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Original Paper

Survival Rates for Primary Malignant Brain Tumours in Europe

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In the framework of EUROCARE, a concerted action between 45 population-based cancer registries, in 17 European countries, survival of patients with primary malignant brain tumours was investigated. Survival analysis was carried out on 16 268 patients diagnosed between 1985 and 1989 and followed-up for at least 5 years. The mean European age-standardised 5-year relative survival was 17% in men and 20% in women, with minimal intercountry variations, except for markedly lower rates in Scotland, Estonia and Poland. The age-specific analysis showed a relatively uniform survival in patients aged more than 65 years at diagnosis, but there were more marked intercountry differences in younger patients. In the 15–44 year age group (25% of the total study population) 5-year relative survival ranged between 55% (Finland and Sweden) and 27% (Poland). Generally, survival decreased with increasing age at diagnosis. The analysis of a temporal trend in survival was carried out on a subset of registries with available data from 1978–1989. Overall, there was an increase in survival over the considered study period, mostly confined to 1-year survival, suggesting that it was mostly related to improved diagnostic techniques. The most important survival increase occurred in the younger patients, both for 1- and 5-year survival, suggesting that younger patients have less biologically aggressive tumours, benefiting from the combined effect of diagnostic accuracy and effective therapies. The most marked survival increase was seen in England and Denmark, countries with low survival rates at the beginning of the study period, whereas in Finland and Germany, where survival was relatively high to begin with, no important temporal trend was seen. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE INCIDENCE of primary malignant brain tumours varies between European countries, being highest in Northern countries such as Sweden, Iceland and Denmark, where the world age-standardised incidence in males is approximately 10 cases/100 000 person/year. In Central and Southern European countries such as the U.K., France, Italy and Spain the figures range between 5–6 per 100 000. The incidence is slightly lower for females, but similar in both sexes in the countries with a high incidence. In most U.S. areas covered by the SEER registries, the incidence of brain tumours is similar to that observed in Central and Southern Europe, with considerable lower values in non-caucasian populations [1]. Incidence and mortality of brain tumours is increasing with time, particularly in the elderly [2, 3] and it is possible that a part of this increase is attributable to improved diagnostic techniques and/or to increased access to healthcare. If there is an artifactual increase due to earlier diagnosis in a country with particularly high level diagnostic techniques, one would also expect a higher survival. However, despite the observed variability in incidence, survival for brain tumours is very poor in all countries. In fact, in Europe 5-year relative survival in males was 18% in the first EUROCARE survey for patients diagnosed between 1983 and 1985 [5]. In the U.S.A. in 1981–1987 5-year relative survival was 23% according to the SEER data [6].

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A temporal improvement in survival has been observed but is limited to selected histotypes such as medulloblastoma, which accounts for a minor proportion of the total incidence and affects younger patients. This improvement has been evident since the 1970s, when chemotherapy and radiotherapy protocols became available. For other more frequent histotypes, which represent most of the total incidence, in particular glioblastoma, there is no evidence of a striking improvement in survival [7, 8]. During the last two decades diagnostic procedures, particularly imaging, have been developed and become available in clinical practice. The availability of non-invasive techniques has made the diagnosis of brain tumours easier than in the past. This is important, particularly in the elderly, where differential diagnosis between brain tumours and stroke is now more accurate. Some authors have explained the modest observed improvements in survival as an effect of earlier and more accurate diagnosis, rather than a real effect of therapies [9].

The aim of this study was to explore geographical differences in survival for brain tumours in Europe and, for those countries with sufficient data, to examine variation in survival over time for the EUROCARE study period (1978–1989).

PATIENTS AND METHODS

Survival analysis was carried out on 16 268 patients suffering from malignant brain tumours as defined by the code 191 of the International Classification of Diseases (ICD-9) [10], diagnosed in 17 countries represented by 38 population-based cancer registries, diagnosed between 1985 and 1989 and followed-up for at least 5 years. Some registries had national or large population coverage (Iceland, Finland, Denmark, Scotland, England, Slovenia, Slovakia and Estonia), some covered up to 20% of the national population (Sweden, The Netherlands, France, Spain, Italy, Switzerland, Germany, Austria and Poland). Only primary malignant tumours were included. Borderline and uncertain behaviour tumours, cases discovered at autopsy, patients first diagnosed with another tumour or known on the basis of their death certificate only (DCO) were excluded. Methods of analysis and criteria of inclusion are fully described in the previous EUROCARE study [5].

Relative survival was computed as the ratio of the observed survival in a given patient group to the expected survival derived from the mortality rates of the general population, according to the Hakulinen method [11]. The overall European mean relative survival was estimated as the weighted average of the relative survival of the individual countries, with weightings proportional to the population size of each country. Age-standardised survival rates were calculated from age-specific rates in the five age groups considered: 15–44, 45–54, 55–64, 65–74 and 75–99 years. The age distribution of cases in the entire European sample was used, for all periods, both sexes and all geographical areas, as the standard distribution. For the analysis of temporal trends in survival, only the registries which contributed to EUROCARE from 1978 to 1989 were considered and the following 3-year periods were defined: 1978–1980, 1981–1983, 1984–1986 and 1987–1989. The relative risk of death (RR) in 1987–1989 versus 1978–1980 was estimated, assuming proportionality of the risk between the periods of diagnosis. RR was calculated by the ratio of the logarithms of the relative survival in the period of interest to the reference one.

RESULTS

Data quality for primary brain tumours, 1985–1989

Table 1 lists the countries represented in EUROCARE II, with the number of cases diagnosed from 1985–1989 in the

Table 1. *Primary malignant brain tumours, number of cases and proportions within age groups, microscopic verification (MV), death certificate only (DCO) and lost to follow-up by country,* 1985–1989 *(EUROCARE* II*)*

Country	No. of cases	% Aged 15–44 years	% Aged 75 + years	% of Males	% MV	% DCO	% Lost to follow-up
Northern Europe							
Iceland	81	31	10	58	75	2	0
Finland	1,165	38	8	52	99	1	0
Sweden*	452	23	9	53	94	0	0
Denmark	1,977	26	11	55	99	0	0
U.K.							
Scotland	1,270	23	11	55	63	2	0
England	6,681	23	10	58	88	5	0.1
Western and Central Europe							
The Netherlands*	143	36	6	52	80	na	1
Germany*	253	26	9	52	71	9	0
Austria*	54	30	9	59	97	9	0
Switzerland*	209	24	12	59	99	1	3
France*	302	28	9	60	82	na	0
Southern Europe							
Spain*	683	19	11	58	54	14	0.4
Italy*	1,345	19	15	56	49	5	0
Eastern Europe							
Slovenia	303	32	3	57	86	4	0.3
Slovakia	811	34	2	54	74	12	0.3
Poland*	269	23	8	48	46	8	2
Estonia	270	33	3	54	98	0	1
Europe	16 268	25	10	56	69	5	0.2

* < 20% of the national population covered. na, data not available.

registries and indicates the percentage of microscopic verification, cases known by death certificate only (DCO) and patients lost to follow-up. Brain tumours were more frequent in males in all countries except Poland. Overall, 25% of patients were aged between 15–44 years at diagnosis and 10% were aged 75 years or more. The proportion of elderly patients was similar in all countries, with the exception of Slovakia, Estonia and Slovenia, where less than 5% were aged 75 years or more. However, there was more variability in younger age groups, ranging between 36–38% in Finland and The Netherlands (countries with a high incidence) to 19% in Italy and Spain (countries with a lower incidence). The highest proportion of microscopic verification was in Finland, Denmark, Estonia and Switzerland, the lowest in Poland, Italy and Spain. The proportions of DCO and that of cases lost to follow-up, both indicators of data quality, were very low in all countries. Only in Slovakia and Spain were the percentages of DCO high, at 12 and 14%, respectively, indicating some failure in the case ascertainment by these registries.

Intercountry variation in survival

Figure 1 shows 5-year age-standardised relative survival in the countries with a sufficient number of cases to compute age-standardisation. Prognosis was very poor, with a mean European 5-year relative survival of 17 and 20% in men and women, respectively. There was little geographic variability in survival and no country had a significantly higher survival than the European mean. The highest rates were seen in Finland for men (21%) and Germany for women (26%). The lowest survival was seen in Estonia (8%) and Poland (10%) for men and in Scotland (13%) for women. Generally, intercountry differences were not statistically significant, except for Estonia (men) and Scotland (women), where the rates were significantly lower than the European mean.

The effect of gender and age on survival

Survival of women was higher than that of men in all countries except Switzerland and Austria, where survival was lower for women or similar between the two sexes. Women had a better survival in all age classes (data not shown).

Table 2 shows 5-year relative survival by age and country. In all countries, survival decreased with increasing age at diagnosis, with the highest survival rates in the 15–44 year age group. Most intercountry differences were confined to patients up to the age of 64 years. For patients aged 65 years and more, survival was equal to or lower than 7% in almost all countries, with the exception of The Netherlands, where the highest survival of the elderly was seen (12% in the 65–74 year age group and 15% in the 75–99 year age group), as well as France and Poland which had relatively high survival for the elderly (12 and 15%, respectively). However, the number of cases in the oldest age groups were small (27 and 21 cases, respectively) and these figures should be considered with caution.

Timetrends in survival

Tables 3 and 4 show temporal trends in survival, for registries which provided data for the whole study period, by age class (15–44, 45–54 , 55–65, 65–74 and 75–99) and 3-year periods (1978–1980, 1981–1983, 1984–1986 and 1987–1989). Relative 1- and 5-year survival rates are reported. To indicate variation of prognosis over time, the relative rate

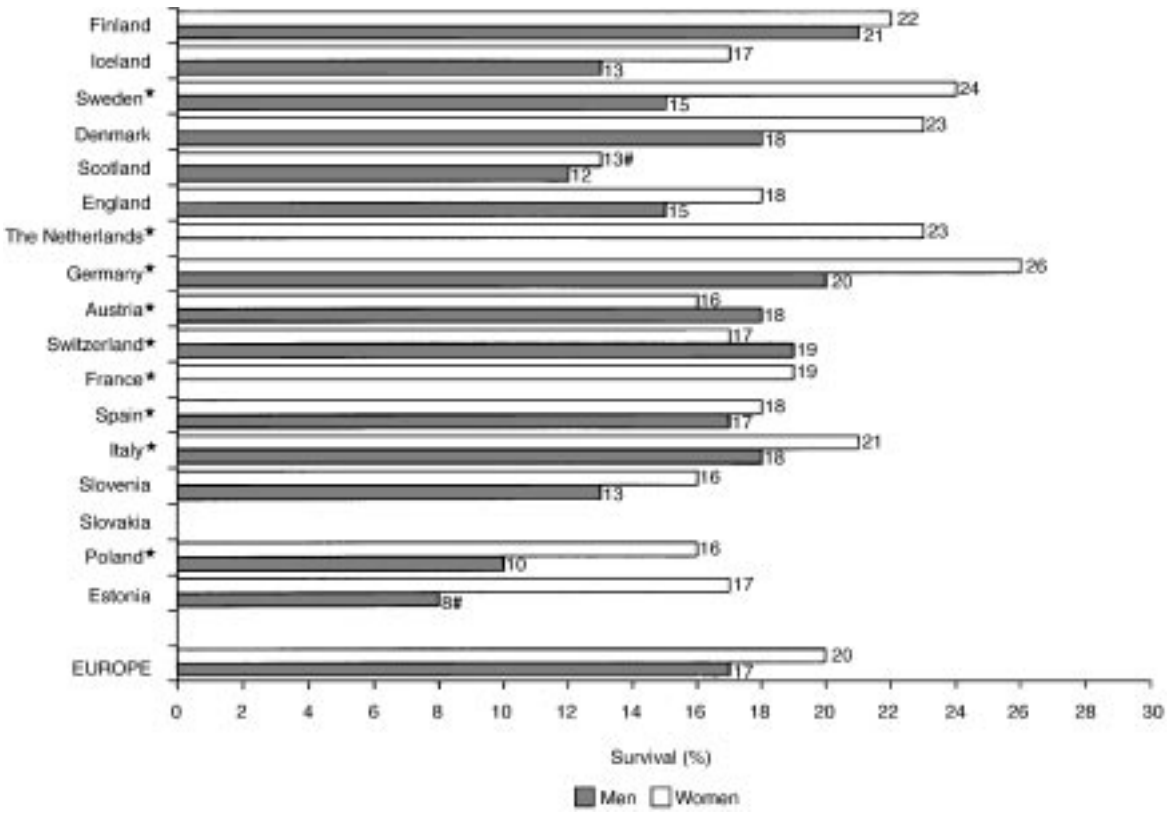

Figure 1. Relative 5-year survival rates (age-standardised) for primary malignant brain tumour patients, 1985–1989. * < 20% of the national population covered. #$P < 0.05$ compared with the European average.

(RR) of death of patients diagnosed in 1978–1980 versus those diagnosed in 1987–1989 is given. A RR over 1 indicates a worst prognosis than that of the reference category.

There was an overall slight increase in survival for all patients from 1978–1980 to 1987–1989, but most improvement was confined to the first year after diagnosis. Five-year relative survival increased only slightly, from 18% in 1978–1980 to 21% in 1987–1989 without age-standardisation (Table 3) and from 16 to 23% with age-standardisation (Table 4), indicating a large part of the increase was due to the ageing of the study population. This increase was practically only evident between 1984 and 1986, and 1987 and 1989. Age-specific rates showed that the increase in survival was more evident in younger patients, up to 54 years of age. From 55–74 years of age, survival was relatively constant over time. In the oldest age group there was some improvement, but absolute survival figures were very low, limiting the clinical significance of this result. In all age groups except the oldest one, the most marked increase was in short-term survival (first and third year from diagnosis) whereas there was little difference in 5-year survival between 1978–1980 and 1987–1989.

Table 4 shows temporal trends of 1- and 5-year survival by gender. Overall in men, survival increased from 1978–1989, with 1-year survival increasing from 33 to 41% ($P < 0.05$) and 5-year survival increasing from 15 to 16% (Table 4a). In most countries where there was an increase, the improvement was more marked in 1 year than in 5-year survival. Five-year survival increased in all countries, except Estonia, Italy, Poland and Scotland. The increase was statistically significant in Denmark and England for both 1- and 5-year survival. This pattern was similar for women, but with higher survival figures than those of men (Table 4b).

Table 2. Five-year relative survival by age and country for all patients with primary malignant brain tumours, 1985–1989 *(EUROCARE* II*)*

	Age at diagnosis					
Country	15–44	45–54	55–64	65–74	75–99	All cases
Northern Europe						
Iceland	40	7	9	0	0	16
Finland	55	23	12	4	0	29
Sweden*	55	19	6	2	4	20
Denmark	49	21	11	5	3	22
U.K.						
Scotland	38	8	2	3	1	13
England	43	16	6	4	4	17
Western and Central Europe						
The Netherlands*	34	20	0	12	15	20
Germany*	54	31	10	5	7	26
Austria*	44	7	9	11	0	20
Switzerland*	44	28	10	0	0	19
France*	46	15	10	0	12	21
Southern Europe						
Spain*	45	9	10	5	6	16
Italy*	46	17	11	5	3	17
Eastern Europe						
Slovenia	39	11	9	0	0	19
Slovakia*	40	18	7	–	–	21
Poland*	27	14	10	3	15	15
Estonia	35	7	6	4	0	16
Europe	45	18	9	4	6	19

* < 20% of the national population covered.

Table 3. Temporal trends of relative 1- *and* 5*-year survival for patients with primary malignant brain tumours by age,* 1978–1989 *(EUROCARE* II*)*

	Period									
	1978–1980		1981–1983		1984–1986		1987–1989		RR 1st/4th	
Age at diagnosis	1-year	5-year	1-year	5-year	1-year	5-year	1-year	5-year	1-year	5-year
15–44	64	39	70	41	73	45	78	45	1.8	1.2
45–54	37	18	41	17	42	16	48	25	1.4	1.2
55–64	29	7	30	8	19	6	32	8	1.1	1.1
65–74	15	5	12	3	12	2	20	5	1.2	1
75–99	3	1	8	1	14	18	7	6	1.3	1.6
All ages	35	18	38	18	35	18	42	21	1.2	1.1

Only registries which contributed data from 1978–1989 were included in the analysis.

Table 4. *Temporal trends in age-standardised relative* 1- *and* 5-*year survival of patients with primary malignant brain tumours by country and gender,* 1978–1989 *(EUROCARE* II*)*

	1978–1980		1981–1983		1984–1986		1987–1989	
	1-year	5-year	1-year	5-year	1-year	5-year	1-year	5-year
(a) Men								
Northern Europe								
Iceland	39	17	35	16	24	3	53	18
Finland	41	18	49	22	46	19	42	22
Sweden*	26	4	27	6	49	14	43†	14
Denmark	31	14	31	15	28	14	38†	21†
U.K.								
Scotland	23	11	19	8	27	14	29	10
England	27	13	26	13	31	14	33†	17†
Western and Central Europe								
Germany*	35	18	39	18	39	22	48	19
Switzerland*	36	15	37	8	‡	‡	62	27
Southern Europe								
Italy*	‡	‡	38	19	38	18	37	9
Eastern Europe								
Poland*	‡	‡	20	8	19	7	26	5
Estonia	19	11	‡	‡	23	6	33	10
Europe	33	15	33	15	35	16	41	16
(b) Women								
Northern Europe								
Iceland	44	22	‡	‡	29	17	40	21
Finland	49	27	48	24	46	24	47	22
Sweden*	32	2	45	6	38	15	49	26
Denmark	31	13	30	16	34	21	36	24
U.K.								
Scotland	24	10	24	12	29	14	29	12
England	30	15	31	17	31	16	34	18
Western and Central Europe								
Germany*	37	20	45	24	32	24	40	27
Switzerland*	37	12	35	12	34	12	58	‡
France*	48	20	‡	‡	33	‡	52	19
Southern Europe								
Italy*	41	21	42	21	39	18	48	21
Eastern Europe								
Poland*	29	18	42	11	‡	‡	52	19
Estonia	26	13	39	15	33	16	39	18
Europe	35	16	39	18	33	19	42	23

* < 20% of the national population covered. †$P < 0.05$ for difference between 1978–1980 versus 1987–1989. ‡Not enough cases to calculate age-standardisation.

DISCUSSION

This study did not indicate any important differences in overall age-standardised survival for brain tumours between European countries, the prognosis still generally remaining very poor. The most striking differences with respect to the European mean survival were the lowest figures of Estonia Poland and Scotland.

In EUROCARE I, a significantly better survival was found in Finland [5] and in this present survey Finland was still amongst the countries with higher survival, but the difference was less marked, as more countries were included in EUROCARE II, some with relatively high survival. In another Finnish population-based study [12] on gliomas diagnosed between 1953 and 1984, cumulative 5-year relative survival was 29% (consistent with the EUROCARE data), which is a relatively high figure compared with that of other European countries. This result can be partially explained by the high proportion of patients operated upon (approximately 80%). The highest survival rates in European countries were similar to those reported by the SEER registries in the U.S.A. [6] and by the South Australian registry [13], which reported a 5-year overall relative survival of 24%, during 1981–1987 and 1977–1990, respectively.

In the present study there was no available information on therapy, but the percentage of microscopic verification, that can indirectly be considered an indicator of attitude to surgery, was 99% in Finland, The Netherlands, Denmark and Switzerland, all countries with high survival rates, except Denmark. Reliable information on other prognostic factors such as sublocalisation and histotype were not available.

Whilst no striking intercountry differences emerged generally, the analysis of age-specific survival revealed that

survival was relatively uniform amongst the older patients, but amongst the youngest the differences between countries were more evident. In the youngest age group (15–44 years), 5-year relative survival ranged from 49–55% in Finland, Sweden, Germany and Denmark and was less than 35% in Estonia, The Netherlands and Poland. From the healthcare perspective, these intercountry differences in the youngest patients are probably more important than those observed considering all the patients. In all countries, survival was higher for younger patients with respect to the older ones. In addition, an improvement in 5-year survival for the youngest ages was seen between 1978 and 1989. These findings indicate that young patients are the most likely to benefit from the efforts in improving therapies.

A better prognosis for younger patients has also been reported by other studies [12, 14]. This could be attributed to particular histotypes occurring mostly in young patients and having a better prognosis (juvenile pilocytic, astrocytoma) and being more sensitive to radiotherapy and chemotherapy (medulloblastoma). However, these are very rare histotypes, and it is more likely that on the whole low-grade glial tumours occur at younger ages, whereas in older patients higher-grade tumours occur more frequently [8, 15]. In order to understand the prognostic role of histotype in EUROCARE, tumours were grouped in broad categories, basically with the aim to separate the most frequent tumours with the poorest prognosis, i.e. glioblastoma and the high-grade astrocytoma from the lower grade glial tumours (data not shown). However, it is well known that histological classification of brain tumours is one of the most controversial and least standardised, even with pathologists from the same country. For example, within the Italian and the English registries, there was a relatively high variability in the proportion of glioblastomas (data not shown). In EUROCARE the distribution by histotype did not help to explain the observed differences. There was heterogeneity among the countries in classifying the histotype, or in some cases it was not available at all. For example, in Finland all brain tumours were classified as 'gliomas', whilst in England and The Netherlands the 'glioblastoma' category was practically unused. This issue needs further investigation in future studies.

A better prognosis for women compared with men was reported, confirming results of other studies [6, 12]. This finding could be explained by the occurrence of higher grade gliomas and glioblastomas in men, with greater biological aggressiveness. However, a better prognosis for many tumours was found generally for women with respect to men in the EUROCARE study, which could indicate a more efficient biological resistance to disease in women [17]. Considering all the European data, there was a 7% increase in survival over the EUROCARE study period, from 1978 to 1989. The decrease in the RR of death was maximal in the first year following diagnosis, but it levelled off during subsequent years of follow-up, suggesting that early diagnosis rather than effective therapies were responsible for most of the improvement. The temporal trend was not uniform between countries. A marked and statistically significant increase in both 1- and 5-year survival was seen in Denmark and England, countries with low survival at the beginning of the study period. An improvement in 1-year survival only, without or with a only slight increase in 5-year survival, was seen in Estonia, Germany, Scotland. In Italy and Poland there was no increase during the study period. Computer tomography (CT) scan was available in clinical practice at the end of the 1970s, but probably its accessibility was different between European countries, depending on the health systems and on the economic conditions of each country. In those countries with high baseline survival rates, such as Finland and Germany, where no trend emerged during the study period, diagnostic imaging facilities may have been available earlier than in other countries. In Denmark and England, the improvement in 1987–1989 could be explained by a delayed access to imaging techniques. Of course, appropriate therapies are the main determinants of prognosis [8]. It is possible that the high incidence in Northern European countries stimulated the organisation of good quality care specifically for brain tumours, for example through centralisation of treatment and dissemination of effective therapeutic protocols.

The analysis by age highlighted that the increases in both the 1- and 5-year survival rate were confined to the youngest and oldest patients. However, in the elderly (75 years of age), the diagnosis of malignant brain tumours can be less reliable than in the younger, since the differential diagnosis between metastasis or stroke can be more difficult, and/or the patients are less investigated. Death certification in the elderly is less accurate and also the number of cases in the 75 + year age group was lower than that of the other groups. These issues limit the importance of the observed improving trend of survival in the oldest age groups. In contrast, the finding of an improvement in prognosis of younger patients is more reliable and suggests that the increase is due to the combined effect of more effective therapies and accurate, earlier diagnosis.

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APPENDIX

The EUROCARE Working Group for this study is: Austria: W. Oberaigner (Cancer Registry of Tirol). Denmark: H. Storm (Danish Cancer Society, 'Institute of Cancer Epidemiology'). Estonia: T. Aareleid (Estonian Cancer Registry). Finland: T. Hakulinen (Finnish Cancer Registry). France: J. Mace-Lesec'h (Calvados General Cancer Registry), P. Arveux (Doubs Cancer Registry), J. Estève (International Agency for Research on Cancer), N. Raverdy (Somme Cancer Registry). Germany: H. Ziegler (Saarland Cancer Registry). Iceland: L. Tryggvadottir, H. Tulinius (Icelandic Cancer Registry). Italy: F. Berrino (Project Leader), P. Crosignani, G. Gatta, A. Micheli, M. Sant (Lombardy Cancer Registry), E. Conti (Latina Cancer Registry), M. Vercelli (Liguria Cancer Registry-NCI, Genova), M. Federico, L. Mangone (Modena Cancer Registry), V. De Lisi (Parma Cancer Registry), R. Zanetti (Piedmont Cancer Registry), L. Gafà, R. Tumino (Ragusa Cancer Registry), F. Falcini (Romagna Cancer Registry), A. Barchielli (Tuscan Cancer Registry), R. Capocaccia, G. De Angelis, F. Valente, A. Verdecchia (National Institute of Health, Rome). Poland: J. Pawlega, J. Rachtan (Cracow Cancer Registry), M. Bielska-Lasota, Z. Wronkowski (Warsaw Cancer Registry). Slovakia: A. Obsitnikova, I. Plesko (National Cancer Registry of Slovakia). Slovenia: V. Pompe-Kirn (Cancer Registry of Slovenia). Spain: I. Izarzugaza (Basque Country Cancer Registry), I. Garau (Mallorca Cancer Registry), E. Ardanaz, C. Moreno (Navarra Cancer Registry), J. Galceran (Tarragona Cancer Registry). Sweden: T. Möller (Southern Swedish Regional Tumour Registry). Switzerland: J. Torhorst (Basel Cancer Registry), C. Bouchardy, L. Raymond (Geneva Cancer Registry). The Netherlands: J.W.W. Coebergh (Eindhoven Cancer Registry). Scotland: A. Gould, R.J. Black (Scottish Cancer Registry). England: T.W. Davies, D. Stockton (East Anglian Cancer Registry), M.P. Coleman (London School of Hygiene and Tropical Medicine), E.M.I. Williams, J. Littler (Merseyside and Cheshire Cancer Registry), D. Forman (Northern and Yorkshire Cancer Registry and Information Service), M.J. Quinn (Office for National Statistics), M. Roche (Oxford Cancer Intelligence Unit), J. Smith (South and West Cancer Intelligence Unit), J. Bell (Thames Cancer Registry), G. Lawrence (West Midlands Cancer Intelligence Unit).