Survival from rare cancer in adults: a population-based study

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Summary

Background **Rare cancers are a challenge to clinical practice, and treatment experience, even in major cancer centres to which rare cancers are usually referred, is often limited. We aimed to study the epidemiology of rare cancers in a large population of several countries.**

Methods **We analysed survival by age, sex, subsite, and morphology in 57 144 adults with 14 selected rare cancers diagnosed 1983–94. Variations in survival over time and between European regions were also assessed for variations in quality of care. We also estimated the adjusted relative excess risk of death for every rare cancer.**

Findings **Overall 5-year relative survival was good (ie, >65%) for placental choriocarcinoma (85·4% [95% CI 81·4–89·5]), thyroid medullary carcinoma (72·4% [69·2–75·5]), ovarian germ-cell cancer (73·0% [70·0–76·0]), lung carcinoid (70·1% [67·3–72·9]), and cervical adenocarcinoma (65·5% [64·3–66·6]); intermediate (ie, 35–65%) for testicular cancer at age 65 years or older (64·0% [59·3–68·7]), sarcoma of extremities (60·0% [58·9–61·2]), digestive-system endocrine cancers (55·6% [54·9–56·3]), anal squamous-cell carcinoma (53·1% [51·5–54·8]), and uterine sarcoma (43·5% [42·0–44·9]); low for carcinoma of adrenal-gland cortex (32·7% [28·3–37·2]) and bladder squamous-cell carcinoma (20·4% [18·8–22·0]); and poor for angiosarcoma of liver (6·4% [1·8–11·0]) and mesothelioma (4·7% [4·3–5·2]). Survival was usually better for women than men and poor in those aged 75 years or older. Survival significantly improved over time for ovarian germ-cell cancer, sarcomas of extremities, digestive-system endocrine tumours, anal squamous-cell carcinoma, and angiosarcoma of liver. Survival in northern Europe was higher than in the other geographic groupings for most cancers.**

Interpretation **Because effective treatments are available for several of the rare cancers we assessed, further research is needed to ascertain why survival is lower in some European countries than in others, particularly in older patients. Audit of best practice for rare cancers with treatment protocols would be useful.**

Introduction

Rare cancers are a challenge to clinical practice. Treatment experience, even in major cancer centres to which rare cancers are usually referred, is often limited, and new treatments are difficult to assess because too few patients are available for adequately powered trials—the gold-standard study design to establish treatment efficacy of new regimens.

However, substantial advances in the treatment of some rare cancers have occurred, particularly for malignant disease that arises during childhood, gastrointestinal stromal cancers, and anal cancer[1–3] as a result of national and international collaborative trials. Nonetheless, for many rare cancers, research is confined to case reports or small retrospective series, for which substantial selection bias occurs and total experience is commonly too limited for any firm conclusions on management to be made.

These problems can be addressed by use of population-based cancer-registries data to avoid selection bias and by compilation of large international databases on rare cancers. The EUROCARE studies,[4–6] the most recent of which is based on 67 population-based cancer registries in 22 European countries, give a unique opportunity to study the epidemiology of rare cancers in a large population from various countries. To our knowledge, no similar large-scale analyses of rare cancers have been reported.

We aimed to analyse survival data for adult European patients with selected rare cancers in relation to major demographic and clinical variables and to assess variations in survival over time and between parts of Europe. Although population-based data for treatment of rare cancers are lacking for the whole European Union, we report survival data to enable comparison of quality of care over time and between European countries.

Methods

We defined rare cancers as those with an annual crude incidence rate of less than 2 per 100 000 for both sexes combined. We selected 14 rare cancers of major clinical and epidemiological interest: angiosarcoma of liver; mesothelioma; adenocarcinoma of uterine cervix; uterine sarcoma; anal squamous-cell carcinoma; testicular cancer in men aged 65 years or older; sarcoma of extremities; placental choriocarcinoma; thyroid medullary carcinoma; bladder squamous-cell carcinoma; adrenal-cortex carcinoma; digestive-system endocrine cancer; lung carcinoid; and ovarian germ-cell cancer. Table 1 lists these cancers with their International Classification of Diseases codes for topography (ICD-9) and morphology (ICD-O).[7,8]

We analysed data from 39 adult cancer registries for 59 021 patients aged 15–99 years diagnosed with a

selected rare cancer between 1983 and 1994. These data were from 18 European countries participating in EUROCARE (table 2). Because these countries differ markedly in terms of economic development, social structure, and health-care structure, we defined four geographic groups (table 2), within which survival from common cancers are much the same.[4–6] All registries gave the most updated follow-up information available for vital status up to Dec 31, 1999. Only primary, first occurrence of cancer at any site, as defined by ICD-O morphology fifth digit behaviour code 3, were included in analyses. Both microscopically verified and microscopically non-verified cases were included, but those known to registries by death-certificate only or discovered incidentally at autopsy were excluded. Patients lost to follow-up—ie, for which registries declared they were unable to update vital-status information—were included in analyses up to the date of the last contact. A total of 57 144 cases were analysed (table 3). Further details of the EUROCARE dataset are available.[4–6]

Because Finland and Sweden use condensed morphological classifications (ie, have less-detailed codes for some cancers), the detail of morphological data was not sufficient for analysis of subgroups for adenocarcinoma of uterine cervix in these two countries, which were thus excluded from analyses of this tumour type. For the same reason, data for Finland were excluded from mesothelioma analyses and those for Sweden from analyses of sarcoma of extremities and sarcoma of uterus. Crude incidence and world-standardised cancer incidence were derived from the EUROCARE dataset (table 3).

We calculated absolute survival of patients with cancer at 1 year, 3 years, and 5 years after diagnosis by the actuarial method, which calculated actual survival in these patients irrespective of whether they died from cancer. We also calculated relative survival 5 years after diagnosis using the Hakulinen method[9] to assess excess mortality for patients with cancer compared with that for the general population. Relative survival is estimated as the ratio of absolute survival to expected age-specific and sex-specific survival of the general population. Age-specific and sex-specific survival of the general population was obtained from actuarial life tables for every cancer registry[10] for the period 1983–99. Materials and methods for construction of life tables are given in the EUROCARE-3 monograph.

Relative-survival ratios were modelled as a function of prognostic covariates, including follow-up, by use of multiple regression on the basis of grouped data, in the framework of generalised linear models with a binomial error structure.[11] The model hazard function is presented as relative excess risk, which estimates the excess hazard for death of patients associated with a given covariate pattern, once the hazard for death of the general population has been taken into account. We assessed the prognostic role of sex, age, period of diagnosis, geographic group, subsite, and morphology. The relative excess risks of death were estimated separately for every cancer, with reference categories of youngest age group, women, 1983–85 diagnosis period, the UK, and the most frequent subsites and morphologies. We used the SEERstat (version 5.2.2) statistical software for univariate analyses of relative

	ICD-9 topography	ICD-O morphology
Adenocarcinoma of uterine cervix	1800–1809	8050, 8140–8141, 8190–8230, 8260–8263, 8310, 8380, 8430–8490, 8510, 8560–8570, 8940
Anal squamous-cell carcinoma	1542, 1543, 1548	8010, 8051–8124
Angiosarcoma of liver	1550, 1551	9120, 9124, 9130, 9133
Sarcoma of uterus	1790, 1800–1809, 1820–1828	8800–9044, 9120–9150, 9560–9589
Sarcoma of extremities	1704–1705, 1707–1708, 1712–1713	8800–9581
Testicular cancer (age ⩾65 years)	1860, 1869	NA
Mesothelioma	NA	9050–9053
Placental choriocarcinoma	181	9100–9101
Medullary carcinoma of thyroid	1939	8510–8511
Squamous-cell carcinoma of bladder	1880–1889	8051–8076
Adrenal-cortex carcinoma	1940	8310, 8370
Digestive-system endocrine tumours	1500–1599	8041–8042, 8150–8155, 8240–8246
Lung carcinoid	1622–1629	8240–8246
Ovarian germ-cell cancer	1830	9060–9102

NA=not applicable (no selection criteria applied).

Table 1: **Rare cancers studied, with ICD topography and morphology codes**

	Patients	Proportion microscopically verified	Proportion death-certificate only	Proportion lost to follow-up
Northern Europe				
Denmark*	5048	99%	0·1%	0·1%
Finland*	2760	100%	0	0·4%
Iceland*	211	100%	0	0
Norway*	3272	100%	0·1%	0·3%
Sweden*	5135	100%	0	0·2%
Western Europe				
France (Bas-Rhin, Calvados, and Côte d'Or)	1338	100%	0	0·8%
Germany (Saarland)	671	99%	0·1%	0
The Netherlands (Eindhoven)	640	100%	0	0
Italy (Latina, Parma, Ragusa, Turin, and Varese)	2488	97%	0·3%	1·0%
Spain (Mallorca, Navarra, and Tarragona)	808	100%	0·2%	0·1%
Switzerland (Basel and Geneva)	629	99%	0	6·8%
UK				
England (East Anglia, Merseyside and Cheshire, Oxford, South West, Thames, Trent, West Midlands, and Yorkshire)	24 690	92%	2·6%	0·1%
Scotland*	4808	92%	0·2%	0
Wales*	1865	96%	0	0
Eastern Europe				
Estonia*	875	100%	0	1·0%
Poland (Krakow)	310	100%	0·3%	1·6%
Slovakia*	2430	100%	1·2%	0
Slovenia*	1043	99%	0	0·6%

*Data from national cancer registry; otherwise regional cancer registries are given in brackets.

Table 2: **Number of cases and proportion microscopically verified, death-certificate only, and lost to follow-up by country**

	Number of cases	Proportion microscopically verified	Proportion death-certificate only	Proportion lost to follow-up	Crude incidence per 100 000/year	World standardised incidence per 100 000/year	Incidence of rare cancer*			Incidence of cancer at site†		
							Minimum (region)	Maximum (region)	Ratio of maximum to minimum	Minimum (region)	Maximum (region)	Ratio of maximum to minimum
Adenocarcinoma of uterine cervix	8686	98%	0	0·3%	2·55	2·27	1·83 (W)	2·78 (N)	1·52	13·99 (W)	24·32 (E)	1·74
Anal squamous-cell carcinoma	5386	94%	1·5%	0·3%	0·73	0·51	0·19 (E)	0·83 (UK)	4·39	0·85 (E)	4·36 (N)	5·15
Angiosarcoma of liver	138	93%	3·1%	0	0·02	0·01	0·01 (E)	0·02 (W)	1·79	2·22 (UK)	8·52 (W)	3·84
Sarcoma of uterus	5686	97%	0·7%	0·1%	1·71	1·31	1·45 (E)	2·16 (N)	1·49	38·95 (W)	48·69 (E)	1·25
Sarcoma of extremities	10 012	96%	0·7%	0·4%	1·53	1·31	1·35 (E)	1·89 (N)	1·40	1·45 (UK)	1·94 (N)	1·33
Testicular cancer (age ⩾65 years)	943	82%	4·7%	0·1%	1·85	1·83	1·64 (E)	1·98 (N)	1·21	40·18 (UK)	53·73 (E)	1·34
Mesothelioma	10 549	90%	3·6%	0·1%	1·37	1·13	0·34 (E)	1·77 (UK)	5·24	0·53 (E)	2·12 (UK)	3·99
Placental choriocarcinoma	308	98%	0	1·0%	0·07	0·09	0·04 (UK)	0·16 (E)	3·61	0·05 (UK)	0·19 (E)	3·68
Medullary carcinoma of thyroid	1100	98%	0·2%	0·6%	0·15	0·13	0·11 (UK)	0·21 (W)	1·89	2·23 (UK)	4·82 (N)	2·16
Squamous-cell carcinoma of bladder	3723	96%	0·5%	0·1%	0·51	0·31	0·18 (E)	0·62 (UK)	3·42	11·42 (E)	27·94 (UK)	2·45
Adrenal-cortex carcinoma	499	97%	0·6%	0	0·07	0·06	0·04 (UK)	0·11 (N)	2·70	0·25 (UK)	0·34 (N)	1·35
Digestive-system endocrine tumours	7693	98%	0·2%	0·3%	1·13	0·84	0·56 (E)	2·20 (N)	3·91	108·33 (E)	135·30 (W)	1·25
Lung carcinoid	1443	98%	0	0·8%	0·20	0·17	0·12 (UK)	0·38 (W)	3·19	52·21 (N)	89·20 (UK)	1·71
Ovarian germ-cell cancer	978	98%	0·5%	1·0%	0·24	0·28	0·22 (UK)	0·39 (E)	1·76	17·72 (W)	25·15 (N)	1·42

W=western Europe. N=northern Europe. E=eastern Europe. *Range of crude incidence (per 100 000/year) for rare cancer by geographic group. †Range of crude incidence (per 100 000/year) for rare-cancer site by geographic group.

Table 3: **Proportion of cases microscopically verified, death-certificate only, and lost to follow-up; crude and standardised incidence rates; and range of incidence across geographic groupings compared with range of incidence across geographic groups for all cancers at same site**

survival and to estimate incidence. For the multiple regression analysis we used Stata software (version 7.0).

Role of the funding source

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

Results

Table 2 shows quality indicators for rare cancer by country. Few cases were classified as death-certificate only. Furthermore, a high proportion of cases (95% overall) were confirmed microscopically, and few patients (0·3% overall) were lost to follow-up. Stage at diagnosis (classified as local, regional, or metastatic) was available only for 40% of patients, ranging from 24% for mesothelioma to 51% for ovarian germ-cell cancer (data not shown). Stage was therefore not included in analyses.

Table 3 shows quality indicators and incidence of every cancer. The ratio of maximum to minimum incidence of rare cancer across geographic groups was lowest for testicular cancer and highest for mesothelioma. The range between the upper and lower ratios for incidence of rare cancer was much the same as that for the incidence of all cancers at every site.

	Absolute survival (%)			Relative survival (%)
	1 year (95% CI)	3-year (95% CI)	5-year (95% CI)	5-year (95% CI)
Adenocarcinoma of uterine cervix	83·2 (82·4–84·0)	67·3 (66·3–68·3)	60·6 (59·6–61·7)	65·5 (64·3–66·6)
Anal squamous-cell carcinoma	76·5 (75·3–77·7)	53·1 (51·7–54·4)	43·3 (41·9–44·6)	53·1 (51·5–54·8)
Angiosarcoma of liver	19·6 (12·8–26·3)	7·9 (3·3–12·5)	5·5 (1·6–9·5)	6·4 (1·8–11·0)
Sarcoma of uterus	63·9 (62·7–65·2)	45·0 (43·7–46·3)	38·5 (37·2–39·7)	43·5 (42·0–44·9)
Sarcoma of extremities	80·1 (79·3–80·9)	60·4 (59·4–61·3)	52·0 (51·0–53·0)	60·0 (58·9–61·2)
Testicular cancer (age ⩾65 years)	68·4 (65·4–71·4)	53·3 (50·1–56·6)	43·9 (40·6–47·1)	64·0 (59·3–68·7)
Mesothelioma	27·8 (26·9–28·6)	6·5 (6·1–7·0)	3·9 (3·5–4·3)	4·7 (4·3–5·2)
Placental choriocarcinoma	90·6 (87·3–93·9)	86·7 (82·8–90·6)	85·1 (81·0–89·1)	85·4 (81·4–89·5)
Medullary carcinoma of thyroid	85·4 (83·2–87·5)	73·2 (70·5–75·8)	65·9 (63·1–68·8)	72·4 (69·2–75·5)
Squamous-cell carcinoma of bladder	33·5 (31·9–35·0)	18·4 (17·1–19·7)	15·2 (14·0–16·3)	20·4 (18·8–22·0)
Adrenal-cortex carcinoma	54·7 (50·3–59·2)	38·1 (33·7–42·4)	30·0 (25·9–34·1)	32·7 (28·3–37·2)
Digestive-system endocrine tumours	68·5 (67·5–69·6)	55·2 (54·1–56·4)	47·4 (46·2–48·5)	55·6 (54·9–56·3)
Lung carcinoid	80·1 (78·0–82·2)	69·8 (67·4–72·2)	63·9 (61·4–66·5)	70·1 (67·3–72·9)
Ovarian germ-cell cancer	81·5 (79·0–83·9)	72·7 (69·9–75·6)	70·8 (67·9–73·7)	73·0 (70·0–76·0)

Table 4: **Absolute survival and relative survival for rare cancers**

	Age									Sex*					
	15–54 years			55–74 years			⩾75 years			Women			Men		
	n	Survival, % (95% CI)	RER†	n	Survival, % (95% CI)	RER (95% CI)	n	Survival, % (95% CI)	RER (95% CI)	n	Survival, % (95% CI)	RER†	n	Survival, % (95% CI)	RER (95% CI)
Adenocarcinoma of uterine cervix	5041	77·6 (76·4–78·8)	1	2623	50·1 (47·9–52·2)	2·82 (2·60–3·07)	1022	29·0 (25·2–32·8)	5·62 (5·06–6·25)	..	..	..	..	..	..
Anal squamous-cell carcinoma	974	64·6 (61·4–67·7)	1	2773	53·4 (51·2–55·5)	1·41 (1·25–1·60)	1639	41·2 (37·6–44·8)	2·35 (2·05–2·69)	3477	55·0 (53·0–57·1)	1	1909	49·5 (46·7–52·4)	1·30 (1·19–1·42)
Angiosarcoma of liver	38	8·0 (0–16·8)	1	75	6·9 (0·5–13·2)	1·18 (0·73–1·89)	25	0·0	2·02 (0·99–4·09)	66	9·8 (1·8–17·7)	1	72	3·3 (0–7·9)	1·71 (1·09–2·66)
Sarcoma of uterus	1868	63·6 (61·3–65·9)	1	2670	32·6 (30·6–34·5)	2·59 (2·35–2·85)	1148	29·5 (25·9–33·1)	3·24 (2·88–3·64)	..	..	..	..	..	..
Sarcoma of extremities	4618	65·7 (64·3–67·1)	1	3468	56·4 (54·5–58·4)	1·73 (2·60–3·16)	1926	46·3 (42·8–49·9)	2·86 (1·11–1·27)	4621	62·3 (60·6–64·0)	1	5391	58·1 (56·5–59·7)	1·19 (1·11–1·27)
Testicular cancer (age ⩾65 years)	..	..	..	560‡	70·4 (65·2–75·7)	1	383	49·5 (40·9–58·1)	1·71 (1·32–2·22)	..	..	..	..	..	..
Mesothelioma	1854	8·6 (7·3–9·9)	1	6397	3·9 (3·4–4·4)	1·34 (1·27–1·42)	2298	3·0 (2·2–4·1)	1·72 (1·60–1·85)	1896	8·1 (6·8–9·5)	1	8653	3·9 (3·5–4·4)	1·15 (1·08–1·21)
Placental choriocarcinoma	171§	91·4 (87·1–95·8)	1	91¶	81·6 (73·4–89·8)	2·28 (1·14–4·58)	46‖	74·3 (61·2–87·4)	4·17 (1·97–8·85)	..	..	..	..	..	..
Medullary carcinoma of thyroid	579	82·5 (79·2–85·8)	1	399	61·8 (56·2–67·4)	2·74 (2·10–3·58)	122	44·5 (31·2–57·9)	5·20 (3·62–7·47)	647	78·2 (74·4–82·1)	1	453	63·7 (58·5–68·9)	1·86 (1·46–2·37)
Squamous-cell carcinoma of bladder	322	32·7 (27·4–38·0)	1	1826	21·5 (19·4–23·6)	1·35 (1·16–1·56)	1575	14·2 (11·7–16·6)	1·88 (1·62–2·19)	1738	18·0 (15·9–20·2)	1	1985	22·6 (20·3–24·9)	0·85 (0·78–0·92)
Adrenal-cortex carcinoma	229	37·1 (30·6–43·6)	1	224	27·9 (21·4–34·3)	1·34 (1·06–1·70)	46	32·6 (14·4–50·9)	1·59 (1·05–2·41)	286	32·3 (26·5–38·1)	1	213	33·3 (26·3–40·4)	0·99 (0·79–1·24)
Digestive-system endocrine tumours	2219	74·6 (73·6–75·6)	1	3788	48·6 (47·7–49·5)	2·26 (2·05–2·50)	1686	38·2 (36·5–39·9)	3·58 (3·19–4·01)	4028	58·1 (57·2–59·0)	1	3665	52·7 (51·8–53·7)	1·19 (1·10–1·28)
Lung carcinoid	613	84·3 (81·2–87·4)	1	717	60·9 (56·7–65·1)	2·97 (2·33–3·78)	113	33·7 (21·7–45·7)	8·24 (5·88–11·54)	731	78·1 (74·5–81·7)	1	712	61·6 (57·4–65·8)	2·08 (1·69–2·56)
Ovarian germ-cell cancer	796	82·8 (80·1–85·5)	1	142	22·9 (15·4–30·3)	6·81 (5·17–8·97)	40	22·3 (3·8–40·8)	10·56 (6·77–16·47)	..	..	..	..	..	..

RER=relative excess risk: adjusted for follow-up, age, diagnosis period, geographic group, sex (excluding uterine, placental, and gonadal sites), subsite (for uterine sarcoma of extremities, mesothelioma and digestive-system endocrine cancer), and morphology (for uterine sarcoma, adenocarcinoma of cervix, testicular cancer, mesothelioma, digestive-system endocrine cancer, and ovarian germ-cell cancer). *Data for sex-specific cancers not reported. †Reference category. ‡65–74 years (reference category). §15–29 years (reference category). ¶30–39 years. ||⩾40 years.

Table 5: **5-year relative survival and adjusted relative excess risk of death by age and sex**

Table 4 shows absolute survival at 1 year, 3 years, and 5 years after diagnosis, and relative survival at 5 years. Placental choriocarcinoma had the highest survival of any of these cancers. For all except placental choriocarcinoma, 1-year absolute survival was 85% or less. For most cancers 5-year absolute survival was 39–85%; angiosarcoma of liver and mesothelioma had poor 5-year absolute survival. 5-year relative survival was usually 1–10% higher than 5-year absolute survival (table 4), depending on mean age of cancer occurrence (data not shown). For testicular cancer, 5-year relative survival was about 20% higher than 5-year absolute survival, since only men aged 65 years or older at diagnosis were included and other causes of death contribute substantially to overall mortality at this age.

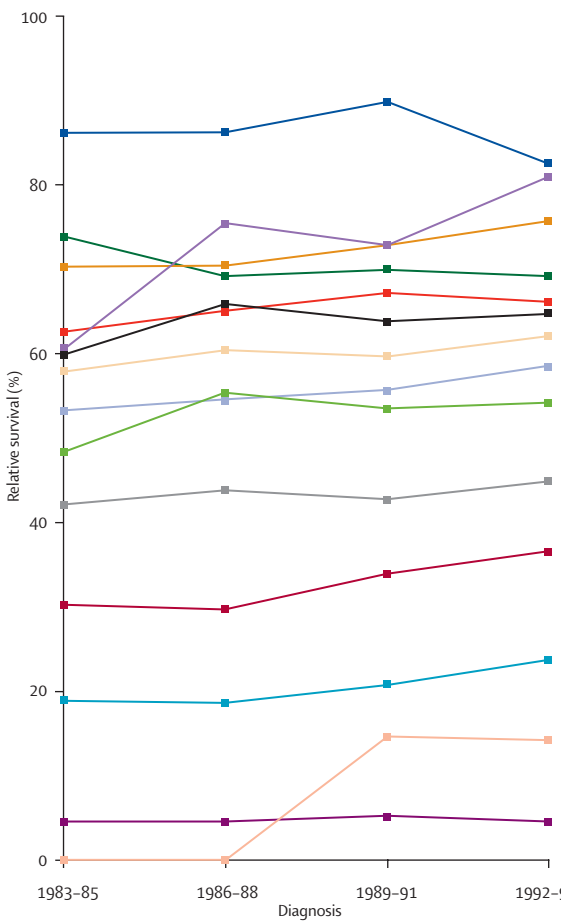
5-year relative survival was more than 50% for most cancers, but was below 50% for uterine sarcoma, adrenal-cortex carcinoma, squamous-cell carcinoma of bladder, and particularly low for angiosarcoma of liver and mesothelioma (table 4).

Survival was generally better for women than for men, even after adjustment for age, geographic group, period of diagnosis, and clinical variables (table 5). Survival from adrenal-cortex carcinoma did not differ between men and women, and survival from squamous-cell carcinoma of bladder was slightly worse in women than men. For all rare cancers, 5-year relative survival decreased with age (table 5). The survival difference between the youngest and oldest groups was significant, except for angiosarcoma of liver, for which we had few data.

The figure and webtable show that except for placental choriocarcinoma, mesothelioma, and lung carcinoid, survival improved over time. Adjusted relative excess risk for the latest versus the first diagnosis period were significantly better for anal squamous cell carcinoma, angiosarcoma of liver, sarcoma of extremities, ovarian germ-cell cancer, and digestive-system endocrine cancers (figure). 5-year survival also improved over time for adenocarcinoma of uterine cervix, sarcoma of uterus, and squamous-cell carcinoma of bladder; however, after adjustment for age, morphology, and other covariates, relative excess risk did not show any significant increase (figure).

See Online for webtable

Survival in northern Europe was higher than in the other geographic groups for most cancers (table 6). The



	Relative excess risk					
	1986–88	(95% CI)	1989–91	(95% CI)	1992–94	(95% CI)
Placental choriocarcinoma	1·15	(0·50–2·62)	0·99	(0·40–2·41)	1·38	(0·61–3·15)
Ovarian germ-cell cancer	0·70	(0·50–0·98)	0·74	(0·54–1·03)	0·57	(0·40–0·80)
Medullary carcinoma of thyroid	1·06	(0·75–1·50)	0·92	(0·65–1·32)	0·88	(0·62–1·25)
Lung carcinoid	1·12	(0·80–1·55)	0·98	(0·70–1·36)	1·07	(0·79–1·45)
Adenocarcinoma of uterine cervix	0·97	(0·87–1·08)	0·91	(0·82–1·02)	0·96	(0·86–1·07)
Testicular cancer at age ⩾65 years	0·84	(0·58–1·23)	1·00	(0·70–1·45)	1·11	(0·78–1·59)
Sarcoma of extremities	0·91	(0·83–1·00)	0·92	(0·84–1·01)	0·87	(0·79–0·95)
Digestive-system endocrine tumours	0·92	(0·82–1·02)	0·95	(0·85–1·05)	0·83	(0·74–0·92)
Anal squamous-cell carcinoma	0·81	(0·71–0·92)	0·88	(0·78–1·00)	0·85	(0·75–0·96)
Sarcoma of uterus	0·99	(0·89–1·10)	0·95	(0·85–1·05)	0·92	(0·83–1·02)
Adrenal-cortex carcinoma	1·19	(0·86–1·65)	1·01	(0·75–1·37)	0·96	(0·70–1·33)
Squamous-cell carcinoma of bladder	1·00	(0·90–1·12)	0·98	(0·87–1·09)	0·93	(0·83–1·04)
Angiosarcoma of liver	0·87	(0·48–1·58)	0·53	(0·28–0·99)	0·52	(0·30–0·89)
Mesothelioma	1·04	(0·97–1·11)	0·98	(0·92–1·05)	0·97	(0·91–1·04)

Figure: **5-year relative survival from rare cancer by period of diagnosis, and relative excess risk of death**
Relative excess risk adjusted by follow-up, age, diagnosis period, geographic group, sex, subsite, and morphology. Reference category 1983–85.

exceptions were: bladder carcinoma, adrenal-cortex carcinoma, and placental choriocarcinoma (for which survival was higher in western Europe than northern Europe); and mesothelioma (for which UK survival was worse than for the rest of Europe and significantly worse than for northern and western Europe)

Table 7 shows 5-year relative survival and adjusted relative excess risk of death from rare cancer by subsite and morphology. We noted that survival varied substantially with morphology. In multiple regression analysis, relative excess risk of death varied significantly with morphology for many sites. For sarcoma of the extremities, short-bone subsites had better survival than did those of long bones (table 7). Survival for digestive-system endocrine cancers that affected the pancreas, liver, and gall bladder was worse than that for those affecting other digestive sites (table 7). Survival for extrapleural mesothelioma (mainly that of the abdomen and pelvis) was better than that for pleural mesothelioma (table 7); however, after adjustment for morphology and age no difference was recorded (table 7).

Discussion

We have shown that survival for rare cancers decreased with increasing age at diagnosis, as for most common cancers. We found that survival was good (ie, >65%) for placental choriocarcinoma, thyroid medullary carcinoma, ovarian germ-cell cancer, lung carcinoid, and cervical adenocarcinoma; intermediate (35–65%) for testicular cancer at age 65 years or older, sarcoma of extremities, digestive-system endocrine cancers, anal squamous-cell carcinoma, and uterine sarcoma; low (20–33%) for carcinoma of the adrenal-gland cortex and bladder squamous-cell carcinoma; and particularly poor (5–6%) for angiosarcoma of liver and mesothelioma.

Apart from age-related biological differences, the oldest patients might not have received a specialist pathological diagnosis as promptly as younger patients, potentially contributing to poor survival. More advanced stage at presentation, reduced access to specialist treatment, and incomplete application of treatment protocols (perhaps because of substantial comorbidity,

	UK*			Northern Europe			Western Europe			Eastern Europe		
	n	Survival, % (95% CI)	RER	n	Survival, % (95% CI)	RER (95% CI)	n	Survival, % (95% CI)	RER (95% CI)	n	Survival, % (95% CI)	RER (95% CI)
Adenocarcinoma of uterine cervix	5275	67·2 (65·7–68·6)	1	1582	68·2 (65·6–70·8)	0·91 (0·82–1·01)	874	61·8 (58·2–65·5)	1·00 (0·88–1·13)	955	54·4 (50·9–58·0)	1·37 (1·22–1·53)
Anal squamous-cell carcinoma	3046	51·9 (49·7–54·2)	1	1479	56·1 (53·0–59·3)	0·89 (0·80–0·98)	699	54·1 (49·5–58·7)	0·88 (0·77–1·01)	162	42·7 (33·4–51·9)	1·35 (1·07–1·70)
Angiosarcoma of liver	69	6·7 (0·2–13·2)	1	42	7·8 (0–17·1)	0·97 (0·59–1·59)	20	0·0	0·86 (0·45–1·64)	7	0·0	0·84 (0·33–2·13)
Sarcoma of uterus	2815	40·4 (38·4–42·5)	1	1344	46·2 (43·2–49·3)	0·86 (0·79–0·94)	890	46·3 (42·6–49·9)	0·87 (0·78–0·97)	637	46·7 (42·4–51·1)	1·03 (0·91–1·16)
Sarcoma of extremities	5314	59·3 (57·7–60·9)	1	2259	64·0 (61·5–66·4)	0·88 (0·80–0·96)	1293	65·6 (62·5–68·7)	0·91 (0·82–1·02)	1146	49·5 (46·2–52·9)	1·47 (1·33–1·63)
Testicular cancer (age ⩾65 years)	491	61·9 (55·3–68·5)	1	298	71·7 (63·3–80·0)	0·86 (0·63–1·19)	94	57·7 (43·9–71·5)	1·10 (0·72–1·68)	60	45·2 (26·3–64·0)	2·02 (1·29–3·18)
Mesothelioma	7098	4·0 (3·5–4·5)	1	2350	5·2 (4·3–6·3)	0·88 (0·84–0·93)	781	7·8 (5·9–10·0)	0·81 (0·74–0·88)	320	8·6 (5·7–12·2)	0·88 (0·78–1·00)
Placental choriocarcinoma	90	85·7 (78·3–93·1)	1	106	84·3 (77·1–91·4)	1·12 (0·54–2·31)	39	92·4 (83·8–101·0)	0·43 (0·13–1·41)	73	85·1 (76·7–93·5)	1·05 (0·47–2·33)
Medullary carcinoma of thyroid	419	68·5 (63·2–73·7)	1	373	75·9 (70·5–81·2)	0·70 (0·53–0·94)	190	77·8 (70·9–84·6)	0·73 (0·50–1·05)	118	66·0 (55·9–76·0)	1·16 (0·80–1·70)
Squamous-cell carcinoma of bladder	2332	20·9 (18·8–22·9)	1	955	17·2 (14·2–20·1)	1·01 (0·92–1·11)	285	25·0 (19·0–31·0)	0·85 (0·72–0·99)	151	22·9 (14·6–31·2)	0·85 (0·69–1·05)
Adrenal cortex carcinoma	154	28·2 (20·5–35·9)	1	219	29·3 (22·7–35·9)	0·98 (0·76–1·27)	59	51·9 (38·1–65·7)	0·54 (0·35–0·84)	67	36·9 (24·4–49·4)	0·82 (0·57–1·19)
Digestive-system endocrine tumours	2538	44·3 (43·1–45·5)	1	3850	64·7 (63·7–65·6)	0·77 (0·70–0·84)	888	54·8 (52·9–56·8)	0·87 (0·77–0·99)	417	39·9 (37·2–42·7)	1·32 (1·14–1·54)
Lung carcinoid	461	67·1 (62·0–72·1)	1	513	72·8 (68·2–77·4)	0·81 (0·63–1·04)	331	70·1 (64·3–75·8)	1·00 (0·76–1·30)	138	70·4 (61·5–79·3)	1·05 (0·73–1·51)
Ovarian germ-cell cancer	444	74·5 (70·1–78·9)	1	253	75·3 (69·4–81·1)	0·71 (0·51–0·98)	107	72·3 (63·3–81·2)	1·46 (0·97–2·18)	174	65·8 (58·5–73·2)	1·56 (1·12–2·17)

RER=relative excess risk, adjusted by follow-up, age, diagnosis period, geographic grouping, sex (excluding uterine, placental, and gonadal sites), subsite (for sarcoma of uterus, sarcoma of extremities, mesothelioma, and digestive-system endocrine tumours), and morphology (for sarcoma of uterus, adenocarcinoma of uterine cervix, testicular cancer at age ⩾65 years, mesothelioma, digestive-system endocrine tumours, and ovarian germ-cell cancer). *Reference category.

Table 6: **5-year relative survival and adjusted relative excess risk of death for rare cancers by geographic group**

compromised immune status, or no protocol tailored for elderly people) may also contribute to poor outcomes in elderly people.[12] However, information on such factors was not systematically obtained by the cancer registries and could not be analysed in this study.

With regard to variations in survival across geographic groups, differences in access to diagnostic facilities and specialised treatments may be important, since these vary markedly across Europe. However, in much of northern and western Europe, multidisciplinary specialist care is well developed. In some countries of eastern Europe, cancer services are commonly provided by oncologists and surgeons who are not specialised in the treatment of particular cancer sites; moreover, few of these eastern European countries participate in clinical trials.[13] In some countries, particularly those in eastern Europe, access to biomarker monitoring or imaging (eg, CT and MRI) might also be restricted.[13,14]

Evidence from the UK suggests that for ovarian cancer and breast cancer, access to specialist centres improves outcome.[15,16] Specialist centres might also offer techniques such as limb-preserving surgery for sarcoma of extremities, or biomarker monitoring of treatment response (particularly for medullary thyroid carcinoma and choriocarcinoma); they are also more likely to give correct pathological diagnosis of difficult-to-diagnose entities than are non-specialist centres.

Cancer registries for northern Europe, Scotland, Wales, Slovenia, Slovakia, and Estonia cover the entire country; other registries participating in this study (ie, those of western Europe; Krakow, Poland; and England) cover variable regions of their respective countries. In these regions, patient selection and local standards of care could affect referral patterns, so findings might not represent those of the country as a whole. Comparisons of national and regional data therefore need to be made cautiously, although this issue concerns mainly western Europe, since more than 50% of the UK population is represented by regional registries.[4]

Stage at diagnosis is an important prognostic factor, and stage distribution is therefore a potential determinant of survival differences by age, sex, or geographical area. However, population-based data for disease stage information was largely incomplete, and our analyses are therefore unable to interpret survival differences in terms of early diagnosis or treatment.

As is noted for common cancers,[17] sex was an important prognostic factor for most rare cancers analysed in that women generally had a better outlook than did men. However, for bladder squamous-cell carcinoma, men had

	n	Survival, % (95% CI)	Relative excess risk* (95% CI)
Subsite (ICD-9 code)			
Sarcoma of uterus			
Cervix (180·0–180·9)	239	45·1 (37·9–52·4)	1 (Reference)
Corpus and uterus, NOS (182·0–182·8, 179)	5447	43·4 (41·9–44·9)	0·99 (0·82–1·18)
Sarcoma of extremities			
Long bones and soft tissue of leg (170·7, 171·3)	7174	57·8 (56·4–59·2)	1 (Reference)
Long bones and soft tissue of arm (170·4, 171·2)	2547	64·2 (61·9–66·5)	0·82 (0·76–0·89)
Short bones of leg (170·8)	142	69·8 (60·7–78·9)	0·63 (0·46–0·88)
Short bones of arm (170·5)	149	90·4 (82·0–98·7)	0·16 (0·07–0·34)
Mesothelioma			
Pleural (163·0–163·9)	9329	4·1 (3·6–4·5)	1 (Reference)
Extrapleural (all but 163·0–163·9)	1220	9·6 (7·9–11·5)	0·97 (0·91–1·04)
Digestive-system endocrine tumours			
Pancreas (157·0–157·9)	941	37·7 (36·0–39·5)	1·99 (1·81–2·20)
Liver and gallbladder (155·0–155·2, 156·0–156·9)	200	17·2 (14·2–20·1)	2·58 (2·13–3·12)
Other digestive sites (150·0–154·9, 158·0–159·9)	6552	59·5 (58·7–60·2)	1 (Reference)
Morphology (ICD-0 code)			
Adenocarcinoma of cervix			
Adenocarcinoma (8050, 8140–8141, 8190–8230, 8260–8263, 8310, 8380, 8430–8490, 8510, 8940)	7300	66·6 (65·4–67·9)	1 (Reference)
Adenosquamous (8560–8570)	1386	59·6 (56·7–62·4)	1·33 (1·21–1·46)
Sarcoma of uterus			
Leiomyosarcoma (8890–8895)	2099	44·2 (43·1–45·4)	1 (Reference)
Endometrial stromal sarcoma (8930)	843	60·2 (58·3–62·1)	0·63 (0·56–0·72)
Müllerian mixed (8933, 8940, 8950, 8980)	1548	38·0 (36·6–39·4)	0·81 (0·73–0·89)
Other specified	730	34·6 (32·6–36·6)	0·92 (0·82–1·03)
Unspecified (8800–8804)	466	38·9 (36·4–41·5)	1·14 (1·00–1·30)
Sarcoma of extremities			
Fibrosarcoma (8810–8812, 8830)	2494	59·4 (56·9–61·8)	1 (Reference)
Osteosarcoma (9180–9195, 9260)	1433	46·6 (43·8–49·4)	2·09 (1·87–2·32)
Chondrosarcoma (9220–9240)	879	72·4 (68·8–76·1)	0·91 (0·78–1·06)
Other specified	4054	66·1 (64·3–67·9)	0·88 (0·80–0·96)
Unspecified (8800–8804)	1152	48·2 (44·8–51·7)	1·70 (1·53–1·90)
Testicular cancer age ⩾65 years			
Seminoma (9060–9064)	546	77·6 (71·6–83·7)	1 (Reference)
Embryonal carcinoma (9070–9071)	29	30·0 (6·9–53·1)	4·47 (2·54–7·89)
Malignant teratoma (9080–9085)	76	51·2 (36·2–66·1)	2·52 (1·62–3·94)
Choriocarcinoma (9100–9101)	10	31·5 (–6·9 to 69·8)	4·88 (2·08–11·47)
Other specified	167	41·7 (30·6–52·7)	2·87 (2·03–4·04)
Unspecified (8000–8002)	115	41·6 (28·4–54·8)	3·04 (2·10–4·39)
Mesothelioma			
Malignant (9950)	9892	4·4 (4·0–4·9)	1 (Reference)
Fibrous (9051)	122	19·4 (12·4–27·8)	0·74 (0·60–0·91)
Epithelioid (9052)	396	8·5 (5·9–11·8)	0·77 (0·68–0·86)
Biphasic (9053)	139	0·8 (0·1–4·2)	1·24 (1·03–1·50)
Digestive-system endocrine tumours			
Well differentiated (8150–8155, 8240–8246)	6718	62·1 (61·4–62·8)	1 (Reference)
Undifferentiated (8041–8042)	975	7·8 (6·8–8·8)	4·60 (4·18–5·06)
Ovarian germ-cell cancer			
Dysgerminoma (9060–9073, 9100–9101)	625	78·1 (74·6–81·6)	1 (Reference)
Teratoma (8240–8243, 9080–9091, 9102)	353	63·6 (58·1–69·1)	1·40 (1·08–1·80)

NOS=Not otherwise specified. *Adjusted for follow-up, age, diagnosis period, geographic group, sex (excluding uterine and gonadal sites), subsite, and morphology.

Table 7: **5-year relative survival and adjusted relative excess risk of death for rare cancers by subsite and morphology**

a better outlook than did women, and survival was much the same for adrenal-cortex carcinoma. Several ideas have been postulated for the better outlook for women compared with men, including: greater awareness by women of their bodies, with consequent earlier diagnosis; different mix of cases due to exposure to various risk factors; and better biological response of women to disease or treatment. With regard to bladder cancer, a stage-adjusted survival advantage in men compared with women has been associated with higher pressure in the male bladder due to longer urethra, thicker detrusor muscle, and presence of prostate; which would hinder blood perfusion and metastatic spread.[18]

We found that survival for many rare cancers has improved over time, particularly for ovarian germ-cell cancer and angiosarcoma of liver. Survival also improved over time for anal squamous-cell carcinoma, sarcoma of extremities, and digestive-system endocrine tumours. For anal squamous-cell carcinoma and ovarian germ-cell cancer, the main improvements were noted between 1983–85 and 1986–88, reflecting the introduction of fluorouracil and radiotherapy for treatment of anal squamous-cell carcinoma in the 1980s,[19] and of cisplatin for ovarian germ-cell cancer in the 1970s.[20] Furthermore, the improvement in survival for patients with angiosarcoma of liver might be linked to improved chemotherapy or wider availability of liver transplantation.[21]

Survival remained stable or increased over time for placental choriocarcinoma, mesothelioma, lung carcinoid, and testicular cancer in men aged 65 years or older. No effective treatments for mesothelioma or lung carcinoid were available during the period of our study.[22,23] Effective treatment has become available for testicular cancer but, as discussed above, might not have been adequately applied in elderly people. For placental choriocarcinoma, the introduction of chemotherapy over the past 25 years has improved survival in clinical studies, including metastatic disease.[24] We recorded high survival for placental choriocarcinoma, but no significant improvement over time; however, a major improvement might have occurred before our study period.

The higher survival noted for the short-bone subsites of sarcoma of the extremities compared with those of long bones has not been reported previously and is not explained by differences in age at diagnosis. Improved radical surgery for sarcoma of extremities has advanced treatment.[25] Differences by subsite for adenocarcinoma of cervix, sarcoma of uterus, and gonadal cancers have been reported[26–28] and are confirmed by our study.

Geographic variation in survival for these cancers might therefore reflect differences in the use of effective treatment protocols. By contrast, little or no treatment advances have been achieved from 1983 to 1994 for squamous-cell carcinoma of bladder, adrenal-cortex carcinoma, and mesothelioma. For these cancers, geographic variation in outcome might reflect differences in diagnosis (eg, accuracy of histological diagnosis for mesothelioma) or in quality of follow-up by cancer registries (eg, loss of information on death).

Bias in our results might arise because of variations in data quality and comparability. However, our major indicators of the quality of cancer-registry data—ie, proportion of cases reported as death-certificate only,

microscopically verified, and lost to follow-up—suggest a high-quality dataset (table 1).

More detailed analysis of the quality of registry data and comparability of diagnoses necessitates an in-depth analysis of cancer-registration documents, and possibly pathological review of all registered, selected rare cancers, both of which are beyond the scope of this study. Inconsistencies in diagnostic and coding criteria can frequently be shown by unlikely geographical variations in incidence. We analysed differences in incidence between geographic groups, and found that incidence ranges for rare cancers were much the same as those for all cancers affecting the same sites (table 3). The most important difference was noted for digestive-system endocrine tumours, the incidence of which varied by a factor of 3·9 between the four geographic groups, whereas incidence of all digestive-system cancers varied only by a factor of 1·2. Fairly high variation in incidence between geographic groups was also recorded for mesothelioma, lung carcinoid, and adrenal-cortex carcinoma. Although such variation could be due to random fluctuation, these data suggests that the comparability of diagnostic criteria will need to be addressed in future studies.

Rare cancers pose particular problems for health-care organisation, clinical decision-making, and translational research. Development and availability of new treatments also depends on designation of orphan drugs. Current definitions of rare cancers are unsatisfactory because of their basis on prevalence (see http://www.rarediseases.org), which is frequently unknown. Addressing these issues needs European-wide networks to generate epidemiological data, coordinate adequately powered multicentre clinical studies, and disseminate information on best practice and treatment advances. The European Commission has recognised the importance of rare diseases, and is encouraging the creation of a European network of excellence.[29]

To conclude, population-based survival studies are essential for assessment of overall effectiveness of health systems in providing cancer care. Substantial regional differences in survival from rare cancers for which there are no effective treatments (eg, mesothelioma) suggest variations in quality of diagnosis and follow-up. For rare cancers that respond well to treatment, differences in regional survival are of greater concern and possibly attributable to variations in treatment availability or cancer awareness in the population. Effective treatments are available for testicular cancer, anal squamous-cell carcinoma, sarcoma of extremities, and sites of reproductive cancer, and further investigation is needed to ascertain why survival from these cancers is low in some European countries, particularly for older patients. Audit of best practice for rare cancers with treatment protocols would also be useful.

Contributors

G Gatta designed the study, analysed data, and wrote the paper; L Ciccolallo analysed data and wrote the paper; F Berrino designed the study; I Kunkler designed the study and reviewed the final draft; R Capoccacia did data preparation and revised the paper; R De Angelis planned and did part of the analysis; M Coleman designed the study; J Faivre and J-M Lutz designed the study and prepared the paper; C Martinez designed the study and reviewed the final draft; T Möller participated in primary data analyses, designed the study, and did presentation of results; and R Sankila designed the study and reviewed the final draft.

Conflict of interest

We declare no conflicts of interest.

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