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The EUROCARE-3 database: methodology of data collection, standardisation, quality control and statistical analysis

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The EUROCARE database contains data on 6.5 million cancer patients diagnosed from 1978 to 1994 in populations covered by 67 cancer registries in 22 European countries. The quality-checked entries specify age, sex, diagnosis date, cancer site, morphology, microscopic confirmation and vital status, as well as containing broad indicators of stage. For EUROCARE-3, which refers to diagnoses from 1990 to 1994, 3389 cases with major data problems and 142 525 second or subsequent cancers were removed, leaving more than 2 million cases for analysis. From these data, observed and relative survival for each cancer site and country were calculated at 1, 3 and 5 years from diagnosis. Overall European survival for each cancer site and for all cancers combined were calculated combining country-specific survival figures. Overall, 1.1% of cases were lost to follow-up, 4.2% were known from death certificates only and 1.2% were known at autopsy only. The percentage of microscopically confirmed cases varied with cancer site and country, and was always higher in northern European countries. Comparison of quality indicators for the EUROCARE-3 database with earlier EUROCARE databases indicates that data quality and standardisation have improved.

Key words: cancer survival, data quality, population-based cancer registries

The EUROCARE database

EUROCARE, which began in 1990, is a collaborative project between European cancer registries. Its purpose is to estimate and compare cancer survival in European populations. The present EUROCARE database includes incidence and life status information on cancer patients diagnosed from 1978 to 1994 and followed-up at least until the end of 1998. EUROCARE has published two major monographs: EUROCARE-1 [1], which analysed survival in ~800 000 cancer cases incident between 1978 and 1985; and EUROCARE-2 [2] which analysed ~1 300 000 cancer patients diagnosed from 1985 to 1989. The present issue of *Annals of Oncology* constitutes the third major EUROCARE monograph (EUROCARE-3) and is concerned with the survival of cancer patients diagnosed in the latest available quinquennium (1990–1994).

This paper describes the methods used for data checking and survival analysis in EUROCARE-3. It also illustrates the most important characteristics of the database and includes an evaluation of registration and follow-up quality.

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Participating registries and populations covered

Sixty-seven registries sent their incidence and follow-up data to EUROCARE-3. Eleven of these registries (Denmark, Estonia, Finland, Iceland, Malta, Norway, Slovakia, Slovenia, Scotland, Sweden and Wales) are national registries covering their entire populations. The other registries are regional registries covering from 3% to 62% of the populations of their respective countries (Table 1). The proportion of the national population covered increased with respect to EUROCARE-2 for Italy (9.7–15.3%), England (49.6–62.6%) and The Netherlands (5.7–23.7%). Five countries are included in EUROCARE-3 that were not present in EUROCARE-2: the Czech Republic, Malta, Norway, Portugal and Wales.

A second German registry, the Munich cancer registry, joined EUROCARE-3 contributing data for cases diagnosed in 1993 and 1994. The relative survival of these Munich cases was very high: the highest in Europe for most cancer sites, and often higher than that observed in the USA [3]. A longer period of incidence and more stage information is necessary to determine whether the high survival in Munich is real or due to case selection—a process which is likely to occur during the early years of population-wide collection by what used to be clinical registry. Munich is therefore included in the database as an individual registry but the data were

Table 1. Population covered (1992, in thousands) and percentage coverage of national population by participating registries[a]

Registry/country	Population (000s)	Percentage coverage	Registry/country	Population (000s)	Percentage coverage
Finland	5023	100	Italy	56 318	
Iceland	267	100	Ferrara	360	0.6
Norway	4618	100	Genoa	725	1.3
Sweden	8918	100	Latina	447	0.8
Denmark	5205	100	Macerata	283	0.5
			Modena	260	0.5
England	49 310		Parma	396	0.7
East Anglia	2089	4.2	Ragusa	285	0.5
Mersey & Cheshire	2412	4.9	Romagna	432	0.8
Oxford	2582	5.2	Sassari	456	0.8
South & West	3320	6.7	Turin	1033	1.8
Thames	6756	13.7	Tuscany	1174	2.1
Trent	4745	9.6	Varese	790	1.4
West Midlands	5278	10.7	Veneto	1977	3.5
Yorkshire	3698	7.5	Italian registries	8618	15.3
English registries	30 880	62.6			
			Malta	365	100
Scotland	5119	100			
Wales	2925	100	Switzerland	6914	
			Basel	435	6.3
Netherlands	15 047		Geneva	386	5.6
Amsterdam	2620	17.4	Swiss registries	821	11.9
Eindhoven	947	6.3			
Dutch registries	3567	23.7	Germany	82 183	
			Munich	1210	1.5
France	56 567		Saarland	1080	1.3
Bas-Rhin	1038	1.8	German registries	2290	2.8
Calvados	625	1.1			
Côte d'Or	499	0.9[b]	Austria	7930	
Isère	1037	1.8[c]	Tyrol	637	8.0
French registries	3199	2.9–5.6[d]			
			Slovenia	2072	100
Portugal	10 019		Czech Republic	10 331	
South Portugal	1145	11.4[e]	West Bohemia	861	8.3
			Slovakia	5344	100
Spain	38 714				
Basque Country	2097	5.4	Poland	38 370	
Granada	791	2.0[f]	Cracow	740	1.9
Mallorca	586	1.5	Warsaw	1626	4.2
Murcia	1080	2.8[g]	Poland	2366	6.1
Navarra	521	1.3			
Tarragona	553	1.4	Estonia	1544	100
Spanish registries	5628	9.6–14.4[d]	European population	403 023	
			Covered population	101 412	25.2–26.3

[a]Specialised childhood registries not included.
[b]Only digestive, gynaecological and haematological.
[c]Only breast.
[d]According to cancer site.
[e]Fifteen cancer sites only.
[f]Seventeen cancer sites only.
[g]Only lung and breast.

not pooled with the other German registry (Saarland) in the main analyses.

Two registries (one digestive and one for all other cancers) cover the region of Calvados (France), while three registries (digestive, gynaecological and haematological) sent data for the region of Côte d'Or (France). Sweden, previously represented by one regional registry, now has complete national coverage in EUROCARE.

Ten specialised childhood cancer registries participated in EUROCARE-3: Brittany, Lorraine and Rhone-Alpes (France), the Dutch Childhood Leukaemia Registry, Germany, Piedmont and Marche (Italy), the Spanish National Childhood Cancer Registries (which sent data for the province of Barcelona), Valencia (Spain) and the UK. Only four of these contributed to EUROCARE-2 [4]. In summary, 67 cancer registries sent data on 53 general and 44 childhood populations. Social, health and cancer control characteristics of the regions covered by these cancer registries are described elsewhere [1, 2, 5].

The cancer cases included in EUROCARE-3 were incident in a total population of 101 million, representing about a quarter of the total population of the 22 countries involved. For six registries (Munich, Sassari, Granada, South Portugal, Isère, Malta and the section of the German Childhood Cancer Registry covering former East Germany), the incidence data did not completely cover the specified incidence period (from 1990 to 1994). In contrast, >50% of registries presented cancer incidence data spanning more than 15 consecutive years.

Four registries (Granada, Isère, Murcia and South Portugal) had adequate follow-up for only a subset of cancer sites and their data were excluded from the analysis of all cancers combined. The three specialist registries of Côte d'Or were also excluded from this analysis because their registration was restricted to specific cancer sites only. Further details of the coverage for childhood cancer are given elsewhere [6].

Data collection and standardisation

Survival data were collected on all malignant cancers as defined by codes 140–172 and 174–208 of the ninth revision of the International Classification of Diseases (ICD-9) and also for cases of non-malignant transitional cell neoplasms of the bladder. Non-melanoma skin cancers were excluded (Table 2).

Each participating cancer registry sent the entire set of its incidence data for which a sufficiently long follow-up was available. This dataset included cases sent to earlier EUROCARE studies in order to update vital status. The data were placed in a central database. Only first primary cancers were included in the survival analyses although data on second and subsequent primaries was retained. Data on multiple tumours is rarely available either at the clinical or population level, and the large EUROCARE database on these tumours constitutes a valuable resource for future studies. According to international rules for ranking multiple cancers, non-malignant neoplasms and non-melanoma skin cancers are ignored as first cancers. Synchronous cancers at a single site are considered one cancer. For synchronous cancers at different sites, that with the worse prognosis is considered as the first.

Data on *in-situ* neoplasms were also collected, but again these were not included in the survival analyses. Since the frequency of *in-situ* neoplasms is related to early diagnosis activity in a population, comparative analysis of *in-situ* frequencies may assist the interpretation of survival differences between populations.

For bladder cancers, standardised rules for including papillomas and non-invasive carcinomas were lacking, therefore transitional cell neoplasms with non-malignant and uncertain behaviour were included among these cancers. Borderline ovarian cancers (ICD-O-2 8342, 8451, 8462, 8472, 8473) [7] were also included, although they were excluded from EUROCARE-2. These lesions were coded as malignant (fifth digit = 3) in International Classification of Diseases for Oncology, second revision (ICD-O-2), but not in previous [8] and subsequent classifications [9].

For each case, the EUROCARE-3 study protocol required the following data: sex; month and year of birth; month and year of diagnosis; month and year of latest vital status ascertainment; vital status; tumour topography (site) code (ICD-9); morphology and behaviour code (ICD-O-2); and information on microscopic confirmation. Basic information on stage (lesion confined to organ, regional extension, distant metastasis, not available) was also supplied if available. Each registry assigned a unique identification code to each case record (that did not allow the individuals to be identified) to facilitate data quality checks.

Site was coded as ICD-7 by the Finnish registry and had to be converted to ICD-9; Slovenian data were converted from ICD-8. Morphology code conversion was necessary for the Finnish, Norwegian and some English registries, and for Slovenian cases incident before 1983. Reconstruction of ICD-O-2 morphology was achieved for almost all of these cases thanks to the active collaboration of personnel in the registries concerned. For this reason EUROCARE-3 contains a higher proportion of cases with consistent morphology codes than previous studies. For all non-solid tumours, ICD-O to ICD-9 conversion was automatic when the morphology code was present. Some lymphomas had topography codes attributing the disease to a specific organ (extra-nodal lymphomas); these were recorded simply as lymphomas.

Automatic checking

Unlikely site–morphology combinations, including the standard International Agency for Research on Cancer (IARC) checks for data submitted to Cancer Incidence in Five Continents [10], were the most frequent problem encountered by the automatic checking procedure. Records containing invalid codes, or impossible or improbable sex–age–site–morphology combinations were sent back to the registries for checking and correction if possible. Records returned after review were automatically re-checked. All records definitively included in the database had fields indicating whether the content had been changed during checking, if it had been reviewed by the registry personnel, and if any problems remained. In the latter case, the problem was categorised as 'major' when missing, invalid or inconsistent values occurred in dates, sex, site or morphology; as 'minor' when unlikely

Table 2. Cancer sites included in EUROCARE-3, by ICD-9 code, with descriptions of the cancer

ICD-9 code	Short description	Full description
140	Lip	Lip (excluding skin of lip)
141	Tongue	
142	Salivary gland	Major salivary glands
143–145	Oral cavity	Gum, floor of mouth, other and unspecified parts of mouth
146	Oropharynx	
147	Nasopharynx	
148	Hypopharynx	
141, 143–148	Head & neck	Tongue, gum, floor of mouth, other and unspecified mouth, oropharynx, nasopharynx, hypopharynx
150	Oesophagus	
151	Stomach	
152	Small intestine	Small intestine (excluding ileocaecal valve)
153	Colon	
154	Rectum	Rectum, rectosigmoid junction, anal canal and anus
153, 154	Colon & rectum	Colon, rectum, recto–sigmoid junction, anal canal and anus
155	Liver, primary	Liver and intrahepatic bile ducts
156	Biliary tract	Gallbladder, ampulla of Vater and extrahepatic bile ducts
157	Pancreas	
160	Nasal cavities	Nasal cavity, accessory sinuses, middle and inner ear
161	Larynx	
162	Lung	Trachea, bronchus and lung
163	Pleura	
170	Bone	Bone, joints and articular cartilage
171	Soft tissues	Connective, subcutaneous and other soft tissues
172	Melanoma of skin	
174, 175	Breast	
180	Cervix uteri	
182	Corpus uteri	
183	Ovary	Ovary and other uterine adnexa
184	Vagina and vulva	Vagina, vulva and other and unspecified female genital organs
185	Prostate	
186	Testis	
187	Penis	Penis and other male genital organs
188	Bladder	Urinary bladder (including benign neoplasms)
189	Kidney	Kidney and other and unspecified urinary organs (excluding urinary bladder)
190.6	Choroid (melanoma)	
191	Brain	
193	Thyroid gland	
200, 202	Non-Hodgkin's lymphoma	
201	Hodgkin's disease	
203	Multiple myeloma	
204.0	Acute lymphatic leukaemia	
204.1	Chronic lymphatic leukaemia	
205.0	Acute myeloid leukaemia	
205.1	Chronic myeloid leukaemia	
204–208	Leukaemia	
140–208	All cancers combined (except non-melanoma skin tumours, 173)	

ICD, International Classification of Diseases.

age–site–morphology combinations were confirmed; and as 'invalid behaviour' for invalid morphology/behaviour combinations.

Site and morphology codes listed in ICD-9 and ICD-O-2, respectively [7, 11], were generally the only ones considered valid by the checking procedure; however, morphology codes introduced in the third revision of the international classification [9] and not present in ICD-O-2 were also admissible. The checking procedure only accepted a behaviour code as valid if the morphology/behaviour combination was present in the ICD-O morphology list. (This contradicts rule F of the coding guidelines [9] stating that any behaviour code can be associated with any morphological type.) Missing morphology codes were accepted only for cases not verified microscopically. For microscopically verified cases, missing values were imputed as 8000/3 for malignant cancers, and as 8000/1 if malignant status was uncertain.

Table 3 summarises the results of the data checking procedure for each registry. Column 4 reports the number of cases received from the registries. Column 5 shows the cases excluded immediately as non-pertinent (usually benign, non-neoplastic disease or duplicate registrations). A total of 6 552 672 records were sent to EUROCARE-3 including the 49 924 records from childhood registries. After rejecting 5010 non-pertinent general cases and 172 non-pertinent childhood cases, the database contained 6 497 638 general records and 49 752 records from childhood registries (Table 3). Column 6 shows the total number of cases accepted in the database. This includes the 99.6% of cases that eventually passed all the quality checks (column 7), a few cases (<0.1%) accepted with invalid behaviour codes (column 8), 0.1% accepted with minor errors (column 9) and 0.2% to be excluded from survival analysis because of major errors (column 10). The latter, however, were retained in the database for possible future correction.

The validation process resulting in the above classification required further manual checking of 61 371 general and 494 childhood case records that were sent back to the registries. Two registries (South & West England and Wales) could not perform this manual checking prior to the EUROCARE-3 analysis.

Some of the cases from childhood cancer registries were also present in general cancer registry files. This occurred in registries of England and Wales, Germany, Italy and The Netherlands. In these cases, only records from childhood registries were used in the analysis of childhood cancer survival.

Cases incident 1990–1994: validity indicators and quality analysis

The characteristics of the 1990–1994 data (for adults) are summarised in Table 4. A total of 2 202 169 cases diagnosed in this period were included in the database (after eliminating non-pertinent cases as described above). A total of 3394 records had major errors while 139 601 records pertained to multiple cancers. These cases were excluded from the survival analyses leaving 2 059 174 records of first primary cancers in adults for analysis. Among these cases, 0.7% had incomplete follow-up, 4.2% were notified to the registry via death certificate only (DCO) and 1.2% were notified via autopsy reports only.

The proportion of multiple tumours was highly variable across registries, ranging from 18% (Mersey, England) to <1% (Murcia, Spain). This suggests imperfect standardisation in the rules for classification/definition of multiple tumours. In general, registries that have been in operation for a long time, and therefore with long follow-up periods—typically northern European registries—have higher proportions of multiple cancers than registries that have been operating for less time. However, the long-established (>15 years) registries of Cracow, Trent, Slovakia and Saarland had <3% multiple tumours and this suggests lower data quality. Similarly, good information quality is suggested by a high proportion of multiple tumours in the database of registries with a short incidence period.

The study protocol stipulated that all cases should have at least 4 years of follow-up. An overall proportion of 0.7% of cases was lost to follow-up before the end of the 4-year period. This proportion was low in most registries, except for 15 registries where >1% of cases were lost, and in six of these >5% of cases. Figures for proportions lost to follow-up have little meaning if only passive follow-up methods are used (as in the Basque Country and in all UK registries except East Anglia).

Thames had the highest proportion of DCO cases (17%), followed by Slovakia (9.1%), Navarra (8.8%) and the Basque Country (7.6%). Six registries had DCO cases in the range 5–7%; while the average value was 4.2%. As noted before, overall 1.2% of cases were found only at autopsy: most registries had values close to this; the only outlier was the registry of the Czech Republic (8.7%). The proportion of deaths that occurred within 1 month was on average 7.1%, with substantially higher values in the UK and Poland.

Table 5 shows the proportions of microscopically (histologically or cytologically) confirmed cases by country for selected cancer sites. Poor prognosis and difficult access cancers, such as those of the lung and digestive tract, had the lowest proportions of microscopically confirmed cases; good survival cancers, such as skin melanoma and breast cancer, had the highest proportions of microscopically confirmed diagnoses. The registries in northern Europe, The Netherlands, Switzerland, France and Munich had the highest proportions (usually >95%) of microscopically verified cases. Poland, Slovakia, most English registries, South Portugal and Ragusa had the lowest proportions (usually <90%).

Table 6 shows 5- and 10-year survival, by country, for a selection of poor survival cancers (acute myeloid leukaemia, cancers of pleura, lung, pancreas, biliary tract, liver and oesophagus) as indirect indicators of follow-up quality. High survival for these cancers suggests (but does not prove) inadequate follow-up procedures. Countries rather than individual registries are listed for maximum comparability. Outlier countries are shown in bold. No country had unbelievably high survival for these sites; however, systematically better survival characterised Spain, Wales and Iceland. For Iceland, with its small population and numerically small numbers of cases, this is more likely due to random variation. For Spain and Wales, the figures suggest follow-up problems.

With the same purpose to indirectly evaluate the quality of the follow-up procedures, 5-year observed survival for stomach and

Table 3. Summary of results of the automated data checking for each registry (general and childhood registries): number of case records received and accepted after checking

Registry	Country	Period of diagnosis		Received		Accepted				
				Total	Excluded	Total	Formally valid	With invalid tumour behaviour	With minor errors	With major errors
Tyrol	A	1988	1997	30 913	49	30 864	30 412	378	47	27
Basel	CH	1981	1992	18 711	3	18 708	18 707	0	1	0
Geneva	CH	1978	1994	28 932	1948	26 984	26 946	0	38	0
West Bohemia	CZ	1988	1994	25 662	0	25 662	25 519	123	17	3
Munich	D	1993	1994	7459	0	7459	7448	0	11	0
Saarland	D	1978	1997	112 636	24	112 612	112 435	4	41	132
Denmark	DK	1978	1994	384 203	0	384 203	382 912	866	365	60
Basque Country	E	1986	1994	66 876	190	66 686	66 612	1	73	0
Granada	E	1991	1994	5169	0	5169	5165	0	4	0
Mallorca	E	1982	1994	16 987	44	16 943	16 907	24	12	0
Murcia	E	1990	1994	3416	0	3416	3415	0	1	0
Navarra	E	1985	1994	18 554	2	18 552	18 539	0	13	0
Tarragona	E	1985	1994	18 628	67	18 561	18 545	2	14	0
Estonia	EST	1978	1994	70 865	0	70 865	70 797	0	67	1
Bas Rhin	F	1978	1996	69 828	0	69 828	69 772	0	56	0
Calvados Digest.	F	1978	1996	11 124	1	11 123	11 121	0	2	0
Calvados Gen.	F	1978	1996	36 687	0	36 687	36 666	0	19	2
Côte d'Or Digest.	F	1978	1994	7888	22	7866	7849	0	11	6
Côte d'Or Gyn.	F	1982	1992	3858	0	3858	3854	0	0	4
Côte d'Or Haem.	F	1980	1997	3208	8	3200	3182	0	0	18
Isère	F	1987	1992	3047	1	3046	3046	0	0	0
Finland	FIN	1978	1994	288 090	1425	286 665	286 472	8	107	78
Ferrara	I	1990	1994	10 804	7	10 797	10 792	0	5	0
Genoa	I	1986	1994	38 895	0	38 895	38 860	5	26	4
Latina	I	1983	1994	14 611	1	14 610	14 597	0	12	1
Macerata	I	1991	1994	6699	0	6699	6694	0	5	0
Modena	I	1988	1994	21 472	0	21 472	21 447	0	24	1
Parma	I	1978	1994	38 295	15	38 280	38 242	6	19	13
Ragusa	I	1981	1994	10 874	0	10 874	10 872	0	2	0
Romagna	I	1986	1994	22 537	5	22 532	22 499	21	12	0
Sassari	I	1992	1994	5673	0	5673	5670	1	2	0
Turin	I	1985	1994	46 836	2	46 834	46 809	0	25	0
Tuscany	I	1985	1994	61 697	6	61 691	61 669	1	21	0
Varese	I	1978	1994	53 824	1	53 823	53 790	0	33	0
Veneto	I	1990	1994	50 774	0	50 774	50 671	0	102	1
Iceland	ICE	1978	2000	20 187	0	20 187	19 991	171	24	1
Malta	MLT	1993	1997	7265	7	7258	7182	54	2	20
Amsterdam	NL	1988	1994	74 197	6	74 191	74 105	6	76	1
Eindhoven	NL	1978	1996	59 778	4	59 774	59 250	321	92	111
Norway	N	1978	1996	324 338	430	323 908	323 423	5	286	194
Cracow	PL	1978	1994	35 622	10	35 612	35 304	0	5	303
Warsaw	PL	1989	1996	48 291	28	48 263	48 244	3	14	2

Table 3. (*Continued*)

Registry	Country	Period of diagnosis		Received		Accepted				
				Total	Excluded	Total	Formally valid	With invalid tumour behaviour	With minor errors	With major errors
Portugal	P	1991	1994	5057	0	5057	5054	0	3	0
Sweden	S	1978	1998	789 732	0	789 732	789 581	0	151	0
Slovakia	SK	1978	1994	237 087	1	237 086	229 379	20	221	7466
Slovenia	SLO	1978	1994	88 355	74	88 281	88 236	7	30	8
East Anglia	UK	1978	1994	161 189	80	161 109	160 730	201	178	0
Mersey	UK	1978	1994	181 059	7	181 052	180 889	71	87	5
Oxford	UK	1978	1994	145 895	179	145 716	144 462	10	54	1190
Scotland	UK	1978	1994	377 883	0	377 883	377 647	6	229	1
South West	UK	1979	1994	482 504	42	482 462	480 485	760	943	274
Thames	UK	1978	1998	553 301	208	553 093	550 211	39	1865	978
Trent	UK	1979	1997	399 476	0	399 476	398 254	6	1207	9
Wales	UK	1978	1994	241 053	0	241 053	239 563	77	158	1255
West Midlands	UK	1978	1994	384 014	113	383 901	383 089	567	220	25
Yorkshire	UK	1978	1994	270 633	0	270 633	269 614	796	178	45
Total	–	–	–	**6 502 648**	**5010**	**6 497 638**	**6 473 626**	**4560**	**7210**	**12 242**
Childhood registries										
Germany (East)	D	1991	1994	1274	0	1274	1266	0	7	8
Germany (West)	D	1980	1994	17 805	0	17 805	17523	0	77	282
Valencia	E	1983	1994	884	0	884	883	0	1	0
Spain National[a]	E	1990	1994	1143	0	1143	1143	0	14	0
Brittany	F	1991	1998	595	2	593	548	0	1	45
Lorraine	F	1983	1994	974	0	974	974	0	6	0
Rhone-Alpes	F	1987	1998	1696	0	1696	1693	0	23	3
Marche	I	1990	1998	275	0	275	275	0	6	6
Piedmont	I	1978	1994	1672	0	1672	1672	0	12	0
Dutch Leukaemia National	NL	1978	1998	2321	0	2321	2321	0	0	0
England & Wales National	UK	1978	1995	21 285	170	21 115	21 115	0	149	0
Total childhood	–	–	–	**49 924**	**172**	**49 752**	**49 413**	**0**	**296**	**344**

[a]The Spanish National Childhood Cancer Registry only contributed cases incident in the province of Barcelona.

colorectal cancers with metastases at diagnosis are shown in Table 7. Because of incomplete stage information, the data are presented only for the 16 registries with stage information for at least half the cases at each site. The 5-year survival of stomach cancer cases with distant metastases at diagnosis ranged from <1% (Côte d'Or, Amsterdam, Norway, Slovenia, Varese and Warsaw) to >4% for Saarland and the Swiss registries. For colorectal cancer, the minimum was 2.6% (Estonia) and the maximum was 9% (Finland and Saarland). In a few cases, e.g. Saarland and Thames, the proportion of 5-year survivors was substantially higher than the average proportion for both stomach and colorectal metastatic cases, suggesting possible follow-up problems; however, stage information is often not available for advanced and non-operated patients. This can selectively bias relative survival figures based on staged cases only.

Statistical methods

Relative survival

Relative survival is the ratio of the observed survival in a group of patients to the survival probability estimated over the same period in a group of people in the general population of similar age and sex. The Hakulinen method was used

Table 4. Summary of characteristics of cancer cases diagnosed from 1990 to 1994, by registry[a]

Registry	Country	Total no. of cases entered in database	Number of major errors	Multiple tumours (%)	Total no. of first primary cases	Lost after <4 years of follow-up (%)	DCO cases (%)	Autopsy cases (%)	Deaths within 1 month (%)
Tyrol	A	15 374	27	1.7	15 090	0	4.6	1.9	2.7
Basel	CH	5057	0	13.7	4364	0.7	0.0	0.0	5.3
Geneva	CH	8631	0	10.1	7758	2.7	1.7	2.6	2.5
West Bohemia	CZ	18 861	3	3.5	18 202	0	2.5	8.7	6.7
Munich	D	7459	0	8.7	6807	8.2	0.0	0.0	0.9
Saarland	D	32 066	1	3.0	31 094	0	6.4	0.1	4.5
Denmark	DK	119 777	5	9.8	108 076	0	0.8	2.2	5.4
Basque Country	E	39 652	0	5.2	37 574	n.a.	7.6	0.0	4.2
Granada	E	5085	0	1.4	5012	0.8	5.2	0.1	3.6
Mallorca	E	11 592	0	2.7	11 282	0.8	4.1	0.0	5.1
Murcia	E	3398	0	0.7	3373	4.3	6.2	0.0	6.4
Navarra	E	10 093	0	4.3	9661	0	8.8	0.7	3.3
Tarragona	E	10 301	0	3.8	9910	0	3.5	0.3	5.2
Estonia	EST	23 794	0	3.5	22 963	0.5	1.0	3.5	7.3
Bas Rhin	F	20 664	0	11.6	18 276	3.3	n.a.	0.6	4.1
Calvados Digest.	F	3375	0	0.0	3375	7.1	n.a.	0.0	6.8
Calvados Gen.	F	10 623	0	0.0	10 623	9.2	n.a.	0.0	1.3
Côte d'Or Digest.	F	2407	5	1.8	2359	3.7	n.a.	0.0	5.0
Côte d'Or Gyn.	F	1229	0	1.2	1214	5.5	n.a.	0.0	2.5
Côte d'Or Haem.	F	948	5	1.3	931	1.1	n.a.	0.0	2.0
Isère	F	1561	0	7.4	1446	9.6	n.a.	0.0	0.4
Finland	FIN	94 757	47	11.6	83 746	0.1	0.8	2.2	4.3
Ferrara	I	10 625	0	1.9	10 418	1.3	2.7	0.1	3.2
Genoa	I	22 472	0	5.0	21 353	0.0	3.2	0.0	3.1
Latina	I	6162	0	3.2	5966	0.0	6.3	0.0	2.3
Macerata	I	6698	0	2.5	6531	0.0	0.5	0.0	2.9
Modena	I	15 637	1	3.1	15 153	1.9	2.3	0.2	3.9
Parma	I	12 684	4	8.1	11 648	0	2.6	0.2	2.8
Ragusa	I	4301	0	2.3	4200	0.2	1.5	0.0	4.2
Romagna	I	12 408	0	4.1	11 904	0.0	1.4	0.3	2.3
Sassari	I	5673	0	4.4	5421	0	0.0	0.0	3.1
Turin	I	23 499	0	6.5	21 961	0.3	5.1	0.0	3.9
Tuscany	I	32 036	0	4.3	30 647	0.4	3.2	0.1	3.8
Varese	I	17 527	0	5.6	16 546	0.3	1.5	0.0	2.7
Veneto	I	50 774	1	2.7	49 421	0.4	4.7	0.8	3.7
Iceland	ICE	4596	0	11.8	4053	0	0.2	3.3	3.5
Malta	MLT	2643	0	1.9	2593	0.2	1.0	0.2	4.5
Amsterdam	NL	50 023	0	0	50 023	1.5	n.a.	0.5	3.9
Eindhoven	NL	17 429	1	9.1	15 850	0.2	n.a.	0.0	3.9
Norway	N	93 274	81	10.8	83 147	0.2	2.0	0.4	5.5
Cracow	PL	11 671	37	1.0	11 517	0.9	3.8	0.9	18.5
Warsaw	PL	30 361	2	0.0	30 359	1.1	6.0	0.1	8.2
Portugal	P	5057	0	0.0	5057	0.5	0.0	0.0	4.8
Sweden	S	197 619	0	10.9	176 050	0.2	n.a.	4.0	4.3

Table 4. (*Continued*)

Registry	Country	Total no. of cases entered in database	Number of major errors	Multiple tumours (%)	Total no. of first primary cases	Lost after <4 years of follow-up (%)	DCO cases (%)	Autopsy cases (%)	Deaths within 1 month (%)
Slovakia	SK	79 685	2661	3.1	74 673	0	9.1	5.1	6.9
Slovenia	SLO	30 183	4	0.4	30 059	0.2	4.2	1.1	6.5
East Anglia	UK	53 623	0	4.0	51 479	16.6	0.2	0.6	7.6
Mersey	UK	60 184	1	18.1	49 260	n.a.	4.1	1.5	6.1
Oxford	UK	49 178	17	4.8	46 785	n.a.	0.6	0.4	9.8
Scotland	UK	122 070	0	7.2	113 329	n.a.	3.4	0.0	9.9
South West	UK	176 080	82	6.0	165 431	n.a.	6.4	0.0	8.7
Thames	UK	136 542	157	4.6	130 157	n.a.	17.4	0.0	9.6
Trent	UK	114 335	2	1.7	112 385	n.a.	3.3	0.0	11.3
Wales	UK	79 914	232	7.8	73 493	n.a.	0.0	0.0	18.7
West Midlands	UK	129 241	8	5.1	122 583	n.a.	2.5	0.4	9.5
Yorkshire	UK	91 261	10	5.1	86 586	n.a.	2.7	0.0	6.7
Total	–	2 202 169	3394	6.3	2 059 174	0.7	4.2	1.2	7.1

[a]Childhood registry cases excluded.
DCO, death certificate only.

to calculate relative survival in EUROCARE-3 [12, 13]. Theoretically, relative survival can exceed 100% if the survival of the patients is greater than the expected survival of the matched general population. This can occur for cancers with high survival probability, if patients lead a healthier life or are better treated for co-morbidities than the reference population. It can also occur by chance with small numbers of patients. In view of this, the cumulative relative survival was constrained to a range between 0 and 100%.

Standard error of the estimated relative survival was obtained using Greenwood's formula [14]. Ninety-five per cent confidence intervals were constrained through a logarithmic transformation to be non-negative. The upper limit can be >1 (or >100% when expressed as a percentage).

European survival

Overall European survival estimates for each cancer site, by age, sex and time since diagnosis, were calculated as the weighted average of the survival for each country or national pool of registries. The weightings applied were the annual sex- and site-specific numbers of incident cases at national level estimated from the available registries' data. The weightings for Germany were based on incidence in former West Germany only. This was done because the only German registry used in calculating European survival estimate was Saarland (West Germany). The weightings used were not age-dependent for practical and theoretical reasons (data availability, simplicity of presentation, comparability of results and stability of estimates). Assuming that the fraction of the national population covered by cancer registration in each country is representative of that of the whole country (this may not be the case, for example, in Germany), the European survival figures can be interpreted as estimates of the average relative survival of all patients diagnosed in the 22 countries considered. Standard errors of European survival were calculated from weighted averages of the corresponding variances of country-specific survival. Confidence intervals for European survival were calculated assuming a normal distribution after log transformation; for this reason, pooled survival estimates and their confidence intervals were always positive but could be greater than 1, although this rarely happened in practice.

Age-adjusted survival

In order to be comparable between different populations, relative survival figures must be either age-specific or age-adjusted. In EUROCARE-3 relative survival tabulated by country is presented as age-adjusted survival. Age-adjusted country-specific survival was calculated by the direct method, using five age classes and, as standard, the age distribution of the whole set of cases analysed for each site. The same standard distribution was used for both sexes. European age-adjusted relative survival is computed in the same way from the corresponding age-specific European survival estimates. European age-adjusted survival figures were generally similar to non-age-adjusted figures although, in a few cases, they can substantially differ. Confidence intervals for age-adjusted relative survival were calculated assuming a normal distribution after logarithmic transformation; however, no constraint was set for the upper interval.

Missing age-specific values

Age-adjusted survival ratios cannot be computed when there are no cases in one or more age classes. This is reflected in missing age-adjusted values for many smaller countries in less frequent cancer sites. The same problem is more serious if geographical comparisons based on age-adjusted values are to be extended at the registry level. An imputation procedure has then been used to fill missing age-specific survival ratios in single cancer registries with an estimate.

A survival model with independent age (a_i), registry (r_k) and follow-up (f_j) interval categorical variables, $\log[-\log(S_{ikj})] = a_i + r_k + f_j$, has been fitted to the whole set of 1990–1994 EUROCARE-3 age-specific relative survival ratios, S_{ik}, stratified by gender and cancer site. Expected survival ratios provided by the models have been used for the imputation of age-specific ratios in those cases in which empirical survival was not available for lack of cases. In any case, age-adjusted ratios have not been calculated for the site–registry–gender combination with three or more age-specific missing values.

Table 5. Microscopically verified cases for selected cancer sites, by registry; cases incident in 1990–1994 (childhood cancer registries excluded)

Registry	Country	Microscopically verified cases, %							
		Stomach	Colon	Biliary tract	Lung	Melanoma	Breast	Prostate	NHL
Tyrol	A	89	91	79	80	99	94	94	97
Basel	CH	100	100	100	100	100	100	100	100
Geneva	CH	96	94	79	92	100	96	92	98
West Bohemia	CZ	84	86	73	88	100	93	92	100
Munich	D	96	98	88	97	99	98	96	100
Saarland	D	87	90	63	76	98	94	93	95
Denmark	DK	94	93	78	85	99	96	91	98
Basque Country	E	87	85	62	81	98	94	76	94
Granada	E	80	86	63	74	98	96	–	97
Mallorca	E	89	90	73	87	100	96	87	97
Murcia	E	–	–	–	79	–	93	–	–
Navarra	E	88	89	71	87	99	97	87	97
Tarragona	E	87	90	65	86	98	96	84	96
Estonia	EST	81	80	82	70	98	92	77	98
Bas Rhin	F	99	99	88	95	100	99	98	100
Calvados	F	97	98	68	99	100	98	99	98
Côte d'Or	F	98	97	82	–	–	97	–	100
Isère	F	–	–	–	–	–	96	–	–
Finland	FIN	95	94	85	89	100	99	97	99
Ferrara	I	85	91	61	77	96	94	84	98
Genoa	I	77	81	66	71	91	91	78	92
Latina	I	82	85	61	67	94	87	82	91
Macerata	I	75	81	56	77	95	91	82	93
Modena	I	85	88	54	69	99	96	90	98
Parma	I	84	91	60	78	99	96	89	98
Ragusa	I	75	76	51	49	96	89	44	96
Romagna	I	92	91	70	82	100	96	84	98
Sassari	I	90	86	61	72	100	96	82	97
Turin	I	87	87	53	72	99	93	88	97
Tuscany	I	77	84	63	62	94	92	75	86
Varese	I	93	93	69	85	100	97	92	98
Veneto	I	86	88	66	73	97	92	81	96
Iceland	ICE	99	97	86	94	100	100	99	100
Malta	MLT	86	91	59	81	97	95	85	97
Amsterdam	NL	98	98	75	95	100	99	98	100
Eindhoven	NL	98	98	79	93	100	99	98	99
Norway	N	95	94	79	91	100	99	95	99
Cracow	PL	54	52	38	70	95	85	52	90
Warsaw	PL	64	60	47	60	91	83	65	84
Portugal	P	81	86	–	–	100	90	72	99
Sweden	S	98	98	92	98	100	99	99	100
Slovakia	SK	74	79	71	71	97	85	79	96
Slovenia	SLO	81	86	72	90	98	94	84	99
East Anglia	UK	53	64	36	44	83	74	63	75

Table 5. (*Continued*)

Registry	Country	Microscopically verified cases, %							
		Stomach	Colon	Biliary tract	Lung	Melanoma	Breast	Prostate	NHL
Mersey	UK	78	79	54	59	98	86	84	85
Oxford	UK	75	80	67	60	100	99	76	100
Scotland	UK	80	83	66	60	99	87	79	90
South West	UK	73	75	66	56	94	82	71	98
South Thames	UK	61	70	48	52	89	76	69	75
Trent	UK	70	74	49	52	94	81	75	84
Wales	UK	44	49	46	39	94	60	50	97
West Midlands	UK	30	32	16	22	98	78	46	37
Yorkshire	UK	82	84	62	65	99	89	83	91
Total	–	78	81	67	67	97	89	83	91

The two registries of Calvados (digestive and general) are considered together; the three registries of Côte d'Or (digestive, gynaecological and haematological) are considered together.
NHL, non-Hodgkin's lymphoma.

Discussion

A major aim of EUROCARE is to analyse cancer survival differences between European countries; however, such comparisons may be confounded by the variable extent of cancer registration. In some countries, 100% of the population is covered by cancer registration, while in other participating countries <10% of the population is covered which may not be representative of the country as a whole. This issue has been extensively discussed elsewhere and will not be repeated here [15, 16]. Note, however, that the number of registries included in EUROCARE-3 was greater than in EUROCARE-2, and that for The Netherlands, Italy, England and Sweden, the percentage coverage of the population increased considerably, yet the overall cancer survival rankings of these four countries did not change.

Three other issues pertaining to data quality must be considered when comparing survival between countries: completeness of case collection; disease definition; and quality of follow-up for vital status. Incomplete registration of incident cases affects survival estimates if the unregistered cases have different prognoses to the registered cases. Cases known only from the death certificate cannot be included in survival analyses because their date of diagnosis is not known. DCO cases may represent patients too ill to be hospitalised or to undergo biopsy; the exclusion of these short survival cases therefore tends to bias survival upwards. However, a high proportion of DCO cases may also be a sign that the registry is missing significant numbers of incident cases. These will include cured patients who will never be detected (the death certificate will not mention the cancer), so the result is an underestimate of true survival. Thus, a high proportion of DCO cases suggests a bias in survival estimates, but does not indicate the direction of that bias. In contrast, a low proportion of cases that would not be detected in the absence of a death certificate (the so-called death certificate-initiated cases) is indicative [1] of more complete registration procedures and therefore of negligible selection bias.

The possible causes and effects of lack of completeness in case registration have been extensively discussed in previous EUROCARE publications [17–20]. The overall proportion of DCO cases was lower in cases diagnosed in 1990–1994 than in earlier EUROCARE incidence periods. In particular, most of the registries that in EUROCARE-2 had >10% of DCO cases had substantially lower percentages in EUROCARE-3. The exception was the English registry of South Thames which has reported high levels of DCO cases in all EUROCARE studies. In spite of this, relative survival in Thames (see electronic data [21]) was comparable with that in other UK registries that had much lower levels of DCO cases. It should also be noted that some registries do not use (Sweden) or do not have access to (Dutch and French registries) death certificates. Selection bias in these registries cannot therefore be detected via this indicator.

With regard to disease definition, the high level of standardisation attained by the participating cancer registries, and the extensive checking procedures employed by EUROCARE-3, mean that extensive misclassification with respect to disease definition and coding can be ruled out for most cancers. However, for head and neck, lung, thyroid and soft tissue cancers, regional variations in sub-site or morphology mix can influence survival estimates; while for ovary, bladder and stomach cancers, the classification of borderline malignancies varies across Europe, again resulting in survival comparability problems. Finally, screening or early diagnostic activity (for breast, cervical and prostate cancers) can complicate the interpretation of inter-country differences in survival when such activities are not similar in all countries. 'High resolution' population-based studies that collect detailed information on stage are necessary to clarify the regional survival difference for such cancer sites. This issue is further discussed elsewhere in this monograph [20].

Table 6. Five- and 10-year relative survival for poor survival cancers (diagnosed in 1990–1994 and 1978–1989, respectively)[a]

Country	Relative survival, years													
	AML		Pleura		Lung		Pancreas		Biliary tract		Liver		Oesophagus	
	5	10	5	10	5	10	5	10	5	10	5	10	5	10
Austria	18	12	6	0	16[b]	7	6	5	**20**	**15**	7	**10**	4	4
Czech Republic	15	5	12	0	8	2	6	3	9	5	2	1	5	0
Denmark	12	0	3	0	7	4	2	1	7	4	2	1	5	3
England	16	8	5	3	7	5	4	3	12	9	7	4	10	7
Estonia	3	3	11	6	8	5	6	1	11	5	2	<1	4	3
Finland	**25**	9	6	3	9	6	3	2	8	7	4	2	8	6
France	**20**	**14**	4	2	14	8	4	3	17	8	8	2	11	4
Germany	17	6	7	8	12	7	5	3	16	13	5	6	12	5
Iceland	**25**	4	–	–	11	9	3	3	**24**	13	–	**13**	**14**	**13**
Italy	13	8	6	2	11	6	5	3	11	9	7	2	8	5
Malta	9	–	–	–	–	–	4	–	–	–	–	–	0	–
Netherlands	17	12	2	3	13	9	3	3	12	9	7	3	9	4
Norway	10	5	4	3	9	6	3	1	9	11	3	2	6	4
Poland	2	2	6	2	7	5	3	5	5	7	2	1	4	2
Scotland	16	7	3	2	7	5	3	3	12	7	5	2	8	4
Slovakia	13	7	9	2	8	**12**	6	9	11	13	4	5	3	7
Slovenia	12	6	7	7	10	5	2	2	7	3	5	1	6	3
Spain	**19**	**13**	**15**	**13**	**13**	**11**	6	6	**19**	**19**	**10**	**8**	**14**	7
Sweden	17	7	5	3	10	7	3	2	9	5	3	1	9	5
Switzerland	18	11	5	0	**13**	9	4	2	13	10	5	<1	**13**	6
Wales	18	**13**	3	**14**	8	**11**	5	**10**	11	**16**	6	**9**	8	**14**
European pool	15	6	6	4	11	6	4	3	12	8	7	3	10	6

[a]Childhood registries excluded.
[b]Outlier countries are shown in bold.
AML, acute myeloid leukaemia.

Difficulties in ascertaining the vital status of incident cases generally result in an overestimation of survival as deaths are missed. Follow-up difficulties may be due to confidentiality constraints, lack of access to death records, or, in registries performing passive follow-up only, linkage failure between death records and registry records. An estimate of the size of the likely bias due to cases erroneously considered alive in passive follow-up was provided by EUROCARE-1 [17]. The relative survival data for poor prognosis cancers presented in Tables 6 and 7 shed further light on this problem, as high survival for such cancers suggests inadequate vital status follow-up. Inadequate follow-up is likely in Spain, Austria and, for 10-year survival, in Wales. The survival data for these countries should therefore be considered as less reliable than for other registries. This analysis also suggests that for the English registries—most of which use passive follow-up—linkage procedures are adequate.

To conclude, a great effort has been devoted by all the EUROCARE-3 participating members to achieve the greatest possible completeness and standardisation of the data (particularly topography and morphology codes). For this reason, the EUROCARE database is more than the sum of its contributing databases, and its value as a resource for cancer surveillance in Europe is considerably greater. It is expected that data quality will continue to improve as wider use is made of this valuable resource in the future.

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Table 7. Five-year observed survival for stomach and colorectal cancers (diagnosed 1990–1994) with metastases at diagnosis, as an indicator of data quality[a]

Registry	Stomach cancer				Colorectal cancer			
	Stage, %	M+	% M+	Survival	Stage, %	M+	% M+	Survival
Amsterdam	84	588	27	0.3	95	967	20	3.1
Basel	89	54	28	7.4	97	151	21	5.1
Côte d'Or Digest.	83	76	21	0.0	95	183	18	4.4
Cracow	79	107	23	1.9	69	186	18	6.5
Denmark	82	705	22	1.0	–	–	–	–
Estonia	86	902	38	1.0	88	700	27	2.6
Finland	78	1633	31	1.6	81	1702	22	9.1
Geneva	92	76	31	3.9	95	178	22	3.8
Norway	97	1099	31	0.6	96	2173	20	3.4
Saarland	55	244	11	4.1	66	398	9	8.5
Slovakia	71	1353	25	1.5	63	1923	15	5.6
Slovenia	82	640	24	0.9	86	667	19	3.3
Thames	61	914	11	2.8	73	2252	12	7.4
Tuscany	73	235	7	2.6	74	306	7	5.9
Varese	82	325	22	0.3	81	373	17	4.3
Warsaw	85	435	34	0.9	79	685	20	3.7

[a]Most non-staged patients were advanced, not treated cases. This table is not appropriate for estimating the survival of metastatic cancer patients; it is intended as a data quality indicator. Colorectal cancer data for Denmark are not shown due to non-comparability of stage coding.

Stage, percentage of cases with information on stage; M+, number of cases with metastases at diagnosis; % M+, percentage of cases metastatic at diagnosis among cases with stage information; survival, 5-year observed survival of metastatic cases.

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