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Differences in colorectal cancer survival between European and US populations: the importance of sub-site and morphology☆

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Abstract

A previous study has shown a lower survival for colorectal cancer in Europe than in the United States of America (USA). It is of interest to examine the extent to which anatomical location and morphological type influence this difference in colorectal cancer survival. We analysed survival for 151 244 European and 53 884 US patients diagnosed with colorectal cancer aged 15–99 years during the period of 1985–1989, obtained from 40 cancer registries that contribute to the EUROCARE study from 17 countries, and nine Surveillance, Epidemiology and End-Results (SEER) registries in the USA. Cases included in the analysis were first primary malignant tumours (ICD-O behaviour code 3 or higher). Relative survival was estimated to correct for competing causes of mortality. The Hakulinen–Tenkanen multiple regression approach was used to examine the prognostic impact of sub-site and ICD-O histology codes. Relative excess risks (RERs) derived from this approach estimate the extent to which the hazard of death differs from that in a reference region after adjustment for mortality in the general population. In order to explore geographical variation, we defined three groups of European registries within which survival rates were known to be broadly similar. The proportion of cases with unspecified sub-site was higher in Europe than the USA (10% versus 2%), but sub-site distributions were broadly similar in the two populations. With the exception of appendix, 5-year survival was 13–22% higher in the USA than in Europe for each anatomical sub-site. The proportion of non-microscopically-verified cases was higher in Europe than the USA (16 versus 3%). Adenocarcinomas arising in a polyp (ICD-O-2 8210, 8261, 8263) were more frequent in the USA than Europe (13 versus 2%). Five-year survival was higher in the USA than Europe for each morphological group, with the exception of non-microscopically-verified cases. When age, gender and sub-site were considered, RERs ranged from 1.52 to 2.40 for the European populations (with the USA as a reference). After inclusion of morphology codes, the range of RERs fell to between 1.28 and 1.86, mainly because of the high frequency of adenocarcinoma in polyps in the USA. This analysis suggests that the large survival advantage for colorectal cancer patients in the USA can only marginally be explained by differences in the distribution of sub-site and morphology. The main explanatory difference is the proportion of adenocarcinoma in polyps.

Keywords: Relative survival; Population-based cancer registries; Colorectal cancer; Morphology; Sub-site; Europe; USA

1. Introduction

Survival for most of the major adult cancers is higher in the United States of America (USA) than in Europe, especially among the oldest patients [1]. In the USA, 5-year relative survival for patients diagnosed with cancers of the colon and rectum during 1985–1989 were 60 and 57%, respectively, while in Europe the figs. were 48% for colon and 44% for rectum. These differences persisted in

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all 17 European populations studied, even the most affluent such as Sweden, Switzerland and The Netherlands.

In international comparisons of cancer survival, the anatomical site of the malignancy is usually defined by the three-digit code in the International Classification of Diseases [2,3], and the morphologic type of the tumours is rarely taken into account. However, survival from some solid tumours is known to vary according to the precise anatomical location (sub-site) within the organ of origin, and by the morphological type of the tumour [4,5]. The distribution of cancers by sub-site and morphology also varies between countries [6].

The aim of this paper was to examine the extent to which anatomical location and morphological type influence the differences in colorectal cancer survival between the USA and Europe.

2. Patients and methods

The European data were contributed by 40 population-based cancer registries in 17 countries: four from Northern Europe (Iceland, Finland, Sweden and Denmark), four from Eastern Europe (Slovenia, Slovakia, Poland and Estonia), and nine from Western Europe (Scotland, England, The Netherlands, Germany, Austria, Switzerland, France, Italy and Spain) as part of the EUROCARE project [7,8]. The American data were taken from the Surveillance, Epidemiology and End Results (SEER) database, which is publicly available [9].

All patients diagnosed with cancer of the colon (ICD-9 153) or rectum (ICD-9 154) aged 15–99 years during the period of 1985–1989 were eligible for inclusion in the analyses, with no selection for race. Only first, primary, malignant tumours (ICD-O-2 behaviour code 3 or higher) were eligible; *in situ* tumours and those of uncertain or borderline malignancy were excluded. Both histologically-verified and non-verified cases were included, but cases known to registries by death certificate only (DCO) and those discovered incidentally at autopsy were excluded.

More detailed information on the two databases is available in two EUROCARE monographs [7,8] published by the International Agency for Research on Cancer, and in the periodic reports on the SEER programme published under the auspices of the National Cancer Institute [9–11].

The anatomical location of tumours was coded to the Ninth Revision of the International Classification of Diseases [3] (ICD-9), and morphology to the second revision of the International Classification of Diseases for Oncology [2] (ICD-O-2). Anatomical sub-sites were defined by the fourth digit of ICD-9, and grouped into four broader categories for analysis: right colon, left colon, colon other and unspecified, and rectum (see Table 2 footnote for detailed breakdown).

The distribution of colorectal cancer cases by morphological group was broadly similar in European and American populations. Twenty-two morphological groupings based on those defined by Berg [12], were used for the survival analysis: adenocarcinoma (11 sub-groups), epidermoid carcinoma, other specified carcinoma (4 sub-groups), sarcoma (2 sub-groups), other specified morphology (2 sub-groups), unspecified morphology and not microscopically-verified.

For seven European registries, and for the SEER data as a whole, information on stage at diagnosis was available in more than 75% of cases. Stage was classified into four categories: lesion confined to site of origin, spread to immediately adjacent tissues and/or regional lymph-nodes, spread to distant organs, and unknown stage. The same stage classification was available for the SEER data.

International comparisons of cancer survival require adjustment for wide international differences in competing causes of death (background mortality), to which cancer patients are also subject [13,14]. Relative survival is the ratio of the survival observed in the cancer patients to the survival expected had they been subject only to the mortality rates of the general population from which they were drawn. Relative survival reflects the excess mortality in cancer patients relative to background mortality. For univariate analysis, relative survival was estimated using the relevant life tables for each population, specific for gender, calendar period and year of age at death, using the Hakulinen method [15]. Regional life tables were needed for regional registries in Europe, and national life tables for the SEER registries and the national registries in Europe. Multiple regression analysis for grouped life table data [16] was used to examine the prognostic impact of sub-site and histology. The relative excess risk of death (RER) in Europe was estimated, with the USA as a reference category.

Since the European data refer to countries at widely differing stages of economic development, and with different social structures and health care systems, we defined three geographical groups of European registries within which survival rates were known to be broadly similar [17]. In Estonia, Poland, Slovakia and Slovenia ('Eastern Europe'), and in England, Scotland and Denmark (United Kingdom (UK) and Denmark) survival rates for colorectal cancer were lower than the average for Europe. The other 10 participating European countries (Austria, France, Finland, Germany, Iceland, Italy, The Netherlands, Spain, Sweden and Switzerland) were combined.

3. Results

The available data included 160 381 cases of colorectal cancer for Europe and 54 471 cases for the USA.

Autopsy-detected cases (0.4% in USA, 0.9% in Europe) were excluded, as were DCO registrations (0.7% in USA, 4.8% in Europe). Total exclusions from the analysis were 9137 cases (5.7%) in Europe and 587 (1.1%) in USA. In all, 205 128 patients were included in the analyses, 151 244 from Europe and 53 884 from the USA (Table 1).

Less than 1% of cases were lost to follow-up the USA (0.9%) or Europe (0.3%), although the proportion ranged from 0 to 2% in the European registries.

In both Europe and the USA, approximately half the cases were in men and half in women; the percentage of men ranged from 45 to 56% among the European countries. The overall proportion of patients aged 75 years or over at diagnosis was also similar in the USA (36%) and Europe (38%), but geographical variation by age was greater between the sub-sites. For colon cancer, 39% of cases in the USA were aged 75 years or over, compared with 40% in Europe, but this proportion varied widely between 45% (Switzerland) and 24% (Slovakia). For rectal cancer, 30% of patients in the USA were aged 75 years or over, compared to 35% in Europe; again the latter proportion varied: between 40% (Switzerland) and 25% (Estonia) (data not tabulated).

Cancers of the right colon were more common in the USA than in Europe: 37 and 26% of the respective totals. Among European countries, these figures ranged from 37 to 18%. By contrast, rectal cancers were more common in Europe: 30% of US cases and 39% of European cases (range 24–53%). Almost all USA cases were microscopically-verified (97%) compared with an average of 84% in Europe (range 63–99%), but in 10 of the 11 Western European countries, the proportion was similar to that of the USA (93–99%) (Table 1).

The sigmoid was the most common sub-site in the colon in both series (42% Europe, 37% USA). The proportion of cases with unspecified sub-site was considerably higher in Europe (10%) than the USA (2%), but sub-site distributions were broadly similar in the two populations (Table 2).

Five-year survival was 13–22% higher in the USA than in Europe for each of the anatomical sub-sites in the colon and rectum (Table 2). The average 5-year survival in Europe was less than 50% for each sub-site: the only exception was for cancers of the appendix (71% in Europe and 64% in the USA, based on 580 European and 290 US cases). Cancers at this sub-site

Table 1
Numbers of cases contributed and characteristics (%) of study populations

	No of cases	Males (%)	Age 75 years and over (%)	Colon			Rectum (%)	Information on stage (%)	Microscopic verification (%)	Unspecified morphology (%)	DCO (%)	Autopsy (%)	Lost to follow-up (%)
				Right (%)	Left (%)	Other (%)							
USA (SEER)	53 884	51	36	37	30	2	30	100	97	0.2	0.7	0.4	0.9
Europe (EUROCARE)	151 244	50	38	26	24	10	39	19	84	2.9	4.8	0.9	0.3
Northern Europe													
Denmark	15707	49	40	28	29	3	40	–	95	6.0	0.0	0.0	0.0
Iceland	366	51	41	37	36	3	24	–	97	0.0	0.0	0.0	0.0
Finland	6946	45	36	33	23	3	41	100	96	0.8	0.4	2.1	0.0
Sweden	4010	50	42	18	25	19	38	–	98	0.2	0.0	0.0	0.0
Western Europe													
Austria	483	45	34	24	24	13	38	–	95	6.0	12.3	0.7	0.0
England	60 711	50	40	25	21	15	38	22	74	0.1	7.9	0.6	0.0
France	4585	53	38	25	30	3	41	27	97	1.1	0.0	0.0	0.9
Germany	3192	47	37	20	23	18	39	–	96	–	5.4	0.3	0.0
Italy	14 991	51	36	24	31	7	36	13	85	0.5	2.5	0.1	1.1
Scotland	13 260	47	40	27	22	18	33	–	86	0.2	3.2	0.0	0.1
Spain	5589	56	32	18	23	14	43	–	93	0.6	7.1	0.3	0.5
Switzerland	1936	51	42	32	29	2	37	100	99	0.1	0.6	4.5	1.6
The Netherlands	3896	51	36	34	27	1	37	–	97	0.1	0.2	0.4	2.0
Eastern Europe													
Estonia	2166	44	26	25	27	1	46	–	84	1.6	0.2	3.5	1.2
Poland	1689	45	31	19	20	13	46	–	63	0.6	7.3	0.4	1.3
Slovakia	8742	57	25	25	23	1	51	–	81	0.2	5.9	3.9	0.0
Slovenia	2975	50	29	25	20	1	53	100	87	0.5	3.8	2.0	0.5

DCO, death certification only; SEER, Survelliance, Epidermiology and End-results.
Countries in bold are those for which national cancer registration data were available. Countries for which data from one or more regional cancer registries are: Sweden (South Sweden); England (East Anglia, Merseyside and Cheshire, Oxford, South Thames, Wessex, West Midlands,Yorkshire); Austria (Tyrol); France (Calvados, Côte d'Or, Doubs, Somme); Germany (Saarland); Switzerland (Basel, Geneva); The Netherlands (Eindhoven, Rotterdam); Italy (Florence, Genoa, Latina, Modena, Parma, Ragusa, Romagna, Turin, Varese); Spain (Basque country, Mallorca, Navarra, Tarragona); Poland (Cracow, Warsaw).
The numbers of cases cited are those included in the analyses. – Information on stage or morphology unavailable.

Table 2
Colorectal cancer: number and proportion (%) of cases and 5-year relative survival (%) by anatomical sub-site, Europe and USA, patients diagnosed 1985–89

Anatomical sub-site	Europe		USA	
	Cases	Survival	Cases	Survival
	No. (%)	%	No. (%)	%
Colon	91 880 (61)	43	37 506 (70)	62
Right colon	38 617 (26)	44	19 676 (37)	59
Caecum	14 747 (10)	43	8233 (15)	59
Appendix	580 (<1)	71	290 (1)	64
Ascending colon	9906 (7)	49	4729 (9)	63
Hepaticflexure	2909 (2)	41	1706 (3)	58
Transverse colon	7793 (5)	42	3289 (6)	59
Splenic fiexure	2682 (2)	39	1429 (3)	56
Left colon	36 594 (24)	48	16 296 (30)	65
Descending colon	5325 (4)	47	2715 (5)	66
Sigmoid colon	31 269 (21)	48	13 581 (25)	67
Other	16 669 (11)	36	1534 (3)	32
Overlapping sites	1055 (1)	40	263 (1)	53
NOS	15 614 (10)	35	1271 (2)	30
Rectum	59 364 (39)	42	16 378 (30)	60
Rectosigmoid junction	9896 (7)	40	5570 (10)	62
Rectum	46 453 (31)	42	9910 (18)	59
Anal canal, anus, other	3015 (2)	46	898 (2)	65

NOS, not otherwise specified.
Right colon: appendix (ICD-9 153.5), caecum (153.4), ascending colon (153.6), hepatic flexure (153.0), transverse colon (153.1), splenic fiexure (153.7). Left colon: descending colon (153.2), sigmoid colon (153.3). 'Other colon': tumours that overlap two or more fourth-digit subcategories within a three-digit rubric (153.8), colon unspecified (153.9). Rectum: rectosigmoid junction (154.0), rectum (154.1), anus, including anal canal (154.2), anus, unspecified (154.3) and other tumours of rectum, rectosigmoid junction and anus (154.8).

have the highest survival, but comprise 1% or less of all colorectal cancers in both populations. Overall survival for cancer of the right colon was lower than cancer of the left colon, both in the USA and Europe. Excluding cancer of the appendix, 5-year survival for the ascending colon was the highest of any sub-site in the right colon, both in Europe (49%) and the USA (63%).

The proportion of cases for which no microscopic verification was available was higher in Europe than the USA (16% versus 3%) (Table 3). Of the microscopically-verified cases, adenocarcinoma represented 96% of cases in the USA and 91% in Europe. The difference was greater for adenocarcinoma in polyp (13% of cases in USA, 2% in Europe). With very few exceptions, 5-year survival was higher in the USA than in Europe for each specific morphological group: for adenocarcinoma in polyp (ICD-O-2 8210, 8261, 8263), survival rates were 89% in the USA and 80% in Europe. Approximately 8% of colorectal cancers were mucinous adenocarcinoma (ICD-O-2 8470, 8480, 8481, 8490) slightly higher in the USA than Europe. As expected, this morphological group had the lowest survival figures among adenocarcinomas.

Survival in Europe was higher than in the USA for cases with unspecified topography (Colon, NOS), cases with unspecified morphology (ICD-O-2 8000-8004) and those that were not microscopically-verified.

The prognostic impact of sub-site and morphology on the colorectal cancer survival differences between the USA and Europe is shown in Table 4. In the simplest model, adjusted for 1-year intervals of follow-up, the relative excess risk (RER) of death was 2.34 in Eastern Europe, 1.98 in the UK and Denmark, and 1.52 in the other European countries. After further adjustment for age and gender (model 2), the RER in Eastern Europe increased slightly, because the population of cases there was younger than average. Further adjustment for subsite (model 3) slightly reduced the RERs in Europe because more European cases were colon NOS and rectal cancers (at higher risk) than in the USA (see Table 2). Further adjustment for morphology (model 4) reduced the excess risks still further, to about 1.9 in Eastern Europe, 1.4 in the UK and Denmark, and 1.3 in the other European countries. This reflects the lower proportion of adenocarcinomas in polyps (with a better prognosis) and the higher proportion of tumours not microscopically-verified in Europe compared with the USA (see Table 3). All RERs were statistically significant at the 5% level. We performed the same analysis on the subset of cases for which sub-site, histology, and microscopic verification were all available; we observed results very close to those reported in Table 4: RERs were 1.9 for Eastern Europe, 1.5 for UK and Denmark, and 1.3 for other countries.

For the seven European registries for which information on stage at diagnosis was available in more than 75% of cases, we also analysed for stage. Stage was inserted into the model before sub-site and morphology. Adjustment for stage only reduced the RERs (range 1.08–1.85; Finland and Slovenia, respectively) in all the European registries considered, except Côte d'Or (France). Minimal changes occurred when sub-site was introduced. However, when morphology was included, RERs reduced still further for Slovenia and England, since these countries had low proportions of adenocarcinoma in polyps. By contrast, the RER for Switzerland increased from 1.22 to 1.29, as the Swiss data had the highest proportion of adenocarcinoma in polyps.

Among these seven registries, Finland (29%) had the highest and Côte d'Or (14%) the lowest percentages of cases with distant metastasis; the figure was 19% for the USA (data not tabulated). In addition, in this instance we excluded the cases that were not microscopically verified and those with missing information on subsite, histology and stage, and reran the analysis. Again, the RERs ranged between 1.6 for Côte d'Or, Varese and Slovenia and 1.08 for Finland. The major difference was found for Varese with 1.58 instead of 1.32, probably due to the slight difference in the proportion of cases with

localised stage between the Varese Cancer Registry and the USA (44.0 versus 41.0).

4. Discussion

This study has analysed survival for colorectal cancer in Europe and the USA taking into account age, subsite and morphology code. Stage was unavailable for the majority of European registries so comparisons taking stage into consideration was only performed between the US and those European registries for which stage information was available.

Nevertheless, a major staging indicator is incorporated into the morphology code adenocarcinoma in polyps. Therefore, adjusting for morphology also partially adjusts for stage.

Our results suggest that the large survival advantage for colorectal cancer patients in the USA, compared with those in Europe, can partly be explained by differences in the distribution of morphological types, but not by differences in the anatomical distribution of tumours within the bowel. Our use of relative survival took international differences in overall mortality into account. Differences in the age distribution of cancer patients had only a minor impact on the survival differences between Europe and the USA. Thus, inclusion of age in the multiple regression analysis only had a marginal impact on the RERs, while stage at diagnosis contributed to the observed differences. After adjusting

Table 3
Coiorectal cancer: number and proportion (1%) of cases and five-year relative survival (1%) by morphology, Europe and USA, patients diagnosed 1985–89

Group[a]	Morphology (ICD-O-2 M code range)	Europe		USA	
		Cases	Survival	Cases	Survival
		No. (%)	%	No. (%)	%
	I. Carcinoma				
	Adenocarcinoma	115 179 (90.9)	47	50 009 (95.8)	62
	Adenocarcinoma in polyp/adenoma	2500 (2.0)	80	6958 (13.3)	89
1	Adenocarcinoma in adenomatous polyp (8210)	1272 (1.0)	80	2549 (4.9)	95
1	Adenocarcinoma in villous adenoma (8261)	1008 (0.8)	79	2818 (5.4)	83
1	Adenocarcinoma in tubulovillous adenoma (8263)	220 (0.2)	82	1591 (3.0)	90
	Mucinous adenocarcinoma	9909 (7.8)	42	4507 (8.6)	53
2	Cystoadenocarcinoma and mucinous adenocarcinoma (8470, 8480)	5628 (4.4)	44	2226 (4.3)	57
2	Mucin-producing adenocarcinoma (8481)	3789 (3.0)	43	2089 (4.0)	52
2	Signet ring cell carcinoma (8490)	492 (0.4)	19	192 (0.4)	18
	Other adenocarcinoma	102 770 (81.1)	47	38 544 (73.9)	59
3	Adenocarcinoma NOS (8140)	95 935 (75.7)	47	38 139 (73.1)	59
3	Papillary adenocarcinoma NOS (8260)	1419 (1.1)	52	138 (0.3)	75
3	Villous adenocarcinoma (8262)	262 (0.2)	68	117 (0.2)	79
3	Adenocarcinoma in adenomatous polyposis coli (8220)	182 (0.1)	68	68 (0.1)	66
3	Other	4972 (3.9)	48	84 (0.2)	40
4	Epidermoid (8051-8130)	1829 (1.4)	51	779 (1.5)	65
	Other specified carcinomas	1599 (1.3)	51	626 (1.2)	77
5	Carcinoid (8240-6)	792 (0.6)	75	546 (1.0)	83
6	Small cell carcinoma (8041-5)	27 (<0.1)	19	20 (<0.1)	31
6	Undifferentiated carcinoma (8012-22, 8030-1, 8230-1, 8510)	768 (0.6)	24	60 (0.1)	23
6	Other	12 (<0.1)	44	– –	–
6	Unspecified (carcinoma NOS)	3896 (3.1)	27	785 (1.5)	43
	II. Sarcoma	170 (0.1)	20	48 (<0.1)	51
7	Leiomyosarcoma (8890-5)	124 (<0.1)	21	40 (<0.1)	57
7	Other	46 (<0.1)	18	8 (<0.1)	17
	Ill. Other specified types	119 (<0.1)	19	33 (<0.1)	23
7	Melanoma (8720-90)	104 (<0.1)	20	31 (<0.1)	20
7	Other	15 (<0.1)	14	2 (<0.1)	59
8	IV. Unspecified (8000-4)	4430 (3.5)	40	98 (0.2)	36
	Total of microscopically-verified	126 730 (100.0)	46	52 186 (100.0)	62
9	V. No microscopic confirmation[b]	24 022 (15.9)	24	1506 (2.8)	9

[a] Nine morphological groups were used in the multiple regression analysis (see Table 4): 1 adenocarcinoma in polypladenoma; 2 mucinous adenocarcinoma; 3 other adenocarcinoma, and adenocarcinoma NOS (reference group); 4 epidermoid carcinoma; 5 carcinoid; 6 other specified carcinoma (except carcinoid), and carcinoma NOS; 7 sarcoma and other specified morphological types; 8 unspecified: 9 no microscopic confirmation. NOS, not otherwise specified.

[b] Percentage of total number of cases. All other percentages relate to the total number of microscopically-verified cases.

Table 4
Relative excess risks of death, colorectal cancer, Europe versus USA, patients diagnosed 1985–1989: age, gender, sub-site, morphology and stage

		Variable(s) added to previous model				
		Basic model	Age and gender	Stage	Sub-site	Morphology
Age, gender, sub-site and morphology						
USA (SEER)		1	1		1	1
Eastern Europe		2.34	2.42		2.40	1.86
UK and Denmark		1.98	1.96		1.87	1.43
Other European countries		1.52	1.52		1.48	1.28
Age, gender, sub-site, morphology and stage						
USA (SEER)		1	1	1	1	1
Slovenia	National	2.35	2.40	1.85	1.82	1.61
England	Thames	1.90	1.86	1.55	1.52	1.32
Italy	Varese	1.54	1.55	1.29	1.34	1.32
Finland	National	1.45	1.45	1.07	1.07	1.08
France	Côte d'Or	1.36	1.34	1.59	1.62	1.57
Switzerland	Basel and Geneva	1.31	1.29	1.22	1.22	1.29

USA is reference category. Eastern Europe: Estonia, Poland, Slovakia, Slovenia; UK and Denmark: England, Scotland, Denmark; Other European countries: Austria, Finland, France, Germany, Iceland, Italy, The Netherlands, Spain, Sweden and Switzerland.
Levels of categorical variables included in models; three age groups: 15–54 years, 55–74 years, 75 years and over; gender: males and females; four sub-sites: right colon, left colon, other colon, rectum; nine morphological groups (see Table 3); four stage categories: tumour confined to the site of origin, tumour spread to immediately adjacent tissues and/or regional lymph-nodes, tumour with metastases in distant organs, no information on stage or stage not available.

for age, gender, stage, sub-site, morphology (in that order), the relative excess risk of death in Finland fell from 45% to 8% (still significant), but the excess risks in other parts of Europe ranged up to 61% (Slovenia). This suggests that while the international differences in survival are partly attributable to differences in the nature of the disease in Europe and America, early detection of colorectal cancer in the USA is also likely to be a major determinant of the US survival advantage.

The patients included in this study were diagnosed during the period 1985–1989, with followup to 1994. The time-lag is partly due to the scale of the EUROCARE project, involving many cancer registries, some with few resources, that had to ensure the completeness and quality of their data for a given calendar period, with at least 5 years of follow-up, before the analysis could take place. Nevertheless, this study was designed to explore the impact of differential case-mix on international comparisons of colorectal cancer survival, and in any case the US–Europe survival differential for patients diagnosed during 1990–1994 is similar to that seen here [18,19].

Because we used individual tumour records from the SEER public-use dataset and the EUROCARE database, it was possible to use the same analytical methods for both datasets: the Hakulinen method for relative survival [15], and the Hakulinen–Tenkanen approach for multiple regression [16].

The main aspects of data quality that may affect the analyses and conclusions are the proportion of cases registered solely from a death certificate (DCO cases), for which the survival time is unknown; the proportion of cases for which microscopic verification (MV) was available, and the proportion of cases that were lost to follow-up. The main differences between the European and US data were for DCO and MV cases. DCO cases were more common in Europe than the USA (5% versus 1%). However, this difference cannot explain the trans-Atlantic difference in survival, since DCO cases generally have poorer survival than patients registered during life [20] and if they could have been included, the difference in survival would have been greater. The considerably higher proportion of cases that were not microscopically verified in Europe than the USA (15.9% versus 2.8%) suggests that, for whatever reason, fewer cancer patients receive surgery in Europe. Another possible contributing factor may be that non-surgical cases are less often registered by SEER registries than in Europe. Furthermore, the higher proportion of European cases for which either sub-site or histology were unspecified may be partly explained by a reduced access to curative surgery.

Missing or unspecified data on detailed aspects of the cancer diagnosis such as sub-site, morphology or stage, characterised a fairly high proportion of European cases. Generally, such unspecified cases have a much poorer prognosis than average cases. This arises because cases that present at a terminal stage often undergo less intensive diagnostic work-up. We found that European cases with unspecified or missing diagnostic data had better survival than the corresponding, but much smaller, group of US patients. Thus, we can consider the US cases as a small subset of poor-prognosis patients, while the much larger European subset may be a mixture of cases with poor prognosis and those with average prognosis. The systematic survival difference between cases

with unspecified diagnostic information is important when these cases are included as a separate category in the multivariate analysis. However, exclusion of all such cases did not materially influence the analysis presented in Table 4.

Five European registries (Côte d'Or, Finland, Oxford, Saarland and Sweden) did not classify any tumours as adenocarcinoma in polyps (ICD-O-2 8210, 8261, 8263), coding them instead simply as adenocarcinoma (8140). Survival for adenocarcinomas arising in a polyp in Europe was substantially higher (80%) than for unspecified adenocarcinoma (47%), and erroneous inclusion of these tumours among the unspecified adenocarcinomas could have inflated survival for the latter category in Europe. The proportion of adenocarcinoma in polyps among European cases increased to 5.3% after exclusion of these registries (cf. 13% in the USA), but the 5-year survival rate for adenocarcinoma NOS barely changed as a result (46% cf. 47%). Most adenocarcinomas in polyps (77%) occurred in the left colon and rectum, and 80% were of localised stage. The two morphological categories were analysed separately in the multivariate analysis, but inclusion of sub-site and stage should have reduced any effect of misclassification.

Race was not considered in this study. Data on race are not collected at cancer registration in Europe. The proportion of non-whites is lower in the EUROCARE than SEER populations: approximately 10% of the US cancer cases were black. White patients have a higher than average survival in the USA [21], so if the analysis had been restricted to US whites, the US–Europe survival differences would have been even larger. For colorectal cancer, race should probably be considered more as a proxy of social class than an indication of a different type of disease.

Colorectal cancers are characterised by a much better response when treated at an early stage, and the large survival differences may therefore reflect the fact that more healthy Americans than Europeans undergo early diagnostic procedures. One indicator of early diagnosis is the proportion of all colorectal cancers that are adenocarcinomas in polyps, and this figure was much higher among US cases than in Europe (13% versus 2%). A survey by the National Health Interview Survey (NHIS) and the Behavioural Risk Factor Surveillance System (BRFSS) [22] suggests that the prevalence of colorectal cancer screening in the USA is high. In 1987, the proportion of healthy people aged 50 years or over who reported undergoing proctoscopy or sigmoidoscopy at some time in the past varied between 24 and 37% by age. In the same population, the proportion who reported having had a faecal occult blood test (FOBT) in the preceding year ranged from 16 to 24%. We do not have equivalent information for Europe, but access to screening or early diagnostic procedures is certainly much lower. The proportion of adenocarcinoma in polyps ranged from 16% for the Swiss registries to less than 1% in Austria, Poland, Slovenia and the UK, which suggests that early diagnostic procedures are much less widely available in Europe than in the parts of the USA covered by the SEER programme.

Geographical variation in colorectal cancer survival was much greater in Europe than the USA. Five-year survival was very low in Eastern Europe (below 25% in Poland, and no more than 35% in Estonia, Poland and Slovenia; while in Western Europe, survival varied from 41% to 54% for colon cancer and from 38 to 53% for rectal cancer [7]. Among patients diagnosed in the nine SEER registry areas during the same period (1985–1989), colorectal cancer survival ranged from 56 to 65% [9]. Differences in the availability of early diagnostic procedures and in access to effective treatment are likely to be the main causes of European survival differences. High survival rates in the USA, with little geographical variation between the SEER registries, could arise from the fact that the SEER registries are not fully representative of the entire US population, as they cover the more affluent areas of the USA [23]. Broadening the comparison to include a wider range of US populations would be an interesting future step.

Stage is a crucial prognostic factor to be considered in explaining colorectal cancer survival differences. Adjustment for stage in this study, even in broad categories, markedly reduced the differences in survival between some European registries and the USA. Unfortunately, stage information was not available for all cases collected by European cancer registries, and the available data were not always directly comparable. A major goal of future studies is to obtain comparable information on stage from large representative samples of cancer patients in each of the contributing cancer registries: this will pinpoint remediable causes of international cancer survival differences and make it possible to quantify the impact of removing them.

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