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Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study

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Abstract

Background

Colorectal cancer survival in the US has consistently been reported as higher than in Europe. The differences have generally been attributed to stage at diagnosis.

Material and methods

21 population-based registries in 7 US states and 9 European countries provided data on Dukes' stage, diagnostic procedures, treatment and follow-up for 12,523 adults (15-99 years) diagnosed with colorectal cancer during 1996-98.

Logistic regression models were used to compare adherence to "standard care" in the US and Europe. Net survival and excess risk of death were estimated with flexible parametric models.

Results

The proportion of Dukes' A and B tumours was similar in the US and Europe, while Dukes' C was more frequent in the US (38% *vs.* 21%) and Dukes' D more frequent in Europe (22% *vs.* 10%).

Resection with curative intent was more frequent in the US (85% *vs.* 75%). Elderly patients (75-99 years) were 70-90% less likely to receive radiotherapy and chemotherapy.

Age-standardised five-year net survival was similar in the US (58%) and Northern and Western Europe (54-56%) and lowest in Eastern Europe (42%).

The mean excess hazard up to 5 years after diagnosis was highest in Eastern Europe, especially among elderly patients and those with Dukes' D tumours.

Conclusions

The wide differences in colorectal cancer survival between Europe and the US in the late 1990s are probably attributable both to earlier stage and more extensive use of surgery and adjuvant treatment.

Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.

Keywords: CONCORD, net survival, excess hazard, cancer registries.

Article Focus

- Why has population-based survival for colorectal cancer been so much higher in the US than in Europe?
- Can differences in stage, diagnostic procedures and/or treatment explain these wide disparities?
- Are evidence-based guidelines for staging and treatment being followed?

Key Messages

- Stage at diagnosis varied more widely between European countries than between US states.
- Evidence-based guidelines do not seem to have been closely followed. The proportion of patients who received surgery with adjuvant chemotherapy and/or radiotherapy was much lower in Europe than the US. Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.
- The wide US-Europe differences in five-year net survival from colorectal cancer in the late 1990s were probably attributable to earlier stage and more extensive use of surgery and adjuvant treatment in the US. Lower survival in Europe was mainly attributable to much lower survival in Eastern countries. This study underlines the need for population-based survival estimates derived from systematic clinical records of stage and treatment for all patients.

Strengths and Limitations

- To our knowledge, this is the first population-based high-resolution study with a direct US-Europe comparison of colorectal cancer survival, using clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods. Clinical records of investigation, stage and treatment are neither complete nor systematic. Cancer registries need resources to obtain these data in a timely manner for all cancer patients.
- Most diagnostic and therapeutic approaches used in the late 1990s remain in widespread use; mesorectal excision for rectal cancer is more recent. It remains relevant to understand the extent to which investigation and treatment are responsible for the persistent international differences in colorectal cancer survival.
- The modelling approach to estimate net survival is a methodological strength.
- Northern Europe was represented only by Finland.

Introduction

Five-year relative survival from cancers of the colon and rectum has been reported as 12-14% higher in the US than in Europe(1). Survival for patients diagnosed during 1985–89 was higher in each of the 9 US states and metropolitan areas covered at that time by the Surveillance, Epidemiology and End Results (SEER) programme than in any of the 22 European countries participating in the EUROCARE-2 study(2).

The differences in 3-year colorectal cancer survival for patients diagnosed during 1990-91 between 10 territories in 5 European countries and the 9 SEER areas were mainly attributable to stage at diagnosis(3).

The first world-wide analysis of cancer survival (CONCORD(1)) provided a systematic comparison of survival for adults (15-99 years) diagnosed with cancer of the breast, colon, rectum or prostate in one of 31 countries during 1990-94 and followed up to 1999. International differences in age-standardised survival were very wide, even after adjustment for differences in mortality from other causes of death. Colorectal cancer survival was higher in the US and Canada than in many other countries. Differences between the US and most European regions were smaller than for patients diagnosed during 1985-89(2). The largest differences were between the US and Eastern Europe.

The CONCORD protocol incorporated studies designed to explain the international variations in survival. These “high-resolution” studies involve systematic collection of detailed clinical and pathological data that are not routinely abstracted by population-based cancer registries from the original medical records of large random samples of patients. The high-resolution study reported here provides a trans-Atlantic comparison of stage, treatment and survival for patients with colorectal cancer.

The aims were (1) to compare the distributions of stage for colorectal cancers in Europe and the US; (2) to determine whether the transatlantic differences in survival persist and, if so, to assess the extent to which they are attributable to differences in stage at diagnosis; and (3) to compare adherence to “standard care” for colorectal cancer in relation to age, stage and cancer site between the US and Europe.

Material and methods

Data on stage, diagnostic procedures, treatment and follow-up were collected for a representative sample of about 13,000 patients aged 15-99 years diagnosed with colorectal cancer (ICD-9(4) codes 1530-1539, 1540-1549) in the US and Europe during 1996-98. A single protocol was used, derived from the EUROCARE high-resolution protocols(5).

The European data were provided by 14 population-based cancer registries in 9 countries, 4 with national coverage (denoted below with an asterisk*). For some analyses, the data were grouped into the four European regions defined by the United Nations (UN, http://unstats.un.org/unsd/methods/m49/m49regin.htm) - Northern Europe: Finland*; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia*, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia*, Poland (Cracow, Kielce), Slovakia*. Estonia is classified by the UN as being in Northern Europe, but cancer survival has resembled that in Eastern European countries(6), and Estonia was included here with Eastern Europe. US data were provided by 7 state-wide registries (California, Colorado, Illinois, Louisiana, New York, Rhode Island, South Carolina) from the National Program of Cancer Registries (NPCR), based at the Centers for Disease Control and Prevention.

For this study, cancer registries in the EUROCARE-3 high-resolution study(7) updated follow-up to at least five years after diagnosis for all patients. North East Netherlands was not included in EUROCARE-3, but the registry routinely collects high-resolution data, and could provide such data on virtually all patients with colorectal cancer.

Most registries provided a random sample of at least 500 patients diagnosed during 1996-98 (1997 in the US). The Finnish cases were a population-based sample of patients diagnosed in the Tampere hospital region, which is considered representative of Finland.

Of 12,941 anonymised records for patients with a malignant neoplasm of the colon or rectum, 418 were excluded: *in situ* (396, 3.1%: collected in the US, but not in Europe) unknown sex (22, 0.2%); benign or uncertain behaviour (1), or age less than 15 or 100 years or over (19, 1.5%). In all, 12,523 patients with a primary, invasive, malignant colorectal neoplasm were included in the comparisons of stage and treatment. For survival analyses, a further 118 patients were excluded: cancer registered only from a death certificate (72; 0.6%); unknown vital status (3; 0.02%); date of last known vital status either unknown or earlier than the date of diagnosis (43; 0.3%); leaving 12,405 patients (99.1% of the 12,523 eligible).

Information on stage, diagnostic examinations and treatment was abstracted from the clinical record, pathology reports, hospital discharge records and other sources, as necessary.

Disease stage was defined according to the TNM (Tumour, Nodes, Metastasis) manual(8) and/or Dukes' stage. Many registries collected both TNM and Dukes' stage, but only Dukes' stage was available for Kielce (Poland) and Finland, so we

used the Dukes' classification in order to include these populations in the stage-specific analyses. Dukes' stage information was more complete than TNM stage, but TNM was used to reconstruct Dukes' stage where necessary. Resected patients for whom no pathology report was available were classified as stage unknown.

Age was categorised as 15-64, 65-74 and 75-99 years. Surgical procedures were divided into sphincter-preserving procedures and those in which continence was not preserved, including all patients with a permanent stoma.

We defined resection for curative intent as resection of all macroscopically evident malignant tissue, with no macroscopic evidence of surgical margin involvement, and excluding polypectomy and trans-anal excision. Radiotherapy and chemotherapy were dichotomised as administered *vs.* not administered or unknown.

Statistical analysis

We analysed the distribution of stage and the number of lymph nodes examined pathologically(8). We report the proportion of patients resected with curative intent and the distributions of stage-specific treatment for colon or rectal cancer. Data sets were excluded if data on stage and/or treatment were missing for 25% or more of patients: Ragusa was excluded from stage-specific analyses, including those on treatment related to stage at diagnosis.

Net survival up to five years after diagnosis was estimated by geographical area (UN region of Europe, country, registry or US state), age and stage, using flexible parametric excess hazard models(9). Net survival is the survival of cancer patients in the hypothetical situation where the cancer may be assumed to be the only possible cause of death; it may be interpreted as cancer survival after controlling for competing causes of death. Net survival was estimated with a modelling approach(9-11) in which the total hazard of death is considered as the sum of the cancer-related mortality hazard (excess hazard), and the hazard of death from other causes (background hazard). The background hazard is derived from life tables of all-cause mortality by sex, single year of age and calendar year in the general population of the geographical area from which the cancer patients are drawn. We constructed period life tables for 1994-2004 with the approaches proposed by Baili et al(12).

Age was included as a continuous variable in all models, in order to avoid the bias in the estimation of net survival that would otherwise arise from differential loss of the oldest patients to competing hazards of death (informative censoring). Both non-linear and time-dependent (interaction with time since diagnosis) effects of age were initially modelled with cubic splines. The proportionality of the effect of tumour stage on the excess hazard was also assessed. Simpler models, with linear and/or proportional effects, were successively tested and selected using the Akaike Information Criterion for goodness of fit(13). We also estimated the instantaneous excess risk (hazard) of death due to colorectal cancer, after subtracting the hazard from all other causes of death(9-11;14;15). We present the mean excess hazard per 1,000 person-years at risk at selected times since diagnosis (1 month, 6 months and 1, 3 and 5 years), both by age group and by stage at diagnosis, after adjustment for age.

Overall (all-ages) net survival estimates were age-standardised with the International Cancer Survival Standard (ICSS) weight(16).

We used a logistic regression model to estimate the odds of colorectal cancer patients in each area being resected with curative intent, the odds of patients with colon cancer at Dukes' stage B or C receiving chemotherapy, and the odds of rectal cancer patients with Dukes' stage A-C being treated with radiotherapy, after adjustment for age and/or tumour site and/or sex.

Survival analyses were performed with *stpm2*(14*)* in Stata version 12 (StataCorp LP, College Station, TX).

Results

We included 12,523 patients with an invasive, primary colorectal cancer: 9,186 patients in 14 registries in 9 European countries and 3,337 patients in 7 US states (Table 1). Microscopic verification was available for 96-98% of the patients in each of the US states and 93% in Europe, ranging from 85% in Ragusa (Italy) to 99% in Kielce (Poland). The proportion of colorectal cancer patients who were male was similar in Europe (53%) and the US (50%), but colon cancer was more frequent in the US (73%) than in Europe (60%). Data were available on stage at diagnosis for 90-93% of patients on both sides of the Atlantic, ranging from 76% (Finland) to 95% or more in 3 of the 14 European registries and from 90% (Colorado and South Carolina) to 97% (Louisiana) in the US.

Early-stage (Dukes' A or B) colorectal cancers were equally common in the US (45%) and Europe (47%), but the stage distributions varied widely, both between US states and between European regions. Tumours in Dukes' stage A were of similar frequency in Europe (17%, range 11-28%) and in the US (17%; 14-23%), and the proportion of Dukes' B tumours were also very comparable (Europe 30%; 25-37%; US 28%; 24-36%). By contrast, Dukes' C tumours were twice as common in the US (38%; 29-46%) as in Europe (21%; 24-30%), while Dukes' D tumours were twice as common in Europe (21%; 11-33%) as in the US (10%; 7-18%). The proportion of tumours with unspecified stage was slightly higher in Europe (10%; 4-24%) than in the US (7%; 3-10%). Exclusion of Finland, with 24% of tumours of unknown stage, did not substantially alter the overall stage distributions in Europe (data not shown).

Patients diagnosed at an advanced stage (i.e. metastatic cases plus unresected cases for which no data on stage were available) were more common in the four European regions (29%; 24-34%) than in the US (20%; 16-23%) (Table 2). In Europe, advanced stage was more common in Southern (30%) and Eastern Europe (34%). The highest proportion of patients with advanced stage in the US (23%, California), was similar to the lowest regional proportion in Europe (24%, Western Europe).

Resection for curative intent was more frequent in the US (85%) than in Europe (75%). The proportion resected with curative intent was remarkably similar in all 7 US states (84-88%). Only Western Europe (84%) showed a proportion as high as that in the US.

Thirty-day post-operative mortality was 5% or less in the US and Europe. Among patients resected with curative intent, the proportion with known stage was around 95% in the US and Europe, with the lowest proportions in Northern Europe (84-90%) (Table 2). In many European registries, data on the number of lymph nodes examined after surgery were not available for most patients (web-appendix Table 2).

Adjuvant chemotherapy and radiotherapy were both administered more frequently in the US than in Europe (Table 3). Among Dukes' B colon cancer patients, 28% received chemotherapy in the US (21-46%) *vs.* 20% in Europe (4-31%). Among Dukes' C colon cancer patients, 56% received chemotherapy in the US (47-64%) vs. 47% in Europe (38-53%). Among Dukes' A-C rectal cancer patients, 47% received radiotherapy in the US (41-52%) vs. 37% in Europe (26-45%).

Relative to Southern Europe (2,912 patients, reference category), the odds of receiving resection for curative intent (*vs.* any other surgical procedure), after adjustment for age and tumour site, were much lower in Eastern Europe (OR=0.46; 0.41-0.52), somewhat lower in Northern Europe (OR=0.88; 95% CI 0.71-1.09); and much higher in Western Europe (OR=1.62; 1.43-1.85) and in the US (OR=1.72; 1.52-1.94) (Table 4).

Patients aged less than 75 years were only half as likely had half the chance to be resected with curative intent as those aged 15-64 years (OR 0.48, 95% confidence interval [CI] 0.43-0.53), after adjustment for region and tumour site.

Patients with colon cancer (reference category) were resected with curative intent more often than patients with rectal cancer (OR 0.73; 0.66-0.79).

Patients with Dukes' B colon cancer received chemotherapy much less often in Western Europe (OR 0.10; 0.06-0.16) and Northern Europe (OR 0.29; 0.15-0.56) than in Southern Europe. For patients with Dukes' C colon cancer, chemotherapy was used less in Western Europe (OR 0.64; 0.48-0.87) and more often in the US (OR 1.56; 1.23-1.98) than in Southern Europe.

Compared to Southern Europe, radiotherapy was administered to patients with rectal cancer in Dukes' stage A-C more often in the US (OR 1.39; 1.10-1.76), less often in Northern Europe (OR 0.58; 0.38-0.89) or Eastern Europe (OR 0.46; 0.36-0.59).

Older patients were only 10% as likely to be treated with radiotherapy and chemotherapy.

Overall, age-standardised net survival at five years was 50% in Europe and 58% in the US (Figure 1). Survival was lower than the US in all European areas, and only in Northern Europe was the figure (56%) close to that in the US. Survival was lower in Western (54%) and in Southern Europe (49%) and lowest in Eastern Europe (42%). Survival varied widely between European countries (from 56% in France and Finland to 37% in Poland), but also between US states (from 64% in Rhode Island to 56% in Illinois and 50% in South Carolina).

Five-year age-standardised net survival was higher in the US for Dukes' stage A (84%) and B (75%) tumours, but higher in Northern Europe for Dukes' C (52%) and D (12%) tumours (Figure 2). The geographic range in survival was much wider for locally advanced disease, from 36% in Eastern Europe to 77% in Northern Europe, and 49% in the US. As with overall survival, stage-specific five-year survival was similar in Northern, Western and Southern Europe and the US. In Eastern Europe, survival for node-positive, locally advanced and metastatic tumours was lower than in other European regions and in the US.

Survival was 5-12% higher in women than in men in all areas, especially in Northern and Western Europe (11-12%) (web-appendix Figure 3).

The mean excess hazard of death at 1 month, 6 months and at 1, 3 and 5 years after diagnosis was higher in Eastern Europe than in all other regions, both for all ages combined and in each of 3 age categories (web-appendix Figure 4). The difference was most marked for elderly patients (75-99 years). No striking differences were found between Northern, Western and Southern Europe and the US. The high

excess hazard of death in Eastern Europe was mainly confined to patients with Dukes' D tumours (web-appendix Figure 5).

Discussion

Transatlantic differences in population-based colorectal cancer survival have raised questions about early diagnosis and the adequacy of investigation and treatment that cannot be addressed with data from clinical trials, which include only selected patient groups.

Patterns-of-care studies and survival studies have been conducted separately in Europe(3;5;7) and the US(17;18). To our knowledge, this is the first population-based high-resolution study that allows direct comparison of colorectal cancer survival between Europe and the US with clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods.

Most of the diagnostic and therapeutic approaches used in the late 1990s remain in widespread use. Understanding their role in international differences in survival remains relevant. Mesorectal excision for rectal cancer is the main exception: it has improved survival from rectal cancer(19;20), but widespread use is more recent. Mesorectal excision was not used in Estonia before 1997, which may partly explain the low survival from rectal cancer(21).

The transatlantic 12% difference in 3-year survival in colorectal cancer survival for patients diagnosed 1990-91(3) was mostly attributed to differences in stage at diagnosis In our study of patients diagnosed in the late 1990s, overall five-year net survival was still higher in the 7 US states (58%) than in the 14 European regions (42-56%). The widest differences with the US were seen in Southern (49%) and Eastern Europe (42%).

The two studies differed in design, however: data from the SEER public-use data set in the US(22) were simply adapted to the EUROCARE-2 high-resolution protocol as far as possible. By contrast, data for this study were collected directly from clinical records on both sides of the Atlantic, with a standard protocol. US coverage changed from the 5 metropolitan areas and 4 states covered by the SEER program to 7 of the state-wide NPCR registries. In the earlier study, differences in background mortality in the US were controlled with a single national life table for 1990, weighted for the proportion of Blacks, Whites and other races. Here, we were able to use state-specific life tables for each of the calendar years 1996-2004.

The tighter control for background mortality and the modelling approach used to estimate net survival are methodological strengths of this study, but these changes do not explain why the transatlantic differences we observe in five-year survival are smaller than the differences in three-year survival for patients diagnosed in the early 1990s(3).

Survival varied widely among European countries, but also between the 7 US states. Survival in Slovenia was lower than in other Southern European countries, and more similar to that in Eastern Europe. In the US, survival was lowest in South Carolina, where Blacks represent approximately 30% of the population (http://www.ipspr.sc.edu/publication/Older%20SC.pdf).

Apart from patients with Dukes' B cancers, where survival was similar in Northern, Western and Southern Europe, stage-specific net survival was rather variable. Survival was highest in the US for Dukes' stage A and B, and in Northern Europe (Finland) for Dukes' stage C and D. This could be due to some misclassification of stage in Finland, where stage data were not available for 24% of cases.

The mean excess hazard of death up to five years after diagnosis was similar in Europe and the US for patients with tumours in Dukes' stage A or B. The hazard was somewhat higher in Eastern Europe for Dukes' stage C, and much higher for Dukes' D disease, especially in the first three years after diagnosis. The very high hazard of death for patients with late-stage disease in Eastern Europe suggests that fewer effective treatment options were available for these patients, although higher levels of co-morbidity may also have restricted the choice.

It was not possible to evaluate the impact of the number of examined lymph nodes on the stage-adjusted excess hazard of death, because information on nodal status was so often unavailable (see web-appendix). It is therefore impossible to assess whether stage migration affects the comparison of stage-specific survival between European regions and the US in the late 1990s, as reported for patients diagnosed in 1990(3).

Adjuvant chemotherapy for colon cancer and adjuvant radiotherapy for rectal cancer were both used more widely in the US than in Europe. Despite the evidence available in the late 1990s on the lack of efficacy of adjuvant chemotherapy for Dukes' B colon cancer, 30% of colon cancer patients in the US received it, and 20% overall in Europe. In Finland and Western Europe, however, adjuvant chemotherapy was rare, in line with the contemporary recommendations, while in Southern and Eastern Europe, adjuvant chemotherapy was used as frequently as in the US.

In contrast, there were striking differences in the use of adjuvant chemotherapy for stage III colon cancer in the late 1990s, particularly within Europe. Given the wide consensus on its effectiveness since 1990, we did not expect to find that such a strong recommendation had been so poorly followed. Co-morbidity and greater toxicity are not valid reasons for under-use of adjuvant chemotherapy in the elderly: toxicity is no greater(23;24) and quality of life no worse(25).

Elderly patients were 90% less likely to receive adjuvant chemotherapy than younger patients. Clinical attitudes appear to differ between the US and Europe, where the proportion of patients receiving adjuvant chemotherapy is much lower. This suggests that a higher proportion of older patients with Dukes' C colon cancer who are fit enough to undergo surgery should receive adjuvant chemotherapy, particularly in Europe.

Radiotherapy is known to be an effective complement to surgery for rectal cancer, in particular to reduce the risk of local recurrence; pre-operative is preferable to post-operative radiotherapy(26), and it is recommended in both Europe and the US(27-30). We were unable to distinguish between the impact of pre- and post-operative radiotherapy, because this information was not systematically available, but fewer patients received radiotherapy in Europe than in the US, and practice in Europe was

strikingly heterogeneous, even within a given country. Age was a strong predictor of the use of radiotherapy. Some older patients are unsuitable for radiotherapy because of co-morbidity, but their 70% lower odds of receiving it cannot be explained by co-morbidity alone; radiotherapy has not yet been deployed to its full potential for older patients with rectal cancer. It is not clear why the evidence on the benefits of radiotherapy was so poorly followed in many regions.

Surgical resection offers the only approach to a definitive cure for colorectal cancer. The proportion of patients resected with curative intent was very similar in the 7 US States (84-88%), but it varied widely between the 9 European countries (from 56% to 86%), and was particularly low in Eastern Europe (mean 62%). A more aggressive approach to surgical treatment for elderly colorectal cancer patients in Europe could improve this situation, although European patients were more often diagnosed at an advanced stage or with unresectable disease. Performance status and co-morbidity can influence whether a patient is considered fit for resection, but data on these factors were not available. The quality of life in Canadian patients aged over 80 who underwent surgery for colorectal cancer was generally comparable to that of younger patients(31).

In this large, population-based study in Europe, however, age alone seems often to have been a limiting factor in the treatment of colorectal cancer. Elderly patients were generally treated less often with surgery, chemotherapy or radiotherapy, despite the evidence that they could benefit from these treatments. Treatment decisions should be taken in the context of multidisciplinary meetings, including a comprehensive geriatric assessment: age alone should not exclude a patient from receiving surgery and/or adjuvant treatment.

Differences in colorectal cancer survival between Europe and the US in the late 1990s were still wide and may be attributable both to earlier stage at diagnosis, higher levels of surgery and more extensive use of adjuvant treatment in the US.

Evidence-based guidelines do not seem to have been followed as closely as they should be: chemotherapy was used too often for Dukes' B disease and not often enough for Dukes' C disease, especially among elderly patients.

The need for population-based survival estimates derived directly from the clinical records on stage at diagnosis and treatment is recognised by clinicians and epidemiologists. A recent comparison of stage-specific cancer survival with population-based data(32), was complicated by inconsistent coding of stage(33); several registries had to be excluded because fewer than half the tumour records contained data on stage. In this high-resolution study, stage data were remarkably complete (76-94% in Europe, 93% in the US), because they were collected directly from clinical records. Ideally, the medical records of cancer patients would systematically include data on investigations and stage at diagnosis; cancer registries would obtain those data for all patients, and stage would be coded consistently. Until then, high-resolution studies would appear to offer the most reliable approach to obtain data on stage and treatment, and to assess survival by stage at diagnosis.

If we want good evidence on whether all patients receive guideline-compliant investigation and treatment and whether this makes a difference to survival, then cancer registries will need more resources to obtain timely and high-quality data on the investigations, the stage and the treatment for all cancer patients.

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Extra results are available in the web-appendix. Raw data are not available.

Contributorship: CA, MS, GG, and MPC contributed to the study design; CL, JF, TA, EA, MBL, SB, RC, ME, JPF, JG, SG, TH, MPZ, JR, CSF, MJS, MJS, TS, GT, RT, MV, HJW, XCW, contributed to data collection; CA performed data quality control; PB prepared the life tables; CA, BR and MPC performed the data analyses; CA, BR, CL, JF, HKW, LS, TA, ME, MV and MPC contributed to interpretation of the findings; CA, BR and MPC drafted the article and CL, JF, HKW, LS, MJS, MBL, MS, TA, XCG, CLo, GG contributed to revisions.

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Table 1. Calendar period of diagnosis, morphological verification, and data on sex, cancer site and stage. Patients with invasive primary colorectal cancer, Europe and US

EUROPE	Registry	No.	Period of diagnosis	Morphologically verified		Males		Colon		Dukes' stage[1] at diagnosis									
										A		B		C		D		Not available	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Estonia	Estonia	560	1997	491	88	250	45	337	60	144	26	151	27	76	14	167	30	22	4
Finland	Finland	523	1996-98	478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
France	Côte d'Or	561	1996-97	544	97	302	54	382	68	112	20	209	37	98	17	114	20	28	5
Italy	Genova	589	1996	529	90	326	55	379	64	71	12	192	33	148	25	131	22	47	8
	Ragusa*	424	1996-98	361	85	233	55	269	63										
	Varese	500	1997	485	97	266	53	332	66	109	22	148	30	105	21	114	23	24	5
Netherlands	North East NL	1,936	1997	1821	94	1002	52	1240	64	280	14	579	30	463	24	332	17	282	15
Poland	Cracow	512	1997-98	463	90	252	49	285	56	128	25	101	20	82	16	158	31	43	8
	Kielce	271	1996	267	99	147	54	133	49	62	23	67	25	41	15	89	33	12	4
Slovakia	Slovakia	581	1996	535	92	351	60	315	54	161	28	147	25	75	13	160	28	38	7
Slovenia	Slovenia	937	1997	871	93	490	52	474	51	131	14	265	28	243	26	209	22	89	9
Spain	Granada	567	1996-97	523	92	312	55	360	63	63	11	191	34	109	19	148	26	56	10
	Navarra	588	1996-97	558	95	354	60	335	57	100	17	188	32	121	21	120	20	59	10
	Tarragona	637	1996-97	603	95	339	53	421	66	71	11	174	27	176	28	146	23	70	11
European registries		**9,186**		**8,529**	**93**	**4,871**	**53**	**5,556**	**60**	**1,493**	**17**	**2,586**	**30**	**1,840**	**21**	**1,948**	**21**	**895**	**10**
Northern Europe		523		478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
Western Europe		2,497		2365	95	1,304	52	1,622	65	392	16	788	32	561	22	446	18	310	12
Southern Europe2		4,242		3930	93	2,320	55	2,570	61	545	14	1158	30	902	24	868	20	345	8
Eastern Europe		1,924		1756	91	1,000	52	1,070	56	495	26	466	24	274	14	574	30	115	6
US																			
	California	495	1997	485	98	242	49	356	72	89	18	137	28	168	34	60	12	41	8
	Colorado	548	1997	536	98	296	54	407	74	85	16	162	30	191	35	56	10	54	10
	Illinois	505	1997	497	98	239	47	384	76	71	14	144	29	224	44	36	7	30	6
	Louisiana	511	1997	502	98	263	51	374	73	115	23	146	29	146	29	90	18	14	3
	New York	492	1997	473	96	248	50	350	71	91	18	114	23	226	46	21	4	40	8
	Rhode Island	418	1997	413	99	195	47	302	72	64	15	149	36	160	38	29	7	16	4
	South Carolina	368	1997	358	97	187	51	265	72	68	18	89	24	150	41	26	7	35	10
US registries		**3,337**		**3,264**	**98**	**1,670**	**50**	**2,438**	**73**	**583**	**17**	**941**	**28**	**1265**	**38**	**318**	**10**	**230**	**7**
Total		**12,523**																	

1 Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Data for Ragusa are not included in the percentages of Dukes' stage for Southern Europe

Table 2. Advanced stage, resection with curative intent, 30-days post-operative mortality and proportion of patients with information on stage: colorectal cancer, Europe and the US, 1996-98

EUROPE	Registry	All cases			Resected with curative intent[2]							
		No.	Advanced stage[1]				Deaths within 30 days		Staged			
									Colon		Rectum	
			No.	%	No.	%	No.	%	No.	%	No.	%
European registries		**8,762**	**2,535**	**29**	**6,584**	**75**	**248**	**4**	**3,895**	**95**	**2,374**	**95**
Northern Europe		523	134	26	385	74	16	4	192	84	142	90
Western Europe[3]		2,497	609	24	2,092	84	24	6	1,299	93	646	92
Southern Europe[4]		3,818	1,131	30	2,912	76	152	5	1,748	97	1,081	97
Eastern Europe		1,924	661	34	1,195	62	56	5	656	98	505	97
US registries		**3,337**	**676**	**20**	**2,832**	**85**	**124**	**4**	**2,039**	**97**	**677**	**93**
	California	495	112	23	415	84	15	4	294	96	102	93
	Colorado	548	113	21	468	85	18	4	335	95	109	93
	Illinois	505	112	22	422	84	21	5	320	97	85	93
	Louisiana	511	105	21	431	84	26	6	315	100	111	97
	New York	492	80	16	411	84	22	5	287	95	102	94
	Rhode Island	418	78	19	369	88	9	2	268	99	93	94
	South Carolina	368	76	21	316	86	13	4	220	96	75	87
Total		**12,099**										

[1] All metastatic cases, plus unresected cases for which no stage data were available

[2] Curative intent: surgery not specified as palliative, or tumour entirely resected

[3] Data for North East Netherlands (1,936) are not included in the proportion of deaths within 30 days of surgery for Western Europe beacuse the date of surgery was not available

[4] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 3. Chemotherapy in Dukes' B and C colon cancer and radiotherapy in Dukes' A-C rectal cancer

EUROPE Registry	Colon Dukes' B[1]			Colon Dukes' C[1]			Rectum Dukes' A-C[1]		
	No.	among whom, chemotherapy		No.	among whom, chemotherapy		No.	among whom, radiotherapy	
		No.	%		No.	%		No.	%
European registries	**1,748**	**343**	**20**	**1,130**	**528**	**47**	**1,850**	**678**	**37**
Northern Europe	110	11	10	50	21	42	118	34	29
Western Europe	591	23	4	346	133	38	411	183	45
Southern Europe[2]	736	209	28	529	265	50	797	331	42
Eastern Europe	259	80	31	154	81	53	480	124	26
US registries	**727**	**200**	**28**	**913**	**508**	**56**	**484**	**228**	**47**
California	108	29	27	114	54	47	65	31	48
Colorado	129	29	22	145	93	64	70	29	41
Illinois	112	28	25	171	88	51	65	33	51
Louisiana	105	22	21	106	59	56	76	33	43
New York	86	24	28	157	81	52	84	44	52
Rhode Island	119	37	31	107	69	64	66	30	45
South Carolina	68	31	46	113	64	57	58	28	48

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 4. Odds of colorectal cancer patients being resected with curative intent, odds of patients with Dukes' B or C colon cancer being treated with chemotherapy and odds of Dukes' stage A-C rectal cancer being treated with radiotherapy: by region, age, cancer site or sex

	Resection for curative intent			Colon Dukes' B[1]			Colon Dukes' C[1]			Rectum stage A - C[1]		
	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
Region												
Northern Europe	385	0.88	0.71 1.09	110	0.29	0.15 0.56	50	0.88	0.46 1.69	118	0.58	0.38 0.89
Western Europe	2,092	1.62	1.43 1.85	591	0.10	0.06 0.16	346	0.64	0.48 0.87	411	1.22	0.95 1.56
Southern Europe[2]	2,912	1.00		736	1.00		529	1.00		797	1.00	
Eastern Europe	1,195	0.46	0.41 0.52	259	0.89	0.64 1.23	154	0.89	0.61 1.32	480	0.46	0.36 0.59
US	2,832	1.72	1.52 1.94	727	1.25	0.97 1.60	913	1.56	1.23 1.98	484	1.39	1.10 1.76
Age (years)												
15-64	3,194	1.00		674	1.00		684	1.00		890	1.00	
65-74	3,195	0.89	0.79 0.99	797	0.61	0.48 0.77	653	0.47	0.37 0.59	784	0.69	0.57 0.84
75-99	3,027	0.48	0.43 0.53	952	0.07	0.05 0.10	655	0.10	0.08 0.13	616	0.30	0.24 0.38
Site												
Colon	6,191	1.00										
Rectum	3,225	0.73	0.66 0.79									
Sex*												
Male										1,324	1.00	
Female										966	0.92	0.77 1.10

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Figure 1. Five-year age standardized net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: country and region.

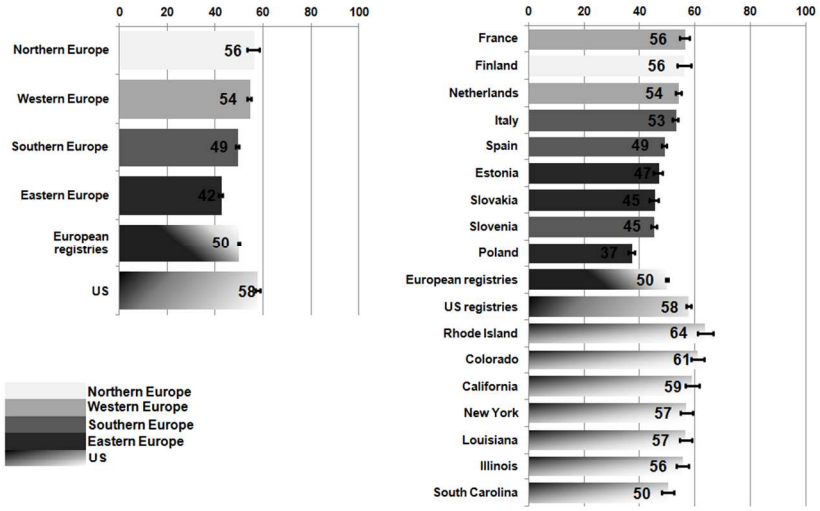
Figure 2. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region and stage at diagnosis.

Figure 3-web appendix. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region and sex.

Figure 4-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by area and age (a), area and sex (b).

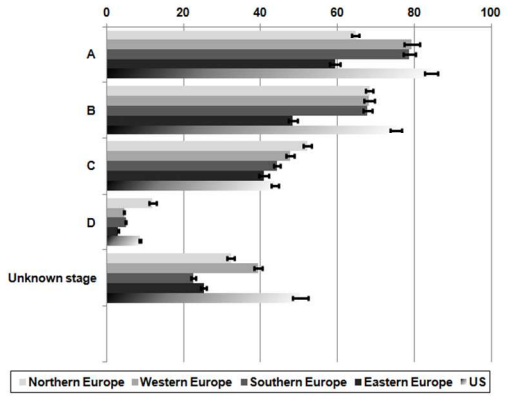
Figure 5-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by stage.

Figure 1. Five-year age standardized net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: country and region.



324x242mm (96 x 96 DPI)

Figure 2. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region and stage at diagnosis



323x245mm (96 x 96 DPI)

Table 2-web appendix. Advanced stage, resection with curative intent, 30-days post-operative mortality, proportion of patients with information on stage and number of lymph nodes examined : colorectal cancer, Europe and the US, 1996-98

EUROPE	Registry	All cases			Resected with curative intent[2]															
		No.	Advanced stage[1]		within				Staged				No. of lymph nodes examined							
									Colon		Rectum		Zero		Up to 11		More than 12		Not available	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Estonia	Estonia	560	188	34	314	56	9	3	192	98	118	99	0	0	149	47	5	2	160	51
Finland	Finland	523	134	26	385	74	16	4	192	84	142	90	49	13	187	49	20	5	129	34
France	Côte d'Or	561	141	25	430	77	24	6	302	100	127	99	62	14	255	59	113	26	0	0
Italy	Genova	589	153	26	503	85	37	7	313	95	164	95	1	0	219	44	171	34	112	22
	Varese	500	133	27	395	79	8	2	270	100	120	96	12	3	201	51	156	39	26	7
Netherland	North East NL	1,936	468	24	1,662	86	n.a	n.a	997	92	519	90	-	-	-	-	-	-	1,662	100
Poland	Cracow	512	187	37	303	59	9	3	146	94	141	96	6	2	210	69	25	8	62	20
	Kielce	271	91	34	211	78	19	9	103	98	97	92	0	0	36	17	3	1	172	82
Slovakia	Slovakia	581	195	34	367	63	19	5	215	100	149	99	7	2	155	42	1	0	204	56
Slovenia	Slovenia	937	283	30	652	70	44	7	322	97	315	98	26	4	243	37	327	50	56	9
Spain	Granada	567	186	33	442	78	30	7	273	96	151	96	4	1	238	54	135	31	65	15
	Navarra	588	172	29	452	77	15	3	259	98	186	98	0	0	201	44	133	29	118	26
	Tarragona	637	204	32	468	73	18	4	311	98	145	96	0	0	174	37	244	52	50	11
European registries		**8,762**	**2,535**	***29***	**6,584**	**75**	**248**	**5**	**3,895**	**95**	**2,374**	**95**	**167**	**3**	**2,268**	**34**	**1,333**	**20**	**2,816**	**43**
Northern Europe		523	134	26	385	74	16	4	192	84	142	90	49	13	187	49	20	5	129	34
Western Europe[3]		2,497	609	24	2,092	84	24	6	1,299	93	646	92	62	3	255	12	113	5	1,662	79
Southern Europe[4]		3,818	1,131	30	2,912	76	152	5	1,748	97	1,081	97	43	1	1,276	44	1,166	40	427	15
Eastern Europe		1,924	661	34	1,195	62	56	5	656	98	505	97	13	1	550	46	34	3	598	50
US																				
	California	495	112	23	415	84	15	4	294	96	102	93	37	9	215	52	156	38	7	2
	Colorado	548	113	21	468	85	18	4	335	95	109	93	24	5	238	51	199	43	7	1
	Illinois	505	112	22	422	84	21	5	320	97	85	93	49	12	191	45	176	42	6	1
	Louisiana	511	105	21	431	84	26	6	315	100	111	97	62	14	226	52	142	33	1	0
	New York	492	80	16	411	84	22	5	287	95	102	94	34	8	216	53	150	36	11	3
	Rhode Island	418	78	19	369	88	9	2	268	99	93	94	37	10	202	55	130	35	0	0
	South Carolina	368	76	21	316	86	13	4	220	96	75	87	28	9	174	55	107	34	7	2
US registries		**3,337**	**676**	**20**	**2,832**	**85**	**124**	**4**	**2,039**	**97**	**677**	**93**	**271**	**10**	**1,462**	**52**	**1,060**	**37**	**39**	**1**
Total		**12,099**																		

[1] All metastatic cases, plus unresected cases for which no stage data were available

[2] Curative intent: surgery not specified as palliative, or tumour entirely resected

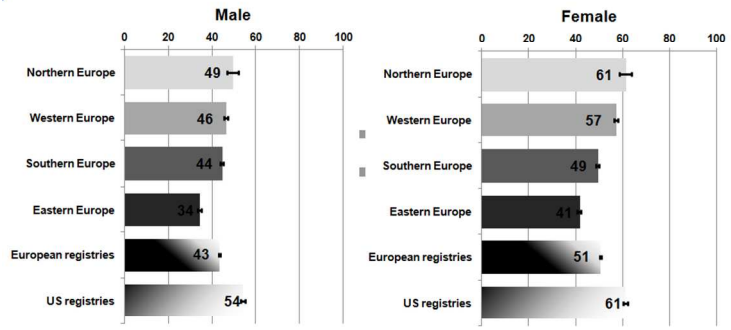
Table 3-web appendix. Chemotherapy in Dukes' B and C colon cancer and radiotherapy in Dukes' A-C rectal cancer

		Colon Dukes' B[1]			Colon Dukes' C[1]			Rectum Dukes' A-C[1]		
EUROPE	**Registry**	**No.**	**among whom,**		**No.**	**among whom,**		**No.**	**among whom,**	
			No.	**%**		**No.**	**%**		**No.**	**%**
Estonia	Estonia	97	8	8	44	19	43	140	36	26
Finland	Finland	110	11	10	50	21	42	118	34	29
France	Côte d'Or	170	22	13	65	33	51	61	27	44
Italy	Genova	122	45	37	93	43	46	109	45	41
	Ragusa	52	20	38	51	28	55	44	6	14
	Varese	106	45	42	63	38	60	85	24	28
Netherlands	North East NL	421	1	0	281	100	36	350	156	45
Poland	Cracow	50	23	46	45	24	53	138	15	11
	Kielce	30	1	3	22	7	32	85	11	13
Slovakia	Slovakia	82	48	59	43	31	72	117	62	53
Slovenia	Slovenia	143	15	10	126	56	44	260	100	38
Spain	Granada	128	47	37	67	36	54	82	37	45
	Navarra	111	39	35	68	37	54	136	82	60
	Tarragona	126	18	14	112	55	49	125	43	34
European registries		**1,748**	**343**	**20**	**1,130**	**528**	**47**	**1,850**	**678**	**37**
Northern Europe		110	11	10	50	21	42	118	34	29
Western Europe		591	23	4	346	133	38	411	183	45
Southern Europe[2]		736	209	28	529	265	50	797	331	42
Eastern Europe		259	80	31	154	81	53	480	124	26
US registries		**727**	**200**	**28**	**913**	**508**	**56**	**484**	**228**	**47**
	California	108	29	27	114	54	47	65	31	48
	Colorado	129	29	22	145	93	64	70	29	41
	Illinois	112	28	25	171	88	51	65	33	51
	Louisiana	105	22	21	106	59	56	76	33	43
	New York	86	24	28	157	81	52	84	44	52
	Rhode Island	119	37	31	107	69	64	66	30	45
	South Carolina	68	31	46	113	64	57	58	28	48

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

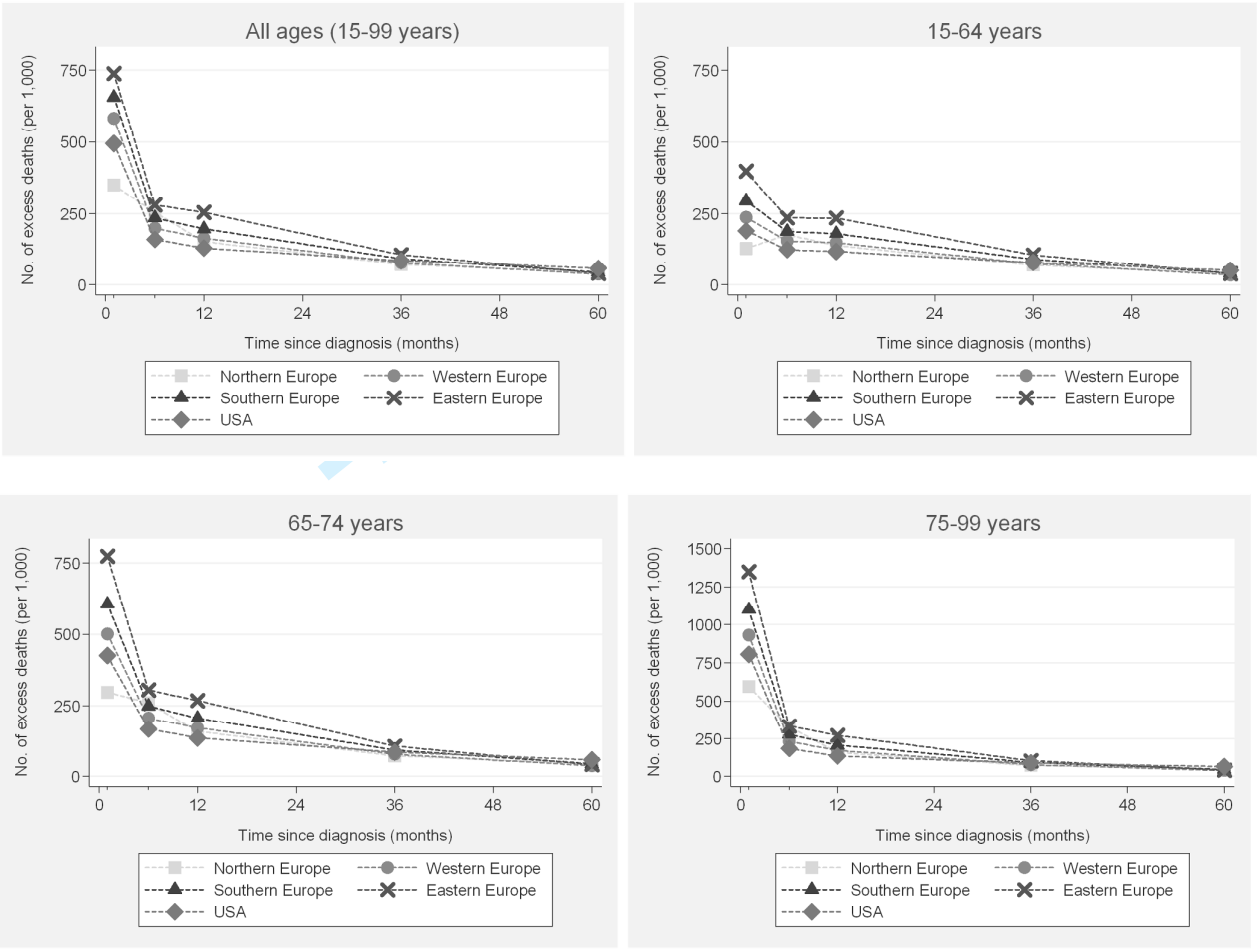
Figure 3-web appendix. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region and sex.



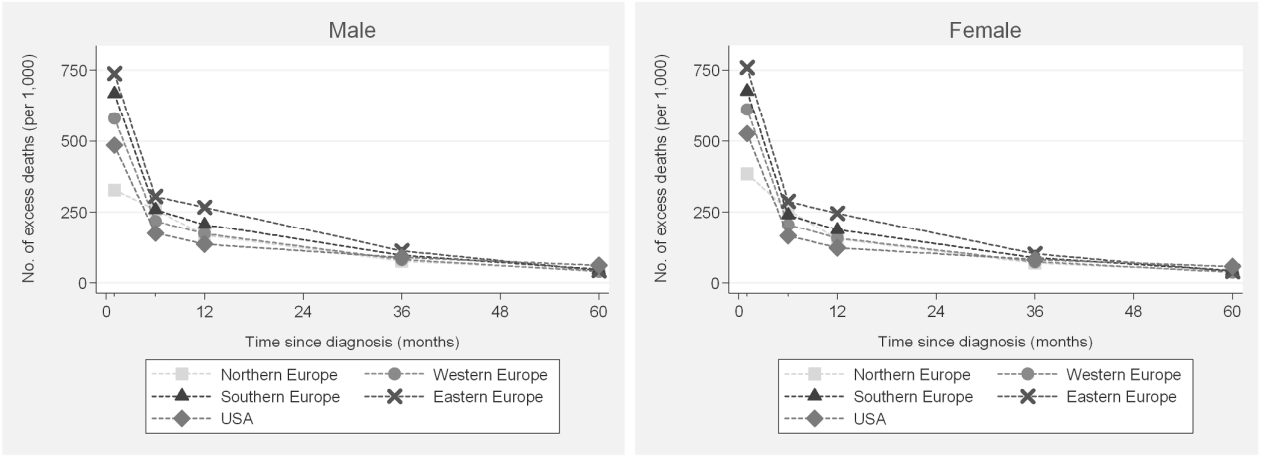
350x160mm (96 x 96 DPI)

Figure 4-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by area and age (a), area and sex (b).

(a)

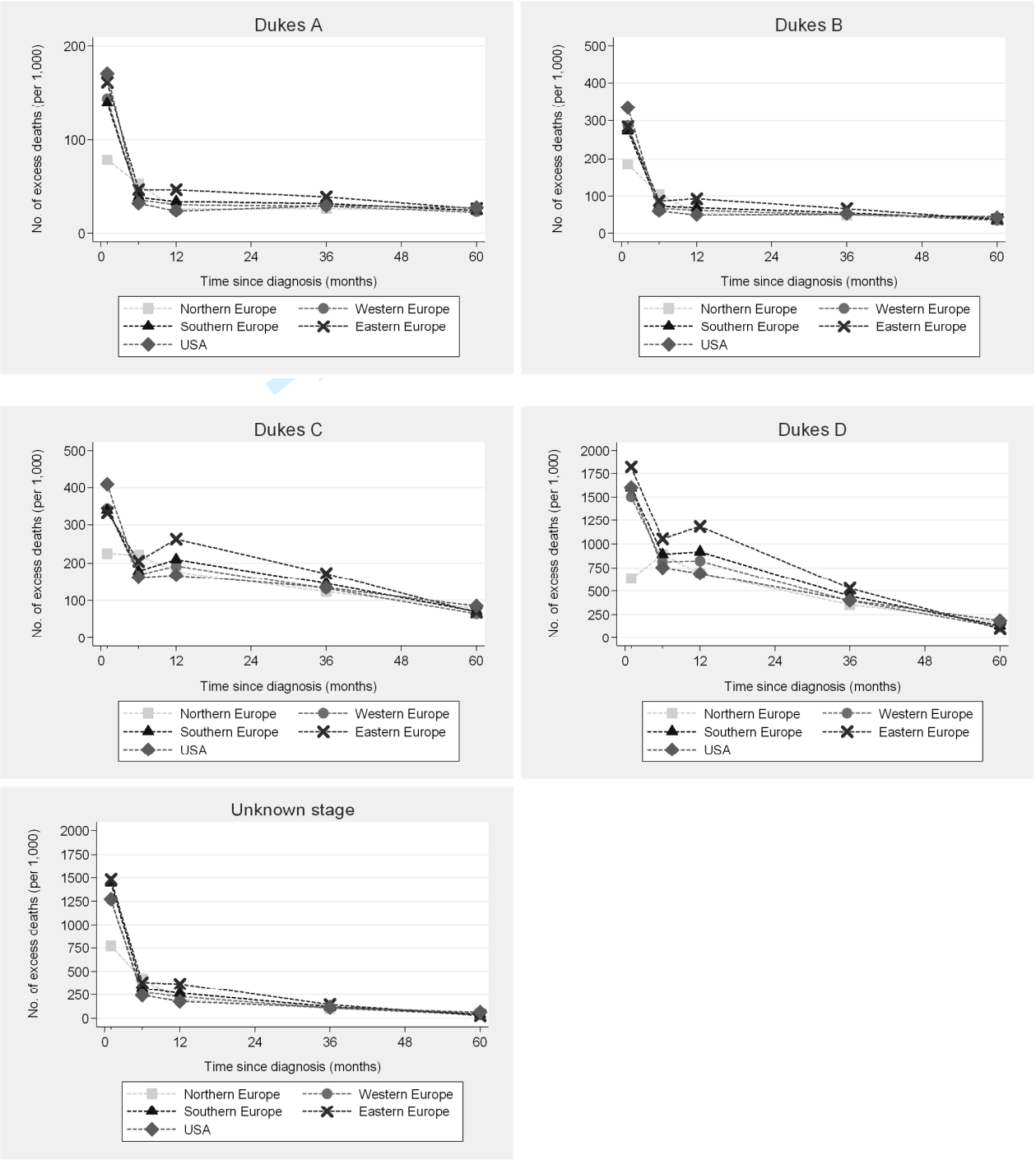


(b)



* Age was modelled as a continuous variable. The data points represent the mean excess hazards within each category of age (a) or sex (b).

Figure 5-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by stage.



* Age was modelled as a continuous variable. The data points represent the mean excess hazards within each category of stage.

Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study

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Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study

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Abstract

Background

Colorectal cancer survival in the US has consistently been reported as higher than in Europe. The differences have generally been attributed to stage at diagnosis.

Material and methods

21 population-based registries in 7 US states and 9 European countries provided data on Dukes' stage, diagnostic procedures, treatment and follow-up for random samples comprising 12,523 adults (15-99 years) diagnosed with colorectal cancer during 1996-98.

Logistic regression models were used to compare adherence to "standard care" in the US and Europe. Net survival and excess risk of death were estimated with flexible parametric models.

Results

The proportion of Dukes' A and B tumours was similar in the US and Europe, while Dukes' C was more frequent in the US (38% *vs.* 21%) and Dukes' D more frequent in Europe (22% *vs.* 10%).

Resection with curative intent was more frequent in the US (85% *vs.* 75%). Elderly patients (75-99 years) were 70-90% less likely to receive radiotherapy and chemotherapy.

Age-standardised five-year net survival was similar in the US (58%) and Northern and Western Europe (54-56%) and lowest in Eastern Europe (42%).

The mean excess hazard up to 5 years after diagnosis was highest in Eastern Europe, especially among elderly patients and those with Dukes' D tumours.

Conclusions

The wide differences in colorectal cancer survival between Europe and the US in the late 1990s are probably attributable both to earlier stage and more extensive use of surgery and adjuvant treatment.

Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.

Keywords: CONCORD, net survival, excess hazard, cancer registries.

Article Focus

- Why has population-based survival for colorectal cancer been so much higher in the US than in Europe?
- Can differences in stage, diagnostic procedures and/or treatment explain these wide disparities?
- Are evidence-based guidelines for staging and treatment being followed?

Key Messages

- Stage at diagnosis varied more widely between European countries than between US states.
- Evidence-based guidelines do not seem to have been closely followed. The proportion of patients who received surgery with adjuvant chemotherapy and/or radiotherapy was much lower in Europe than the US. Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.
- The wide US-Europe differences in five-year net survival from colorectal cancer in the late 1990s were probably attributable to earlier stage and more extensive use of surgery and adjuvant treatment in the US. Lower survival in Europe was mainly attributable to much lower survival in Eastern countries. This study underlines the need for population-based survival estimates derived from systematic clinical records of stage and treatment for all patients.

Strengths and Limitations

- To our knowledge, this is the first population-based high-resolution study with a direct US-Europe comparison of colorectal cancer survival, using clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods. Clinical records of investigation, stage and treatment are neither complete nor systematic. Cancer registries need resources to obtain these data in a timely manner for all cancer patients.
- Most diagnostic and therapeutic approaches used in the late 1990s remain in widespread use; mesorectal excision for rectal cancer is more recent. It remains relevant to understand the extent to which investigation and treatment are responsible for the persistent international differences in colorectal cancer survival.
- The modelling approach to estimate net survival is a methodological strength.
- Northern Europe was represented only by Finland.

Conflict of interest: none.

Ethical approval and data sharing agreement:

The study was approved by the US Centers for Disease Control (CDC, Atlanta GA) Institutional Review board #3551.

Informed consent of data subjects was not required; this was a records-based epidemiology study. No interview or contact with any patient was required, and no action was to be taken in respect of any individual whose data were included in the study, e.g. to alter their treatment. It is not practical to obtain informed consent from individual data subjects for their inclusion in studies of this type. It would involve attempting to contact many thousands of persons up to 15 years since they were first diagnosed. A substantial proportion would have died; many others would have moved, still others might not have been informed of the diagnosis. Contact would need to be made via the treating physician, whose identity was unknown. Consent could only have been sought by the cancer registries, since they alone know who the patients actually are, but none of the registries has the resources required. It would involve disproportionate effort, it would be substantially incomplete and it would take years to achieve, and the results would be irretrievably biased, invalidating the study.

Introduction

Five-year relative survival from cancers of the colon and rectum has been reported as 12-14% higher in the US than in Europe[1]. Survival for patients diagnosed during 1985–89 was higher in each of the 9 US states and metropolitan areas covered at that time by the Surveillance, Epidemiology and End Results (SEER) programme than in any of the 22 European countries participating in the EUROCARE-2 study[2].

The differences in 3-year colorectal cancer survival for patients diagnosed during 1990-91 between 10 territories in 5 European countries and the 9 SEER areas were mainly attributable to stage at diagnosis[3].

The first world-wide analysis of cancer survival (CONCORD[1]) provided a systematic comparison of survival for adults (15-99 years) diagnosed with cancer of the breast, colon, rectum or prostate in 31 countries during 1990-94 and followed up to 1999. International differences in age-standardised survival were very wide, even after adjustment for differences in mortality from other causes of death. Colorectal cancer survival was higher in the US and Canada than in many other countries. Differences between the US and most European regions were smaller than for patients diagnosed during 1985-89[2]. The largest differences were between the US and Eastern Europe.

The CONCORD protocol incorporated studies designed to explain the international variations in survival. These “high-resolution” studies involve systematic collection of detailed clinical and pathological data that are not routinely abstracted by population-based cancer registries from the original medical records of large random samples of patients. The high-resolution study reported here provides a trans-Atlantic comparison of stage, treatment and survival for patients with colorectal cancer.

The aims were (1) to compare the distributions of stage for colorectal cancers in Europe and the US; (2) to determine whether the transatlantic differences in survival persist and, if so, to assess the extent to which they are attributable to differences in stage at diagnosis; and (3) to compare adherence to “standard care”[4] for colorectal cancer in relation to age, stage and cancer site between the US and Europe.

Material and methods

Data on stage, diagnostic procedures, treatment and follow-up were collected for a representative sample of about 13,000 patients aged 15-99 years diagnosed with colorectal cancer (ICD-9[5] codes 1530-1539, 1540-1549) in the US and Europe during 1996-98. A single protocol was used, derived from the EUROCARE high-resolution protocols[6].

The European data were provided by 14 population-based cancer registries in 9 countries, 4 with national coverage (denoted below with an asterisk*). For some analyses, the data were grouped into the four European regions defined by the United Nations (UN, http://unstats.un.org/unsd/methods/m49/m49regin.htm) - Northern Europe: Finland*; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia*, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia*, Poland (Cracow, Kielce), Slovakia*. Estonia is classified by the UN as being in Northern Europe, but cancer survival has resembled that in Eastern European countries[7], and Estonia was included here with Eastern Europe. US data were provided by 7 state-wide registries (California, Colorado, Illinois, Louisiana, New York, Rhode Island, South Carolina) from the National Program of Cancer Registries (NPCR), based at the Centers for Disease Control and Prevention.

For this study, cancer registries in the EUROCARE-3 high-resolution study[8] updated follow-up to at least five years after diagnosis for all patients. North East Netherlands was not included in EUROCARE-3, but the registry routinely collects high-resolution data, and could provide such data on virtually all patients with colorectal cancer.

Most registries provided a random sample of at least 500 patients diagnosed during 1996-98 (1997 in the US). The Finnish cases were a population-based sample of patients diagnosed in the Tampere hospital region, which is considered representative of Finland.

Of 12,941 anonymised records for patients with a malignant neoplasm of the colon or rectum, 418 were excluded: *in situ* (396, 3.1%: collected in the US, but not in Europe) unknown sex (22, 0.2%); benign or uncertain behaviour (1), or age less than 15 or 100 years or over (19, 1.5%). In all, 12,523 patients with a primary, invasive, malignant colorectal neoplasm were included in the comparisons of stage and treatment. For survival analyses, a further 118 patients were excluded: cancer registered only from a death certificate (72; 0.6%); unknown vital status (3; 0.02%); date of last known vital status either unknown or earlier than the date of diagnosis (43; 0.3%); leaving 12,405 patients (99.1% of the 12,523 eligible).

Information on stage, diagnostic examinations and treatment was abstracted from the clinical record, pathology reports, hospital discharge records and other sources, as necessary.

Disease stage was defined according to the TNM (Tumour, Nodes, Metastasis) manual[9] and/or Dukes' stage. Many registries collected both TNM and Dukes' stage, but only Dukes' stage was available for Kielce (Poland) and Finland, so we used the Dukes' classification in order to include these populations in the stage-specific

analyses. Dukes' stage information was more complete than TNM stage, but TNM was used to reconstruct Dukes' stage where necessary. For descriptive purposes, we defined patients with 'advanced stage' as those with metastatic disease or those who had been operated on, but for whom no pathology report was available. This broad category was not used in stage-specific survival analyses, which are based on Dukes' stage, where available.

Age was categorised as 15-64, 65-74 and 75-99 years.

We defined resection for curative intent as resection of all macroscopically evident malignant tissue, with no macroscopic evidence of surgical margin involvement, and excluding polypectomy and trans-anal excision. Radiotherapy and chemotherapy were dichotomised as administered *vs.* not administered or unknown.

Statistical analysis

We analysed the distribution of stage and the number of lymph nodes examined pathologically[9]. We report the proportion of patients resected with curative intent and the distributions of stage-specific treatment for colon or rectal cancer. Data sets were excluded if data on stage and/or treatment were missing for 25% or more of patients: Ragusa was excluded from stage-specific analyses, including those on treatment related to stage at diagnosis.

Net survival up to five years after diagnosis was estimated by geographical area (UN region of Europe, country, registry or US state), age and stage, using flexible parametric excess hazard models[10]. Net survival is the survival of cancer patients in the hypothetical situation where the cancer may be assumed to be the only possible cause of death; it may be interpreted as cancer survival after controlling for competing causes of death. Net survival was estimated with a modelling approach[10-12] in which the total hazard of death is considered as the sum of the cancer-related mortality hazard (excess hazard), and the hazard of death from other causes (background hazard). The background hazard is derived from life tables of all-cause mortality by sex, single year of age and calendar year in the general population of the geographical area from which the cancer patients are drawn. We constructed period life tables for 1994-2004 with the approaches proposed by Baili et al[13].

Age was included as a continuous variable in all models, in order to avoid the bias in the estimation of net survival that would otherwise arise from differential loss of the oldest patients to competing hazards of death (informative censoring). Both non-linear and time-dependent (interaction with time since diagnosis) effects of age were initially modelled with cubic splines. The proportionality of the effect of tumour stage on the excess hazard was also assessed. Simpler models, with linear and/or proportional effects, were successively tested and selected using the Akaike Information Criterion for goodness of fit[14]. We also estimated the instantaneous excess risk (hazard) of death due to colorectal cancer, after subtracting the hazard from all other causes of death[10-12;15;16]. We present the mean excess hazard per 1,000 person-years at risk at selected times since diagnosis (1 month, 6 months and 1, 3 and 5 years), both by age group and by stage at diagnosis, after adjustment for age.

Overall (all-ages) net survival estimates were age-standardised with the International Cancer Survival Standard (ICSS) weight[17].

We used a logistic regression model to estimate the odds of colorectal cancer patients in each area being resected with curative intent, the odds of patients with colon cancer at Dukes' stage B or C receiving chemotherapy, and the odds of rectal cancer patients with Dukes' stage A-C being treated with radiotherapy, after adjustment for age and/or tumour site and/or sex.

Survival analyses were performed with *stpm2*[15] in Stata version 12 (StataCorp LP, College Station, TX).

Results

We included 12,523 patients with an invasive, primary colorectal cancer: 9,186 patients in 14 registries in 9 European countries and 3,337 patients in 7 US states (Table 1). Microscopic verification was available for 96-98% of the patients in each of the US states and 93% in Europe, ranging from 85% in Ragusa (Italy) to 99% in Kielce (Poland). The proportion of colorectal cancer patients who were male was similar in Europe (53%) and the US (50%), but colon cancer was more frequent in the US (73%) than in Europe (60%). Data were available on stage at diagnosis for 90-93% of patients on both sides of the Atlantic, ranging from 76% (Finland) to 95% or more in 3 of the 14 European registries and from 90% (Colorado and South Carolina) to 97% (Louisiana) in the US.

Early-stage (Dukes' A or B) colorectal cancers were equally common in the US (45%) and Europe (47%), but the stage distributions varied widely, both between US states and between European regions. Tumours in Dukes' stage A were of similar frequency in Europe (17%, range 11-28%) and in the US (17%; 14-23%), and the proportion of Dukes' B tumours were also very comparable (Europe 30%; 25-37%; US 28%; 24-36%). By contrast, Dukes' C tumours were twice as common in the US (38%; 29-46%) as in Europe (21%; 24-30%), while Dukes' D tumours were twice as common in Europe (21%; 11-33%) as in the US (10%; 7-18%). The proportion of tumours with unspecified stage was slightly higher in Europe (10%; 4-24%) than in the US (7%; 3-10%). Exclusion of Finland, with 24% of tumours of unknown stage, did not substantially alter the overall stage distributions in Europe (data not shown).

Patients diagnosed at an advanced stage (i.e. metastatic cases plus unresected cases for which no data on stage were available) were more common in the four European regions (29%; 24-34%) than in the US (20%; 16-23%) (Table 2). In Europe, advanced stage was more common in Southern (30%) and Eastern Europe (34%). The highest proportion of patients with advanced stage in the US (23%, California), was similar to the lowest regional proportion in Europe (24%, Western Europe).

Resection for curative intent was more frequent in the US (85%) than in Europe (75%). The proportion resected with curative intent was remarkably similar in all 7 US states (84-88%). Only Western Europe (84%) showed a proportion as high as that in the US.

Thirty-day post-operative mortality was 5% or less in the US and Europe. Among patients resected with curative intent, the proportion with known stage was around 95% in the US and Europe, with the lowest proportions in Northern Europe (84-90%) (Table 2). In many European registries, data on the number of lymph nodes examined after surgery were not available for most patients (web-appendix Table 2).

Adjuvant chemotherapy and radiotherapy were both administered more frequently in the US than in Europe (Table 3). Among Dukes' B colon cancer patients, 28% received chemotherapy in the US (21-46%) *vs.* 20% in Europe (4-31%). Among Dukes' C colon cancer patients, 56% received chemotherapy in the US (47-64%) vs. 47% in Europe (38-53%). Among Dukes' A-C rectal cancer patients, 47% received radiotherapy in the US (41-52%) vs. 37% in Europe (26-45%).

Relative to Southern Europe (2,912 patients, reference category), the odds of receiving resection for curative intent (*vs.* any other surgical procedure), after adjustment for age and tumour site, were much lower in Eastern Europe (OR=0.46; 0.41-0.52), somewhat lower in Northern Europe (OR=0.88; 95% CI 0.71-1.09); and much higher in Western Europe (OR=1.62; 1.43-1.85) and in the US (OR=1.72; 1.52-1.94) (Table 4).

Patients aged less than 75 years were only half as likely to be resected with curative intent as those aged 15-64 years (OR 0.48, 95% confidence interval [CI] 0.43-0.53), after adjustment for region and tumour site.

Patients with colon cancer (reference category) were resected with curative intent more often than patients with rectal cancer (OR 0.73; 0.66-0.79).

Patients with Dukes' B colon cancer received chemotherapy much less often in Western Europe (OR 0.10; 0.06-0.16) and Northern Europe (OR 0.29; 0.15-0.56) than in Southern Europe. For patients with Dukes' C colon cancer, chemotherapy was used less in Western Europe (OR 0.64; 0.48-0.87) and more often in the US (OR 1.56; 1.23-1.98) than in Southern Europe.

Compared to Southern Europe, radiotherapy was administered to patients with rectal cancer in Dukes' stage A-C more often in the US (OR 1.39; 1.10-1.76), less often in Northern Europe (OR 0.58; 0.38-0.89) or Eastern Europe (OR 0.46; 0.36-0.59).

Older patients were only 10% as likely to be treated with radiotherapy and chemotherapy.

Overall, age-standardised net survival at five years was 50% in Europe and 58% in the US (Figure 1). Survival was lower than the US in all European areas, and only in Northern Europe was the figure (56%) close to that in the US. Survival was lower in Western (54%) and in Southern Europe (49%) and lowest in Eastern Europe (42%). Survival varied widely between European countries (from 56% in France and Finland to 37% in Poland), but also between US states (from 64% in Rhode Island to 56% in Illinois and 50% in South Carolina).

Five-year age-standardised net survival was higher in the US for Dukes' stage A (84%) and B (75%) tumours, but higher in Northern Europe for Dukes' C (52%) and D (12%) tumours (Figure 2). The geographic range in survival was much wider for locally advanced disease, from 36% in Eastern Europe to 77% in Northern Europe, and 49% in the US. As with overall survival, stage-specific five-year survival was similar in Northern, Western and Southern Europe and the US. In Eastern Europe, survival for node-positive, locally advanced and metastatic tumours was lower than in other European regions and in the US.

Survival was 5-12% higher in women than in men in all areas, especially in Northern and Western Europe (11-12%) (web-appendix Figure 3).

The mean excess hazard of death at 1 month, 6 months and at 1, 3 and 5 years after diagnosis was higher in Eastern Europe than in all other regions, both for all ages combined and in each of 3 age categories (web-appendix Figure 4). The difference was most marked for elderly patients (75-99 years). No striking differences were found between Northern, Western and Southern Europe and the US. The high

excess hazard of death in Eastern Europe was mainly confined to patients with Dukes' D tumours (web-appendix Figure 5).

Discussion

Transatlantic differences in population-based colorectal cancer survival have raised questions about early diagnosis and the adequacy of investigation and treatment that cannot be addressed with data from clinical trials, which include only selected patient groups.

Patterns-of-care studies and survival studies have been conducted separately in Europe[3;6;8] and the US[18;19]. To our knowledge, this is the first population-based high-resolution study that allows direct comparison of colorectal cancer survival between Europe and the US with clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods.

Most of the diagnostic and therapeutic approaches used in the late 1990s remain in widespread use. Understanding their role in international differences in survival remains relevant. Mesorectal excision for rectal cancer is the main exception: it has improved survival from rectal cancer[20;21], but widespread use is more recent. Mesorectal excision was not used in Estonia before 1997, which may partly explain the low survival from rectal cancer[22].

The transatlantic 12% difference in 3-year survival in colorectal cancer survival for patients diagnosed 1990-91[3] was mostly attributed to differences in stage at diagnosis In our study of patients diagnosed in the late 1990s, overall five-year net survival was still higher in the 7 US states (58%) than in the 14 European regions (42-56%). The widest differences with the US were seen in Southern (49%) and Eastern Europe (42%).

The two studies differed in design, however: data from the SEER public-use data set in the US[23] were simply adapted to the EUROCARE-2 high-resolution protocol as far as possible. By contrast, data for this study were collected directly from clinical records on both sides of the Atlantic, with a standard protocol. US coverage changed from the 5 metropolitan areas and 4 states covered by the SEER program to 7 of the state-wide NPCR registries. In the earlier study, differences in background mortality in the US were controlled with a single national life table for 1990, weighted for the proportion of Blacks, Whites and other races. Here, we were able to use state-specific life tables for each of the calendar years 1996-2004.

The tighter control for background mortality and the modelling approach used to estimate net survival are methodological strengths of this study, but these changes do not explain why the transatlantic differences we observe in five-year survival are smaller than the differences in three-year survival for patients diagnosed in the early 1990s[3].

Survival varied widely among European countries, but also between the 7 US states. Survival in Slovenia was lower than in other Southern European countries, and more similar to that in Eastern Europe. In the US, survival was lowest in South Carolina, where Blacks represent approximately 30% of the population (http://www.ipspr.sc.edu/publication/Older%20SC.pdf).

Apart from patients with Dukes' B cancers, where survival was similar in Northern, Western and Southern Europe, stage-specific net survival was rather variable. Survival was highest in the US for Dukes' stage A and B, and in Northern Europe (Finland) for Dukes' stage C and D. This could be due to some misclassification of stage in Finland, where stage data were not available for 24% of cases.

The mean excess hazard of death up to five years after diagnosis was similar in Europe and the US for patients with tumours in Dukes' stage A or B. The hazard was somewhat higher in Eastern Europe for Dukes' stage C, and much higher for Dukes' D disease, especially in the first three years after diagnosis. The very high hazard of death for patients with late-stage disease in Eastern Europe suggests that fewer effective treatment options were available for these patients, although higher levels of co-morbidity may also have restricted the choice.

It was not possible to evaluate the impact of the number of examined lymph nodes on the stage-adjusted excess hazard of death, because information on nodal status was so often unavailable (see web-appendix). It is therefore impossible to assess whether stage migration affects the comparison of stage-specific survival between European regions and the US in the late 1990s, as reported for patients diagnosed in 1990[3].

We did not have information on whether or not patients in this study had undergone faecal occult blood testing or sigmoidoscopy before diagnosis. Opportunistic testing with these procedures was common in the US in the late 1990s. Almost 40% of respondents to the Behavioural Risk Factor Surveillance System (www.cdc.gov/mmwr/preview/mmwrhtml/00056494.htm) survey in 1997 reported having had a faecal occult blood test at some time in the past, and 42% reported a previous sigmoidoscopy or proctoscopy. Removal of premalignant polyps or *in situ* neoplasms may thus have been more frequent than in Europe. This would be expected to reduce incidence, shift the spectrum of malignancy to the right, and reduce survival in the US. In fact, incidence in the US is higher, the stage distribution less advanced, and survival higher than in Europe.

Adjuvant chemotherapy for colon cancer and adjuvant radiotherapy for rectal cancer were both used more widely in the US than in Europe. Despite the evidence available in the late 1990s on the lack of efficacy of adjuvant chemotherapy for Dukes' B colon cancer, 30% of colon cancer patients in the US received it, and 20% overall in Europe. In Finland and Western Europe, however, adjuvant chemotherapy was rare, in line with the contemporary recommendations, while in Southern and Eastern Europe, adjuvant chemotherapy was used as frequently as in the US.

In contrast, there were striking differences in the use of adjuvant chemotherapy for stage III colon cancer in the late 1990s, particularly within Europe. Given the wide consensus on its effectiveness since 1990, we did not expect to find that such a strong recommendation had been so poorly followed. Co-morbidity and greater toxicity are not valid reasons for under-use of adjuvant chemotherapy in the elderly: toxicity is no greater[24;25] and quality of life no worse[26].

Elderly patients were 90% less likely to receive adjuvant chemotherapy than younger patients. Clinical attitudes appear to differ between the US and Europe, where the proportion of patients receiving adjuvant chemotherapy is much lower. This suggests that a higher proportion of older patients with Dukes' C colon cancer who are fit enough to undergo surgery should receive adjuvant chemotherapy, particularly in Europe.

Radiotherapy is known to be an effective complement to surgery for rectal cancer, in particular to reduce the risk of local recurrence; pre-operative is preferable to post-operative radiotherapy[27], and it is recommended in both Europe and the US[28-31]. We were unable to distinguish between the impact of pre- and post-operative radiotherapy, because this information was not systematically available, but fewer patients received radiotherapy in Europe than in the US, and practice in Europe was strikingly heterogeneous, even within a given country. Age was a strong predictor of the use of radiotherapy. Some older patients are unsuitable for radiotherapy because of co-morbidity, but their 70% lower odds of receiving it cannot be explained by co-morbidity alone; radiotherapy has not yet been deployed to its full potential for older patients with rectal cancer. It is not clear why the evidence on the benefits of radiotherapy was so poorly followed in many regions.

Surgical resection offers the only approach to a definitive cure for colorectal cancer. The proportion of patients resected with curative intent was very similar in the 7 US States (84-88%), but it varied widely between the 9 European countries (from 56% to 86%), and was particularly low in Eastern Europe (mean 62%). A more aggressive approach to surgical treatment for elderly colorectal cancer patients in Europe could improve this situation, although European patients were more often diagnosed at an advanced stage or with unresectable disease. Performance status and co-morbidity can influence whether a patient is considered fit for resection, but data on these factors were not available. The quality of life in Canadian patients aged over 80 who underwent surgery for colorectal cancer was generally comparable to that of younger patients[32].

In this large, population-based study in Europe, however, age alone seems often to have been a limiting factor in the treatment of colorectal cancer. Elderly patients were generally treated less often with surgery, chemotherapy or radiotherapy, despite the evidence that they could benefit from these treatments. Treatment decisions should be taken in the context of multidisciplinary meetings, including a comprehensive geriatric assessment: age alone should not exclude a patient from receiving surgery and/or adjuvant treatment.

Differences in colorectal cancer survival between Europe and the US in the late 1990s were still wide and may be attributable both to earlier stage at diagnosis, higher levels of surgery and more extensive use of adjuvant treatment in the US.

Evidence-based guidelines do not seem to have been followed as closely as they should be: chemotherapy was used too often for Dukes' B disease and not often enough for Dukes' C disease, especially among elderly patients.

The need for population-based survival estimates derived directly from the clinical records on stage at diagnosis and treatment is recognised by clinicians and

epidemiologists. A recent comparison of stage-specific cancer survival with population-based data[33], was complicated by inconsistent coding of stage[34]; several registries had to be excluded because fewer than half the tumour records contained data on stage. In this high-resolution study, stage data were remarkably complete (76-94% in Europe, 93% in the US), because they were collected directly from clinical records. Ideally, the medical records of cancer patients would systematically include data on investigations and stage at diagnosis; cancer registries would obtain those data for all patients, and stage would be coded consistently. Until then, high-resolution studies would appear to offer the most reliable approach to obtain data on stage and treatment, and to assess survival by stage at diagnosis.

If good evidence is required on whether all patients receive guideline-compliant investigation and treatment, and whether this makes a difference to survival, then cancer registries will need to be able to obtain timely and high-quality data on the investigations, the stage and the treatment for all cancer patients.

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Extra results are available in the web-appendix. Raw data are not available.

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Table 1. Calendar period of diagnosis, morphological verification, and data on sex, cancer site and stage. Patients with invasive primary colorectal cancer, Europe and US

										Dukes' stage[1] at diagnosis									
EUROPE	Registry	No.	Period of diagnosis	Morphologically verified		Males		Colon		A		B		C		D		Not available	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Estonia	Estonia	560	1997	491	88	250	45	337	60	144	26	151	27	76	14	167	30	22	4
Finland	Finland	523	1996-98	478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
France	Côte d'Or	561	1996-97	544	97	302	54	382	68	112	20	209	37	98	17	114	20	28	5
Italy	Genova	589	1996	529	90	326	55	379	64	71	12	192	33	148	25	131	22	47	8
	Ragusa*	424	1996-98	361	85	233	55	269	63										
	Varese	500	1997	485	97	266	53	332	66	109	22	148	30	105	21	114	23	24	5
Netherlands	North East NL	1,936	1997	1821	94	1002	52	1240	64	280	14	579	30	463	24	332	17	282	15
Poland	Cracow	512	1997-98	463	90	252	49	285	56	128	25	101	20	82	16	158	31	43	8
	Kielce	271	1996	267	99	147	54	133	49	62	23	67	25	41	15	89	33	12	4
Slovakia	Slovakia	581	1996	535	92	351	60	315	54	161	28	147	25	75	13	160	28	38	7
Slovenia	Slovenia	937	1997	871	93	490	52	474	51	131	14	265	28	243	26	209	22	89	9
Spain	Granada	567	1996-97	523	92	312	55	360	63	63	11	191	34	109	19	148	26	56	10
	Navarra	588	1996-97	558	95	354	60	335	57	100	17	188	32	121	21	120	20	59	10
	Tarragona	637	1996-97	603	95	339	53	421	66	71	11	174	27	176	28	146	23	70	11
European registries[2]		**9,186**		**8,529**	**93**	**4,871**	**53**	**5,556**	**60**	**1,493**	**17**	**2,586**	**30**	**1,840**	**21**	**1,948**	**21**	**895**	**10**
Northern Europe		523		478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
Western Europe		2,497		2365	95	1,304	52	1,622	65	392	16	788	32	561	22	446	18	310	12
Southern Europe[3]		4,242		3930	93	2,320	55	2,570	61	545	14	1158	30	902	24	868	20	345	8
Eastern Europe		1,924		1756	91	1,000	52	1,070	56	495	26	466	24	274	14	574	30	115	6
US																			
	California	495	1997	485	98	242	49	356	72	89	18	137	28	168	34	60	12	41	8
	Colorado	548	1997	536	98	296	54	407	74	85	16	162	30	191	35	56	10	54	10
	Illinois	505	1997	497	98	239	47	384	76	71	14	144	29	224	44	36	7	30	6
	Louisiana	511	1997	502	98	263	51	374	73	115	23	146	29	146	29	90	18	14	3
	New York	492	1997	473	96	248	50	350	71	91	18	114	23	226	46	21	4	40	8
	Rhode Island	418	1997	413	99	195	47	302	72	64	15	149	36	160	38	29	7	16	4
	South Carolina	368	1997	358	97	187	51	265	72	68	18	89	24	150	41	26	7	35	10
US registries		**3,337**		**3,264**	**98**	**1,670**	**50**	**2,438**	**73**	**583**	**17**	**941**	**28**	**1265**	**38**	**318**	**10**	**230**	**7**
Total		**12,523**																	

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow , Kielce), Slovakia

[3] Data for Ragusa are not included in the percentages of Dukes' stage for Southern Europe

Table 2. Advanced stage, resection with curative intent, 30-days post-operative mortality and proportion of patients with information on stage: colorectal cancer, Europe and the US, 1996-98

		All cases			Resected with curative intent[2]							
			Advanced stage[1]				Deaths within 30 days		Staged			
									Colon		Rectum	
EUROPE	Registry	No.	No.	%	No.	%	No.	%	No.	%	No.	%
European registries[3]		**8,762**	**2,535**	**29**	**6,584**	**75**	**248**	**4**	**3,895**	**95**	**2,374**	**95**
Northern Europe		523	134	26	385	74	16	4	192	84	142	90
Western Europe[4]		2,497	609	24	2,092	84	24	6	1,299	93	646	92
Southern Europe[5]		3,818	1,131	30	2,912	76	152	5	1,748	97	1,081	97
Eastern Europe		1,924	661	34	1,195	62	56	5	656	98	505	97
US registries		**3,337**	**676**	**20**	**2,832**	**85**	**124**	**4**	**2,039**	**97**	**677**	**93**
	California	495	112	23	415	84	15	4	294	96	102	93
	Colorado	548	113	21	468	85	18	4	335	95	109	93
	Illinois	505	112	22	422	84	21	5	320	97	85	93
	Louisiana	511	105	21	431	84	26	6	315	100	111	97
	New York	492	80	16	411	84	22	5	287	95	102	94
	Rhode Island	418	78	19	369	88	9	2	268	99	93	94
	South Carolina	368	76	21	316	86	13	4	220	96	75	87
Total		**12,099**										

[1] All metastatic cases, plus unresected cases for which no stage data were available
[2] Curative intent: surgery not specified as palliative, or tumour entirely resected
[3] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow , Kielce), Slovakia
[4] Data for North East Netherlands (1,936) are not included in the proportion of deaths within 30 days of surgery for Western Europe beacuse the date of surgery was not available
[5] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 3. Chemotherapy in Dukes' B and C colon cancer and radiotherapy in Dukes' A-C rectal cancer

		Colon Dukes' B[1]			Colon Dukes' C[1]			Rectum Dukes' A-C[1]		
EUROPE	**Registry**	**No.**	**among whom, chemotherapy**		**No.**	**among whom, chemotherapy**		**No.**	**among whom, radiotherapy**	
			No.	**%**		**No.**	**%**		**No.**	**%**
European registries[2]		**1,748**	**343**	**20**	**1,130**	**528**	**47**	**1,850**	**678**	**37**
Northern Europe		110	11	10	50	21	42	118	34	29
Western Europe		591	23	4	346	133	38	411	183	45
Southern Europe[3]		736	209	28	529	265	50	797	331	42
Eastern Europe		259	80	31	154	81	53	480	124	26
US registries		**727**	**200**	**28**	**913**	**508**	**56**	**484**	**228**	**47**
	California	108	29	27	114	54	47	65	31	48
	Colorado	129	29	22	145	93	64	70	29	41
	Illinois	112	28	25	171	88	51	65	33	51
	Louisiana	105	22	21	106	59	56	76	33	43
	New York	86	24	28	157	81	52	84	44	52
	Rhode Island	119	37	31	107	69	64	66	30	45
	South Carolina	68	31	46	113	64	57	58	28	48

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 4. Odds of colorectal cancer patients being resected with curative intent, odds of patients with Dukes' B or C colon cancer being treated with chemotherapy and odds of Dukes' stage A-C rectal cancer being treated with radiotherapy: by region, age, cancer site or sex

	Resection for curative intent				Colon Dukes' B[1]				Colon Dukes' C[1]				Rectum stage A - C[1]			
	No.	OR	95% CI		No.	OR	95% CI		No.	OR	95% CI		No.	OR	95% CI	
Region[2]																
Northern Europe	385	0.88	0.71	1.09	110	0.29	0.15	0.56	50	0.88	0.46	1.69	118	0.58	0.38	0.89
Western Europe	2,092	1.62	1.43	1.85	591	0.10	0.06	0.16	346	0.64	0.48	0.87	411	1.22	0.95	1.56
Southern Europe[3]	2,912	1.00			736	1.00			529	1.00			797	1.00		
Eastern Europe	1,195	0.46	0.41	0.52	259	0.89	0.64	1.23	154	0.89	0.61	1.32	480	0.46	0.36	0.59
US	2,832	1.72	1.52	1.94	727	1.25	0.97	1.60	913	1.56	1.23	1.98	484	1.39	1.10	1.76
Age (years)																
15-64	3,194	1.00			674	1.00			684	1.00			890	1.00		
65-74	3,195	0.89	0.79	0.99	797	0.61	0.48	0.77	653	0.47	0.37	0.59	784	0.69	0.57	0.84
75-99	3,027	0.48	0.43	0.53	952	0.07	0.05	0.10	655	0.10	0.08	0.13	616	0.30	0.24	0.38
Site																
Colon	6,191	1.00														
Rectum	3,225	0.73	0.66	0.79												
Sex																
Male													1,324	1.00		
Female													966	0.92	0.77	1.10

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Figure 1. Five-year age standardized net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: country and region[1].

Figure 1 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 2. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region[1] and stage at diagnosis.

Figure 2 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 3-web appendix. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region[1] and sex.

Figure 3 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 4-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and age (a), region[1] and sex (b).

Figure 4 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 5-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and stage.

Figure 5 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study

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Abstract

Background

Colorectal cancer survival in the US has consistently been reported as higher than in Europe. The differences have generally been attributed to stage at diagnosis.

Material and methods

21 population-based registries in 7 US states and 9 European countries provided data on Dukes' stage, diagnostic procedures, treatment and follow-up for random samples comprising 12,523 adults (15-99 years) diagnosed with colorectal cancer during 1996-98.

Logistic regression models were used to compare adherence to "standard care" in the US and Europe. Net survival and excess risk of death were estimated with flexible parametric models.

Results

The proportion of Dukes' A and B tumours was similar in the US and Europe, while Dukes' C was more frequent in the US (38% *vs.* 21%) and Dukes' D more frequent in Europe (22% *vs.* 10%).

Resection with curative intent was more frequent in the US (85% *vs.* 75%). Elderly patients (75-99 years) were 70-90% less likely to receive radiotherapy and chemotherapy.

Age-standardised five-year net survival was similar in the US (58%) and Northern and Western Europe (54-56%) and lowest in Eastern Europe (42%).

The mean excess hazard up to 5 years after diagnosis was highest in Eastern Europe, especially among elderly patients and those with Dukes' D tumours.

Conclusions

The wide differences in colorectal cancer survival between Europe and the US in the late 1990s are probably attributable both to earlier stage and more extensive use of surgery and adjuvant treatment.

Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.

Keywords: CONCORD, net survival, excess hazard, cancer registries.

Article Focus

- Why has population-based survival for colorectal cancer been so much higher in the US than in Europe?
- Can differences in stage, diagnostic procedures and/or treatment explain these wide disparities?
- Are evidence-based guidelines for staging and treatment being followed?

Key Messages

- Stage at diagnosis varied more widely between European countries than between US states.
- Evidence-based guidelines do not seem to have been closely followed. The proportion of patients who received surgery with adjuvant chemotherapy and/or radiotherapy was much lower in Europe than the US. Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.
- The wide US-Europe differences in five-year net survival from colorectal cancer in the late 1990s were probably attributable to earlier stage and more extensive use of surgery and adjuvant treatment in the US. Lower survival in Europe was mainly attributable to much lower survival in Eastern countries. This study underlines the need for population-based survival estimates derived from systematic clinical records of stage and treatment for all patients.

Strengths and Limitations

- To our knowledge, this is the first population-based high-resolution study with a direct US-Europe comparison of colorectal cancer survival, using clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods. Clinical records of investigation, stage and treatment are neither complete nor systematic. Cancer registries need resources to obtain these data in a timely manner for all cancer patients.
- Most diagnostic and therapeutic approaches used in the late 1990s remain in widespread use; mesorectal excision for rectal cancer is more recent. It remains relevant to understand the extent to which investigation and treatment are responsible for the persistent international differences in colorectal cancer survival.
- The modelling approach to estimate net survival is a methodological strength.
- Northern Europe was represented only by Finland.

Conflict of interest: none.

Ethical approval and data sharing agreement:

The study was approved by the US Centers for Disease Control (CDC, Atlanta GA) Institutional Review board #3551.

Informed consent of data subjects was not required; this was a records-based epidemiology study. No interview or contact with any patient was required, and no action was to be taken in respect of any individual whose data were included in the study, e.g. to alter their treatment. It is not practical to obtain informed consent from individual data subjects for their inclusion in studies of this type. It would involve attempting to contact many thousands of persons up to 15 years since they were first diagnosed. A substantial proportion would have died; many others would have moved, still others might not have been informed of the diagnosis. Contact would need to be made via the treating physician, whose identity was unknown. Consent could only have been sought by the cancer registries, since they alone know who the patients actually are, but none of the registries has the resources required. It would involve disproportionate effort, it would be substantially incomplete and it would take years to achieve, and the results would be irretrievably biased, invalidating the study.

Introduction

Five-year relative survival from cancers of the colon and rectum has been reported as 12-14% higher in the US than in Europe[1]. Survival for patients diagnosed during 1985–89 was higher in each of the 9 US states and metropolitan areas covered at that time by the Surveillance, Epidemiology and End Results (SEER) programme than in any of the 22 European countries participating in the EUROCARE-2 study[2].

The differences in 3-year colorectal cancer survival for patients diagnosed during 1990-91 between 10 territories in 5 European countries and the 9 SEER areas were mainly attributable to stage at diagnosis[3].

The first world-wide analysis of cancer survival (CONCORD[1]) provided a systematic comparison of survival for adults (15-99 years) diagnosed with cancer of the breast, colon, rectum or prostate in 31 countries during 1990-94 and followed up to 1999. International differences in age-standardised survival were very wide, even after adjustment for differences in mortality from other causes of death. Colorectal cancer survival was higher in the US and Canada than in many other countries. Differences between the US and most European regions were smaller than for patients diagnosed during 1985-89[2]. The largest differences were between the US and Eastern Europe.

The CONCORD protocol incorporated studies designed to explain the international variations in survival. These "high-resolution" studies involve systematic collection of detailed clinical and pathological data that are not routinely abstracted by population-based cancer registries from the original medical records of large random samples of patients. The high-resolution study reported here provides a trans-Atlantic comparison of stage, treatment and survival for patients with colorectal cancer.

The aims were (1) to compare the distributions of stage for colorectal cancers in Europe and the US; (2) to determine whether the transatlantic differences in survival persist and, if so, to assess the extent to which they are attributable to differences in stage at diagnosis; and (3) to compare adherence to "standard care"[4] for colorectal cancer in relation to age, stage and cancer site between the US and Europe.

Material and methods

Data on stage, diagnostic procedures, treatment and follow-up were collected for a representative sample of about 13,000 patients aged 15-99 years diagnosed with colorectal cancer (ICD-9[5] codes 1530-1539, 1540-1549) in the US and Europe during 1996-98. A single protocol was used, derived from the EUROCARE high-resolution protocols[6].

The European data were provided by 14 population-based cancer registries in 9 countries, 4 with national coverage (denoted below with an asterisk*). For some analyses, the data were grouped into the four European regions defined by the United Nations (UN, http://unstats.un.org/unsd/methods/m49/m49regin.htm) - Northern Europe: Finland*; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia*, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia*, Poland (Cracow, Kielce), Slovakia*. Estonia is classified by the UN as being in Northern Europe, but cancer survival has resembled that in Eastern European countries[7], and Estonia was included here with Eastern Europe. US data were provided by 7 state-wide registries (California, Colorado, Illinois, Louisiana, New York, Rhode Island, South Carolina) from the National Program of Cancer Registries (NPCR), based at the Centers for Disease Control and Prevention.

For this study, cancer registries in the EUROCARE-3 high-resolution study[8] updated follow-up to at least five years after diagnosis for all patients. North East Netherlands was not included in EUROCARE-3, but the registry routinely collects high-resolution data, and could provide such data on virtually all patients with colorectal cancer.

Most registries provided a random sample of at least 500 patients diagnosed during 1996-98 (1997 in the US). The Finnish cases were a population-based sample of patients diagnosed in the Tampere hospital region, which is considered representative of Finland.

Of 12,941 anonymised records for patients with a malignant neoplasm of the colon or rectum, 418 were excluded: *in situ* (396, 3.1%: collected in the US, but not in Europe) unknown sex (22, 0.2%); benign or uncertain behaviour (1), or age less than 15 or 100 years or over (19, 1.5%). In all, 12,523 patients with a primary, invasive, malignant colorectal neoplasm were included in the comparisons of stage and treatment. For survival analyses, a further 118 patients were excluded: cancer registered only from a death certificate (72; 0.6%); unknown vital status (3; 0.02%); date of last known vital status either unknown or earlier than the date of diagnosis (43; 0.3%); leaving 12,405 patients (99.1% of the 12,523 eligible).

Information on stage, diagnostic examinations and treatment was abstracted from the clinical record, pathology reports, hospital discharge records and other sources, as necessary.

Disease stage was defined according to the TNM (Tumour, Nodes, Metastasis) manual[9] and/or Dukes' stage. Many registries collected both TNM and Dukes' stage, but only Dukes' stage was available for Kielce (Poland) and Finland, so we used the Dukes' classification in order to include these populations in the stage-specific

analyses. Dukes' stage information was more complete than TNM stage, but TNM was used to reconstruct Dukes' stage where necessary. For descriptive purposes, we defined patients with 'advanced stage' as those with metastatic disease or those who had been operated on, but for whom no pathology report was available. This broad category was not used in stage-specific survival analyses, which are based on Dukes' stage, where available.

Age was categorised as 15-64, 65-74 and 75-99 years.

We defined resection for curative intent as resection of all macroscopically evident malignant tissue, with no macroscopic evidence of surgical margin involvement, and excluding polypectomy and trans-anal excision. Radiotherapy and chemotherapy were dichotomised as administered *vs.* not administered or unknown.

Statistical analysis

We analysed the distribution of stage and the number of lymph nodes examined pathologically[9]. We report the proportion of patients resected with curative intent and the distributions of stage-specific treatment for colon or rectal cancer. Data sets were excluded if data on stage and/or treatment were missing for 25% or more of patients: Ragusa was excluded from stage-specific analyses, including those on treatment related to stage at diagnosis.

Net survival up to five years after diagnosis was estimated by geographical area (UN region of Europe, country, registry or US state), age and stage, using flexible parametric excess hazard models[10]. Net survival is the survival of cancer patients in the hypothetical situation where the cancer may be assumed to be the only possible cause of death; it may be interpreted as cancer survival after controlling for competing causes of death. Net survival was estimated with a modelling approach[10-12] in which the total hazard of death is considered as the sum of the cancer-related mortality hazard (excess hazard), and the hazard of death from other causes (background hazard). The background hazard is derived from life tables of all-cause mortality by sex, single year of age and calendar year in the general population of the geographical area from which the cancer patients are drawn. We constructed period life tables for 1994-2004 with the approaches proposed by Baili et al[13].

Age was included as a continuous variable in all models, in order to avoid the bias in the estimation of net survival that would otherwise arise from differential loss of the oldest patients to competing hazards of death (informative censoring). Both non-linear and time-dependent (interaction with time since diagnosis) effects of age were initially modelled with cubic splines. The proportionality of the effect of tumour stage on the excess hazard was also assessed. Simpler models, with linear and/or proportional effects, were successively tested and selected using the Akaike Information Criterion for goodness of fit[14]. We also estimated the instantaneous excess risk (hazard) of death due to colorectal cancer, after subtracting the hazard from all other causes of death[10-12;15;16]. We present the mean excess hazard per 1,000 person-years at risk at selected times since diagnosis (1 month, 6 months and 1, 3 and 5 years), both by age group and by stage at diagnosis, after adjustment for age.

Overall (all-ages) net survival estimates were age-standardised with the International Cancer Survival Standard (ICSS) weight[17].

We used a logistic regression model to estimate the odds of colorectal cancer patients in each area being resected with curative intent, the odds of patients with colon cancer at Dukes' stage B or C receiving chemotherapy, and the odds of rectal cancer patients with Dukes' stage A-C being treated with radiotherapy, after adjustment for age and/or tumour site and/or sex.

Survival analyses were performed with *stpm2*[15] in Stata version 12 (StataCorp LP, College Station, TX).

Results

We included 12,523 patients with an invasive, primary colorectal cancer: 9,186 patients in 14 registries in 9 European countries and 3,337 patients in 7 US states (Table 1). Microscopic verification was available for 96-98% of the patients in each of the US states and 93% in Europe, ranging from 85% in Ragusa (Italy) to 99% in Kielce (Poland). The proportion of colorectal cancer patients who were male was similar in Europe (53%) and the US (50%), but colon cancer was more frequent in the US (73%) than in Europe (60%). Data were available on stage at diagnosis for 90-93% of patients on both sides of the Atlantic, ranging from 76% (Finland) to 95% or more in 3 of the 14 European registries and from 90% (Colorado and South Carolina) to 97% (Louisiana) in the US.

Early-stage (Dukes' A or B) colorectal cancers were equally common in the US (45%) and Europe (47%), but the stage distributions varied widely, both between US states and between European regions. Tumours in Dukes' stage A were of similar frequency in Europe (17%, range 11-28%) and in the US (17%; 14-23%), and the proportion of Dukes' B tumours were also very comparable (Europe 30%; 25-37%; US 28%; 24-36%). By contrast, Dukes' C tumours were twice as common in the US (38%; 29-46%) as in Europe (21%; 24-30%), while Dukes' D tumours were twice as common in Europe (21%; 11-33%) as in the US (10%; 7-18%). The proportion of tumours with unspecified stage was slightly higher in Europe (10%; 4-24%) than in the US (7%; 3-10%). Exclusion of Finland, with 24% of tumours of unknown stage, did not substantially alter the overall stage distributions in Europe (data not shown).

Patients diagnosed at an advanced stage (i.e. metastatic cases plus unresected cases for which no data on stage were available) were more common in the four European regions (29%; 24-34%) than in the US (20%; 16-23%) (Table 2). In Europe, advanced stage was more common in Southern (30%) and Eastern Europe (34%). The highest proportion of patients with advanced stage in the US (23%, California), was similar to the lowest regional proportion in Europe (24%, Western Europe).

Resection for curative intent was more frequent in the US (85%) than in Europe (75%). The proportion resected with curative intent was remarkably similar in all 7 US states (84-88%). Only Western Europe (84%) showed a proportion as high as that in the US.

Thirty-day post-operative mortality was 5% or less in the US and Europe. Among patients resected with curative intent, the proportion with known stage was around 95% in the US and Europe, with the lowest proportions in Northern Europe (84-90%) (Table 2). In many European registries, data on the number of lymph nodes examined after surgery were not available for most patients (web-appendix Table 2).

Adjuvant chemotherapy and radiotherapy were both administered more frequently in the US than in Europe (Table 3). Among Dukes' B colon cancer patients, 28% received chemotherapy in the US (21-46%) *vs.* 20% in Europe (4-31%). Among Dukes' C colon cancer patients, 56% received chemotherapy in the US (47-64%) vs. 47% in Europe (38-53%). Among Dukes' A-C rectal cancer patients, 47% received radiotherapy in the US (41-52%) vs. 37% in Europe (26-45%).

Relative to Southern Europe (2,912 patients, reference category), the odds of receiving resection for curative intent (*vs.* any other surgical procedure), after adjustment for age and tumour site, were much lower in Eastern Europe (OR=0.46; 0.41-0.52), somewhat lower in Northern Europe (OR=0.88; 95% CI 0.71-1.09); and much higher in Western Europe (OR=1.62; 1.43-1.85) and in the US (OR=1.72; 1.52-1.94) (Table 4).

Patients aged less than 75 years were only half as likely to be resected with curative intent as those aged 15-64 years (OR 0.48, 95% confidence interval [CI] 0.43-0.53), after adjustment for region and tumour site.

Patients with colon cancer (reference category) were resected with curative intent more often than patients with rectal cancer (OR 0.73; 0.66-0.79).

Patients with Dukes' B colon cancer received chemotherapy much less often in Western Europe (OR 0.10; 0.06-0.16) and Northern Europe (OR 0.29; 0.15-0.56) than in Southern Europe. For patients with Dukes' C colon cancer, chemotherapy was used less in Western Europe (OR 0.64; 0.48-0.87) and more often in the US (OR 1.56; 1.23-1.98) than in Southern Europe.

Compared to Southern Europe, radiotherapy was administered to patients with rectal cancer in Dukes' stage A-C more often in the US (OR 1.39; 1.10-1.76), less often in Northern Europe (OR 0.58; 0.38-0.89) or Eastern Europe (OR 0.46; 0.36-0.59).

Older patients were only 10% as likely to be treated with radiotherapy and chemotherapy.

Overall, age-standardised net survival at five years was 50% in Europe and 58% in the US (Figure 1). Survival was lower than the US in all European areas, and only in Northern Europe was the figure (56%) close to that in the US. Survival was lower in Western (54%) and in Southern Europe (49%) and lowest in Eastern Europe (42%). Survival varied widely between European countries (from 56% in France and Finland to 37% in Poland), but also between US states (from 64% in Rhode Island to 56% in Illinois and 50% in South Carolina).

Five-year age-standardised net survival was higher in the US for Dukes' stage A (84%) and B (75%) tumours, but higher in Northern Europe for Dukes' C (52%) and D (12%) tumours (Figure 2). The geographic range in survival was much wider for locally advanced disease, from 36% in Eastern Europe to 77% in Northern Europe, and 49% in the US. As with overall survival, stage-specific five-year survival was similar in Northern, Western and Southern Europe and the US. In Eastern Europe, survival for node-positive, locally advanced and metastatic tumours was lower than in other European regions and in the US.

Survival was 5-12% higher in women than in men in all areas, especially in Northern and Western Europe (11-12%) (web-appendix Figure 3).

The mean excess hazard of death at 1 month, 6 months and at 1, 3 and 5 years after diagnosis was higher in Eastern Europe than in all other regions, both for all ages combined and in each of 3 age categories (web-appendix Figure 4). The difference was most marked for elderly patients (75-99 years). No striking differences were found between Northern, Western and Southern Europe and the US. The high

excess hazard of death in Eastern Europe was mainly confined to patients with Dukes' D tumours (web-appendix Figure 5).

Discussion

Transatlantic differences in population-based colorectal cancer survival have raised questions about early diagnosis and the adequacy of investigation and treatment that cannot be addressed with data from clinical trials, which include only selected patient groups.

Patterns-of-care studies and survival studies have been conducted separately in Europe[3;6;8] and the US[18;19]. To our knowledge, this is the first population-based high-resolution study that allows direct comparison of colorectal cancer survival between Europe and the US with clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods.

Most of the diagnostic and therapeutic approaches used in the late 1990s remain in widespread use. Understanding their role in international differences in survival remains relevant. Mesorectal excision for rectal cancer is the main exception: it has improved survival from rectal cancer[20;21], but widespread use is more recent. Mesorectal excision was not used in Estonia before 1997, which may partly explain the low survival from rectal cancer[22].

The transatlantic 12% difference in 3-year survival in colorectal cancer survival for patients diagnosed 1990-91[3] was mostly attributed to differences in stage at diagnosis In our study of patients diagnosed in the late 1990s, overall five-year net survival was still higher in the 7 US states (58%) than in the 14 European regions (42-56%). The widest differences with the US were seen in Southern (49%) and Eastern Europe (42%).

The two studies differed in design, however: data from the SEER public-use data set in the US[23] were simply adapted to the EUROCARE-2 high-resolution protocol as far as possible. By contrast, data for this study were collected directly from clinical records on both sides of the Atlantic, with a standard protocol. US coverage changed from the 5 metropolitan areas and 4 states covered by the SEER program to 7 of the state-wide NPCR registries. In the earlier study, differences in background mortality in the US were controlled with a single national life table for 1990, weighted for the proportion of Blacks, Whites and other races. Here, we were able to use state-specific life tables for each of the calendar years 1996-2004.

The tighter control for background mortality and the modelling approach used to estimate net survival are methodological strengths of this study, but these changes do not explain why the transatlantic differences we observe in five-year survival are smaller than the differences in three-year survival for patients diagnosed in the early 1990s[3].

Survival varied widely among European countries, but also between the 7 US states. Survival in Slovenia was lower than in other Southern European countries, and more similar to that in Eastern Europe. In the US, survival was lowest in South Carolina, where Blacks represent approximately 30% of the population (http://www.ipspr.sc.edu/publication/Older%20SC.pdf).

Apart from patients with Dukes' B cancers, where survival was similar in Northern, Western and Southern Europe, stage-specific net survival was rather variable. Survival was highest in the US for Dukes' stage A and B, and in Northern Europe (Finland) for Dukes' stage C and D. This could be due to some misclassification of stage in Finland, where stage data were not available for 24% of cases.

The mean excess hazard of death up to five years after diagnosis was similar in Europe and the US for patients with tumours in Dukes' stage A or B. The hazard was somewhat higher in Eastern Europe for Dukes' stage C, and much higher for Dukes' D disease, especially in the first three years after diagnosis. The very high hazard of death for patients with late-stage disease in Eastern Europe suggests that fewer effective treatment options were available for these patients, although higher levels of co-morbidity may also have restricted the choice.

It was not possible to evaluate the impact of the number of examined lymph nodes on the stage-adjusted excess hazard of death, because information on nodal status was so often unavailable (see web-appendix). It is therefore impossible to assess whether stage migration affects the comparison of stage-specific survival between European regions and the US in the late 1990s, as reported for patients diagnosed in 1990[3].

We did not have information on whether or not patients in this study had undergone faecal occult blood testing or sigmoidoscopy before diagnosis. Opportunistic testing with these procedures was common in the US in the late 1990s. Almost 40% of respondents to the Behavioural Risk Factor Surveillance System (www.cdc.gov/mmwr/preview/mmwrhtml/00056494.htm) survey in 1997 reported having had a faecal occult blood test at some time in the past, and 42% reported a previous sigmoidoscopy or proctoscopy. Removal of premalignant polyps or *in situ* neoplasms may thus have been more frequent than in Europe. This would be expected to reduce incidence, shift the spectrum of malignancy to the right, and reduce survival in the US. In fact, incidence in the US is higher, the stage distribution less advanced, and survival higher than in Europe.

Adjuvant chemotherapy for colon cancer and adjuvant radiotherapy for rectal cancer were both used more widely in the US than in Europe. Despite the evidence available in the late 1990s on the lack of efficacy of adjuvant chemotherapy for Dukes' B colon cancer, 30% of colon cancer patients in the US received it, and 20% overall in Europe. In Finland and Western Europe, however, adjuvant chemotherapy was rare, in line with the contemporary recommendations, while in Southern and Eastern Europe, adjuvant chemotherapy was used as frequently as in the US.

In contrast, there were striking differences in the use of adjuvant chemotherapy for stage III colon cancer in the late 1990s, particularly within Europe. Given the wide consensus on its effectiveness since 1990, we did not expect to find that such a strong recommendation had been so poorly followed. Co-morbidity and greater toxicity are not valid reasons for under-use of adjuvant chemotherapy in the elderly: toxicity is no greater[24;25] and quality of life no worse[26].

Elderly patients were 90% less likely to receive adjuvant chemotherapy than younger patients. Clinical attitudes appear to differ between the US and Europe, where the proportion of patients receiving adjuvant chemotherapy is much lower. This suggests that a higher proportion of older patients with Dukes' C colon cancer who are fit enough to undergo surgery should receive adjuvant chemotherapy, particularly in Europe.

Radiotherapy is known to be an effective complement to surgery for rectal cancer, in particular to reduce the risk of local recurrence; pre-operative is preferable to post-operative radiotherapy[27], and it is recommended in both Europe and the US[28-31]. We were unable to distinguish between the impact of pre- and post-operative radiotherapy, because this information was not systematically available, but fewer patients received radiotherapy in Europe than in the US, and practice in Europe was strikingly heterogeneous, even within a given country. Age was a strong predictor of the use of radiotherapy. Some older patients are unsuitable for radiotherapy because of co-morbidity, but their 70% lower odds of receiving it cannot be explained by co-morbidity alone; radiotherapy has not yet been deployed to its full potential for older patients with rectal cancer. It is not clear why the evidence on the benefits of radiotherapy was so poorly followed in many regions.

Surgical resection offers the only approach to a definitive cure for colorectal cancer. The proportion of patients resected with curative intent was very similar in the 7 US States (84-88%), but it varied widely between the 9 European countries (from 56% to 86%), and was particularly low in Eastern Europe (mean 62%). A more aggressive approach to surgical treatment for elderly colorectal cancer patients in Europe could improve this situation, although European patients were more often diagnosed at an advanced stage or with unresectable disease. Performance status and co-morbidity can influence whether a patient is considered fit for resection, but data on these factors were not available. The quality of life in Canadian patients aged over 80 who underwent surgery for colorectal cancer was generally comparable to that of younger patients[32].

In this large, population-based study in Europe, however, age alone seems often to have been a limiting factor in the treatment of colorectal cancer. Elderly patients were generally treated less often with surgery, chemotherapy or radiotherapy, despite the evidence that they could benefit from these treatments. Treatment decisions should be taken in the context of multidisciplinary meetings, including a comprehensive geriatric assessment: age alone should not exclude a patient from receiving surgery and/or adjuvant treatment.

Differences in colorectal cancer survival between Europe and the US in the late 1990s were still wide and may be attributable both to earlier stage at diagnosis, higher levels of surgery and more extensive use of adjuvant treatment in the US.

Evidence-based guidelines do not seem to have been followed as closely as they should be: chemotherapy was used too often for Dukes' B disease and not often enough for Dukes' C disease, especially among elderly patients.

The need for population-based survival estimates derived directly from the clinical records on stage at diagnosis and treatment is recognised by clinicians and

epidemiologists. A recent comparison of stage-specific cancer survival with population-based data[33], was complicated by inconsistent coding of stage[34]; several registries had to be excluded because fewer than half the tumour records contained data on stage. In this high-resolution study, stage data were remarkably complete (76-94% in Europe, 93% in the US), because they were collected directly from clinical records. Ideally, the medical records of cancer patients would systematically include data on investigations and stage at diagnosis; cancer registries would obtain those data for all patients, and stage would be coded consistently. Until then, high-resolution studies would appear to offer the most reliable approach to obtain data on stage and treatment, and to assess survival by stage at diagnosis.

If good evidence is required on whether all patients receive guideline-compliant investigation and treatment, and whether this makes a difference to survival, then cancer registries will need to be able to obtain timely and high-quality data on the investigations, the stage and the treatment for all cancer patients.

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Extra results are available in the web-appendix. Raw data are not available.

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Table 1. Calendar period of diagnosis, morphological verification, and data on sex, cancer site and stage. Patients with invasive primary colorectal cancer, Europe and US

										Dukes' stage[1] at diagnosis									
EUROPE	Registry	No.	Period of diagnosis	Morphologically verified		Males		Colon		A		B		C		D		Not available	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Estonia	Estonia	560	1997	491	88	250	45	337	60	144	26	151	27	76	14	167	30	22	4
Finland	Finland	523	1996-98	478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
France	Côte d'Or	561	1996-97	544	97	302	54	382	68	112	20	209	37	98	17	114	20	28	5
Italy	Genova	589	1996	529	90	326	55	379	64	71	12	192	33	148	25	131	22	47	8
	Ragusa*	424	1996-98	361	85	233	55	269	63										
	Varese	500	1997	485	97	266	53	332	66	109	22	148	30	105	21	114	23	24	5
Netherlands	North East NL	1,936	1997	1821	94	1002	52	1240	64	280	14	579	30	463	24	332	17	282	15
Poland	Cracow	512	1997-98	463	90	252	49	285	56	128	25	101	20	82	16	158	31	43	8
	Kielce	271	1996	267	99	147	54	133	49	62	23	67	25	41	15	89	33	12	4
Slovakia	Slovakia	581	1996	535	92	351	60	315	54	161	28	147	25	75	13	160	28	38	7
Slovenia	Slovenia	937	1997	871	93	490	52	474	51	131	14	265	28	243	26	209	22	89	9
Spain	Granada	567	1996-97	523	92	312	55	360	63	63	11	191	34	109	19	148	26	56	10
	Navarra	588	1996-97	558	95	354	60	335	57	100	17	188	32	121	21	120	20	59	10
	Tarragona	637	1996-97	603	95	339	53	421	66	71	11	174	27	176	28	146	23	70	11
European registries[2]		**9,186**		**8,529**	**93**	**4,871**	**53**	**5,556**	**60**	**1,493**	**17**	**2,586**	**30**	**1,840**	**21**	**1,948**	**21**	**895**	**10**
Northern Europe		523		478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
Western Europe		2,497		2365	95	1,304	52	1,622	65	392	16	788	32	561	22	446	18	310	12
Southern Europe[3]		4,242		3930	93	2,320	55	2,570	61	545	14	1158	30	902	24	868	20	345	8
Eastern Europe		1,924		1756	91	1,000	52	1,070	56	495	26	466	24	274	14	574	30	115	6
US																			
	California	495	1997	485	98	242	49	356	72	89	18	137	28	168	34	60	12	41	8
	Colorado	548	1997	536	98	296	54	407	74	85	16	162	30	191	35	56	10	54	10
	Illinois	505	1997	497	98	239	47	384	76	71	14	144	29	224	44	36	7	30	6
	Louisiana	511	1997	502	98	263	51	374	73	115	23	146	29	146	29	90	18	14	3
	New York	492	1997	473	96	248	50	350	71	91	18	114	23	226	46	21	4	40	8
	Rhode Island	418	1997	413	99	195	47	302	72	64	15	149	36	160	38	29	7	16	4
	South Carolina	368	1997	358	97	187	51	265	72	68	18	89	24	150	41	26	7	35	10
US registries		**3,337**		**3,264**	**98**	**1,670**	**50**	**2,438**	**73**	**583**	**17**	**941**	**28**	**1265**	**38**	**318**	**10**	**230**	**7**
Total		**12,523**																	

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow , Kielce), Slovakia

[3] Data for Ragusa are not included in the percentages of Dukes' stage for Southern Europe

Table 2. Advanced stage, resection with curative intent, 30-days post-operative mortality and proportion of patients with information on stage: colorectal cancer, Europe and the US, 1996-98

		All cases			Resected with curative intent[2]							
			Advanced stage[1]				Deaths within 30 days		Staged			
									Colon		Rectum	
EUROPE	Registry	No.	No.	%	No.	%	No.	%	No.	%	No.	%
European registries[3]		**8,762**	**2,535**	**29**	**6,584**	**75**	**248**	**4**	**3,895**	**95**	**2,374**	**95**
Northern Europe		523	134	26	385	74	16	4	192	84	142	90
Western Europe[4]		2,497	609	24	2,092	84	24	6	1,299	93	646	92
Southern Europe[5]		3,818	1,131	30	2,912	76	152	5	1,748	97	1,081	97
Eastern Europe		1,924	661	34	1,195	62	56	5	656	98	505	97
US registries		**3,337**	**676**	**20**	**2,832**	**85**	**124**	**4**	**2,039**	**97**	**677**	**93**
	California	495	112	23	415	84	15	4	294	96	102	93
	Colorado	548	113	21	468	85	18	4	335	95	109	93
	Illinois	505	112	22	422	84	21	5	320	97	85	93
	Louisiana	511	105	21	431	84	26	6	315	100	111	97
	New York	492	80	16	411	84	22	5	287	95	102	94
	Rhode Island	418	78	19	369	88	9	2	268	99	93	94
	South Carolina	368	76	21	316	86	13	4	220	96	75	87
Total		**12,099**										

[1] All metastatic cases, plus unresected cases for which no stage data were available

[2] Curative intent: surgery not specified as palliative, or tumour entirely resected

[3] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow , Kielce), Slovakia

[4] Data for North East Netherlands (1,936) are not included in the proportion of deaths within 30 days of surgery for Western Europe beacuse the date of surgery was not available

[5] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 3. Chemotherapy in Dukes' B and C colon cancer and radiotherapy in Dukes' A-C rectal cancer

		Colon Dukes' B[1]			Colon Dukes' C[1]			Rectum Dukes' A-C[1]		
EUROPE	**Registry**	**No.**	**among whom, chemotherapy**		**No.**	**among whom, chemotherapy**		**No.**	**among whom, radiotherapy**	
			No.	**%**		**No.**	**%**		**No.**	**%**
European registries[2]		**1,748**	**343**	**20**	**1,130**	**528**	**47**	**1,850**	**678**	**37**
Northern Europe		110	11	10	50	21	42	118	34	29
Western Europe		591	23	4	346	133	38	411	183	45
Southern Europe[3]		736	209	28	529	265	50	797	331	42
Eastern Europe		259	80	31	154	81	53	480	124	26
US registries		**727**	**200**	**28**	**913**	**508**	**56**	**484**	**228**	**47**
	California	108	29	27	114	54	47	65	31	48
	Colorado	129	29	22	145	93	64	70	29	41
	Illinois	112	28	25	171	88	51	65	33	51
	Louisiana	105	22	21	106	59	56	76	33	43
	New York	86	24	28	157	81	52	84	44	52
	Rhode Island	119	37	31	107	69	64	66	30	45
	South Carolina	68	31	46	113	64	57	58	28	48

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 4. Odds of colorectal cancer patients being resected with curative intent, odds of patients with Dukes' B or C colon cancer being treated with chemotherapy and odds of Dukes' stage A-C rectal cancer being treated with radiotherapy: by region, age, cancer site or sex

	Resection for curative intent				Colon Dukes' B[1]				Colon Dukes' C[1]				Rectum stage A - C[1]			
	No.	OR	95% CI		No.	OR	95% CI		No.	OR	95% CI		No.	OR	95% CI	
Region[2]																
Northern Europe	385	0.88	0.71	1.09	110	0.29	0.15	0.56	50	0.88	0.46	1.69	118	0.58	0.38	0.89
Western Europe	2,092	1.62	1.43	1.85	591	0.10	0.06	0.16	346	0.64	0.48	0.87	411	1.22	0.95	1.56
Southern Europe[3]	2,912	1.00			736	1.00			529	1.00			797	1.00		
Eastern Europe	1,195	0.46	0.41	0.52	259	0.89	0.64	1.23	154	0.89	0.61	1.32	480	0.46	0.36	0.59
US	2,832	1.72	1.52	1.94	727	1.25	0.97	1.60	913	1.56	1.23	1.98	484	1.39	1.10	1.76
Age (years)																
15-64	3,194	1.00			674	1.00			684	1.00			890	1.00		
65-74	3,195	0.89	0.79	0.99	797	0.61	0.48	0.77	653	0.47	0.37	0.59	784	0.69	0.57	0.84
75-99	3,027	0.48	0.43	0.53	952	0.07	0.05	0.10	655	0.10	0.08	0.13	616	0.30	0.24	0.38
Site																
Colon	6,191	1.00														
Rectum	3,225	0.73	0.66	0.79												
Sex																
Male													1,324	1.00		
Female													966	0.92	0.77	1.10

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Figure 1. Five-year age standardized net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: country and region[1].

Figure 1 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 2. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region[1] and stage at diagnosis.

Figure 2 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 3-web appendix. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region[1] and sex.

Figure 3 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 4-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and age (a), region[1] and sex (b).

Figure 4 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 5-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and stage.

Figure 5 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

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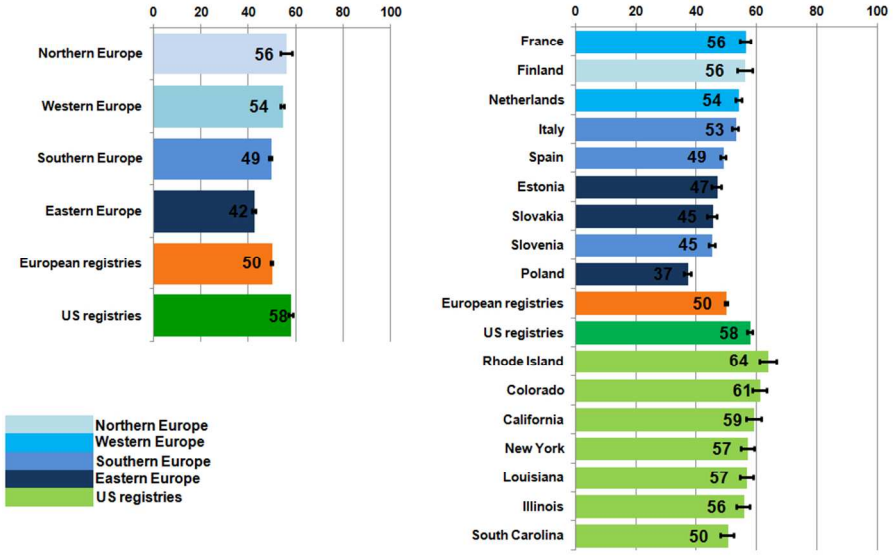

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Figure 2. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region and stage at diagnosis

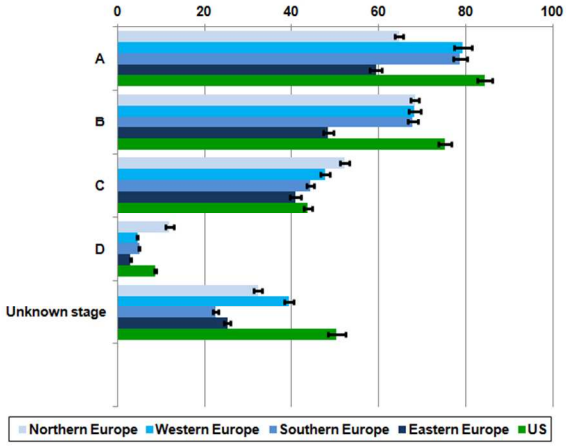

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Table 2-web appendix. Advanced stage, resection with curative intent, 30-days post-operative mortality, proportion of patients with information on stage and number of lymph nodes examined : colorectal cancer, Europe and the US, 1996-98

		All cases			Resected with curative intent[2]															
			Advanced stage[1]		Deaths within 30 days				Staged				No. of lymph nodes examined							
									Colon		Rectum		Zero		Up to 11		More than 12		Not available	
EUROPE	Registry	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Estonia	Estonia	560	188	34	314	56	9	3	192	98	118	99	0	0	149	47	5	2	160	51
Finland	Finland	523	134	26	385	74	16	4	192	84	142	90	49	13	187	49	20	5	129	34
France	Côte d'Or	561	141	25	430	77	24	6	302	100	127	99	62	14	255	59	113	26	0	0
Italy	Genova	589	153	26	503	85	37	7	313	95	164	95	1	0	219	44	171	34	112	22
	Varese	500	133	27	395	79	8	2	270	100	120	96	12	3	201	51	156	39	26	7
Netherland	North East NL	1,936	468	24	1,662	86	n.a	n.a	997	92	519	90	-	-	-	-	-	-	1,662	100
Poland	Cracow	512	187	37	303	59	9	3	146	94	141	96	6	2	210	69	25	8	62	20
	Kielce	271	91	34	211	78	19	9	103	98	97	92	0	0	36	17	3	1	172	82
Slovakia	Slovakia	581	195	34	367	63	19	5	215	100	149	99	7	2	155	42	1	0	204	56
Slovenia	Slovenia	937	283	30	652	70	44	7	322	97	315	98	26	4	243	37	327	50	56	9
Spain	Granada	567	186	33	442	78	30	7	273	96	151	96	4	1	238	54	135	31	65	15
	Navarra	588	172	29	452	77	15	3	259	98	186	98	0	0	201	44	133	29	118	26
	Tarragona	637	204	32	468	73	18	4	311	98	145	96	0	0	174	37	244	52	50	11
European registries[3]		**8,762**	**2,535**	***29***	**6,584**	**75**	**248**	**5**	**3,895**	**95**	**2,374**	**95**	**167**	**3**	**2,268**	**34**	**1,333**	**20**	**2,816**	**43**
Northern Europe		523	134	26	385	74	16	4	192	84	142	90	49	13	187	49	20	5	129	34
Western Europe[4]		2,497	609	24	2,092	84	24	6	1,299	93	646	92	62	3	255	12	113	5	1,662	79
Southern Europe[5]		3,818	1,131	30	2,912	76	152	5	1,748	97	1,081	97	43	1	1,276	44	1,166	40	427	15
Eastern Europe		1,924	661	34	1,195	62	56	5	656	98	505	97	13	1	550	46	34	3	598	50
US																				
	California	495	112	23	415	84	15	4	294	96	102	93	37	9	215	52	156	38	7	2
	Colorado	548	113	21	468	85	18	4	335	95	109	93	24	5	238	51	199	43	7	1
	Illinois	505	112	22	422	84	21	5	320	97	85	93	49	12	191	45	176	42	6	1
	Louisiana	511	105	21	431	84	26	6	315	100	111	97	62	14	226	52	142	33	1	0
	New York	492	80	16	411	84	22	5	287	95	102	94	34	8	216	53	150	36	11	3
	Rhode Island	418	78	19	369	88	9	2	268	99	93	94	37	10	202	55	130	35	0	0
	South Carolina	368	76	21	316	86	13	4	220	96	75	87	28	9	174	55	107	34	7	2
US registries		**3,337**	**676**	**20**	**2,832**	**85**	**124**	**4**	**2,039**	**97**	**677**	**93**	**271**	**10**	**1,462**	**52**	**1,060**	**37**	**39**	**1**
Total		**12,099**																		

[1] All metastatic cases, plus unresected cases for which no stage data were available

[2] Curative intent: surgery not specified as palliative, or tumour entirely resected

[3] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow , Kielce), Slovakia

[4] Data for North East Netherlands (1,936) are not included in the proportion of deaths within 30 days of surgery for Western Europe beacuse the date of surgery was not available

[5] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 3-web appendix. Chemotherapy in Dukes' B and C colon cancer and radiotherapy in Dukes' A-C rectal cancer

EUROPE	Registry	Colon Dukes' B[1] No.	among whom, No.	%	Colon Dukes' C[1] No.	among whom, No.	%	Rectum Dukes' A-C[1] No.	among whom, No.	%
Estonia	Estonia	97	8	8	44	19	43	140	36	26
Finland	Finland	110	11	10	50	21	42	118	34	29
France	Côte d'Or	170	22	13	65	33	51	61	27	44
Italy	Genova	122	45	37	93	43	46	109	45	41
	Ragusa	52	20	38	51	28	55	44	6	14
	Varese	106	45	42	63	38	60	85	24	28
Netherlands	North East NL	421	1	0	281	100	36	350	156	45
Poland	Cracow	50	23	46	45	24	53	138	15	11
	Kielce	30	1	3	22	7	32	85	11	13
Slovakia	Slovakia	82	48	59	43	31	72	117	62	53
Slovenia	Slovenia	143	15	10	126	56	44	260	100	38
Spain	Granada	128	47	37	67	36	54	82	37	45
	Navarra	111	39	35	68	37	54	136	82	60
	Tarragona	126	18	14	112	55	49	125	43	34
European registries[2]		**1,748**	**343**	**20**	**1,130**	**528**	**47**	**1,850**	**678**	**37**
Northern Europe		110	11	10	50	21	42	118	34	29
Western Europe		591	23	4	346	133	38	411	183	45
Southern Europe[3]		736	209	28	529	265	50	797	331	42
Eastern Europe		259	80	31	154	81	53	480	124	26
US registries		**727**	**200**	**28**	**913**	**508**	**56**	**484**	**228**	**47**
	California	108	29	27	114	54	47	65	31	48
	Colorado	129	29	22	145	93	64	70	29	41
	Illinois	112	28	25	171	88	51	65	33	51
	Louisiana	105	22	21	106	59	56	76	33	43
	New York	86	24	28	157	81	52	84	44	52
	Rhode Island	119	37	31	107	69	64	66	30	45
	South Carolina	68	31	46	113	64	57	58	28	48

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

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Figure 3-web appendix. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region and sex

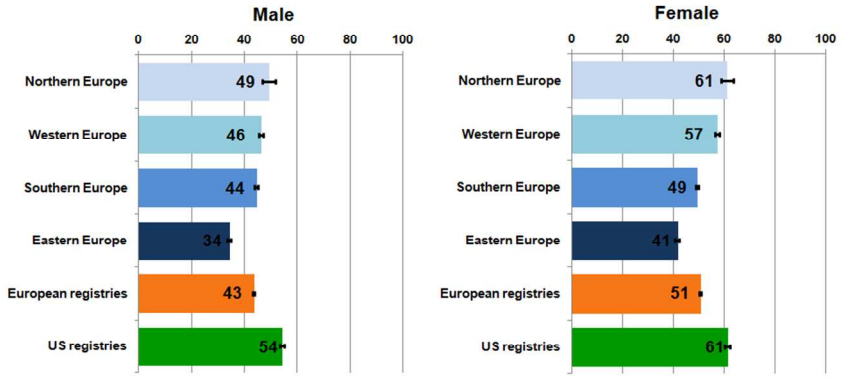

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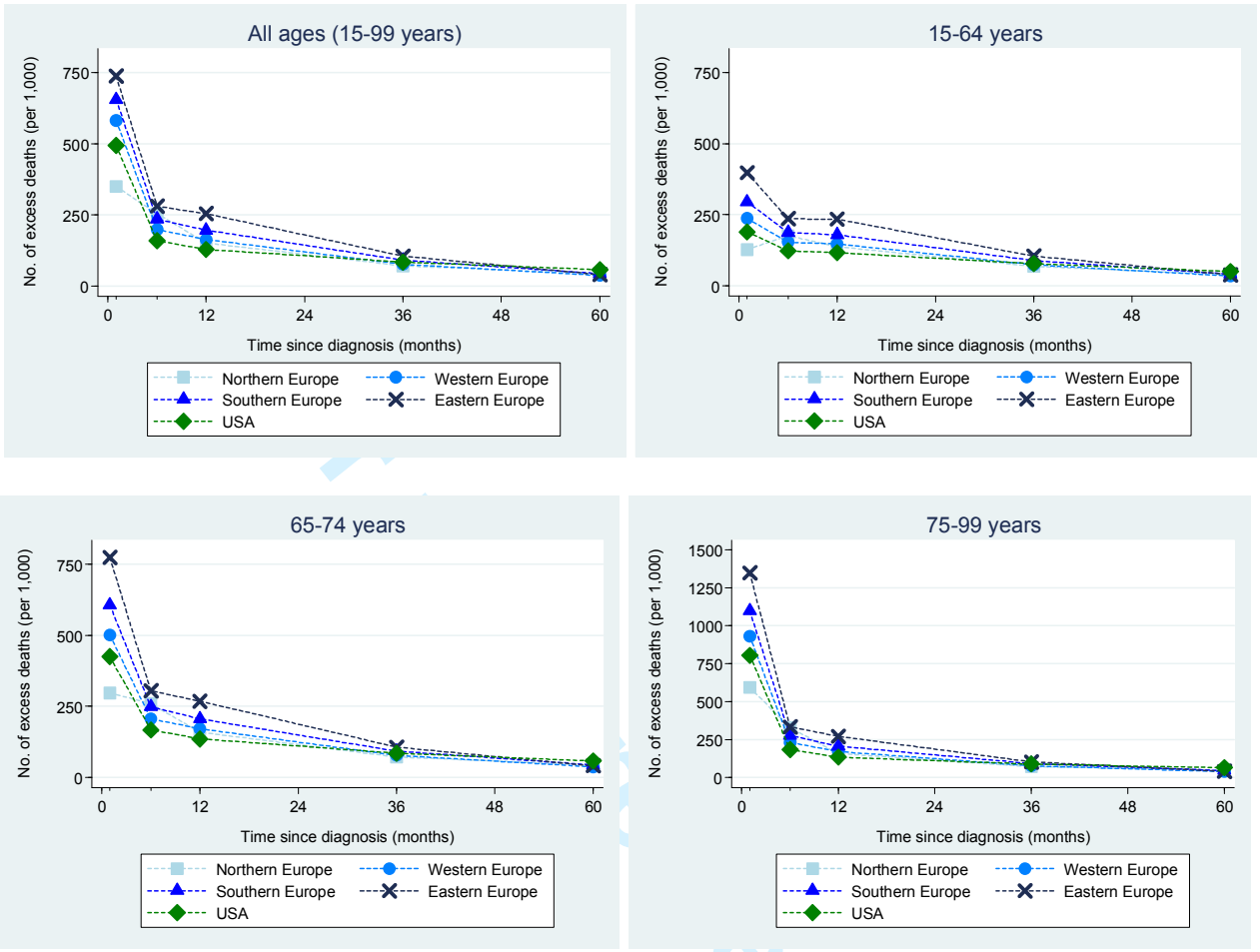
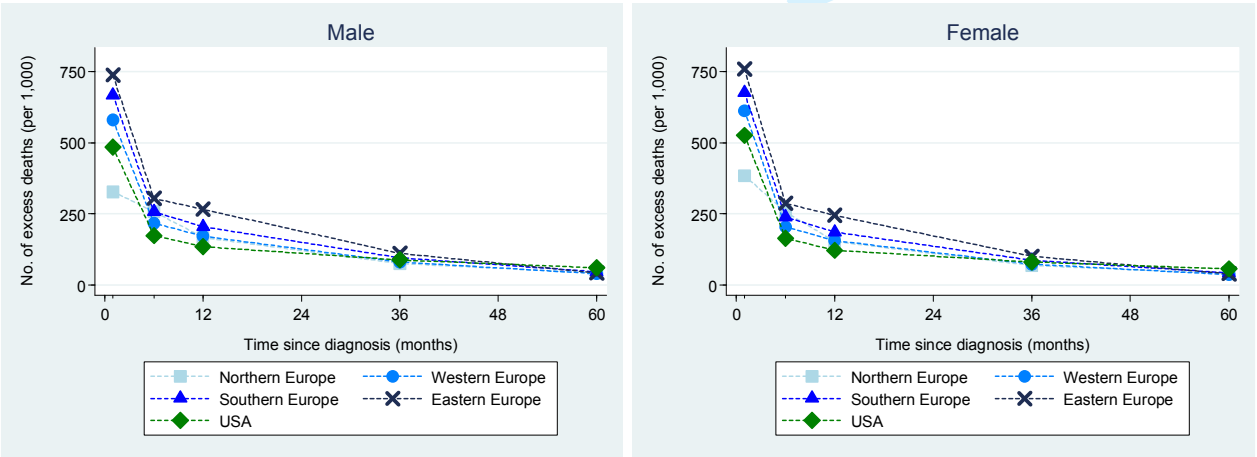
Figure 4-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and age (a), region[1] and sex (b).

(a)

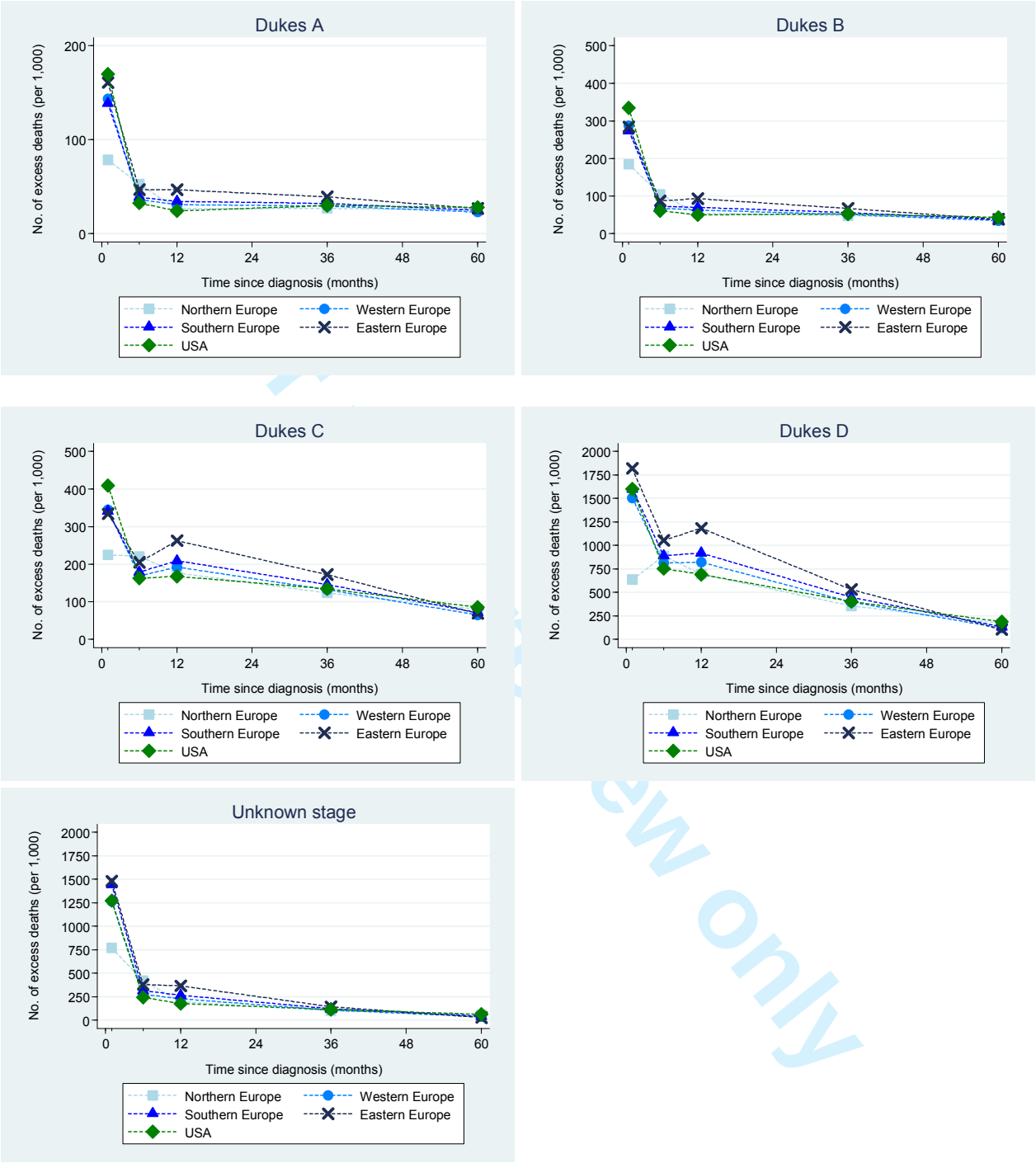


(b)



* Age was modelled as a continuous variable. The data points represent the mean excess hazards within each category of age (a) or sex (b).

Figure 5-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and stage.



* Age was modelled as a continuous variable. The data points represent the mean excess hazards within each category of stage.

Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study

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Keywords:	EPIDEMIOLOGY, Gastrointestinal tumours < ONCOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS

Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study

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Abstract

Background

Colorectal cancer survival in the US has consistently been reported as higher than in Europe. The differences have generally been attributed to stage at diagnosis.

Material and methods

21 population-based registries in 7 US states and 9 European countries provided data on Dukes' stage, diagnostic procedures, treatment and follow-up for random samples comprising 12,523 adults (15-99 years) diagnosed with colorectal cancer during 1996-98.

Logistic regression models were used to compare adherence to "standard care" in the US and Europe. Net survival and excess risk of death were estimated with flexible parametric models.

Results

The proportion of Dukes' A and B tumours was similar in the US and Europe, while Dukes' C was more frequent in the US (38% *vs.* 21%) and Dukes' D more frequent in Europe (22% *vs.* 10%).

Resection with curative intent was more frequent in the US (85% *vs.* 75%). Elderly patients (75-99 years) were 70-90% less likely to receive radiotherapy and chemotherapy.

Age-standardised five-year net survival was similar in the US (58%) and Northern and Western Europe (54-56%) and lowest in Eastern Europe (42%).

The mean excess hazard up to 5 years after diagnosis was highest in Eastern Europe, especially among elderly patients and those with Dukes' D tumours.

Conclusions

The wide differences in colorectal cancer survival between Europe and the US in the late 1990s are probably attributable both to earlier stage and more extensive use of surgery and adjuvant treatment.

Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.

Keywords: CONCORD, net survival, excess hazard, cancer registries.

Article Focus

- Why has population-based survival for colorectal cancer been so much higher in the US than in Europe?
- Can differences in stage, diagnostic procedures and/or treatment explain these wide disparities?
- Are evidence-based guidelines for staging and treatment being followed?

Key Messages

- Stage at diagnosis varied more widely between participating European countries than between participating US states.
- Evidence-based guidelines do not seem to have been closely followed. The proportion of patients who received surgery with adjuvant chemotherapy and/or radiotherapy was much lower in Europe than the US. Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.
- The wide US-Europe differences in five-year net survival from colorectal cancer in the late 1990s were probably attributable to earlier stage and more extensive use of surgery and adjuvant treatment in the US. Lower survival in Europe was mainly attributable to much lower survival in Eastern countries. This study underlines the need for population-based survival estimates derived from systematic clinical records of stage and treatment for all patients.

Strengths and Limitations

- To our knowledge, this is the first population-based high-resolution study with a direct US-Europe comparison of colorectal cancer survival, using clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods. Some of these clinical records of investigation, stage and treatment are not complete, systematic, or timely because they are not collected through routine cancer surveillance reporting for all cancer patients.
- Most diagnostic and therapeutic approaches used in the late 1990s remain in widespread use; mesorectal excision for rectal cancer is more recent. It remains relevant to understand the extent to which investigation and treatment are responsible for the persistent international differences in colorectal cancer survival.
- The modelling approach to estimate net survival is a methodological strength.
- Northern Europe was represented only by Finland.

Conflict of interest: none.

Ethical approval and data sharing agreement:

The study was approved by the US Centers for Disease Control (CDC, Atlanta GA) Institutional Review board #3551.

Informed consent of data subjects was not required; this was a records-based epidemiology study. No interview or contact with any patient was required, and no action was to be taken in respect of any individual whose data were included in the study, e.g. to alter their treatment. It is not practical to obtain informed consent from individual data subjects for their inclusion in studies of this type. It would involve attempting to contact many thousands of persons up to 15 years since they were first diagnosed. A substantial proportion would have died; many others would have moved, still others might not have been informed of the diagnosis. Contact would need to be made via the treating physician, whose identity was unknown. Consent could only have been sought by the cancer registries, since they alone know who the patients actually are, but none of the registries has the resources required. It would involve disproportionate effort, it would be substantially incomplete and it would take years to achieve, and the results would be irretrievably biased, invalidating the study.

Introduction

Five-year relative survival from cancers of the colon and rectum has been reported as 12-14% higher in the US than in Europe[1]. Survival for patients diagnosed during 1985–89 was higher in each of the 9 US states and metropolitan areas covered at that time by the Surveillance, Epidemiology and End Results (SEER) programme than in any of the 22 European countries participating in the EUROCARE-2 study[2].

The differences in 3-year colorectal cancer survival for patients diagnosed during 1990-91 between 10 territories in 5 European countries and the 9 SEER areas were mainly attributable to stage at diagnosis[3].

The first world-wide analysis of cancer survival (CONCORD[1]) provided a systematic comparison of survival for adults (15-99 years) diagnosed with cancer of the breast, colon, rectum or prostate in 31 countries during 1990-94 and followed up to 1999. International differences in age-standardised survival were very wide, even after adjustment for differences in mortality from other causes of death. Colorectal cancer survival was higher in the US and Canada than in many other countries. Differences between the US and most European regions were smaller than for patients diagnosed during 1985-89[2]. The largest differences were between the US and Eastern Europe.

The CONCORD protocol incorporated studies designed to explain the international variations in survival. These “high-resolution” studies involve systematic collection of detailed clinical and pathological data that are not routinely abstracted by population-based cancer registries from the original medical records of large random samples of patients. The high-resolution study reported here provides a trans-Atlantic comparison of stage, treatment and survival for patients with colorectal cancer.

The aims were (1) to compare the distributions of stage for colorectal cancers in Europe and the US; (2) to determine whether the transatlantic differences in survival persist and, if so, to assess the extent to which they are attributable to differences in stage at diagnosis; and (3) to compare adherence to “standard care”[4] for colorectal cancer in relation to age, stage and cancer site between the US and Europe.

Material and methods

Data on stage, diagnostic procedures, treatment and follow-up were collected for a representative sample of about 13,000 patients aged 15-99 years diagnosed with colorectal cancer (ICD-9[5] codes 1530-1539, 1540-1549) in the US and Europe during 1996-98. A single protocol was used, derived from the EUROCARE high-resolution protocols[6].

The European data were provided by 14 population-based cancer registries in 9 countries, 4 with national coverage (denoted below with an asterisk*). For some analyses, the data were grouped into the four European regions defined by the United Nations (UN, http://unstats.un.org/unsd/methods/m49/m49regin.htm) - Northern Europe: Finland*; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia*, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia*, Poland (Cracow, Kielce), Slovakia*. Estonia is classified by the UN as being in Northern Europe, but cancer survival has resembled that in Eastern European countries[7], and Estonia was included here with Eastern Europe. US data were provided by 7 state-wide registries (California, Colorado, Illinois, Louisiana, New York, Rhode Island, South Carolina) from the National Program of Cancer Registries (NPCR), based at the Centers for Disease Control and Prevention.

For this study, cancer registries in the EUROCARE-3 high-resolution study[8] updated follow-up to at least five years after diagnosis for all patients. North East Netherlands was not included in EUROCARE-3, but the registry routinely collects high-resolution data, and could provide such data on virtually all patients with colorectal cancer.

Most registries provided a random sample of at least 500 patients diagnosed during 1996-98 (1997 in the US). The Finnish cases were a population-based sample of patients diagnosed in the Tampere hospital region, which is considered representative of Finland.

Of 12,941 anonymised records for patients with a malignant neoplasm of the colon or rectum, 418 were excluded: *in situ* (396, 3.1%: collected in the US, but not in Europe) unknown sex (22, 0.2%); benign or uncertain behaviour (1), or age less than 15 or 100 years or over (19, 1.5%). In all, 12,523 patients with a primary, invasive, malignant colorectal neoplasm were included in the comparisons of stage and treatment. For survival analyses, a further 118 patients were excluded: cancer registered only from a death certificate (72; 0.6%); unknown vital status (3; 0.02%); date of last known vital status either unknown or earlier than the date of diagnosis (43; 0.3%); leaving 12,405 patients (99.1% of the 12,523 eligible).

Information on stage, diagnostic examinations and treatment was abstracted from the clinical record, pathology reports, hospital discharge records and other sources, as necessary.

Disease stage was defined according to the TNM (Tumour, Nodes, Metastasis) manual[9] and/or Dukes' stage. Many registries collected both TNM and Dukes' stage, but only Dukes' stage was available for Kielce (Poland) and Finland, so we used the Dukes' classification in order to include these populations in the stage-specific

analyses. Dukes' stage information was more complete than TNM stage, but TNM was used to reconstruct Dukes' stage where necessary. For descriptive purposes, we defined patients with 'advanced stage' as those with metastatic disease or those who had been operated on, but for whom no pathology report was available. This broad category was not used in stage-specific survival analyses, which are based on Dukes' stage, where available.

Age was categorised as 15-64, 65-74 and 75-99 years.

We defined resection for curative intent as resection of all macroscopically evident malignant tissue, with no macroscopic evidence of surgical margin involvement, and excluding polypectomy and trans-anal excision. Radiotherapy and chemotherapy were dichotomised as administered *vs.* not administered or unknown.

Statistical analysis

We analysed the distribution of stage and the number of lymph nodes examined pathologically[9]. We report the proportion of patients resected with curative intent and the distributions of stage-specific treatment for colon or rectal cancer. Data sets were excluded if data on stage and/or treatment were missing for 25% or more of patients: Ragusa was excluded from stage-specific analyses, including those on treatment related to stage at diagnosis.

Net survival up to five years after diagnosis was estimated by geographical area (UN region of Europe, country, registry or US state), age and stage, using flexible parametric excess hazard models[10]. Net survival is the survival of cancer patients in the hypothetical situation where the cancer may be assumed to be the only possible cause of death; it may be interpreted as cancer survival after controlling for competing causes of death. Net survival was estimated with a modelling approach[10-12] in which the total hazard of death is considered as the sum of the cancer-related mortality hazard (excess hazard), and the hazard of death from other causes (background hazard). The background hazard is derived from life tables of all-cause mortality by sex, single year of age and calendar year in the general population of the geographical area from which the cancer patients are drawn. We constructed period life tables for 1994-2004 with the approaches proposed by Baili et al[13].

Age was included as a continuous variable in all models, in order to avoid the bias in the estimation of net survival that would otherwise arise from differential loss of the oldest patients to competing hazards of death (informative censoring). Both non-linear and time-dependent (interaction with time since diagnosis) effects of age were initially modelled with cubic splines. The proportionality of the effect of tumour stage on the excess hazard was also assessed. Simpler models, with linear and/or proportional effects, were successively tested and selected using the Akaike Information Criterion for goodness of fit[14]. We also estimated the instantaneous excess risk (hazard) of death due to colorectal cancer, after subtracting the hazard from all other causes of death[10-12;15;16]. We present the mean excess hazard per 1,000 person-years at risk at selected times since diagnosis (1 month, 6 months and 1, 3 and 5 years), both by age group and by stage at diagnosis, after adjustment for age.

Overall (all-ages) net survival estimates were age-standardised with the International Cancer Survival Standard (ICSS) weight[17].

We used a logistic regression model to estimate the odds of colorectal cancer patients in each area being resected with curative intent, the odds of patients with colon cancer at Dukes' stage B or C receiving chemotherapy, and the odds of rectal cancer patients with Dukes' stage A-C being treated with radiotherapy, after adjustment for age and/or tumour site and/or sex.

Survival analyses were performed with *stpm2*[15] in Stata version 12 (StataCorp LP, College Station, TX).

Results

We included 12,523 patients with an invasive, primary colorectal cancer: 9,186 patients in 14 registries in 9 European countries and 3,337 patients in 7 US states (Table 1). Microscopic verification was available for 96-98% of the patients in each of the US states and 93% in Europe, ranging from 85% in Ragusa (Italy) to 99% in Kielce (Poland). The proportion of colorectal cancer patients who were male was similar in Europe (53%) and the US (50%), but colon cancer was more frequent in the US (73%) than in Europe (60%). Data were available on stage at diagnosis for 90-93% of patients on both sides of the Atlantic, ranging from 76% (Finland) to 95% or more in 3 of the 14 European registries and from 90% (Colorado and South Carolina) to 97% (Louisiana) in the US.

Early-stage (Dukes' A or B) colorectal cancers were equally common in the US (45%) and Europe (47%), but the stage distributions varied widely, both between US states and between European regions. Tumours in Dukes' stage A were of similar frequency in Europe (17%, range 11-28%) and in the US (17%; 14-23%), and the proportion of Dukes' B tumours were also very comparable (Europe 30%; 25-37%; US 28%; 24-36%). By contrast, Dukes' C tumours were twice as common in the US (38%; 29-46%) as in Europe (21%; 24-30%), while Dukes' D tumours were twice as common in Europe (21%; 11-33%) as in the US (10%; 7-18%). The proportion of tumours with unspecified stage was slightly higher in Europe (10%; 4-24%) than in the US (7%; 3-10%). Exclusion of Finland, with 24% of tumours of unknown stage, did not substantially alter the overall stage distributions in Europe (data not shown).

Patients diagnosed at an advanced stage (i.e. metastatic cases plus unresected cases for which no data on stage were available) were more common in the four European regions (29%; 24-34%) than in the US (20%; 16-23%) (Table 2). In Europe, advanced stage was more common in Southern (30%) and Eastern Europe (34%). The highest proportion of patients with advanced stage in the US (23%, California), was similar to the lowest regional proportion in Europe (24%, Western Europe).

Resection for curative intent was more frequent in the US (85%) than in Europe (75%). The proportion resected with curative intent was remarkably similar in all 7 US states (84-88%). Only Western Europe (84%) showed a proportion as high as that in the US.

Thirty-day post-operative mortality was 5% or less in the US and Europe. Among patients resected with curative intent, the proportion with known stage was around 95% in the US and Europe, with the lowest proportions in Northern Europe (84-90%) (Table 2). In many European registries, data on the number of lymph nodes examined after surgery were not available for most patients (web-appendix Table 2).

Adjuvant chemotherapy and radiotherapy were both administered more frequently in the US than in Europe (Table 3). Among Dukes' B colon cancer patients, 28% received chemotherapy in the US (21-46%) *vs.* 20% in Europe (4-31%). Among Dukes' C colon cancer patients, 56% received chemotherapy in the US (47-64%) vs. 47% in Europe (38-53%). Among Dukes' A-C rectal cancer patients, 47% received radiotherapy in the US (41-52%) vs. 37% in Europe (26-45%).

Relative to Southern Europe (2,912 patients, reference category), the odds of receiving resection for curative intent (*vs.* any other surgical procedure), after adjustment for age and tumour site, were much lower in Eastern Europe (OR=0.46; 0.41-0.52), somewhat lower in Northern Europe (OR=0.88; 95% CI 0.71-1.09); and much higher in Western Europe (OR=1.62; 1.43-1.85) and in the US (OR=1.72; 1.52-1.94) (Table 4).

Patients aged less than 75 years were only half as likely to be resected with curative intent as those aged 15-64 years (OR 0.48, 95% confidence interval [CI] 0.43-0.53), after adjustment for region and tumour site.

Patients with colon cancer (reference category) were resected with curative intent more often than patients with rectal cancer (OR 0.73; 0.66-0.79).

Patients with Dukes' B colon cancer received chemotherapy much less often in Western Europe (OR 0.10; 0.06-0.16) and Northern Europe (OR 0.29; 0.15-0.56) than in Southern Europe. For patients with Dukes' C colon cancer, chemotherapy was used less in Western Europe (OR 0.64; 0.48-0.87) and more often in the US (OR 1.56; 1.23-1.98) than in Southern Europe.

Compared to Southern Europe, radiotherapy was administered to patients with rectal cancer in Dukes' stage A-C more often in the US (OR 1.39; 1.10-1.76), less often in Northern Europe (OR 0.58; 0.38-0.89) or Eastern Europe (OR 0.46; 0.36-0.59).

Older patients were only 10% as likely to be treated with radiotherapy and chemotherapy.

Overall, age-standardised net survival at five years was 50% in Europe and 58% in the US (Figure 1). Survival was lower than the US in all European areas, and only in Northern Europe was the figure (56%) close to that in the US. Survival was lower in Western (54%) and in Southern Europe (49%) and lowest in Eastern Europe (42%). Survival varied widely between European countries (from 56% in France and Finland to 37% in Poland), but also between US states (from 64% in Rhode Island to 56% in Illinois and 50% in South Carolina).

Five-year age-standardised net survival was higher in the US for Dukes' stage A (84%) and B (75%) tumours, but higher in Northern Europe for Dukes' C (52%) and D (12%) tumours (Figure 2). The geographic range in survival was much wider for locally advanced disease, from 36% in Eastern Europe to 77% in Northern Europe, and 49% in the US. As with overall survival, stage-specific five-year survival was similar in Northern, Western and Southern Europe and the US. In Eastern Europe, survival for node-positive, locally advanced and metastatic tumours was lower than in other European regions and in the US.

Survival was 5-12% higher in women than in men in all areas, especially in Northern and Western Europe (11-12%) (web-appendix Figure 3).

The mean excess hazard of death at 1 month, 6 months and at 1, 3 and 5 years after diagnosis was higher in Eastern Europe than in all other regions, both for all ages combined and in each of 3 age categories (web-appendix Figure 4). The difference was most marked for elderly patients (75-99 years). No striking differences were found between Northern, Western and Southern Europe and the US. The high

excess hazard of death in Eastern Europe was mainly confined to patients with Dukes' D tumours (web-appendix Figure 5).

Discussion

Transatlantic differences in population-based colorectal cancer survival have raised questions about early diagnosis and the adequacy of investigation and treatment that cannot be addressed with data from clinical trials, which include only selected patient groups.

Patterns-of-care studies and survival studies have been conducted separately in Europe[3;6;8] and the US[18;19]. To our knowledge, this is the first population-based high-resolution study that allows direct comparison of colorectal cancer survival between Europe and the US with clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods.

The participating cancer registries are population-based registries that register all persons diagnosed in the territory they cover. This study included large, randomly selected subsets of all persons diagnosed with colorectal cancer during 1996-98, in each territory. These samples are not intended to be "representative" of all colorectal cancer patients in Europe or the US, but they are representative of all colorectal cancer patients diagnosed during 1996-98 in the territory of each registry, and the findings are generalisable to the populations from which they are drawn.

Most of the diagnostic and therapeutic approaches used in the late 1990s remain in widespread use. Understanding their role in international differences in survival remains relevant. Mesorectal excision for rectal cancer is the main exception: it has improved survival from rectal cancer[20;21], but widespread use is more recent. Mesorectal excision was not used in Estonia before 1997, which may partly explain the low survival from rectal cancer[22].

The transatlantic 12% difference in 3-year survival in colorectal cancer survival for patients diagnosed 1990-91[3] was mostly attributed to differences in stage at diagnosis In our study of patients diagnosed in the late 1990s, overall five-year net survival was still higher in the 7 US states (58%) than in the 14 European regions (42-56%). The widest differences with the US were seen in Southern (49%) and Eastern Europe (42%).

The two studies differed in design, however: data from the SEER public-use data set in the US[23] were simply adapted to the EUROCARE-2 high-resolution protocol as far as possible. By contrast, data for this study were collected directly from clinical records on both sides of the Atlantic, with a standard protocol. US coverage changed from the 5 metropolitan areas and 4 states covered by the SEER program to 7 of the state-wide NPCR registries. In the earlier study, differences in background mortality in the US were controlled with a single national life table for 1990, weighted for the proportion of Blacks, Whites and other races. Here, we were able to use state-specific life tables for each of the calendar years 1996-2004.

The tighter control for background mortality and the modelling approach used to estimate net survival are methodological strengths of this study, but these changes do not explain why the transatlantic differences we observe in five-year survival are

smaller than the differences in three-year survival for patients diagnosed in the early 1990s[3].

Survival varied widely among European countries, but also between the 7 US states. Survival in Slovenia was lower than in other Southern European countries, and more similar to that in Eastern Europe. In the US, survival was lowest in South Carolina, where Blacks represent approximately 30% of the population (http://www.ipspr.sc.edu/publication/Older%20SC.pdf).

Apart from patients with Dukes' B cancers, where survival was similar in Northern, Western and Southern Europe, stage-specific net survival was rather variable. Survival was highest in the US for Dukes' stage A and B, and in Northern Europe (Finland) for Dukes' stage C and D. This could be due to some misclassification of stage in Finland, where stage data were not available for 24% of cases.

The mean excess hazard of death up to five years after diagnosis was similar in Europe and the US for patients with tumours in Dukes' stage A or B. The hazard was somewhat higher in Eastern Europe for Dukes' stage C, and much higher for Dukes' D disease, especially in the first three years after diagnosis. The very high hazard of death for patients with late-stage disease in Eastern Europe suggests that fewer effective treatment options were available for these patients, although higher levels of co-morbidity may also have restricted the choice.

It was not possible to evaluate the impact of the number of examined lymph nodes on the stage-adjusted excess hazard of death, because information on nodal status was so often unavailable (see web-appendix). It is therefore impossible to assess whether stage migration affects the comparison of stage-specific survival between European regions and the US in the late 1990s, as reported for patients diagnosed in 1990[3].

We did not have information on whether or not patients in this study had undergone faecal occult blood testing or sigmoidoscopy before diagnosis. Opportunistic testing with these procedures was common in the US in the late 1990s. Almost 40% of respondents to the Behavioural Risk Factor Surveillance System (www.cdc.gov/mmwr/preview/mmwrhtml/00056494.htm) survey in 1997 reported having had a faecal occult blood test at some time in the past, and 42% reported a previous sigmoidoscopy or proctoscopy. Removal of premalignant polyps or *in situ* neoplasms may thus have been more frequent than in Europe. This would be expected to reduce incidence, shift the spectrum of malignancy to the right, and reduce survival in the US. In fact, incidence in the US is higher, the stage distribution less advanced, and survival higher than in Europe.

Adjuvant chemotherapy for colon cancer and adjuvant radiotherapy for rectal cancer were both used more widely in the US than in Europe. Despite the evidence available in the late 1990s on the lack of efficacy of adjuvant chemotherapy for Dukes' B colon cancer, 30% of colon cancer patients in the US received it, and 20% overall in Europe. In Finland and Western Europe, however, adjuvant chemotherapy was rare, in line with the contemporary recommendations, while in Southern and Eastern Europe, adjuvant chemotherapy was used as frequently as in the US.

In contrast, there were striking differences in the use of adjuvant chemotherapy for stage III colon cancer in the late 1990s, particularly within Europe. Given the wide consensus on its effectiveness since 1990, we did not expect to find that such a strong recommendation had been so poorly followed. Co-morbidity and greater toxicity are not valid reasons for under-use of adjuvant chemotherapy in the elderly: toxicity is no greater[24;25] and quality of life no worse[26].

Elderly patients were 90% less likely to receive adjuvant chemotherapy than younger patients. Clinical attitudes appear to differ between the US and Europe, where the proportion of patients receiving adjuvant chemotherapy is much lower. This suggests that a higher proportion of older patients with Dukes' C colon cancer who are fit enough to undergo surgery should receive adjuvant chemotherapy, particularly in Europe.

Radiotherapy is known to be an effective complement to surgery for rectal cancer, in particular to reduce the risk of local recurrence; pre-operative is preferable to post-operative radiotherapy[27], and it is recommended in both Europe and the US[28-31]. We were unable to distinguish between the impact of pre- and post-operative radiotherapy, because this information was not systematically available, but fewer patients received radiotherapy in Europe than in the US, and practice in Europe was strikingly heterogeneous, even within a given country. Age was a strong predictor of the use of radiotherapy. Some older patients are unsuitable for radiotherapy because of co-morbidity, but their 70% lower odds of receiving it cannot be explained by co-morbidity alone; radiotherapy has not yet been deployed to its full potential for older patients with rectal cancer. It is not clear why the evidence on the benefits of radiotherapy was so poorly followed in many regions.

Surgical resection offers the only approach to a definitive cure for colorectal cancer. The proportion of patients resected with curative intent was very similar in the 7 US States (84-88%), but it varied widely between the 9 European countries (from 56% to 86%), and was particularly low in Eastern Europe (mean 62%). A more aggressive approach to surgical treatment for elderly colorectal cancer patients in Europe could improve this situation, although European patients were more often diagnosed at an advanced stage or with unresectable disease. Performance status and co-morbidity can influence whether a patient is considered fit for resection, but data on these factors were not available. The quality of life in Canadian patients aged over 80 who underwent surgery for colorectal cancer was generally comparable to that of younger patients[32].

In this large, population-based study in Europe, however, age alone seems often to have been a limiting factor in the treatment of colorectal cancer. Elderly patients were generally treated less often with surgery, chemotherapy or radiotherapy, despite the evidence that they could benefit from these treatments. Treatment decisions should be taken in the context of multidisciplinary meetings, including a comprehensive geriatric assessment: age alone should not exclude a patient from receiving surgery and/or adjuvant treatment.

Differences in colorectal cancer survival between Europe and the US in the late 1990s were still wide and may be attributable both to earlier stage at diagnosis, higher levels of surgery and more extensive use of adjuvant treatment in the US.

Evidence-based guidelines do not seem to have been followed as closely as they should be: chemotherapy was used too often for Dukes' B disease and not often enough for Dukes' C disease, especially among elderly patients.

The need for population-based survival estimates derived directly from the clinical records on stage at diagnosis and treatment is recognised by clinicians and epidemiologists. A recent comparison of stage-specific cancer survival with population-based data[33], was complicated by inconsistent coding of stage[34]; several registries had to be excluded because fewer than half the tumour records contained data on stage. In this high-resolution study, stage data were remarkably complete (76-94% in Europe, 93% in the US), because they were collected directly from clinical records. Ideally, the medical records of cancer patients would systematically include data on investigations and stage at diagnosis; cancer registries would obtain those data for all patients, and stage would be coded consistently. Until then, high-resolution studies would appear to offer the most reliable approach to obtain data on stage and treatment, and to assess survival by stage at diagnosis.

If good evidence is required on whether all patients receive guideline-compliant investigation and treatment, and whether this makes a difference to survival, then cancer registries will need to be able to obtain timely and high-quality data on the investigations, the stage and the treatment for all cancer patients.

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Extra results are available in the web-appendix. Raw data are not available.

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Table 1. Calendar period of diagnosis, morphological verification, and data on sex, cancer site and stage. Patients with invasive primary colorectal cancer, Europe and US

										Dukes' stage[1] at diagnosis									
			Period of diagnosis	Morphologically verified		Males		Colon		A		B		C		D		Not available	
EUROPE	**Registry**	**No.**		**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Estonia	Estonia	560	1997	491	88	250	45	337	60	144	26	151	27	76	14	167	30	22	4
Finland	Finland	523	1996-98	478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
France	Côte d'Or	561	1996-97	544	97	302	54	382	68	112	20	209	37	98	17	114	20	28	5
Italy	Genova	589	1996	529	90	326	55	379	64	71	12	192	33	148	25	131	22	47	8
	Ragusa*	424	1996-98	361	85	233	55	269	63										
	Varese	500	1997	485	97	266	53	332	66	109	22	148	30	105	21	114	23	24	5
Netherlands	North East NL	1,936	1997	1821	94	1002	52	1240	64	280	14	579	30	463	24	332	17	282	15
Poland	Cracow	512	1997-98	463	90	252	49	285	56	128	25	101	20	82	16	158	31	43	8
	Kielce	271	1996	267	99	147	54	133	49	62	23	67	25	41	15	89	33	12	4
Slovakia	Slovakia	581	1996	535	92	351	60	315	54	161	28	147	25	75	13	160	28	38	7
Slovenia	Slovenia	937	1997	871	93	490	52	474	51	131	14	265	28	243	26	209	22	89	9
Spain	Granada	567	1996-97	523	92	312	55	360	63	63	11	191	34	109	19	148	26	56	10
	Navarra	588	1996-97	558	95	354	60	335	57	100	17	188	32	121	21	120	20	59	10
	Tarragona	637	1996-97	603	95	339	53	421	66	71	11	174	27	176	28	146	23	70	11
European registries[2]		**9,186**		**8,529**	**93**	**4,871**	**53**	**5,556**	**60**	**1,493**	**17**	**2,586**	**30**	**1,840**	**21**	**1,948**	**21**	**895**	**10**
Northern Europe		523		478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
Western Europe		2,497		2365	95	1,304	52	1,622	65	392	16	788	32	561	22	446	18	310	12
Southern Europe[3]		4,242		3930	93	2,320	55	2,570	61	545	14	1158	30	902	24	868	20	345	8
Eastern Europe		1,924		1756	91	1,000	52	1,070	56	495	26	466	24	274	14	574	30	115	6
US																			
	California	495	1997	485	98	242	49	356	72	89	18	137	28	168	34	60	12	41	8
	Colorado	548	1997	536	98	296	54	407	74	85	16	162	30	191	35	56	10	54	10
	Illinois	505	1997	497	98	239	47	384	76	71	14	144	29	224	44	36	7	30	6
	Louisiana	511	1997	502	98	263	51	374	73	115	23	146	29	146	29	90	18	14	3
	New York	492	1997	473	96	248	50	350	71	91	18	114	23	226	46	21	4	40	8
	Rhode Island	418	1997	413	99	195	47	302	72	64	15	149	36	160	38	29	7	16	4
	South Carolina	368	1997	358	97	187	51	265	72	68	18	89	24	150	41	26	7	35	10
US registries		**3,337**		**3,264**	**98**	**1,670**	**50**	**2,438**	**73**	**583**	**17**	**941**	**28**	**1265**	**38**	**318**	**10**	**230**	**7**
Total		**12,523**																	

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow , Kielce), Slovakia

[3] Data for Ragusa are not included in the percentages of Dukes' stage for Southern Europe

Table 2. Advanced stage, resection with curative intent, 30-days post-operative mortality and proportion of patients with information on stage: colorectal cancer, Europe and the US, 1996-98

		All cases			Resected with curative intent[2]							
			Advanced stage[1]		Deaths within 30 days				Staged			
									Colon		Rectum	
EUROPE	Registry	No.	No.	%	No.	%	No.	%	No.	%	No.	%
European registries[3]		**8,762**	**2,535**	**29**	**6,584**	**75**	**248**	**4**	**3,895**	**95**	**2,374**	**95**
Northern Europe		523	134	26	385	74	16	4	192	84	142	90
Western Europe[4]		2,497	609	24	2,092	84	24	6	1,299	93	646	92
Southern Europe[5]		3,818	1,131	30	2,912	76	152	5	1,748	97	1,081	97
Eastern Europe		1,924	661	34	1,195	62	56	5	656	98	505	97
US registries		**3,337**	**676**	**20**	**2,832**	**85**	**124**	**4**	**2,039**	**97**	**677**	**93**
	California	495	112	23	415	84	15	4	294	96	102	93
	Colorado	548	113	21	468	85	18	4	335	95	109	93
	Illinois	505	112	22	422	84	21	5	320	97	85	93
	Louisiana	511	105	21	431	84	26	6	315	100	111	97
	New York	492	80	16	411	84	22	5	287	95	102	94
	Rhode Island	418	78	19	369	88	9	2	268	99	93	94
	South Carolina	368	76	21	316	86	13	4	220	96	75	87
Total		**12,099**										

[1] All metastatic cases, plus unresected cases for which no stage data were available
[2] Curative intent: surgery not specified as palliative, or tumour entirely resected
[3] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia
[4] Data for North East Netherlands (1,936) are not included in the proportion of deaths within 30 days of surgery for Western Europe beacuse the date of surgery was not available
[5] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 3. Chemotherapy in Dukes' B and C colon cancer and radiotherapy in Dukes' A-C rectal cancer

		Colon Dukes' B[1]			Colon Dukes' C[1]			Rectum Dukes' A-C[1]		
EUROPE	**Registry**	**No.**	**among whom, chemotherapy**		**No.**	**among whom, chemotherapy**		**No.**	**among whom, radiotherapy**	
			No.	**%**		**No.**	**%**		**No.**	**%**
European registries[2]		**1,748**	**343**	**20**	**1,130**	**528**	**47**	**1,850**	**678**	**37**
Northern Europe		110	11	10	50	21	42	118	34	29
Western Europe		591	23	4	346	133	38	411	183	45
Southern Europe[3]		736	209	28	529	265	50	797	331	42
Eastern Europe		259	80	31	154	81	53	480	124	26
US registries		**727**	**200**	**28**	**913**	**508**	**56**	**484**	**228**	**47**
	California	108	29	27	114	54	47	65	31	48
	Colorado	129	29	22	145	93	64	70	29	41
	Illinois	112	28	25	171	88	51	65	33	51
	Louisiana	105	22	21	106	59	56	76	33	43
	New York	86	24	28	157	81	52	84	44	52
	Rhode Island	119	37	31	107	69	64	66	30	45
	South Carolina	68	31	46	113	64	57	58	28	48

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 4. Odds of colorectal cancer patients being resected with curative intent, odds of patients with Dukes' B or C colon cancer being treated with chemotherapy and odds of Dukes' stage A-C rectal cancer being treated with radiotherapy: by region, age, cancer site or sex

	Resection for curative intent				Colon Dukes' B[1]				Colon Dukes' C[1]				Rectum stage A - C[1]			
	No.	OR	95% CI		No.	OR	95% CI		No.	OR	95% CI		No.	OR	95% CI	
Region[2]																
Northern Europe	385	0.88	0.71	1.09	110	0.29	0.15	0.56	50	0.88	0.46	1.69	118	0.58	0.38	0.89
Western Europe	2,092	1.62	1.43	1.85	591	0.10	0.06	0.16	346	0.64	0.48	0.87	411	1.22	0.95	1.56
Southern Europe[3]	2,912	1.00			736	1.00			529	1.00			797	1.00		
Eastern Europe	1,195	0.46	0.41	0.52	259	0.89	0.64	1.23	154	0.89	0.61	1.32	480	0.46	0.36	0.59
US	2,832	1.72	1.52	1.94	727	1.25	0.97	1.60	913	1.56	1.23	1.98	484	1.39	1.10	1.76
Age (years)																
15-64	3,194	1.00			674	1.00			684	1.00			890	1.00		
65-74	3,195	0.89	0.79	0.99	797	0.61	0.48	0.77	653	0.47	0.37	0.59	784	0.69	0.57	0.84
75-99	3,027	0.48	0.43	0.53	952	0.07	0.05	0.10	655	0.10	0.08	0.13	616	0.30	0.24	0.38
Site																
Colon	6,191	1.00														
Rectum	3,225	0.73	0.66	0.79												
Sex																
Male													1,324	1.00		
Female													966	0.92	0.77	1.10

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Figure 1. Five-year age standardized net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: country and region[1].

Figure 1 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 2. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region[1] and stage at diagnosis.

Figure 2 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 3-web appendix. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region[1] and sex.

Figure 3 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 4-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and age (a), region[1] and sex (b).

Figure 4 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 5-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and stage.

Figure 5 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Colorectal cancer survival in the US and Europe: a CONCORD high-resolution study

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Abstract

Background

Colorectal cancer survival in the US has consistently been reported as higher than in Europe. The differences have generally been attributed to stage at diagnosis.

Material and methods

21 population-based registries in 7 US states and 9 European countries provided data on Dukes' stage, diagnostic procedures, treatment and follow-up for random samples comprising 12,523 adults (15-99 years) diagnosed with colorectal cancer during 1996-98.

Logistic regression models were used to compare adherence to "standard care" in the US and Europe. Net survival and excess risk of death were estimated with flexible parametric models.

Results

The proportion of Dukes' A and B tumours was similar in the US and Europe, while Dukes' C was more frequent in the US (38% *vs.* 21%) and Dukes' D more frequent in Europe (22% *vs.* 10%).

Resection with curative intent was more frequent in the US (85% *vs.* 75%). Elderly patients (75-99 years) were 70-90% less likely to receive radiotherapy and chemotherapy.

Age-standardised five-year net survival was similar in the US (58%) and Northern and Western Europe (54-56%) and lowest in Eastern Europe (42%).

The mean excess hazard up to 5 years after diagnosis was highest in Eastern Europe, especially among elderly patients and those with Dukes' D tumours.

Conclusions

The wide differences in colorectal cancer survival between Europe and the US in the late 1990s are probably attributable both to earlier stage and more extensive use of surgery and adjuvant treatment.

Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.

Keywords: CONCORD, net survival, excess hazard, cancer registries.

Article Focus

- Why has population-based survival for colorectal cancer been so much higher in the US than in Europe?
- Can differences in stage, diagnostic procedures and/or treatment explain these wide disparities?
- Are evidence-based guidelines for staging and treatment being followed?

Key Messages

- Stage at diagnosis varied more widely between participating European countries than between participating US states.
- Evidence-based guidelines do not seem to have been closely followed. The proportion of patients who received surgery with adjuvant chemotherapy and/or radiotherapy was much lower in Europe than the US. Elderly patients received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could have benefited.
- The wide US-Europe differences in five-year net survival from colorectal cancer in the late 1990s were probably attributable to earlier stage and more extensive use of surgery and adjuvant treatment in the US. Lower survival in Europe was mainly attributable to much lower survival in Eastern countries. This study underlines the need for population-based survival estimates derived from systematic clinical records of stage and treatment for all patients.

Strengths and Limitations

- To our knowledge, this is the first population-based high-resolution study with a direct US-Europe comparison of colorectal cancer survival, using clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods. Some of these clinical records of investigation, stage and treatment are not complete, systematic, or timely because they are not collected through routine cancer surveillance reporting for all cancer patients.
- Most diagnostic and therapeutic approaches used in the late 1990s remain in widespread use; mesorectal excision for rectal cancer is more recent. It remains relevant to understand the extent to which investigation and treatment are responsible for the persistent international differences in colorectal cancer survival.
- The modelling approach to estimate net survival is a methodological strength.
- Northern Europe was represented only by Finland.

Conflict of interest: none.

Ethical approval and data sharing agreement:

The study was approved by the US Centers for Disease Control (CDC, Atlanta GA) Institutional Review board #3551.

Informed consent of data subjects was not required; this was a records-based epidemiology study. No interview or contact with any patient was required, and no action was to be taken in respect of any individual whose data were included in the study, e.g. to alter their treatment. It is not practical to obtain informed consent from individual data subjects for their inclusion in studies of this type. It would involve attempting to contact many thousands of persons up to 15 years since they were first diagnosed. A substantial proportion would have died; many others would have moved, still others might not have been informed of the diagnosis. Contact would need to be made via the treating physician, whose identity was unknown. Consent could only have been sought by the cancer registries, since they alone know who the patients actually are, but none of the registries has the resources required. It would involve disproportionate effort, it would be substantially incomplete and it would take years to achieve, and the results would be irretrievably biased, invalidating the study.

Introduction

Five-year relative survival from cancers of the colon and rectum has been reported as 12-14% higher in the US than in Europe[1]. Survival for patients diagnosed during 1985–89 was higher in each of the 9 US states and metropolitan areas covered at that time by the Surveillance, Epidemiology and End Results (SEER) programme than in any of the 22 European countries participating in the EUROCARE-2 study[2].

The differences in 3-year colorectal cancer survival for patients diagnosed during 1990-91 between 10 territories in 5 European countries and the 9 SEER areas were mainly attributable to stage at diagnosis[3].

The first world-wide analysis of cancer survival (CONCORD[1]) provided a systematic comparison of survival for adults (15-99 years) diagnosed with cancer of the breast, colon, rectum or prostate in 31 countries during 1990-94 and followed up to 1999. International differences in age-standardised survival were very wide, even after adjustment for differences in mortality from other causes of death. Colorectal cancer survival was higher in the US and Canada than in many other countries. Differences between the US and most European regions were smaller than for patients diagnosed during 1985-89[2]. The largest differences were between the US and Eastern Europe.

The CONCORD protocol incorporated studies designed to explain the international variations in survival. These “high-resolution” studies involve systematic collection of detailed clinical and pathological data that are not routinely abstracted by population-based cancer registries from the original medical records of large random samples of patients. The high-resolution study reported here provides a trans-Atlantic comparison of stage, treatment and survival for patients with colorectal cancer.

The aims were (1) to compare the distributions of stage for colorectal cancers in Europe and the US; (2) to determine whether the transatlantic differences in survival persist and, if so, to assess the extent to which they are attributable to differences in stage at diagnosis; and (3) to compare adherence to “standard care”[4] for colorectal cancer in relation to age, stage and cancer site between the US and Europe.

Material and methods

Data on stage, diagnostic procedures, treatment and follow-up were collected for a representative sample of about 13,000 patients aged 15-99 years diagnosed with colorectal cancer (ICD-9[5] codes 1530-1539, 1540-1549) in the US and Europe during 1996-98. A single protocol was used, derived from the EUROCARE high-resolution protocols[6].

The European data were provided by 14 population-based cancer registries in 9 countries, 4 with national coverage (denoted below with an asterisk*). For some analyses, the data were grouped into the four European regions defined by the United Nations (UN, http://unstats.un.org/unsd/methods/m49/m49regin.htm) - Northern Europe: Finland*; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia*, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia*, Poland (Cracow, Kielce), Slovakia*. Estonia is classified by the UN as being in Northern Europe, but cancer survival has resembled that in Eastern European countries[7], and Estonia was included here with Eastern Europe. US data were provided by 7 state-wide registries (California, Colorado, Illinois, Louisiana, New York, Rhode Island, South Carolina) from the National Program of Cancer Registries (NPCR), based at the Centers for Disease Control and Prevention.

For this study, cancer registries in the EUROCARE-3 high-resolution study[8] updated follow-up to at least five years after diagnosis for all patients. North East Netherlands was not included in EUROCARE-3, but the registry routinely collects high-resolution data, and could provide such data on virtually all patients with colorectal cancer.

Most registries provided a random sample of at least 500 patients diagnosed during 1996-98 (1997 in the US). The Finnish cases were a population-based sample of patients diagnosed in the Tampere hospital region, which is considered representative of Finland.

Of 12,941 anonymised records for patients with a malignant neoplasm of the colon or rectum, 418 were excluded: *in situ* (396, 3.1%: collected in the US, but not in Europe) unknown sex (22, 0.2%); benign or uncertain behaviour (1), or age less than 15 or 100 years or over (19, 1.5%). In all, 12,523 patients with a primary, invasive, malignant colorectal neoplasm were included in the comparisons of stage and treatment. For survival analyses, a further 118 patients were excluded: cancer registered only from a death certificate (72; 0.6%); unknown vital status (3; 0.02%); date of last known vital status either unknown or earlier than the date of diagnosis (43; 0.3%); leaving 12,405 patients (99.1% of the 12,523 eligible).

Information on stage, diagnostic examinations and treatment was abstracted from the clinical record, pathology reports, hospital discharge records and other sources, as necessary.

Disease stage was defined according to the TNM (Tumour, Nodes, Metastasis) manual[9] and/or Dukes' stage. Many registries collected both TNM and Dukes' stage, but only Dukes' stage was available for Kielce (Poland) and Finland, so we used the Dukes' classification in order to include these populations in the stage-specific

analyses. Dukes' stage information was more complete than TNM stage, but TNM was used to reconstruct Dukes' stage where necessary. For descriptive purposes, we defined patients with 'advanced stage' as those with metastatic disease or those who had been operated on, but for whom no pathology report was available. This broad category was not used in stage-specific survival analyses, which are based on Dukes' stage, where available.

Age was categorised as 15-64, 65-74 and 75-99 years.

We defined resection for curative intent as resection of all macroscopically evident malignant tissue, with no macroscopic evidence of surgical margin involvement, and excluding polypectomy and trans-anal excision. Radiotherapy and chemotherapy were dichotomised as administered *vs.* not administered or unknown.

Statistical analysis

We analysed the distribution of stage and the number of lymph nodes examined pathologically[9]. We report the proportion of patients resected with curative intent and the distributions of stage-specific treatment for colon or rectal cancer. Data sets were excluded if data on stage and/or treatment were missing for 25% or more of patients: Ragusa was excluded from stage-specific analyses, including those on treatment related to stage at diagnosis.

Net survival up to five years after diagnosis was estimated by geographical area (UN region of Europe, country, registry or US state), age and stage, using flexible parametric excess hazard models[10]. Net survival is the survival of cancer patients in the hypothetical situation where the cancer may be assumed to be the only possible cause of death; it may be interpreted as cancer survival after controlling for competing causes of death. Net survival was estimated with a modelling approach[10-12] in which the total hazard of death is considered as the sum of the cancer-related mortality hazard (excess hazard), and the hazard of death from other causes (background hazard). The background hazard is derived from life tables of all-cause mortality by sex, single year of age and calendar year in the general population of the geographical area from which the cancer patients are drawn. We constructed period life tables for 1994-2004 with the approaches proposed by Baili et al[13].

Age was included as a continuous variable in all models, in order to avoid the bias in the estimation of net survival that would otherwise arise from differential loss of the oldest patients to competing hazards of death (informative censoring). Both non-linear and time-dependent (interaction with time since diagnosis) effects of age were initially modelled with cubic splines. The proportionality of the effect of tumour stage on the excess hazard was also assessed. Simpler models, with linear and/or proportional effects, were successively tested and selected using the Akaike Information Criterion for goodness of fit[14]. We also estimated the instantaneous excess risk (hazard) of death due to colorectal cancer, after subtracting the hazard from all other causes of death[10-12;15;16]. We present the mean excess hazard per 1,000 person-years at risk at selected times since diagnosis (1 month, 6 months and 1, 3 and 5 years), both by age group and by stage at diagnosis, after adjustment for age.

Overall (all-ages) net survival estimates were age-standardised with the International Cancer Survival Standard (ICSS) weight[17].

We used a logistic regression model to estimate the odds of colorectal cancer patients in each area being resected with curative intent, the odds of patients with colon cancer at Dukes' stage B or C receiving chemotherapy, and the odds of rectal cancer patients with Dukes' stage A-C being treated with radiotherapy, after adjustment for age and/or tumour site and/or sex.

Survival analyses were performed with *stpm2*[15] in Stata version 12 (StataCorp LP, College Station, TX).

Results

We included 12,523 patients with an invasive, primary colorectal cancer: 9,186 patients in 14 registries in 9 European countries and 3,337 patients in 7 US states (Table 1). Microscopic verification was available for 96-98% of the patients in each of the US states and 93% in Europe, ranging from 85% in Ragusa (Italy) to 99% in Kielce (Poland). The proportion of colorectal cancer patients who were male was similar in Europe (53%) and the US (50%), but colon cancer was more frequent in the US (73%) than in Europe (60%). Data were available on stage at diagnosis for 90-93% of patients on both sides of the Atlantic, ranging from 76% (Finland) to 95% or more in 3 of the 14 European registries and from 90% (Colorado and South Carolina) to 97% (Louisiana) in the US.

Early-stage (Dukes' A or B) colorectal cancers were equally common in the US (45%) and Europe (47%), but the stage distributions varied widely, both between US states and between European regions. Tumours in Dukes' stage A were of similar frequency in Europe (17%, range 11-28%) and in the US (17%; 14-23%), and the proportion of Dukes' B tumours were also very comparable (Europe 30%; 25-37%; US 28%; 24-36%). By contrast, Dukes' C tumours were twice as common in the US (38%; 29-46%) as in Europe (21%; 24-30%), while Dukes' D tumours were twice as common in Europe (21%; 11-33%) as in the US (10%; 7-18%). The proportion of tumours with unspecified stage was slightly higher in Europe (10%; 4-24%) than in the US (7%; 3-10%). Exclusion of Finland, with 24% of tumours of unknown stage, did not substantially alter the overall stage distributions in Europe (data not shown).

Patients diagnosed at an advanced stage (i.e. metastatic cases plus unresected cases for which no data on stage were available) were more common in the four European regions (29%; 24-34%) than in the US (20%; 16-23%) (Table 2). In Europe, advanced stage was more common in Southern (30%) and Eastern Europe (34%). The highest proportion of patients with advanced stage in the US (23%, California), was similar to the lowest regional proportion in Europe (24%, Western Europe).

Resection for curative intent was more frequent in the US (85%) than in Europe (75%). The proportion resected with curative intent was remarkably similar in all 7 US states (84-88%). Only Western Europe (84%) showed a proportion as high as that in the US.

Thirty-day post-operative mortality was 5% or less in the US and Europe. Among patients resected with curative intent, the proportion with known stage was around 95% in the US and Europe, with the lowest proportions in Northern Europe (84-90%) (Table 2). In many European registries, data on the number of lymph nodes examined after surgery were not available for most patients (web-appendix Table 2).

Adjuvant chemotherapy and radiotherapy were both administered more frequently in the US than in Europe (Table 3). Among Dukes' B colon cancer patients, 28% received chemotherapy in the US (21-46%) *vs.* 20% in Europe (4-31%). Among Dukes' C colon cancer patients, 56% received chemotherapy in the US (47-64%) vs. 47% in Europe (38-53%). Among Dukes' A-C rectal cancer patients, 47% received radiotherapy in the US (41-52%) vs. 37% in Europe (26-45%).

Relative to Southern Europe (2,912 patients, reference category), the odds of receiving resection for curative intent (*vs.* any other surgical procedure), after adjustment for age and tumour site, were much lower in Eastern Europe (OR=0.46; 0.41-0.52), somewhat lower in Northern Europe (OR=0.88; 95% CI 0.71-1.09); and much higher in Western Europe (OR=1.62; 1.43-1.85) and in the US (OR=1.72; 1.52-1.94) (Table 4).

Patients aged less than 75 years were only half as likely to be resected with curative intent as those aged 15-64 years (OR 0.48, 95% confidence interval [CI] 0.43-0.53), after adjustment for region and tumour site.

Patients with colon cancer (reference category) were resected with curative intent more often than patients with rectal cancer (OR 0.73; 0.66-0.79).

Patients with Dukes' B colon cancer received chemotherapy much less often in Western Europe (OR 0.10; 0.06-0.16) and Northern Europe (OR 0.29; 0.15-0.56) than in Southern Europe. For patients with Dukes' C colon cancer, chemotherapy was used less in Western Europe (OR 0.64; 0.48-0.87) and more often in the US (OR 1.56; 1.23-1.98) than in Southern Europe.

Compared to Southern Europe, radiotherapy was administered to patients with rectal cancer in Dukes' stage A-C more often in the US (OR 1.39; 1.10-1.76), less often in Northern Europe (OR 0.58; 0.38-0.89) or Eastern Europe (OR 0.46; 0.36-0.59).

Older patients were only 10% as likely to be treated with radiotherapy and chemotherapy.

Overall, age-standardised net survival at five years was 50% in Europe and 58% in the US (Figure 1). Survival was lower than the US in all European areas, and only in Northern Europe was the figure (56%) close to that in the US. Survival was lower in Western (54%) and in Southern Europe (49%) and lowest in Eastern Europe (42%). Survival varied widely between European countries (from 56% in France and Finland to 37% in Poland), but also between US states (from 64% in Rhode Island to 56% in Illinois and 50% in South Carolina).

Five-year age-standardised net survival was higher in the US for Dukes' stage A (84%) and B (75%) tumours, but higher in Northern Europe for Dukes' C (52%) and D (12%) tumours (Figure 2). The geographic range in survival was much wider for locally advanced disease, from 36% in Eastern Europe to 77% in Northern Europe, and 49% in the US. As with overall survival, stage-specific five-year survival was similar in Northern, Western and Southern Europe and the US. In Eastern Europe, survival for node-positive, locally advanced and metastatic tumours was lower than in other European regions and in the US.

Survival was 5-12% higher in women than in men in all areas, especially in Northern and Western Europe (11-12%) (web-appendix Figure 3).

The mean excess hazard of death at 1 month, 6 months and at 1, 3 and 5 years after diagnosis was higher in Eastern Europe than in all other regions, both for all ages combined and in each of 3 age categories (web-appendix Figure 4). The difference was most marked for elderly patients (75-99 years). No striking differences were found between Northern, Western and Southern Europe and the US. The high

excess hazard of death in Eastern Europe was mainly confined to patients with Dukes' D tumours (web-appendix Figure 5).

Discussion

Transatlantic differences in population-based colorectal cancer survival have raised questions about early diagnosis and the adequacy of investigation and treatment that cannot be addressed with data from clinical trials, which include only selected patient groups.

Patterns-of-care studies and survival studies have been conducted separately in Europe[3;6;8] and the US[18;19]. To our knowledge, this is the first population-based high-resolution study that allows direct comparison of colorectal cancer survival between Europe and the US with clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, then subjected to standard quality control procedures and analysed centrally with the same statistical methods.

The participating cancer registries are population-based registries that register all persons diagnosed in the territory they cover. This study included large, randomly selected subsets of all persons diagnosed with colorectal cancer during 1996-98, in each territory. These samples are not intended to be "representative" of all colorectal cancer patients in Europe or the US, but they are representative of all colorectal cancer patients diagnosed during 1996-98 in the territory of each registry, and the findings are generalisable to the populations from which they are drawn.

Most of the diagnostic and therapeutic approaches used in the late 1990s remain in widespread use. Understanding their role in international differences in survival remains relevant. Mesorectal excision for rectal cancer is the main exception: it has improved survival from rectal cancer[20;21], but widespread use is more recent. Mesorectal excision was not used in Estonia before 1997, which may partly explain the low survival from rectal cancer[22].

The transatlantic 12% difference in 3-year survival in colorectal cancer survival for patients diagnosed 1990-91[3] was mostly attributed to differences in stage at diagnosis In our study of patients diagnosed in the late 1990s, overall five-year net survival was still higher in the 7 US states (58%) than in the 14 European regions (42-56%). The widest differences with the US were seen in Southern (49%) and Eastern Europe (42%).

The two studies differed in design, however: data from the SEER public-use data set in the US[23] were simply adapted to the EUROCARE-2 high-resolution protocol as far as possible. By contrast, data for this study were collected directly from clinical records on both sides of the Atlantic, with a standard protocol. US coverage changed from the 5 metropolitan areas and 4 states covered by the SEER program to 7 of the state-wide NPCR registries. In the earlier study, differences in background mortality in the US were controlled with a single national life table for 1990, weighted for the proportion of Blacks, Whites and other races. Here, we were able to use state-specific life tables for each of the calendar years 1996-2004.

The tighter control for background mortality and the modelling approach used to estimate net survival are methodological strengths of this study, but these changes do not explain why the transatlantic differences we observe in five-year survival are

smaller than the differences in three-year survival for patients diagnosed in the early 1990s[3].

Survival varied widely among European countries, but also between the 7 US states. Survival in Slovenia was lower than in other Southern European countries, and more similar to that in Eastern Europe. In the US, survival was lowest in South Carolina, where Blacks represent approximately 30% of the population (http://www.ipspr.sc.edu/publication/Older%20SC.pdf).

Apart from patients with Dukes' B cancers, where survival was similar in Northern, Western and Southern Europe, stage-specific net survival was rather variable. Survival was highest in the US for Dukes' stage A and B, and in Northern Europe (Finland) for Dukes' stage C and D. This could be due to some misclassification of stage in Finland, where stage data were not available for 24% of cases.

The mean excess hazard of death up to five years after diagnosis was similar in Europe and the US for patients with tumours in Dukes' stage A or B. The hazard was somewhat higher in Eastern Europe for Dukes' stage C, and much higher for Dukes' D disease, especially in the first three years after diagnosis. The very high hazard of death for patients with late-stage disease in Eastern Europe suggests that fewer effective treatment options were available for these patients, although higher levels of co-morbidity may also have restricted the choice.

It was not possible to evaluate the impact of the number of examined lymph nodes on the stage-adjusted excess hazard of death, because information on nodal status was so often unavailable (see web-appendix). It is therefore impossible to assess whether stage migration affects the comparison of stage-specific survival between European regions and the US in the late 1990s, as reported for patients diagnosed in 1990[3].

We did not have information on whether or not patients in this study had undergone faecal occult blood testing or sigmoidoscopy before diagnosis. Opportunistic testing with these procedures was common in the US in the late 1990s. Almost 40% of respondents to the Behavioural Risk Factor Surveillance System (www.cdc.gov/mmwr/preview/mmwrhtml/00056494.htm) survey in 1997 reported having had a faecal occult blood test at some time in the past, and 42% reported a previous sigmoidoscopy or proctoscopy. Removal of premalignant polyps or *in situ* neoplasms may thus have been more frequent than in Europe. This would be expected to reduce incidence, shift the spectrum of malignancy to the right, and reduce survival in the US. In fact, incidence in the US is higher, the stage distribution less advanced, and survival higher than in Europe.

Adjuvant chemotherapy for colon cancer and adjuvant radiotherapy for rectal cancer were both used more widely in the US than in Europe. Despite the evidence available in the late 1990s on the lack of efficacy of adjuvant chemotherapy for Dukes' B colon cancer, 30% of colon cancer patients in the US received it, and 20% overall in Europe. In Finland and Western Europe, however, adjuvant chemotherapy was rare, in line with the contemporary recommendations, while in Southern and Eastern Europe, adjuvant chemotherapy was used as frequently as in the US.

In contrast, there were striking differences in the use of adjuvant chemotherapy for stage III colon cancer in the late 1990s, particularly within Europe. Given the wide consensus on its effectiveness since 1990, we did not expect to find that such a strong recommendation had been so poorly followed. Co-morbidity and greater toxicity are not valid reasons for under-use of adjuvant chemotherapy in the elderly: toxicity is no greater[24;25] and quality of life no worse[26].

Elderly patients were 90% less likely to receive adjuvant chemotherapy than younger patients. Clinical attitudes appear to differ between the US and Europe, where the proportion of patients receiving adjuvant chemotherapy is much lower. This suggests that a higher proportion of older patients with Dukes' C colon cancer who are fit enough to undergo surgery should receive adjuvant chemotherapy, particularly in Europe.

Radiotherapy is known to be an effective complement to surgery for rectal cancer, in particular to reduce the risk of local recurrence; pre-operative is preferable to post-operative radiotherapy[27], and it is recommended in both Europe and the US[28-31]. We were unable to distinguish between the impact of pre- and post-operative radiotherapy, because this information was not systematically available, but fewer patients received radiotherapy in Europe than in the US, and practice in Europe was strikingly heterogeneous, even within a given country. Age was a strong predictor of the use of radiotherapy. Some older patients are unsuitable for radiotherapy because of co-morbidity, but their 70% lower odds of receiving it cannot be explained by co-morbidity alone; radiotherapy has not yet been deployed to its full potential for older patients with rectal cancer. It is not clear why the evidence on the benefits of radiotherapy was so poorly followed in many regions.

Surgical resection offers the only approach to a definitive cure for colorectal cancer. The proportion of patients resected with curative intent was very similar in the 7 US States (84-88%), but it varied widely between the 9 European countries (from 56% to 86%), and was particularly low in Eastern Europe (mean 62%). A more aggressive approach to surgical treatment for elderly colorectal cancer patients in Europe could improve this situation, although European patients were more often diagnosed at an advanced stage or with unresectable disease. Performance status and co-morbidity can influence whether a patient is considered fit for resection, but data on these factors were not available. The quality of life in Canadian patients aged over 80 who underwent surgery for colorectal cancer was generally comparable to that of younger patients[32].

In this large, population-based study in Europe, however, age alone seems often to have been a limiting factor in the treatment of colorectal cancer. Elderly patients were generally treated less often with surgery, chemotherapy or radiotherapy, despite the evidence that they could benefit from these treatments. Treatment decisions should be taken in the context of multidisciplinary meetings, including a comprehensive geriatric assessment: age alone should not exclude a patient from receiving surgery and/or adjuvant treatment.

Differences in colorectal cancer survival between Europe and the US in the late 1990s were still wide and may be attributable both to earlier stage at diagnosis, higher levels of surgery and more extensive use of adjuvant treatment in the US.

Evidence-based guidelines do not seem to have been followed as closely as they should be: chemotherapy was used too often for Dukes' B disease and not often enough for Dukes' C disease, especially among elderly patients.

The need for population-based survival estimates derived directly from the clinical records on stage at diagnosis and treatment is recognised by clinicians and epidemiologists. A recent comparison of stage-specific cancer survival with population-based data[33], was complicated by inconsistent coding of stage[34]; several registries had to be excluded because fewer than half the tumour records contained data on stage. In this high-resolution study, stage data were remarkably complete (76-94% in Europe, 93% in the US), because they were collected directly from clinical records. Ideally, the medical records of cancer patients would systematically include data on investigations and stage at diagnosis; cancer registries would obtain those data for all patients, and stage would be coded consistently. Until then, high-resolution studies would appear to offer the most reliable approach to obtain data on stage and treatment, and to assess survival by stage at diagnosis.

If good evidence is required on whether all patients receive guideline-compliant investigation and treatment, and whether this makes a difference to survival, then cancer registries will need to be able to obtain timely and high-quality data on the investigations, the stage and the treatment for all cancer patients.

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Extra results are available in the web-appendix. Raw data are not available.

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Table 1. Calendar period of diagnosis, morphological verification, and data on sex, cancer site and stage. Patients with invasive primary colorectal cancer, Europe and US

										Dukes' stage[1] at diagnosis									
EUROPE	Registry	No.	Period of diagnosis	Morphologically verified		Males		Colon		A		B		C		D		Not available	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Estonia	Estonia	560	1997	491	88	250	45	337	60	144	26	151	27	76	14	167	30	22	4
Finland	Finland	523	1996-98	478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
France	Côte d'Or	561	1996-97	544	97	302	54	382	68	112	20	209	37	98	17	114	20	28	5
Italy	Genova	589	1996	529	90	326	55	379	64	71	12	192	33	148	25	131	22	47	8
	Ragusa*	424	1996-98	361	85	233	55	269	63										
	Varese	500	1997	485	97	266	53	332	66	109	22	148	30	105	21	114	23	24	5
Netherlands	North East NL	1,936	1997	1821	94	1002	52	1240	64	280	14	579	30	463	24	332	17	282	15
Poland	Cracow	512	1997-98	463	90	252	49	285	56	128	25	101	20	82	16	158	31	43	8
	Kielce	271	1996	267	99	147	54	133	49	62	23	67	25	41	15	89	33	12	4
Slovakia	Slovakia	581	1996	535	92	351	60	315	54	161	28	147	25	75	13	160	28	38	7
Slovenia	Slovenia	937	1997	871	93	490	52	474	51	131	14	265	28	243	26	209	22	89	9
Spain	Granada	567	1996-97	523	92	312	55	360	63	63	11	191	34	109	19	148	26	56	10
	Navarra	588	1996-97	558	95	354	60	335	57	100	17	188	32	121	21	120	20	59	10
	Tarragona	637	1996-97	603	95	339	53	421	66	71	11	174	27	176	28	146	23	70	11
European registries[2]		**9,186**		**8,529**	**93**	**4,871**	**53**	**5,556**	**60**	**1,493**	**17**	**2,586**	**30**	**1,840**	**21**	**1,948**	**21**	**895**	**10**
Northern Europe		523		478	91	247	47	294	56	61	12	174	33	103	20	60	11	125	24
Western Europe		2,497		2365	95	1,304	52	1,622	65	392	16	788	32	561	22	446	18	310	12
Southern Europe[3]		4,242		3930	93	2,320	55	2,570	61	545	14	1158	30	902	24	868	20	345	8
Eastern Europe		1,924		1756	91	1,000	52	1,070	56	495	26	466	24	274	14	574	30	115	6
US																			
	California	495	1997	485	98	242	49	356	72	89	18	137	28	168	34	60	12	41	8
	Colorado	548	1997	536	98	296	54	407	74	85	16	162	30	191	35	56	10	54	10
	Illinois	505	1997	497	98	239	47	384	76	71	14	144	29	224	44	36	7	30	6
	Louisiana	511	1997	502	98	263	51	374	73	115	23	146	29	146	29	90	18	14	3
	New York	492	1997	473	96	248	50	350	71	91	18	114	23	226	46	21	4	40	8
	Rhode Island	418	1997	413	99	195	47	302	72	64	15	149	36	160	38	29	7	16	4
	South Carolina	368	1997	358	97	187	51	265	72	68	18	89	24	150	41	26	7	35	10
US registries		**3,337**		**3,264**	**98**	**1,670**	**50**	**2,438**	**73**	**583**	**17**	**941**	**28**	**1265**	**38**	**318**	**10**	**230**	**7**
Total		**12,523**																	

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow , Kielce), Slovakia

[3] Data for Ragusa are not included in the percentages of Dukes' stage for Southern Europe

Table 2. Advanced stage, resection with curative intent, 30-days post-operative mortality and proportion of patients with information on stage: colorectal cancer, Europe and the US, 1996-98

		All cases			Resected with curative intent[2]							
			Advanced stage[1]		Deaths within 30 days				Staged			
									Colon		Rectum	
EUROPE	Registry	No.	No.	%	No.	%	No.	%	No.	%	No.	%
European registries[3]		**8,762**	**2,535**	**29**	**6,584**	**75**	**248**	**4**	**3,895**	**95**	**2,374**	**95**
Northern Europe		523	134	26	385	74	16	4	192	84	142	90
Western Europe[4]		2,497	609	24	2,092	84	24	6	1,299	93	646	92
Southern Europe[5]		3,818	1,131	30	2,912	76	152	5	1,748	97	1,081	97
Eastern Europe		1,924	661	34	1,195	62	56	5	656	98	505	97
US registries		**3,337**	**676**	**20**	**2,832**	**85**	**124**	**4**	**2,039**	**97**	**677**	**93**
	California	495	112	23	415	84	15	4	294	96	102	93
	Colorado	548	113	21	468	85	18	4	335	95	109	93
	Illinois	505	112	22	422	84	21	5	320	97	85	93
	Louisiana	511	105	21	431	84	26	6	315	100	111	97
	New York	492	80	16	411	84	22	5	287	95	102	94
	Rhode Island	418	78	19	369	88	9	2	268	99	93	94
	South Carolina	368	76	21	316	86	13	4	220	96	75	87
Total		**12,099**										

1 All metastatic cases, plus unresected cases for which no stage data were available

2 Curative intent: surgery not specified as palliative, or tumour entirely resected

3 Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

4 Data for North East Netherlands (1,936) are not included in the proportion of deaths within 30 days of surgery for Western Europe beacuse the date of surgery was not available

5 Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 3. Chemotherapy in Dukes' B and C colon cancer and radiotherapy in Dukes' A-C rectal cancer

		Colon Dukes' B[1]			Colon Dukes' C[1]			Rectum Dukes' A-C[1]		
EUROPE	**Registry**	**No.**	**among whom, chemotherapy**		**No.**	**among whom, chemotherapy**		**No.**	**among whom, radiotherapy**	
			No.	**%**		**No.**	**%**		**No.**	**%**
European registries[2]		**1,748**	**343**	**20**	**1,130**	**528**	**47**	**1,850**	**678**	**37**
Northern Europe		110	11	10	50	21	42	118	34	29
Western Europe		591	23	4	346	133	38	411	183	45
Southern Europe[3]		736	209	28	529	265	50	797	331	42
Eastern Europe		259	80	31	154	81	53	480	124	26
US registries		**727**	**200**	**28**	**913**	**508**	**56**	**484**	**228**	**47**
	California	108	29	27	114	54	47	65	31	48
	Colorado	129	29	22	145	93	64	70	29	41
	Illinois	112	28	25	171	88	51	65	33	51
	Louisiana	105	22	21	106	59	56	76	33	43
	New York	86	24	28	157	81	52	84	44	52
	Rhode Island	119	37	31	107	69	64	66	30	45
	South Carolina	68	31	46	113	64	57	58	28	48

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 4. Odds of colorectal cancer patients being resected with curative intent, odds of patients with Dukes' B or C colon cancer being treated with chemotherapy and odds of Dukes' stage A-C rectal cancer being treated with radiotherapy: by region, age, cancer site or sex

	Resection for curative intent				Colon Dukes' B[1]				Colon Dukes' C[1]				Rectum stage A - C[1]			
	No.	OR	95% CI		No.	OR	95% CI		No.	OR	95% CI		No.	OR	95% CI	
Region[2]																
Northern Europe	385	0.88	0.71	1.09	110	0.29	0.15	0.56	50	0.88	0.46	1.69	118	0.58	0.38	0.89
Western Europe	2,092	1.62	1.43	1.85	591	0.10	0.06	0.16	346	0.64	0.48	0.87	411	1.22	0.95	1.56
Southern Europe[3]	2,912	1.00			736	1.00			529	1.00			797	1.00		
Eastern Europe	1,195	0.46	0.41	0.52	259	0.89	0.64	1.23	154	0.89	0.61	1.32	480	0.46	0.36	0.59
US	2,832	1.72	1.52	1.94	727	1.25	0.97	1.60	913	1.56	1.23	1.98	484	1.39	1.10	1.76
Age (years)																
15-64	3,194	1.00			674	1.00			684	1.00			890	1.00		
65-74	3,195	0.89	0.79	0.99	797	0.61	0.48	0.77	653	0.47	0.37	0.59	784	0.69	0.57	0.84
75-99	3,027	0.48	0.43	0.53	952	0.07	0.05	0.10	655	0.10	0.08	0.13	616	0.30	0.24	0.38
Site																
Colon	6,191	1.00														
Rectum	3,225	0.73	0.66	0.79												
Sex																
Male													1,324	1.00		
Female													966	0.92	0.77	1.10

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Figure 1. Five-year age standardized net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: country and region[1].

Figure 1 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 2. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region[1] and stage at diagnosis.

Figure 2 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 3-web appendix. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region[1] and sex.

Figure 3 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

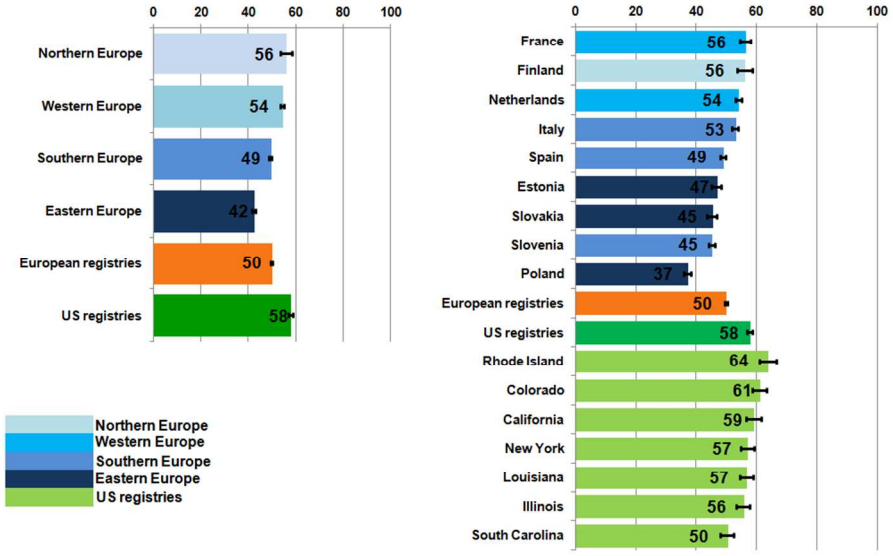
Figure 4-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and age (a), region[1] and sex (b).

Figure 4 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 5-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and stage.

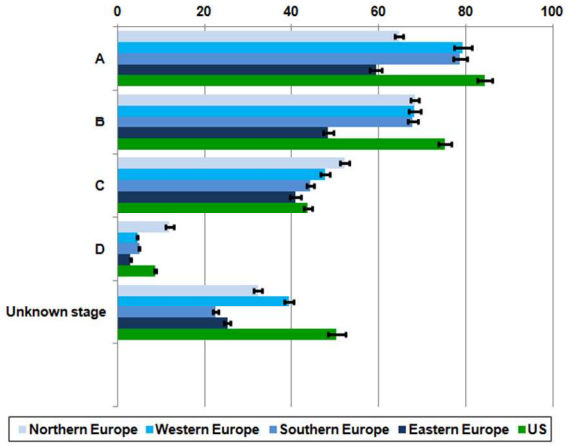
Figure 5 footnote: [1] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

Figure 1. Five-year age standardized net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: country and region.



297x190mm (96 x 96 DPI)

Figure 2. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region and stage at diagnosis



285x159mm (96 x 96 DPI)

Table 2-web appendix. Advanced stage, resection with curative intent, 30-days post-operative mortality, proportion of patients with information on stage and number of lymph nodes examined : colorectal cancer, Europe and the US, 1996-98

		All cases			Resected with curative intent[2]															
			Advanced stage[1]		Deaths within 30 days				Staged				No. of lymph nodes examined							
									Colon		Rectum		Zero		Up to 11		More than 12		Not available	
EUROPE	Registry	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Estonia	Estonia	560	188	34	314	56	9	3	192	98	118	99	0	0	149	47	5	2	160	51
Finland	Finland	523	134	26	385	74	16	4	192	84	142	90	49	13	187	49	20	5	129	34
France	Côte d'Or	561	141	25	430	77	24	6	302	100	127	99	62	14	255	59	113	26	0	0
Italy	Genova	589	153	26	503	85	37	7	313	95	164	95	1	0	219	44	171	34	112	22
	Varese	500	133	27	395	79	8	2	270	100	120	96	12	3	201	51	156	39	26	7
Netherland	North East NL	1,936	468	24	1,662	86	n.a	n.a	997	92	519	90	-	-	-	-	-	-	1,662	100
Poland	Cracow	512	187	37	303	59	9	3	146	94	141	96	6	2	210	69	25	8	62	20
	Kielce	271	91	34	211	78	19	9	103	98	97	92	0	0	36	17	3	1	172	82
Slovakia	Slovakia	581	195	34	367	63	19	5	215	100	149	99	7	2	155	42	1	0	204	56
Slovenia	Slovenia	937	283	30	652	70	44	7	322	97	315	98	26	4	243	37	327	50	56	9
Spain	Granada	567	186	33	442	78	30	7	273	96	151	96	4	1	238	54	135	31	65	15
	Navarra	588	172	29	452	77	15	3	259	98	186	98	0	0	201	44	133	29	118	26
	Tarragona	637	204	32	468	73	18	4	311	98	145	96	0	0	174	37	244	52	50	11
European registries[3]		**8,762**	**2,535**	***29***	**6,584**	**75**	**248**	**5**	**3,895**	**95**	**2,374**	**95**	**167**	**3**	**2,268**	**34**	**1,333**	**20**	**2,816**	**43**
Northern Europe		523	134	26	385	74	16	4	192	84	142	90	49	13	187	49	20	5	129	34
Western Europe[4]		2,497	609	24	2,092	84	24	6	1,299	93	646	92	62	3	255	12	113	5	1,662	79
Southern Europe[5]		3,818	1,131	30	2,912	76	152	5	1,748	97	1,081	97	43	1	1,276	44	1,166	40	427	15
Eastern Europe		1,924	661	34	1,195	62	56	5	656	98	505	97	13	1	550	46	34	3	598	50
US																				
	California	495	112	23	415	84	15	4	294	96	102	93	37	9	215	52	156	38	7	2
	Colorado	548	113	21	468	85	18	4	335	95	109	93	24	5	238	51	199	43	7	1
	Illinois	505	112	22	422	84	21	5	320	97	85	93	49	12	191	45	176	42	6	1
	Louisiana	511	105	21	431	84	26	6	315	100	111	97	62	14	226	52	142	33	1	0
	New York	492	80	16	411	84	22	5	287	95	102	94	34	8	216	53	150	36	11	3
	Rhode Island	418	78	19	369	88	9	2	268	99	93	94	37	10	202	55	130	35	0	0
	South Carolina	368	76	21	316	86	13	4	220	96	75	87	28	9	174	55	107	34	7	2
US registries		**3,337**	**676**	**20**	**2,832**	**85**	**124**	**4**	**2,039**	**97**	**677**	**93**	**271**	**10**	**1,462**	**52**	**1,060**	**37**	**39**	**1**
Total		**12,099**																		

[1] All metastatic cases, plus unresected cases for which no stage data were available

[2] Curative intent: surgery not specified as palliative, or tumour entirely resected

[3] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow , Kielce), Slovakia

[4] Data for North East Netherlands (1,936) are not included in the proportion of deaths within 30 days of surgery for Western Europe beacuse the date of surgery was not available

[5] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Table 3-web appendix. Chemotherapy in Dukes' B and C colon cancer and radiotherapy in Dukes' A-C rectal cancer

EUROPE	Registry	Colon Dukes' B[1] No.	among whom, No.	%	Colon Dukes' C[1] No.	among whom, No.	%	Rectum Dukes' A-C[1] No.	among whom, No.	%
Estonia	Estonia	97	8	8	44	19	43	140	36	26
Finland	Finland	110	11	10	50	21	42	118	34	29
France	Côte d'Or	170	22	13	65	33	51	61	27	44
Italy	Genova	122	45	37	93	43	46	109	45	41
	Ragusa	52	20	38	51	28	55	44	6	14
	Varese	106	45	42	63	38	60	85	24	28
Netherlands	North East NL	421	1	0	281	100	36	350	156	45
Poland	Cracow	50	23	46	45	24	53	138	15	11
	Kielce	30	1	3	22	7	32	85	11	13
Slovakia	Slovakia	82	48	59	43	31	72	117	62	53
Slovenia	Slovenia	143	15	10	126	56	44	260	100	38
Spain	Granada	128	47	37	67	36	54	82	37	45
	Navarra	111	39	35	68	37	54	136	82	60
	Tarragona	126	18	14	112	55	49	125	43	34
European registries[2]		**1,748**	**343**	**20**	**1,130**	**528**	**47**	**1,850**	**678**	**37**
Northern Europe		110	11	10	50	21	42	118	34	29
Western Europe		591	23	4	346	133	38	411	183	45
Southern Europe[3]		736	209	28	529	265	50	797	331	42
Eastern Europe		259	80	31	154	81	53	480	124	26
US registries		**727**	**200**	**28**	**913**	**508**	**56**	**484**	**228**	**47**
	California	108	29	27	114	54	47	65	31	48
	Colorado	129	29	22	145	93	64	70	29	41
	Illinois	112	28	25	171	88	51	65	33	51
	Louisiana	105	22	21	106	59	56	76	33	43
	New York	86	24	28	157	81	52	84	44	52
	Rhode Island	119	37	31	107	69	64	66	30	45
	South Carolina	68	31	46	113	64	57	58	28	48

[1] Dukes' stages A, B, C and D correspond to TNM categories stage I, II, III and IV

[2] Northern Europe: Finland; Western Europe: France (Côte d'Or), the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa, Varese), Slovenia, Spain (Granada, Navarra, Tarragona); Eastern Europe: Estonia, Poland (Cracow, Kielce), Slovakia

[3] Data for Ragusa (424) are not included in the percentages of Dukes' stage for Southern Europe

Figure 3-web appendix. Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the US in the late 1990s: region and sex

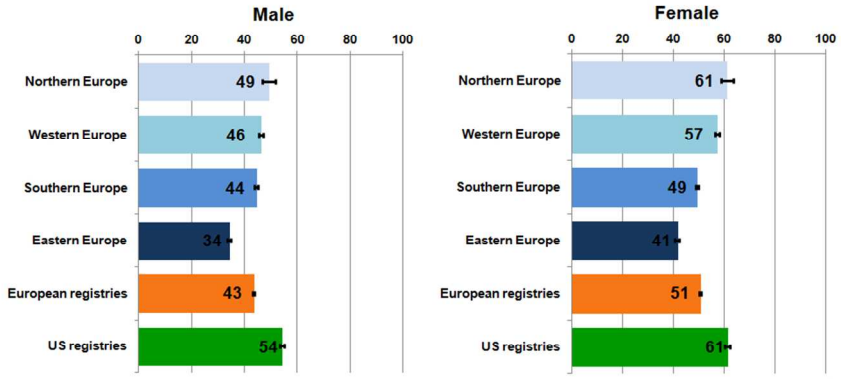


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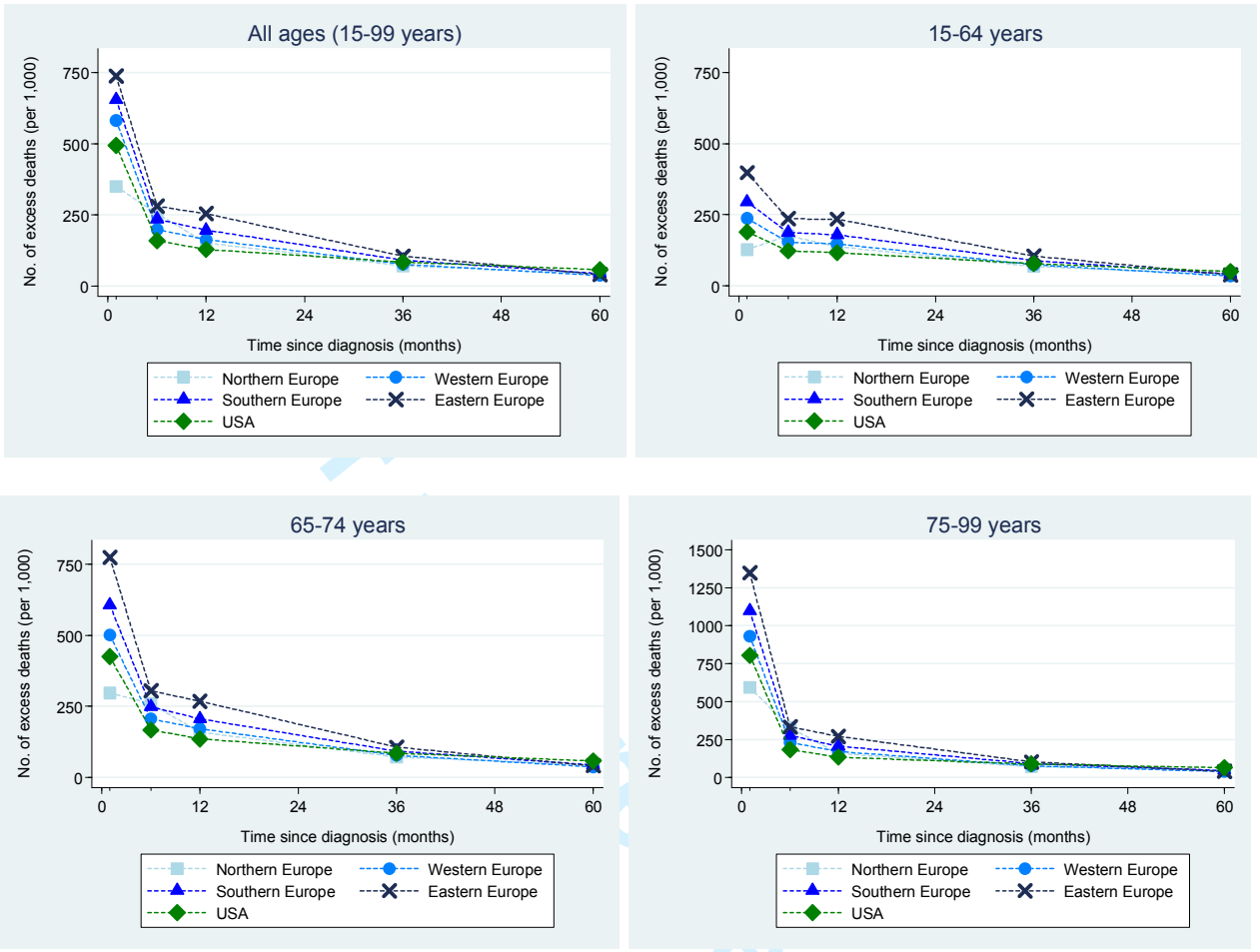
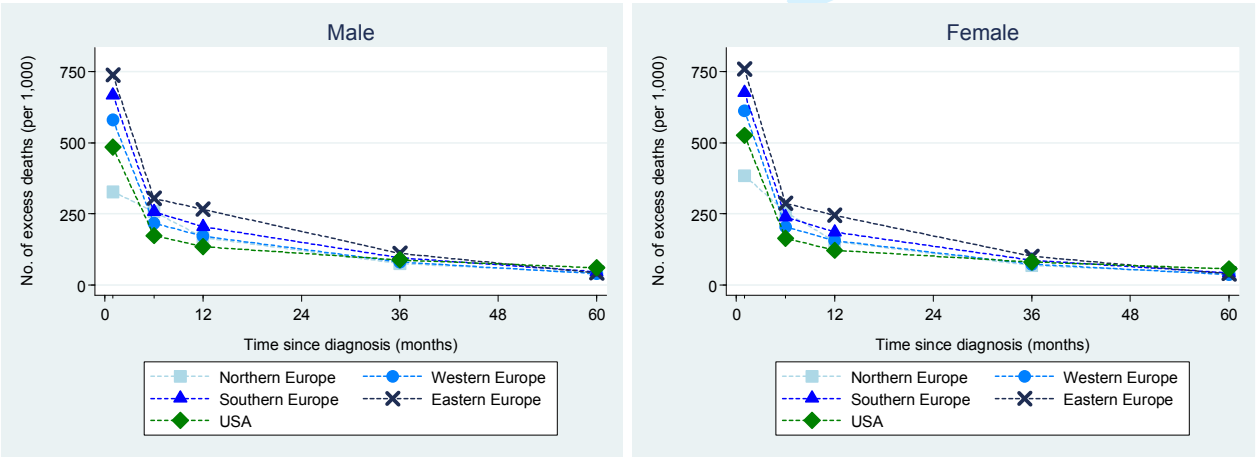
Figure 4-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and age (a), region[1] and sex (b).

(a)

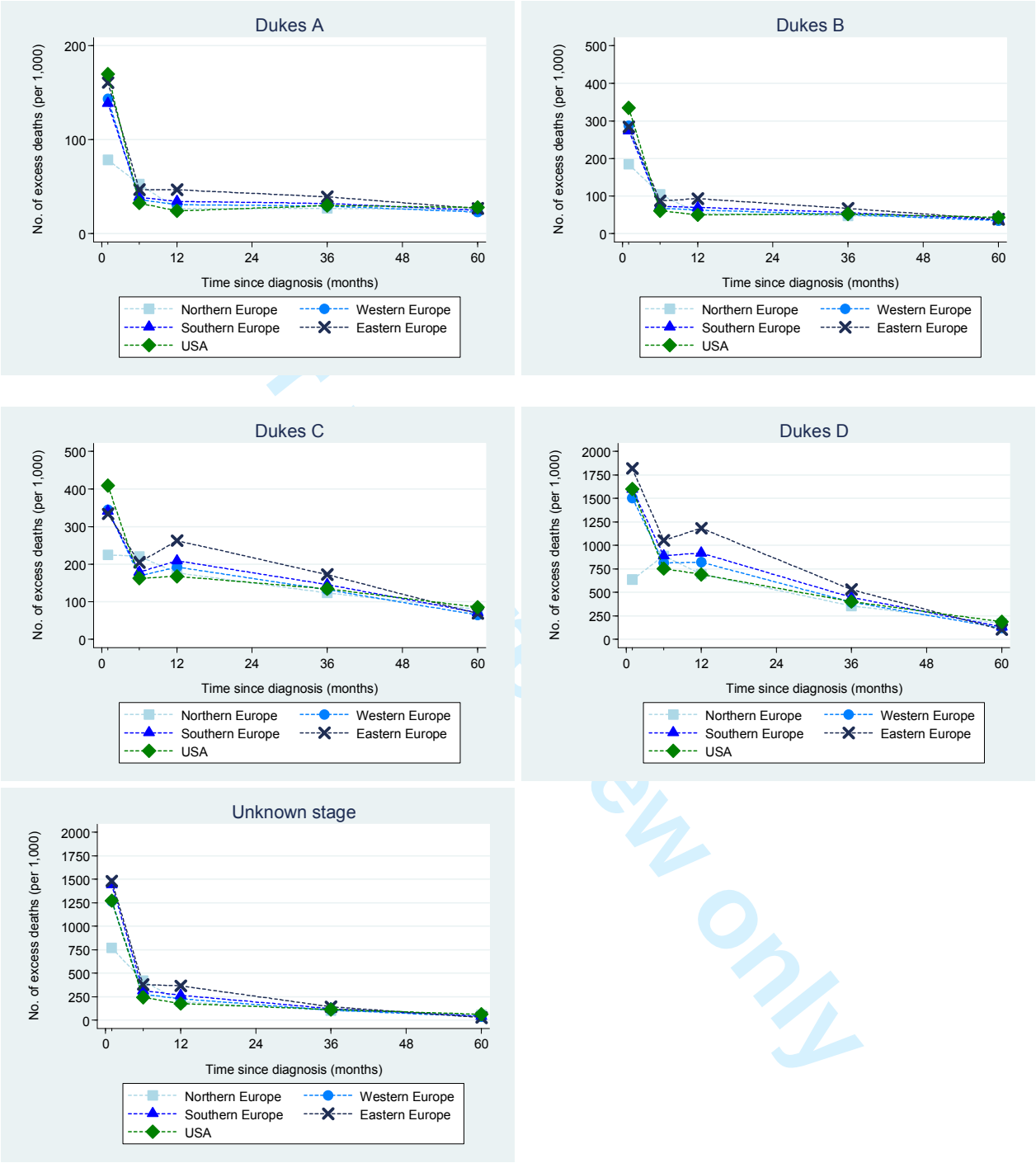


(b)



* Age was modelled as a continuous variable. The data points represent the mean excess hazards within each category of age (a) or sex (b).

Figure 5-web appendix. Mean excess hazard of death per 1,000 person-years at selected points since diagnosis, by region[1] and stage.



* Age was modelled as a continuous variable. The data points represent the mean excess hazards within each category of stage.