Allemani, C; Rachet, B; Weir, HK; Richardson, LC; Lepage, C; Faivre, J; Gatta, G; Capocaccia, R; Sant, M; Baili, P; Lombardo, C; Aareleid, T; Ardanaz, E; Bielska-Lasota, M; Bolick, S; Cress, R; Elferink, M; Fulton, JP; Galceran, J; Gzdz, S; Hakulinen, T; Primic-Zakelj, M; Rachtan, J; Diba, CS; Snchez, MJ; Schymura, MJ; Shen, T; Tagliabue, G; Tumino, R; Vercelli, M; Wolf, HJ; Wu, XC; Coleman, MP (2013) Colorectal cancer survival in the USA and Europe: a CONCORD high-resolution study. BMJ open, 3 (9). e003055. ISSN 2044-6055 DOI: https://doi.org/10.1136/bmjopen-2013-003055

Downloaded from: http://researchonline.lshtm.ac.uk/1217019/

DOI: 10.1136/bmjopen-2013-003055

Usage Guidelines

Please refer to usage guidelines at http://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: Creative Commons Attribution Non-commercial http://creativecommons.org/licenses/by-nc/3.0/
Colorectal cancer survival in the USA and Europe: a CONCORD high-resolution study


ABSTRACT

Objectives: To assess the extent to which stage at diagnosis and adherence to treatment guidelines may explain the persistent differences in colorectal cancer survival between the USA and Europe.

Design: A high-resolution study using detailed clinical data on Dukes’ stage, diagnostic procedures, treatment and follow-up, collected directly from medical records by trained abstractors under a single protocol, with standardised quality control and central statistical analysis.

Setting and participants: 21 population-based registries in seven US states and nine European countries provided data for random samples comprising 12,523 adults (15–99 years) diagnosed with colorectal cancer during 1996–1998.

Outcome measures: Logistic regression models were used to compare adherence to ‘standard care’ in the USA 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 USA and Europe, while that of Dukes’ C was more frequent in the USA (38% vs 21%) and of Dukes’ D more frequent in Europe (22% vs 10%). Resection with curative intent was more frequent in the USA (85% vs 75%). Elderly patients (75–99 years) were 70–90% less likely to receive radiotherapy and chemotherapy. Age-standardised 5-year net survival was similar in the USA (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 USA in the late 1990s are probably attributable to earlier stage and more extensive use of surgery and adjuvant treatment in the USA.

ARTICLE SUMMARY

Article focus

▪ Why has population-based survival for colorectal cancer been so much higher in the USA 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

▪ The stage at diagnosis varied more widely between the participating European countries than between the 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 in the USA. 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 5-year net survival from colorectal cancer in the late 1990s were probably attributable to the earlier stage and more extensive use of surgery and adjuvant treatment in the USA. Lower survival in Europe was mainly attributable to the 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.

Elderly patients with colorectal cancer received surgery, chemotherapy or radiotherapy less often than younger patients, despite evidence that they could also have benefited.
ARTICLE SUMMARY

Strengths and limitations of this study

- 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, which was 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 patients with cancer.

- Most of the 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 USA than in Europe.1 Survival for patients diagnosed during 1985–1989 was higher in each of the 9 US states and metropolitan areas covered at that time by the Surveillance, Epidemiology and End Results (SEER) Program 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 1990–1991 between 10 territories in five European countries and the nine SEER areas were mainly attributable to the stage at diagnosis.3

The first worldwide analysis of cancer survival (CONCORD4) 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 1990–1994 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 USA and Canada than in many other countries. Differences between the USA and most European regions were smaller than for patients diagnosed during 1985–1989.5 The largest differences were between the USA and Eastern Europe.

The CONCORD protocol incorporated studies designed to explain the international variations in survival. These ‘high-resolution’ studies involve the 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 transatlantic 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 USA; (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’5 for colorectal cancer in relation to age, stage and cancer site between the USA 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 (International Classiﬁcation of Diseases, ninth revision (ICD-9))5 codes 1530–1539, 1540–1549) in the USA and Europe during 1996–1998. 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 nine countries, four 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) and the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa and Varese), Slovenia* and Spain (Granada, Navarra and Tarragona); Eastern Europe: Estonia*, Poland (Cracow and Kielce) and Slovakia*. Estonia is classiﬁed by the UN as being in Northern Europe, but cancer survival has resembled that in Eastern Europe countries7 and Estonia was included here with Eastern Europe. US data were provided by seven statewide registries (California, Colorado, Illinois, Louisiana, New York, Rhode Island and 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 study8 updated follow-up to at least 5 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 1996–1998 (1997 in the USA). The Finnish cases were a population-based sample of patients diagnosed in the Tampere hospital region, which is considered representative of Finland.

Of the 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 USA, but not in Europe); unknown sex (22, 0.2%); benign or uncertain behaviour (1), or age less than 15 or 100 years. URL: http://unstats.un.org/unsd/methods/m49/m49regin.htm
or over (19.1%). In all, 12 523 patients with a primary, invasive and 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%) and 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 tumour, nodes, metastasis (TNM) manual and/or Dukes’ stage. Many registries collected TNM and Dukes’ stage, but only Dukes’ stage was available for Kielce (Poland) and Finland, so we used Dukes’ classification in order to include these populations in the stage-specific analyses. Dukes’ stage information was more complete than that in the 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, excluding polypectomy and transanal excision. Radiotherapy and chemotherapy were dichotomised as administered versus 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 the stage at diagnosis.

Net survival up to 5 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 patients with cancer 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 approach10–12 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 patients with cancer 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). The 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 1000 person-years at risk at selected times since diagnosis (1 and 6 months, and 1, 3 and 5 years), by age group as well as by stage at diagnosis, after adjustment for age.

The 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 patients with colorectal cancer 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 patients with rectal cancer 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 stpm215 in Stata V.12 (StataCorp LP, College Station, Texas, USA).

RESULTS
We included 12 523 patients with an invasive, primary colorectal cancer: 9186 patients in 14 registries in nine European countries and 3337 patients in seven 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 patients with colorectal cancer who were men was similar in Europe (55%) and the USA (50%), but colon cancer was more frequent in the USA (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 USA.

Early-stage (Dukes’ A or B) colorectal cancers were equally common in the USA (45%) and Europe (47%).
<table>
<thead>
<tr>
<th>EUROPE</th>
<th>Registry</th>
<th>Period of diagnosis</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estonia</td>
<td>Estonia</td>
<td>1997</td>
<td>491</td>
<td>88</td>
<td>250</td>
<td>45</td>
<td>337</td>
<td>60</td>
<td>144</td>
<td>26</td>
<td>151</td>
<td>27</td>
<td>76</td>
<td>14</td>
</tr>
<tr>
<td>Finland</td>
<td>Finland</td>
<td>1996–1998</td>
<td>478</td>
<td>91</td>
<td>247</td>
<td>47</td>
<td>294</td>
<td>56</td>
<td>61</td>
<td>12</td>
<td>174</td>
<td>33</td>
<td>103</td>
<td>20</td>
</tr>
<tr>
<td>France</td>
<td>Côte d’Or</td>
<td>1996–1997</td>
<td>544</td>
<td>97</td>
<td>302</td>
<td>54</td>
<td>382</td>
<td>68</td>
<td>112</td>
<td>20</td>
<td>209</td>
<td>37</td>
<td>98</td>
<td>17</td>
</tr>
<tr>
<td>Italy</td>
<td>Genova</td>
<td>1996</td>
<td>529</td>
<td>90</td>
<td>326</td>
<td>55</td>
<td>379</td>
<td>64</td>
<td>71</td>
<td>12</td>
<td>192</td>
<td>33</td>
<td>148</td>
<td>25</td>
</tr>
<tr>
<td>Netherlands</td>
<td>North East Netherlands</td>
<td>1997</td>
<td>1821</td>
<td>94</td>
<td>1002</td>
<td>52</td>
<td>1240</td>
<td>64</td>
<td>280</td>
<td>14</td>
<td>579</td>
<td>30</td>
<td>463</td>
<td>24</td>
</tr>
<tr>
<td>Poland</td>
<td>Cracow</td>
<td>1997</td>
<td>529</td>
<td>90</td>
<td>326</td>
<td>55</td>
<td>379</td>
<td>64</td>
<td>71</td>
<td>12</td>
<td>192</td>
<td>33</td>
<td>148</td>
<td>25</td>
</tr>
<tr>
<td>Kielce</td>
<td>1996</td>
<td>267</td>
<td>99</td>
<td>147</td>
<td>54</td>
<td>133</td>
<td>49</td>
<td>62</td>
<td>23</td>
<td>67</td>
<td>25</td>
<td>41</td>
<td>15</td>
<td>89</td>
</tr>
<tr>
<td>Slovakia</td>
<td>1996</td>
<td>535</td>
<td>92</td>
<td>351</td>
<td>60</td>
<td>315</td>
<td>54</td>
<td>161</td>
<td>28</td>
<td>147</td>
<td>25</td>
<td>75</td>
<td>13</td>
<td>160</td>
</tr>
<tr>
<td>Slovenia</td>
<td>1997</td>
<td>871</td>
<td>93</td>
<td>490</td>
<td>52</td>
<td>474</td>
<td>51</td>
<td>131</td>
<td>14</td>
<td>265</td>
<td>28</td>
<td>243</td>
<td>26</td>
<td>209</td>
</tr>
<tr>
<td>Navarra</td>
<td>1997</td>
<td>558</td>
<td>95</td>
<td>354</td>
<td>60</td>
<td>335</td>
<td>57</td>
<td>100</td>
<td>17</td>
<td>188</td>
<td>32</td>
<td>121</td>
<td>21</td>
<td>120</td>
</tr>
<tr>
<td>European registries‡</td>
<td>9186</td>
<td>8529</td>
<td>93</td>
<td>4871</td>
<td>53</td>
<td>5556</td>
<td>60</td>
<td>1493</td>
<td>17</td>
<td>2586</td>
<td>30</td>
<td>1840</td>
<td>21</td>
<td>1948</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>523</td>
<td>478</td>
<td>91</td>
<td>247</td>
<td>47</td>
<td>294</td>
<td>56</td>
<td>61</td>
<td>12</td>
<td>174</td>
<td>33</td>
<td>103</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Western Europe</td>
<td>2497</td>
<td>2365</td>
<td>95</td>
<td>1304</td>
<td>52</td>
<td>1622</td>
<td>65</td>
<td>392</td>
<td>16</td>
<td>788</td>
<td>32</td>
<td>561</td>
<td>22</td>
<td>446</td>
</tr>
<tr>
<td>Southern Europe†</td>
<td>4242</td>
<td>3930</td>
<td>93</td>
<td>2320</td>
<td>52</td>
<td>2570</td>
<td>61</td>
<td>545</td>
<td>14</td>
<td>1158</td>
<td>30</td>
<td>902</td>
<td>24</td>
<td>868</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>1924</td>
<td>1756</td>
<td>91</td>
<td>1000</td>
<td>52</td>
<td>1070</td>
<td>56</td>
<td>495</td>
<td>26</td>
<td>466</td>
<td>24</td>
<td>274</td>
<td>14</td>
<td>574</td>
</tr>
</tbody>
</table>

| USA | California | 1997 | 485 | 96 | 242 | 49 | 356 | 72 | 89 | 18 | 137 | 28 | 168 | 34 | 60 | 12 | 41 | 8 |
| Colorado | 1997 | 536 | 98 | 296 | 54 | 437 | 74 | 85 | 16 | 162 | 30 | 191 | 35 | 50 | 10 | 54 | 10 |
| Illinois | 1997 | 497 | 98 | 239 | 47 | 384 | 76 | 71 | 14 | 144 | 29 | 224 | 44 | 36 | 7 | 30 | 6 |
| Louisiana | 1997 | 502 | 98 | 263 | 51 | 374 | 73 | 115 | 23 | 146 | 29 | 146 | 29 | 90 | 18 | 14 | 3 |
| New York | 1997 | 473 | 96 | 248 | 50 | 350 | 71 | 91 | 18 | 114 | 23 | 226 | 46 | 21 | 4 | 40 | 8 |
| Rhode Island | 1997 | 413 | 99 | 195 | 47 | 302 | 72 | 64 | 15 | 149 | 36 | 160 | 38 | 29 | 7 | 16 | 4 |
| South Carolina | 1997 | 358 | 97 | 187 | 51 | 265 | 72 | 68 | 18 | 89 | 24 | 150 | 41 | 26 | 7 | 35 | 10 |
| US registries | 3337 | 3264 | 98 | 1670 | 50 | 2438 | 73 | 523 | 17 | 241 | 28 | 1265 | 38 | 318 | 10 | 230 | 7 |

| Total | 12523 |

*‘Dukes’ stage A–D correspond to TNM stage categories I–IV.
†Data for Ragusa are not included in the percentages of Dukes’ stage for Southern Europe.
‡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.

but the stage distributions varied widely between the US states and between the European regions. Tumours in Dukes’ stage A were of similar frequency in Europe (17%, range 11–28%) and in the USA (17%, 14–23%), and the proportion of Dukes’ B tumours were also very comparable (Europe 30%, 25–37%; USA 28%, 24–36%). In contrast, Dukes’ C tumours were twice as common in the USA (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 USA (10%, 7–18%). The proportion of tumours with unspecified stage was slightly higher in Europe (10%, 4–24%) than in the USA (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 (ie, metastatic cases plus unrected cases for which no data on stage were available) were more common in the four European regions (29%, 24–34%) than in the USA (20%, 16–23%; table 2). In Europe, advanced stage was more common in Southern Europe (30%) and Eastern Europe (34%). The highest proportion of patients at an advanced stage in the USA (23%, California) was similar to the lowest regional proportion in Europe (24%, Western Europe).

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

Thirty-day postoperative mortality was 5% or less in the USA and Europe. Among patients resected with curative intent, the proportion with a known stage was around 95% in the USA 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 (see web-appendix table S1).

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

Relative to Southern Europe (2912 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, 95% CI 0.41 to 0.52), somewhat lower in Northern Europe (OR 0.88, 0.71 to 1.09) and much higher in Western Europe (OR 1.62, 1.43 to 1.85) and in the USA (OR 1.72, 1.52 to 1.94; table 4).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Advanced stage, resection with curative intent, 30-day postoperative mortality and proportion of patients with information on stage: colorectal cancer, Europe and the USA, 1996–1998</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All cases</td>
</tr>
<tr>
<td></td>
<td>Advanced stage†</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EUROPE</strong></td>
<td><strong>Registry</strong></td>
</tr>
<tr>
<td>European registries‡</td>
<td>Northern Europe</td>
</tr>
<tr>
<td></td>
<td>Western Europe§</td>
</tr>
<tr>
<td></td>
<td>Southern Europe¶</td>
</tr>
<tr>
<td></td>
<td>Eastern Europe</td>
</tr>
<tr>
<td>US registries</td>
<td>California</td>
</tr>
<tr>
<td></td>
<td>Colorado</td>
</tr>
<tr>
<td></td>
<td>Illinois</td>
</tr>
<tr>
<td></td>
<td>Louisiana</td>
</tr>
<tr>
<td></td>
<td>New York</td>
</tr>
<tr>
<td></td>
<td>Rhode Island</td>
</tr>
<tr>
<td></td>
<td>South Carolina</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
</tr>
</tbody>
</table>

†All metastatic cases, plus unrected cases for which no stage data were available.
*Curative intent: surgery not specified as palliative or tumour entirely resected.
‡Northern Europe: Finland; Western Europe: France (Côte d’Or) and the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa and Varese), Slovenia and Spain (Granada, Navarra and Tarragona); Eastern Europe: Estonia, Poland (Cracow and Kielce) and Slovakia.
§Data for North East Netherlands (1936) are not included in the percentages of Dukes’ stage for Western Europe because the date of surgery was not available.
¶Data for Ragusa (424) are not included in the percentages of Dukes’ stage for Southern Europe.
Patients aged 75 years or more were only half as likely to be resected with curative intent as those aged 15–64 years (OR 0.48, 95% CI 0.43 to 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 to 0.79).

Patients with Dukes’ B colon cancer received chemotherapy much less often in Western Europe (OR 0.10, 0.06 to 0.16) and Northern Europe (OR 0.29, 0.15 to 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 to 0.87) and more often in the USA (OR 1.56, 1.23 to 1.98) than in Southern Europe.

Radiotherapy was administered to patients with rectal cancer in Dukes’ stage A–C more often in the USA (OR 1.39, 1.10 to 1.76) and less often in Northern Europe (OR 0.58, 0.38 to 0.89) or Eastern Europe (OR 0.46, 0.36 to 0.59), compared to Southern Europe.

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

Overall, age-standardised net survival at 5 years was 50% in Europe and 58% in the USA (figure 1). Survival was lower in all European areas than in the USA, and only in Northern Europe was the figure (56%) close to that in the USA. Survival was lower in Western Europe (54%) and in Southern Europe (49%) and lowest in Eastern Europe (42%). Survival varied widely not only 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 USA than in Europe for Dukes’ stage A (84%) and B (75%) tumours, but higher in Northern Europe than in the USA for Dukes’ C (52%) and D (12%) tumours (figure 2). The geographical range in survival was much wider for locally advanced disease, from 36% in Eastern Europe to 77% in Northern Europe and 49% in the USA. As with overall survival, stage-specific 5-year survival was similar in Northern, Western and Southern Europe and the USA. In Eastern Europe, survival for node-positive, locally advanced and metastatic tumours was lower than in other European regions and the USA.

Survival was 5–12% higher in women than in men in all areas, especially in Northern and Western Europe (11–12%; see web-appendix figure S1).

The mean excess hazard of death at 1 and 6 months, and at 1, 3 and 5 years after diagnosis was higher in Eastern Europe than in all other regions, for all ages combined as well as in each of the three age categories (see web-appendix figure S2). The difference was most marked for elderly patients (75–99 years). No striking differences were found between Northern, Western and Southern Europe and the USA. The high excess hazard of death in Eastern Europe was mainly confined to patients with Dukes’ D tumours (see web-appendix figure S3).

**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 and the USA, and the USA. 

---

**Table 3** Chemotherapy in Dukes’ B and C colon cancer and radiotherapy in Dukes’ A–C rectal cancer

<table>
<thead>
<tr>
<th>EUROPE</th>
<th>Registry</th>
<th>Colon Dukes’ B*</th>
<th>Colon Dukes’ C*</th>
<th>Rectum Dukes’ A–C*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Among whom, chemotherapy</td>
<td>N</td>
<td>Among whom, chemotherapy</td>
</tr>
<tr>
<td><strong>EUROPE</strong></td>
<td><strong>Registy</strong></td>
<td><strong>N</strong></td>
<td><strong>%</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>European registries†</td>
<td>1748</td>
<td>343</td>
<td>20</td>
<td>1130</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>110</td>
<td>11</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Western Europe</td>
<td>591</td>
<td>23</td>
<td>4</td>
<td>346</td>
</tr>
<tr>
<td>Southern Europe‡</td>
<td>736</td>
<td>209</td>
<td>28</td>
<td>529</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>259</td>
<td>80</td>
<td>31</td>
<td>154</td>
</tr>
<tr>
<td><strong>US registries</strong></td>
<td><strong>1748</strong></td>
<td><strong>343</strong></td>
<td><strong>20</strong></td>
<td><strong>1130</strong></td>
</tr>
<tr>
<td>California</td>
<td>108</td>
<td>29</td>
<td>27</td>
<td>114</td>
</tr>
<tr>
<td>Colorado</td>
<td>129</td>
<td>29</td>
<td>22</td>
<td>145</td>
</tr>
<tr>
<td>Illinois</td>
<td>112</td>
<td>28</td>
<td>25</td>
<td>171</td>
</tr>
<tr>
<td>Louisiana</td>
<td>105</td>
<td>22</td>
<td>21</td>
<td>106</td>
</tr>
<tr>
<td>New York</td>
<td>86</td>
<td>24</td>
<td>28</td>
<td>157</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>119</td>
<td>37</td>
<td>31</td>
<td>107</td>
</tr>
<tr>
<td>South Carolina</td>
<td>68</td>
<td>31</td>
<td>46</td>
<td>113</td>
</tr>
</tbody>
</table>

*Dukes’ stage A–D correspond to TNM stage categories I–IV.
†Northern Europe: Finland; Western Europe: France (Côte d’Or) and the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa and Varese), Slovenia and Spain (Granada, Navarra and Tarragona); Eastern Europe: Estonia, Poland (Cracow and Kielce) and Slovakia.
‡Data for Ragusa (424) are not included in the percentages of Dukes’ stage for Southern Europe.
To our knowledge, this is the first population-based high-resolution study that allows direct comparison of colorectal cancer survival between Europe and the USA with clinical data on investigation and treatment collected directly from medical records by trained abstractors with a single protocol, which is 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 1996–1998 in each territory. These samples are not intended to be ‘representative’ of all patients with colorectal cancer in Europe or the USA, but they are representative of all patients with colorectal cancer diagnosed during 1996–1998 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, but its widespread use is more recent. Mesorectal excision was not used in Estonia before 1997, which may partly explain the low survival from rectal cancer.

The transatlantic 12% difference in the 3-year survival in colorectal cancer survival for patients diagnosed during 1990–1991 was mostly attributed to the differences in stage at diagnosis. In our study of patients diagnosed in the late 1990s, the overall 5-year net survival was still higher in the 7 US states (58%) than in the 14 European regions (49–56%). The widest differences with the USA 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 USA were simply from the SEER Program to seven of the state-wide NPCR registries. In the earlier study, differences in background mortality in the USA were controlled with a single national life table for 1990, weighted for the proportion of African-American patients, white patients 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 the methodological strengths of this study, but these changes do not explain why the transatlantic differences we observed in 5-year survival are smaller than the differences in 3-year survival for patients diagnosed in the early 1990s.

Survival varied widely not only among European countries, but also between the seven US states. Survival in Slovenia was lower than in other Southern European

---

**Table 4** Odds of colorectal cancer patients with cancer 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

<table>
<thead>
<tr>
<th>Region†‡</th>
<th>Resection for curative intent</th>
<th>Colon Dukes’ B*</th>
<th>Colon Dukes’ C*</th>
<th>Rectum Dukes’ A–C*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
<td>95%CI</td>
<td>N</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–64</td>
<td>3194</td>
<td>1.00</td>
<td></td>
<td>674</td>
</tr>
<tr>
<td>65–74</td>
<td>3195</td>
<td>0.89</td>
<td>0.79</td>
<td>0.99</td>
</tr>
<tr>
<td>75–99</td>
<td>3027</td>
<td>0.48</td>
<td>0.43</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>6191</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>3225</td>
<td>0.73</td>
<td>0.66</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>966</td>
<td>0.92</td>
<td>0.77</td>
<td>1.10</td>
</tr>
</tbody>
</table>

*Dukes’ stage A–D correspond to TNM stage categories I–IV.
†Northern Europe: Finland; Western Europe: France (Côte d’Or) and the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa and Varese), Slovenia and Spain (Granada, Navarra and Tarragona); Eastern Europe: Estonia, Poland (Cracow and Kielce) and Slovakia.
‡Data for Ragusa (424) are not included in the percentages of Dukes’ stage for Southern Europe.
countries and more similar to that in Eastern Europe. In
the USA, survival was lowest in South Carolina, where
African-American patients represent approximately 30% of
the population (http://www.ipspr.sc.edu/publication/
Older%20SC.pdf).

Apart from patients with Dukes’ B cancers, where sur-
vival was similar in Northern, Western and Southern
Europe, stage-specific net survival was rather variable.
Survival was highest in the USA 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 the stage data were not available
for 24% of cases.

The mean excess hazard of death up to 5 years after
diagnosis was similar in Europe and the USA 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 3 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 comorbidity 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 USA 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 USA
in the late 1990s. Almost 40% of respondents to the
Behavioural Risk Factor Surveillance System (http://
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 pre-
malignant 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 USA.
In fact, incidence in the USA is higher, the stage distri-
bution is less advanced, and survival is higher than in
Europe.

Adjuvant chemotherapy for colon cancer and adjuvant
radiotherapy for rectal cancer were used more widely in
the USA 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
patients with colon cancer received it in the USA, and

Figure 1 Five-year age standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and
the USA in the late 1990s: country and region. Note—Northern Europe: Finland; Western Europe: France (Côte d’Or) and the
Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa and Varese), Slovenia and Spain (Granada,
Navarre and Tarragona); Eastern Europe: Estonia, Poland (Cracow and Kielce) and Slovakia.
Figure 2  Five-year age-standardised net survival (%), patients diagnosed with primary invasive colorectal cancer in Europe and the USA in the late 1990s: region* and stage at diagnosis. *Northern Europe: Finland; Western Europe: France (Côte d’Or) and the Netherlands (North East Netherlands); Southern Europe: Italy (Genova, Ragusa and Varese), Slovenia and Spain (Granada, Navarra and Tarragona); Eastern Europe: Estonia, Poland (Cracow and Kielce) and Slovakia.

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 USA.

In contrast, there were striking differences in the use of adjuvant chemotherapy for Dukes’ C stage 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 would be so poorly followed. Comorbidity and greater toxicity are not valid reasons for the underuse of adjuvant chemotherapy in the elderly: toxicity is not greater\(^{24, 25}\) and quality of life is not worse.\(^{26}\)

Elderly patients were 90% less likely to receive adjuvant chemotherapy than younger patients. Clinical attitudes appear to differ between the USA 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; preoperative radiotherapy is preferable to postoperative radiotherapy\(^{27}\) and it is recommended in Europe and the USA.\(^{28-31}\) We were unable to distinguish between the impact of preoperative and postoperative radiotherapy, because this information was not systematically available, but fewer patients received radiotherapy in Europe than in the USA and the 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 comorbidity, but their 70% lower odds of receiving it cannot be explained by comorbidity 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 seven US states (84–88%), but it varied widely between the nine European countries (from 56% to 86%) and was particularly low in Eastern Europe (mean 62%). A more aggressive approach to surgical treatment for elderly patients with colorectal cancer in Europe could improve this situation, although European patients were more often diagnosed at an advanced stage or with unresectable disease. Performance status and comorbidity 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 years 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 often seems 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 USA in the late 1990s were still wide and may be attributable to the earlier stage at diagnosis, higher levels of surgery and more extensive use of adjuvant treatment in the USA.

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 the 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 the stage\(^{34}\); several registries had to be excluded because fewer than half the tumour records contained data on stage. In this high-resolution study, the stage data were remarkably complete (76–94% in Europe and 93% in the USA), because they were collected directly from clinical records. Ideally, the medical records of patients with cancer would systematically include data on...
investigations and stage at diagnosis; cancer registries would obtain those data for all patients and the 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 patients with cancer.

Author affiliations

1Cancer Research UK Cancer Survival Group, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
2Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
3Côte-d’Or Digestive Cancer Registry, Faculté de Médecine, Dijon Cédex, France
4Evaluative Epidemiology Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
5National Center of Epidemiology, Surveillance and Promotion of Health, National Institute of Health, Rome, Italy
6Descriptive Studies and Health Planning Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
7Alleanza Contro il Cancro, Rome, Italy
8Department of Epidemiology and Biostatistics, National Institute for Health Development, Tallinn, Estonia
9Navarra Cancer Registry, Navarra Public Health Institute, Navarra, Spain
10CIBER Epidemiology and Public Health CIBERESP, Madrid, Spain
11National Institute of Public Health, National Institute of Hygiene, Warszawa, Poland
12SC Department of Health and Environmental Control, South Carolina Central Cancer Registry, Office of Public Health Statistics and Information Systems, Columbia, South Carolina, USA
13Public Health Institute, Cancer Registry of Greater California, Sacramento, California, USA
14Comprehensive Cancer Centre the Netherlands, Utrecht, The Netherlands
15Rhode Island Department of Health, Rhode Island Cancer Registry, Providence, Rhode Island, USA
16Tarragona Cancer Registry, Foundation Society for Cancer Research and Prevention, Pere Virgili Health Research Institute, Tarragona, Spain
17Świętokrzyskie Centrum Onkologii (Holycross Cancer Centre), Kielce, Poland
18Faculty of Health Sciences, Jan Kochanowski University of Humanities and Sciences in Kielce, Kielce, Poland
19Finnish Cancer Registry, Helsinki, Finland
20Epidemiology and Cancer Registry, Institute of Oncology Ljubljana, Ljubljana, Slovenia
21Cracow Cancer Registry, Centre of Oncology, M Skłodowska-Curie Memorial Cancer Institute, Krakow, Poland
22National Cancer Registry of Slovakia, National Health Information Center, Bratislava, Slovakia
23Andalusian School of Public Health, Granada, Spain
24CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
25New York State Department of Health, New York State Cancer Registry, Albany, New York, USA
26Illinois Department of Public Health, Illinois State Cancer Registry, Springfield, Illinois, USA
27Cancer Registry and Environmental Epidemiology Division, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
28Cancer Registry and Histopathology Unit, Civile-MP Arezzo Hospital, ASP Ragusa, Ragusa, Italy
29UOS Epidemiologia Descrittiva, USM-IST (IRCCS Azienda Ospedaliera Universitaria San Martino—IST Istituto Nazionale per la Ricerca sul Cancro), Largo R Benzi, Genova, Italy
30Sez. Epidemiologia Descrittiva, Dipartimento di Scienze della Salute, Università di Genova, Genova, Italy
31Cancer Prevention and Control Division, University of Colorado Cancer Center, Colorado School of Public Health, Aurora, Colorado, USA
32Louisiana Tumor Registry, LSU Health Sciences Center School of Public Health, New Orleans, Louisiana, USA

Acknowledgements Some of the data for this study were collected with the support of the Compagnia di San Paolo, Turin, Italy. Alleanza Contro il Cancro, the Italian Cancer Network (http://www.alleanzacontroilcancro.it) supported a CONCORD Working Group meeting for this study in London, 29–30 September 2010. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Contributors CA, MS, GG and MPC contributed to the study design. CL, JF, TA, EA, MBL, SB, RC, ME, JPF, JG, SG, TH, MPZ, JR, CSD, MJSa, MJSb, TS, GT, RT, MV, HJW and 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, LCR, TA, ME, MV and MPC contributed to the interpretation of the findings. CA, BR and MPC drafted the article and CL, JF, HKW, LCR, MJS, MBL, MS, TA, XCW, CLo and GG contributed to the revisions of the manuscript. All authors have read and approved the final version of the manuscript.

Funding Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Cancer Prevention and Control, Cancer Surveillance Branch, Atlanta, GA; Louisiana Tumor Registry, School of Public Health, Louisiana State University, New Orleans, LA (cooperative agreement #US5/CCU 62(306); CDC/NPCR contractor. Atlanta, GA; New York State Cancer Registry, New York State Department of Health, Albany, NY (cooperative agreement #US5/CCU 220322); Colorado Central Cancer Registry, Colorado Department of Public Health and Environment, Denver, CO (cooperative agreement #US5/CCU 820326); Illinois State Cancer Registry, Illinois Department of Public Health, Springfield, IL (cooperative agreement #US5/CCU 520378); South Carolina Central Cancer Registry, Columbia; SC (cooperative agreement #US5/CCU 420312); California Cancer Registry, Sacramento, CA (cooperative agreement #US5/CCU 920352); Rhode Island Cancer Registry, Rhode Island Department of Health, Providence, RI (cooperative agreement #US5/CCU 520378); University of Kentucky, Lexington KY (UKRF 3049024672-12-568). Support was also obtained from the Health Department of the Navarra Government, Spain (research grant 79/2000). The participation of Estonia was partly supported by the Estonian Ministry of Education and Research (SF0940026s07).

Competing interests None.

Ethics approval The study was approved by the US Centers for Disease Control (CDC, Atlanta, Georgia, USA), Institutional Review Board #3551.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Additional results are available on the web appendix. No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/3.0/

REFERENCES
