The economic burden of colorectal cancer across Europe: a population-based cost-of-illness study

Raymond Hugo Henderson, Declan French, Timothy Maughan, Richard Adams, Claudia Allemani, Pamela Minicozzi, Michel P Coleman, Ethna McFerran, Richard Sullivan, Mark Lawler

Summary

Background Colorectal cancer is one of the leading causes of cancer morbidity and mortality in Europe. We aimed to ascertain the economic burden of colorectal cancer across Europe using a population-based cost-of-illness approach.

Methods In this population-based cost-of-illness study, we obtained 2015 activity and costing data for colorectal cancer in 33 European countries (EUR-33) from global and national sources. Country-specific aggregate data were acquired for health-care, mortality, morbidity, and informal care costs. We calculated primary, outpatient, emergency, and hospital care, and systemic anti-cancer therapy (SACT) costs, as well as the costs of premature death, temporary and permanent absence from work, and unpaid informal care due to colorectal cancer. Colorectal cancer health-care costs per case were compared with colorectal cancer survival and colorectal cancer personnel, equipment, and resources across EUR-33 using univariable and multivariable regression. We also compared hospital care and SACT costs against 2009 data for the 27 EU countries.

Findings The economic burden of colorectal cancer across Europe in 2015 was €19·1 billion. The total non-health-care cost of €11·6 billion (60·6% of total economic burden) consisted of loss of productivity due to disability (€6·3 billion [33·0%]), premature death (€3·0 billion [15·9%]), and opportunity costs for informal carers (€2·2 billion [11·6%]). The €7·5 billion (39·4% of total economic burden) of direct health-care costs consisted of hospital care (€3·3 billion [43·4%] of health-care costs), SACT (€1·9 billion [25·6%]), and outpatient care (€1·3 billion [17·7%]), primary care (€0·7 billion [9·3%]), and emergency care (€0·3 billion [3·9%]). The mean cost for managing a patient with colorectal cancer varied widely between countries (€259–36 295). Hospital-care costs as a proportion of health-care costs varied considerably (24·1–84·8%), with a decrease of 21·2% from 2009 to 2015 in the EU. Overall, hospital care was the largest proportion (43·4%) of health-care expenditure, but pharmaceutical expenditure was far higher than hospital-care expenditure in some countries. Countries with similar gross domestic product per capita had widely varying health-care costs. In the EU, overall expenditure on pharmaceuticals increased by 213·7% from 2009 to 2015.

Interpretation Although the data analysed include non-homogenous sources from some countries and should be interpreted with caution, this study is the most comprehensive analysis to date of the economic burden of colorectal cancer in Europe. Overall spend on health care in some countries did not seem to correspond with patient outcomes. Spending on improving outcomes must be appropriately matched to the challenges in each country, to ensure tangible benefits. Our results have major implications for guiding policy and improving outcomes for this common malignancy.

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Introduction

Colorectal cancer represents one of the most substantial cancer burdens in Europe. In 2009, colorectal cancer accounted for 11·5% of all new cancer diagnoses in the 27 EU countries,[1,2] with health-care costs of over €5·5 billion.[3] Together with economic losses from morbidity and mortality (indirect costs) and informal care costs, the total economic burden was more than €13 billion. However, since 2009, the health-care and economic landscapes have markedly changed. Increasing incidence of colorectal cancer and advances in therapeutic innovation (intravenous precision and targeted treatments, and oral targeted therapies) have contributed to greater management costs.[4,5] Colorectal cancer remains the second most common cause of cancer death in Europe.[6] Age-standardised 5-year net survival is highest in northern, western, and southern Europe and lowest in central and eastern European countries.[7]

Understanding the comparative economic burden of colorectal cancer across Europe, using up-to-date intelligence and robust methodologies, is crucial for delivering evidence-based public policy frameworks that governments can use to guide appropriate investment to help reduce the morbidity and mortality associated with this common cancer.

Research in context

Evidence before this study

Colorectal cancer is one of the most commonly diagnosed cancer in Europe, and the second most common cause of cancer death. We searched MEDLINE using the terms "economic burden", "colorectal cancer", and "Europe" for study designs such as economic burden and cost-of-illness studies published up until Dec 31, 2020. No language restrictions were applied. A previous study on cancer, using data from 2009, which only analysed the costs of colorectal cancer and did not derive any correlations with drivers, determinants, and outcomes for this disease, indicated that direct and indirect costs of colorectal cancers in the 27 EU countries were approximately €13 billion. However, no previous study has focused specifically on the economic burden of colorectal cancer in Europe, and Europe's health-care systems and economic landscape have changed substantially since 2009.

Added value of this study

This study represents the most comprehensive analysis of the economic burden of colorectal cancer in Europe to date. Using high-quality granular data from a variety of sources, the epidemiology of colorectal cancer and its consequential financial effect on patients and their carers, on health-care infrastructure, and on society were defined for the 27 EU countries plus Iceland, Norway, Serbia, Switzerland, Turkey, and the UK. The economic burden of colorectal cancer across Europe in 2015 totalled €19·1 billion, with over 60% of the total cost associated with loss of productivity and opportunity costs for informal carers. Direct health-care costs represented less than 40% of the total cost. Countries with similar gross domestic product per capita had widely varying health-care expenditures. Expenditure on pharmaceuticals increased by over 200% between 2009 and 2015. In some countries, however, increased expenditure did not align with improved outcomes—eg, some central and eastern European countries outspent northern and western European countries, especially on pharmaceutical medicines, but still had poorer outcomes.

Implications of all the available evidence

Comprehensive evaluation of the economic burden of colorectal cancer can provide vital intelligence to underpin better health policy implementation and more appropriate resource allocation. Upfront investment in colorectal cancer infrastructure is more likely to not only reduce colorectal cancer deaths, but also to lessen the economic burden. Increased expenditure on pharmaceutical medicines might not necessarily be reflected in improved outcomes, particularly in central and eastern European countries, emphasising the need to use resources most appropriately for this common malignancy.

A comparative European analysis allows precise mapping of the health economic landscape, and its relationship to colorectal cancer outcomes, by capturing individual components that contribute to the overall economic burden. The granularity of the information that can be extracted allows specific expenditure patterns to be discerned—eg, precise costs of individual chemotherapy or targeted therapy in each country. This economic intelligence can help identify activities and associated expenditures in individual countries that might be examples of best practice that can be shared with European partners, or these data might highlight inappropriate use of scarce resources that should be redirected to more patient-focused and value-based activities. We aimed to define the economic burden of colorectal cancer in 33 European countries (EUR-33; the 27 EU countries plus Iceland, Norway, Serbia, Switzerland, Turkey, and the UK). We aim to highlight how this intelligence can inform approaches to improve key health and socioeconomic outcomes for European citizens and societies.

See Online for appendix

Methods

Study design

In this population-based cost-of-illness study, we evaluated the cost of colorectal cancer, defined as invasive malignancies of the colon, rectum, and anus by the International Classification of Diseases, 10th revision (codes C18 to C21). For the EUR-33, we acquired activity data from 2015 related to colorectal cancer management and associated costs using a published framework in which costs for health care, productivity losses, and informal care were determined for lung, breast, colorectal, and prostate cancer in the 27 EU countries.[3] Resource use in 2015 was assessed for all prevalent patients (ie, patients newly diagnosed and patients receiving ongoing care) in each country.

We determined the value of resources used from the costs in each country and, when possible, used either colorectal cancer-specific or cancer-specific costs (table 1). Costs were expressed in local currency units and standardised between countries using purchasing power parity (PPP) for hospital services; PPP indicators were obtained from Eurostat and applied to our datasets.[8] PPP measures the price of a basket of goods (in this case, hospital services) in each country relative to the mean of the 27 EU countries.

We derived aggregate activity and costing data from global and national sources, and ranked the activity data sources and costings by colorectal cancer-specific reliability from A+ (best) to E (worst; appendix pp 1–7).

Health-care expenditure

We compiled activities and costs for hospital, outpatient, primary, and emergency care from colorectal cancer-specific or cancer-specific data. Colorectal cancer prevalence was applied to cancer-specific or general disease data to obtain colorectal cancer-specific values (table 1). Several countries did not have national data for emergency care (Croatia, Lithuania, Luxembourg, Romania, and Serbia) or hospital care (Estonia). We estimated the data for these countries by using corresponding proportions extrapolated from countries with similar health-care expenditure per person, life expectancy, and geographical location. To test the robustness of the hospital-care cost data, we did a sensitivity analysis by replacing colorectal cancer-specific or cancer-specific hospital-care cost data with mean hospital-care expenditure data gathered from Eurostat[9] and then repeated the analysis.

Colectomy activity data were available for each country (from Eurostat), but these data did not distinguish between colorectal cancer and other diseases, such as Crohn's disease or ulcerative colitis. Similarly, Eurostat cost data were only available for generalised domains (eg, long-term care or laboratory services), so attributable costs could not be estimated

	Primary care activity	Outpatient care activity	Accident and emergency care activity	Hospital care activity	Systemic anti-cancer therapy activity	Primary care costs	Outpatient care costs	Accident and emergency care costs	Hospital care costs	Systemic anti-cancer therapy costs
Austria	B	B	B	A+	A+	B	A	B	A+	A+
Belgium	B	B	B	A+	A+	B	A	B	A	A+
Bulgaria	B	B	B	A+	A+	B	B	E	C	A+
Croatia	B	B	C	A+	A+	B	B	B	C	A+
Cyprus	B	A	B	A+	C	B	A	B	A	C
Czech Republic	B	A	B	A+	A+	B	B	B	C	A+
Denmark	B	A+	A+	A+	C	C	A	A	A	C
Estonia	B	A	B	C	A+	C	B	C	B	A+
Finland	B	A	B	A+	A+	B	A	B	A	A+
France	B	B	B	A+	A+	B	A	B	A	A+
Germany	B	A	B	A+	A+	B	A	B	A	A+
Greece	B	B	B	A+	A+	B	B	B	A+	A+
Hungary	B	B	B	A+	A+	B	A+	B	A+	A+
Iceland	B	A	B	A+	C	B	A	B	A	C
Ireland	B	B	B	A+	A+	B	A+	A+	A	A+
Italy	B	B	B	A+	A+	A	A	A	A	A+
Latvia	A+	A+	B	A+	A+	A+	A+	B	A+	A+
Lithuania	B	B	C	A+	A+	B	A	B	A	A+
Luxembourg	B	B	C	A+	A+	B	A	B	C	A+
Malta	B	B	B	A+	C	C	D	B	B	C
Netherlands	B	A+	B	A+	C	B	A+	A+	A+	C
Norway	B	A	B	A+	A+	B	B	B	A+	A+
Poland	B	B	B	A+	A+	B	A	B	A+	A+
Portugal	B	B	B	A+	A+	B	A	B	C	A+
Romania	B	B	C	A+	A+	D	D	E	C	A+
Serbia	B	B	C	A+	A+	B	B	B	A+	A+
Slovakia	B	A	B	A+	A+	D	B	B	C	A+
Slovenia	B	A	B	A+	A+	D	D	B	A+	A+
Spain	B	A	B	A+	A+	B	A	A	A	A+
Sweden	B	A	B	A+	A+	B	A	B	A+	A+
Switzerland	B	B	B	A+	A+	B	A+	C	A+	A+
Turkey	B	B	B	A+	A+	B	B	B	B	A+
UK	B	A+	B	A+	A+	A+	A+	A+	A+	A+

A+=national colorectal cancer data. Colorectal cancer-specific health-care activity and expenditure data were obtained for that country's population. A=national cancer-specific data. Cancer-specific health-care activity and expenditure data were obtained for that country's population. B=national data but not colorectal cancer specific. All-cause health-care activity data were obtained but not all data were on colorectal cancer. We evaluated colorectal cancer-specific resource use by multiplying all-cause national data by the percentage of ambulatory visits due to colorectal cancer out of all ambulatory visits if available. If colorectal cancer-related ambulatory information was not available we used the percentage of hospital discharges due to colorectal cancer out of all discharges to assign that country's health-care use. Costs were directly obtained from sources such as national fee schedules, national reports, and published studies. C=no national data. That country's activity data were obtained for all diseases from similar countries, and colorectal cancer activity data were estimated using the approach defined in B. Costs were acquired from national expenditure figures (eg, primary care, outpatient care, emergency care, and hospital care) using the respective total activity levels (eg, cost per hospital day was estimated by dividing the total hospital expenditure by the total number of hospital days). D=estimates derived costs and prices used in the WHO-CHOICE analysis. E=derived from the predictions of linear regression analyses of the unit costs of countries with available data.

Table 1: **Sources used to obtain health-care activity and unit costs by category and country**

For more on **IQVIA** see https://www.iqvia.com

For more on the **International Agency for Research on Cancer** see https://www.iarc.who.int/

for colorectal cancer. For all countries, systemic anticancer therapy (SACT) expenditures for colorectal cancer (split by drug into chemotherapy and targeted therapy; appendix pp 4–5) were supplied by IQVIA Oncology data (2015).

Population data were accessed from Eurostat.[10] 5-year prevalence estimates at the end of 2012 were sourced from the International Agency for Research on Cancer. We extrapolated these estimates to calculate total prevalence at the end of 2015 (appendix p 8), which allowed us to calculate health-care costs for each prevalent case.

We determined the proportion of health-care costs for colorectal cancer in EUR-33 (calculated from total health-care expenditure); we also calculated the proportion of hospital-care costs and the proportion of pharmaceutical medicine costs (both calculated from total colorectal cancer health-care costs).

We compared hospital care and SACT costs from our study with 2009 data from the 27 EU member states,[3] and as a validity check of data sources, hospital care costs were exchanged for mean hospital care expenditure data from Eurostat.[3,9]

Informal care costs

Informal care costs are an opportunity cost—ie, they comprise the financial loss to caregivers, such as lost earnings or leisure time in providing unpaid care for relatives or friends. For each country, we calculated informal care costs from the prevalence statistics and the probability that patients were receiving such care from wave 6 of the Survey of Health, Ageing and Retirement in Europe (SHARE).[11] SHARE gathered data on 60 000 people in 17 EUR-33 countries in 2015. We calculated probabilities for the remaining 16 countries using pooled data from similar countries (appendix pp 9–13). SHARE data informed an ordered logistic regression, applied to estimate the number of hours of informal care required by patients with colorectal cancer. Hours were multiplied by the probability of receiving care and the mean or minimum hourly wage, depending on whether the caregiver was employed or unemployed (appendix pp 9–13).

Productivity losses from colorectal cancer

We estimated the costs to the overall economy in each country from lost earnings due to morbidity and premature mortality (appendix p 14).

For mortality costs, we extracted the number of deaths by age (15–65 years), sex, and country from Eurostat.[12] Number of working years lost (years lost) were calculated by subtracting the age of death from colorectal cancer from the effective retirement age in each country.[13,14] Age-specific and gender-specific employment rates[15] for EUR-33 were applied to the years lost. To account for lost future earnings, we multiplied years lost by wages[16] and converted them to current prices. We calculated total earnings lost using the following equation:

$$\text{Total earnings lost} = X\left(\frac{1}{i} - \frac{1}{i(1+i)^n}\right)$$

where n is years lost, i is the discount rate (either 0·0%, 3·5%, or 10·0%), and X is the annual earnings lost due to colorectal cancer death. X was calculated using the following equation:

$$X = 230 \text{ days} \times \text{daily wage} \times \text{employment rate} \times \text{activity rate}$$

We summed lost earnings by age group, sex, and country to give total economic losses from premature death, applying the human capital approach. The human capital approach was applied rather than the friction cost approach because it takes the perspective of the patient and society rather than that of employers and is less affected by labour market conditions than the friction cost approach.[17–19] For temporary earnings lost (appendix pp 14–15) patient sick-days were calculated as a proportion of total sick-days for each country using the following formula:

$$\text{Temporary earnings lost} = \text{sick days due to colorectal cancer} \times \text{daily wage}$$

For morbidity costs, we calculated lost earnings from permanent absence (permanent earnings lost) from the total number of individuals collecting disability benefits in each country,[20] applying colorectal cancer 5-year net survival over the lifetime of each patient, from 5-year age groupings, and applying the discount rate using the human capital approach (appendix pp 15–16):

$$\text{Permanent earnings lost} = \phi Y\left(\frac{1}{i+\delta} - \frac{\phi^n}{(i+\delta)(1+i)^n}\right)$$

where n is years lost, i is the discount rate (either 0·0%, 3·5%, or 10·0%), δ is the conditional probability of not surviving, ϕ is the conditional probability of survival,

$$\text{Conditional probability of survival} = \phi = 1 - \delta$$

and Y is the annual earnings lost due to colorectal cancer disablement. We calculated Y using the following formula:

$$Y = 230 \text{ days} \times \text{daily wage} \times \text{employment rate}$$

Lost earnings were summed for temporary and permanent absences to give total morbidity losses.

Statistical analysis

We examined countries for associations with colorectal cancer-related health-care costs per capita and per case

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	Health-care costs							Productivity costs		Informal care costs, € (%)	Total non-health-care expenditure costs, € (%)	Total costs, €
	Primary care costs, € (%)	Outpatient care costs, € (%)	Emergency care costs, € (%)	Hospital care costs, € (%)	Systemic anti-cancer therapy costs, € (%)	Total health-care expenditure costs, € (%)	Percentage of total health-care expenditure	Mortality costs, € (%)	Morbidity costs, € (%)			
Austria	28 027 (13·9%)	3883 (1·9%)	28 773 (14·3%)	104 808* (52·0%)	36 240* (18·0%)	201 730 (57·0%)	0·9%	24 605 (7·0%)	105 584 (29·9%)	21 738 (6·1%)	151 927 (43·0%)	353 657
Belgium	8084 (5·3%)	24 062 (15·8%)	6061 (4·0%)	75 941† (49·9%)	38 088* (25·0%)	152 235 (38·7%)	0·5%	29 765 (7·6%)	169 360 (43·0%)	42 169 (10·7%)	241 294 (61·3%)	393 530
Bulgaria	3596 (2·5%)	10 716 (7·5%)	1509 (1·1%)	38 194 (26·9%)	88 194* (62·0%)	142 209 (55·3%)	0·7%	38 105 (14·8%)	43 959 (17·1%)	32 858 (12·8%)	114 922 (44·7%)	257 131
Croatia	13 207 (16·3%)	10 735 (13·3%)	16 353 (20·2%)	22 167 (27·4%)	18 349* (22·7%)	80 811 (35·4%)	1·0%	28 599 (12·5%)	92 407 (40·5%)	26 509 (11·6%)	147 515 (64·6%)	228 327
Cyprus	62 (5·3%)	376 (31·9%)	19 (1·6%)	575† (48·8%)	145 (12·3%)	1177 (19·4%)	0·1%	1874 (30·9%)	2015 (33·3%)	993 (16·4%)	4881 (80·6%)	6058
Czech Republic	5173 (7·2%)	7271 (10·1%)	513 (0·7%)	36 140 (50·0%)	23 190* (32·1%)	72 287 (30·8%)	0·3%	46 433 (19·8%)	81 512 (34·7%)	34 644 (14·8%)	162 589 (69·2%)	234 876
Denmark	5756 (7·0%)	32 740† (39·9%)	5† (0·01%)	36 841† (44·9%)	6738 (8·2%)	82 080 (28·4%)	0·4%	45 637 (15·8%)	123 114 (42·6%)	38 353 (13·3%)	207 104 (71·6%)	289 185
Estonia	2251 (10·7%)	1458 (6·9%)	7301 (34·7%)	8767† (41·6%)	1286* (6·1%)	21 063 (25·8%)	0·8%	9446 (11·6%)	46 390 (56·8%)	4845 (5·9%)	60 681 (74·2%)	81 744
Finland	3967 (6·5%)	100‡ (0·2%)	2582 (4·2%)	39 815† (64·9%)	14 906* (24·3%)	61 369 (35·1%)	0·4%	22 270 (12·7%)	69 884 (40·0%)	21 331 (12·2%)	113 485 (64·9%)	174 854
France	25 088 (3·5%)	58 324 (8·2%)	8113 (1·1%)	295 779† (41·4%)	326 844* (45·8%)	714 149 (36·0%)	0·3%	167 233 (8·4%)	854 026 (43·0%)	250 470 (12·6%)	1 271 729 (64·0%)	1 985 878
Germany	71 404 (7·7%)	239 040‡ (25·8%)	5164 (0·6%)	389 986† (42·2%)	219 530* (23·7%)	925 124 (33·6%)	0·3%	537 834 (19·5%)	888 870 (32·3%)	401 728 (14·6%)	1 828 432 (66·4%)	2 753 556
Greece	6071 (10·3%)	8040 (13·7%)	2892 (4·9%)	37 835* (64·4%)	3878* (6·6%)	58 716 (52·1%)	0·4%	17 141 (15·2%)	17 682 (15·7%)	19 201 (17·0%)	54 025 (47·9%)	112 741
Hungary	70 028 (9·0%)	275 643 (35·6%)	21 314 (2·8%)	240 126* (31·0%)	167 137* (21·6%)	774 247 (76·3%)	2·2%	130 796 (12·9%)	19 623 (1·9%)	90 391 (8·9%)	240 810 (23·7%)	1 015 057
Iceland	400 (11·4%)	531 (15·2%)	16 (0·4%)	2202† (62·9%)	350 (10·0%)	3500 (18·1%)	0·4%	3219 (16·6%)	12 445 (64·3%)	203 (1·0%)	15 867 (81·9%)	19 367
Ireland	4230 (7·7%)	13 496 (24·6%)	1374 (2·5%)	22 092† (40·3%)	13 646* (24·9%)	54 838 (40·9%)	0·4%	31 956 (23·9%)	35 671 (26·6%)	11 485 (8·6%)	79 113 (59·1%)	133 950
Italy	49 547 (4·9%)	65 256 (6·5%)	84 832 (8·5%)	561 445† (56·1%)	240 355* (24·0%)	1 001 435 (56·3%)	0·7%	210 357 (11·8%)	310 752 (17·5%)	256 220 (14·4%)	777 330 (43·7%)	1 778 765
Latvia	218* (0·9%)	4993* (20·3%)	2875 (11·7%)	13 618* (55·3%)	2910* (11·8%)	24 614 (26·7%)	0·5%	10 184 (11·1%)	47 128 (51·2%)	10 116 (11·0%)	67 427 (73·3%)	92 041
Lithuania	2187 (7·8%)	10 135 (36·0%)	5741 (20·4%)	7101† (25·2%)	3026* (10·7%)	28 191 (23·2%)	0·3%	16 677 (13·7%)	64 698 (53·1%)	12 168 (10·0%)	93 543 (76·8%)	121 734
Luxembourg	241 (4·5%)	477 (8·8%)	34 (0·6%)	4571 (84·8%)	69* (1·3%)	5393 (28·4%)	0·4%	1383 (7·3%)	11 019 (58·0%)	1196 (6·3%)	13 598 (71·6%)	18 990
Malta	204 (6·8%)	206 (6·9%)	117 (3·9%)	2081 (69·6%)	380 (12·7%)	2989 (28·2%)	0·3%	1266 (11·9%)	5196 (49·0%)	1164 (11·0%)	7626 (71·8%)	10 615
Netherlands	12 965 (5·7%)	136 965* (60·2%)	2119 (0·9%)	56 882* (25·0%)	18 757* (8·2%)	227 688 (38·1%)	0·4%	113 872 (19·1%)	183 270 (30·7%)	72 036 (12·1%)	369 177 (61·9%)	596 865
Norway	1419 (6·6%)	4964 (23·1%)	242 (1·1%)	10 744* (50·1%)	4088* (19·1%)	21 456 (4·5%)	0·1%	36 526 (7·7%)	395 589 (83·4%)	20 540 (4·3%)	452 655 (95·5%)	474 110
Poland	14 812 (3·4%)	48 002 (10·9%)	4630 (1·0%)	319 045* (72·2%)	55 262* (12·5%)	441 750 (33·9%)	0·6%	194 261 (14·9%)	510 206 (39·2%)	156 923 (12·0%)	861 390 (66·1%)	1 303 140
Portugal	10 804 (8·3%)	9102 (7·0%)	13 376 (10·3%)	71 326 (54·9%)	25 265* (19·5%)	129 874 (36·3%)	0·6%	88 455 (24·7%)	98 252 (27·5%)	41 147 (11·5%)	227 855 (63·7%)	357 728
Romania	158 074 (26·6%)	144 683 (24·3%)	5645 (0·9%)	143 408 (24·1%)	143 178* (24·1%)	594 988 (46·7%)	1·2%	255 330 (20·0%)	320 482 (25·1%)	104 283 (8·2%)	680 096 (53·3%)	1 275 083
Serbia	19 716 (16·4%)	16 436 (13·7%)	1847 (1·5%)	69 097* (57·6%)	12 826* (10·7%)	119 922 (42·0%)	0·2%	58 812 (20·6%)	67 765 (23·8%)	38 716 (13·6%)	165 294 (58·0%)	285 216

(Table 2 continues on next page)

	Health-care costs							Productivity costs		Informal care costs, € (%)	Total non-health-care expenditure costs, € (%)	Total costs, €
	Primary care costs, € (%)	Outpatient care costs, € (%)	Emergency care costs, € (%)	Hospital care costs, € (%)	Systemic anti-cancer therapy costs, € (%)	Total health-care expenditure costs, € (%)	Percentage of total health-care expenditure	Mortality costs, € (%)	Morbidity costs, € (%)			
(Continued from previous page)												
Slovakia	15 175 (9·5%)	56 843 (35·5%)	2711 (1·7%)	42 608 (26·6%)	42 832* (26·7%)	160 169 (50·3%)	1·1%	29 577 (9·3%)	102 393 (32·2%)	26 165 (8·2%)	158 135 (49·7%)	318 305
Slovenia	2217 (7·0%)	1190 (3·7%)	494 (1·6%)	20 493* (64·6%)	7340* (23·1%)	31 733 (49·8%)	0·7%	13 498 (21·2%)	9063 (14·2%)	9377 (14·7%)	31 938 (50·2%)	63 672
Spain	73 983 (20·3%)	3771 (1·0%)	28 158‡ (7·7%)	132 213† (36·3%)	125 704* (34·6%)	363 829 (38·0%)	0·4%	159 962 (16·7%)	311 698 (32·5%)	122 516 (12·8%)	594 175 (62·0%)	958 004
Sweden	9429 (17·8%)	5085‡ (9·6%)	1995‡ (3·8%)	25 817* (48·7%)	10 718* (20·2%)	53 044 (22·3%)	0·2%	56 082 (23·6%)	92 555 (38·9%)	36 333 (15·3%)	184 970 (77·7%)	238 014
Switzerland	5736 (6·4%)	7211 (8·0%)	1318 (1·5%)	59 099* (65·5%)	16 825* (18·7%)	90 188 (35·8%)	0·4%	41 961 (16·7%)	99 378 (39·5%)	20 107 (8·0%)	161 447 (64·2%)	251 635
Turkey	27 677 (5·1%)	118 300 (22·0%)	13 098 (2·4%)	264 723 (49·1%)	114 961* (21·3%)	538 760 (57·3%)	0·6%	197 274 (21·0%)	140 802 (15·0%)	63 380 (6·7%)	401 455 (42·7%)	940 215
UK	52 426 (14·5%)	17 090* (4·7%)	23 980 (6·6%)	116 957* (32·4%)	150 946* (41·8%)	361 398 (17·9%)	0·2%	424 785 (21·1%)	992 158 (49·2%)	236 363 (11·7%)	1 653 307 (82·1%)	2 014 705
EUR-33	704 177 (9·3%)	1 337 122 (17·7%)	295 198 (3·9%)	3 272 496 (43·4%)	1 933 941 (25·6%)	7 542 956 (39·4%)	0·5%	3 045 177 (15·9%)	6 324 948 (33·0%)	2 225 668 (11·6%)	11 595 793 (60·6%)	19 138 749

Colorectal cancer health-care costs (primary, outpatient, emergency, and hospital care) and systemic anti-cancer therapy percentages are the proportion of that country's total colorectal cancer health-care costs; percentage of total health-care expenditure is the proportion of the total colorectal cancer economic burden that was attributable to health-care expenditure; percentages of productivity costs are the proportion of total colorectal cancer economic burden. Data are adjusted for purchasing power parity. Totals do not match the sum of costs because of rounding. EUR-33=33 European countries, defined as the 27 EU countries plus Iceland, Norway, Serbia, Switzerland, Turkey, and the UK. *Colorectal cancer activity and costs. †Colorectal cancer activity and other cancer costs. ‡General cancer activity and other cancer costs.

Table 2: **Costs (× €1000) of colorectal cancer in 33 European countries and proportion of health-care costs by country, 2015**

using log-linear univariable regression, dependent on gross domestic product (GDP; euros per capita), total health-care expenditure (euros per capita), disability-adjusted life-years (per 1000), incidence (crude rate per 1000 per year), total prevalence (per 1000), mortality (crude rate per 1000 per year), and age-standardised 5-year net survival (%). Drivers, determinants, and outcomes of colorectal cancer originated from 2015 data, except survival, which was for patients diagnosed during 2010–14.[7] Additionally, we analysed the relationship between colorectal cancer-related health-care costs per capita and per case and colorectal cancer incidence and colorectal cancer survival using log-linear multivariable regression.

For individual countries, we used multivariable regression to investigate the association between colorectal cancer survival and a set of independent variables: numbers of oncologists (2015 data), CT scanners (2015 data), CT scans (2015 data), radiologists (2015 data), radiotherapy machines (2015 data), and surgical oncologists (2018 data).

An explanatory variable was deemed statistically significant if its p value was less than 0·05. Stata software v.14.2 was used for regression analyses.

Sensitivity analyses were done on the discount rate and the costs due to health care, mortality, morbidity, and informal care. We also evaluated discount rates (0·0%, 3·5%, and 10·0%) for productivity losses due to morbidity and premature mortality. Effects on the total economic costs were determined for a 20% variation in each category.[3]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In 2015, the cost of colorectal cancer for the EUR-33 was €19·1 billion (PPP adjusted; table 2), broken down into €7·5 billion (39·4% of the total economic burden) of health-care costs (€12 per citizen or €2351 per patient), and non-health-care costs of €11·6 billion (60·6% of the total economic burden). The €7·5 billion attributable to health-care costs comprised hospital-care costs (€3·3 billion [43·4% of health-care costs]), SACT (€1·9 billion [25·6%]), outpatient-care costs (€1·3 billion [17·7%]), primary-care costs (€0·7 billion [9·3%]), and emergency-care costs (€0·3 billion [3·9%]). The €11·6 billion of non-health-care costs consisted of loss of productivity due to disability (€6·3 billion [33·0%]), premature death (€3·0 billion [15·9%]), and opportunity costs for informal carers (€2·2 billion [11·6%]). A map of the geographical spread of costs for each region or country is shown in the appendix (p 25).

Hospital-care costs as a proportion of health-care costs diverged considerably between nations, from €143·4 million (24·1%) of €594·9 million in Romania to €4·6 million (84·8%) of €5·4 million in Luxembourg. Hospitalisation accounted for the largest proportion of health-care costs both overall and individually in 27 of the EUR-33. However, in Bulgaria, France, and the UK, hospital-care expenditure was lower than expenditure on SACT—eg, in Bulgaria €38·2 million (26·9%) of €142·2 million of health-care costs was spent on hospital care and €88·2 million (62·0%) was spent on SACT. Hungary, Romania, and Slovakia had the largest expenditures on colorectal cancer health care per case, with expenditures on SACT being a large component (from €167·1 million [21·6%] of €774·2 million in Hungary to €42·8 million [26·7%] of €160·2 million in Slovakia) of overall costs (figure 1). SACT expenditure as a percentage of aggregate colorectal cancer-related health-care costs was lowest in Luxembourg (€68 891 [1·3%] of €5·4 million) and highest in Bulgaria (€88·2 million [62·0%] of €142·2 million). The mean cost for managing a patient with colorectal cancer varied from €259 in Cyprus to €36 295 in Hungary, with the mean cost per case in EUR-33 being €2351 (95% CI 1571–5745; figure 1); the differences in SACT expenditure showed a similar variation of €32 per patient in Cyprus versus €7835 per patient in Hungary. EUR-33 countries with similar GDP per capita have widely varying colorectal cancer health-care expenditures—eg, Austria (€4054 per patient, PPP) spent over four times more than Sweden (€1090 per patient, PPP; figure 1).

The greatest divergence observed within colorectal cancer health-care costs was in unit cost of an emergency hospital attendance, from €15 in Cyprus to €1511 in Hungary with a mean of €276 (95% CI 155–397) per emergency visit (appendix p 19). Substantial variation was also seen in the number of contacts with health-care services. Colorectal cancer-related hospital days (inpatient days) varied from 3 days per 1000 people per year in Turkey to 26 days per 1000 in Germany with an overall mean of 13 days (95% CI 11–15) per 1000 people per year (appendix p 20). Colorectal cancer health-care costs per capita varied widely within the EUR-33 (from €1 in Cyprus to €79 in Hungary); the mean cost of colorectal cancer was equivalent to €12 (95% CI 10–19) per capita (PPP adjusted; figure 1)

Informal-care costs were €2·2 billion (11·6%) of the €19·1 billion total economic burden of colorectal cancer

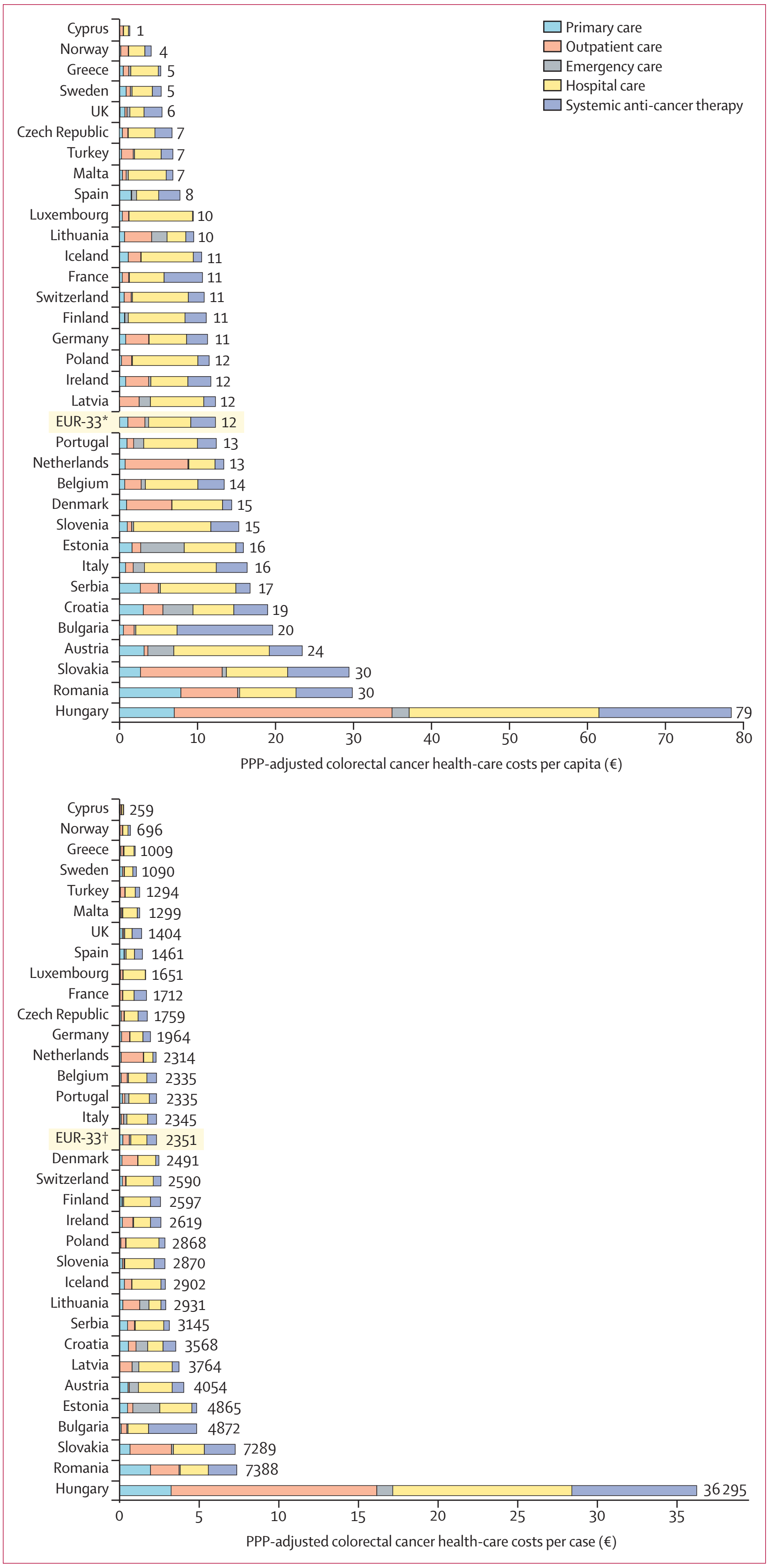

Figure 1: **Health-care costs of colorectal cancer per capita and per case in 33 European countries in 2015, by health-care service category, adjusted for PPP**

EUR-33=33 European countries, defined as the 27 EU countries plus Iceland, Norway, Serbia, Switzerland, Turkey, and the UK. PPP=purchasing power parity. *The EUR-33 entry was calculated by totalling the amount for each health-care domain and then dividing by the population in the EUR-33. †The EUR-33 entry was calculated by totalling the amount for each health-care domain and then dividing by the total number of colorectal cases in the EUR-33.

(table 2), ranging from 1·0% (€0·2 million) in Iceland to 17·1% (€19·2 million) in Greece (PPP adjusted).

Mean productivity unit costs diverged by country; losses in daily earnings ranged from €99 in Cyprus and Greece to €219 in Denmark with a mean of €138 (95% CI 128–149) of daily earnings lost (PPP adjusted; appendix p 19). There was substantial deviation in number of years or days lost because of premature death and morbidity. Losses due to colorectal cancer deaths amounted to €3·0 billion (15·9% of the total colorectal cancer economic burden), ranging from €24·6 million (7·0%) in Austria to €1·9 million (30·9%) in Cyprus (table 2). Morbidity losses totalled €6·3 billion (33·0% of total colorectal cancer economic burden), ranging from €19·6 million (1·9%) in Hungary to €395·6 million (83·4%) in Norway.

Results of the log-linear univariable regression revealed a strong positive relationship between health-care expenditure and GDP (per capita p=0·0010; per case p<0·0001), a strong positive relationship between health-care costs and disability-adjusted life-years (per capita p=0·0010; per case p=0·0010), a positive relationship between health-care costs and incidence (per capita p=0·041), a strong negative relationship between health-care costs and prevalence (per capita p=0·046; per case p<0·0001), and a strong positive relationship between health-care costs and mortality (per capita p<0·0001; per case p<0·0001; appendix pp 28–37).

A log-linear multivariable regression model (appendix p 23) was created by regressing colorectal cancer health-care costs on two independent variables (incidence rate and 5-year net survival). The R^2 statistics (per capita R^2=0·21; per case R^2=0·21) and F test (per capita F-test p=0·029; per case F-test p=0·028) indicated a significant association between this set of independent variables and colorectal cancer health-care costs.

Our sensitivity analysis (appendix p 38) indicated the largest effect on total colorectal cancer costs resulted from discounting the present value of future earnings lost to mortality or morbidity (0·0%, 3·5% baseline, 10·0% [baseline is the reference to which 0·0% and 10·0% discount rates are compared]), resulting in a range of €17·1 billion to €21·9 billion, with the second-largest effect from a 20% variation in health-care costs (€17·6 billion to €20·7 billion).

EUR-33 colorectal cancer SACT expenditure was €1·9 billion. Detailed SACT expenditure breakdowns were unavailable for Cyprus, Denmark, Iceland, Luxembourg, Malta, and the Netherlands; in-depth analysis was done for the remaining 27 European countries (EUR-27), revealing substantial variations in deployment of both chemotherapeutic and targeted pharmaceutical medicine across Europe in 2015 (tables 3, 4).

With regard to non-targeted SACTs, expenditure on fluorouracil and its oral analogue capecitabine was €167·3 million (8·8% of the €1·9 billion total EUR-27 colorectal cancer SACT expenditure). Fluorouracil was prescribed in all countries except Estonia, with Latvia having the highest proportional spend and Italy the lowest. All countries prescribed capecitabine, with Estonia having the highest proportional spend and Bulgaria the lowest. Expenditure on oxaliplatin was €180·4 million (9·5%) of total EUR-27 colorectal cancer SACT costs. All countries except Estonia prescribed oxaliplatin; the UK had the highest proportional spend and Greece the lowest. Expenditure on folic acid (including calcium folinate, calcium levofolinate, and calcium mefolinate) was €131·9 million (6·9%) of total EUR-27 colorectal cancer SACT costs; table 3). Folic acid, its derivatives, and precursors were prescribed in all countries, with Greece the highest proportional spend and Slovakia the lowest. Expenditure on irinotecan was €119·2 million (6·2%) of EUR-27 total colorectal cancer SACT costs. All countries except Estonia prescribed irinotecan; Croatia had the highest proportional spend and Slovenia the lowest. Expenditure on raltitrexed was €5·6 million (0·3%) of total colorectal cancer SACT costs for EUR-27. Raltitrexed was only prescribed in 12 of the EUR-27; Spain had the highest proportional spend and Switzerland the lowest.

Of the colorectal cancer-targeted SACTs available in 2015 in the EUR-27 (table 4), bevacizumab was the most prescribed. Expenditure in 2015 was €771·4 million (40·4% of the €1·9 billion total EUR-27 colorectal cancer SACT expenditure), the largest proportional expenditure of all EUR-27 colorectal cancer-targeted SACT. All countries evaluated prescribed bevacizumab, ranging from €540 (0·02% of national SACT expenditure) for Latvia to €30·9 million (72·2%) for Slovakia. The smallest targeted SACT expenditure was for aflibercept, which made up €36·2 million (1·9%) of total EUR-27 colorectal cancer SACT costs. Only 16 of the EUR-27 used aflibercept (table 4), with Belgium having the largest proportional expenditure. Cetuximab had the second-largest proportional targeted SACT expenditure of the EUR-27. In Serbia, cetuximab expenditure was twice as high as bevacizumab expenditure. Cetuximab was not prescribed in Estonia or Greece and was rarely prescribed in Lithuania. Panitumumab had the third-highest proportional targeted SACT spend, representing €176·2 million (9·2%) of the total EUR-27 colorectal cancer SACT costs. Sweden had the highest proportional expenditure and Romania the lowest. Panitumumab was not prescribed in Estonia, Latvia, Lithuania, or Poland. Regorafenib expenditure was €41·5 million (2·2% of the total EUR-27 colorectal cancer SACT costs). Slovenia had the highest proportional spend, and Romania the lowest; Bulgaria, the Czech Republic, Estonia, Greece, Latvia, and Serbia did not prescribe regorafenib. Overall, evaluating country-specific activities, France had the highest 2015 expenditure on targeted colorectal cancer therapies (€191·2 million) both in terms of overall spend and for individual colorectal cancer-targeted SACTs (except regorafenib, for which Germany had the highest spend [€11·6 million]). The financial outlay on colorectal cancer-targeted SACT ranged from €41 065

	Enhances chemotherapy	Inhibits synthesis of DNA		Inhibits topoisomerase I	Blocks DNA replication	Inhibits synthesis of DNA	Total non-targeted therapy costs, € (%)	All anti-neoplastic colorectal cancer therapy costs, €††
	Precursors and derivatives (folic acid†) costs, € (%)	Converted to fluorouracil (capecitabine‡) costs, € (%)	Pyrimidine antimetabolite (fluorouracil§) costs, € (%)	Derivative of camptothecin (irinotecan¶) costs, € (%)	Platinum-based (oxaliplatin||) costs, € (%)	Antimetabolite (raltitrexed**) costs, € (%)		
Austria	986 319 (2·7%)	923 356 (2·5%)	629 549 (1·7%)	2 940 936 (8·1%)	3 308 488 (9·1%)	189 126 (0·5%)	8 977 776 (24·8%)	36 239 965
Belgium	1 305 152 (3·4%)	935 229 (2·5%)	869 514 (2·3%)	3 144 464 (8·3%)	2 502 284 (6·6%)	44 047 (0·1%)	8 800 690 (23·1%)	38 088 456
Bulgaria	2 237 552 (2·5%)	1 378 601 (1·6%)	920 110 (1·0%)	715 255 (0·8%)	1 144 288 (1·3%)	0	6 395 807 (7·3%)	88 193 548
Croatia	1 264 755 (6·9%)	2 542 940 (13·9%)	573 731 (3·1%)	2 730 842 (14·9%)	1 419 059 (7·7%)	0	8 531 326 (46·5%)	18 348 575
Czech Republic	1 953 082 (8·4%)	5 214 121 (22·5%)	1 059 486 (4·6%)	918 093 (4·0%)	1 004 493 (4·3%)	67 732 (0·3%)	10 217 007 (44·1%)	23 190 441
Estonia	332 061 (25·8%)	912 838 (71·0%)	0	0	0	0	1 244 899 (96·8%)	1 285 964
Finland	750 284 (5·0%)	947 870 (6·4%)	91 996 (0·6%)	246 781 (1·7%)	125 716 (0·8%)	0	2 162 647 (14·5%)	14 905 661
France	25 102 950 (7·7%)	11 853 940 (3·6%)	3 605 989 (1·1%)	44 433 823 (13·6%)	49 496 367 (15·1%)	1 155 659 (0·4%)	135 648 727 (41·5%)	326 844 133
Germany	10 955 441 (5·0%)	8 454 864 (3·9%)	6 902 851 (3·1%)	8 672 863 (4·0%)	10 921 509 (5·0%)	0	45 907 528 (20·9%)	219 529 790
Greece	3 013 148 (77·7%)	283 576 (7·3%)	355 874 (9·2%)	49 452 (1·3%)	18 624 (0·5%)	0	3 720 674 (95·9%)	3 877 944
Hungary	9 706 987 (5·8%)	6 811 697 (4·1%)	2 656 437 (1·6%)	4 737 203 (2·8%)	8 753 951 (5·2%)	518 077 (0·3%)	33 184 352 (19·9%)	167 137 032
Ireland	2 046 229 (15·0%)	511 034 (3·7%)	308 835 (2·3%)	1 002 645 (7·3%)	1 524 421 (11·2%)	0	5 393 165 (39·5%)	13 645 980
Italy	26 447 747 (11·0%)	13 505 286 (5·6%)	1 156 030 (0·5%)	12 260 239 (5·1%)	34 033 790 (14·2%)	675 774 (0·3%)	88 078 867 (36·6%)	240 355 400
Latvia	1 224 205 (42·1%)	282 407 (9·7%)	278 123 (9·6%)	193 706 (6·7%)	149 016 (5·1%)	0	2 127 457 (73·1%)	2 910 482
Lithuania	1 356 664 (44·8%)	760 348 (25·1%)	232 225 (7·7%)	49 034 (1·6%)	27 269 (0·9%)	0	2 425 541 (80·2%)	3 025 579
Norway	166 619 (4·1%)	141 642 (3·5%)	56 706 (1·4%)	82 521 (2·0%)	87 319 (2·1%)	1784 (0·04%)	536 591 (13·1%)	4 087 663
Poland	2 617 683 (4·7%)	5 610 485 (10·2%)	4 374 401 (7·9%)	2 520 057 (4·6%)	1 155 329 (2·1%)	0	16 277 955 (29·5%)	55 261 501
Portugal	1 381 216 (5·5%)	912 046 (3·6%)	842 178 (3·3%)	556 811 (2·2%)	361 423 (1·4%)	55 444 (0·2%)	4 109 118 (16·3%)	25 265 277
Romania	3 652 834 (2·6%)	18 026 752 (12·6%)	1 065 008 (0·7%)	6 654 256 (4·6%)	4 670 313 (3·3%)	0	34 069 164 (23·8%)	143 178 245
Serbia	1 414 882 (11·0%)	1 321 685 (10·3%)	1 182 843 (9·2%)	638 919 (5·0%)	584 817 (4·6%)	0	5 143 145 (40·1%)	12 826 458
Slovakia	299 786 (0·7%)	3 207 155 (7·5%)	522 942 (1·2%)	571 589 (1·3%)	501 450 (1·2%)	0	5 102 922 (11·9%)	42 832 005
Slovenia	91 797 (1·3%)	541 909 (7·4%)	88 900 (1·2%)	20 513 (0·3%)	118 998 (1·6%)	0	862 118 (11·7%)	7 339 853
Spain	5 486 699 (4·4%)	9 968 595 (7·9%)	2 830 719 (2·3%)	3 786 620 (3·0%)	16 112 570 (12·8%)	1 926 143 (1·5%)	40 111 345 (31·9%)	125 703 928
Sweden	932 157 (8·7%)	320 036 (3·0%)	214 155 (2·0%)	126 897 (1·2%)	121 382 (1·1%)	0	1 714 626 (16·0%)	10 717 858
Switzerland	923 639 (5·5%)	999 980 (5·9%)	382 001 (2·3%)	1 107 392 (6·6%)	2 401 410 (14·3%)	5296 (0·03%)	5 819 718 (34·6%)	16 824 717
Turkey	15 310 280 (13·3%)	10 324 711 (9·0%)	2 790 506 (2·4%)	3 183 667 (2·8%)	3 483 595 (3·0%)	369 345 (0·3%)	35 462 105 (30·8%)	114 960 919
UK	10 922 763 (7·2%)	16 998 329 (11·3%)	9 599 635 (6·4%)	17 829 611 (11·8%)	36 388 435 (24·1%)	588 804 (0·4%)	92 327 577 (61·2%)	150 945 772
EUR-27[a]	131 884 946 (6·9%)	123 693 447 (6·5%)	43 592 760 (2·3%)	119 176 206 (6·2%)	180 418 333 (9·5%)	5 599 248 (0·3%)	604 364 939 (31·7%)	1 907 523 146

Percentages are the proportion of all systemic anti-cancer therapy costs for colorectal cancer for that country (reported in the final column). Data are adjusted for purchasing power parity. EUR-27=27 European countries. *Not including Cyprus, Denmark, Iceland, Luxembourg, Malta, and Netherlands. †Calcium folinate (Leucovorin); calcium levofolinate (Leoleucovorin); calcium mefolinate (Prefolic). ‡Capecitabine (Xeloda). §Fluorouracil (Adrucil). ¶Irinotecan (Camptosar). ||Oxaliplatin (Eloxatin). **Raltitrexed (Tomudex). ††Other anti-neoplastics are regorafenib, aflibercept, bevacizumab, cetuximab, and panitumumab (see table 4).

***Table 3*: Colorectal non-targeted systemic anti-cancer therapy costs and proportions by mechanism of action and country*, 2015**

(3·2% national SACT expenditure) in Estonia to €81·8 million (92·7%) in Bulgaria (table 4).

Our multivariable regression model (appendix p 24) indicated a significant association between the set of independent variables (numbers of oncologists, CT scanners, CT scans, radiologists, and radiotherapy machines [2015 data]; and surgical oncologists [2018 data]) and 5-year net survival for 2010–14 (R^2=0·48; F-test p=0·0053) across the EUR-33.

11 central and eastern European countries were in the top half of the EUR-33 for colorectal cancer health-care costs per case (appendix p 21). However, except for the number of radiologists, there was a paucity of colorectal cancer-related hospital personnel, resources, and activities (numbers of oncologists, CT scanners, CT scans, radiotherapy machines, surgical oncologists) in central and eastern European countries. All central and eastern European countries were in the bottom half of the EUR-33 for 5-year net survival. Of the northern European countries, Norway was in the bottom half of EUR-33 colorectal cancer health-care costs per case and in the top half for colorectal cancer-related hospital resources, and activities, except for surgical oncologists. All Scandinavian countries (Denmark, Finland, Iceland,

	VEGFR-2 (blocks angiogenesis)	VEGF (blocks angiogenesis)		EGFR (blocks cell growth)		Total targeted colorectal cancer therapy costs, € (%)	All antineoplastic colorectal cancer therapy costs, € (%)**
	Protein tyrosine kinase inhibitor (regorafenib†) costs, € (%)	Recombinant fusion protein (aflibercept‡) costs, € (%)	Monoclonal antibody (bevacizumab§) costs, € (%)	Monoclonal antibody (cetuximab¶) costs, € (%)	Monoclonal antibody (panitumumab‖) costs, € (%)		
Austria	1 856 061 (5·1%)	1 280 752 (3·5%)	16 762 754 (46·3%)	3 568 758 (9·8%)	3 793 864 (10·5%)	27 262 189 (75·2%)	36 239 965
Belgium	617 834 (1·6%)	1 989 914 (5·2%)	15 666 851 (41·1%)	6 492 516 (17·0%)	4 520 651 (11·9%)	29 287 766 (76·9%)	38 088 456
Bulgaria	0	1 809 672 (2·1%)	51 440 032 (58·3%)	9 287 732 (10·5%)	19 260 305 (21·8%)	81 797 742 (92·7%)	88 193 548
Croatia	15 263 (0·1%)	0	6 967 729 (38·0%)	1 903 230 (10·4%)	931 027 (5·1%)	9 817 249 (53·5%)	18 348 575
Czech Republic	0	0	5 041 238 (21·7%)	5 654 713 (24·4%)	2 277 483 (9·8%)	12 973 434 (55·9%)	23 190 441
Estonia	0	0	41 065 (3·2%)	0	0	41 065 (3·2%)	1 285 964
Finland	667 272 (4·5%)	294 792 (2·0%)	7 667 219 (51·4%)	766 582 (5·1%)	3 347 149 (22·5%)	12 743 014 (85·5%)	14 905 661
France	9 429 089 (2·9%)	8 881 514 (2·7%)	105 286 828 (32·2%)	40 210 785 (12·3%)	27 387 189 (8·4%)	191 195 406 (58·5%)	326 844 133
Germany	11 578 475 (5·3%)	6 165 377 (2·8%)	93 405 151 (42·5%)	36 668 010 (16·7%)	25 805 249 (11·8%)	173 622 262 (79·1%)	219 529 790
Greece	0	0	142 775 (3·7%)	0	14 495 (0·4%)	157 270 (4·1%)	3 877 944
Hungary	583 504 (0·3%)	0	69 620 860 (41·7%)	37 806 350 (22·6%)	25 941 966 (15·5%)	133 952 680 (80·1%)	167 137 032
Ireland	542 564 (4·0%)	43 626 (0·3%)	4 987 243 (36·5%)	1 376 957 (10·1%)	1 302 424 (9·5%)	8 252 815 (60·5%)	13 645 980
Italy	6 628 776 (2·8%)	4 859 591 (2·0%)	89 514 923 (37·2%)	29 048 496 (12·1%)	22 224 747 (9·2%)	152 276 533 (63·4%)	240 355 400
Latvia	0	0	540 (0·02%)	782 484 (26·9%)	0	783 025 (26·9%)	2 910 482
Lithuania	127 636 (4·2%)	0	470 955 (15·6%)	1447 (0·05%)	0	600 038 (19·8%)	3 025 579
Norway	247 871 (6·1%)	6349 (0·2%)	1 875 724 (45·9%)	320 362 (7·8%)	1 100 766 (26·9%)	3 551 072 (86·9%)	4 087 663
Poland	139 688 (0·3%)	0	31 773 039 (57·5%)	7 070 819 (12·8%)	0	38 983 546 (70·5%)	55 261 501
Portugal	146 111 (0·6%)	42 169 (0·2%)	10 009 941 (39·6%)	8 770 595 (34·7%)	2 187 342 (8·7%)	21 156 158 (83·7%)	25 265 277
Romania	18 706 (0·01%)	0	97 540 744 (68·1%)	11 446 864 (8·0%)	102 767 (0·1%)	109 109 081 (76·2%)	143 178 245
Serbia	0	0	2 379 362 (18·6%)	5 108 630 (39·8%)	195 320 (1·5%)	7 683 313 (59·9%)	12 826 458
Slovakia	15 407 (0·04%)	1 037 062 (2·4%)	30 937 601 (72·2%)	2 419 556 (5·6%)	3 319 457 (7·7%)	37 729 083 (88·1%)	42 832 005
Slovenia	573 550 (7·8%)	189 453 (2·6%)	3 430 366 (46·7%)	1 288 553 (17·6%)	995 814 (13·6%)	6 477 735 (88·3%)	7 339 853
Spain	2 113 837 (1·7%)	5 854 552 (4·7%)	45 394 797 (36·1%)	17 692 027 (14·1%)	14 537 370 (11·6%)	85 592 582 (68·1%)	125 703 928
Sweden	215 693 (2·0%)	199 920 (1·9%)	4 656 360 (43·4%)	924 201 (8·6%)	3 007 058 (28·1%)	9 003 232 (84·0%)	10 717 858
Switzerland	757 010 (4·5%)	523 387 (3·1%)	6 344 265 (37·7%)	2 243 032 (13·3%)	1 137 306 (6·8%)	11 005 000 (65·4%)	16 824 717
Turkey	3 336 729 (2·9%)	0	41 993 661 (36·5%)	23 030 635 (20·0%)	11 137 788 (9·7%)	79 498 814 (69·2%)	114 960 919
UK	1 896 274 (1·3%)	2 992 494 (2·0%)	28 000 170 (18·5%)	24 105 573 (16·0%)	1 623 684 (1·1%)	58 618 195 (38·8%)	150 945 772
EUR-27*	41 507 351 (2·2%)	36 170 625 (1·9%)	771 352 191 (40·4%)	277 988 909 (14·6%)	176 151 221 (9·2%)	1 303 170 298 (68·3%)	1 907 523 146

Percentages are the proportion of all systemic anti-cancer therapy costs for colorectal cancer, for that country (reported in the final column). Data are adjusted for purchasing power parity. EGFR=epidermal growth factor receptor. EUR-27=27 European countries. VEGF=vascular endothelial growth factor. VEGFR-2=vascular endothelial growth factor receptor 2. *Not including Cyprus, Denmark, Iceland, Luxembourg, Malta, and Netherlands. †Regorafenib (Stivarga). ‡Aflibercept (Zaltrap). §Bevacizumab (Avastin). ¶Cetuximab (Erbitux). ‖Panitumumab (Vectibix). **Other anti-neoplastics are calcium folinate, calcium levofolinate, calcium mefolinate, capecitabine, fluorouracil, folic acid, irinotecan, oxaliplatin, and raltitrexed (see table 3).

Table 4: **Colorectal targeted systemic anti-cancer therapy costs and proportions by mechanism of action and country*, 2015**

Norway, and Sweden) were in the top half for age-standardised 5-year net survival and in the bottom half for SACT expenditure (except Finland). For western European countries, Switzerland was at the midpoint for health-care expenditure as a proportion of total health-care costs and in the top half for colorectal cancer-related hospital resources, and activities (except surgical oncologists), and all western European countries were in the top half for survival. For southern European countries, no discernible pattern was observed.

12 of the 13 countries (Germany was the exception) with the highest 5-year net survival spent at least twice as much on hospital-based care as on SACT (appendix p 21).

Colorectal cancer health-care costs per case are shown on a colorectal cancer survival map of Europe in figure 2. The colorectal cancer health-care costs per case were low in countries where survival was high, such as Germany, Norway, and Sweden, but high in countries where survival was low, such as Bulgaria, Hungary, Romania, and Slovakia.

Compared with the 2009 health economic study for all cancers for 27 member states of the EU,[3] overall costs have increased by 31·7% (€14·5 billion to €19·1 billion, after adjusting for inflation); however, health-care costs have only increased by 23·0% (from €6·1 billion to €7·5 billion). We only did specific comparisons with the 2009 EU data for hospital-care and SACT costs to evaluate changes over time, because activity with regard to hospital care and expenditure on SACT are directly comparable. Overall, hospital-care costs decreased by

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Colorectal cancer health-care costs per case, € (PPP adjusted)

EUR-33	2351	Latvia	3764
Austria	4054	Lithuania	2931
Belgium	2335	Luxembourg	1651
Bulgaria	4872	Malta	1299
Croatia	3568	Netherlands	2314
Cyprus	259	Norway	696
Czech Republic	1759	Poland	2868
Denmark	2491	Portugal	2335
Estonia	4865	Romania	7388
Finland	2597	Serbia	3145
France	1712	Slovakia	7289
Germany	1964	Slovenia	2870
Greece	1009	Spain	1461
Hungary	36 295	Sweden	1090
Iceland	2902	Switzerland	2590
Ireland	2619	Turkey	1294
Italy	2345	UK	1404

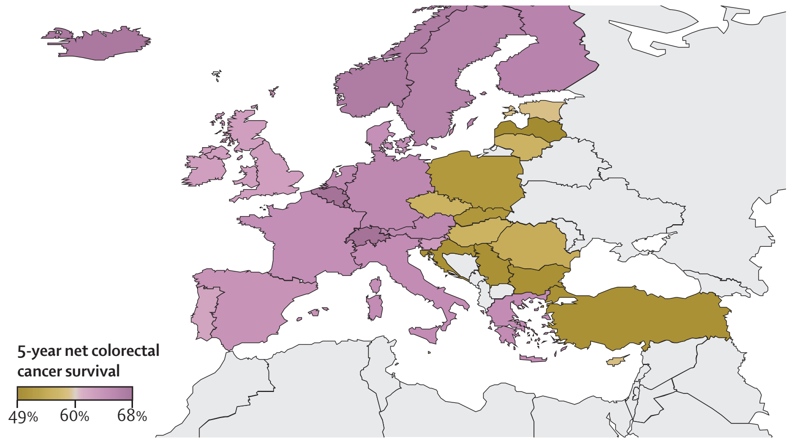

Figure 2: **Geographical spread of colorectal cancer survival and colorectal cancer health-care costs per case in 2015**
EUR-33=33 European countries, defined as the 27 EU countries plus Iceland, Norway, Serbia, Switzerland, Turkey, and the UK. PPP=purchasing power parity.

21·2% in the EU, from €3·6 billion to €2·8 billion (appendix p 22). The greatest percentage increases in hospital-care costs were in Hungary (222·1%), Portugal (154·7%), Malta (96·4%), and Austria (84·5%; appendix p 22). Expenditure on SACTs increased by 213·7% between 2009 and 2015. The largest increases in SACT expenditures were in Bulgaria (817·8%), Ireland (473·1%), Hungary (398·2%), and Austria (369·2%). All EU countries increased their SACT expenditure from 2009 to 2015, except Cyprus (–83·4%), Luxembourg (–79·6%), and Greece (–75·0%; appendix p 22).

Hospital care costs increased by 43·6% from €3·3 billion to €4·7 billion when colorectal cancer or cancer-specific costs were used instead of mean hospital care expenditure data from Eurostat.[9] The top five countries, Hungary, Romania, Slovakia, Bulgaria, and Estonia, and the bottom country (Cyprus) and the country third from the bottom (Greece) retained their rankings, as did Latvia. There was movement between rankings for the remaining countries. The average cost for hospital care rankings and colorectal cancer cost for hospital care rankings (where possible) are shown in the appendix (pp 26–27).

Discussion

This study represents the most comprehensive analysis to date on the economic burden of colorectal cancer across Europe. By 2015, the economic burden of colorectal cancer across Europe had increased to over €19 billion. Direct health-care costs represented less than 40% of the total cost of colorectal cancer, with about 60% being due to loss of productivity and opportunity costs for informal carers. Countries with similar GDP per capita had substantially different health-care expenditures. Expenditure on pharmaceuticals increased by over 200% between 2009 and 2015 in EU countries. Some central and eastern European countries spent more than their western European counterparts, especially on pharmaceutical medicines, but still had poorer outcomes. This study provides valuable intelligence for policy makers and health-care providers to inform their decision making on service prioritisation and budget allocation to improve outcomes. More broadly, we recommend that colorectal cancer be considered as an indicator to show how cancer systems are performing overall from an economic perspective. Previously, we reported on the overall financial burden of cancer in the EU, which only included economic cost data for colorectal cancer without any correlations with drivers, determinants, and outcomes of the disease.[3] This present study focuses solely on colorectal cancer, substantially extends the previous analysis, expands coverage from 27 to 33 countries, and produces much more comprehensive colorectal cancer-specific economic data, particularly concerning SACT use. Hospital-specific PPP adjustments[8] were made throughout to enable like-for-like comparisons between EUR-33 countries. It should be stressed at the outset, that although we endeavoured to source homogenous colorectal cancer data for analysis, this was not always possible.

Our analysis indicates that countries with higher colorectal cancer incidence and mortality had higher health-care costs and, conversely, countries with the highest colorectal cancer survival had lower costs, reflecting both the higher costs of treating colorectal cancer presenting at a late stage and the higher costs incurred within less efficient health-care systems.[21] Higher 5-year net survival correlated significantly with better resourcing, shown by metrics such as the number of oncologists (surgical, medical), CT scanners, CT scans, and radiotherapy equipment. The highest survival estimates in Norway and Switzerland appear to be related to expenditure on the core components of colorectal cancer treatment, including surgery, radiotherapy, and human resources, rather than SACT expenditure.[22] Studies suggest that central and eastern European countries require an investment and restructuring of public health, personnel, and equipment allocation to avoid having patients first present at hospital with late stage colorectal cancer.[23–25] Our 2015 data would support this assertion. We have shown that hospital-care costs have continued to increase in most central and eastern European countries, due in large part to a continued hospital-centric approach, whereas hospital-care costs have decreased in some northern and western European countries such as France, Germany, Spain, the Netherlands, and the UK compared with 2009. In Bulgaria, increased use of targeted therapy is associated with a reduction in hospital costs. This finding was for 2015 data only, and was found by ranking the greatest expenditure on targeted SACT as a proportion of all SACT (table 4) and comparing hospital care costs (table 2). From the 2015 rankings (table 3), Estonia, Greece, Latvia, and Lithuania, preference for chemotherapy expenditure as a high proportion of all SACT expenditure is associated with increases in hospital costs; adverse effects related to chemotherapy might have contributed to these high hospital costs.

Some of the health systems with less resources in Europe had higher costs and lower survival than European countries with more resources: a double value burden. 11 countries from central and eastern Europe had the highest expenditure on colorectal cancer per case. However, these countries are all in the bottom half for 5-year net survival, indicating that greater expenditure is not necessarily associated with improved outcomes.[7] Unequal access to screening[26] and late-stage diagnosis might partially explain lower survival, but less effective and efficient deployment of cancer care is also a major factor.[27] In 2015 hospital-care costs for colorectal cancer were €479 (95% CI €385–573) per hospital stay (after adjusting for inflation; appendix p 19), but overall hospital-care costs have decreased by 21% (from €3·6 billion to €2·8 billion) since 2009, because of shorter inpatient stays than in the 2009 study.[3]

Our data indicate that SACT costs have more than tripled since 2009 (213·7%), and are supported by a 2018 study on overall oncology costs across Europe.[28] Most of these drug costs are due to increases in use of targeted SACT.[28] However, there are wide variations in SACT expenditure across Europe, with an 818% increase in Bulgaria and a 398% increase in Hungary since 2009, which are not reflected in improved outcomes; some of these increases might be due to shortages of chemotherapies, potentially leading to an overspend in targeted therapies.[29] Substantial reductions in SACT expenditure since 2009 (of around 80%) were seen in Cyprus, Greece, and Luxembourg. Reductions for Cyprus and Greece are probably due to the direct consequence of the 2008 economic crisis. Decreases in Luxembourg might reflect the increasing willingness of patients to seek cross-border care.[30] Although five eastern European countries are ranked in the bottom half of the EUR-33 for SACT expenditure as a proportion of total colorectal cancer health-care expenditure (appendix p 21), our data and those of others reveal that some central and eastern European countries have outpaced their western European counterparts in SACT expenditure,[31] but this expenditure is not reflected in any therapeutic gain for their patients.

Several studies have reported on the costs of cancer care in Europe over the past 6 years. One study highlighted that cancer health-care costs are relatively low compared with the overall cancer burden, but a second study showed substantial increases in cancer drug spending over the past 5 years.[28,32] Looking at the overall cancer burden in the 2018 study, the data are similar to our results for overall colorectal cancer burden (€21·3 billion *vs* our calculation of €19·1 billion) and findings from the 2015 study by Schlueter and colleagues align with our figure of 0·47% for the proportion of total health-care costs, when colorectal cancer as a proportion of all cancer diagnosis and the number of colorectal cancer cases are considered.[28,32] However, the partial implementation of PPP adjustments in these studies makes country-by-country health-care cost comparisons unachievable.

There are several limitations to our study. First, accuracy of this analysis is dependent on the data sources, which, outside of hospital-care activity and SACT costs, are absent for some countries, specifically sources of epidemiological and financial data that can be allocated to either colorectal cancer or cancer in general. In some cases, we had to rely on non-homogenous B-grade data (activity of cost data for any disease), particularly for emergency care, possibly contributing to the variations between countries. Furthermore, the assumption that colorectal cancer visits to a general practitioner might equate to the proportion of colorectal cancer hospital discharges might not always be correct, and thus our primary care projections should be interpreted with caution. Additionally, the SHARE data set is constrained by the number of countries included; however, the dataset was updated after 2015 to include eight further countries, increasing its utility.

Second, Hungary is somewhat of an outlier in these analyses. Hungary has the highest incidence, mortality, and disability-adjusted life-years, coupled with the lowest prevalence and disability payments of all EUR-33 countries. Studies have shown that Hungary has both the highest incidence of colorectal cancer and highest associated mortality, not only in the EU but also globally, arising from a combination of factors including lifestyle choices, scarcity of colorectal cancer screening awareness, frequent metastatic presentation, and a potential genetic component. Similar results are seen for Croatia and Slovakia, which also have high costs of colorectal cancer per case.[33–36]

Third, colorectal cancer costs increase as the disease progresses, with estimates of €4000 for stage I presentation to €40 000 for late-stage presentation.[25] A colorectal cancer screening programme can help attenuate metastatic presentation, but few countries reach the EU goal of 65% participation in screening programmes in people aged 50–74 years, with the Netherlands and Slovenia as exceptions.[25,37] Ideally, we would have liked to use incident cases by stage of presentation and have tracked costs and epidemiology of each cohort, but unfortunately we could not find a corresponding dataset for these analyses.

Fourth, data sourced from IQVIA were aggregated cost volumes by therapy and by country, and it was not possible to determine the unit costs of each therapy, making it difficult to deduce relative volumes of combination therapies or lines of treatment.

Fifth, a key driver of colorectal cancer costs is productivity losses; in this study we used the human capital approach rather than the friction cost approach, as colorectal cancer is both a terminal illness and contributes to long-term disability. The previous 2009 study focused on the friction cost approach, making it difficult to draw conclusions between the productivity loss components in 2009 and 2015.

Despite these limitations, this study is the most comprehensive and granular to date of the economic burden of colorectal cancer across Europe and its implications for colorectal cancer care and colorectal cancer outcomes.

Colorectal cancer is a major economic burden throughout Europe, particularly due to disability, premature death, and loss of productivity. There is substantial variation in overall expenditure to reduce cancer burden across the EUR-33, but this variation is not associated with patient outcomes. This finding strongly suggests that many countries need to understand why, despite increasing expenditure, their colorectal cancer outcomes remain so poor.

A substantial misspend on colorectal cancer care also appears to exist in many central and eastern European countries and should be addressed within an overall systems-improvement approach for better value and improved outcomes. Expenditure on targeted SACT is rapidly escalating, not only in northern and western European countries, but also in central and eastern European countries, despite an apparent lack of evidence for their effectiveness in significantly improving survival.

Our data reinforce the need for greater public policy focus on outcomes, value, and affordability in colorectal cancer care. This policy could use the European Society of Medical Oncology's Magnitude of Benefit Scale for new chemotherapy regimens,[38] to ensure more measurable gains from systemic interventions in colorectal and other common cancers. Our analysis adds substantial policy and public health intelligence for implementing value-based care and prioritising the distribution of public research funds to areas of recognised need, as articulated in the Critical Research Gaps Analysis in Colorectal Cancer.[39] Crucially, as the adverse effect of COVID-19 is recognised, especially on patients with colorectal cancer,[40] and mitigation strategies are developed,[41] we must ensure that spending on improving colorectal cancer outcomes takes into account the challenges that are relevant in each country or region, particularly in the context of Europe's Beating Cancer Plan, to ensure tangible benefits for all European citizens, patients, and society.

Contributors

RHH, DF, RS, and ML developed the concept of the paper and the plan for analysis. MPC, CA, and PM validated the morbidity model. DF reviewed the model in total. DF, RS, and ML and verified underlying data and methodology and supervised the project. RHH did the literature search, plotted figures, study design, data collection, data analysis, data interpretation, and writing of the original draft of the manuscript with ML. All authors were involved in the review and editing of the manuscript. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Declaration of interests

RHH is an employee at Diaceutics. RA reports grants from AstraZeneca and MSD; consulting fees from AstraZeneca, Merck, and Bayer; speaker fees from Amgen, Merck, and Servier; and support for attending meetings from Amgen, Bristol Myers Squibb, and Merck. TM reports consulting fees from AstraZeneca; participation on a Pierre Fabre Independent Data Monitoring Committee and a Pfizer steering committee; and receipt of material from Almac Diagnostics, Indica labs and Psioxus. EM reports support from Cancer Focus Northern Ireland and has given advice to the Royal College of Nursing. ML reports support from MRC, Cancer Research UK, and HDRUK; an unrestricted educational grant from Pfizer; and honoraria from Pfizer, EMD Serono, and Roche unrelated to the work. All other authors declare no competing interests.

Data sharing

The data on which this study is based (including the Cancer Today 2012 data from the International Agency for Research on Cancer, which is no longer available online) are available at https://data.mendeley.com/datasets/tnjw2gd8nm/draft?a=5c9fce82-00c5-4e21-972b-42d4af18e26a.

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Editorial note: the *Lancet* Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

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