COLORECTAL CANCER

Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery

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Gut 2005;**54**:268–273. doi: 10.1136/gut.2004.044214

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Revised version received 16 June 2004
Accepted for publication 23 June 2004

Background: Population based colorectal cancer survival among patients diagnosed in 1985–89 was lower in Europe than in the USA (45% *v* 59% five year relative survival).
Aims: To explain this difference in survival using a new analytic approach for patients diagnosed between 1990 and 1991.
Subjects: A total of 2492 European and 11 191 US colorectal adenocarcinoma patients registered by 10 European and nine US cancer registries.
Methods: We obtained clinical information on disease stage, number of lymph nodes examined, and surgical treatment. We analysed three year relative survival, calculating relative excess risks of death (RERs, referent category US patients) adjusted for age, sex, site, surgery, stage, and number of nodes examined, using a new multivariable approach.
Results: We found that 85% of European patients and 92% of US patients underwent surgical resection. Three year relative survival was 69% for US patients and 57% for European patients. After adjustment for age, sex, and site, the RER was significantly high in all 10 European populations, ranging from 1.07 (95% confidence interval 0.86–1.32) (Modena, Italy) to 2.22 (1.79–2.76) (Thames, UK). After further adjustment for stage, surgical resection, and number of nodes examined (a determinant of stage), RERs ranged from 0.77 (0.62–0.96) to 1.59 (1.28–1.97). For some European registries the excess risk was small and not statistically significant.
Conclusions: US-Europe survival differences in colorectal cancer are large but seem to be mostly attributable to differences in stage at diagnosis. There are wide variations in diagnostic and surgical practice between Europe and the USA.

Differences in colorectal cancer survival between European and American patients are substantial[1] and are particularly marked in the oldest patients. The excess risk of death among European patients relative to US patients in the first year after diagnosis was much higher than in subsequent years.[1] This pattern is likely to be attributable to differences in stage at diagnosis and in postoperative mortality. Information on stage and treatment is not routinely collected by all population based cancer registries however, and only limited clinical information, such as subsite and morphology, was taken into account in previous studies.[1 2] Prognosis varies with morphology, and adjustment for the different distribution of morphological types between Europe and the USA reduced somewhat the range of relative excess risks in Europe.[3] The proportion of colorectal cancers coded as adenocarcinoma in polyp, which have a better prognosis, was also higher in the USA.[3]

Stage specific survival comparisons are likely to be confounded by the stage migration phenomenon[4] due to the unequal availability of new diagnostic techniques used to determine stage. We were able to address this problem with information on a major staging procedure—examination of nodes in the resected surgical specimen—available in the EUROCARE High Resolution database[5 6] and in the SEER database.[7]

The approaches available to date for modelling relative survival have had theoretical limitations (for example, distributional assumptions applied to the number of observed deaths) or technical limitations due to the nature of the specialised software. Dickman and colleagues[8] recently developed a new approach to modelling relative survival in the framework of generalised linear models, which avoids some of these problems.

The aim of this study was to examine the extent to which disease stage, staging procedures, and treatment explain the differences in cancer survival between colorectal cases diagnosed in 1990 in European and US populations.

PATIENTS AND METHODS

Ten population based cancer registries from Italy (I), France (F), Spain (E), the Netherlands (NL), and the UK contributed to the European data as part of the EUROCARE High Resolution study[2] (table 1). Each European registry was asked to provide a representative sample of consecutive cases of colorectal cancer (including the anus; ICD-9 site codes 1530–1548)[9] incident in 1990 (Eindhoven contributed cases registered in 1991 and 1992, Modena in 1990–91), with detailed information on diagnostic and treatment procedures from the original clinical records, and with a potential follow up of at least three years. The American data were taken from the SEER public use database (April 2000 issue) selecting the same ICD-9 codes (''Recode ICD-O-2 to 9'' variable).[7]

A total of 2492 European patients were included. Only patients with a first primary, invasive, malignant adenocarcinoma of the large bowel were considered: these tumours represent more than 90% of all colorectal malignancies in both Europe and the USA[3] (in what follows they are referred to as ''colorectal cancers'' for simplicity). Cases known to the

Abbreviations: RER, relative excess risk; F, France; I, Italy; E, Spain; NL, The Netherlands; UK, United Kingdom; US, United States; DCO, death certificate only; FOBT, faecal occult blood test

Table 1 Number (%) of colorectal cancer cases included in the analyses for Europe and the USA: period of diagnosis, sex, age, site, country, and registry. EUROCARE and SEER data, patients diagnosed 1990–91

		No of cases	Period of diagnosis	Males (%)	Aged ⩾75 y (%)	Colon (%)
USA	9 SEER registries	11191	1990	51	39	72
Europe	10 EUROCARE registries	2492	1990–91	52	38	61
Italy	Varese	445	1990	53	37	62
	Modena	306	1990–91	52	32	65
France	Calvados	262	1990	47	40	52
	Somme	228	1990	60	38	64
	Côte d'Or	237	1990	54	46	66
Netherlands	Rotterdam	202	1990	54	40	63
	Eindhoven	256	1991	52	33	68
Spain	Granada	173	1990	51	31	54
UK	Mersey	207	1990	48	47	58
	Thames	176	1990	47	43	55

registry through death certificate only (DCO) or discovered incidentally at autopsy were also excluded.

All patients diagnosed with colorectal cancer (including the anus) in 1990 and included in the SEER database were extracted. After application of the same eligibility criteria used for European patients, we included 11 191 US patients. More detailed information on the high resolution EUROCARE data has been published previously.[2] The SEER database is described in periodic reports published by the National Cancer Institute.[10]

Relative survival is the ratio of the observed (absolute) survival of cancer patients and the survival that would have been expected if the patients had had the same age and sex specific mortality (background or competing mortality) as the general population. Relative survival rates were calculated by the Hakulinen method.[11] Age and sex specific general population mortality rates were obtained from life tables for each registry, centred on 1990. The life tables for Europe are described in the EUROCARE-2 monograph.[12] Race specific life tables for the USA were derived from the SEER CD-ROM: we used a single combined life table, weighted according to the race distribution in the US cases in the study.

To model relative survival rates, we used Stata[13] to apply a new multivariable approach in the framework of generalised linear models[8] with a Poisson error structure, based on collapsed data (that is, numbers of observed and expected deaths and the time at risk are summed for each combination of covariates) and using exact survival times for individuals. When modelling the hazard function, we estimate excess hazard ratios, or relative excess risks (RERs), which can be seen as the excess hazard due to diagnosis of cancer once the known baseline hazard (general population mortality) has been taken into account. We estimated RERs for each registry, taking into account the different distributions of age at diagnosis (<65, 65–74, ⩾75 years), sex, site (colon/rectum), stage, number of examined nodes as a diagnostic determinant of stage, and surgical treatment. The referent category for geographic comparisons was the USA (RER = 1), which had the largest number of cases. In order to provide more clinically meaningful groups, we combined Dukes' stage classification[14] with surgical treatment—resected or unresected—and with number of examined nodes into the following 10 categories: ''resected'' patients with Dukes' stage A; Dukes' B with fewer than 6 nodes examined; Dukes' B with 6–11 nodes; Dukes' B with 12 or more nodes; Dukes' C with fewer than 6 nodes; Dukes' C with 6–11 nodes; Dukes' C with 12 or more nodes; Dukes' D; Dukes' stage not known; and ''unresected'' patients (with any stage). Hereinafter this variable will be cited as ''stage/resection/nodes''.

Resected patients were defined as those who underwent surgery to remove the primary bowel tumour whether or not resection was judged radical. Palliative surgery was included in the ''unresected'' category. We defined the categories of the number of lymph nodes according to the indication that at least 12 lymph nodes should be examined for accurate staging[15]: the category with fewer than six nodes examined

Table 2 Three year relative survival (%) and percentage of cases by Dukes' stage, number of lymph nodes examined, and surgical resection, by registry: EUROCARE and SEER data, colorectal cancer patients diagnosed 1990–91

Registry (No of cases)		3 year relative survival (%)	Dukes' stage*				Unstaged cases: resected?		12 or more nodes examined†	Resected
			A	B	C	D	Yes	No		
USA (11 191)		69	24	30	23	18	2	3	28	92
Europe (2492)		57	14	34	21	21	3	7	13	85
Italy	Varese (445)	56	19	31	17	27	2	4	21	82
	Modena (306)	67	9	39	24	17	3	7	11	88
France	Calvados (262)	63	10	35	20	24	4	8	23	85
	Somme (228)	58	14	29	19	21	6	11	4	84
	Côte d'Or (237)	60	21	36	25	14	1	3	20	93
Netherlands	Rotterdam (202)	57	19	39	20	15	0	6	2	86
	Eindhoven (256)	62	15	40	19	21	3	2	4	92
Spain	Granada (173)	51	7	34	23	19	4	13	31	77
UK	Mersey (207)	52	11	29	23	23	5	9	15	82
	Thames (176)	44	12	30	24	23	2	9	10	80

*A, localised within bowel wall; B, penetrates the bowel wall; C, spread to the regional lymph nodes; D, distant metastases.
†For resected patients only.

Table 3 Relative excess risk of death (and 95% confidence interval) three years after diagnosis, by registry, adjusted for sex, age, site, and stage/resection/nodes (regression model). EUROCARE and SEER data, colorectal cancer patients diagnosed 1990–91

Registry	No of cases	Model 1 (registry)	Model 2 (Model 1+sex, age, site)	Model 3 (Model 2+stage/ resection/nodes*)
USA (SEER)	11 191	1	1	1
Varese (I)	445	1.50	1.52	1.09
		1.28–1.76	1.30–1.77	0.93–1.27
Modena (I)	306	1.05	1.07	0.77
		0.85–1.31	0.86–1.32	0.62–0.96
Calvados (F)	262	1.26	1.28	1.04
		1.00–1.59	1.02–1.61	0.84–1.29
Somme (F)	228	1.46	1.45	1.01
		1.17–1.83	1.16–1.81	0.81–1.25
Côte d'Or (F)	237	1.40	1.39	1.55
		1.12–1.76	1.11–1.74	1.23–1.94
Rotterdam (NL)	202	1.37	1.39	1.15
		1.07–1.76	1.09–1.77	0.89–1.47
Eindhoven (NL)	256	1.21	1.25	1.06
		0.97–1.52	1.00–1.56	0.85–1.33
Granada (E)	173	1.81	1.90	1.29
		1.43–2.30	1.50–2.40	1.02–1.64
Mersey (UK)	207	1.84	1.80	1.52
		1.48–2.29	1.45–2.23	1.23–1.88
Thames (UK)	176	2.21	2.22	1.59
		1.78–2.75	1.79–2.76	1.28–1.97

F, France; I, Italy; E, Spain; NL, The Netherlands; UK, United Kingdom.

includes nodes not examined, missing number but examined, and not known if examined or not.

RESULTS

The distribution of cases by sex, age, and cancer site in the USA and Europe, and by European registry, is given in table 1. The proportion of males was the same overall in the USA and Europe, but ranged from 47% (Calvados and Thames) to 60% (Somme) in Europe. Thirty nine per cent of American patients and 38% of European patients were over 74 years of age, ranging from 31% (Granada) to 47% (Mersey). Colon cancer represented the majority of colorectal adenocarcinomas in both series, especially in the SEER registries (72%), and the European registries ranged from 52% to 68%, with an average of 61%.

Relative survival three years after diagnosis was high in the US registries (69%) and Modena (I) (67%), relatively high in Calvados (F) (63%), Eindhoven (NL) (62%), and Côte d'Or (F) (60%), and low in Thames (UK) (44%) (see table 2). The European average was 57%.

The proportion of patients with Dukes' stages A or B was higher in the USA (54%) than in Europe (48%). In particular, it was high in the Dutch registries (58% and 55%) and Côte d'Or (57%) but intermediate in the Italian registries (50% and 48%), low in Granada (E) (41%) and Thames (42%), and the lowest in Mersey (UK) (40%). Varese (I) had the highest proportion of cases with distant metastases (Dukes' D) (27%), followed by Calvados (F) (24%), and the English registries (23%).

The percentage of patients for whom 12 or more lymph nodes were examined by the pathologist was 13% in Europe and 28% in the USA (table 2). The proportion also varied widely within Europe, from less than 5% in the Dutch registries and Somme (F) to 31% in Granada. More patients were surgically resected in the USA (92%) than in Europe (85%), ranging from 77% in Granada to 93% in Côte d'Or.

Relative excess risks of death three years after diagnosis, adjusted for age, sex, site, and stage/resection/nodes are presented for each registry in table 3. In the simplest model—comparing European registries with the SEER data (model 1)—all RERs, with the exception of those for Modena and Eindhoven, were significantly higher than 1, ranging from 1.26 to 2.21.

After adjustment for age, sex, and primary site (model 2), the majority of RERs increased slightly. The exceptions were Somme, with a high proportion of males, and Côte d'Or and Mersey, with a high proportion of cases aged 75 years or over, which had lower survival (see table 1).

Adjustment for stage/resection/nodes (model 3) produced lower RERs in all registries except Côte d'Or. This is due to the unfavourable pattern of stage, resection, and number of examined nodes in most European registries relative to the USA (lower proportion of localised cases, higher proportion of metastatic cases, lower proportion of resected cases, or lower proportion of 12 or more lymph nodes examined, see table 2). The RER for Côte d'Or increased after adjustment for stage/resection/nodes (model 3) because cases in this registry had the most favourable distribution of stage and resection (57% early stage, 14% metastatic, and 93% resected, an earlier stage distribution than the SEER data).

Cases from Modena had a low proportion of examined nodes, were more advanced, and underwent fewer resections than US cases (see table 2); therefore, as the unadjusted relative survival for patients from Modena was similar to that of US patients (67% *v* 69%), the overall adjustment produced a low risk (RER 0.77 (95% confidence interval (CI) 0.62–0.99)). The proportion of cases with 12 or more nodes examined was also low in Somme (4%), Rotterdam (2%), Eindhoven (4%), and Thames (10%) (table 2). Patients classified in those areas are likely to have been less accurately staged, and therefore probably have more advanced disease than patients classified to the same stage in other areas (stage migration).

Three year relative survival for US patients was the similar or higher than for European patients in each category of Dukes' stage and the number of nodes examined (table 4). Survival was 94% (USA) compared with 93% (Europe) for Dukes' A cases and 16% in both regions for Dukes' D cases. Survival was higher in the USA for those who did not undergo surgical resection (15% *v* 11%) while cases for which

Table 4 Three year relative survival (%) and relative excess risks (RER) of death* within three years of diagnosis (with 95% confidence intervals (CI)), by Dukes' stage, surgical resection, and number of examined nodes: EUROCARE and SEER data on colorectal cancer patients diagnosed 1990–91

		USA (SEER)			Europe (EUROCARE)			Relative excess risk of death	
Dukes' stage and surgical resection	No of nodes examined	Patients	3 y survival (%)	95% CI	Patients	3 y survival (%)	95% CI	RER	95% CI
All patients		11 191	69	67.6–69.7	2492	57	54.3–60.1		
Resected									
Dukes' A		2602	94	92.2–95.5	353	93	88.2–97.3	1	
Dukes' B	12 or more	1142	94	91.2–96.3	128	91	82.2–97.1	1.18	0.79–1.76
	6–11	1032	89	85.8–91.9	207	85	77.9–91.4	2.05	1.47–2.87
	<6	1165	80	76.5–82.7	508	74	69.4–79.0	4.04	3.05–5.35
Dukes' C	12 or more	1001	70	66.1–72.8	99	66	54.4–75.7	5.82	4.40–7.69
	6–11	872	63	59.1–66.6	154	53	44.2–62.1	7.54	5.72–9.93
	<6	728	62	57.9–66.2	261	48	41.5–55.1	8.65	6.58–11.38
Dukes' D		1484	16	13.9–17.9	334	16	12.0–20.3	30.38	23.51–39.27
Unstaged		275	68	60.6–74.0	77	69	55.2–80.3	6.56	4.71–9.14
Unresected		890	15	12.1–17.3	371	11	7.8–15.1	44.49	34.28–57.76

*RERs derived from regression model 3 (table 3) and adjusted for registry, sex, age, and subsite (see text).

Dukes' stage was not known had a three year survival of 69% in Europe and 68% in the USA.

The number of examined nodes is a determinant of staging accuracy: US patients had a higher survival than European patients in each subgroup of Dukes' stage defined by the number of lymph nodes examined but differences were larger for less accurately staged cases (fewer than six nodes examined), both in Dukes' B (80% *v* 74%) and Dukes' C (62% *v* 48%) stage tumours.

The relative excess risks of death for stage/resection/nodes, mutually adjusted for registry, age, sex, and site, are also shown in table 4.

As for unadjusted relative survival rates, the relative excess risk of death was higher with successively smaller numbers of nodes examined: thus the relative excess risk of death for resected patients with a Dukes' B tumour (relative to Dukes' A resected tumours as the referent category) ranged from 1.18 in cases with the most accurate staging (12 or more lymph nodes examined) to 4.04 in less accurately staged cases. The RER of death for resected patients with Dukes' C tumours was about six times higher when 12 or more lymph nodes were examined (RER 5.82 (95% CI 4.40–7.69)) and more than eight times higher in cases with fewer than six nodes examined (RER 8.65 (95% CI 6.58–11.38)). The risk of death for unresected patients (RER 44.49) was even higher than that for metastatic but resected cases (RER 30.38) whereas resected cases with unknown stage had a risk six times that of patients with very early stage disease.

The RERs for the other covariates of model 3 are not tabulated. Excess mortality was highest during the first year (referent category), decreasing to 0.60 (95% CI 0.54–0.66) during the third year after diagnosis. The relative excess risk for women (RER 1.10 (95% CI 1.03–1.17)) was 10% higher than for men (referent group). Relative to patients aged less than 65 years (referent category), the RER increased from 1.19 to 1.47 with increasing age at diagnosis. After adjustment for stage/resection/nodes, the relative excess risk of death within three years of diagnosis was 17% lower for rectal cancer patients than for colon cancer patients (referent category) (RER 0.83 (95% CI 0.77–0.89)).

DISCUSSION

The results of this analysis suggest that the survival advantage for colorectal cancer patients in the USA, compared with those in Europe, can be partly explained by trans Atlantic differences in diagnostic and surgical practice. Approximately 90% of American patients were surgically treated, more than a quarter had at least 12 nodes examined, and more than 50% had localised disease at diagnosis, indicating earlier diagnosis in the USA. With the exclusion of Somme (F) and Modena (I)—where risk was not raised compared with the SEER data—the RER of death for patients in the European registry areas ranged from 4% to 59% after adjustment for age, sex, site, stage at diagnosis, number of lymph nodes examined, and whether the patient underwent resection. For European registry areas where excess risks were still high (approximately 1.5-fold) after full adjustment for stage, surgery, and stage migration, such as Mersey and Thames (UK), Côte d'Or (F), and Granada (E), the differences were compatible with less effective treatment. For other registry areas such as Varese (I), Rotterdam (NL), Eindhoven (NL), Somme (F), and Calvados (F), the data suggest that the most likely explanation for lower survival than in the USA is later stage at diagnosis.

We have previously reported that the proportion of adenocarcinomas arising in a polyp (ICD-O-2 8210, 8261, and 8263)[3 16] in patients diagnosed during 1985–89 was higher in the USA than Europe, suggesting that American patients have less advanced disease at diagnosis than their European counterparts. This difference was confirmed for patients diagnosed in 1990 (14.7% *v* 6.2%) reported here. We included adenocarcinoma in polyp (yes/no) in our modelling strategy because of this marked difference in frequency between the USA and Europe, and because it has a better prognosis than other adenocarcinomas,[2] in order to examine survival in a more clinically homogeneous subset of patients within Duke's stage A or B. Adjustment for the proportion of adenocarcinoma in polyp further reduced the RER in some registries, reflecting the lower proportion of such patients in Europe, but three registries (Modena, Côte d'Or, and Thames) did not classify any tumours as adenocarcinoma in polyp and therefore this covariate was not retained in the final model.

The higher frequency of adenocarcinoma in polyp in the USA is likely to be the result of more widespread use of early diagnostic procedures. Endoscopy and faecal occult blood tests (FOBT) have both been actively recommended by the American Cancer Society. A survey showed that in 1987, 24% of people aged 50 years or over had undergone an endoscopy at some time in the past, this proportion increasing to 38% by 1992. The percentage of people aged 50 years or over who reported undergoing FOBT within one year increased from 15% in 1987 to 18% in 1992.[17 18] We do not have equivalent information for Europe but some large scale trials were

undertaken in the UK, Denmark, Sweden, and France.[19] Low barrier endoscopy has been offered in the Netherlands since 1981 but was not part of a mass screening programme.[20] It is only since 2000 that the European Union has recommended that member states implement colorectal cancer screening.

Thirty day postoperative mortality in SEER colorectal cancer patients aged 65 years and older, diagnosed in 1991–96, was 4.5% (colon)[21] and 3.3% (rectum),[22] while in colorectal cancer patients diagnosed in 1988–91 in Côte d'Or it was 7.2%.[23] This difference, together with the high proportion of resections (93%), of patients with more than 12 examined nodes (20%), and of localised disease (57%) in Côte d'Or may help explain why the RER of death for Côte d'Or increased after full adjustment for stage/resection/nodes.

The quality of the EUROCARE High Resolution data has been discussed.[2] The sample was designed to be broadly representative of all patients diagnosed in 1990 and included in the participating registries (some registries provided data on all cases incident in 1990). The registries cannot be considered representative of Europe but the range of survival rates between them was similar to that between Northern Europe, Denmark, the UK, and other Western European countries.[24] The range of three year relative survival rates between US registries (63–73%) was narrower than between European registries (44–67%) in our data.

The SEER and EUROCARE data have been compared.[1 3] Distribution by race was not considered here because race is not available in the EUROCARE database. We chose not to restrict the analysis to US whites as an equivalent exclusion could not be done for European patients, and our aim was an overall population based comparison of survival between the USA and Europe. Ethnic origin may also be considered as a proxy of social class in the USA.[25] The difference in proportion of DCO cases (2–3% in EUROCARE *v* 0.5% in SEER) cannot explain the observed survival differences because such cases generally have poorer survival than cancer patients registered in life, and the difference in itself is negligible. Very few cases were lost to follow up in either series (0 in EUROCARE, 0.17% in SEER). Almost 100% of SEER cases were microscopically verified compared with 85% in the EUROCARE series; fewer European patients received surgical treatment. Information on stage was available for most patients in both series: the European average for patients with unknown stage was 10%, with a minimum in Côte d'Or (4%) and a maximum in Granada (17%), but in resected patients this proportion was 3% (range 0%-6%, see table 2). Information on stage was missing in only 5% of cases in the SEER data (2% in resected cases).

At the time of collection of the data for this project, the Thames Cancer Registry was attaining approximately 90% primary case ascertainment for colorectal cancer.[26] The missing cases are expected to be selectively non-fatal cases because in the UK deaths among cancer patients are routinely notified to the registries. The main outcome parameters in this study reported for Thames (the unfavourable stage distribution, the low relative survival, and the sensitivity of the RER to adjustment for stage) may all be partly or largely due to this deficit in the Thames data.*

Estimation and modelling of relative survival enabled us to adjust for covariates as well as for general population mortality. Background mortality varies widely within Europe, and regional or national life tables were used as appropriate, although for the USA the life tables were national. The extent to which the populations covered by the nine SEER registries reflect the general mortality of the entire US population is controversial: there are indications that SEER covers more affluent areas of the USA.[27] If US national mortality rates were higher than mortality in the SEER areas, relative survival for the SEER areas would tend to be overestimated because expected survival (the denominator of relative survival) is derived from these rates, and would be correspondingly low. Only three years of follow up data were available in our European data but excess mortality more than three years after diagnosis was much lower than in the first three years (the relative survival curve approaches a plateau), and three year relative survival is a reasonable proxy for five year survival in international comparisons.[1]

With the new approach we studied potential interactions between time since diagnosis and other relevant variables in order to detect and account for non-proportional excess hazards by time since diagnosis. We found several minor interactions but decided not to include them in the final model as they did not materially change the goodness of fit of the model (deviance divided by degrees of freedom) and were difficult to interpret clinically. Similarly, the statistical interaction between cancer registry and surgical treatment detected in previous analyses[2] (not shown), which revealed different patterns of risk of death between registries among resected and unresected patients, was not included here. The new analytic method also proved useful for studying goodness of fit and regression diagnostics for the statistical models within a widely available statistical software package.

We attempted to enhance the comparability of the results by using a standard analytic protocol, with the same data definitions and the same analytical methods. A common protocol for data collection is the next logical step. This has been implemented in the CONCORD Study (First CONCORD Investigators' Meeting, Toronto, Canada, 2002), an ongoing large trans Atlantic collaborative study with the aim of measuring and explaining differences in cancer survival between Europe, the USA, and other areas.

Stage is the most important prognostic factor in explaining international differences in colorectal cancer survival. The use of information on the determinants of stage partially addresses the problem of stage migration as adjustment for the number of lymph nodes examined improves the comparability of cases classified to the same stage (see table 4). However, residual confounding cannot be completely ruled out as a possible explanation for adjusted differences.

To improve the effectiveness of treatment and hence the survival of European patients with colorectal cancer, relative to that of US patients, we suggest that European countries pay more attention to early detection, in particular by implementing population based screening programmes, as recommended by the European Union. Effort should also be directed to the reduction of postoperative mortality with a multidisciplinary approach to hospital care (high hospital procedure volume and best intraoperative technique) as this has been shown to contribute to the improvement in survival.[25]

ACKNOWLEDGEMENTS

The EUROCARE Study was financed through the BIOMED Programme of the European Community and by the "Europe against Cancer" programme (project number S12.117414 "Differences in the survival of colorectal cancer patients between Europe and USA"). The SEER Programme is a cancer surveillance programme of the National Cancer Institute, USA.

The authors are extremely grateful to all of the cancer registries involved in the study. They are also indebted to Maria Rosa Ruzza for

* The possible impact on survival analysis of such selective loss was tested by a simulation approach. Twenty cases, corresponding to 10% of the Thames cases and randomly selected among those still alive at the end of follow up, were duplicated and added to the data. When running model 3 on this augmented data set, the estimated RERs for Thames decreased from 1.59 to 1.48, on average over 10 replications (range 1.45–1.50). Unadjusted estimates of the RER (model 1) decreased from 2.21 to 1.83.

her help in the quality control of the data and wish to thank Paul Dickman, Andy Sloggett, and Timo Hakulinen for their assistance in applying the new statistical approach they developed for relative survival modelling.

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Conflict of interest: None declared.

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