Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet—a population-based study

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Summary

Background Rare cancers pose challenges for diagnosis, treatments, and clinical decision making. Information about rare cancers is scant. The RARECARE project defined rare cancers as those with an annual incidence of less than six per 100 000 people in European Union (EU). We updated the estimates of the burden of rare cancers in Europe, their time trends in incidence and survival, and provide information about centralisation of treatments in seven European countries.

Methods We analysed data from 94 cancer registries for more than 2 million rare cancer diagnoses, to estimate European incidence and survival in 2000–07 and the corresponding time trends during 1995–2007. Incidence was calculated as the number of new cases divided by the corresponding total person-years in the population. 5-year relative survival was calculated by the Ederer-2 method. Seven registries (Belgium, Bulgaria, Finland, Ireland, the Netherlands, Slovenia, and the Navarra region in Spain) provided additional data for hospitals treating about 220 000 cases diagnosed in 2000–07. We also calculated hospital volume admission as the number of treatments provided by each hospital rare cancer group sharing the same referral pattern.

Findings Rare cancers accounted for 24% of all cancers diagnosed in the EU during 2000–07. The overall incidence rose annually by 0·5% (99·8% CI 0·3–0·8). 5-year relative survival for all rare cancers was 48·5% (95% CI 48·4 to 48·6), compared with 63·4% (95% CI 63·3 to 63·4) for all common cancers. 5-year relative survival increased (overall 2·9%, 95% CI 2·7 to 3·2), from 1999–2001 to 2007–09, and for most rare cancers, with the largest increases for haematological tumours and sarcomas. The amount of centralisation of rare cancer treatment varied widely between cancers and between countries. The Netherlands and Slovenia had the highest treatment volumes.

Interpretation Our study benefits from the largest pool of population-based registries to estimate incidence and survival of about 200 rare cancers. Incidence trends can be explained by changes in known risk factors, improved diagnosis, and registration problems. Survival could be improved by early diagnosis, new treatments, and improved case management. The centralisation of treatment could be improved in the seven European countries we studied.

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Introduction

The RARECARE project[1] defined rare cancers as those with an annual incidence of less than six per 100 000 people in the European Union (EU), and showed that about one in five cancers diagnosed in the EU were rare and slightly more than 4 million people with a rare cancer diagnosis were living in the EU population. Because of their low numbers, the almost 200 rare cancers listed by RARECARE pose challenges for diagnosis, treatments, and clinical decision making. Clinical trials into such cancers are rare too, and it is hard to build up new knowledge and expertise.

The broad consensus suggests that diagnostic pathological confirmation and primary treatment of rare cancers, in particular, should be centralised in reference centres, collaborative networks, or both, with multidisciplinary approaches[2] and very specific expertise. Additionally, clinical and translational research calls for a high level of centralisation and international collaboration. To what extent appropriate policies for patients with rare cancer are implemented at the country level has seldom been studied. As a consequence, information for policy makers and stakeholders is scarce for many of these rare tumours.

The project Information Network on Rare Cancers (RARECAREnet) is designed to update epidemiological information about rare cancers in the EU,[3] to provide indicators at the country level, time trends, and to study to what extent treatment is centralised in Europe.

In this study, we provide current incidence and survival estimates based on data collected from 94 population-based cancer registries, for 198 rare cancers diagnosed in 2000–07 and for 12 major families of rare cancers. We also present data for the levels of centralisation for rare cancers in selected European countries.

Methods

Patients

We extracted data from two databases. The first, the descriptive analysis database, is a subset of the EUROCARE-5 database,[4] which includes incidence and follow-up data provided by European population-based

Research in context

Evidence before the study

The surveillance of rare cancer in Europe (RARECARE) project provided data from European population-based cancer registries to provide for the first time the burden of rare cancers in Europe. The RARECARE definition of rare cancer was an incidence of less than six cases per 100 000 people per year. A list of rare cancers was created, combining the topography and morphology codes from the International Classification of Diseases for Oncology (ICD-O-3). The list was produced after consultations by a group of pathologists, clinicians and epidemiologists, and was endorsed by the main European cancer organisations. The definition and the list were employed in several European and extra-European countries. The European Commission (EC) based the recent launch of the Joint Action on Rare Cancer in line with this definition. Estimates indicated that about one in five new cancers were rare and slightly more than 4 million people diagnosed with rare cancers lived in Europe. Outcomes (5-year relative survival) were worse for patients with rare cancers than for patients with common cancers.

There is general agreement that treatment of rare cancers should be concentrated in specialised multidisciplinary centres, and that international collaboration is needed for research on these cancers. However, there is no knowledge about the extent of centralisation of rare cancer treatment at the population level.

Added value of this study

With the new project 'Information network on rare cancer' (RARECAREnet), we updated the burden of rare cancer and provided indicators of the centralisation of patients with rare cancer in seven European countries. We estimated about 650 000 new diagnoses of rare cancers occur yearly in Europe, with an incidence of 115 of 100 000 per year. The incidence rose by 0·5% annually, due to overdiagnosis (eg, thyroid carcinoma) or improved diagnosis (eg, neuroendocrine tumours [NET], gastrointestinal stromal tumour [GIST]) or increases in exposure to risk factors (such as HPV). 5-year survival for rare cancers (49%) is still lower than for common cancers (63%), but has risen, from 46% in 1999–2001 to 49% in 2005–07. Significant progress was reported for some poor-prognosis cancers, such as chronic myeloid leukaemia, gastroenteropancreatic tumours (GEP), soft tissue sarcoma of viscera, plasmocytoma or multiple myeloma, and oesophageal cancers. Seven European countries provided data to study the extent of hospital centralisation for rare cancers and these data showed that, overall, centralisation of rare cancer treatment varied widely between countries and was generally low.

Implication of all the evidence

Rare cancers are a specific group of rare diseases requiring, compared with other rare diseases, the largest expenditure for drugs. The rare disease community has strongly lobbied the EC to increase investment in research, management, and social support for these diseases. This very large population-based study on rare cancers thus provides useful information for public health. The EC recognised the results of RARECARE and RARECAREnet and launched a European Joint Action for Rare Cancers in 2016 aiming to help member states with their national health plans. The EC also recently approved two specific rare cancer European Reference Networks (ERN), for childhood and solid cancers, to exchange management of very rare cancers or to treat patients from small countries. Both initiatives can use these data, with national and European health-care institutions, to address the issue of rare cancers better.

Lower survival of patients with rare cancer might be explained by difficulties in clinical research, as well as their specific biological characteristics, and our results have shown that non-optimal organisation of care can have a role too. There is ample room for improving the levels of centralisation of treatment and clinical expertise in seven European countries. These results were discussed in national meetings, and confirmed the need for improving the centralisation of rare cancer treatment in fewer, more specialised hospitals. Our data offer a starting point to measure the effects of new policies on rare cancers.

Data provided by cancer registries are essential, but their quality has to improve, especially on morphology, hospital and treatment definitions. Basic information on stage and the determinants of stage needs to be collected routinely. The European network of cancer registries should work to boost these improvements and make wider use of the data on rare cancers.

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cancer registries for patients with cancer diagnosed between Jan 1, 1978, and Dec 31, 2007. Vital status was updated to Dec 31, 2008. From the 117 cancer registries participating in EUROCARE-5, we excluded specialised paediatric cancer registries, the Swedish and Turin cancer registries, because they did not participate in the RARECAREnet study, and the Danish cancer registry, because it did not provide the morphology detail needed to define rare cancers. Details of the RARECAREnet database can be found in the report on the project website.[5] To analyse incidence, we excluded 11 anatomical-site-specific cancer registries to avoid incomplete coverage of some cancer entities affecting multiple sites such as neuroendocrine tumours. We excluded cases identified only by death certificate or incidentally discovered at autopsy from the analysis because they do not report time of survival. Cases lost to follow-up were considered as censored at the date of last contact. We included multiple primaries in the same patient.

The second database was used for the study of hospitals of treatment and hospital volume, which includes data from seven European cancer registries: the national cancer registries of Belgium, Bulgaria, Finland, Ireland, the Netherlands, Slovenia, and the regional cancer

registry of Navarra (Spain). The Navarra cancer registry, although regional, was added because of the regional organisation of the Spanish health-care system. These cancer registries were selected to reflect the variability of incidence and survival in Europe,[1,5] and because they could provide detailed data for all 198 rare cancers included in the RARECAREnet list. Variables included in the database were: sex, date of birth, date of diagnosis, topography and morphology codes from the International Classification of Disease for Oncology version 3 (ICDO-3) grading, pathological and clinical TNM Classification of Malignant Tumours (TNM) staging, simplified stage (localised, regional extension, metastatic), treatment (surgery, radiotherapy, systemic, other, or none), vital status, date of last follow-up or death, hospital of diagnosis, and hospital of treatment. The hospital of diagnosis was defined as the hospital where the pathology examination was done or requested. The hospital of treatment(s) was defined as the hospital where a specific treatment (eg, surgery) or the first course of systemic therapy (eg, chemotherapy) was given. Up to five different types of treatment within 1 year from the date of diagnosis were considered as a primary treatment. Vital status was further updated in this second database, with respect to the first descriptive analysis database, to Dec 31, 2012.

Analysis

The rationale for the definition of rare cancer entities and their classification in terms of ICD-O codes are reported elsewhere.[1,2,5] Classification was structured to avoid any overlap among rare entities. For example, gastroenteropancreatic neuroendocrine tumours and gastrointestinal stromal tumours were under the families of neuroendocrine tumours and sarcomas, but not also in digestive rare cancers.

From the first database, we estimated incidence as the number of new cases arising in 2000–07 divided by the corresponding total person-years (male and female) in the general population. The European standard population was used for direct age standardisation. New cases in 2013 in EU28 (28 member states of EU) were calculated by multiplying age-specific and sex-specific incidence rates in 2000–07 by the corresponding European population classified in 5-year age classes on Jan 1, 2013.

We estimated incidence variation by restricting the analysis to cases diagnosed in the two sub-periods 1999–2002 and 2003–07, and presented the results in a funnel plot. Annual percentage change was calculated as the ratio between incidence rates for the two sub-periods to the power of 1 over 4·5, the inverse of the mean difference in time between the two sub-periods.

We estimated 5-year relative survival as the ratio of observed to expected survival in the general population, matched by age, sex, calendar year, and geographical area, and calculated by the Ederer-2 method.[6] We estimated relative survival time trends using the period approach and considering three follow-up periods: 1999–2001 (cohorts diagnosed in Jan 1, 1995, to Dec 31, 2001), 2002–04 (cohorts diagnosed in Jan 1,1998 to Dec 31, 2004), and 2005–07 (cohorts diagnosed in Jan 1, 2001, to Dec 31, 2007). We presented relative survival changes as a funnel plot.

The volume (number) of treatments provided by each hospital was calculated from the second database for major cancer groups, defined by aggregating all the solid rare cancers into 38 groups sharing the same referral pattern. For example, all seven head and neck tumours identified as clinically distinct rare entities[1] are usually referred to head and neck specialised services, and we considered these as a single group. Haematological rare tumours do not always require hospitalisation and we did not consider these in the volume analysis. We then computed hospital volume for each of the 38 groups as the annual number of any treatment delivered by the hospital, for all the cancers in that group. We regarded repeated admissions to the same hospital for the same cancer and the same treatment type (ie, surgery, radiotherapy, or systemic therapy) as a single admission and counted as one treatment in the analyses. Repeated admissions for several treatment types (such as radiotherapy and subsequent surgery) given to a patient in the same hospital were counted as separate treatments. Untreated patients were assigned to the hospital of diagnosis. The total number of treatments provided by each hospital for a given group of rare cancers was then divided by the number of years of observation to provide its mean annual hospital volume. Pearson's correlation coefficient was used to evaluate the association, across cancers, between mean admission volume and incidence.

Finally, for each patient we calculated the mean annual volume of the hospital(s) where they were treated to obtain a patient-specific measure with a much less skewed distribution with respect to the hospital-specific volume. The mean value of this measure for all the patients diagnosed with a given group of rare cancers in a certain country gives a cancer-specific and country-specific measure of the level of expertise that patients can expect for the treatment of their tumour. We called this calculation the mean admission volume indicator.

Role of the funding source

The funders had no role in study design, collection, analysis or interpretation of data, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Survival estimates in 2000–07 for all rare cancers were based on 1994346 diagnoses, observed by 94 cancer registries. 1984147 rare cancer diagnoses were considered for incidence estimates in 2000–07, collected by 83 cancer registries from 1566 million person-years of observation.

62 828 (3%) of 1 984 147 cases were identified by death certificate only or incidentally at autopsy ranging from a maximum of 4412 (10%) of 44 755 cases in Slovakia, to 265 (<1%) of 60 377 cases in Scotland. Data for incidence time trends came from 42 cancer registries for 1995–2007, and included 2 268 602 cases, and 1900 million person-years of observation. Survival time trend analysis was based on 1 649 309 rare cancer diagnoses from 45 cancer registries providing uninterrupted data from at least Jan 1, 1995, to Dec 31, 2007.

For the study of hospitals of treatment and hospital volume, we received data for about 348 000 rare cancers diagnosed in the period 2000–07. However, national data from Belgium were limited to 2004–07, and those from Navarra to 2000–05. Cases diagnosed in Bulgaria and the Netherlands during 2000–04 were removed on account of incomplete national coverage of hospital information. 223 081 rare cancer cases were included in the hospital volume study database. Non-specific morphologies (8000, 8001, 8010, 8800, 9800, 9590) were found in 4588 (2%), with the highest proportion in Finland (1268 [4%] of 30 740 cases). 37 959 (17%) of 223 081 cases were removed because hospital information was missing.

Table 1 shows the incidence and survival estimates for each of the 198 rare cancers, for 63 groups of rare cancers, for the 12 wider families in which rare cancers are hierarchically grouped, and for six common cancer groups. Haematological malignancies, rare cancers of female genital organs and of the digestive tract, and head and neck cancers were families with the highest overall incidence rates (from 19 to 28 per 100 000 people per year). Thoracic cancers, male

	Crude incidence rate per 100 000 people per year	95% CI	Observed cases in 83 cancer registries in 2000–07	Estimated new cases in 2013 in EU28	5-year relative survival (%)	95% CI	Observed cases in 94 cancer registries in 2000–07
Rare: head and neck cancers	18·82	16·76–16·89	263 565	84 989	52·1%	51·8–52·3	254 563
Epithelial tumours of nasal cavity and sinuses	0·45	0·44–0·46	7046	2282	47·3%	45·8–48·8	6867
Squamous cell carcinoma with variants of nasal cavity and sinuses	0·35	0·34–0·36	5465	1770	49·5%	47·8–51·2	5444
Lymphoepithelial carcinoma of nasal cavity and sinuses	0·00	0·00–0·00	31	10	70·8%	50·7–99·0	31
Undifferentiated carcinoma of nasal cavity and sinuses	0·02	0·02–0·02	286	93	30·5%	24·3–38·2	283
Intestinal-type adenocarcinoma of nasal cavity and sinuses	0·00	0·00–0·00	42	14	65·0%	48·9–86·4	42
Epithelial tumours of nasopharynx	0·47	0·46–0·49	7439	2580	48·9%	47·5–50·2	7276
Squamous cell carcinoma with variants of nasopharynx	0·36	0·35–0·37	5613	1941	48·5%	47·0–50·1	5589
Papillary adenocarcinoma of nasopharynx	0·00	0·00–0·00	17	6	58·7%	36·2–95·3	17
Epithelial tumours of major salivary glands and salivary-gland-type tumours	1·39	1·37–1·41	21 794	7059	62·8%	62·0–63·7	21 364
Epithelial tumours of major salivary glands	0·96	0·95–0·98	15 053	4876	60·8%	59·8–61·8	14 703
Salivary-gland-type tumours of head and neck	0·43	0·42–0·44	6741	2183	67·1%	65·7–68·6	6683
Epithelial tumours of hypopharynx and larynx	6·33	6·29–6·37	99 176	31 545	52·0%	51·6–52·4	96 793
Squamous cell carcinoma with variants of hypopharynx	1·27	1·25–1·28	19 828	6422	25·1%	24·4–25·9	19 878
Squamous cell carcinoma with variants of larynx	4·61	4·58–4·64	72 210	23 389	60·5%	60·1–61·0	71 928
Epithelial tumours of oropharynx	3·32	3·29–3·35	52 017	16 848	40·9%	40·4–41·4	50 843
Squamous cell carcinoma with variants of oropharynx	3·12	3·09–3·14	48 812	15 810	41·3%	40·8–41·8	48 401
Epithelial tumours of oral cavity and lip	4·78	4·75–4·81	74 890	24 257	56·7%	56·2–57·1	73 101
Squamous cell carcinoma with variants of oral cavity	3·51	3·48–3·54	54 931	17 792	48·0%	47·5–48·6	54 229
Squamous cell carcinoma with variants of lip	1·02	1·00–1·04	15 984	5177	89·5%	88·5–90·5	15 899
Epithelial tumours of eye and adnexa	0·04	0·04–0·05	679	247	80·6%	75·9–85·6	673
Squamous cell carcinoma with variants of eye and adnexa	0·03	0·02–0·03	421	136	88·9%	83·0–95·2	422
Adenocarcinoma with variants of eye and adnexa	0·01	0·01–0·01	134	43	58·7%	49·1–70·1	134
Epithelial tumours of middle ear	0·03	0·03–0·04	524	170	44·1%	38·5–49·6	488
Squamous cell carcinoma with variants of middle ear	0·02	0·02–0·03	377	122	37·6%	31·8–44·4	370
Adenocarcinoma with variants of middle ear	0·00	0·00–0·00	50	16	83·8%	70·5–99·5	50
Rare: digestive cancers	21·94	21·86–22·01	343 635	112 351	15·3%	15·2–15·5	321 375
Epithelial tumours of oesophagus	7·81	7·77–7·85	122 344	40 068	12·0%	11·8–12·2	119 522
Squamous cell carcinoma with variants of oesophagus	3·36	3·33–3·39	52 597	17 036	11·7%	11·3–12·0	53 225
Adenocarcinoma with variants of oesophagus	3·26	3·24–3·29	51 138	16 564	13·9%	13·5–14·2	51 250
Salivary-gland-type tumours of oesophagus	0·00	0·00–0·01	63	20	13·7%	6·4–29·0	64
Undifferentiated carcinoma of oesophagus	0·04	0·04–0·05	695	225	6·8%	4·9–9·4	712

(Table 1 continues on next page)

	Crude incidence rate per 100 000 people per year	95% CI	Observed cases in 83 cancer registries in 2000–07	Estimated new cases in 2013 in EU28	5-year relative survival (%)	95% CI	Observed cases in 94 cancer registries in 2000–07
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Rare epithelial tumours of stomach	0·33	0·32–0·34	5146	1886	15·9%	14·7–17·1	5157
Squamous cell carcinoma with variants of stomach	0·12	0·11–0·12	1807	585	17·5%	15·6–19·7	1800
Salivary-gland-type tumours of stomach	0·00	0·00–0·00	39	13	25·1%	12·7–49·9	40
Undifferentiated carcinoma of stomach	0·21	0·20–0·22	3300	1069	14·9%	13·5–16·4	3317
Epithelial tumours of small intestine	0·77	0·76–0·79	12 132	3930	27·3%	26·3–28·3	11 544
Adenocarcinoma with variants of small intestine	0·59	0·58–0·60	9219	2986	27·9%	26·8–29·0	9193
Squamous cell carcinoma with variants of small intestine	0·01	0·01–0·01	133	43	34·8%	26·8–45·3	133
Rare epithelial tumour of colon	0·13	0·13–0·14	2074	737	54·8%	52·0–57·7	2075
Squamous cell carcinoma with variants of colon	0·03	0·02–0·03	400	130	37·1%	31·8–43·4	395
Fibromixoma and low-grade mucinous adenocarcinoma of the appendix	0·11	0·10–0·11	1674	542	58·8%	55·7–62·1	1680
Rare epithelial tumours of rectum	0·11	0·11–0·12	1764	635	47·2%	44·4–50·2	1777
Squamous cell carcinoma with variants of rectum	0·11	0·11–0·12	1764	571	47·2%	44·4–50·2	1777
Epithelial tumours of anal canal	1·16	1·14–1·18	18 155	5880	56·5%	55·5–57·4	18 020
Squamous cell carcinoma with variants of anal canal	0·81	0·80–0·82	12 691	4111	63·0%	61·9–64·1	12 847
Adenocarcinoma with variants of anal canal	0·25	0·25–0·26	3970	1286	41·9%	39·9–43·9	3945
Paget's disease of anal canal	0·00	0·00–0·00	21	7	62·9%	38·0–104·0	21
Rare epithelial tumours of pancreas	0·07	0·07–0·08	1159	414	20·2%	17·4–23·3	1116
Squamous cell carcinoma with variants of pancreas	0·02	0·02–0·03	361	117	5·9%	3·6–9·6	347
Acinar cell carcinoma of pancreas	0·03	0·03–0·03	449	145	19·0%	14·8–24·3	427
Mucinous cystadenocarcinoma of pancreas	0·01	0·01–0·01	109	35	35·9%	26·3–49·0	106
Intraductal papillary mucinous carcinoma invasive of pancreas	0·01	0·01–0·01	173	56	31·8%	23·6–42·9	171
Solid pseudopapillary carcinoma of pancreas	0·00	0·00–0·00	44	14	67·7%	52·8–86·8	42
Serous cystadenocarcinoma of pancreas	0·00	0·00–0·00	4	1	NE	NE	4
Carcinoma with osteoclast-like giant cells of pancreas	0·00	0·00–0·00	19	6	NE	NE	19
Epithelial tumours of liver and intrahepatic bile tract	7·10	7·06–7·14	111 271	36 261	10·1%	9·9–10·3	98 765
Hepatocellular carcinoma of liver and intrahepatic bile tract	3·22	3·19–3·25	50 461	16 344	14·0%	13·7–14·4	46 896
Hepatocellular carcinoma, fibrolamellar of liver and intrahepatic bile tract	0·02	0·02–0·03	387	125	28·1%	23·3–33·8	390
Cholangiocarcinoma of intrahepatic bile tract	0·97	0·95–0·99	15 201	4924	6·0%	5·6–6·6	13 845
Adenocarcinoma with variants of liver and intrahepatic bile tract	0·41	0·40–0·42	6457	2091	6·6%	5·9–7·4	6311
Undifferentiated carcinoma of liver and intrahepatic bile tract	0·02	0·01–0·02	240	78	2·7%	1·2–6·4	219
Squamous cell carcinoma with variants of liver and intrahepatic bile tract	0·01	0·01–0·01	147	48	14·6%	9·1–23·4	143
Bile duct cystadenocarcinoma of intrahepatic bile tract	0·00	0·00–0·00	38	12	23·6%	11·5–48·5	34
Epithelial tumours of gallbladder and extrahepatic biliary tract	4·44	4·41–4·48	69 590	22 540	13·6%	13·2–13·9	63 889
Adenocarcinoma with variants of gallbladder	1·35	1·33–1·36	21 085	6830	14·5%	14·0–15·1	20 338
Adenocarcinoma with variants of extrahepatic biliary tract	1·44	1·42–1·46	22 510	7291	19·2%	18·6–19·8	22 234
Squamous cell carcinoma of gallbladder and extrahepatic biliary tract	0·03	0·03–0·03	496	161	8·8%	6·3–12·3	476
Rare: thoracic cancers	6·80	6·76–6·84	106 573	37 277	13·4%	13·1–13·6	104 670
Epithelial tumour of trachea	0·11	0·11–0·12	1771	574	18·0%	16·0–20·3	1697
Squamous cell carcinoma with variants of trachea	0·06	0·06–0·07	1017	329	12·2%	10·0–14·9	1008
Adenocarcinoma with variants of trachea	0·01	0·01–0·01	164	53	15·7%	10·3–24·0	158
Salivary-gland-type tumours of trachea	0·01	0·01–0·01	175	57	70·1%	62·0–79·2	174
Rare epithelial tumour of lung	4·37	4·34–4·40	68 452	24 930	14·9%	14·6–15·2	67 936
Adenosquamous carcinoma of lung	0·29	0·29–0·30	4607	1492	21·9%	20·5–23·4	4566
Large-cell carcinoma of lung	3·81	3·78–3·84	59 714	19 342	13·9%	13·5–14·2	59 332
Salivary-gland-type tumours of lung	0·06	0·05–0·06	879	285	40·4%	36·8–44·4	866
Sarcomatoid carcinoma of lung	0·21	0·20–0·22	3255	1054	17·5%	16·0–19·2	3183

(Table 1 continues on next page)

	Crude incidence rate per 100 000 people per year	95% CI	Observed cases in 83 cancer registries in 2000–07	Estimated new cases in 2013 in EU28	5-year relative survival (%)	95% CI	Observed cases in 94 cancer registries in 2000–07
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Epithelial tumours of thymus	0·18	0·17–0·19	2795	905	64·3%	62·1–66·6	2729
Malignant thymoma	0·14	0·14–0·15	2268	735	69·3%	67·0–71·8	2248
Squamous cell carcinoma of thymus	0·01	0·01–0·01	114	37	40·4%	30·4–53·7	112
Undifferentiated carcinoma of thymus	0·00	0·00–0·00	36	12	13·3%	5·1–34·8	36
Lymphoepithelial carcinoma of thymus	0·00	0·00–0·00	12	4	55·0%	29·2–103·6	11
Adenocarcinoma with variants of thymus	0·00	0·00–0·00	45	15	37·3%	21·7–64·1	44
Malignant mesothelioma	2·14	2·12–2·16	33 552	10 868	5·3%	4·9–5·6	32 330
Mesothelioma of pleura and pericardium	1·83	1·81–1·85	28 676	9288	4·6%	4·2–4·9	27 893
Mesothelioma of peritoneum and tunica vaginalis	0·13	0·13–0·14	2065	669	13·2%	11·5–15·1	1965
Rare: female genital cancers	22·73	22·66–22·81	356 151	113 796	57·7%	57·5–57·9	347 015
Rare epithelial tumours of breast	4·12	4·09–4·16	64 605	22 980	91·4%	91·0–91·8	64 368
Mammary Paget's disease of breast	0·41	0·40–0·42	6488	2101	85·9%	84·6–87·3	6508
Special types of adenocarcinoma of breast	3·06	3·04–3·09	48 012	15 551	95·2%	94·8–95·6	47 974
Metaplastic carcinoma of breast	0·10	0·10–0·11	1576	510	65·0%	61·9–68·3	1583
Salivary-gland-type tumours of breast	0·06	0·05–0·06	868	281	90·9%	87·6–94·2	870
Epithelial tumour of male breast	0·52	0·51–0·53	8098	5376	77·0%	75·5–78·5	7882
Rare epithelial tumours of corpus uteri	0·70	0·69–0·72	11 038	3932	44·3%	43·2–45·5	11 013
Squamous cell carcinoma with variants of corpus uteri	0·06	0·06–0·07	1003	325	58·2%	54·6–62·1	989
Adenoid cystic carcinoma of corpus uteri	0·00	0·00–0·00	5	2	64·1%	31·3–131·1	5
Clear cell adenocarcinoma, not otherwise specified of corpus uteri	0·16	0·16–0·17	2527	819	58·6%	56·2–61·2	2532
Serous (papillary) carcinoma of corpus uteri	0·08	0·07–0·08	1227	397	40·0%	36·5–43·9	1225
Mullerian mixed tumour of corpus uteri	0·40	0·39–0·41	6276	2033	36·9%	35·5–38·4	6263
Epithelial tumours of cervix uteri	6·28	6·24–6·32	98 321	28 898	65·4%	65·1–65·8	96 821
Squamous cell carcinoma with variants of cervix uteri	4·73	4·70–4·76	74 105	24 003	66·8%	66·5–67·2	73 810
Adenocarcinoma with variants of cervix uteri	0·91	0·89–0·92	14 252	4616	67·4%	66·5–68·3	14 221
Undifferentiated carcinoma of cervix uteri	0·03	0·03–0·03	480	155	35·3%	30·9–40·4	478
Mullerian mixed tumour of cervix uteri	0·02	0·01–0·02	257	83	34·3%	28·1–41·7	256
Epithelial tumour of ovary and fallopian tube	9·38	9·33–9·43	146 908	45 382	37·5%	37·2–37·8	141 240
Adenocarcinoma with variants of ovary	5·95	5·92–5·99	93 263	30 208	38·7%	38·3–39·1	92 814
Mucinous adenocarcinoma of ovary	0·77	0·76–0·78	12 066	3908	59·9%	58·9–60·9	12 010
Clear cell adenocarcinoma of ovary	0·30	0·29–0·31	4753	1540	55·5%	53·8–57·2	4761
Primary peritoneal serous or papillary carcinoma of ovary	0·08	0·08–0·09	1280	415	21·9%	19·1–25·2	1280
Mullerian mixed tumour of ovary	0·14	0·14–0·15	2255	730	21·4%	19·5–23·6	2242
Adenocarcinoma with variant of fallopian tube	0·17	0·16–0·18	2683	869	59·1%	56·8–61·6	2672
Non-epithelial tumours of ovary	0·25	0·25–0·26	3977	1288	82·0%	80·6–83·5	3970
Sex cord tumours of ovary	0·13	0·12–0·13	2006	650	78·8%	76·5–81·1	1998
Malignant or immature teratomas of ovary	0·05	0·05–0·06	833	270	83·4%	80·6–86·3	829
Germ cell tumour of ovary	0·07	0·07–0·08	1138	369	86·6%	84·4–88·8	1143
Epithelial tumours of vulva and vagina	1·97	1·95–2·00	30 938	11 215	58·1%	57·3–58·8	30 238
Squamous cell carcinoma with variants of vulva and vagina	1·69	1·67–1·71	26 422	8558	59·8%	59·0–60·7	26 277
Adenocarcinoma with variants of vulva and vagina	0·07	0·07–0·08	1120	363	45·8%	42·3–49·6	1112
Paget's disease of vulva and vagina	0·05	0·04–0·05	746	242	88·0%	83·7–92·6	744
Undifferentiated carcinoma of vulva and vagina	0·01	0·00–0·01	85	28	25·6%	15·8–41·6	85
Trophoblastic tumour of placenta	0·02	0·02–0·03	363	100	89·3%	85·3–92·2	361
Choriocarcinoma of placenta	0·02	0·02–0·02	352	114	89·8%	86·5–93·3	350

(Table 1 continues on next page)

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(Continued from previous page)							
Rare: male genital and urogenital cancers	7·09	7·05–7·14	111 128	38 138	73·6%	73·3–74·0	109 102
Rare epithelial tumours of prostate	0·60	0·59–0·61	9437	3563	75·4%	74·0–76·9	9291
Squamous cell carcinoma with variants of prostate	0·02	0·02–0·02	291	94	41·1%	34·1–49·5	287
Infiltrating duct carcinoma of prostate	0·51	0·50–0·53	8064	2612	78·7%	77·2–80·3	7945
Transitional cell carcinoma of prostate	0·06	0·06–0·07	960	311	57·7%	53·4–62·4	941
Salivary-gland-type tumours of prostate	0·01	0·01–0·01	122	40	78·5%	64·4–95·7	118
Testicular and paratesticular cancers	3·29	3·27–3·32	51 605	16 061	94·9%	94·7–95·2	51 011
Paratesticular adenocarcinoma with variants	0·00	0·00–0·00	22	7	82·5%	65·3–104·1	22
Non-seminomatous testicular cancer	1·27	1·25–1·28	19 835	6425	92·9%	92·5–93·3	19 714
Seminomatous testicular cancer	1·82	1·80–1·84	28 516	9236	97·5%	97·3–97·8	28 326
Spermatocytic seminoma	0·03	0·03–0·03	502	163	95·3%	91·8–99·0	502
Teratoma with malignant transformation	0·00	0·00–0·00	20	6	91·4%	78·6–106·2	20
Testicular sex cord cancer	0·02	0·02–0·02	340	110	82·3%	77·3–87·6	337
Epithelial tumours of penis	0·66	0·65–0·67	10 368	3887	67·5%	66·2–68·9	10 210
Squamous cell carcinoma with variants of penis	0·62	0·60–0·63	9646	3124	68·9%	67·5–70·2	9621
Adenocarcinoma with variants of penis	0·01	0·00–0·01	88	29	49·0%	36·2–66·4	86
Rare epithelial tumours of kidney	0·05	0·04–0·05	723	261	18·8%	15·8–22·4	704
Squamous cell carcinoma spindle cell type of kidney	0·01	0·01–0·01	190	62	22·0%	16·0–30·2	190
Squamous cell carcinoma with variants of kidney	0·03	0·03–0·04	533	173	17·7%	14·4–21·7	514
Epithelial tumours of pelvis and ureter	1·58	1·57–1·60	24 826	9187	48·8%	48·0–49·7	24 017
Transitional cell carcinoma of pelvis and ureter	1·41	1·39–1·43	22 099	7158	51·3%	50·4–52·2	21 607
Squamous cell carcinoma with variants of pelvis and ureter	0·02	0·02–0·03	372	121	15·0%	11·2–20·2	366
Adenocarcinoma with variants of pelvis and ureter	0·02	0·02–0·02	326	106	43·0%	36·7–50·5	320
Epithelial tumours of urethra	0·13	0·13–0·14	2077	784	44·5%	41·6–47·5	2050
Transitional cell carcinoma of urethra	0·09	0·08–0·09	1390	450	42·9%	39·5–46·7	1387
Squamous cell carcinoma with variants of urethra	0·02	0·02–0·02	329	107	51·1%	44·6–58·5	329
Adenocarcinoma with variants of urethra	0·01	0·01–0·01	190	62	52·0%	43·2–62·6	189
Rare epithelial tumours of bladder	0·65	0·64–0·67	10 226	3819	32·3%	31·2–33·5	10 152
Squamous cell carcinoma with variants of bladder	0·36	0·35–0·36	5566	1803	24·3	22·9–25·7	5534
Adenocarcinoma with variants of bladder	0·30	0·29–0·31	4653	1507	41·9%	40·1–43·8	4614
Salivary-gland-type tumours of bladder	0·00	0·00–0·00	7	2	NE	NE	7
Extragonadal germ cell tumours	0·12	0·11–0·12	1862	576	69·6%	67·3–71·8	1851
Non-seminomatous germ cell tumours	0·06	0·05–0·06	915	296	62·5%	59·2–66·0	909
Seminomatous germ cell tumours	0·01	0·01–0·01	130	42	85·9%	79·1–93·3	130
Germ cell tumours of CNS	0·04	0·03–0·04	574	186	82·5%	79·2–85·9	572
Rare: neuroendocrine tumours	3·51	3·43–3·58	54 942	19 587	53·5%	53·0–54·1	54 331
GEP, well differentiated not functioning endocrine carcinoma of pancreas and digestive tract	1·01	1·00–1·03	15 852	5134	72·0%	71·1–73·0	15 656
GEP, well differentiated functioning endocrine carcinoma of pancreas and digestive tract	0·03	0·02–0·03	411	133	61·3%	55·9–67·3	407
GEP, poorly differentiated endocrine carcinoma	0·67	0·65–0·68	10 421	3375	35·0%	33·9–36·2	10 456
GEP, mixed endocrine–exocrine carcinoma	0·01	0·01–0·01	147	48	25·9%	18·2–37·0	141
Endocrine carcinoma of thyroid gland	0·24	0·23–0·25	3796	1230	83·6%	82·1–85·2	3793
Neuroendocrine carcinoma of skin	0·19	0·19–0·20	3024	979	55·9%	53·2–58·7	2997
Typical and atypical carcinoid of the lung	0·39	0·38–0·40	6160	1995	81·1%	79·9–82·5	6058
Neuroendocrine carcinoma of other sites	0·90	0·89–0·92	14 120	4573	23·9%	23·0–24·8	13 958
Pheochromocytoma, malignant	0·04	0·04–0·04	650	211	70·1%	65·9–74·5	612
Paraganglioma	0·02	0·02–0·02	347	112	56·3%	50·6–62·6	342

(Table 1 continues on next page)

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(Continued from previous page)							
Rare: cancers of the endocrine organs	5·35	5·32–5·39	83 836	28 322	88·1%	87·8–88·4	82 523
Carcinomas of pituitary gland	0·04	0·03–0·04	582	206	63·7%	58·9–69·0	511
Carcinomas of thyroid gland	5·07	5·03–5·10	79 418	26 768	90·5%	90·2–90·8	78 533
Carcinomas of parathyroid gland	0·03	0·02–0·03	410	143	80·8%	75·8–86·2	395
Carcinomas of adrenal gland	0·22	0·21–0·23	3424	1205	32·1%	30·2–34·0	3103
Rare: sarcomas	5·86	5·83–6·00	91 878	31 916	59·5%	57·4–58·2	90 568
Soft tissue sarcoma	4·71	4·68–4·74	73 795	25 851	56·7%	56·3–57·1	72 696
Soft tissue sarcoma of head and neck	0·26	0·25–0·27	4087	1324	59·8%	57·7–61·8	4062
Soft tissue sarcoma of limbs	1·10	1·08–1·11	17 178	5564	67·7%	66·8–68·6	17 094
Soft tissue sarcoma of superficial trunk	0·50	0·49–0·51	7813	2531	48·1%	46·8–49·5	7723
Soft tissue sarcoma of mediastinum	0·03	0·03–0·03	465	151	23·4%	19·3–28·3	457
Soft tissue sarcoma of heart	0·01	0·01–0·02	216	70	14·4%	9·8–21·0	203
Soft tissue sarcoma of breast	0·18	0·18–0·19	2865	928	74·5%	72·5–76·5	2864
Soft tissue sarcoma of uterus	0·55	0·54–0·56	8657	2804	52·0%	50·8–53·2	8568
Other soft tissue sarcomas of genitourinary tract	0·20	0·19–0·21	3160	1024	50·4%	48·3–52·5	3107
Soft tissue sarcoma of viscera	0·38	0·37–0·39	6004	1945	42·1%	40·6–43·6	5915
Soft tissue sarcoma of paratestis	0·03	0·03–0·04	510	165	87·2%	82·2–92·4	510
Soft tissue sarcoma of retroperitoneum and peritoneum	0·31	0·30–0·32	4911	1591	38·8%	37·1–40·5	4854
Soft tissue sarcoma of pelvis	0·20	0·19–0·20	3090	1001	47·4%	45·3–49·6	3064
Soft tissue sarcoma of skin	0·30	0·29–0·31	4737	1534	90·2%	88·8–91·7	4728
Soft tissue sarcoma of paraorbit	0·01	0·01–0·01	117	38	63·3%	52·9–75·7	115
Soft tissue sarcoma of brain and other parts of nervous system	0·17	0·17–0·18	2723	882	54·5%	52·3–56·7	2695
Embryonal rhabdomyosarcoma of soft tissue	0·05	0·05–0·06	836	271	66·2%	62·8–69·8	825
Alveolar rhabdomyosarcoma of soft tissue	0·03	0·03–0·04	519	168	36·0%	31·7–40·8	515
Ewing's sarcoma of soft tissue	0·06	0·06–0·07	998	323	44·9%	41·5–48·5	992
Bone sarcoma	0·85	0·84–0·87	13 376	4382	58·6%	57·6–59·6	13 216
Osteogenic sarcoma	0·21	0·21–0·22	3330	1079	51·4%	49·5–53·4	3282
Chondrogenic sarcomas	0·26	0·25–0·27	4107	1330	70·0%	68·2–71·7	4060
Notochordal sarcomas, chordoma	0·07	0·07–0·08	1145	371	62·5%	58·2–67·2	755
Vascular sarcomas	0·01	0·01–0·01	129	42	45·1%	36·4–55·9	129
Ewing's sarcoma	0·12	0·12–0·13	1943	629	52·8%	50·4–55·3	1932
Epithelial tumours, adamantinoma	0·01	0·01–0·02	213	69	87·2%	81·0–93·9	210
Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	0·02	0·02–0·02	304	98	46·2%	40·1–53·1	302
Gastrointestinal stromal sarcoma	0·30	0·29–0·31	4706	1683	72·3%	70·4–74·1	4781
Rare: cancers of the CNS	7·56	7·51–8·00	118 391	36 343	21·3%	21·0–21·6	111 838
Tumours of CNS	7·36	7·32–7·40	115 289	35 339	20·3%	20·0–20·6	108 752
Astrocytic tumours of CNS	4·99	4·95–5·02	78 118	25 303	15·0%	14·8–15·3	77 195
Oligodendroglial tumours of CNS	0·39	0·38–0·40	6148	1991	51·8%	50·4–53·3	6124
Ependymal tumours of CNS	0·21	0·20–0·21	3212	1040	72·7%	71·0–74·5	3190
Choroid plexus carcinoma of CNS	0·01	0·01–0·01	98	32	57·7%	48·3–68·8	95
Malignant meningiomas	0·16	0·16–0·17	2564	830	61·1%	58·8–63·4	2509
Embryonal tumours of CNS	0·20	0·19–0·21	3102	1005	56·1%	54·2–58·1	3092
Rare: skin cancers and non-cutaneous melanoma	1·22	1·18–1·25	21 878	7086	70·2%	69·3–71·1	21 637
Malignant melanoma of mucosa	0·15	0·14–0·15	2279	738	20·3%	18·3–22·6	2277
Malignant melanoma of uvea	0·70	0·69–0·72	11 022	3570	71·0%	69·8–72·2	10 872
Adnexal carcinoma of skin	0·30	0·29–0·31	4684	1517	86·1%	83·9–88·0	4661
Kaposi's sarcoma	0·25	0·24–0·26	3893	1261	78·9%	77·1–80·8	3830

(Table 1 continues on next page)

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(Continued from previous page)							
Rare: embryonal tumours	0·34	0·33–0·35	5363	1822	78·6%	77·4–79·8	5239
Neuroblastoma and ganglioneuroblastoma	0·10	0·10–0·11	1566	507	64·6%	62·1–67·3	1553
Nephroblastoma	0·13	0·12–0·13	1965	636	88·2%	86·6–89·7	1936
Retinoblastoma	0·05	0·05–0·06	860	279	96·5%	95·1–97·9	801
Hepatoblastoma	0·02	0·02–0·03	357	116	76·8%	72·2–81·7	352
Pleuropulmonary blastoma	0·00	0·00–0·00	9	3	53·5%	28·3–101·1	9
Pancreatoblastoma	0·00	0·00–0·00	39	13	34·3%	20·7–56·9	35
Olfactory neuroblastoma	0·03	0·03–0·03	498	161	64·0%	59·2–69·2	489
Odontogenic malignant tumours	0·00	0·00–0·01	69	22	61·6%	49·0–77·5	69
Rare: haematological malignancies	27·73	27·65–27·82	434 469	156 099	50·5%	50·3–50·7	423 741
Rare lymphoid diseases	18·09	18·02–18·16	283 399	100 343	55·8%	55·5–56·0	279 794
Hodgkin's lymphoma, classical	2·46	2·44–2·49	38 588	12 499	81·4%	80·9–81·8	38 389
Hodgkin's lymphoma nodular lymphocyte predominance	0·09	0·09–0·10	1483	480	93·6%	91·8–95·3	1507
Precursor B-cell or T-cell lymphoblastic leukaemia or lymphoma (and Burkitt's leukaemia or lymphoma)	1·46	1·44–1·47	22 795	7383	58·1%	57·4–58·8	22 496
T-cell cutaneous lymphoma (Sezary syndrome, mycosis fungoides)	0·35	0·34–0·36	5526	1790	81·5%	80·0–83·1	5482
Other T-cell lymphomas and natural killer cell neoplasms	0·62	0·60–0·63	9656	3128	39·0%	37·9–40·2	9635
Diffuse B-cell lymphoma	4·32	4·29–4·35	67 645	21 910	53·4%	52·9–53·9	67 907
Follicular B-cell lymphoma	2·19	2·17–2·22	34 346	11 125	77·0%	76·4–77·6	34 545
Hairy cell leukaemia	0·28	0·27–0·29	4375	1417	89·8%	88·3–91·3	4387
Plasmacytoma or multiple myeloma (and heavy chain diseases)	5·71	5·67–5·75	89 440	28 970	35·3%	34·8–35·7	86 496
Mantle cell lymphoma	0·56	0·55–0·57	8748	2834	44·0%	42·6–45·4	8797
Prolymphocytic leukaemia, B cell	0·05	0·05–0·06	804	260	30·8%	26·9–35·2	788
Acute myeloid leukaemia and related precursor neoplasms	3·81	3·77–3·84	59 608	21 557	19·2%	18·8–19·6	56 709
Acute promyelocytic leukaemia with t(15;17) with variants	0·12	0·11–0·13	1876	608	63·2%	60·8–65·7	1880
Acute myeloid leukaemia	3·50	3·47–3·53	54 789	17 746	17·5%	17·1–17·8	52 305
Myeloproliferative neoplasms	3·31	3·28–3·34	51 888	18 805	68·3%	67·7–68·9	50 624
Chronic myeloid leukaemia	1·12	1·10–1·13	17 473	5660	54·9%	54·0–55·9	16 599
Other myeloproliferative neoplasms	2·17	2·14–2·19	33 954	10 998	75·0%	74·3–75·7	33 599
Mast cell tumour	0·03	0·03–0·03	461	149	71·4%	66·2–77·1	454
Myelodysplastic syndrome and myelodysplastic or myeloproliferative diseases	2·47	2·45–2·50	38 738	15 116	31·1%	30·5–31·8	37 792
Myelodysplastic syndrome with 5q syndrome	0·01	0·01–0·01	156	51	48·0%	38·3–60·3	178
Other myelodysplastic syndrome	2·14	2·12–2·16	33 542	10 864	32·2%	31·5–32·9	32 576
Chronic myelomonocytic leukaemia	0·29	0·28–0·30	4542	1471	21·3%	19·8–23·0	4575
Atypical chronic myeloid leukaemia BCR/ABL negative	0·02	0·01–0·02	239	77	28·2%	21·7–36·5	248
Histiocytic and dendritic cell neoplasms	0·05	0·05–0·06	828	278	59·9%	56·1–63·9	817
Histiocytic malignancies	0·04	0·04–0·05	656	212	63·4%	59·4–67·8	645
Lymph-node accessory cell tumours	0·01	0·01–0·01	172	56	45·6%	37·1–56·0	172
All rare tier 2 tumours	114·99	114·82–115·16	1 801 443	636 753	48·5%	48·4–48·6	1 751 601
Common: digestive tumours	91·80	91·65–91·95	1 438 094	490 051	41·4%	41·3–45·8	1 365 575
Epithelial tumours of stomach	17·10	17·03–17·16	267 832	92 067	21·2%	21·0–21·4	253 439
Adenocarcinoma with variants of stomach	14·18	14·12–14·24	222 145	71 954	22·7%	22·5–22·9	221 604
Epithelial tumours of colon	43·88	43·77–43·98	687 386	234 319	54·2%	54·0–54·4	664 118
Adenocarcinoma with variants of colon	38·85	38·75–38·95	608 637	197 139	57·9%	57·7–58·0	604 459
Epithelial tumours of rectum	17·98	17·92–18·05	281 697	95 187	53·8%	53·6–54·1	276 024
Adenocarcinoma with variants of rectum	16·45	16·39–16·52	257 723	83 477	55·8%	55·6–56·1	258 469
Epithelial tumours of pancreas	12·84	12·79–12·90	201 179	68 478	4·1%	4·0–4·2	182 579
Adenocarcinoma with variants of pancreas	7·96	7·92–8·01	124 744	40 405	4·1%	4·0–4·2	119 154

(Table 1 continues on next page)

	Crude incidence rate per 100 000 people per year	95% CI	Observed cases in 83 cancer registries in 2000–07	Estimated new cases in 2013 in EU28	5-year relative survival (%)	95% CI	Observed cases in 94 cancer registries in 2000–07
(Continued from previous page)							
Common: thoracic tumours	53·02	52·91–53·14	830 611	281 332	10·1%	10·0–10·2	779 539
Epithelial tumour of lung	53·02	52·91–53·14	830 611	281 332	10·1%	10·0–10·2	779 539
Squamous cell carcinoma with variants of lung	12·31	12·25–12·36	192 771	62 439	13·8%	13·6–14·0	190 051
Adenocarcinoma with variants of lung	11·63	11·58–11·68	182 175	59 007	16·0%	15·8–16·2	179 385
Poorly differentiated endocrine carcinoma of lung	7·91	7·86–7·95	123 888	40 128	5·9%	5·7–6·0	121 904
Common: female genital tumours	74·17	74·03–74·30	1 161 864	394 087	82·2%	82·1–82·3	1 131 902
Epithelial tumours of breast	63·52	63·40–63·65	995 119	318 878	82·4%	82·3–82·5	961 378
Invasive ductal carcinoma of breast	46·56	46·45–46·66	729 345	236 237	85·4%	85·3–85·6	723 998
Invasive lobular carcinoma of breast	7·75	7·71–7·80	121 455	39 340	86·2%	85·9–86·5	120 973
Epithelial tumours of corpus uteri	10·64	10·59–10·70	166 745	75 209	81·2%	80·9–81·4	164 787
Adenocarcinoma with variants of corpus uteri	9·93	9·88–9·98	155 550	50 383	83·0%	82·7–83·2	154 968
Common: male genital and urogenital tumours	85·27	85·13–85·42	1 335 876	462 665	75·9%	75·8–76·0	1 277 743
Epithelial tumours of prostate	55·06	54·95–55·18	862 576	301 113	84·0%	83·8–84·1	842 467
Adenocarcinoma with variants of prostate	48·86	48·75–48·97	765 405	247 917	88·1%	88·0–88·3	762 360
Epithelial tumours of kidney	12·66	12·61–12·72	198 402	65 848	60·5%	60·2–60·7	187 324
Renal cell carcinoma with variants	10·08	10·03–10·13	157 886	51 140	68·5%	68·2–68·8	153 460
Epithelial tumours of bladder	17·55	17·48–17·61	274 896	95 704	60·4%	60·1–60·6	266 941
Transitional cell carcinoma of bladder	15·68	15·62–15·74	245 681	79 577	62·7%	62·4–63·0	243 620
Common: skin tumours and non-cutaneous melanoma	69·08	68·95–69·21	1 082 244	350 542	95·6%	95·5–95·7	1 048 046
Malignant skin melanoma	14·06	14·00–14·12	220 206	71 325	83·8%	83·6–84·1	216 317
Epithelial tumours of skin	55·03	54·91–55·14	862 038	279 217	98·8%	98·7–99·0	837 895
Basal cell carcinoma of skin	40·75	40·65–40·85	638 347	206 763	101·6%	101·5–101·8	634 953
Squamous cell carcinoma with variants of skin	14·28	14·22–14·34	223 691	72 454	89·7%	89·4–90·1	221 487
Common: haematological malignancies	11·03	10·98–11·08	172 794	58 286	60·5%	60·2–60·8	166 040
Lymphoid diseases	11·03	10·98–11·08	172 794	58 286	60·5%	60·2–60·8	166 040
Other non-Hodgkin, mature B-cell lymphoma	6·37	6·33–6·41	99 729	32 303	68·3%	67·8–68·7	97 389
All common tumours	384·37	384·07–384·78	6 021 483	2 036 963	63·4%	63·3–63·4	5 633 710

The first tier entities are not a sum of the second tiers included because of the not otherwise specified entities. EU28=European Union (28 member states). GEP=gastroenteric-pancreatic tumour. NE=not estimable.

***Table 1*: Estimates of incidence and survival for rare and common cancers**

genital and urological tumours, endocrine organ tumours, CNS tumours, and sarcomas had overall incidences from 4 to 8 per 100 000 people per year. Rare skin cancers and non-cutaneous melanoma, and embryonal cancers were the families with the lowest incidences (1·22 and 0·34 per 100 000). Overall, rare cancers accounted for 24% of all cancers diagnosed in EU28 during 2000–07; the majority were solid cancers (76%). For sex-specific rare cancers, we also provide sex-specific incidence (appendix p 4).

5-year relative survival of all rare cancers was 48·5% (95% CI 48·4–48·6), compared with 63·4% (95% CI 63·3–63·4) for all common cancers. Rare cancers also had lower survival within the families of digestive cancers (15·3% [95% CI 15·2–15·5] for rare cancers *vs* 41·4% [41·3–41·5] for common cancers), female genital cancers (57·7% [57·5–57·9] *vs* 82·2% [82·1–82·3]), male genital and urological cancers (73·6% [73·3–74·0] *vs* 75·9% [75·8–76·0]), skin cancers (70·2% [69·3–71·1] *vs* 95·6% [95% CI 95·5–95·7]), and haematological tumours (50·5% [50·3–50·7] *vs* 60·5% [60·2–60·8]). The only exception was the thoracic cancer family (13·4% [13·1–13·6] *vs* 10·1% [10·0–10·2]), for which common cancers included poorly differentiated endocrine carcinoma of the lung with a very poor prognosis (5·9% [5·7–6·0] after 5 years. Families including only rare cancers had 5-year relative survival ranging from high, as for embryonal tumours (78·6% [95% CI 77·4–79·8]) and endocrine organ tumours (88·1% [87·8–88·4]), to intermediate, for sarcomas (59·5% [57·4–58·2]), neuroendocrine tumours (53·5% [53·0–54·1]), and head and neck tumours (52·1% [51·8–52·3]), and low for CNS tumours (21·3% [21·0–21·6]).

Time trends of incidence and survival for rare cancers are in figures 1 and 2. Cancers whose incidence variation fell outside the confidence interval shown in figure 1 are listed in table 2, with the age-standardised incidence estimates for 1999–2002 and 2003–07, the corresponding annual percentage change and 3 standard-error confidence intervals. Rare cancer dots in the plot seem to be

See Online for appendix

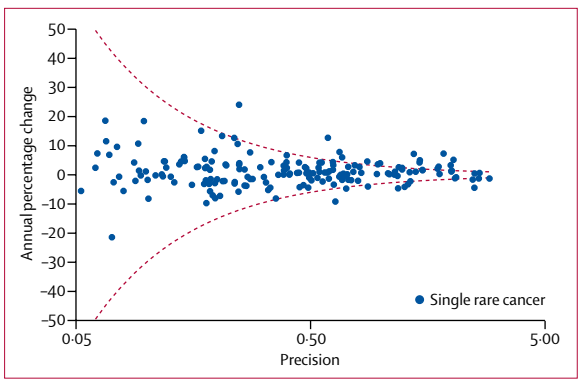

***Figure 1*: Annual percentage changes in age-adjusted incidence rates of rare cancers (1999–2007)**
Funnel plot in which each dot represents a single rare cancer, the y-axis displays the estimated difference in terms of annual percentage change of age-adjusted incidence, and the x-axis the corresponding precision in terms of the inverse of its standard error. 3 standard-error confidence bounds for estimated zero changes[7] are represented by two symmetrical lines progressively approaching the x-axis with increasing x values. Dots lying above or below the area between them correspond respectively to tumours with 99·8% significantly higher or lower incidence rates.

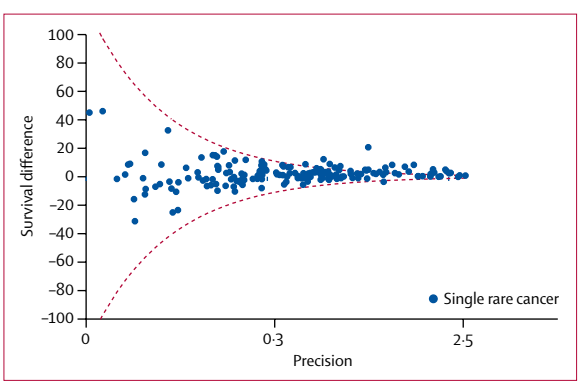

***Figure 2*: Difference in 5-year relative survival for rare cancers (1999–2001 *vs* 2005–07)**
Funnel plot in which each dot represents a single rare cancer, the y-axis displays the estimated difference between 5-year relative survival in 2005–07 and 1999–2001, and the x-axis the corresponding precision in terms of the inverse of its standard error. 3 standard-error confidence bounds for estimated zero changes[7] are represented by two symmetrical lines progressively approaching the x-axis with increasing x values. Dots lying above or below the area between them correspond respectively to tumours with 99·8% significantly higher or lower incidence rates.

distributed fairly symmetrically around the zero-change line, indicating no major systematic shifts in incidence. The average annual percentage change of all rare cancers was 0·5% (99·8% CI 0·3–0·8). Incidence increased for 16 rare cancers and incidence decreased for 10 rare cancers, but with changes falling outside the 99·8% confidence limits. Time trends of rare cancers did not substantially differ from those of common cancers (data not shown), whose average annual change was 0·9%. Only prostate and skin cancers had an annual percentage change of more than 2%, while only epithelial cancers of the stomach decreased more than 2% (data not shown).

Survival increased from 1999–2001 to 2005–07 for most rare cancers. The cloud of points in figure 2 is skewed upward from the zero line, corresponding to a mean increase in survival, averaged over all the entities, of 2·9% (95% CI 2·7–3·2). Survival for 24 rare cancers was significantly increased (table 3), whereas survival was significantly reduced for only one cancer (other myelodysplastic syndromes). Rare cancers with the largest survival increases were mainly haematological: chronic myeloid leukaemia, diffuse B cell lymphoma, follicular lymphoma, precursor B/T cell lymphoblastic leukaemia or lymphoma, and multiple myeloma. Sarcomas were well represented among the top tumours with increasing survival, specifically of the viscera, trunk, and Kaposi's sarcoma. Survival increases higher than 5 percentage points were also observed for infiltrating ductal carcinoma of the prostate (12·3 percentage points [99·8% CI 6·4–18·2]), poorly differentiated endocrine carcinoma of the digestive system (7·5 percentage points [2·7–12·2]), and squamous cell carcinoma of the oropharynx (7·1 percentage points [5·0–9·2]). There were no major improvements in survival for rare cancers of the colon, rectum, breast, or kidney, differently from the corresponding groups of common cancers.[8]

The extent of centralisation of rare cancer treatment is presented in figures 3 and 4 presenting mean admission volume, overall and by country, for 38 cancer groups ranked by decreasing incidence. We used a logarithmic scale for the x-axis to make the graph readable despite large mean admission volume variability (from 0·2 to 82·6 treatments per year) across the considered cancers. The mean number of admissions is in the appendix (p 3–4). Pooled mean admission volume (figures 3 and 4) ranged from a maximum of 82·6 treatments per year for head and neck tumours to less than 0·5 treatments per year for placenta (choriocarcinoma), and some embryonal and endocrine tumours. The higher the incidence, the larger the mean admission volume of treating hospitals. The association between cancer incidence and mean admission volume in the pool of countries was very strong (Pearson's correlation coefficient 0·88), although there are several outliers. For example, epithelial tumours of the ovary had a higher incidence but a lower mean admission volume than CNS tumours (35 *vs* 20 cases treated per year). Treatment of patients with epithelial tumours of the ovary was thus spread among a larger number of hospitals compared with CNS tumours. Similarly, the incidence of soft tissue sarcomas was 5 times higher than bone sarcomas, but soft tissue sarcomas were treated centrally less than bone sarcoma. Treatment for thyroid cancers, uveal melanoma, and several embryonal tumours appeared to be fairly concentrated in a few hospitals with relatively high volumes. By contrast, tumours of the urinary tract, gastroenteropancreatic neuroendocrine tumours, small intestine, non-epithelial ovary cancers, and

	1999–2002 age-standardised incidence	2003–07 age-standardised incidence	Annual percentage change	99·8% CI
Gastrointestinal stromal sarcoma	0·098	0·258	24·1%	12·0 to 36·2
Gastroenteric-pancreatic tumour, poorly differentiated endocrine carcinoma of pancreas and digestive system	0·361	0·618	12·7%	7·7 to 17·8
Other T-cell lymphomas and natural killer cell neoplasms	0·395	0·555	7·8%	3·3 to 12·4
Diffuse B-cell lymphoma	2·837	3·894	7·3%	5·7 to 8·9
Other myeloproliferative neoplasms	1·530	2·092	7·2%	5·0 to 9·4
Mantle cell lymphoma	0·367	0·477	6·0%	1·6 to 10·4
Carcinomas of thyroid gland	3·470	4·353	5·2%	3·7 to 6·6
Other myelodysplastic syndrome	1·395	1·738	5·0%	3·0 to 7·1
Squamous cell carcinoma with variants of anal canal	0·595	0·728	4·6%	1·2 to 8·0
Follicular B-cell lymphoma	1·676	2·021	4·2%	2·2 to 6·3
Cholangiocarcinoma of intrahepatic bile tract	0·685	0·816	4·0%	0·9 to 7·0
Neuroendocrine carcinoma of other sites	0·683	0·801	3·6%	0·5 to 6·7
Adenocarcinoma with variants of oesophagus	2·725	3·153	3·3%	1·8 to 4·8
Squamous cell carcinoma with variants of oropharynx	2·412	2·732	2·8%	1·1 to 4·5
Adenocarcinoma with variants of extrahepatic biliary tract	0·969	1·088	2·6	0·1 to 5·1
Hepatocellular carcinoma of liver and intrahepatic bile tract	2·068	2·273	2·1%	0·4 to 3·8
Squamous cell carcinoma with variants of cervix uteri	4·536	4·287	–1·2%	–2·4 to –0·1
Adenocarcinoma with variants of ovary	5·351	5·053	–1·3%	–2·3 to –0·2
Squamous cell carcinoma with variants of larynx	3·853	3·578	–1·6%	–2·8 to –0·4
Chronic myeloid leukaemia	0·991	0·854	–3·2%	–5·5 to –0·9
Infiltrating duct carcinoma of prostate	0·412	0·343	–4·0%	–7·4 to –0·6
Squamous cell carcinoma with variants of lip	0·838	0·693	–4·1%	–6·5 to –1·8
Large cell carcinoma of lung	3·440	2·806	–4·4%	–5·6 to –3·2
Mucinous adenocarcinoma of ovary	0·813	0·657	–4·6%	–7·2 to –2·1
Adenocarcinoma with variants of bladder	0·265	0·213	–4·7%	–8·9 to –0·5
Undifferentiated carcinoma of stomach	0·189	0·123	–9·2%	–13·9 to –4·5

Data are rare cancers lying outside the 3 standard-error confidence bounds in figure 1.

***Table 2*: Age-standardised incidence in 1999–2002 and 2003–07**

neuroendocrine tumours of the skin were treated in centres with an even lower mean admission volume than would be expected because of their very low occurrence.

With some exceptions, country-specific patterns of mean admission volume were similar to the pooled data. By contrast with what was found in the other countries, the management of epithelial ovarian cancers was highly centralised in Bulgaria and Slovenia. Patients with CNS tumours were treated in highly centralised structures in all countries except Finland and Navarra. Treatment for uveal melanoma and retinoblastoma was not centralised in Bulgaria or in Navarra. Slovenia and the Netherlands had the highest centralisation patterns, whereas mean admission volume for the majority of cancers was very low in Navarra due also to the small population size.

Table 4 shows the annual number of cases diagnosed, the number of top-volume hospitals treating at least 75% of national cases, and the average annual numbers of treatments provided for each country and for 29 rare cancers. For head and neck cancers, 75% of patients were centralised in two top hospitals in Slovenia (2 million population, 266 treatments per hospital per year), and 12 top hospitals in the Netherlands (17 million population, 201 treatments per hospital per year). The level of centralisation was lower in the other countries, resulting in a caseload of 145 in the ten Bulgarian top hospitals, 106 in the 29 Belgian hospitals, and 83 in the six hospitals in Finland, 77 in the two hospitals in Navarra, and 63 in the seven hospitals in Ireland. The Netherlands and Slovenia had the highest treatment volume for 12 of 29 cancers.

Discussion

Rare cancers make up one quarter of all malignancies. They are a very heterogeneous group of almost 200 cancers, mostly solid, constituting from 2% of all skin cancers up to 32% of all female genital cancers. We confirmed that 5-year survival is lower for rare cancers than common cancers (49% *vs* 63%), and for all rare cancer families compared with their more common counterparts, except thoracic cancers. The disadvantage persisted even after excluding common cancers with good prognosis, such as prostate, breast, and skin cancer. Several factors help explain these differences: the biology

	1999–2001 5-year relative survival	2005–07 5-year relative survival	Difference	99·8% CI
Chronic myeloid leukaemia	37·2	57·9	20·7	17·4 to 24·1
Infiltrating duct carcinoma of prostate	67·5	79·8	12·3	6·4 to 18·2
Soft tissue sarcoma of viscera	34·7	43·7	9·0	3·6 to 14·4
Kaposi's sarcoma	75·4	84·2	8·8	1·4 to 16·2
Diffuse B-cell lymphoma	46·9	55·2	8·4	6·5 to 10·2
Follicular B-cell lymphoma	69·5	77·9	8·4	5·9 to 10·8
Poorly differentiated endocrine carcinoma of pancreas and digestive system	25·3	32·7	7·5	2·7 to 12·2
Squamous cell carcinoma with variants of oropharynx	37·5	44·5	7·1	5·0 to 9·2
Soft tissue sarcoma of superficial trunk	43·9	50·4	6·5	1·4 to 11·6
Precursor B/T cell lymphoblastic leukaemia or lymphoma (and Burkitt's leukaemia/lymphoma)	54·3	60·8	6·4	3·8 to 9·1
Plasmacytoma or multiple myeloma (and heavy chain diseases)	29·8	35·0	5·2	3·8 to 6·7
Carcinomas of thyroid gland	85·6	90·6	5·0	3·8 to 6·3
Adenocarcinoma with variants of cervix uteri	63·8	68·8	5·0	1·7 to 8·3
Well differentiated not functioning endocrine carcinoma of pancreas and digestive system	67·7	72·6	4·9	1·5 to 8·4
Soft tissue sarcoma of limbs	63·9	68·4	4·4	1·0 to 7·9
Adenocarcinoma with variants of oesophagus	9·9	13·8	3·9	2·6 to 5·1
Squamous cell carcinoma with variants of oral cavity	46·1	49·7	3·7	1·7 to 5·6
Squamous cell carcinoma with variants of hypopharynx	22·2	25·6	3·4	0·5 to 6·3
Other myeloproliferative neoplasms	70·8	74·0	3·2	0·6 to 5·9
Squamous cell carcinoma with variants of cervix uteri	65·1	68·1	3·0	1·6 to 4·5
Large cell carcinoma of lung	10·9	13·6	2·7	1·6 to 3·9
Adenocarcinoma with variants of extrahepatic biliary tract	16·2	18·7	2·6	0·2 to 5·0
Squamous cell carcinoma with variants of oesophagus	9·5	12·0	2·5	1·3 to 3·7
Hepatocellular carcinoma of liver and intrahepatic biliary tract	11·0	13·0	2·0	0·5 to 3·5
Other myelodysplastic syndrome	33·8	30·2	–3·5	–6·3 to –0·8

Data are rare cancers lying outside the 3 standard-errors confidence bounds in figure 2.

***Table 3*: Age-standardised 5-year relative survival in 1999–2001 and 2005–07**

of the diseases, adequacies of diagnosis and treatment, scarcity of effective therapies, or insufficient evidence-based treatment guidelines.

A novelty of this study is the analysis of incidence and survival trends. Overall, incidence rose by 0·5% a year from 1999 up to 2007. The increase was substantial for several rare cancers. Some of the increases can probably be attributed to improvements in pathological diagnosis, new entity codes in the ICD-O-3, and to the time needed to adapt the coding procedures. This is the case for gastrointestinal stromal tumours, large cell carcinomas of the lung, neuroendocrine tumours, and many haematological cancers.[9–11] For other rare cancers, increases in incidence might be due to improvements in pathological diagnosis, similar to neuroendocrine tumours. For thyroid carcinoma several authors have suggested an increase in overdiagnosis.[12] However, increased exposure to risk factors might explain higher incidence rates for some cancers; such as exposure to HPV for oropharynx and anal canal squamous cell cancers[13,14] and perhaps increasing obesity or gastro-oesophageal reflux for adenocarcinoma of the oesophagus.[15] The low incidence of squamous cell carcinoma of the cervix might reflect organised cervical screening programmes. The drop in incidence for some of the rare cancers was due to the still falling prevalence of smoking.[16]

Relative survival improved by about 3% overall over the study period, slightly less than for common cancers (5·5%, data not shown), suggesting that investments were more focused on common cancers. Also, overdiagnosis is expected to affect more common cancers than rare cancers. Improvement to relative survival was greatest for chronic myeloid leukaemia with a 5-year gain in survival of 21% across the study years, largely explained by the widespread use of new and more effective treatments, such as targeted treatments and more effective stem-cell transplantation.[17] For many other haematological cancers, new (targeted) drugs in combination with radiotherapy, and improvements in transplantation are responsible for the effects on prognosis.[18] Survival also improved for some groups of sarcoma (viscera, trunk, and limbs) for which multidisciplinary approaches and centralisation of treatments might take the credit; similarly, for neuro-endocrine tumours,[19] biliary tract, liver,[20] and oesophageal cancers,[15] for which there are now more specific and effective treatments and protocols. For oesophageal cancers, earlier detection through Barrett's oesophagus surveillance practices might also contribute to improvements in relative survival. For oropharyngeal cancers, the larger proportion of less aggressive tumours attributed to HPV might have influenced the survival gain.[21] For carcinoma of the thyroid and infiltrating ductal carcinoma of the prostate, early diagnosis is probably the major contributing factor to improved relative survival. Early diagnosis would also have contributed to a rise in the proportion of cases that are clinically irrelevant, although this is hard to estimate.[12,22] As for incidence, some of the apparent survival gains might be due to classification changes,[9] such as for large cell carcinomas of the lung that have a relatively new ICD-O morphology code.

Myeloproliferative neoplasms and myelodysplastic syndromes were not considered cancers until the WHO classification was changed in 2001, and their registration started even later.[9] Generally, the increases in incidence of some rare cancers could be due to more specific diagnosis and coding by cancer registry.

Our hospital volume analysis represents, to our knowledge, the first attempt to systematically study the place of treatment of rare cancers from population-based cancer registry data. Many potentially relevant indications

***Figure 3*: Mean admission volume by country and cancers ranked by pooled incidence level**

Data are for pooled countries, Belgium, Bulgaria, and Finland.


Incidence
Head and neck 14·50
Epithelial ovary 6·67
Oesophagus 4·66
CNS 4·61
Soft tissue sarcoma 4·23
Thyroid 3·59
Testis 2·94
Biliary tract 1·80
Urinary tract 1·75
Gastroenteric-pancreatic neuroendocrine tumour 1·64
Vagina 1·51
Liver 1·22
Mesothelioma 1·14
Bone sarcoma 0·83
Anal canal 0·69
Penis 0·54
Melanoma of uvea 0·53
Small Intestine 0·43
Neuroendocrine of skin 0·29
Non-epithelial ovary 0·24
Endocrine of thyroid 0·19
Thymus 0·16
Nephroblastoma 0·15
Melanoma of mucosa 0·14
Embryonal CNS 0·12
Adrenal cortex 0·12
Neuroblastoma 0·09
Retinoblastoma 0·09
Trachaea 0·07
Eye 0·04
Olfactory neuroblastoma 0·04
Placenta 0·03
Hepatoblastoma 0·02
Middle ear 0·02
Parathyroid 0·02
Pituitary 0·01
Parcreatoblastoma 0·00
Pleuropulmonary blastoma 0·00
Pooled
Belgium
Bulgaria
Finland
0
1
10
100
Mean admission volume (logarithmic)
Mean admission volume (logarithmic)


Ireland
Head and neck
Epithelial ovary
Oesophagus
CNS
Soft tissue sarcoma
Thyroid
Testis
Biliary tract
Urinary tract
Gastroenteric-pancreatic neuroendocrine tumour
Vagina
Liver
Mesothelioma
Bone sarcoma
Anal canal
Penis
Melanoma of uvea
Small Intestine
Neuroendocrine of skin
Non-epithelial ovary
Endocrine of thyroid
Thymus
Nephroblastoma
Melanoma of mucosa
Embryonal CNS
Adrenal cortex
Neuroblastoma
Retinoblastoma
Trachaea
Eye
Olfactory neuroblastoma
Placenta
Hepatoblastoma
Middle ear
Parathyroid
Pituitary
Parcreatoblastoma
Pleuropulmonary blastoma
Netherlands
Slovenia
Navarra
0
1
10
100
Mean admission volume (logarithmic)

can be drawn from this seldom used source of information. However, several important limitations should be recognised. Seven cancer registries cannot be considered as statistically representative of the whole European population. Bulgaria, Finland, and Navarra only provided information about, at most, three treatments: the first surgical, systemic, and radiotherapy treatments. However, we estimated from the data of the other cancer registries that this problem only relates to about 1% of all patients.

The mean admission volume estimates, based on individual patient data and blind administrative coding of hospitals, will depend on how cancer services were organised and coded. We cannot know if, for some rare cancers and in some countries, hospitals were linked in organised networks during the study period, thus overcoming an apparent dispersion of treating structures. For example, patients with localised sarcomas or head and neck cancers were frequently treated by small or peripheral hospitals.[23] If several hospitals provided different services but acted cooperatively as a single specialist centre, their estimated volume will depend on whether they were identified as single or separate units. Our data do not allow detailed identification of protocols used in the considered hospitals. Hospital volume can therefore be considered as only a partial quality indicator, mainly pointing to level of experience in protocol application and general management of patients with rare cancer.

To address the volume–survival assocation is beyond the scope of this paper, but centralisation of care has been suggested to improve outcomes for rare cancers.[24] This is particularly true when optimal treatment requires complex surgery or high-technology radiotherapy equipment. Diagnosis and treatment in reference centres are expected to be more accurate because they benefit from large numbers of cases, which are often discussed in a multidisciplinary setting involving expert professionals. Often centralised sites are connected to research centres participating in international debates and research. Disadvantages of centralisation are the need for patients to locate to the centralised site, and the risk of a longer waiting list, with consequent discomfort and possible negative effects on outcome.[25] Sometimes centralisation was only moderately perceived by oncologists as a solution to be endorsed for patients with rare cancers.[26]

For many of the solid rare cancers, centralisation did not seem to have been completely achieved during the study period. However, most cases had been diagnosed more than 10 years ago when centralisation for patients with cancer did not necessarily have much priority. Centralisation seemed to be more widely implemented for rare cancers requiring highly specific technologies (particularly radiotherapy and nuclear medicine) and for those with long-established evidence-based guidelines for diagnosis and treatment. This was the case for many paediatric tumours, uveal melanoma, anal canal cancers, adrenal cortex cancers and, for specific surgical expertise, in CNS cancers and bone sarcomas.

The degree of centralisation varied across Europe, and to a large extent was affected by the population size. In countries with a small population it is easier to concentrate patients in a single hospital or few hospitals. High admission volumes are more likely to be achieved in reference centres in larger-population countries.

The results of this part of the study were discussed in the participating countries at dedicated meetings attended by public health planners, oncologists, surgeons, representatives of Ministries of Health, and patient associations. Although the general pattern of dispersion was recognised, almost all the countries were working at different levels to implement centralisation, or network-based organisations for treatment, or both, while still following country-specific priorities.[27]

In Belgium, where all patients with cancer can be treated in any hospital with an oncology care programme, the level of centralisation was low. A plan is now under way for the development of hospital networks between centres of expertise and other oncology care services and programmes. Centralisation was already happening while we did this study in the Netherlands, mostly for surgical treatment. This was reflected in the high admission volumes in this country for many rare cancers (see appendix p 3).

In Bulgaria, patients with rare cancers were operated in all hospitals with surgical departments, whereas radiotherapy was concentrated in 17 centres and systemic therapy in 14 oncological hospitals. A problem was the quality of diagnosis, mainly due to inadequate facilities to diagnose many complex rare cancers. The definition of national and international pathways for second opinions from expert pathologists was deemed important by participants, for improving quality of rare cancer diagnoses. With this in mind, the European Reference Networks should offer a good opportunity to improve pathologist training through dedicated training schemes and fellowships across Europe. Cancer registration remains vital for monitoring progress in rare cancer diagnosis and treatment for these patients.

In Finland, more than 60% of patients with rare cancer were treated in five university hospitals. Centralisation in single national structures was only observed for uveal melanoma and retinoblastoma. Further centralisation for other rare cancers is impeded by the spread of the population over large areas and by administrative constraints on regional health authorities for referring patients with cancer to the closest university hospital.

Irish public health authorities, during the period covered by the study, identified centres to treat rare or particularly complex cancers. However, patients were not always correctly referred to them. This highlights the

Figure 4: **Mean admission volume by country and cancers ranked by pooled incidence level**
Data are for Ireland, The Netherlands, Slovenia, and Navarra.

	Belgium (10·5*)			Bulgaria (7·7*)			Finland (5·3*)			Ireland (4·2*)			Netherlands (16·3*)			Slovenia (2·0*)			Navarra (0·6*)		
	Cases	H75	Treat	Cases	H75	Treat	Cases	H75	Treat	Cases	H75	Treat	Cases	H75	Treat	Cases	H75	Treat	Cases	H75	Treat
Head and neck	2098	29	105·6	1180	10	145·1	439	6	82·2	368	7	63·0	2439	12	201·4	395	2	266·1	125	2	76·6
Epithelial ovary	760	50	19·5	627	16	52·3	370	10	44·5	261	15	21·0	1118	47	30·2	158	3	82·0	38	1	45·5
Oesophagus	689	31	29·3	77	14	5·2	163	8	21·6	289	9	37·1	1422	31	42·0	49	2	32·9	24	2	15·7
CNS	623	20	48·4	412	13	41·7	57	4	19·1	229	3	106·3	912	14	84·0	97	2	78·7	47	2	32·0
Soft tissue sarcoma	500	35	16·6	372	21	18·4	165	7	25·6	157	17	10·6	802	33	26·4	81	2	47·4	32	2	17·4
Thyroid	576	34	14·2	220	12	20·4	286	12	22·8	98	11	9·6	418	31	17·1	109	1	260·3	43	2	36·8
Testis	244	40	8·4	180	19	12·4	101	9	14·3	144	12	15·6	609	42	18·4	93	3	48·8	10	3	4·4
Biliary tract	214	44	4·9	183	23	6·5	147	13	11·3	122	14	7·7	582	38	12·2	47	3	13·2	43	2	19·7
Gastroenteric-pancreatic neuroendocrine tumour	287	46	5·6	30	21	1·3	148	13	9·3	61	20	2·7	355	44	6·9	22	3	6·8	10	3	2·9
Liver	250	22	11·0	107	12	7·6	165	11	12·8	68	12	4·6	236	36	5·2	29	2	14·4	49	3	14·5
Urinary tract	292	48	6·7	67	17	4·1	48	12	3·9	24	10	2·3	419	46	7·7	30	3	8·9	19	3	8·2
Mesothelioma	184	25	8·7	34	10	3·7	64	9	6·8	25	11	2·0	481	43	9·8	21	1	22·3	9	2	4·6
Vagina	172	35	5·8	120	9	14·0	70	5	14·8	40	9	4·7	296	14	21·8	42	2	21·9	8	2	4·7
Bone sarcoma	81	10	10·2	55	13	4·6	28	3	9·6	30	7	5·2	195	5	43·3	15	2	10·4	3	2	2·4
Anal canal	95	27	5·3	39	12	4·1	24	7	4·6	30	9	4·4	135	22	7·2	15	1	23·6	4	2	3·6
Melanoma of uvea	43	2	21·9	17	7	2·7	6	1	5·5	29	4	5·7	156	2	80·2	13	1	11·9	3	3	0·8
Penis	63	43	1·4	39	17	2·4	21	10	2·1	20	15	1·2	109	26	3·7	9	4	2·0	4	3	1·2
Small intestine	62	37	1·9	15	13	1·1	26	13	2·1	27	20	1·3	120	38	2·6	5	4	1·3	2	2	1·0
Neuroendocrine carcinoma of skin	46	32	1·9	1	3	0·4	0			15	18	0·8	77	37	2·3	4	4	1·1	0		
Non-epithelial ovary	20	19	1·3	43	17	3·2	8	9	1·1	8	15	0·6	32	24	1·4	4	3	1·7	1	3	0·3
Endocrine carcinoma of thyroid	31	22	1·4	10	9	1·2	8	8	1·2	5	10	0·5	32	13	2·7	5	1	10·3	1	1	1·7
Thymus	22	20	1·4	7	8	1·3	4	5	1·1	5	5	1·3	36	15	2·8	3	2	2·1	2	2	1·3
Nephroblastoma	18	4	7·4	6	3	2·8	8	3	4·7	7	1	13·4	30	4	16·9	3	1	4·8	0	1	0·3
Melanoma of mucosa	14	24	0·8	2	5	0·8	10	7	1·7	6	11	0·6	34	13	3·0	4	3	1·5	1	2	0·3
Adrenal cortex	13	14	1·1	13	10	1·3	6	7	0·9	5	11	0·4	25	15	1·5	3	2	1·4	1	2	0·4
Embryonal CNS	21	9	4·2	14	9	2·5	6	3	3·1	9	3	6·3	0				2	4·2	2	1	5·2
Neuroblastoma	15	4	5·7	8	5	1·7	1	1	2·1	7	2	5·4	12	4	6·2	1	2	1·3	1	1	1·8
Retinoblastoma	10	1	14·0	3	5	0·5	3	2	1·5	3	2	1·8	22	1	30·7	1	1	1·1	1	2	0·5
Trachea	10	18	0·9	5	4	1·1	4	5	0·9	2	4	0·4	11	11	1·1	3	1	3·8	1	1	0·5

*Population in millions. Number of hospitals providing 75% of treatments (H75), mean annual number of treatments (treat) provided by H75 hospitals, by country and cancer group.

Table 4: **Annual number of cases of rare tumours by country**

need for strong political commitment to ensure centralisation, to make sure all patients with rare cancer receive the highest quality of care.

Cancer care was highly centralised in Slovenia. Additionally, the major hospitals were organised on a task-specific basis: radiotherapy was only provided by the National Cancer Center, whereas surgical treatment was more often done in two other major hospitals. Reducing delays in diagnosis and treatment was recognised in Slovenia as one of the major challenges to improve rare cancer outcomes.

Navarra is a relatively small region of Spain, a country with a highly regionalised health organisation. No hospital with national recruitment for rare cancers was operating in Navarra, and 98% of resident patients with rare cancer were treated locally, the majority in the two largest regional hospitals. However, the admission volumes of Navarra hospitals were much lower than in all the other participating countries, even considering some underestimation due to unregistered patients coming from outside the region. This suggests some disadvantages in organising rare cancer treatment on a regional or local basis.

To conclude, to our knowledge, this is the largest study that estimates the burden of rare cancer for Europe, including trends in incidence and survival rates. This study also provides indicators of rare cancer treatment management. In seven European countries we observed, with few exceptions, a low level of centralisation of treatment for rare cancers. We recognise the importance of population-based cancer registries in descriptive studies like this, to ensure surveillance. However, the quality of the data needs to be improved when morphology, hospital, and treatment definitions are considered. To this aim, we suggest the use of specific

data quality indicators, the planning of periodic sample-based quality studies and, above all, a wider use of these variables in population-based studies, with related sensitivity analysis. Furthermore, the international classification for cancer have to rapidly include the new entities on the basis of molecular and genomic categorisation. Genomic categorisation is a necessary condition for updating a new rare cancers list.

The European Network of Cancer Registries (ENCR) should work to boost these quality improvements and make wider use of the data on rare cancers. The Joint Action of Rare Cancers[28] and the European Network for Rare Diseases will profit from these data, which are also useful for national and European policies to improve care for patients with rare cancer. The RARECAREnet project website includes a search tool with data for all the countries that contributed data.[3]

Contributions

GG, RC, and AT designed the study and wrote the article. RC, LB, SM, and RDA did the statistical analyses. LB, RDA, SM, EA, HC, ND, MKL, SS, JMvdZ, LVE, OV, MPZ, LAA, FB, IK, RO, and CAS revised the paper and contributed to data interpretation. All authors reviewed and approved the final version. Members of the working group collected data.

Declaration of interests

We declare no competing interests.

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