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

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ABSTRACT

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

Methods: Activity and costing data were evaluated for healthcare expenditure, informal care costs and productivity losses in 33 European countries. Country-specific aggregate data were acquired for healthcare, mortality, morbidity, and informal care costs. Primary, outpatient, emergency, and hospital care, and systemic anti-cancer therapy (SACT) costs were calculated. Costs of premature death, temporary and permanent absence from work, and unpaid informal care due to CRC were determined. CRC healthcare costs per case were compared to CRC survival and CRC personnel, equipment, and resources across Europe.

Findings: The economic burden of CRC across Europe in 2015 was €19·1 billion. Over sixty percent of the total cost (€11·6B, 60·6%) arose from loss of productivity due to disability (€6·3B, 33·0%), premature death (€3·0B, 15·9%) and opportunity costs for informal carers (€2·2B, 11·6%). Direct healthcare costs represented nearly forty percent of the total (€7·5B, 39·4%), comprising hospital care (€3·3B, 43·4% of healthcare costs), SACT (€1·9B, 25·6%), and outpatient (€1·3B, 17·7%), primary (€0·7B; 9·3%) and emergency care (€0·3B, 3·9%).

The average cost for managing a CRC patient varied widely between countries (€259-€36,295). Hospital care costs showed considerable variation as a proportion of healthcare costs (24%-85%) with a decrease of 21% from 2009 to 2015. Overall, hospital care comprised the largest proportion of healthcare expenditure, but it was significantly outstripped by pharmaceutical expenditure in some countries. Countries with similar GDP *per capita* had widely varying healthcare expenditures. Expenditure on pharmaceuticals rose by 214% from 2009 to 2015.

Interpretation: Although the data analysed include non-homogenous sources from certain countries and should be interpreted with a degree of caution, this study nonetheless represents the most comprehensive analysis to date of the economic burden of colorectal cancer in Europe. Substantial variation in overall spend on healthcare costs in certain countries is not in direct correlation to patient outcomes. Spending on improving outcomes must be appropriate to the challenges in each country, in order to ensure tangible benefits for European citizens, patients and society. Our results have major implications for guiding policy and improving outcomes for this common malignancy.

Research in Context

Evidence before this study

Colorectal cancer (CRC) is one of the most common diagnosed cancer in Europe, and the second most common cause of cancer death. A previous study on cancer, employing data from 2009 which included a limited analysis of CRC, indicated that CRCs direct and indirect costs in the EU-27 were approximately 13 billion euro. However, no previous study has focussed specifically on the economic burden of CRC in Europe, while Europe's healthcare systems and economic landscape have changed significantly since 2009.

Added value of this study

This study represents the most comprehensive analysis of the economic burden of CRC in Europe to date. Using high-quality granular data from a variety of sources, the epidemiology of CRC and its consequential financial impact on patients and their carers, on healthcare infrastructure and on society were defined for the EUR-33, (the EU-27 plus Iceland, Norway, Serbia, Switzerland, Turkey, and the United Kingdom).

The economic burden of CRC across Europe in 2015 totalled €19·1 billion. Of this, over 60% of the total cost was associated with loss of productivity and opportunity costs for informal carers. Direct healthcare costs only represented less than 40% of the total cost. Countries with similar GDP *per capita* had widely varying healthcare expenditures. Expenditure on pharmaceuticals rose by over 200% between 2009 and 2015.

In certain countries however, increased expenditure did not align with improved outcomes e.g. a number of Central and Eastern European (CEE) 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 CRC can provide vital intelligence to underpin better health policy implementation and more appropriate resource allocation. Upfront investment in CRC infrastructure is more likely to not only reduce CRC deaths, but also to lessen the economic burden. Increased expenditure on pharmaceutical medicines may not necessarily be reflected in improved outcomes, particularly in CEE countries, emphasising the need to use precious resources most appropriately for this common malignancy.

INTRODUCTION

Colorectal cancer (CRC) is one of the most significant cancer burdens in Europe. In 2009, it accounted for 11·5% of all new cancer diagnoses (EU-27), [1,2] with healthcare costs over €5·5 billion (B).[3] Together with economic losses from morbidity and mortality (indirect costs) and informal care costs, the total economic burden was more than €13B.

However, since 2009, the healthcare and economic landscapes have significantly changed. Increasing incidence of CRC and advances in therapeutic innovation (both intravenous precision and targeted treatments, as well as oral targeted CRC therapies) have contributed to greater management costs.[4,5] CRC 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 (CEE) countries.[7]

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

A comparative European analysis allows precise mapping of the health economic landscape and its relationship to CRC 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, for example, precise costs of individual chemotherapy or targeted therapy in each country. This economic intelligence can help underpin identification of activities and associated expenditures in individual countries that may be examples of best practice that can be shared with European partners, or it may represent inappropriate use of scarce resources that should be redirected to more patient-focussed and value-based activities. Here, we define the economic burden of CRC in 33 European countries (EUR-33: the 27 EU countries plus Iceland, Norway, Serbia, Switzerland, Turkey, and the United Kingdom (UK)). It should be stressed at the outset, that while we endeavoured to source homogenous CRC data for analysis, this was not always possible. Nevertheless, we highlight how this intelligence can inform approaches to improve key health and socioeconomic outcomes for European citizens and societies.

METHODS

We defined CRC as invasive malignancies of the colon, rectum, and anus, using the International Classification of Diseases, 10th revision (codes C18 to C21). For the EUR-33 in 2015, activity data related to CRC management and associated costs were acquired using a published framework in which costs for healthcare, productivity losses, and informal care were determined for lung, breast, colorectal and prostate cancer in the EU-27.[3] Resource use was assessed for all prevalent patients in each country in 2015, to include patients newly diagnosed in that year and those receiving ongoing care.

The value of resources used was determined from the costs in each country and, where possible, either CRC-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.[8] PPP measures the price of a basket of goods (in this case, hospital services) in each country relative to the EU-27 mean.

Aggregate activity and costing data were derived from global and national sources. Activity data sources and costings were ranked (see Appendix p1-7).

Healthcare expenditure

Activities and costs for hospital, outpatient, primary and emergency care were compiled from CRC-specific or cancer-specific data. CRC prevalence was applied to cancer-specific or general disease data to obtain CRC-specific figures (Table 1). Several countries did not have national data for emergency care (Croatia, Luxembourg, Lithuania, Romania, Serbia) or hospital care (Estonia). Data for these countries were estimated by using corresponding proportions extrapolated from countries with similar healthcare expenditure per person, life expectancy and geographic location. To test the robustness of the hospital-care cost data, a sensitivity analysis was performed by replacing CRC- or cancer-specific hospital-care cost data with average hospital-care expenditure data gathered from Eurostat[9] and the analysis was repeated.

Colectomy activity data were available for each country (Eurostat), but these did not distinguish between CRC and other diseases, such as Crohn's disease/Ulcerative Colitis. Similarly, Eurostat cost data were only available for generalised domains (e.g. long-term care, laboratory services), so attributable costs could not be estimated for CRC. For all countries, systemic anti-cancer therapy (SACT) expenditures for CRC (split by drug into chemotherapy and targeted therapy [see Appendix p4, p5]) were supplied by IQVIA Oncology data (2015).[10]

Population data were accessed from Eurostat.[11] Five-year prevalence estimates at the end of 2012 were sourced from the International Agency for Research on Cancer (IARC)[12]. Extrapolation to total prevalence at the end of 2015 was applied (see Appendix p8), permitting calculation of healthcare costs for each prevalent case.

Calculations for CRC in EUR-33 were performed to determine the proportion of healthcare costs (calculated from total healthcare expenditure (THE)); the proportion of hospital-care costs and the proportion of pharmaceutical medicine costs (both calculated from total CRC healthcare costs).

Hospital care and SACT costs from our study were compared to 2009 data, and as a validity check of data sources, hospital care costs were exchanged for average hospital care expenditure data from Eurostat.[3,9]

Informal care costs

Informal care costs reflect an opportunity cost, i.e. the financial loss to caregivers (e.g. lost earnings, leisure time) in providing unpaid care for relatives or friends. For each country, informal care costs were calculated from the prevalence statistics and the probability that patients were receiving such care (Wave 6: Survey of Health, Ageing and Retirement in Europe (SHARE)).[13] SHARE gathered data on 60,000 people in 17 EUR-33 countries in 2015. Probabilities for the remaining 16 countries were calculated using pooled data from similar countries (see Appendix p9-p13). SHARE data informed an ordered logistic regression, applied to estimate the number of hours of informal care required by CRC patients. Hours were multiplied by the probability of receiving care and the average or minimum hourly wage, depending on whether the caregiver was employed or unemployed (see Appendix p9-13).

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 (see Appendix p14).

For mortality costs, we extracted the number of deaths by age (15-65 years), gender and country from Eurostat.[14] Number of working years lost (years lost) were calculated by subtracting the age of CRC death from the effective retirement age in each country.[15,16] Age- and gender-specific employment rates[17] for EUR-33 were applied to the years lost. To account for lost future earnings, years lost were multiplied by wages[18] and converted to current prices (see Box 1). Lost earnings were summed by age group, gender and country to give total economic losses from premature death, applying the human capital approach (HCA). HCA was applied rather than the friction cost approach (FCA) because it takes the perspective of the patient and society rather than that of employers, and is less affected by labour market conditions.[19–21]

For temporary morbidity costs (see Appendix p14, p15), patient sick-days were calculated as a proportion of total sick-days for each country:

$$Temporary\ earnings\ lost\ (HCA) = CRC\ sick - days \times Daily\ wage$$

Lost earnings from permanent absence (permanent earnings lost) were calculated from the total number of individuals collecting disability benefits in each country,[22] applying CRC 5-year net survival over the lifetime of each patient, from 5-year age groupings, and discounting at 0%, 3·5%, and 10% using HCA (see Box 2 and Appendix p15, p 16).

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

Statistical analysis

Countries were examined for relationships in CRC-related healthcare costs *per capita* and per case using log-linear univariable regression, dependent on gross domestic product (GDP, euro *per capita*), THE (euro *per capita*), disability-adjusted life-years (DALYs, per 1,000), incidence (crude rate per 1,000 per year), total prevalence (per 1,000), mortality (crude rate per 1,000 per year) and age-standardised 5-year net survival (%). Drivers, determinants, and outcomes of CRC originated from 2015 data, except survival, which was for patients diagnosed during 2010-2014.[7] Additionally, a log-linear multivariable regression was conducted between CRC-related healthcare costs *per capita* and per case and CRC incidence and CRC survival.

Countries were investigated for association in a multivariable regression between CRC survival and a set of independent variables; numbers of oncologists (2015), computed tomography [CT] scanners (2015), CT scans (2015), radiologists (2015), radiotherapy machines (2015), and surgical oncologists (2018).

An explanatory variable was deemed statistically significant if its p-value was <5%. Stata software v·14·2 (StataCorp, College Station, TX, USA) was employed for regression analyses.

Sensitivity analysis

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

Role of the funding source

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RESULTS

The economic burden of colorectal cancer

In 2015, costs for the EUR-33 were €19·1Billion (B) (Table 2 – PPP adjusted), broken down as follows: (1) healthcare costs: €7·5B (€12/citizen or €2,351/patient; 39·4% of total); (2) mortality costs: €3·0B (15·9%); (3) morbidity costs: €6·3B (33·0%); (4) informal-care costs: €2·2B (11·6%). Non-healthcare costs represented 60·6% of total CRC costs, due to loss of productivity resulting from either premature CRC-specific death/disability, or opportunity costs for informal carers. The remaining €7·5B (39·4%) attributable to healthcare costs comprised hospital-care costs (€3·3B; 43·4% of healthcare costs), SACT (€1·9B; 25·6% of healthcare costs), outpatient, primary, and emergency-care costs (€1·3B; 17·7%); (€0·7B; 9·3%); (€0·3B; 3·9%), of healthcare costs, respectively. Costs for each region/country are indicated in Appendix p25.

Hospital-care costs as a proportion of healthcare costs diverged considerably between nations, from 24% (Romania) to 85% (Luxembourg). Hospitalisation accounted for the largest proportion of healthcare costs both overall, and individually in 27 of the EUR-33. However, in Bulgaria, France, and UK, hospital-care expenditure was lower than expenditure on SACT, e.g., in Bulgaria 27% of healthcare costs (€38·2M) was spent on hospital care while 62% (€88·2M) was spent on SACT. Hungary, Romania, and Slovakia had the largest expenditures on CRC healthcare per case, with expenditures on SACT a large component (22% to 27%) of overall costs (Figure 1). SACT as a percentage of aggregate CRC-related healthcare costs were lowest in Luxembourg (1%) and highest in Bulgaria (62%). The average cost for managing a CRC patient varied from €259 (Cyprus) to €36,295 (Hungary) (Figure 1), also reflected in the differences in SACT expenditure, €32/patient (Cyprus) versus €7,835/patient (Hungary). EUR-33 countries with similar GDP *per capita* have widely varying CRC healthcare expenditures, e.g., Austria (€4,054/patient, PPP) spent over four-fold more than Sweden (€1,090/patient, PPP) (Figure 1).

The greatest divergence observed within CRC healthcare costs was in unit cost of an emergency hospital attendance, from €15 (Cyprus) to €1,511 (Hungary) with a mean of €276 (95% CI €155-€397) per emergency visit (see Appendix p20). Significant variation was also documented in the number of contacts with healthcare services. CRC-related hospital days (inpatient days) varied from 3 per 1,000 persons per year (Turkey) to 26 per 1,000 (Germany) with a mean 13 (95% 11-

15) per 1,000 persons per year (see Appendix p21). CRC healthcare costs *per capita* varied widely within the EUR-33 (from Cyprus: €1; to Hungary: €79); the average cost of CRC was equivalent to €12 *per capita* (Figure 1, PPP adjusted)

Informal care costs and productivity losses

Informal-care costs were €2·2B (11·6% of the economic burden of CRC) (Table 2), ranging from 1·0% (Iceland; €0·2Million (M)) to 17·1% (Greece; €19·2M) (PPP-adjusted).

Average productivity unit costs diverged by country; losses in daily earnings ranging from €99 (Cyprus/Greece) to €219 (Denmark) with a mean of €138 (95% CI €128-€149) daily earnings (see Appendix p20 - PPP adjusted). There was significant deviation in number of years/days lost because of premature death and morbidity. Losses due to CRC deaths were 15·9% of total CRC economic burden (€3·0B), ranging from 7·0% (Austria; €24·6M) to 30·9% (Cyprus; €1·9M) (Table 2). Morbidity losses represented 33·0% of the economic CRC burden (€6·3B), ranging from 1·9% (Hungary; €19·6M) to 83·4% (Norway; €395·6M).

Drivers, determinants, and outcomes of CRC healthcare costs

Results of the log-linear univariable regression revealed: a strong positive relationship between healthcare expenditure and GDP (*per capita*, $p < 0{\cdot}001$; per case, $p < 0{\cdot}002$), a strong positive relationship between healthcare costs and DALYs (*per capita*, $p < 0{\cdot}001$; per case $< 0{\cdot}001$), a positive relationship between healthcare costs and incidence (*per capita*, $p < 0{\cdot}041$), a strong negative relationship between healthcare costs and prevalence (*per capita*, $p < 0.046$; per case, $p < 0{\cdot}001$), and a strong positive relationship between healthcare costs and mortality (*per capita*, $p < 0{\cdot}001$; per case, $p < 0{\cdot}001$) (see Appendix p29-p37).

A log-linear multivariable regression model (see Appendix p23) was created by regressing CRC healthcare costs on two independent variables (incidence rate and 5-year net survival). The R^2 statistics (*per capita*=0·21; per case=0·21) and F (*per capita*=0·03; per case= 0·03) indicated a significant association between this set of independent variables and CRC healthcare costs.

Sensitivity analysis

Sensitivity analysis (see Appendix p38) indicated the largest effect on total CRC costs resulted from discounting the present value of future earnings lost to mortality/morbidity (0%, 3·5% baseline, 10%), resulting in a range of €17·1B-€21·9B, with the second-largest effect from a 20% variation in healthcare costs (€17·6B-€20·7B).

Systemic Therapy

EUR-33 CRC SACT expenditure was €1·9B. Unfortunately, for Cyprus, Denmark, Iceland, Luxembourg, Malta, and Netherlands, detailed SACT expenditure breakdowns were unavailable; in-depth analysis was performed for the remaining EUR-27, revealing significant variations in deployment of both chemotherapeutic and targeted pharmaceutical medicine across Europe in 2015 (Tables 3,4).

Chemotherapy

Expenditure on 5-FU and its oral analogue capecitabine was €167M (9% of total EUR-27 CRC SACT expenditure). 5-FU was prescribed in all countries except Estonia, with Latvia having the highest proportional spend (€278,123; 10%) and Italy the lowest (€1M; 0·5%).). All countries prescribed capecitabine, with Estonia having the highest proportional spend (€912,858; 71%) and Bulgaria the lowest (€1M; 2%).

Expenditure on oxaliplatin was 9% of total EUR-27 CRC SACT costs. All countries except Estonia prescribed oxaliplatin; the UK had the highest proportional spend (€36M; 24%) and Greece the lowest (€18,624; 0·5%).

Expenditure on Folic acid (including calcium folinate, calcium levofolinate, calcium mefolinate) was €132M, 7% of total EUR-27 CRC SACT costs (Table 3). Folic acid, its derivatives and precursors were prescribed in all countries, with Greece the highest proportional spend (€3M; 78%) and Slovakia the lowest (€299,786; 0·7%).

Expenditure on irinotecan was 6% of EUR-27 total CRC SACT costs. All countries except Estonia prescribed irinotecan; Croatia had the highest proportional spend (€2·7M; 15%) and Slovenia the lowest (€20,513; 0·3%).

Expenditure on raltitrexed was 0·3% of total CRC SACT costs for EUR-27. Raltitrexed was only prescribed in 12 of the EUR-27; Spain had the highest proportional spend (€2M; 2%) and Switzerland the lowest (€5,296; 0·03%).

Targeted Therapy

Of the CRC-targeted SACT available in 2015 in the EUR-27 (Table 4), bevacizumab was the most prescribed. Expenditure in 2015 was €771M (40%), the largest proportional expenditure of all EUR-27 CRC-targeted SACT. All countries evaluated prescribed bevacizumab, ranging from 0·02% (€540) for Latvia to 72% (€30·9M) for Slovakia. The smallest targeted SACT expenditure was for aflibercept, 2% of total EUR-27 CRC SACT costs. Only 16 of EUR-27 used aflibercept (Table 4), with Belgium having the largest proportional expenditure (€2M; 5%).

Cetuximab had the second-largest proportional targeted SACT expenditure of the EUR-27 (€278M; 15%). In Serbia, cetuximab expenditure (€5·1M; 40%) represented more than twice the costs as bevacizumab (€2·4M; 19%). Cetuximab was not prescribed in Estonia or Greece and was rarely prescribed in Lithuania (€1,447; 0·05%).

Panitumumab had the third-highest proportional targeted SACT spend, representing 9% of the total EUR-27 CRC SACT costs. Sweden had the highest proportional expenditure, 28% (€3M) and Romania the lowest at 0·07% (€102,767). Panitumumab was not prescribed in Estonia, Latvia, Lithuania, or Poland.

Regorafenib expenditure was €42M (2% of total CRC SACT costs for EUR-27). Slovenia had the highest proportional spend, (€440,510; 8%) and Romania the lowest (€18,706; 0·01%); Bulgaria, the Czech Republic, Estonia, Greece, Latvia, and Serbia did not prescribe regorafenib.

Overall, evaluating country-specific activities, France had the highest 2015 expenditure (€191M), both in overall spend and for individual CRC-targeted SACT (excepting regorafenib, for which Germany had the highest spend (€11·6M)). The financial outlay on CRC-targeted SACT ranged from 3% (€41,065 (Estonia)) to 93% (€81·8M (Bulgaria)) (Table 4).

Colorectal cancer expenditure by Region, Resources and Survival

A multivariable regression model (see Appendix p24) was created by regressing CRC survival on a set of independent variables (numbers of oncologists, computed tomography [CT] scanners, CT scans, radiologists, radiotherapy machines, surgical oncologists, (all corresponding to 2015 except for surgical oncologists (2018)) for the EUR-33. Results indicated a significant association between the set of independent variables and 5-year net survival (2010-2014) (R^2=0·48; F=0·005).

Eleven of the CEE countries were in the top half of the EUR-33 for CRC healthcare costs per case (see Appendix p21). However, except for the number of radiologists, there was a paucity of CRC-related hospital personnel, resources, and activities (numbers of oncologists, CT scanners, CT scans, radiotherapy machines, surgical oncologists) in CEE countries. All CEE countries were in the bottom half of the EUR-33 for five-year net survival.

Of the Northern European countries, Norway was in the bottom half of EUR-33 CRC healthcare costs per case and in the top half for CRC-related hospital resources, and activities, except surgical oncologists. All Scandinavian countries 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 appeared at the midpoint for healthcare expenditure as a proportion of total healthcare costs and in the top half for CRC-related hospital resources, and activities (except surgical oncologists), while all Western European countries were in the top half for survival.

For Southern European countries, no discernible pattern was observed.

Twelve of the thirteen countries (Germany was the exception) with the highest five-year net survival spent at least twice as much on hospital-based care as on SACT.

CRC healthcare costs per case were portrayed on a CRC survival map of Europe using Tableau software (Figure 2). The CRC healthcare 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.

Costs comparisons for colorectal cancer: 2009 versus 2015

Compared to the 2009 health economic study for all cancers for EU-27,[3] overall costs have increased by 32% (€14·5B to €19·1B, after adjusting for inflation), while healthcare costs have only increased by 23% (€6·1B to €7·5B). We only performed specific comparisons with 2009 data for hospital-care and SACT costs to evaluate changes over time, as activity in the former and expenditure in the latter are directly comparable. Overall, hospital-care costs decreased by 21% for the EU-27 from €3·6B to €2·8B (see Appendix p22). The greatest percentage increase for hospital-care costs were in Hungary (+222%), Portugal (+155%), Malta (+96%), and Austria

(+84%) (see Appendix p22). The largest increases in SACT expenditures were in Bulgaria (+818%), Ireland (+473%), Hungary (+398%), and Austria (+369%). All EUR-33 countries increased their SACT expenditure from 2009 to 2015, except Cyprus (-83%), Luxembourg (-80%), and Greece (-75%) (see Appendix p22).

Internal validity of hospital care data

Hospital care costs rose by 44% from €3·3B to €4·7B when CRC/cancer-specific costs were switched for average hospital care expenditure data from Eurostat.[9] The top and bottom three countries retained their ranking for costs per case, while Lithuania moved from 10th to 21st position, Italy moved from 19th to 13th position, the Netherlands moved from 22nd to 19th position) and Portugal moved from 20th to 18th position. The remaining countries remained in their rank position or switched up/down with their nearest neighbour.

DISCUSSION

This study represents the most comprehensive analysis to date on the economic burden of CRC across Europe. By 2015, the economic burden of CRC across Europe had increased to over €19 billion. Direct healthcare costs represented less than 40% of the total cost, with 60% being due to loss of productivity and opportunity costs for informal carers. Countries with similar GDP *per capita* had significantly different healthcare expenditures. Expenditure on pharmaceuticals rose by over 200% between 2009 and 2015. Certain Central and Eastern European (CEE) 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 healthcare providers to inform their decision-making on service prioritisation and budget allocation, in order to improve outcomes. More broadly, we recommend that CRC be considered as a bellwether indicator, reflecting how cancer systems are performing overall from an economic perspective. Previously, we reported on the overall financial burden of cancer in the EU, which included limited economic cost data for CRC.[3] This study focusses solely on CRC, significantly extends the previous analysis, expands coverage from 27 to 33 countries, and produces much more comprehensive CRC-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.

Our analysis indicates that those countries with higher CRC incidence and mortality had higher healthcare costs and conversely, those countries with the highest CRC survival had lower costs, reflecting both the higher costs of treating CRC presenting at a late stage and the higher costs incurred within less efficient healthcare systems.[23] Higher 5-year net survival correlated significantly with better resourcing, demonstrated by metrics including the number of oncologists (surgical, medical), CT scanners and scans performed, and radiotherapy equipment, etc. The highest survival estimates in Norway and Switzerland appear to be related to expenditure on the core components of CRC treatment, including surgery, radiotherapy and human resources, rather than SACT expenditure.[24] Recent studies suggest that Central and Eastern European (CEE) countries require an investment and restructuring of public health, personnel and equipment allocation, in order to avoid having patients first present at hospital with late stage CRC.[25–27] Our 2015 data would support this assertion. We have shown that, hospital care costs have continued to increase in most CEE countries, due in large part to a continued hospital-centric approach, whereas the hospital costs have decreased in France, Germany, Spain, the Netherlands, and the UK compared to 2009. In the case of Bulgaria, increased use of targeted therapy is associated with a reduction in hospital costs. In Estonia, Greece, Latvia, and Lithuania, a preference for chemotherapy is associated with increases in hospital costs; adverse effects related to chemotherapy might contribute to these increases.

Some of the poorer performing health systems in Europe were associated with higher costs and lower survival: a double value burden. Eleven countries from CEE had the highest expenditure on CRC 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 [28] and late-stage diagnosis may partially explain lower survival, but less effective and efficient deployment of cancer care is also a major factor.[29] Overall, CRC hospital-care costs for the EUR-33 have remained relatively consistent at €471 (95% CI €385-€573) per hospital stay (after adjusting for inflation), but overall costs have diminished by 21% (€3·6B to €2·8B), due to shorter inpatient stays compared to the 2009 study.[3]

Our data indicate that SACT costs have more than tripled since 2009 (over 214%) confirmed by a recent 2018 study on overall oncology costs across Europe. The majority of these drug costs are due to increases in targeted SACT.[30] However, there are wide variations across Europe, with 400-800% increases in Bulgaria and Hungary respectively, which are not reflected in improved outcomes; some of these increases may be due to shortages of chemotherapies, potentially leading to an overspend in targeted therapies.[31] Significant reductions (~80%) were seen in Cyprus, Greece and Luxembourg. Reductions for Cyprus and Greece are likely due to the direct consequence of the 2008 economic crisis. Decreases in Luxembourg may reflect the increasing willingness of patients to seek cross-border care.[32] While five Eastern European countries that spend the least on SACT proportionally are in the bottom-half of the EUR-33, our data and those of others reveal that certain CEE countries have outpaced their WE counterparts in SACT expenditure,[33] but this is not reflected in any therapeutic gain for their patients.

Several recent papers have reported on the costs of cancer care in Europe. One study highlighted that cancer healthcare costs are relatively low compared to the overall cancer burden, while a second study showed significant increases in cancer drug spending over the last 5 years.[30,34] Looking at the overall cancer burden in the 2018 study, the data are comparable with our results for overall CRC burden (€21.3B versus our calculation of €19.1B) and the 2015 Schlueter *et al.* paper aligns with our figure of 0.47% for the percent of total healthcare costs, when CRC as a proportion of all cancer diagnosis and the number of CRC cases are considered.[30,34] However, the lack of full implementation of PPP adjustments in these studies makes country-by-country healthcare costs comparisons unachievable.

There are several limitations to our study. Firstly, accuracy of this analysis is dependent on the data sources which, outside of hospital care activity and SACT costs, are lacking for certain countries for epidemiological and financial data which can be specifically allocated to either CRC or cancer in general. In a proportion of cases, we had to rely on non-homogenous B grade data, particularly for emergency care, possibly contributing to the variations between countries. Furthermore, the assumption that CRC GP visits may equate to proportion of CRC hospital discharges may not always be the case, 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 it has been updated post 2015 to include eight further countries, increasing its utility.

Secondly, Hungary is somewhat of an outlier in these analyses; it exhibits the highest incidence, mortality and DALYs, coupled with the lowest prevalence and disability payments. Recent studies have highlighted that Hungary has both the highest incidence and mortality in the EU and globally, arising from a combination of factors including lifestyle choices, lack of CRC screening awareness, frequent metastatic presentation, and a potential genetic component. Similar results are seen in Croatia, and Slovakia, two other countries seen with a high CRC per case costs.[35–38]

Thirdly, CRC costs increase as the disease progresses, with estimates of €4,000 for stage I to €40,000 for late-stage presentation.[27] While a CRC screening programme can help attenuate metastatic presentation, few countries reach the EU goal of 65% participation in screening programmes in the 50-74 year old cohort, with the Netherlands and Slovenia as exceptions.[27,39] Ideally, we would have liked to employ incident cases by stage of presentation and tracked costs and epidemiology of each cohort, unfortunately we could find no corresponding data set to perform these analyses.

Fourthly, 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.

Fifthly, a key driver of CRC costs is the productivity losses; here we employed the human capital approach rather than the friction cost approach (FCA), as CRC is both a terminal illness and contributes to long-term disability. The prior 2009 study focused on FCA, making it difficult to draw conclusions between the productivity losses components in 2009 and 2015.

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

CONCLUSION

CRC 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. This variation is not correlated with patient outcomes. This strongly suggests that many countries need to understand why, despite increasing expenditure, their CRC outcomes remain so poor.

A significant mis-spend on CRC care also appears to exist in many CEE countries. This 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 CEE 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. This could deploy the European Society of Medical Oncology's Magnitude of Benefit Scale for new chemotherapy regimens,[40] to ensure more measurable gains from systemic interventions in colorectal and other common cancers. Our analysis adds significant 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.[41] Crucially, as the adverse impact of COVID is recognised, particularly on patients with CRC, and mitigation strategies are developed,[42] we must ensure that spending on improving CRC outcomes is appropriate to the challenges that are relevant in each country or region, particularly in the context of Europe's Beating Cancer Plan, in order to ensure tangible benefits for all European citizens, patients and society.

Contributors

RH, DF, RS and ML developed the concept of the paper and the plan for analysis, MC, CA, and PA validated the morbidity model. DF reviewed the model in total and verified underlying data and methodology while supervising project with RS and ML. RH conducted literature search, plotted figures, performed 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.

Declaration of interest

RH is an employee at Diaceutics PLC. RA reports grants from AstraZeneca and MSD, consulting fees from AstraZeneca, Merck KGgA, and Bayer, speaker fees from Amgen, Merck KGgA, and Servier, and support for attending meetings from Amgen, BMS, and Merck KGgA. TM reports support from MRC and Cancer Research UK, consulting fees from AstraZeneca, participation on Pierre Fabre IDMC, Pfizer steering committee, and receipt of material from Almac Diagnostics, Indica labs and Psioxus. EMF reports support and grants from Cancer Focus NI and Health Data Research UK, and advice to RCN. EMcF reports support from Cancer Focus Northern Ireland and Health data Research UK (HDRUK). ML reports support from MRC, Cancer Research UK, HDRUK, an unrestricted educational grant from Pfizer, and honoraria from Pfizer, EMD Serono, and Roche unrelated to the work.

Data Sharing

The data on which this study is based are available at:
Henderson, Raymond (2021), "Defining the economic burden of colorectal cancer across Europe", Mendeley Data, V2, https://data.mendeley.com/datasets/tnjw2gd8nm/draft?a=5c9fce82-00c5-4e21-972b-42d4af18e26a

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$$Annual\ earnings\ lost\ (CRC\ death) = 230\ days \times Daily\ wage \times Employment\ rate \times Activity\ rate = X$$

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

$$discount\ rate = i$$

$$years\ lost = n$$

where i=0%, 3·5% or 10%

Box 1 Formulae for future lost earnings due to mortality.

$$Annual\ earnings\ lost\ (CRC\ disablement) = 230\ days \times Daily\ wage \times Employment\ rate = Y$$

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

$$conditional\ probability\ of\ survival = \ \varphi = 1 - \delta$$

$$discount\ rate = i$$

$$years\ lost = n$$

where i=0%, 3·5% or 10%

Box 2 Formulae for future lost earnings due to morbidity.

Country	Primary care activity	Outpatient care activity	A&E care activity	Hospital care activity	SACT activity	Primary care costs	Outpatient care costs	A&E care costs	Hospital care costs	SACT costs
Austria (AT)	B	B	B	A*	A*	B	A	B	A*	A*
Belgium (BE)	B	B	B	A*	A*	B	A	B	A	A*
Bulgaria (BG)	B	B	B	A*	A*	B	B	E	C	A*
Croatia (HR)	B	B	C	A*	A*	B	B	B	C	A*
Cyprus (CY)	B	A	B	A*	C	B	A	B	A	C
Czech Rep. (CZ)	B	A	B	A*	A*	B	B	B	C	A*
Denmark (DK)	B	A*	A*	A*	C	C	A	A	A	C
Estonia (EE)	B	A	B	C	A*	C	B	C	B	A*
Finland (FI)	B	A	B	A*	A*	B	A	B	A	A*
France (FR)	B	B	B	A*	A*	B	A	B	A	A*
Germany (DE)	B	A	B	A*	A*	B	A	B	A	A*
Greece (EL)	B	B	B	A*	A*	B	B	B	A*	A*
Hungary (HU)	B	B	B	A*	A*	B	A*	B	A*	A*
Iceland (IS)	B	A	B	A*	C	B	A	B	A	C
Ireland (IE)	B	B	B	A*	A*	B	A*	A*	A	A*
Italy (IT)	B	B	B	A*	A*	A	A	A	A	A*
Latvia (LV)	A*	A*	B	A*	A*	A*	A*	B	A*	A*
Lithuania (LT)	B	B	C	A*	A*	B	A	B	A	A*
Luxembourg (LU)	B	B	C	A*	A*	B	A	B	C	A*
Malta (MT)	B	B	B	A*	C	C	D	B	B	C
Netherlands (NL)	B	A*	B	A*	C	B	A*	A*	A*	C
Norway (NO)	B	A	B	A*	A*	B	B	B	A*	A*
Poland (PL)	B	B	B	A*	A*	B	A	B	A*	A*
Portugal (PT)	B	B	B	A*	A*	B	A	B	C	A*
Romania (RO)	B	B	C	A*	A*	D	D	E	C	A*
Serbia (RS)	B	B	C	A*	A*	B	B	B	A*	A*
Slovakia (SK)	B	A	B	A*	A*	D	B	B	C	A*
Slovenia (SI)	B	A	B	A*	A*	D	D	B	A*	A*
Spain (ES)	B	A	B	A*	A*	B	A	A	A	A*
Sweden (SE)	B	A	B	A*	A*	B	A	B	A*	A*
Switzerland (CH)	B	B	B	A*	A*	B	A*	C	A*	A*
Turkey (TR)	B	B	B	A*	A*	B	B	B	B	A*
United Kingdom (UK)	B	A*	B	A*	A*	A*	A*	A*	A*	A*

Table 1. Sources used to obtain healthcare activity and unit costs, by category and country

SACT – systemic anti-cancer therapy

A*. National CRC data: CRC-specific healthcare activity and expenditure data were obtained for that country's population;

A. National cancer-specific data: Cancer-specific healthcare activity and expenditure data were obtained for that country's population;

B. National data but not CRC-specific: All-cause healthcare activity data are obtained but not due solely to CRC. We evaluated CRC-specific resource use by multiplying all-cause national data by the percentage of ambulatory visits due to CRC out of all ambulatory visits, if available. If CRC-related ambulatory information was not available, we used the percentage of hospital discharges due to CRC out of all discharges to assign that country's healthcare utilisation. Costs directly obtained from sources such as national fee schedules, national reports, published studies, etc;

C. No national data: that country’s activity data are obtained for all diseases from similar countries and assigned it into CRC using the approach defined in (B). Costs acquired from national expenditure figures (e.g. primary care, outpatient care, emergency care, hospital care) using the respective total activity levels. For example, cost per hospital day is 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.

	Healthcare Costs													Productivity Costs						
Country	Primary care		Outpatient care		Emergency care		Hospital care		SACT		Total healthcare		% of THE	Mortality		Morbidity		Informal care		TOTAL COSTS
	Cost (€)	%	Cost (€)	%	Cost (€)	%	Cost (€)	%	Cost (€)	%	Cost (€)	%		Cost (€)	%	Cost (€)	%	Cost (€)	%	
Austria	28,027	14	3,883	2	28,773	14	104,808[a]	52	36,240[a]	18	201,730	57	0·91	24,605	7	105,584	30	21,738	6	353,657
Belgium	8,084	5	24,062	16	6,061	4	75,941[b]	50	38,088[a]	25	152,235	39	0·46	29,765	8	169,360	43	42,169	11	393,530
Bulgaria	3,596	3	10,716	8	1,509	1	38,194	27	88,194[a]	62	142,209	55	0·66	38,105	15	43,959	17	32,858	13	257,131
Croatia	13,207	16	10,735	13	16,353	20	22,167	27	18,349[a]	23	80,811	35	0·99	28,599	13	92,407	40	26,509	12	228,327
Cyprus	62	5	376	32	19	2	575[b]	49	145	12	1,177	19	0·11	1,874	31	2,015	33	993	16	6,058
Czech Rep.	5,173	7	7,271	10	513	1	36,140	50	23,190[a]	32	72,287	31	0·30	46,433	20	81,512	35	34,644	15	234,876
Denmark	5,756	7	32,740[b]	40	5[b]	0·01	36,841[b]	45	6,738	8	82,080	28	0·35	45,637	16	123,114	43	38,353	13	289,185
Estonia	2,251	11	1,458	7	7,301	35	8,767[b]	42	1,286[a]	6	21,063	26	0·82	9,446	12	46,390	57	4,845	6	81,744
Finland	3,967	6	100[c]	0·2	2,582	4	39,815[b]	65	14,906[a]	24	61,369	35	0·36	22,270	13	69,884	40	21,331	12	174,854
France	25,088	4	58,324	8	8,113	1	295,779[b]	41	326,844[a]	46	714,149	36	0·35	167,233	8	854,026	43	250,470	13	1,985,878
Germany	71,404	8	239,040[c]	26	5,164	1	389,986[b]	42	219,530[a]	24	925,124	34	0·32	537,834	20	888,870	32	401,728	15	2,753,556
Greece	6,071	10	8,040	14	2,892	5	37,835[a]	64	3,878[a]	7	58,716	52	0·40	17,141	15	17,682	16	19,201	17	112,741
Hungary	70,028	9	275,643	36	21,314	3	240,126[a]	31	167,137[a]	22	774,247	76	2·19	130,796	13	19,623	2	90,391	9	1,015,057
Iceland	400	11	531	15	16	0·4	2,202[b]	63	350	10	3,500	18	0·44	3,219	17	12,445	64	203	1	19,367
Ireland	4,230	8	13,496	25	1,374	3	22,092[b]	40	13,646[a]	25	54,838	41	0·43	31,956	24	35,671	27	11,485	9	133,950
Italy	49,547	5	65,256	7	84,832	8	561,445[b]	56	240,355[a]	24	1,001,435	56	0·70	210,357	12	310,752	17	256,220	14	1,778,765
Latvia	218[a]	1	4,993[a]	20	2,875	12	13,618[a]	55	2,910[a]	12	24,614	27	0·49	10,184	11	47,128	51	10,116	11	92,041
Lithuania	2,187	8	10,135	36	5,741	20	7,101[b]	25	3,026[a]	11	28,191	23	0·32	16,677	14	64,698	53	12,168	10	121,734
Luxembourg	241	4	477	9	34	1	4,571	85	69[a]	1	5,393	28	0·39	1,383	7	11,019	58	1,196	6	18,990
Malta	204	7	206	7	117	4	2,081	70	380	13	2,989	28	0·26	1,266	12	5,196	49	1,164	11	10,615
Netherlands	12,965	6	136,965[a]	60	2,119	1	56,882[a]	25	18,757[a]	8	227,688	38	0·43	113,872	19	183,270	31	72,036	12	596,865
Norway	1,419	7	4,964	23	242	1	10,744[a]	50	4,088[a]	19	21,456	5	0·14	36,526	8	395,589	83	20,540	4	474,110
Poland	14,812	3	48,002	11	4,630	1	319,045[a]	72	55,262[a]	13	441,750	34	0·59	194,261	15	510,206	39	156,923	12	1,303,140
Portugal	10,804	8	9,102	7	13,376	10	71,326	55	25,265[a]	19	129,874	36	0·56	88,455	25	98,252	27	41,147	12	357,728
Romania	158,074	27	144,683	24	5,645	1	143,408	24	143,178[a]	24	594,988	47	1·17	255,330	20	320,482	25	104,283	8	1,275,083
Serbia	19,716	16	16,436	14	1,847	2	69,097[a]	58	12,826[a]	11	119,922	42	0·19	58,812	21	67,765	24	38,716	14	285,216
Slovakia	15,175	9	56,843	35	2,711	2	42,608	27	42,832[a]	27	160,169	50	1·12	29,577	9	102,393	32	26,165	8	318,305
Slovenia	2,217	7	1,190	4	494	2	20,493[a]	65	7,340[a]	23	31,733	50	0·74	13,498	21	9,063	14	9,377	15	63,672
Spain	73,983	20	3,771	1	28,158[c]	8	132,213[b]	36	125,704[a]	35	363,829	38	0·45	159,962	17	311,698	33	122,516	13	958,004
Sweden	9,429	18	5,085[c]	10	1,995[c]	4	25,817[a]	49	10,718[a]	20	53,044	22	0·18	56,082	24	92,555	39	36,333	15	238,014
Switzerland	5,736	6	7,211	8	1,318	1	59,099[a]	66	16,825[a]	19	90,188	36	0·41	41,961	17	99,378	39	20,107	8	251,635
Turkey	27,677	5	118,300	22	13,098	2	264,723	49	114,961[a]	21	538,760	57	0·57	197,274	21	140,802	15	63,380	7	940,215
UK	52,426	15	17,090[a]	5	23,980	7	116,957[a]	32	150,925[a]	42	361,377	18	0·17	424,785	21	992,158	49	236,363	12	2,014,683
EUR-33	704,177	9	1,337,122	18	295,198	4	3,272,496	43	1,933,941	26	7,542,934	39	0·47	3,045,177	16	6,324,948	33	2,225,668	12	19,138,728

Table 2. Costs (x €1,000's) of colorectal cancer in 33 European countries and proportion of healthcare costs, by country, 2015.

CRC healthcare costs and SACT percentages are a proportion of total CRC healthcare costs; percentage of THE is the CRC expenditure fraction; percentage of productivity costs is the proportion of total CRC economic burden. Adjusted for purchasing power parity (PPP). Totals do not match the sum of costs because of rounding. a - CRC activity and costs, b – CRC activity and other cancer costs, c – general cancer activity and other cancer costs.

GDP - gross domestic product; SACT – systemic anti-cancer therapy; THE – total healthcare expenditure.

MOA:	Enhances chemotherapy		Inhibits synthesis of DNA				Inhibits topoisomerase I		Blocks DNA replication		Inhibits synthesis of DNA	
Type:	**Precusors and derivatives**		**Converted to fluorouracil**		**Pyrimidine antimetabolite**		**Derivative of camptothecin**		**Platinum-based**		**Antimetabolite**	
Name[a]:	**Folic acid**		**Capecitabine**		**Fluorouracil**		**Irinotecan**		**Oxaliplatin**		**Raltitrexed**	
Country[b]	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**	**%**
Austria	986,319	2·72	923,356	2·55	629,549	1·74	2,940,936	8·12	3,308,488	9·13	189,126	0·52
Belgium	1,305,152	3·43	935,229	2·46	869,514	2·28	3,144,464	8·26	2,502,284	6·57	44,047	0·12
Bulgaria	2,237,552	2·54	1,378,601	1·56	920,110	1·04	715,255	0·81	1,144,288	1·30	0	0·00
Croatia	1,264,755	6·89	2,542,940	13·86	573,731	3·13	2,730,842	14·88	1,419,059	7·73	0	0·00
Czech Rep·	1,953,082	8·42	5,214,121	22·48	1,059,486	4·57	918,093	3·96	1,004,493	4·33	67,732	0·29
Estonia	332,061	25·82	912,838	70·98	0	0·00	0	0·00	0	0·00	0	0·00
Finland	750,284	5·03	947,870	6·36	91,996	0·62	246,781	1·66	125,716	0·84	0	0·00
France	25,102,950	7·68	11,853,940	3·63	3,605,989	1·10	44,433,823	13·59	49,496,367	15·14	1,155,659	0·35
Germany	10,955,441	4·99	8,454,864	3·85	6,902,851	3·14	8,672,863	3·95	10,921,509	4·97	0	0·00
Greece	3,013,148	77·70	283,576	7·31	355,874	9·18	49,452	1·28	18,624	0·48	0	0·00
Hungary	9,706,987	5·81	6,811,697	4·08	2,656,437	1·59	4,737,203	2·83	8,753,951	5·24	518,077	0·31
Ireland	2,046,229	15·00	511,034	3·74	308,835	2·26	1,002,645	7·35	1,524,421	11·17	0	0·00
Italy	26,447,747	11·00	13,505,286	5·62	1,156,030	0·48	12,260,239	5·10	34,033,790	14·16	675,774	0·28
Latvia	1,224,205	42·06	282,407	9·70	278,123	9·56	193,706	6·66	149,016	5·12	0	0·00
Lithuania	1,356,664	44·84	760,348	25·13	232,225	7·68	49,034	1·62	27,269	0·90	0	0·00
Norway	166,619	4·08	141,642	3·47	56,706	1·39	82,521	2·02	87,319	2·14	1,784	0·04
Poland	2,617,683	4·74	5,610,485	10·15	4,374,401	7·92	2,520,057	4·56	1,155,329	2·09	0	0·00
Portugal	1,381,216	5·47	912,046	3·61	842,178	3·33	556,811	2·20	361,423	1·43	55,444	0·22
Romania	3,652,834	2·55	18,026,752	12·59	1,065,008	0·74	6,654,256	4·65	4,670,313	3·26	0	0·00
Serbia	1,414,882	11·03	1,321,685	10·30	1,182,843	9·22	638,919	4·98	584,817	4·56	0	0·00
Slovakia	299,786	0·70	3,207,155	7·49	522,942	1·22	571,589	1·33	501,450	1·17	0	0·00
Slovenia	91,797	1·25	541,909	7·38	88,900	1·21	20,513	0·28	118,998	1·62	0	0·00
Spain	5,486,699	4·36	9,968,595	7·93	2,830,719	2·25	3,786,620	3·01	16,112,570	12·82	1,926,143	1·53
Sweden	932,157	8·70	320,036	2·99	214,155	2.00	126,897	1·18	121,382	1·13	0	0·00
Switzerland	923,639	5·49	999,980	5·94	382,001	2·27	1,107,392	6·58	2,401,410	14·27	5,296	0·03
Turkey	15,310,280	13·32	10,324,711	8·98	2,790,506	2·43	3,183,667	2·77	3,483,595	3·03	369,345	0·32
UK	10,922,763	7·24	16,998,329	11·26	9,599,635	6·36	17,829,611	11·81	36,388,435	24·11	588,804	0·39
EUR-27	131,884,946	6·91	123,693,447	6·48	43,592,760	2·29	119,176,206	6·25	180,418,333	9·46	5,599,248	0·29

Table 3. 2015 colorectal non-targeted systemic anti-cancer therapy costs and proportions, by country.

a. (Generic – Commercial name) Non-targeted: Calcium Folinate – Leucovorin; Calcium Levofolinate – Leoleucovorin; Calcium Mefolinate – Prefolic; Capecitabine - Xeloda; Fluorouracil – Adrucil; Irinotecan - Camptosar; Oxaliplatin – Eloxatin; Raltitrexed - Tomudex.

b. Cyprus, Denmark, Iceland, Malta, Luxembourg, and Netherlands not included.

Percentage columns are a proportion of all SACT costs for that country. Adjusted for purchasing power parity (PPP). MOA – mechanism of action.

Target - MOA:	VEGFR-2 - blocks angiogenesis		VEGF - blocks angiogenesis				EGFR - blocks cell growth						
Type:	**Protein tyrosine kinase inhibitor**		**Recombinant fusion protein**		**Monoclonal antibody**		**Monoclonal antibody**		**Monoclonal antibody**		**Total targeted CRC therapies**		**All anti-neoplastic CRC therapies[c]**
Name[a]:	**Regorafenib**		**Aflibercept**		**Bevacizumab**		**Cetuximab**		**Panitumumab**				
Country[d]	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**	**%**	**Cost (€)**
Austria	1,856,061	5·12	1,280,752	3·53	16,762,754	46·25	3,568,758	9·85	3,793,864	10·47	27,262,189	75·23	36,239,965
Belgium	617,834	1·62	1,989,914	5·22	15,666,851	41·13	6,492,516	17·05	4,520,651	11·87	29,287,766	76·89	38,088,456
Bulgaria	0	0.00	1,809,672	2·05	51,440,032	58·33	9,287,732	10·53	19,260,305	21·84	81,797,742	92·75	88,193,548
Croatia	15,263	0·08	0	0.00	6,967,729	37·97	1,903,230	10·37	931,027	5·07	9,817,249	53·50	18,348,575
Czech Rep·	0	0.00	0	0.00	5,041,238	21·74	5,654,713	24·38	2,277,483	9·82	12,973,434	55·94	23,190,441
Estonia	0	0.00	0	0.00	41,065	3·19	0	0.00	0	0.00	41,065	3·19	1,285,964
Finland	667,272	4·48	294,792	1·98	7,667,219	51·44	766,582	5·14	3,347,149	22·46	12,743,014	85·49	14,905,661
France	9,429,089	2·88	8,881,514	2·72	105,286,828	32·21	40,210,785	12·30	27,387,189	8·38	191,195,406	58·50	326,844,133
Germany	11,578,475	5·27	6,165,377	2·81	93,405,151	42·55	36,668,010	16·70	25,805,249	11·75	173,622,262	79·09	219,529,790
Greece	0	0.00	0	0.00	142,775	3·68	0	0.00	14,495	0·37	157,270	4·06	3,877,944
Hungary	583,504	0·35	0	0.00	69,620,860	41·65	37,806,350	22·62	25,941,966	15·52	133,952,680	80·15	167,137,032
Ireland	542,564	3·98	43,626	0·32	4,987,243	36·55	1,376,957	10·09	1,302,424	9·54	8,252,815	60·48	13,645,980
Italy	6,628,776	2·76	4,859,591	2·02	89,514,923	37·24	29,048,496	12·09	22,224,747	9·25	152,276,533	63·35	240,355,400
Latvia	0	0.00	0	0.00	540	0·02	782,484	26·89	0	0.00	783,025	26·90	2,910,482
Lithuania	127,636	4·22	0	0.00	470,955	15·57	1,447	0·05	0	0.00	600,038	19·83	3,025,579
Norway	247,871	6·06	6,349	0·16	1,875,724	45·89	320,362	7·84	1,100,766	26·93	3,551,072	86·87	4,087,663
Poland	139,688	0·25	0	0.00	31,773,039	57·50	7,070,819	12·80	0	0.00	38,983,546	70·54	55,261,501
Portugal	146,111	0·58	42,169	0·17	10,009,941	39·62	8,770,595	34·71	2,187,342	8·66	21,156,158	83·74	25,265,277
Romania	18,706	0·01	0	0.00	97,540,744	68·13	11,446,864	7·99	102,767	0·07	109,109,081	76·21	143,178,245
Serbia	0	0.00	0	0.00	2,379,362	18·55	5,108,630	39·83	195,320	1·52	7,683,313	59·90	12,826,458
Slovakia	15,407	0·04	1,037,062	2·42	30,937,601	72·23	2,419,556	5·65	3,319,457	7·75	37,729,083	88·09	42,832,005
Slovenia	573,550	7·81	189,453	2·58	3,430,366	46·74	1,288,553	17·56	995,814	13·57	6,477,735	88·25	7,339,853
Spain	2,113,837	1·68	5,854,552	4·66	45,394,797	36·11	17,692,027	14·07	14,537,370	11·56	85,592,582	68·09	125,703,928
Sweden	215,693	2·01	199,920	1·87	4,656,360	43·44	924,201	8·62	3,007,058	28·06	9,003,232	84.00	10,717,858
Switzerland	757,010	4·50	523,387	3·11	6,344,265	37·71	2,243,032	13·33	1,137,306	6·76	11,005,000	65·41	16,824,717
Turkey	3,336,729	2·90	0	0.00	41,993,661	36·53	23,030,635	20·03	11,137,788	9·69	79,498,814	69·15	114,960,919
UK	1,896,274	1·26	2,992,494	1·98	28,000,170	18·55	24,105,573	15·97	1,623,684	1·08	58,618,195	38·83	150,945,772
EUR-27	41,507,351	2·18	36,170,625	1·90	771,352,191	40·44	277,988,909	14·57	176,151,221	9·23	1,303,170,298	68·32	1,907,523,146

Table 4. 2015 colorectal targeted systemic anti-cancer therapy costs and proportions, by country.

a. Targeted: Aflibercept - Zaltrap; Bevacizumab -Avastin; Cetuximab – Erbitux; Panitumumab – Vectibix; Regorafenib – Stivarga.

b. No 2015 data for ramucirumab as not released onto European market until 2016, but 2016 and 1st quarter 2017 data were available.

c. Other anti-neoplastics: Calcium Folinate, Calcium Levofolinate, Calcium Mefolinate, Capecitabine, Fluorouracil, Folic acid, Irinotecan, Oxaliplatin, and Raltitrexed (see Table 6).

d. Cyprus, Denmark, Iceland, Malta, Luxembourg, and Netherlands not included.

EGFR - epidermal growth factor receptor; MOA – mechanism of action VEGF - vascular endothelial growth factor; VEGFR-2 - vascular endothelial growth factor receptor 2.

Percentage columns are a proportion of all SACT costs for that country. Adjusted for purchasing power parity (PPP)

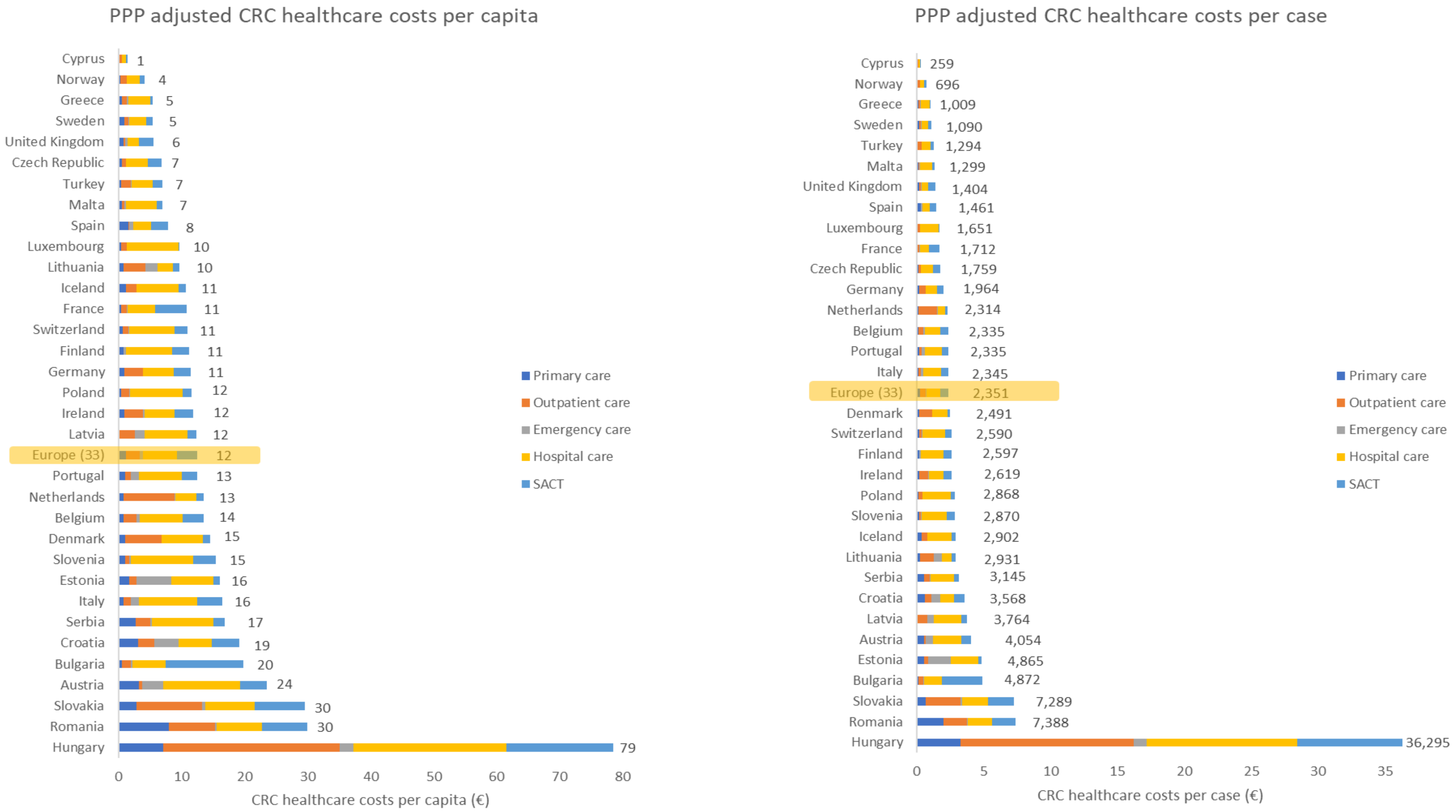

Figure 1. Healthcare costs of colorectal cancer per capita and per case in 33 European countries in 2015, by healthcare service category, adjusted for purchasing power parity (PPP).

SACT – systemic anti-cancer therapy

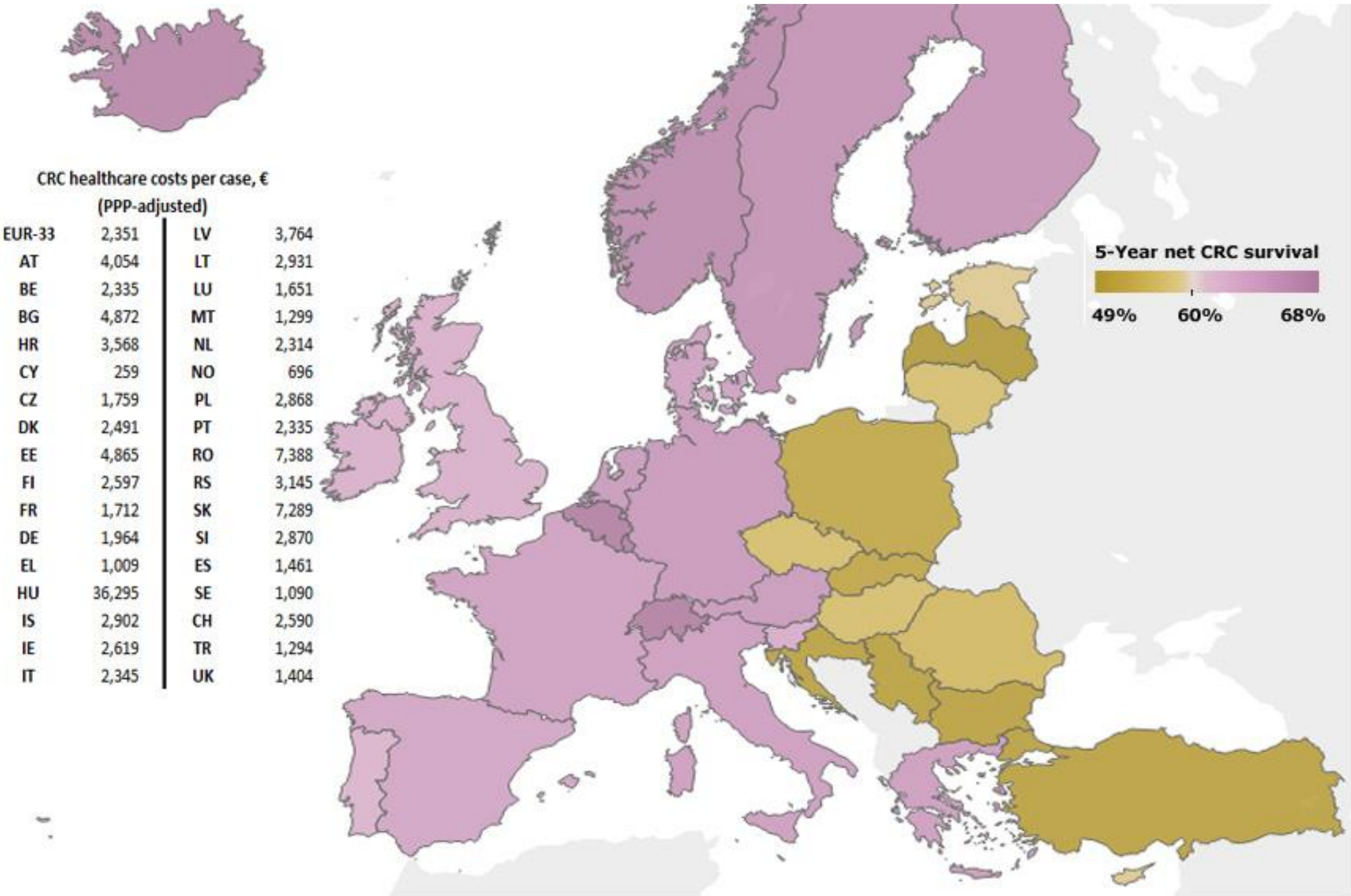

Figure 2. Geographical spread of colorectal cancer (CRC) survival and CRC healthcare costs per case in 2015.