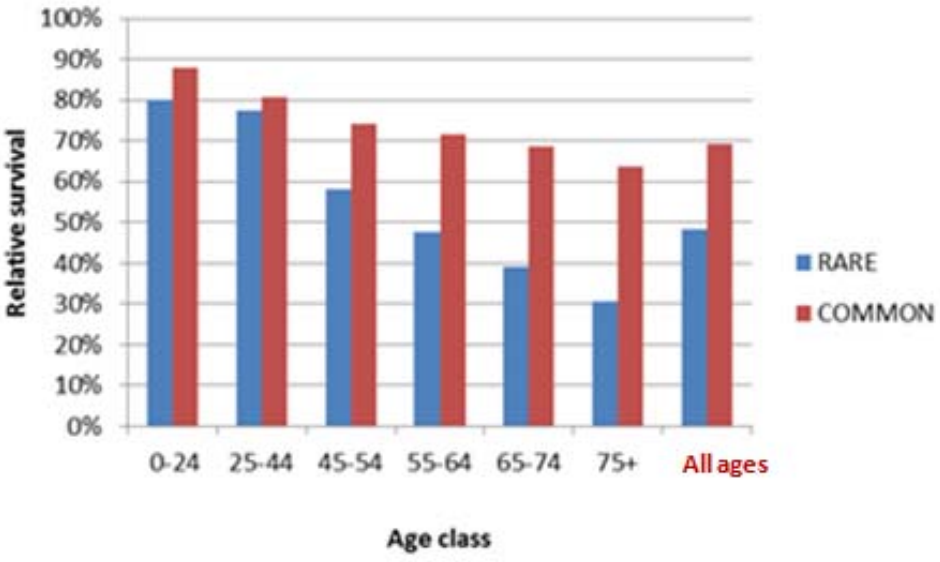
Table 18. Rare entities with significant survival time trends changes

cancer entity	1999-01 Relative Survival	2005-07 Relative Survival	Difference	St. Error
Lymphoepithelial carcinoma of nasal cavity and sinuses	11.5%	96.9%	85.4	13.6
Chronic myeloid leukemia	37.2%	57.9%	20.7	1.1
GEP, well diff funct endocrine carcinoma of pancreas and dig. tract	41.6%	59.4%	17.8	7.1
Infiltrating duct carcinoma of prostate	67.5%	79.8%	12.3	2.0
Soft tissue sarcoma of viscera	34.7%	43.7%	9.0	1.8
Kaposi's sarcoma	75.4%	84.2%	8.8	2.5
Diffuse B lymphoma	46.9%	55.3%	8.4	0.6
Follicular B lymphoma	69.5%	77.9%	8.4	0.8
GEP, poorly differentiated endocrine carcinoma	25.3%	32.7%	7.5	1.6
Squamous cell carcinoma with variants of oropharynx	37.5%	44.5%	7.1	0.7
Soft tissue sarcoma of superficial trunk	43.9%	50.4%	6.5	1.7
Precursor B/T lymphoblastic (and Burkitt) leuk/lymphoma	54.3%	60.8%	6.4	0.9
Adenocarcinoma with variants of bladder	36.0%	42.0%	6.0	2.2
Soft tissue sarcoma of retroperitoneum and peritoneum	33.6%	38.9%	5.3	2.1
Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	29.8%	35.0%	5.2	0.5
Carcinoma of thyroid gland	85.6%	90.6%	5.0	0.4

As expected, the majority of improvements occurred for the haematological malignancies, for which new effective treatments have become available over the study period. This is the case for chronic myeloid leukemia, multiple myeloma/plasmocitoma and many lymphoid neoplasms. The survival improvement of the carcinoma of thyroid was probably due to the inclusion of small and indolent lesions discovered with the increasing use of imaging. Similarly the survival improvement of the duct carcinoma of prostate is due to the large use of the prostatic specific antigen (PSA) test and niddle biopsies. Interestingly better outcomes have been observed for some types of sarcoma and for two groups of endocrine GEP carcinomas and adenocarcinoma of bladder. For these rare cancers more in depth analyses will be carried out.
Also the impressive increase of nasal cavities lymphoepitelial carcinoma, which is an exceptional entity, will be discussed with pathologists and clinicians to unsderstand if the improvement was real or due to a change in the definition of the entity.
Relative survival of all rare cancers combined differs according to EU region, but not as much as for most common cancers. Five-year age-adjusted survival varied from about 41.5% in Eastern Region and UK and Ireland, to 48.1% in the Northern Region. Due to the large number of patients, all the differences are of course highly significant.

Instead, relative survival of rare cancers strongly and regularly decreases with age (Figure 4), dropping from 80% for children, adolescents and youg adults patients to 30% for those aged 75 or more. Of course, even more pronounced are the age related variation of absolute survival (from 80% to 20%, respectively). The age pattern does not substantially differs between sex.

Figure 4. Five year relative survival by age class



Regarding outcome by sex, as for common cancers, also in rare cancers women showed a better outcome: 5-year survival was 53% and 44% in women and men, respectively.

Prevalence

The estimated 15-year prevalence of all the 198 rare cancer entites combined was 635 per 100,000 persons, corresponding to about 3,180,000 citizens resident in the EU28 countries at the beginning of the year 2008. The corresponding figures for 2-year prevalence and 5-year prevalence were 168 and 329 per 100,000, respectively. The detailed 15-year prevalence figures for each (rare and common) entities are

reported in the observed 15-year prevalence file available on the project web-site. The fifteen-year prevalence for all the rare tumours were under the 50 per 100,000, that is the cut off utilized in Europe for the definition of rare disease. Epithelial tumours of lung and stomach have prevalence rates lower than 50 per 100,000 but annual incidence rates higher than 6 per 100,000. These tumours are then classified as common according to our incidence-based definition, but rare according to the standard EU prevalence-based criterion. All these tumours have very poor survival and therefore low prevalence figures, even in presence of a high occurrence, at least for the European population.
Complete prevalence will be provided in a close future, we are aware that 15-year prevalence is lower than complete prevalence for malignancies with a good prognosis and occurring in young patients.

Dissemination of results
The results of the stratified analysis, together with the above estimated indicators, will be published on the web-site of RARECARENet project, to inform clinicians, patients and health planners. A search toll based on aggregated data of this analysis will be publicly available. A publication plan will include objectivies of major interest for clinicians and health care providers.

CONCLUSIONS

In the years 2000-2007, about 3,250,000 European citizens (EU-28 countries) lived with a past diagnosis of rare tumours during the last 15 years, corresponding to a proportion of 635 per 100,000. The annual European incidence rates of all the rare cancers was 115 per 100,000, for a total number of about 585,000 new diagnoses per year, 22% of the global incidence of cancer in Europe. The age-adjusted incidence trend slightly increased, from 87.9 to 89.3 per 100,000/year, the raise was lower than that observed for common cancers.
Overall survival was poorer in rare than common cancer patients: 5-year relative survival figures were 48 and 69%, respectively. Outcome for all rare cancers combined slightly improves: only 3 percent points for 5-year survival, from 44% in the period 1999-2001 to 49% in 2005-2007. The increase for common cancers was higher. The majority of improvements occurred for the haematological rare tumours, for which new effective treatments have become available over the study period. Five-year survival reduced with increasing age, dropping from 80% for children and youg adults patients to 30% for those aged 75 or more. As for common cancers, also in rare cancers women showed a better outcome: 5-year survival was 53% and 44% in women and men, respectively. Fifteen-year prevalence was lower 50 per 100,000, the European cut off of the rare disease definition, for all the rare cancer indentified with this project.

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