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Comparing Cancer Care and Economic Outcomes Across Health Systems: Challenges and Opportunities

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Advancing Comparative Studies of Patterns of Care and Economic Outcomes in Cancer: Challenges and Opportunities

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Cancer is a leading cause of morbidity and mortality worldwide (1). Cancer also accounts for a substantial proportion of health-care expenditures as well as productivity losses due to morbidity and premature death (2). Because incidence increases with age for most cancer sites (3,4), and populations are aging in most developed countries, prevalence is expected to increase appreciably in the future (2,5–8). Additionally, ongoing improvements in early detection and use of effective treatments are associated with improved survival following diagnosis, also increasing cancer prevalence. As a result of these trends, related medical expenditures (6) and costs associated with morbidity (9) and premature mortality (10,11) are expected to be even larger in the future. Moreover, health-care delivery trends, in particular the increasing use of expensive new chemotherapy drugs (12,13), are projected to be associated with increased costs of cancer care in the future. Measuring and projecting the economic burden associated with cancer and identifying effective policies for minimizing its impact are increasingly important issues for health-care policy makers and health-care systems at multiple levels.

Internationally and regionally, there is tremendous diversity in organization and financing of health-care systems, health-care utilization, and cancer care delivery, all of which are associated with variation in cancer outcomes and spending. Selected cancer statistics, measures of health-care services utilization, and overall spending obtained from the Organisation for Economic Co-operation and Development (OECD) (14,15) are listed in Table 1 for several countries with data featured in this monograph. As shown in Table 1, these measures vary significantly by country (14). In 2009, the average cancer mortality rate for women across 34 OECD countries was 124 per 100 000, ranging from 111 per 100 000 in France to 143 per 100 000 in Canada. General health-care utilization, such as the average length of a hospital stay, number of physician visits, or the use of imaging per 1000 individuals, also varies substantially across country. For example, the rate of magnetic resonance imaging (MRI) exams is 97.7 per 1000 individuals in the United States, but 46.3 per 1000 on average across the OECD countries. Other measures such as recent cervical cancer screening range from 39.0% of women aged 20–69 in Italy to 85.9% in the United States, with an average of 61.1% across OECD countries.

Large differences in health-care expenditures, ranging from $2964 per capita in Italy to $8233 in the United States (in US dollars, adjusted for purchasing power parity), are also reported. The OECD average per capita spending was $3265. Within health-care spending, the percentage of public expenditures ranged from 48.2% in the United States to 83.2% in the United Kingdom, with an OECD average of 72.2%. Other components of health-care systems, including coordination of care delivery, administrative costs, negotiation and payment of hospitals, physicians, pharmaceuticals, and input prices, also vary by country and organization of health systems (16).

This diversity in health-care delivery, expenditures, and cancer outcomes suggests that comparative studies between health-care systems and/or countries might inform evaluation, development, or modification of policies related to cancer screening, treatment, and programs of care delivery (eg, hospice care for cancer patients at the end of life). Such comparisons of cancer patient outcomes between different models of health-care delivery can help identify best practices, serve as benchmarking of "high-quality" or "high-value" cancer outcomes and related costs, or be used as contemporary "usual care" comparisons to evaluate the introduction of cancer control interventions. This concept of using cross-national comparisons of health outcomes to identify lessons learned in countries with high-quality outcomes and reduce health disparities elsewhere is highlighted in the recent Institute of Medicine report, *U.S. Health in International Perspective: Shorter Lives, Poorer Health* (17). At the same time, underlying differences in the distribution of population characteristics, cultural attitudes, social and health-care policies, availability of specialists and primary care providers and relative mix of specialty care, physical environments, and data availability make between-health system and between-country comparisons complex (17). As described by Karanikolos et al. in this monograph (18), health systems can influence cancer outcomes through the comprehensiveness of health insurance coverage, the rate at which effective innovative treatments are introduced, and the quality of care as measured by timely and equitable access to diagnostic and specialty care, and coordination of that care.

Some of the observed and measured variation in health outcomes and utilization across countries also reflects differences in types of data sources available and comprehensiveness of

Table 1. Cancer incidence and mortality rates and selected health-care delivery and expenditure characteristics by country*

		United States	United Kingdom	Canada	Italy	France	OECD average for 34 countries
Cancer statistics†	Cancer incidence rates per 100 000 (2008)	300.2	269.4	296.6	274.3	300.4	260.9
	Colorectal cancer, 5-year relative survival rate (2004–2009 or available years)	64.5	53.3	63.4		57.0	59.9‡
	Cancer mortality rates per 100 000 (2009 or nearest year)						
	Females	130	141	143	117	111	124
	Males	185	199	205	212	221	208
Health services utilization (2010 or nearest year)	Average length of hospital stay in days	4.9	7.7	7.7	6.7	5.7	7.1
	Average annual number of physician visits per capita	3.9	5.0	5.5	—	6.9	6.4
	Cervical cancer screening in women aged 20–69, %	85.9§	78.7§	75.3§	39.0‖	72.4§	61.1¶
	MRI exams per 1000 persons	97.7	40.8	46.7	—	60.2	46.3
	CT exams per 1000 persons	265	76.4	126.9		145.4	123.8
Overall health-care spending# (2010 or nearest year)	Health-care spending per capita	$8233	$3433	$4445	$2964	$3974	$3265
	Out-of-pocket health-care spending per capita	$970	$306	$631	$528	$290	$558
	% public expenditure on health	48.2%	83.2%	71.1%	79.6%	77.0%	72.2%

* Data from Organisation for Economic Co-operation and Development (OECD) (15). CT = computed tomography; MRI = magnetic resonance imaging.

† Incidence and mortality rates age-standardized.

‡ Colorectal cancer 5-year relative survival based on 16 countries.

§ Cervical cancer screening measured by survey.

‖ Cervical cancer screening measured by program data.

¶ Cervical cancer screening measured by OECD average from 17 countries.

Spending in US dollars adjusted for purchasing power parity.

population coverage for the data source. Cancer incidence is typically collected in geographically defined, population-based cancer registries using consistent definitions, although the degree of registry population coverage varies and can be limited to cities or larger regions, or cover entire countries. Within countries, substantial geographical variation in cancer incidence has been reported, even after controlling for some key population characteristics (19). On the other hand, the cervical cancer screening measures reported by the OECD are based on self-report from household surveys in some countries, but health-care delivery program data in other countries. Self-report has been shown to overstate screening rates compared with medical record data (20), suggesting that the wide range in cervical cancer screening among the selected countries in Table 1 (ie, 39.0%–85.9%) reflects in part the data sources used for the comparison. Thus, variations in the comprehensiveness or the particular characteristics of data sources can also lead to apparent differences in outcomes, utilization, and expenditures.

Variation in data sources is one of many factors complicating comparative studies of cancer outcomes, utilization, and expenditures. For example, international comparisons of 5-year survival rates and costs of care following colorectal cancer diagnosis will also be influenced by the age structure of and risk factor prevalence within the populations, underlying prevalence of screening and distribution of stage of disease at diagnosis, methods of identifying relevant patients (eg, registry, hospital discharges), access to guideline-consistent initial and surveillance care, policies related to coverage of relevant treatment strategies following diagnosis, and competing causes of death. Thus, the complexity of estimating the impact on costs of simultaneous trends in cancer incidence, survival, and patterns of care requires that multidisciplinary approaches be adopted.

In September 2010, the National Cancer Institute, University of Roma Tor Vergata, Instituto Superiore di Sanità, and Institute of Research on Population and Social Policies, National Research Council, co-sponsored a meeting "Combining Epidemiology and Economics for Measurement of Cancer Costs" to discuss interdisciplinary approaches for estimation of the burden of cancer and the feasibility of international and health-care system comparative studies of cancer outcomes (21). That meeting was the basis for initiating this monograph. It contains an overview of key aspects of health-care systems (18), several systematic reviews of published studies of patterns of care and costs associated with cancer (22–24), and a series of comparative papers either between countries (25,26) or between health systems within a country (27,28). The final section begins with an illustration of how simulation modeling can inform cancer care decision making (29). It concludes with a future directions paper that examines the opportunities and challenges associated with improving the scientific quality and usefulness of comparative studies of the burden of cancer and interventions to reduce it (30).

Systematic Reviews of the Literature Describing Patterns of Cancer Care and Economic Outcomes

Patterns of cancer care are directly related to cancer outcomes and associated costs. In some settings, actual payments or expenditures are not available, and instead, standardized unit costs are applied to service frequency. Thus, an understanding and documentation of patterns of care are a necessary, but not sufficient, first step for understanding the variation in the cost of care and other economic outcomes. This section of the monograph consists of systematic

reviews of the published literature describing treatment patterns and associated economic outcomes, using colorectal cancer as an illustrative example. In addition to providing contemporary information about patient receipt of cancer treatment and associated costs in multiple countries, these reviews offer an overview of relevant data sources and a critical assessment of the completeness of reporting and comparability across studies.

Butler et al. (22) and Chawla et al. (23) conducted companion systematic reviews of published studies of patterns of care following colorectal cancer diagnosis, including initial treatment with surgery, chemotherapy, and radiation therapy; surveillance following initial treatment; and end-of-life care. They abstracted study characteristics, including study country, data sources for identifying cancer patients and health services, study sample size, patient characteristics, type(s) of care measured, and key findings. Importantly, underlying population characteristics, population representativeness, patient and tumor characteristics associated with prognosis (eg, age, stage at diagnosis), data sources, and types of care evaluated and their measurement varied widely both within and across countries. For example, analyses using the ongoing linkage of SEER cancer registry and Medicare claims data (31) in the United States are restricted to Medicare beneficiaries age 65 and older with fee-for-service coverage. Although the majority of newly diagnosed cancer patients are age 65 and older, findings from these SEER–Medicare studies are not necessarily generalizable to the population younger than 65 or to populations in the same age group with other types of health insurance coverage within the United States. Additionally, these studies may not be representative of the entire United States in cross-country comparisons. On the other hand, studies conducted solely in the hospital setting may include all hospitalized patients of all ages, but do not have key information about cancer diagnosis (eg, stage at diagnosis) or may include only inpatient care and not have longitudinal information about ongoing care or vital status. Thus, studies of rectal cancer surgery conducted only in the hospital setting may be incomplete with regard to important trends in the use of neoadjuvant therapy and sphincter-sparing surgery. Importantly, any comparative study based on these data sources will need to be restricted to the subset of patient populations and types of care that can be consistently measured in both data sources. Studies are rarely stratified by these key characteristics, and hence comparisons between published studies are difficult. Further, diversity in health-care systems and health insurance coverage of cancer care makes cross-country comparisons of patterns of care and associated costs all the more challenging.

Yabroff et al. (24) conducted a systematic review of studies of the economic burden associated with colorectal cancer and report *direct medical care costs*, including inpatient care, outpatient or ambulatory services, surgery, chemotherapy and radiation therapy; other *direct non–medical care costs*, such as transportation to and from medical care, time spent by family members providing home care, and patient time; and *productivity or "indirect" costs*, which represent lost or impaired work or leisure time due to morbidity or early death from disease, and are typically measured from the societal or employer perspective. Unlike direct medical costs, which can be measured from health insurance payments or the application of standardized cost or reimbursement rates to services, direct non–medical costs and indirect costs are not typically measured explicitly. In addition to abstracting and reporting types of costs at the aggregate and per capita levels, they report study country, health-care delivery setting, methods for identifying incident and prevalent colorectal cancer patients, types of medical services included, patient characteristics, and key findings, presented in terms of both incidence-based and prevalence-based estimates. When these myriad study characteristics vary together, as is typically the case, even patterns of care or cost calculations with seemingly the same objective are difficult to compare directly. Moreover, complicating factors such as features of the health-care delivery system, accompanying payer models, and data availability all vary by country.

These three systematic reviews offer recommendations for developing data infrastructure and for standardizing measures and reporting of patient characteristics associated with patterns of care or economic outcomes (eg, stage at diagnosis, comorbidity), with the goal of improving comparability across studies. They also identify areas for improving the comprehensiveness of analyses of patterns of care and the economic burden of cancer, particularly those aspects that are understudied, such as end-of-life care, patient and caregiver time costs, and productivity losses. Ultimately, findings suggest that valid cost comparisons can be developed de novo with explicit standardization of patient populations, types of medical services included, measures of costs, choice of methods, and specification of the context (eg, within- or between-health systems in a country vs cross-country).

Comparative Studies

As described previously and shown in Table 1, aggregate data can be useful in highlighting differences across countries in health-care delivery, expenditures, and outcomes. Similarly, a recent historical evaluation of cervical cancer screening prevalence and mortality rates in the United States and the Netherlands offers insight into the differential impact of screening frequency, age of initiation and cessation of screening, and insurance coverage policies in the two countries (32). However, a better understanding of the impact of cancer control interventions and associated costs requires individual-level information about patient outcomes and costs in comparable patient populations, with complete information about treatment by stage at diagnosis and other factors that might impact both outcomes and costs. Yet few comparative studies have assessed patterns or costs of cancer care, in part due to absence of standardized data elements measured in the same manner across settings.

This section of the monograph consists of four comparative studies of cancer care across health systems or countries, with the common goals of providing examples and lessons learned that might be applied to other comparative studies, as well as recommendations for future research. One approach is the supplementation of existing data systems using common standards and data quality control measures to allow comparability. EUROCARE (33,34), a collaborative research project measuring cancer survival in Europe using population-based cancer registry data from more than 20 countries, and the CONCORD program (35), covering population-based cancer registries in more than 30 countries, are prime examples of this approach. These collaborative efforts use

standardized measures for comparability of cancer data to conduct more detailed systematic comparisons of survival following diagnosis for most adult cancers, accounting for underlying population characteristics, such as age structure, competing (ie, noncancer) mortality rates, and race. In this monograph, Gatta et al. use data from EUROCARE-4, supplemented with macroeconomic and health system data from the OECD and the European Observatory on Health Care Systems, to evaluate survival rates for breast, colorectal, and prostate cancer across 19 countries (26). This study uses results from EUROCARE-4 "high-resolution" studies, which include detailed information on stage at diagnosis, staging procedures, and treatment for a sample of cancer patients in each registry. Specifically, they evaluated the association between several summary measures—including total national expenditure on health, investments in health-care infrastructure, and availability of medical devices or equipment—and a classification of the health-care system based on the funding model, adherence to standard cancer care, and 5-year relative survival as an outcome measure. This novel study serves as a model for evaluating macroeconomic measures when assessing differences in cancer outcomes across countries, with the goal of identifying best practices and improving cancer survival throughout Europe. The authors also highlight differences in measures across countries and inconsistencies in population completeness from cancer registries in different countries.

The additional information required for the "high-resolution" studies derived from the EUROCARE project is not routinely collected and requires an additional effort from population-based cancer registries. Similarly, in the United States, the National Cancer Institute and Centers for Disease Control and Prevention conduct cancer registry–based patterns of care studies with more detailed data collection for a sample of newly diagnosed cancer patients about health insurance, characteristics of the hospital where surgery was performed, staging, testing for treatment response (eg, K-RAS), and receipt of adjuvant therapies, including chemotherapy, hormonal therapy, and biological modifiers and immunotherapy (36,37). A related approach to conducting comparative studies across country or health systems capitalizes on existing and sustained linkages of cancer registry and administrative health data (eg, SEER–Medicare), and then study teams work to ensure the consistency of patient populations, services and costs measured, and appropriate methods for evaluation of patient outcomes (38,39). In this monograph, Gigli et al. (25) conducted a comparative study of colorectal cancer care in elderly populations in the United States and Italy. Study teams in both countries had expertise with their respective cancer registry and administrative data, and reimbursement policies. They applied the same selection criteria to identify similar cohorts of newly diagnosed elderly colorectal cancer patients in the linked SEER–Medicare data in the United States and cancer registry data linked to information on hospital discharge cards in two regions in Italy. They identified cancer services with comprehensive information for the cohorts in both countries during the period of the study and compared patterns of colorectal cancer treatment during the first year following diagnosis, including hospitalizations, receipt of surgery, chemotherapy, and radiation therapy. They also compared the timeliness of surgery following diagnosis and adjuvant therapy following surgery. Although patterns of care within stage at diagnosis were generally similar, they found greater use of adjuvant therapy in the US cohort, a higher percentage of open abdominal surgeries in the Italian cohort (and more use of endoscopic procedures in the US cohort), and more hospital days in the Italian cohort, despite similar numbers of hospitalizations. Additionally, a greater percentage of patients in Italy were diagnosed with advanced disease at diagnosis, suggesting that further evaluation of colorectal cancer screening prevalence, even at the aggregate level, might also be informative. More detailed evaluation of patient outcomes and related costs would also provide more information about the impact of the observed variation in treatment. Finally, in appraising one of the few examples of "head-to-head" comparisons in cancer care between the United States and a European country, where there are many structural differences in health-care delivery and reimbursement, the authors emphasized the importance of ensuring the comparability of populations and the completeness of treatment information.

Fishman et al. (27) also conducted a comparative study with administrative data linked to cancer registries, but within the United States and between fee-for-service and managed care delivery systems. Specifically, they selected an elderly population with newly diagnosed colorectal, prostate, breast, and lung cancers from either SEER–Medicare with fee-for-service coverage, or state-based registry data linked to Medicare Advantage–managed care plans in a subset of the Cancer Research Network (CRN) (40). They report differences, by health-care system, in stage of disease at diagnosis and in inpatient and outpatient care in the 6-month period preceding and 6 months after the cancer diagnosis. Their findings illustrate the importance of differences in the underlying patient characteristics and the mix of inpatient and outpatient care under the two systems. These findings add to the limited research evaluating cancer care in managed care compared with fee-for-service settings in the United States (41,42) and point to the critical importance of comprehensive and comparable data when comparing outcomes across systems. This study also highlights the potential of comparative studies of cancer care and outcomes in evaluating different organizational models of care.

The complications arising in comparative studies of patterns of care are compounded when one tries to assess and contrast cancer care costs in different settings. In addition to structural differences in the organization and financing of health care and systematic variation in patient characteristics and patterns of care, differences in the costs of care across health-care systems also reflect differences in input prices. In the final paper of this section, O'Keeffe-Rosetti et al. (28) describe the development of a standardized relative resource cost algorithm (SRRCA) for comparative studies of the costs of cancer care between different health systems, specifically Medicare fee-for-service and Medicare-managed care in the United States. The SRRCA adapts 15 payment systems used by Medicare to reimburse fee-for-service providers for covered services to health-care utilization data, so that the observed variation in expenditures reflects only variations in the mix and volume of the various medical care services delivered to patients, and not variation in prices in the same inputs.

The SRRCA can be applied in multiple managed care plans and across fee-for-service delivery systems to create consistent relative cost data for economic analyses. These Medicare payment systems are developed separately for short-term stays in general hospitals, inpatient rehabilitation facilities and long-term care hospitals, psychiatric hospitals, physician services, hospital outpatient services, ambulatory surgical centers, laboratory services, skilled nursing facilities, home health services, outpatient dialysis, hospice, ambulance services, durable medical equipment, and pharmacy care. Importantly, the SRRCA can be systematically applied to service use in individuals with and without cancer, allowing for comparison of cancer patients and noncancer control populations across health-care delivery settings, thus informing a wide variety of research questions. Data harmonization issues, more specifically those related to consistency of utilization and resource intensity definitions and measures, will determine how well the SRRCA can be adapted for international comparisons. As highlighted by the authors, a challenging but important task is focusing on differences in utilization, health outcomes, and expenditures across systems and countries to improve the quality of cancer care.

Policy Applications and Future Directions

The final section of this monograph describes a prostate cancer simulation model from the Cancer Intervention and Surveillance Modeling Network (CISNET) project (43). In this paper, Etzioni et al illustrate how a detailed and calibrated natural history of disease model can be used to inform policy decisions about the harms and benefits of cancer control interventions (29). This section also contains a future directions paper that synthesizes key themes, including the importance of data infrastructure development and standardization of measures and data collection, to promote comparability in analyses of patient populations, cancer diagnosis information, treatment, and components of economic burden (30). Finally, we draw on a wealth of international knowledge and experience in highlighting the utility of comparative studies and in formulating future directions and research priorities.

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Health Systems Performance and Cancer Outcomes

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Do the characteristics of health systems influence cancer outcomes? Although caveats are required when undertaking international comparisons of both health systems and cancer outcomes, observed differences cannot solely be explained by data problems or economic development. Health systems can influence cancer outcomes through three mechanisms: coverage, innovation, and quality of care. First, in countries where population coverage is incomplete, patients may find certain services excluded or face substantial copayments or deductibles. Second, there are variations in the rate at which innovative treatments are introduced, reflecting in particular the need for publicly funded health systems to compare costs and benefits of increasingly expensive treatments given demands for other treatments. Third, systematic differences in quality of care (early diagnosis, timely and equitable access to specialist care, and existence of systematic coordination between these activities) may lead to variations in cancer outcomes.

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This monograph looks at international variations in the care provided to people with cancer in different countries. A key issue in evaluating these variations is the extent to which health systems might impact on outcomes. This paper reviews, first, the basis on which such judgments can be made, in particular the international comparability of cancer registration, and, second, the characteristics of health systems that might impact on the effectiveness of the care that is provided.

Measuring Outcomes

At the outset, one must define what a health system is. There are many different definitions, varying in respect of the boundaries of the system, each with implications for assessing outcomes. Thus, the 2000 World Health Report included "all activities whose primary purpose is to promote, restore and maintain health" (1). However, in this chapter, we refer to a narrower health-care system defined as the "combined functioning of public health and personal healthcare services" that are under the "direct control of identifiable agents, especially ministries of health" (2).

The first step in assessing the contribution of health systems to cancer outcomes is to collect the necessary data. The most important in a series of international comparisons of cancer survival have been the four successive European Cancer Registry (EUROCARE) projects, covering 20 European countries (3) and the CONCORD program, covering 101 population-based cancer registries in 31 countries on five continents (4). EUROCARE-5 will cover 27 countries in Europe in 2012, and CONCORD-2, now in progress, will cover 50 countries worldwide.

At the national level, many hospital-based registries also exist: The outcome data they provide relate to a catchment area rather than to a defined population, but they often collect more detailed data on stage at diagnosis, which is a key prognostic factor as well as an indicator of the quality of primary care and the referral system. The most widely used example is the US National Cancer Data Base (NCDB), which covers about 1400 facilities and about 70% of cases of cancer in the United States.

However, there are still substantial gaps in coverage by cancer registries. For example, the 20-country EUROCARE-4 project has national (100%) coverage in 10 participating countries, but in some the coverage up to 2000 has been low (Germany 1%, Czech Republic 8%, Poland 9%) (5). Ill-founded concerns about data protection and consent in a few countries have sometimes impeded the creation or expansion of registries. In Germany and Hungary, cancer registries were shut down in the early 1990s. The previously successful national registry in Estonia was prevented from operating effectively from 1996 (6); imminent failure of cancer registration required emergency legislation in the United Kingdom in 2000 (7), and in the United States, the US Department of Veterans Affairs has more recently declined to supply data due to concerns about disclosure (8). This is despite evidence that the vast majority of the public are unconcerned by this use of personal data (9).

It is, however, important to be aware of a number of methodological and comparability issues when exploring any potential association between outcomes and health systems. The US Surveillance, Epidemiology and End Results (SEER) program systematically underrepresents African Americans and poorer people, leading to an overestimate of national survival levels (4,10). There are also considerable international variations in the performance of registries, measured, for example, by the percentage of cases that are reported only at death (11). Finally, especially for cancers that can be detected early by screening, it is necessary to take account of the possibility of lead-time bias, whereby the existence of a screening program leads to the detection of more cancers at an early stage in their natural history, but where subsequent treatment does not affect the point at which the patient

dies. This will artificially increase the recorded survival but at no benefit to the patient, and indeed may cause harm given the longer period of psychological distress (12).

A corollary is the incomplete availability of data on health systems. Despite heroic efforts to standardize data collection in recent years, in particular by the Organisation for Economic Co-operation and Development, there are still many problems in undertaking quantitative comparisons of health systems (13). The first problem, of relevance when comparing measures such as expenditure, is how to define the boundaries of the health system. Although there has been much progress in developing national health accounts, there are still difficulties in allocating costs at interfaces, such as those between health and social care and between clinical care and research. The second is the comparability of inputs. The skills, roles, and task profiles of many health workers vary among countries. So do the sources of data and the units in which these inputs are measured. For example, are numbers of health professionals based on headcounts or whole-time equivalents? Do they capture those employed in all sectors (such as prison health or the military)? In countries with predominantly statutory systems, do the data include the private sector?

Collectively, there are many definitional problems. Consequently, when reading the remainder of this paper, it is important to recognize that a degree of caution is required when interpreting the findings that are reported. Nonetheless, the available data show clear differences in survival from many cancers among countries (14). Some of this variation can be attributed to differences in resources available for health care. For example, a study of cancer survival in European countries found a close correlation between survival from all cancers combined and both gross national product and total expenditure on health (15). However, there is considerable evidence that the way in which the resources are actually used is also important (16).

How Might the Organization of Health Systems Impact on Cancer Outcomes?

Health systems can influence the outcome of any disease in a population through three mechanisms. First, and self-evidently, only those with effective coverage by or access to the health system can benefit from it. Hence, although there has been considerable progress worldwide in achieving universal coverage, there are many parts of the world where that is still no more than an aspiration. Even in advanced industrialized countries there may be gaps. The most notorious example is the United States, and although recent legislation seeks to address this in part (17), even when it is implemented, some 23 million people will be left without insurance (18). Those without health insurance do receive some care in the United States, even if limited; they have some access to emergency care. However, many of those who are considered to have coverage may find themselves excluded from a wide range of services, especially if they have preexisting conditions, or they may face substantial copayments or deductibles. Although this creates significant methodological challenges to researchers, the United States does provide one of the main sources of evidence on the effect of incomplete coverage or access to health care.

Second, there is innovation. There have been enormous strides in the management of many cancers since the early 20th century, with cure rates for some cancers exceeding 90%. The number of new treatments is expanding steadily, although this is bringing challenges as the cost of drug development is the same whether the drug concerned is a so-called "blockbuster," given for many years to large numbers of patients with common chronic disorders, or for several months to small numbers of patients with rare cancers. Inevitably, however, the unit cost of the latter is vastly higher, and where the benefit is marginal in terms of survival or quality of life, publicly funded health systems must take account of the opportunity cost. Hence, there is a judgment to be made about what is affordable, leading, entirely appropriately, to international differences in access to certain innovative drugs.

Third, health systems may vary in the quality of care, although, in practice, the variation within a health system is likely to swamp any systematic differences that might be expected. Nonetheless, there may be some systematic differences between health systems that can be linked to variation in cancer outcomes. The existence, or otherwise, of a comprehensive, integrated approach to cancer management falls within this category.

Coverage and Access to Health Care

There is now a wealth of research showing substantial differences in the United States in the stage at diagnosis and the processes of care delivered to patients with different forms of coverage (19). Typically, among those aged under 65, before the age when all patients become eligible for Medicare, comparisons are made between those covered by private insurance, those without insurance, and those enrolled in Medicaid, which provides basic coverage for the poor. However, a degree of caution is required in interpreting the data because about one-third of those with Medicaid cover have only become eligible as a result of being diagnosed with cancer (20). The following examples are illustrative of what is a consistent pattern.

A study of incident cases diagnosed in Florida in 1994, where stage at diagnosis and insurance status were known, found increased odds ratios (OR) for late presentation (stage III or IV) among persons who were uninsured compared with those with private insurance (21). The increased risks were 67% for colorectal cancer, 159% for melanoma, 43% for breast cancer, and 47% for prostate cancer. Delayed presentation was also found among those enrolled in Medicaid, with an 87% increase for breast cancer and as much as 369% increase for melanoma. All these differences were statistically significant.

A comparison of the management of almost 7000 patients with invasive breast cancer in one American state between 1996 and 2005 found that women who were uninsured, compared with privately insured women, presented with larger tumors, were much less likely to be node-negative, were less likely to be accessing breast-conserving surgery (where indicated), and very much less likely to be accessing reconstructive surgery (22). Among uninsured women, 15.5% underwent no surgical treatment at all, compared with only 4.3% of those with private insurance, consistent with the overall picture of later presentation. Another study used data on patients diagnosed between 1998 and 2004 recorded on the US

NCDB (23). Uninsured patients and those enrolled in Medicaid were significantly more likely than privately insured patients to present with advanced-stage cancer. The differences were greatest for cancers that can potentially be detected early. Patients lacking insurance were twice as likely to present with late-stage colorectal cancer (stage III or IV) as those with private insurance (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.9–2.1), whereas those enrolled in Medicaid were 1.6-fold more likely to present late (95% CI 1.5–1.7). For advanced-stage melanoma, the odds ratios were 2.3 (2.1–2.5) for uninsured patients and 3.3 (3.0–3.6) for those enrolled in Medicaid compared with privately insured patients. Very similar findings were obtained in a study of over 500 000 women, diagnosed with breast cancer between 1998 and 2003, also on the NCDB (24). Similar findings were obtained in a survey of women diagnosed in 2004–2005 (25).

All the studies that have examined the impact of race found that black and Hispanic patients had an increased risk of advanced-stage disease at diagnosis, regardless of insurance status, compared with white patients.

A recent study sought explicitly to assess the future impact of health-care reform in the United States, again using the NCDB (26). It took those patients diagnosed with a range of cancers in the age group 55–74 years. It then compared those aged 55–64 years and who had private insurance with three other groups. The first comprised those in the same age group who were uninsured. The second comprised those in the age group 65–74 years with basic Medicare coverage: although it provides access to health care, it involves substantial deductibles and copayments, which may still restrict access to care. The fourth group comprised those enrolled in Medicare Advantage schemes, in which individuals pay extra for a range of additional benefits that, in general, do not involve deductibles or copayments but instead have a fixed rate fee for a consultation. In keeping with the previous research, this study found a significantly higher risk among the uninsured of first attendance with advanced cancers of the prostate, lung and bronchus, breast, colon and rectum, uterine corpus, bladder, and thyroid, and for melanoma. Those with basic Medicare also had an increased risk of presenting with late-stage disease, although to a much lesser extent, for melanoma and thyroid cancers. They were also more likely to present late with the same cancers as the uninsured, although again the increased risk was lower. However, there was no significant difference between those under 65 with private insurance and those over 65 with Medicare Advantage.

Collectively, this evidence is entirely consistent with other evidence showing that those Americans without insurance are less likely to seek care when they feel it necessary, or to undergo routine healthchecks (27) or cancer screening (28). However, it also raises the question of whether late presentation is the only reason for worse cancer survival among those without adequate coverage. This is difficult to determine, as much of the literature has focused on characteristics that often coincide with being uninsured, such as African American race and low income. However, the evidence from the survival analysis within Veterans Affairs health-care service shows that the ethnic disparities typically present between white and African Americans can be attenuated if the provider delivers high-quality health care and achieves equal access (29–30). Ayanian et al. found higher death rates from breast cancer at between 54 and 89 months after diagnosis for women who were uninsured or enrolled in Medicaid, compared with those with private insurance, after adjusting for stage at diagnosis and, as one would expect, the relative disadvantage was confined to those with local or regional disease rather than those with distant metastases at presentation (31). Robbins et al. also found significantly lower survival among those under 65 years with rectal cancer who lacked insurance. This persisted after adjustment for treatment (surgical procedure, margins at primary site, chemo- and radiotherapy, etc.) and stage. They estimated that differences in stage and treatment accounted for approximately 53% of the excess mortality, whereas other factors accounted for approximately 17% (32). Kwok et al. found that uninsured patients and those enrolled with Medicaid and who had head and neck cancer had a significantly greater probability of dying than those with private insurance, after adjustment for a wide range of variables, including stage at diagnosis (hazard ratio 1.50, 95% CI 1.07–2.11) (33). In a population-based study in Kentucky, McDavid et al. found lower 3-year survival in uninsured than privately insured patients with cancers of the colorectum, breast, lung, and prostate, after adjustment for age group, sex, race, and stage at diagnosis (34). The reasons for such differences in survival are not entirely clear, although Wu et al. found that women with breast cancer but without insurance coverage were less likely to receive chemotherapy according to accepted guidelines (35).

In those countries with universal coverage, socioeconomic factors may also have an impact on access to health services. Research from the United Kingdom indicates that women living in deprived areas are less likely to access cervical (36) and breast screening (37). Poorer socioeconomic groups had a longer delay in diagnosis for prostate cancer, whereas no differences by socioeconomic groups were identified for other types of cancer (colon, lung, ovary, breast, and non-Hodgkin lymphoma) (38). Differences in cancer survival between socioeconomic groups were partially attributed to stage at diagnosis and access to optimal treatment (39).

Therefore, in assessing the impact of health systems on overall cancer outcomes, an important consideration is whether they provide timely and effective care to the entire population.

Innovation

The political division of Europe during the Cold War provided an important natural experiment, because countries in the Soviet bloc were unable to access a number of innovative technologies. The impact of obtaining access to innovative treatment has been neatly illustrated by a comparison of mortality from testicular cancer in the two parts of Germany (40). Death rates in the west began to decline from the mid-1970s, whereas they remained high in the east until 1989 when reunification made modern treatments available. However, now, at least in high-income countries, differences are more subtle and they are also considerably more controversial. A series of reports from the Karolinska Institute, Stockholm (41–43), assessed patients' access to cancer medication in high-income countries through sales and uptake of oncology drugs. The reports highlighted large variations across countries in relation to level of uptake of new drugs, sales of select drugs, and time period over which cancer drugs became available. This highlighted how the impact of innovation reflects not only the investment in

development of new chemical entities but also the investment by payers in making them available to patients. In the latest report, from 2009 (43), the authors suggest that differences in the level and speed of uptake of cancer drugs lead to inequalities in access to medication among the EU countries. The 2007 report (42) purported to show that access to new drugs was linked to improved survival and larger reductions in cancer mortality rates. Findings such as these have led some authors to advocate accelerating the approval process of new drugs and increased funding to purchase them (44).

The Swedish research was, however, funded by the pharmaceutical industry, which has an obvious strong vested interest in speeding up access to its products, even if the benefit they provide may be limited and the cost may be high. This work has also faced severe criticism for overestimating relative survival and failing to demonstrate robust temporal associations between the introduction of new drugs and cancer outcomes (45).

A literature review by Morgan et al. (46) found that chemotherapy made a relatively small contribution to cancer survival overall. Using data from trials that reported a significant benefit due solely to chemotherapy, they calculated the absolute number of patients who would benefit from chemotherapy for each of 22 cancers, the proportion of those who would achieve a benefit, and the percentage increase in 5-year survival that would be expected due solely to cytotoxic chemotherapy. Although the overall 5-year survival from these cancers was about 60%, the contribution of chemotherapy was estimated to be about 2.3% in Australia and 2.1% in the United States.

Given the importance of considering cost-effectiveness of innovative treatment, a key question about health systems is their ability to incorporate such considerations within their decision-making processes. It is intuitive, but also supported by evidence, that this is easier in countries with single payers or mechanisms by which payers can work together, as in European national health services (47). In their comparison of UK and US health systems, which noted the challenges of comparability, Faden et al. (48) contend that the British National Health Service is fairer in providing access to end-of-life treatment to patients, as it has mechanisms of dealing with the availability of expensive cancer drugs not routinely covered by the state, in contrast with Medicaid beneficiaries, for whom the treatment is subject to copayment (40).

Quality

Early detection of cancer is crucial for increasing the chances of successful treatment and subsequent survival. Implementation of population-based cancer screening programs varies widely internationally. In the European Union, there are screening programs in 22 of the 27 EU countries for breast cancer, whereas 15 have cervical screening programs and 12 screen for colorectal cancer (49). However, these programs vary in eligibility criteria, recall systems, and uptake rates. Thus, in practice, coverage of cervical cancer screening in the EU ranges between 10% and 79% of eligible women (50). Countries also vary in the extent to which their systems are organized or opportunistic, with consequences for the quality of the intervention. Thus, a Finnish woman can expect to undergo seven smears in her lifetime, whereas a German woman may have 50 or more, yet cervical cancer mortality in Finland is half that in Germany (42).

Another aspect of quality is the speed of access to specialized care. A recent analysis of survival trends (51) shows a persisting survival deficit for cancers of the bowel, lung, breast, and ovary in the United Kingdom and Denmark, compared with Sweden, Norway, Canada, and Australia. Artifacts due to loss to follow-up, representativeness of the registries, and data quality were ruled out as potential causes of such variation in survival during the period 1995–2007 (51). The authors suggest that the most likely reason is late diagnosis and delay in obtaining definitive treatment (51–53) as well as some variations in diagnostic and surgical practice (54–55). A subsequent study that looked at the completeness of stage data and implications for comparability in stage-specific cancer survival in these countries for the same cancer types showed that, after standardizing staging across registries, survival estimates were consistent with previous findings, despite the presence of stage migration in some regions (56).

Other work has suggested that the low 1-year cancer survival in the United Kingdom and Denmark could reflect the gate-keeping role of general practitioners (57). A shortage of trained personnel and equipment to undertake screening has also been invoked as an explanation for the performance of Denmark, whereas a report by the King's Fund, in the United Kingdom (58), makes the case for improved early diagnosis and access to specialist care.

One way of quantifying the impact of early treatment on survival is by measuring avoidable deaths from cancer, defined as "the component of excess cancer mortality that would not occur if the relative survival were at the higher level seen in a comparator population, instead of what was actually observed"(59). A comparison of cancer survival in the United Kingdom in relation to the mean for European countries participating in the EUROCARE study (59) found that, in the 15 years between 1985 and 1999, avoidable premature mortality in Britain constituted about 6–7% of total cancer-related mortality, with the highest share of that avoidable mortality attributable to cancers of the breast (18%), prostate (14%), colon (9%), stomach (8%), and lung (2%). The authors also noted that, even with universal coverage, about half of the avoidable premature mortality in the United Kingdom can be attributed to socioeconomic inequalities. The importance of inequalities receives more support from a population-based study on avoidable deaths from cancer in England (60), which suggests that, for cancers included in UK national screening programs (cervical, breast), improving the uptake of screening among deprived population would dramatically reduce the number of premature deaths. A study of avoidable cancer deaths in Finland also showed how inequalities in cancer survival could exist even in one of the most equitable societies in Europe, where health-care standards are high, thus emphasizing the importance of early diagnosis for everyone (61). Not unexpectedly, a series of studies by Gorey et al. (62–64) shows how the Canadian health-care system achieves much more equitable access to services than does the United States, largely attributed to universal coverage by health insurance in Canada.

Survivorship, as another measure of quality of care for cancer patients, has been used increasingly in the United States since 2006. Care after cancer, including screening for recurrences and late effects of cancer therapies, is not standardized there, and transition

to posttreatment care may be more complex in the absence of comprehensive survivorship care plans (65).

The cure fraction, defined as the proportion of survivors (technically, the relative survival) when the death rate in the cancer patients is no longer significantly higher than the death rate in the general population, is potentially a very useful measure of the overall effectiveness of cancer care. It can only be derived from population-based cancer survival analysis. However, robust international comparisons with this indicator are not yet widely available.

The management of cancer requires coordination of a wide range of health system inputs, ensuring ready access to relevant expertise when needed. Intuitively, this may be easier where services are concentrated in a few large centres, potentially bringing additional benefits from greater experience by the health professionals involved. There is an extensive literature on the association between volume and outcome, although there are many methodological problems involved (66). However, a recent systematic review concludes that better outcomes are achieved at higher treatment volumes, especially for complex cancer surgery and specifically for pancreatectomy, esphagectomy, gastrectomy, and rectal resection (67).

A related question is whether the creation of a systematic cancer plan to bring these elements together makes a difference. One study took advantage of a natural experiment following the introduction of such a plan in England in 2000. Neighboring Wales had reorganized its services in the 1990s. The evaluation concluded that improvements in 1-year survival in England, which had lagged behind those in Wales before full implementation of the cancer plan in 2004, then overtook it, although there was no difference in 3-year survival trends (68). The authors concluded that the English cancer plan had probably had some beneficial effect, but a definitive judgment could not be reached.

In Denmark, national cancer pathways have been introduced in 2008 as a response to the intense debate in the media and among the medical professionals on "internal waiting times" and their impact on the relatively poor survival in Denmark compared with other countries (69), but the impact on cancer outcomes is not yet visible.

Conclusions

Health systems do impact on cancer outcomes, although our scope to discover why is handicapped by constraints on both our ability to define and describe health systems and our ability to achieve robust international comparisons of cancer survival. Health systems have an impact on cancer outcomes through three broad mechanisms: first, by ensuring population coverage and access to care; second, by ensuring access to innovative treatment; third, by ensuring that the care that is accessed is of high quality. Although all three are necessary, the first is most important. However, there is clearly considerable further scope to increase our knowledge on these important relationships if we are to provide more meaningful input into policy debates about how best to improve cancer control.

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Patterns of Colorectal Cancer Care in the United States and Canada: A Systematic Review

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Colorectal cancer is the third most common cancer in the United States and Canada. Given the high incidence and increased survival of colorectal cancer patients, prevalence is increasing over time in both countries. Using MEDLINE, we conducted a systematic review of the literature published between 2000 and 2010 to describe patterns of colorectal cancer care. Specifically we examined data sources used to obtain treatment information and compared patterns of cancer-directed initial care, post-diagnostic surveillance care, and end-of-life care among colorectal cancer patients diagnosed in the United States and Canada. Receipt of initial treatment for colorectal cancer was associated with the anatomical position of the tumor and extent of disease at diagnosis, in accordance with consensus-based guidelines. Overall, care trends were similar between the United States and Canada; however, we observed differences with respect to data sources used to measure treatment receipt. Differences were also present between study populations within country, further limiting direct comparisons. Findings from this review will allow researchers, clinicians, and policy makers to evaluate treatment receipt by patient, clinical, or system characteristics and identify emerging trends over time. Furthermore, comparisons between health-care systems in the United States and Canada can identify disparities in care, allow the evaluation of different models of care, and highlight issues regarding the utility of existing data sources to estimate national patterns of care.

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Colorectal cancer is the third most common cancer (1) in the United States and Canada. In 2012, approximately 140 000 new patients were expected to be diagnosed in the United States (2) and 22 000 were expected in Canada (3). Although curable when detected early, colorectal cancer is the second leading cause of cancer death in North America, resulting in approximately 58 000 deaths per year (1). Recent improvements in the early diagnosis and treatment of colorectal cancer have led to increased survival (4–6). However, changes in treatment, especially the use of new chemotherapeutic agents, have been linked to increased costs for care (7). Given the high incidence and increased survival of colorectal cancer patients, it is beneficial for researchers, clinicians, and policy makers to characterize treatment receipt, identify populations of patients who do not receive optimal care, and quantify economic and health-care system resources needed to treat this growing population.

Although similar demographically, both with sizeable immigrant populations, the United States' multipayer system and Canada's universal single-payer system offer differing platforms to explore how patient treatment data are collected, managed, and used to measure care patterns. Comparisons across country and health-care systems will allow the evaluation of different models of care delivery and can highlight issues regarding health-care practices and standards of care. In this systematic review of the literature, we describe patterns of care for patients diagnosed with colorectal cancer in the United States and Canada and evaluate data resources for capturing and measuring treatment patterns in both countries. Findings from this study may have implications for health-care delivery, treatment, and outcomes for patients diagnosed with colorectal cancer.

Methods

We used the MEDLINE database to identify articles on colorectal cancer care published in English between January 2000 and December 2010. Our search strategy combined the Medical Subject Heading (MeSH) term "Colorectal Neoplasms" with additional headings or text strings related to patterns of care, yielding 717 articles (see Appendix 1 for more details). Articles were hierarchically excluded for the following reasons: 1) the article did not report original research on receipt of colorectal cancer care; 2) the study was based on biological specimens, a nonhuman population, simulation model, or hypothetical cohort; 3) the study did not report receipt of cancer-directed initial care, postdiagnostic surveillance care, or end-of-life care; 4) the article reported results from a clinical study or controlled trial evaluating a specific treatment; 5) the study did not include information on patterns of care; 6) the study included fewer than 200 cancer patients; 7) the study did not report data for colorectal cancer care separately. After exclusions, we selected studies that were conducted in the United States or Canada. Studies conducted in Europe, Australia, and New Zealand are evaluated in a separate article (8). The reference lists of the retained articles (n = 52) were examined to identify additional studies and were evaluated by the exclusion criteria described above. An additional 21 studies

were identified from reference lists and a total of 73 studies are included in this systematic review of the literature.

For each article, we used a standard format to record cohort characteristics (ie, tumor site, stage, year of diagnosis or year of death in studies of end-of-life care, sample size, age distribution); health-care delivery setting and data sources used to identify patients and their health services (ie, cancer registry data, medical records, claims, surveys); and a summary of key findings on the receipt of care. Items were recorded as "Not Reported" if the information was not explicitly stated or could not be reasonably inferred from the summary statistics presented. Four reviewers participated in data abstraction. To ensure consistency between reviewers, we completed three quality control checks, where each reviewer abstracted the same three studies and compared abstracted findings.

With respect to patterns of colorectal cancer care, we abstracted the proportion of patients receiving specific types of initial care, postdiagnostic surveillance care, and end-of-life care. Cancer-directed initial care consisted of surgery, radiotherapy, chemotherapy, and multicomponent care where multiple types of care were reported together and could not be abstracted separately. The summaries of postdiagnostic surveillance and end-of-life care patterns are presented in the text only, given the small number of studies. We also documented patient population and health-care provider characteristics that were associated with receipt of care and whether the associations were positive or negative. These characteristics included patient sex, race and/or ethnicity, marital status, stage of disease at diagnosis, delivery setting, and provider practice patterns (eg, cancer patient volume). We reported patterns of care across the continuum of care from initial treatment following diagnosis to postdiagnostic surveillance and, finally, end-of-life care. When appropriate, we attempted to identify when care was guideline-concordant. In each table, studies are ordered by date of publication.

Results

Study Characteristics

Of the 73 studies included in this review (9–81), 62 were conducted in the United States and 11 were conducted in Canada (Table 1). The number of published articles on colorectal cancer care increased across the study period more rapidly in Canada, with a majority published between 2008 and 2010. Patterns of cancer-directed initial care represented the greatest number of studies for both the United States (76%) and Canada (82%), followed by studies on postdiagnostic surveillance care. Studies that reported end-of-life care were only identified in the United States (8%). With respect to cancer-directed initial care, nearly half of US studies reported on the receipt of chemotherapy (48%); in Canada, surgery, radiotherapy, and chemotherapy were assessed in similar proportions. Several studies that included a description of cancer-directed initial care fell into two or more categories used to describe "Type of care reported" or "Type of initial care reported." Thus, these two study characteristics were not mutually exclusive.

Most colorectal cancer patients and health services data were identified by registry data linked to medical records, insurance claims, or physician surveys in the United States (53%); in Canada, all studies were conducted using data of this type (100%). Registry data alone accounted for patient and health services information in 18% of US studies. The remaining data sources in the United States included medical claims alone (5%) or other data sources, including special studies designed to assess treatment receipt and outcomes for cancer patients (24%). In both countries, similar numbers of studies assessed treatment for colon, rectal, and colorectal tumors, where "colorectal tumors" describe studies that assessed both colon and rectal tumor sites together and could not be abstracted separately. Several studies assessed two or more tumor sites; thus, our cohort characteristic titled "Tumor site reported" is not mutually exclusive. Several studies were represented across multiple tables or multiple times within a single table. In the United States, the majority of studies included 5000 or more patients. And in Canada, all study populations included less than 5000 patients. Health services data sources for the United States and Canada are described in Tables 2 and 3.

Cancer-Directed Initial Care—Surgery, Radiotherapy, Chemotherapy, and Multicomponent Care

The receipt of surgical care for colorectal cancer was reported in 16 US studies and 4 Canadian studies (Table 4). Health services data were obtained from a variety of sources, including state or provincial registries with or without linkage to medical claims or patient records, hospital discharge data (eg, the Healthcare Cost and Utilization Project [HCUP]), or the National Cancer Data Base. Study cohorts were drawn from single institutions and national-, state-, or provincial-based populations. Most studies reported receipt of surgery near or above 80% in both the United States and Canada. Surgery as the sole treatment modality decreased across time, giving way to treatment plans that included neoadjuvant or adjuvant therapy (13,31). Older and uninsured patients had the highest proportions of emergency resections (23), and several studies reported an increasing trend over time for the proportion of rectal cancer patients receiving sphincter-sparing surgery. Surgery receipt varied by anatomical location of the tumor, race, sex, and age.

Twenty-one studies reported patterns of care for the receipt of radiotherapy in the United States and Canada (Table 5). Surveillance, Epidemiology, and End Results (SEER) registries alone or linked to Medicare claims were used to identify radiotherapy receipt for a plurality of US studies. Similarly, all studies of radiotherapy use in Canada obtained data from provincially based cancer registries augmented by treatment data from medical records (ie, CancerCare Manitoba and the British Columbia Cancer Agency). Patients with stage II–III, local, or regional rectal cancer had the greatest representation within studies of radiotherapy; for this subset, rates of radiotherapy use increased from approximately 15% in the mid-1970s to 50% or greater in the first decade of the 21st century. This upward trend was evident in both Canada and the United States (13,35) and is in accordance with findings from randomized controlled trials that have demonstrated survival benefits from the use of radiotherapy in the treatment of early-stage rectal cancer (82).

Patterns of care for the receipt of chemotherapy were reported in 29 US studies and 5 Canadian studies (Table 6).

Table 1. Characteristics of studies examining the receipt of colorectal cancer in the United States and Canada

Characteristic	United States (n = 62)		Canada (n = 11)	
	No.	%	No.	%
Study publication year				
2000–2003	18	29.0	3	27.3
2004–2007	24	38.7	1	9.1
2008–2010	20	32.3	7	63.6
Patient identification and health services data source				
Registry-linked medical records/claims/surveys	33	53.2	11	100.0
Registry only	11	17.7	0	0.0
Medical claims only	3	4.8	0	0.0
Other	15	24.2	0	0.0
Type of care reported*				
Initial care	47	75.8	9	81.8
Postdiagnostic surveillance care	11	17.7	2	18.2
End-of-life care	5	8.1	0	0.0
Type of initial care reported*				
Surgery	15	24.2	5	45.5
Radiation	17	27.4	4	36.4
Chemotherapy	30	48.4	5	45.5
Multicomponent	13	21.0	4	36.4
Lower bound for year of diagnosis				
Prior to 1990	8	12.9	4	36.4
1990–1999	41	66.1	4	36.4
2000 and later	9	14.5	3	27.3
Not reported	4	6.5	0	0.0
Tumor site reported*				
Colon	22	35.5	3	27.3
Rectum	19	30.6	5	45.5
Colorectal	24	38.7	4	36.4
Lower bound for age for inclusion				
<65	32	51.6	8	72.7
≥65	29	46.8	0	0.0
Not reported	1	1.6	3	27.3
Number of cancer patients				
<500	8	12.9	5	45.5
500–999	6	9.7	1	9.1
1000–4999	14	22.6	5	45.5
5000–9999	12	19.4	0	0.0
≥10 000	22	35.5	0	0.0

* Not mutually exclusive.

SEER–Medicare or state registry data linked to Medicare claims provided treatment information for a majority of studies in the United States. The remaining US studies obtained data through hospital registries, a health maintenance organization (HMO) insurance network, or special studies of cancer patients (eg, the National Comprehensive Cancer Network's (NCCN) Colon/Rectum Cancer Outcomes Database). As in other studies of initial care for Canada, chemotherapy treatment data were obtained from provincial registries linked to supplemental data sources. Several methods and definitions were used to assess chemotherapy receipt, even within studies, yielding a wide range of estimates. In the United States, lower use of chemotherapy was observed among patients with Medicaid coverage and those with comorbidities. And although black and white patients received consultation with an oncologist in similar proportions, white patients were significantly more likely to receive chemotherapy compared with black patients (34,50).

Seventeen studies reported receipt of multicomponent care for the treatment of colorectal cancer in the United States or Canada (Table 7). Among studies that referenced published guidelines for the receipt of adjuvant therapy, adherence ranged between approximately 50% and 80%. Patients and health services data were identified from various sources, including SEER Patterns of Care, the National Cancer Data Base, and provincial registries in Canada.

Postdiagnostic Surveillance Care

Patterns of care for the postdiagnostic surveillance of colorectal cancer were reported in 13 studies and were most commonly discussed in the context of achieving various guideline recommendations. Eleven studies were conducted in the United States (52,66–70,74,77–79,81) and two studies were conducted in Canada (65,72). SEER–Medicare data were used to assess postdiagnostic surveillance for a majority of the US studies. Data for the remaining studies in both the United States and Canada were obtained

Table 2. Characteristics of data sources used to measure patterns of colorectal cancer care in the United States*

Percentage of studies	Data source	Data type	Population coverage	Patient data		Health services data				
				Date of diagnosis	Stage at diagnosis	Surgery	Radiotherapy	Chemotherapy	Post-diagnosis surveillance	End of life
40%	SEER–Medicare	Registry linked to Medicare claims	≥65 y diagnosed and treated in SEER regions	√	√	√	√	√	√	√
10%	SEER	Registry	17 US regions	√	√	√	√			
10%	State registry linked†	Registry linked to supplemental data source	State	√	√	√	√	√	√	√
8%	State registry alone†	Registry	State	√	√	√	√	√	√	√
7%	HCUP–NIS	Hospital discharge data	Nation			√				
7%	Special study (eg, CanCORS)† ‡	Varies	Varies	√	√	√	√	√	√	√
5%	Single institution†	Hospital medical records	Institution	√	√	√	√	√	√	√
5%	Medical claims alone	Medical claims	Medical insurance beneficiaries			√	√	√	√	√
3%	NCI Patterns of Care	Registry linked to physician surveys	17 US regions	√	√	√	√	√		
3%	NCDB		Nation	√	√	√	√	√		
3%	NCCN CRC outcomes database	Chart review	Patients treated at 8 NCI comprehensive cancer centers	√	√	√	√	√		

* CanCORS = Cancer Care Outcome Research and Surveillance Consortium; CRC = colorectal cancer; HCUP–NIS = Healthcare Cost and Utilization Project–Nationwide Inpatient Sample; NCCN = National Comprehensive Cancer Network; NCDB = National Cancer Data Base; NCI = National Cancer Institute; SEER = Surveillance, Epidemiology, and End Results.

† Availability of health services data may vary by state, study, or institution.

‡ Availability of patient data may vary by study.

Table 3. Characteristics of data sources used to measure patterns of colorectal cancer care in Canada*

				Patient data		Health services data				
Percentage of studies	**Data source**	**Data type**	**Population coverage**	**Date of diagnosis**	**Stage at diagnosis**	**Surgery**	**Radiotherapy**	**Chemotherapy**	**Postdiagnosis surveillance**	**End of life**
18%	Multiple provincial registry data linked†	Registry linked to chart review or EHRs	Multiple provinces	√	√	√	√	√	√	
18%	British Columbia Cancer Agency	Registry linked to medical insurance claims	Province	√	√	√	√	√		
18%	CancerCare Manitoba	Registry linked to medical insurance claims	Province	√	√	√	√	√		
18%	Alberta Cancer Registry linked	Registry linked to EHRs, hospital discharge records, or other administrative records	Province	√	√	√		√		
18%	Single institutions†	Registry linked to medical records	Institution	√	√	√	√	√	√	
9%	Ontario Cancer Registry linked	Registry linked to pathology reports	Province	√	√	√				

* EHR = electronic health record.

† Availability of health services data may vary by province or institution.

Table 4. Patterns of care for the initial receipt of surgery for colorectal cancer in the United States and Canada*

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
Colon	Hardiman, 2009 (9)	United States	Any	1998–2004	10 433	≥80, 30	Oregon; patients and health services data identified through the Oregon State Cancer Registry	Overall, patients aged ≥80 were as likely to receive surgery as were younger patients; older patients were less likely to have surgery if they had regional, distant, or unknown disease
Rectal	Pisu, 2010 (10)	United States	I–III	1999–2003	675	≥65, 100	Alabama; patients identified through registry; health services data from Medicare claims	Overall, 90% of patients received surgery; surgery receipt increased with increased stage (stage I: 85%, stage II: 93%, stage III: 95%)
	Ricciardi, 2010 (11)	United States	NR	NR	19 912	NR	Multiple states; patients and health services data identified through the HCUP–NIS	50% of discharges had a sphincter-sparing procedure; county-level data showed geographical variability in the receipt of sphincter-sparing techniques; one-fourth of counties treated ≥60% of patients with nonrestorative surgical techniques
	Latosinsky, 2009 (12)	Canada	I–III	1984–1997	333	Range 22–88	Manitoba; patients and health services data obtained through CancerCare Manitoba, which houses registry and treatment data	47% of patients received anterior resection, 51% received APR, 2% received Hartmann's procedure; 53% of patients received a permanent stoma
	Demers, 2008 (13)	Canada	NR	1985–1999	2925	≥60, 79	Manitoba; patients and health services data obtained through CancerCare Manitoba, which houses registry and treatment data	74% of patients received surgery; surgery alone was the most common treatment modality across the study period, though surgery alone decreased from 60% to 40% between 1985 and 1999
	Esnaola, 2008 (14)	United States	I–III	2003–2005	35 695	≥65, 51	Multiple states; patients identified from the NCDB; health services data obtained by medical record abstraction	Older patients (≥75) were less likely to receive surgery compared with younger patients (<55); older patients were more likely to receive local excision instead of definitive, segmental resection; compared with white patients, black patients were less likely to receive surgery
	Chang, 2007 (15)	United States	I–III	1991–2002	21 390	Median 68	Multiple states; patients and health services data identified from SEER	11% of patients did not receive cancer-directed surgery, 15% of patients received local excision, 44% of patients received LAR, 26% of patients received APR, and 4% of patients received multivisceral resection
	Ricciardi, 2007 (16)	United States	NR	NR	117 773	Mean 66	Multiple states; patients and health services data identified through the HCUP–NIS	Among patients who received surgery, 40% received sphincter-sparing procedures; the proportion of sphincter-sparing surgery increased from approximately 30% in 1988 to approximately 50% in 2003

(Table continues)

Table 4 (Continued).

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
	Morris, 2006 (17)	United States	I–IV	1992–1999	10 940	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	Segmental resection was performed on 56% of black patients and 62% of white patients (P = .005); APR was more common among blacks (30%) than whites (28%); the proportion of transanal resection was similar in both groups
	Purves, 2005 (18)	United States	NR	NR	477	≥65, 25	Multiple states; patients and health services data identified through the HCUP–NIS	46% of patients had an APR and 54% had a sphincter-sparing procedure; patients treated by surgeons who had higher caseloads were more likely to undergo a sphincter-sparing procedure
	Morris, 2004 (19)	United States	Any	1988–1999	52 864	≥35, 100	Multiple states; patients and health services data identified from SEER	96% of white patients and 94% of black patients received surgery; among these, 63% and 57% of white and black patients, respectively, received a sphincter-sparing procedure; overall, black patients were less likely to receive any type of surgery
	Phang, 2003 (20)	Canada	0–IV	1996	481	Median 70	British Columbia; patients identified through the British Columbia Cancer Agency; health services data from chart review and physician surveys	The majority of rectal cancers were resected: 51% by anterior resection, 33% by APR, 5% by Hartmann's procedure, and 1% by proctocolectomy
	Shroen, 2001 (21)	United States	I–IV	1994–1996	637	Range 22–94	California; patients and health services data identified from the Cancer Surveillance Program (Sacramento)	More than 93% of patients received surgery; 22% of patients with middle rectum tumors and 55% of those with lower rectum tumors received APR; LAR was associated with female sex, tumor location, and treatment at a major teaching hospital
Colorectal	Chan, 2010 (22)	Canada	IV	2000–2002	411	≥70, 40	British Columbia; patients and health services data identified through the British Columbia Cancer Agency	70% of patients underwent resection of the primary tumor; those who did not receive resection were more likely to have rectal tumors
	Diggs, 2007 (23)	United States	Any	2002	26 269	≥65, 79	Multiple states; patients and health services data identified through the HCUP–NIS	Patients ≥85 y were most likely to undergo emergency resection; for patients aged <65 y, emergency resection receipt was highest among those who were uninsured
	Cook, 2005 (24)	United States	IV	1988–2000	17 658	≥50, 91	Multiple states; patients and health services data identified from SEER	66% of patients received resection; women, blacks, rectal cancer patients, and patients with leftsided colon cancers were less likely to have surgery

(Table continues)

Table 4 (Continued).

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
	Temple, 2004 (25)	United States	IV	1990–1991	9011	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	72% of patients received cancer-directed surgery; age ≥75 y, rectal lesions, leftsided colon tumors, and lower SES were associated with decreased likelihood of undergoing surgery
	Wudel, 2002 (26)	United States	I–IV	1990–1999	668	Median 69, 74‡	Tennessee; data were collected through cancer registry databases at a university medical center and a city hospital in the Nashville area	There was no difference in curative resection by race or hospital; at the university hospital, 74% of black patients and 81% of white patients received curative surgery; at the city hospital, 73% of black patients and 78% of white patients received curative surgery
	Roetzheim, 2000 (27)	United States	Any	1994	9551	Mean 72	Florida; patients identified through the Florida Cancer Data System; health services data from statewide hospital and ambulatory surgical centers, freestanding RT centers, and diagnostic imaging centers	Overall, 80% of patients received surgery; a higher proportion of female, married, Medicare HMO, regional stage, and colon cancer patients received surgery
	Simunovic, 2000 (28)	Canada	NR	1990	1072	≥20, 100	Ontario; patients identified through the registry and health services data from pathology report review	31% of patients received APRs; 32% of all procedures were performed in high-volume hospitals

* APR = abdominoperineal resection; HCUP–NIS = Healthcare Cost and Utilization Project–Nationwide Inpatient Sample; HMO = health maintenance organization; LAR = lower anterior resection; NCDB = National Cancer Data Base; NR = not reported; RT = radiotherapy; SEER = Surveillance, Epidemiology, and End Results; SES = socioeconomic status.

† For studies where age distributions were not explicitly stated, we include measures of mean, median, or range as reflected in the original study's presentation.

‡ Median shown at university medical center, city hospital, respectively.

Table 5. Patterns of care for the initial receipt of radiotherapy for colorectal cancer in the United States and Canada*

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
Colon	Dunn, 2010 (29)	United States	I–III	1988–2005	187 004	≥60, 81	Multiple states; patients and health services data identified from SEER	Less than 10% of nonmetastatic patients received RT; patients diagnosed in 1988 were 2.5 times more likely to receive RT than those diagnosed in 2005
Rectal	Kuo, 2010 (30)	United States	II	1994–2003	329	Range 28–93	California; patients and health services data identified through the registry's Desert Sierra Cancer Surveillance Program	54% of patients received pelvic RT; among these, 71% received RT postoperatively
	Lin, 2010 (31)	United States	II–III	1998–2005	8978	≥18, 100	Multiple states; patients and health services data identified from SEER	31% of patients received preoperative RT, 37% received postoperative RT, and 31% received no RT
	Pisu, 2010 (10)	United States	I–III	1999–2003	675	≥65, 100	Alabama; patients identified through registry; health services data from Medicare claims	15% of patients received neoadjuvant RT, 25% received adjuvant RT; over time, a higher proportion of patients received preoperative RT compared with postoperative RT
	Latosinsky, 2009 (12)	Canada	I–III	1984–1997	333	Range 22–88	Manitoba; patients and health services data obtained through CancerCare Manitoba, which houses registry and treatment data	47% of patients received adjuvant RT; receipt of RT increased by stage; 1% of patients received neoadjuvant RT
	Romanus, 2009 (32)	United States	I–IV	2005–2008	2042	≥65, 50	Multiple states; patients and health services data obtained from the NCCN Outcomes Database Project	93% of stage III patients aged ≤80 y and who underwent curative surgery received RT within 6 mo of diagnosis
	Demers, 2008 (13)	Canada	NR	1985–1999	2925	≥60, 79	Manitoba; patients and health services data from CancerCare Manitoba (cancer registry and treatment data)	Receipt of RT increased 32% to 40% between 1985 and 1999
	Dobie, 2008 (33)	United States	II–III	1992–1999	2886	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	55% of all patients received RT; 48% of stage II and 62% of stage III patients received RT
	Morris, 2008 (34)	United States	II–III	1992–1999	2716	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	57% of blacks and 65% of whites consulted with a radiation oncologist; among these, 74% of blacks and 83% of whites received RT after consultation
	Chang, 2007 (15)	United States	I–III	1991–2002	21 390	Median 68	Multiple states; patients and health services data identified through SEER	47% of patients received adjuvant RT; increasing age was associated with decreased receipt of RT
	Morris, 2006 (34)	United States	I–IV	1992–1999	10 940	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	Among patients with stage II to IV disease, black patients were less likely to receive RT compared with white patients (25% vs 34%)
	Baxter, 2005 (35)	United States	Local regional	1976–2005	45 627	≥18, 100	Multiple states; patients and health services data identified from SEER	Overall, 32% of patients received RT; receipt increased 15% to 42% from 1976 to 2000; younger age, male sex, and regional spread was associated with RT use

(Table continues)

Table 5 (Continued).

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
	Morris, 2004 (19)	United States	Any	1988–1999	52 864	≥35, 100	Multiple states; patients and health services data identified from SEER	47% of white patients and 44% of black patients received any RT; 7% of white patients and 7% of black patients received neoadjuvant RT
	Phang, 2003 (20)	Canada	0–IV	1996	481	Median 70	British Columbia; patients were identified through the British Columbia Cancer Agency; chart review and physician surveys were used to obtain health services data	60% of stage II and stage III patients received RT; of these, 89% received postoperative radiation and 11% received neoadjuvant radiation
	Neugut, 2002 (36)	United States	II–III	1991–2002	55 204	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	Overall, 48% of patients received RT following surgery; 11% of patients received RT only for adjuvant therapy
	Schrag, 2001 (37)	United States	II–III	1992–1996	1411	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	57% of patients received RT; increasing age was associated with decreased likelihood of RT receipt
	Shroen, 2001 (21)	United States	I–IV	1994–1996	637	Range 22–94	California; patients and health services data identified from the Cancer Surveillance Program (Sacramento)	14% of stage I, 53% of stage II, 63% of stage III, and 30% of stage IV patients received RT
Colorectal	Chan, 2010 (22)	Canada	IV	2000–2002	411	≥70, 40%	British Columbia; patients and health services data identified through the British Columbia Cancer Agency	63% of resected and 58% of nonresected rectal cancer patients received RT
	Ayanian, 2003 (38)	United States	II–III	1996–1997	1956	≥18, 100%	California; patients were identified from the registry; health services data obtained from physician surveys or hospital records	Based on registry data, 58% of patients received RT; this proportion increased to 64% with additional data obtained from physician surveys or hospital records; black and older patients were less likely to receive RT
	Wudell, 2002 (26)	United States	I–IV	1990–1999	668	Median 69, 74‡	Tennessee; data were collected through cancer registry databases at a university medical center and a city hospital in the Nashville area	There was no significant difference in RT receipt by race or hospital; at the university hospital, 7% of black patients and 10% of white patients received RT; at the city hospital, 7% of black patients and 6% of white patients received RT
	Roetzheim, 2000 (27)	United States	Any	1994	9551	Mean 72	Florida; patients identified through the Florida Cancer Data System; health services data were obtained from statewide hospital and ambulatory surgical centers, freestanding RT centers, and diagnostic imaging centers	Overall, 26% of patients received RT; a higher proportion of male, married, lower income, smoking, Medicaid, distant stage, and rectal cancer patients received surgery

* NCCN = National Comprehensive Cancer Network; NR = not reported; RT = radiotherapy; SEER = Surveillance, Epidemiology, and End Results.

† For studies where age distributions were not explicitly stated, we include measures of mean, median, or range as reflected in the original study's presentation.

‡ Median shown at university medical center, city hospital, respectively.

Table 6. Patterns of care for the initial receipt of chemotherapy for colorectal cancer in the United States and Canada*

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
Colon	Kirkpatrick, 2010 (39)	United States	II	1995–2003	287	≥65, 69	Texas; patients identified through the Baylor University Medical Center tumor registry; health services data from chart review	Among patients receiving resection, 56% were referred to a medical oncologist, 28% received adjuvant chemotherapy; receipt of chemotherapy was associated with age at diagnosis, comorbidity score, tumor grade, and stage
	Winget, 2010 (40)	Canada	III	1999–2000	772	≥70, 56	Alberta; patients identified from the registry; health services data obtained from hospital discharge data and EMRs	Among patients who received surgery, 80% received an oncologist consultation within 6 mo of diagnosis; 63% of patients with an oncologist consultation received chemotherapy
	Earle, 2009 (41)	United States	II	2005–2008	258	≥65, 46	Multiple states; patients and health services data identified from the NCCN Colon/Rectum Cancer Outcomes Database	46% of patients received chemotherapy; 77% of patients who initiated chemotherapy completed at least 4 mo of therapy; an oxaliplatin-containing regimen was used for 67% of patients
	Hardiman, 2009 (9)	United States	Any	1998–2004	10 433	≥80, 30	Oregon; patients and health services data identified through the Oregon State Cancer Registry	Patients aged ≥80 y received chemotherapy less often than younger patients; older patients who did receive chemotherapy were less likely to receive multiple agents
	Hershman, 2009 (42)	United States	NR	1991–2002	13 422	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	Study cohort was limited to patients who received chemotherapy; 17% received erythropoiesis-stimulating agents
	Wirtzfeld, 2009 (43)	Canada	I–III	1999–2000	419	NR	Newfoundland and Labrador, Ontario; patient and health services data from the Newfoundland and Labrador Familial Colorectal Cancer Registry, the Ontario Familial Colorectal Cancer Registry, medical record review, and questionnaire	0% of stage I, 37% of stage II, and 92% of stage III colon cancer patients received chemotherapy
	Romanus, 2009 (32)	United States	I–IV	2005–2008	2042	≥65, 50	Multiple states; patients and health services data obtained from the NCCN Outcomes Database Project	90% of stage III patients aged ≤80 y received chemotherapy within 4 mo of diagnosis
	Bradley, 2008 (44)	United States	I–IV	1997–2000	4675	≥66, 100	Michigan; patients identified from the registry; health services data identified from Medicare and Medicaid insurance claims	Oncologist consultations were received by 81% of Medicaid beneficiaries and 85% of Medicare-only beneficiaries; 23% of Medicaid beneficiaries and 34% of Medicare-only beneficiaries initiated chemotherapy; of these, 48% of Medicaid beneficiaries and 62% of Medicare-only beneficiaries completed chemotherapy regimens

(Table continues)

Table 6 (Continued).

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
	Quah, 2007 (45)	United States	I–III	1990–2001	1327	Median 70	New York; patients and health services data identified from the MSKCC Colorectal Service Database and chart review	Younger patients (≤40 y) were more likely to receive chemotherapy compared with older patients: 39% vs 14% of stage II patients, 87% vs 80% of stage III patients
	Dobie, 2006 (46)	United States	III	1992–1996	5778	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	Researchers classified receipt of chemotherapy using both liberal (1 claim-day in a month) and conservative (3 claim-days in a month) definitions; by the conservative definition, 16% initiated and 38% completed chemotherapy; by the liberal definition, 12% initiated and 42% completed chemotherapy
	Luo, 2006 (47)	United States	III	1992–1999	8978	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	78% of patients saw an oncologist within 6 mo of diagnosis; 59% of patients received chemotherapy within 6 mo of diagnosis; consultation with a medical oncologist, younger age, white race, being married, and later year of diagnosis were associated with receipt of chemotherapy
	McGory, 2006 (48)	United States	III	1994–2001	13 231	Mean 69	California; patients identified from the registry; health services data from California Patient Discharge Database	48% of patients received chemotherapy
	Neugut, 2006 (49)	United States	III	1995–1999	3733	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	More than 30% of patients were treated with chemotherapy for 1 to 4 mo; chemotherapy treatment for 5–7 mo was associated with younger age, more recent year of diagnosis, being married, having a tumor of well/moderately differentiated grade, and having no comorbidities
	Baldwin, 2005 (50)	United States	III	1992–1996	5294	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	There was no difference in the proportions of white and black patients who received consultation with an oncologist (79% and 79%, respectively, $P = 0.922$); however, a significant difference in treatment receipt was observed where 70% of whites and 60% of blacks received chemotherapy ($P < 0.001$)

(Table continues)

Table 6 (Continued).

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
	Jessup, 2005 (51)	United States	III	1990–2002	85 934	≥60, 79	Multiple states; patients and health services data from the National Cancer Data Base	Use of adjuvant chemotherapy increased from 39% in 1990 to 64% in 2002; these percentages include the use of both chemotherapy and biological response-modifiers (primarily 5-FU, levamisole, and BCG vaccine)
	Keating, 2005 (52)	United States	III	1993–1999	48 027	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	Increases in market share of managed care by county was not associated with receipt of adjuvant chemotherapy (P = .94)
	Wu, 2004 (53)	United States	III	2001	303	≥65, 63	Louisiana; patients identified from the registry; health services data from medical records of patients treated in CoC and non-CoC hospitals	Receipt of chemotherapy based on race/sex was as follows: 65% white/male, 66% white/female, 72% black/male, 66% black/female; 75% of patients treated at CoC hospital and 54% at non-CoC hospital
	Sundararajan, 2002 (54)	United States	III–IV	1992–1996	4768	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	4% of patients received chemotherapy that did not include 5-FU, whereas 52% received 5-FU-based therapy; younger age was strongly associated with receiving 5-FU treatment
	Schrag, 2001 (55)	United States	III	1991–1996	6262	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	55% of all patients received chemotherapy; older age was associated with decreased likelihood of receipt of chemotherapy
	Sundararajan, 2001 (56)	United States	III	1992–1996	4998	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	Approximately 50% of patients received 5-FU during the study period; use of 5-FU increased by 10% between 1992 and 1996
Rectal	Kuo, 2010 (30)	United States	II	1994–2003	329	Range 28–93	California; patients and health services data identified through the registry's Desert Sierra Cancer Surveillance Program	45% of patients received chemotherapy; among these, 11% of patients received chemotherapy only in addition to surgery
	Pisu, 2010 (10)	United States	I–III	1999–2003	675	≥65, 100	Alabama; patients identified through registry; health services data from Medicare claims	11% of patients received neoadjuvant chemotherapy; 37% received adjuvant chemotherapy
	Romanus, 2009 (32)	United States	I–IV	2005–2008	2042	≥65, 50	Multiple states; patients and health services data obtained from the NCCN Outcomes Database Project	81% of stage II/III patients aged ≤80 y received chemotherapy within 4 mo of diagnosis
	Demers, 2008 (13)	Canada	NR	1985–1999	2925	≥60, 79	Manitoba; patients and health services data from CancerCare Manitoba (cancer registry and treatment data)	Receipt of chemotherapy increased 13% to 37% between 1985 and 1999

(Table continues)

Table 6 (Continued).

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
	Dobie, 2008 (33)	United States	II–III	1992–1999	2886	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	52% of all patients received chemotherapy; 42% of stage II and 63% of stage III patients received chemotherapy
	Morris, 2008 (34)	United States	II–III	1992–1999	2716	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	73% of blacks and 75% of whites consulted with a medical oncologist; following consultation, 54% of blacks and 70% of whites received chemotherapy
	Morris, 2006 (17)	United States	I–IV	1992–1999	10 940	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	Among patients with stage II to IV disease, black patients were less likely to receive chemotherapy compared with white patients (27% vs 40%)
	Phang, 2003 (20)	Canada	0–IV	1996	481	Median 70	British Columbia; patients were identified through the British Columbia Cancer Agency; chart review and physician surveys were used to obtain health services data	60% of stage II and stage III patients received adjuvant chemotherapy
	Neugut, 2002 (36)	United States	II–III	1991–2002	55 204	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	Overall, 51% of patients received adjuvant chemotherapy with 5-FU-containing regimens; 14% of patients received a 5-FU regimen only in addition to surgery
	Shroen, 2001 (21)	United States	I–IV	1994–1996	637	Range 22–94	Sacramento, California; patients and health services data identified from the Cancer Surveillance Program	11% of stage I patients, 54% of stage II patients, 70% of stage III patients, and 55% of stage IV patients received chemotherapy
Colorectal	Chan, 2010 (22)	Canada	IV	2000–2002	411	≥70, 40	British Columbia; patients and health services data identified through the British Columbia Cancer Agency	61% of resected patients and 58% nonresected patients received chemotherapy
	Hendren, 2010 (57)	United States	III	1998–2005	17 108	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare; patients receiving RT were excluded	66% of patients received adjuvant chemotherapy; surgical complications were associated with nonreceipt of chemotherapy
	Oliveria, 2004 (58)	United States	I–IV	1997–1999	217	Mean 72	Massachusetts; patient and health services data obtained from HMO administrative data and medical record review	48% of stage I patients, 60% of stage II patients, 87% of stage III patients, and 67% of stage IV patients received consultation with an oncologist; among those who received consultation with an oncologist, 14% of stage I patients, 44% of stage II patients, 67% of stage III patients, and 61% of stage IV patients received chemotherapy

(Table continues)

Table 6 (Continued).

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
	Ayanian, 2003 (38)	United States	II–III	1996–1997	1956	≥18, 100	California; patients were identified from the registry; health services data obtained from physician surveys or hospital records	Based on registry data, 59% of patients received chemotherapy; this proportion increased to 67% with additional data obtained from physician surveys or hospital records; older and unmarried patients were less likely to receive chemotherapy
	Wudel, 2002 (26)	United States	I–IV	1990–1999	668	Median 69, 74‡	Tennessee; data were collected through cancer registry databases, a university medical center, and a city hospital in the Nashville area	There was no difference in chemotherapy receipt by race or hospital; at the university hospital, 16% of black patients and 21% of white patients received chemotherapy; at the city hospital, 16% of black patients and 25% of white patients received chemotherapy
	Roetzheim, 2000 (27)	United States	Any	1994	9551	Mean 72	Florida; patients identified through the Florida Cancer Data System; health services data were obtained from statewide hospital and ambulatory surgical centers, freestanding RT centers, and diagnostic imaging centers	Overall, 21% of patients received chemotherapy; a higher proportion of married, smoking, uninsured, distant stage, and rectal cancer patients received surgery

* 5-FU = 5-Fluorouracil; CoC = Commission on Cancer; BCG = Bacillus Calmette–Guérin; EMR = electronic medical record; HMO = health maintenance organization; MSKCC = Memorial Sloan-Kettering Cancer Center; NCCN = National Comprehensive Cancer Network; NR = not reported; RT = radiotherapy; SEER = Surveillance, Epidemiology, and End Results.

† For studies where age distributions were not explicitly stated, we include measures of mean, median, or range as reflected in the original study's presentation.

‡ Median shown at university medical center, city hospital, respectively.

Table 7. Patterns of care for the initial receipt of multicomponent therapy for colorectal cancer in the United States and Canada*

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
Colon	Cree, 2009 (59)	Canada	III	2004	3280	≥65, 70	Alberta, Manitoba, and Saskatchewan; patients identified from registry; health services data from medical record review and/or through cancer registry	53% of stage III patients received standard care (surgery + chemotherapy and/or RT), as per the NIH Consensus Conference statement
	Cronin, 2006 (60)	United States	II–III	2000	475	≥20, 100	Multiple states; patients and health services data obtained from SEER registries and supplemental Patterns of Care physician surveys	61% of stage III patients received guideline therapy (surgery + 5-FU + leucovorin/levamisole); notably, due to a lack of consensus on guideline treatment for stage II disease, these patients were not included in survival or regression analyses
	VanEenwyk, 2002 (61)	United States	III	1996–1997	632	≥65, 71	Washington; patients identified from the registry linked to hospital discharge data	38% of patients did not receive adjuvant therapy (any chemotherapy or RT) in their treatment plan; older age, not having private health insurance, and living in a lower income area was associated with not having an adjuvant therapy treatment plan
Rectal	Pisu, 2010 (10)	United States	I–III	1999–2003	675	≥65, 100	Alabama; patients identified through registry; health services data from Medicare claims	17% of patients received chemoradiation
	Cree, 2009 (59)	Canada	II–III	2004	3280	≥65, 70	Alberta, Manitoba, and Saskatchewan; patients identified from registry; health services data from medical record review and/or through cancer registry	51% of stage II–III rectal cancer patients received standard care (surgery + chemotherapy and/or RT), as per the NIH Consensus Conference statement
	Latosinsky, 2009 (12)	Canada	I–III	1984–1997	333	Range 27–96	Manitoba; patients identified from the registry; health services data identified from medical records	Chemotherapy was administered concomitantly for more than 80% of patients who received RT
	Demers, 2008 (13)	Canada	NR	1985–1999	2925	≥60, 79	Manitoba; patients and health services data from CancerCare Manitoba (cancer registry and treatment data)	The combination of major surgery and perioperative chemoradiation increased from 1% to 25% between 1985 and 1999
	Dobie, 2008 (33)	United States	II–III	1992–1999	2886	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	45% of patients received both chemotherapy and RT; 38% of stage II and 54% of stage III patients received both chemotherapy and RT
	Esnaola, 2008 (14)	United States	I–III	2003–2005	35 695	≥65, 51	Multiple states; patients identified from the NCDB; health services data obtained by medical record abstraction	Increasing age was associated with lower use of chemoradiation
	Morris, 2008 (34)	United States	II–III	1992–1999	2716	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	Following consultation with an oncologist, 77% of whites and 61% of blacks received both chemotherapy and RT
	Cronin, 2006 (60)	United States	II–III	2000	352	≥20, 100	Multiple states; patients and health services data obtained from SEER registries and supplemental Patterns of Care physician surveys	55% of stage II and 53% of stage III rectal cancer patients received guideline therapy (surgery + 5-FU + RT)

(Table continues)

Table 7 (Continued).

Site	First author, year (ref.)	Country	Stage	Diagnosis year	Sample size	Age, y, %†	Health delivery setting and data sources	Findings
	McGory, 2006 (48)	United States	III	1994–2001	13 231	Mean 69	California; patients identified from the registry; health services data from California Patient Discharge Database	52% of stage I and 62% of stage II patients received chemoradiation
	Keating, 2005 (52)	United States	III	1993–1999	48 027	≥66, 100	Multiple states; patients and health services data identified from SEER–Medicare	Increases in market share of managed care by county were associated with receipt of adjuvant chemoradiation for patients with stage II or stage III cancer; rates peaked in areas with a market share of managed care between 1% and 10% ($P = 0.001$).
	Dharma-Wardene, 2002 (62)	Canada	NR	1985–1999	2925	Median 69	Manitoba; patients identified from registry and health services data obtained from CancerCare Manitoba	The combination of major surgery and perioperative chemoradiation increased from 1% to 25% between 1985 and 1999
	Neugut, 2002 (36)	United States	II–III	1991–2002	55 204	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	37% of patients received surgery with RT and 5-FU chemotherapy
	VanEenwyk, 2002 (61)	United States	III	1996–1997	632	≥65, 71	Washington; patients identified from the registry linked to hospital discharge data	27% of patients did not receive adjuvant therapy (any chemotherapy or RT); older age and later stage were associated with not having an adjuvant therapy treatment plan
	Schrag, 2001 (37)	United States	II–III	1992–1996	1411	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	Overall, 42% of patients received chemoradiation; increasing age reduced likelihood of treatment receipt
	Shroen, 2001 (21)	United States	I–IV	1994–1996	637	Range 22–94	California (Sacramento); patients and health services data identified from the Cancer Surveillance Program	Evaluated by NIH Consensus Conference recommendations, 44% of stage II patients and 60% of stage III patients received recommended therapy (surgery + RT + chemotherapy)
Colorectal	White, 2008 (63)	United States	I–III	1991–2002	55 204	≥65, 100	Multiple states; patients and health services data identified from SEER–Medicare	77% of white patients and 74% of black patients received standard therapy according to NCI Physician Data Query guidelines
	Potosky, 2002 (64)	United States	II–III	1987–1995	4706	≥20, 100	Multiple states; patients and health services data obtained from SEER registries and supplemental Patterns of Care physician surveys	Standard therapy = 5-FU + levamisole/leucovorin for stage III colon patients, 5-FU with or without RT for stage II/III rectal patients; 78% of patients <55 y received standard therapy; 58% of whites, compared with 47% of blacks, received standard therapy

* 5-FU = 5-Fluorouracil; NCDB = National Cancer Data Base; NCI = National Cancer Institute; NIH = National Institutes of Health; NR = not reported; RT = radiotherapy; SEER = Surveillance, Epidemiology, and End Results.

† For studies where age distributions were not explicitly stated, we include measures of mean, median, or range as reflected in the original study's presentation.

from registry linkages to medical claims, medical record review, or from a national research project designed to survey patterns of care and care outcomes for cancer patients (ie, Cancer Care Outcomes Consortium [CanCORS]). Physical examinations of the bowel or colon (eg, colonoscopy, sigmoidoscopy) accounted for a majority of surveillance methods reported, followed by carcinoembryonic antigen (CEA) testing, physician office visits, and scans of the abdomen, pelvis, or chest.

Because various established guidelines were used to evaluate adherence to postdiagnostic surveillance at varying time points following initial treatment, studies reported disparate proportions for receipt of care. In the United States, receipt of surveillance care ranged between 26% and 83% for bowel or colon examinations, and between 60% and 92% for physician office visits. In Canada, 59% to 71% of patients received CEA testing compared with 47% of patients in a US population (65,66). The use of scans for colorectal cancer surveillance has not been included in any published guidelines at the time of this publication; however, US studies reported 7% to 59% for the use of X-ray or positron emission tomographic scans. Receipt of surveillance care was independently associated with race, age, and treatment facility; blacks, older patients, and patients treated in community vs teaching hospitals were less likely to receive care (65,69,77).

End-of-Life Care

Five studies reported the receipt of end-of-life care for colorectal cancer patients (71,73,75,76,80). These studies were all conducted in the United States and evaluated the use of palliative chemotherapy, hospice care, and hospital or emergency room services. Notably, four of the five studies acquired health services data from Medicare claims. The exception, McCarthy et al. (76), obtained data from a special study seeking to assess patient outcomes (ie, Study to Understand Patient Prognoses and Preferences for Outcomes and Risks of Treatments [SUPPORT]).

Discussion

In this study, we evaluated contemporary patterns of colorectal cancer care in the United States and Canada, as identified through a systematic review of 73 studies. Although direct comparisons between and within the two countries were limited by differences in study populations and research methods, we generally observed similar patterns of cancer-directed initial care, including rates of surgical treatment, use of adjuvant chemotherapy, and use of radiation therapy in the United States and Canada. Few studies measured postdiagnostic surveillance or end-of-life care. Our findings highlighted research gaps related to treatment practices in the absence of consensus-based guidelines. In addition, the time required to link data sources used to measure patterns of care results in data lags that can affect promising research, as in the case of the SEER–Medicare linkage (83). Researchers, clinicians, and policy makers can use findings from this review in efforts to quantify future economic and health-care resources that will be needed to improve treatment, outcomes, and access to care for colorectal cancer patients treated in the United States and Canada.

Findings for cancer-directed surgery in both the United States and Canada showed that most patients were resected, although the specific types of surgery received varied. Since 2000, surgical resection as the sole treatment modality for any colorectal cancer has declined with the addition of neoadjuvant and adjuvant treatment. In recent years, permanent colostomies have occurred less frequently and sphincter-sparing procedures have become a viable option for more rectal cancer patients when radiotherapy is given preoperatively (84). Moreover, the role of radiotherapy among colorectal cancer patients is largely restricted to those with rectal cancer. For these patients, the use of radiotherapy increased over time, whereas rates for colon cancer patients remained stagnant at 20% or less (27,29). This observation is consistent with recommendations for the treatment of colorectal cancer (85), which endorse radiotherapy for patients with rectal cancer, specifically those with stage II or III disease. In contrast, receipt of radiotherapy is only indicated for stage IV colon cancer patients or those who have experienced recurrence. The receipt of neoadjuvant radiotherapy for rectal cancer patients also increased over time (31). Shrinking the tumor preoperatively through neoadjuvant therapy maximizes options for surgical resection and is likely to affect observed patterns of both surgical and adjuvant care.

Receipt of chemotherapy increased over time, but varied considerably across studies, ranging between 28% and 90% in the United States and between 0% and 92% in Canada. Chemotherapy receipt was associated with anatomical site of the tumor, stage of disease, and patient insurance status; such wide variation in treatment receipt was due to differences in study populations and research methods. For US and Canadian studies that had comparable patient populations, receipt of chemotherapy was generally similar. Among those receiving chemotherapy, 5-Fluorouracil (5-FU)-based regimens were commonly administered, particularly for patients with stage II–IV colon cancer where such treatment is recommended by guidelines (85). However, with the advent of effective but expensive drugs (86) and use of supportive agents (87), costs associated with chemotherapy are expected to increase over time, potentially introducing an additional barrier for patients to receive appropriate care. Few studies in our review addressed the use of newer chemotherapeutic or biological agents, due, in part, to lags in the availability of data on cancer drugs. Future research should evaluate the specific agents used in colorectal cancer care.

Consensus-based guidelines provided the context for many of the studies that assessed multicomponent care in our review; however, guideline adherence varied by study population setting and year of diagnosis, likely because practice guidelines vary in their treatment recommendations. One study assessing treatment in relation to NCCN guidelines among a network of NCCN institutions reported that although guideline adherence varied, the reported receipt of guideline care remained high (>80%), as may be expected among US comprehensive cancer centers (32). In contrast, a population-based study conducted by Shroen et al. demonstrated that only 44% of stage II and 60% of stage III rectal cancer patients obtained recommended therapy, as outlined by the National Institutes of Health Consensus Conference (21).

Comparisons of treatment receipt between and within the United States and Canada are limited for early- and late-stage colorectal cancer patients because of the lack of consensus-based guidelines for the two patient groups. Nearly 40% of colorectal cancer patients receive a diagnosis of localized disease, and approximately one-quarter of patients are diagnosed with distant disease. This results in a substantial number of patients whose treatment plans cannot be evaluated in relation to a standard of care (88). Controlled trials for these patient populations will play a large role in guideline development. However, it should be noted that treatment plans vary at the discretion of the treating physician along with patient preferences for care, despite the existence of guideline recommendations.

Few studies of postdiagnostic surveillance were identified for our review, and most were conducted in the context of achieving guideline recommendations. Because there was no general consensus on frequency and time to follow-up care across guidelines, proportions of care receipt varied widely. Coordinated development of evidence-based guidelines for postdiagnostic colorectal cancer surveillance is needed to improve patient care, and evaluation of their implementation will be important for future research.

Few studies in our literature review addressed end-of-life care for colorectal cancer patients. This is may be expected because end-of-life studies tend to group all cancer patients together and do not report receipt of care separately by cancer site. However, because palliative care is not cancer-directed, this component of end-of-life care may be relatively consistent for all cancer patients. Of the five end-of-life care studies we identified, four were conducted among US patients with Medicare coverage, which promotes the use of hospice care. Future research describing end-of-life care will be important, particularly in Canada, where we did not identify any study and where the availability of hospice care varies by province.

A significant proportion of patients did not receive expected surgical or adjuvant care based on tumor site and disease stage, particularly patients who were nonwhite, older age, or who reported comorbidities. In the United States, blacks were least likely to receive any component of colorectal cancer care. However, we identified particularly worrisome findings in our review for chemotherapy use in the context of disparities by race. Although black and white colon cancer patients received consultation with an oncologist in similar proportions, blacks were significantly less likely to receive chemotherapy (34,50). The Canadian studies included in our review generally did not provide data on treatment receipt stratified by race. Studies assessing the association between race and treatment receipt in Canada's universal health-care system would add to the current body of knowledge regarding disparities in health-care access because barriers to care are assumed to be mitigated in this population. In the United States, more studies of Asian and Hispanic populations, which were underrepresented in our review, are needed to inform efforts that seek to improve care. Older patients and individuals with comorbidities were also consistently less likely to obtain recommended care (36,45,47,61). However, these patient populations typically have contraindications to treatment; thus, data on performance status in future research will allow for improved assessments of patterns of care. Ongoing efforts to improve measurement of comorbidities and to evaluate potential barriers of access to care will inform future efforts to reduce treatment disparities.

Though trends in the receipt of care were generally similar between the two countries, we observed differences in the United States and Canada with respect to data resources used to identify colorectal cancer treatment. Health-care payers in each country are central to the availability of patient treatment data. Canada's universal health coverage provides centralized systems health services data, thereby creating a potential resource that would allow for the continuous observation of patients. However, few provinces or territories have linked registry data to insurance claims. In the United States, varying forms of health-care coverage yield multiple data sources that can be used to measure patterns of care. But the disparate resources pose a challenge in the accurate assessment of care patterns for the US population as a whole. Additionally, measuring patterns of care is limited by discontinuity between data sources and lags in data availability for both countries. In the United States, ongoing state-based efforts to link registry data with multiple health insurance datasets may lead to a more comprehensive view of cancer care patterns (89–91). In Canada, the Canadian Partnership Against Cancer (CPAC) heads several initiatives that seek to improve cancer surveillance, including efforts to reduce information gaps at the national, provincial, and territorial levels (92).

In conclusion, this review summarizes a substantial volume of literature on colorectal cancer treatment practices in the United States and Canada, providing a basis for researchers who seek to address research gaps within colorectal cancer populations. Future work in assessing patterns of care for colorectal cancer patients in the United States and Canada should seek to include more studies in the areas of postdiagnostic surveillance and end-of-life care, which were both underrepresented in our review. Although guidelines provide insight on specific aspects of care, ongoing evaluation of the receipt of all types of colorectal cancer care for all stages and tumor sites will be important in identifying over- and underuse of health services. Further, where guideline consensuses do not exist, as in the case of postdiagnostic surveillance care, descriptions of metrics used to assess receipt of care will enable comparisons across studies. Future work should also address challenges to the interpretation of care patterns, including the use of various staging systems, alternating use of clinical or pathological staging, and contraindications to treatment that are not consistently captured or are absent from data sources. High-quality research on patterns of colorectal cancer care will aid policy makers in quantifying the resources needed to treat this population, while addressing disparities, projecting future costs, and ultimately improving care and cancer outcomes.

Appendix 1

Search No.	Limits: English, Journal Article, Humans, Publication Date from 2000 to 2010
1	"Colorectal Neoplasms/drug therapy"[Mesh] OR "Colorectal Neoplasms/radiotherapy"[Mesh] OR "Colorectal Neoplasms/surgery"[Mesh] OR "Colorectal Neoplasms/therapy"[Mesh]
2	"Physician's Practice Patterns"[Mesh]
3	"Guideline Adherence"[Mesh]
4	"Health Services/statistics and numerical data"[Majr] OR "Health Services/trends"[Majr] OR "Health Services/utilization"[Majr]
5	"Quality of Health Care/statistics and numerical data"[Majr] OR "Quality of Health Care/trends"[Majr] OR "Quality of Health Care/utilization"[Majr]
6	"Chemotherapy, Adjuvant/statistics and numerical data"[Mesh] OR "Chemotherapy, Adjuvant/trends"[Mesh] OR "Chemotherapy, Adjuvant/utilization"[Mesh]
7	"Neoadjuvant Therapy/statistics and numerical data"[Mesh] OR "Neoadjuvant Therapy/trends"[Mesh] OR "Neoadjuvant Therapy/utilization"[Mesh]
8	"Radiotherapy, Adjuvant/statistics and numerical data"[Mesh] OR "Radiotherapy, Adjuvant/trends"[Mesh] OR "Radiotherapy, Adjuvant/utilization"[Mesh]
9	"Neoplasm Recurrence, Local/prevention and control"[Majr]
10	"Terminal Care"[Mesh]
11	"Patterns of Care"[Keyword String][Abstract or Title]
12	Search No. 1 AND (No. 2 OR No. 3 OR No. 4 OR No. 5 OR No. 6 OR No. 7 OR No. 8 OR No. 9 OR No. 10 OR No. 11)
13	Select studies conducted in the United States or Canada

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Patterns of Colorectal Cancer Care in Europe, Australia, and New Zealand

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Colorectal cancer is the second most common cancer in women and the third most common in men worldwide. In this study, we used MEDLINE to conduct a systematic review of existing literature published in English between 2000 and 2010 on patterns of colorectal cancer care. Specifically, this review examined 66 studies conducted in Europe, Australia, and New Zealand to assess patterns of initial care, post-diagnostic surveillance, and end-of-life care for colorectal cancer. The majority of studies in this review reported rates of initial care, and limited research examined either post-diagnostic surveillance or end-of-life care for colorectal cancer. Older colorectal cancer patients and individuals with comorbidities generally received less surgery, chemotherapy, or radiotherapy. Patients with lower socioeconomic status were less likely to receive treatment, and variations in patterns of care were observed by patient demographic and clinical characteristics, geographical location, and hospital setting. However, there was wide variability in data collection and measures, health-care systems, patient populations, and population representativeness, making direct comparisons challenging. Future research and policy efforts should emphasize increased comparability of data systems, promote data standardization, and encourage collaboration between and within European cancer registries and administrative databases.

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In 2008, an estimated 2.1 million individuals were diagnosed with colorectal cancer worldwide, with nearly 60% residing in developed regions (1,2). Globally, colorectal cancer is the second most common cancer in women and third in men (1,2). Although rates vary significantly by regions of the world, Australia/New Zealand and Western Europe have among the highest estimated incidence rates of colorectal cancer (1,2). For both genders, Central and Eastern Europe have the highest mortality rates because of colorectal cancer worldwide (1,2). Given that the likelihood of developing colorectal cancer increases with older age, global prevalence is rising over time because of growing proportions of elderly (1,2). Better methods of screening and early detection and advances in treatment are also improving survival, further contributing to increasing prevalence (1,2). Undoubtedly, these increases have significant implications for health-care costs, delivery, and service utilization associated with this disease.

Given high rates of mortality and incidence for colorectal cancer in certain parts of Europe, this region of the world is an important area of international focus. Available comparative research on cancer in European countries has primarily come from studies conducted by EUROCARE, a research collaboration between several European population-based cancer registries that began in 1990 (3). EUROCARE was designed to develop standardized measures for improved comparability of cancer data between European countries and explore trends in patterns of cancer treatment and survival (3). Findings from these studies have demonstrated considerable variation in age-adjusted 5-year survival by country and region, with the highest colorectal cancer survival rates in northern European countries and the lowest in Eastern European countries (4–9).

A study comparing colorectal cancer survival in Europe to the United States during the period of 1985–1989 found that 5-year survival ranged from 13% to 22% higher in the United States depending upon tumor subsite (10). Verdecchia et al. compared data from 47 European registries to data from Surveillance, Epidemiology, and End Results (SEER) and noted higher mean survival in the United States compared with Europe for multiple cancers, including colorectal cancer, for patients diagnosed in 1995–1999 and followed up to December 2003 (7). Although limited, existing studies have suggested that differences in stage at diagnosis, postoperative mortality, and access to care may be factors that partially explain variations in outcomes between European nations (11–13).

With the larger goal of improving delivery of population-based care for colorectal cancer, assessment of current practices is a necessary first step. Therefore, we conducted this systematic review of published studies to evaluate patterns of initial care following diagnosis, post-diagnostic surveillance, and end-of-life care for colorectal cancer in Europe, Australia, and New Zealand. Examination of this literature will provide a deeper understanding of care patterns and trends over time and may identify disparities in treatment. Assessment of data comparability between nations can also inform data collection and in combination with patient outcomes and cost data, assist resource allocation, health-care delivery, and research and policy efforts targeting colorectal cancer treatment.

Methods

Study Selection and Criteria

The MEDLINE database was used to identify articles on colorectal cancer care published in English between January 2000 and

December 2010. The Medical Subject Heading (MeSH) term "Colorectal Neoplasms" was combined with additional headings or text strings related to patterns of care, such as "physician's practice patterns," "guideline adherence," "chemotherapy," and "radiotherapy" (see Appendix). In total, this search strategy yielded 717 articles.

Articles were hierarchically excluded according to the following criteria: 1) article was an editorial, letter, essay, commentary, conference paper, note, published guideline, highlight, or review; 2) study was based on biological specimens, nonhuman population, simulation model, or hypothetical cohort; 3) study did not report receipt of initial, post-diagnostic surveillance, or end-of-life colorectal cancer care; 4) study reported results from a clinical study or controlled trial evaluating a specific treatment; 5) study included only outcome measures, such as survival; 6) study had sample size of less than 200 cancer patients; and 7) study did not report data for colorectal cancer care separately from other cancer sites.

Data Abstraction

After applying the exclusion criteria to the 717 identified articles, a total of 105 studies were retained and abstracted by four individuals. Additionally, because electronic searches may not include all relevant studies, we reviewed the reference lists of these 105 articles and published reviews of colorectal cancer treatment (14–25) to identify additional studies for possible inclusion. Through this process, the study team identified 34 additional articles that were also included and abstracted. In total 139 studies were abstracted and a subset of 66 articles reporting patterns of colorectal cancer care in countries outside of North America were included in this systematic review (25–90).

The countries represented in this review include Australia, France, Germany, Italy, Spain, the Netherlands, New Zealand, Norway, Sweden, and the United Kingdom. Additionally, one study included in the review compared data from cancer registries in multiple European countries: Genoa and Varese, Italy; Côte-d'Or, France; Granada, Navarra, and Tarragona, Spain; Tampere, Finland; Estonia; Slovenia; Slovakia; and Krakow and Kielce, Poland. The remaining 73 articles were included in the companion review conducted by Butler et al., which examines patterns of colorectal cancer care in the United States and Canada (91).

A standardized abstraction form was used to record information on study characteristics and principal findings, including initial care and treatment (eg, surgery, radiotherapy [RT], chemotherapy), post-diagnostic surveillance, and end-of-life care. We also abstracted several study characteristics, including reporting of stage, year of diagnosis or treatment, sample size, patient age, health delivery setting, and data sources. In order to ensure comparability between reviewers, three quality control reviews were conducted and compared for uniformity in abstraction procedures. After each quality control review, adjustments were made to increase consistency in data abstraction. By the last quality review, it was determined that comparability among the four reviewers had been achieved, and studies that were abstracted prior to this point were revisited for secondary abstraction.

Data Analyses

Data are presented for initial care following colorectal cancer diagnosis, post-diagnostic surveillance, and end-of-life care. We abstracted "chemoradiation" or "any adjuvant therapy" as reported in the underlying studies and classified treatment as "multicomponent care" when one particular form of treatment could not be separately abstracted from other treatment types.

Several studies reported multiple types of care, such as rates of surgery as well as chemotherapy. These studies were reported in both tables on surgery and chemotherapy. As a result, some studies may appear in the data tables more than once. Tables presenting studies with findings on receipt of initial care are organized by cancer site and then by year of publication, beginning with the most recent year of publication. Given the limited number of studies focusing on either post-diagnostic surveillance (n = 7) or end-of-life care (n = 1), findings from these studies are described in the text only.

Results

Study Characteristics

Out of the total 66 papers included in the review, the vast majority focused on initial treatment for colorectal cancer (Table 1). Limited research examined either post-diagnostic surveillance or end-of-life care. With respect to distribution by country, the majority of studies were conducted in France (22.7%), the Netherlands (18.2%), the United Kingdom (16.7%), and Australia (12.1%) (Figure 1). Categories for components of care were not mutually exclusive. Nearly three-quarters of studies reported rates of surgery (69.7%), whereas approximately half of studies reported rates of radiation treatment (48.5%) and chemotherapy (51.5%).

As shown in Table 2, the data sources for measuring patterns of care varied significantly in terms of population coverage (eg, single institution vs national) and availability of information about cancer diagnosis, stage at diagnosis, and health services reported. Studies from certain countries, such as France and the Netherlands, relied more heavily on registry data, with several studies using the French network of cancer registries (FRANCIM) or the Eindhoven registry as the data source. By contrast, studies conducted in countries such as Italy, New Zealand, and the United Kingdom relied more heavily on hospital data sources that were comprised of either single or multiple institutions. Studies from other countries had mixed data sources that ranged from national health insurance commissions for pharmaceuticals to single institutions to registries in a particular geographic region or area.

Initial Treatment

Surgery. Forty-six articles included in the review reported rates of surgical treatment and spanned several countries (Table 3), including France (19.6%), the United Kingdom (19.6%), Australia (15.2%), and the Netherlands (15.2%). Among studies that were not exclusively limited to patients undergoing surgery, rates of resection varied from 54% to 85% (36,57) depending upon cancer site, stage, patient age, disease stage, and study time period. One study was conducted as a European collaboration comparing rates of resection with curative intent across eight European countries (28) and found significant variation of resection rates by country, ranging from 44% in Kielce (Poland) to 86% in Genoa (Italy).

Table 1. Characteristics of colorectal cancer care studies from Europe, Australia, and New Zealand (n = 66)

Characteristics	No. of studies	Percentage of studies
Study publication year		
2000–2003	16	24.2
2004–2007	35	53.0
2008–2010	15	22.7
Tumor site reported (not mutually exclusive)*		
Colon	29	43.9
Rectum	45	68.2
Colorectal (combined)	11	16.7
Type of care measured		
Initial treatment only	58	87.9
Initial treatment + post-diagnostic surveillance	5	7.6
Post-diagnostic surveillance only	2	3.0
End of life	1	1.5
Component(s) of care reported (not mutually exclusive)*		
Initial care		
Surgery	46	69.7
Radiation	32	48.5
Chemotherapy	34	51.5
Multicomponent	11	16.7
Post-diagnostic surveillance	7	10.6
End-of-life care	1	1.5
Cancer patient identification/data source		
Registry	20	30.3
Medical records/hospital data	21	31.8
Registry + medical records/hospital data	9	13.6
Registry + physician survey	8	12.1
Other	5	7.6
Not reported	3	4.5
Study design		
Retrospective cohort	54	81.8
Prospective cohort	10	15.2
Cross-sectional	2	3.0
Lower-bound year of diagnosis		
Prior to 1990	11	16.7
1990–1999	28	42.4
2000 and later	8	12.1
Not reported	19	28.8
Age distribution		
Mean/median age <65	9	13.6
Mean/median age >65+	49	74.2
Not reported	8	12.1
Number of cancer patients		
<500	16	24.2
500–999	15	22.7
1000–4999	20	30.3
5000–9999	5	7.6
10 000+	10	15.2

* Exceeds 100% because some studies counted in more than one category; percentages for components of care and cancer site were derived by dividing reported number of studies by total number of studies (n = 66); several articles examined both colon and rectal cancers separately; therefore, these studies were counted twice when reporting site of cancer.

Most studies reported trends in rates of surgery over time and described variation in rates by patient characteristics (ie, age, gender, socioeconomic status, disease severity, comorbidities), hospital setting or volume, and geographical location. Several studies reported increasing or stable rates of surgery for both colon and rectal cancers over time (27,30,32,36,66,68,79). However, three studies contrasted decreasing trends for abdominoperineal resection (APR) with increasing trends sphincter-sparing surgery (27,83,86). Additionally, a small number of studies compared trends over time to the implementation of guidelines or national consensus statements (32,46,49,52,66,74).

With respect to patient characteristics, several studies found that younger patients were more likely to receive resections (28,30,37,45,55,66,72,78,79). However, other studies indicated mixed findings for rates of surgical treatment by patient age depending upon type of surgery, time period, and disease severity (26,31,79). Studies also reported mixed findings regarding the association of female gender with the likelihood of receiving surgical treatment (31,38,55,84). Although many studies did not report information on patient socioeconomic status, two UK studies found that patients with lower socioeconomic status were less likely to receive surgical treatment (31,38). Additionally, several studies noted that patients

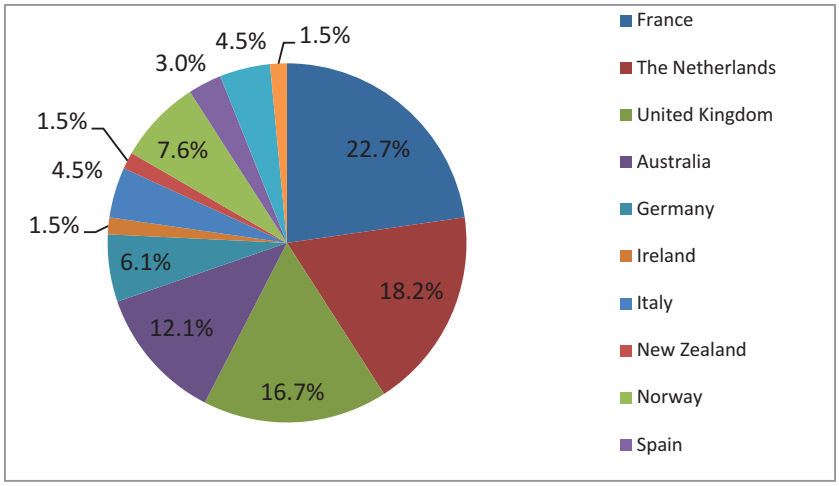

Figure 1. Percentage of studies by country.

with metastatic tumors and comorbidities were often less likely to receive surgical treatment for colorectal cancer (45,55,66,79).

Variation in rates of surgical treatment was also observed by hospital setting and patient volume for several studies. Presentation to the emergency room was associated with a lower likelihood of receiving resections (31,38,45,84). Hospital type, such as private vs public hospital, was associated with variations in surgical treatment patterns (55,59,76). Additionally, higher hospital volume was associated with lower rates of APR in two studies (42,85). A number of studies also highlighted regional variation in rates of surgery for both colon and rectal cancers (57,63,69,79). Although the majority of studies did not report urban/rural residence, two studies found that individuals living in urban areas were more likely to receive surgery (57,79).

Radiation treatment. The majority of the 32 total studies reporting on patterns of RT were conducted in the Netherlands (25.0%), France (21.9%), Australia (12.5%), Norway (9.4%), and the United Kingdom (9.4%) (Table 4). Rates of overall RT use varied widely, ranging from 1% to 75% in studies reviewed, depending upon patient age, stage of disease, and study time period (57,81). Studies typically reported increasing or stable rates of RT over time; for instance, one study conducted in the Netherlands found a 16% increase over the study period, with 47% receiving RT in 1998–2002 and 63% receiving RT in 2003–2006 (34). Several studies noted the declining rates of postoperative RT balanced by increasing rates of preoperative RT as a general trend over time (27,30,34,43,57,68,73,83,88). This trend was seen for patients of all age groups, although multiple studies indicated that older patients were less likely to receive either pre- or postoperative RT overall (26,28,30,34,48,78,88).

Some studies indicated that later stage of diagnosis and tumor status were significant predictors of RT use, with sicker patients being more likely to have RT administered (26,48,60,78,88). Two studies found that female patients were less likely to receive preoperative RT (26,35). Variation in RT use by hospital setting, hospital volume, and surgery type was also reported by several studies (26,34,48,51,72,88). Lastly, some studies reported regional variation in RT rates (26,28).

Chemotherapy. Thirty-four studies reported patterns of chemotherapy use for colorectal cancer, and these were most commonly conducted in France (35.3%), Australia (17.6%), the Netherlands (17.6%), and the United Kingdom (8.8%) (Table 5). Overall, chemotherapy use varied substantially between studies, ranging from 0% to 95%, depending upon stage, patient age, and study time period (52,73). The single study making national comparisons between European countries found wide variation by cancer registry, ranging from 24% in Krakow to 73% in Slovakia (28).

Many studies noted increasing trends of chemotherapy use over time, particularly toward the later part of the 1990s (30,44,54,64,66,68,73,79,82). Several studies also indicated that younger patients were more likely to receive chemotherapy compared with older patients, though some highlighted rising rates of chemotherapy use among the elderly over time (28–30,40,46,47,60,61,66,68,69,78,79). Additionally, more advanced tumor stage greatly increased the likelihood of chemotherapy receipt (30,40,49,50,54,61,63–66,68,73,78,79).

Although studies exhibited inconsistent reporting of comorbidities, two studies found that patients with previous malignancies or chronic obstructive pulmonary disease were less likely to receive chemotherapy (60,61). Chemotherapy receipt was less likely among both women and patients with lower socioeconomic status in one study (61). Several studies also highlighted variation in chemotherapy rates by hospital setting (eg, general vs university; private vs public), hospital volume, and emergency room admissions (29,40,54,61,68,77).

Multicomponent care. Out of the 11 studies reporting on patterns of multicomponent care, four were conducted in the Netherlands, three in Germany, and the remaining in Australia, Italy, the United Kingdom, and Norway (Table 6). Studies exhibited variation in stage, patient age, and date of diagnosis. Sources of data varied, though data were most commonly from registries (63.6%) (26,30,37,60,65,73,81). Most studies reported on treatment that combined chemotherapy and radiation, such as chemoradiation or neoadjuvant RT combined with chemotherapy. Predominant findings included higher rates of therapy use over

Table 2. Characteristics of selected data sources for measuring patterns of colorectal cancer care in Europe, Australia, and New Zealand*

				Information about cancer patients		Health services reported		
Country	**Data source**	**Type of data**	**Population coverage**	**Date of diagnosis**	**Stage at diagnosis**	**Surgery**	**Chemotherapy**	**Radiation**
Australia	Multiple hospitals	Hospital records	Four hospitals in Western Australia; 1.8–2 million	√	√	√		
	Victoria Cancer Registry	Registry	State in southeast Australia	√		√		
	Health Insurance Commission through PBS	Insurance claims for pharmaceuticals	National				√	
France	Burgundy Registry of Digestive Cancers	Registry, physician survey	Region	√	√	√	√	√
	Calvados Registry of Gastrointestinal Tumors	Registry	Administrative district in north of France	√	√	√	√	
	FRANCIM	Registry, hospital data, physician survey	10% of French population in eight administrative areas	√		√	√	
	Multiple hospitals	Medical records	81 hospitals	Date of surgery	√	√	√	
Germany	Multiple hospitals	Hospital databases/medical records	75 hospitals in five states: Bradenburg, Saxony, Saxony-Anhalt, Thuringia, Mecklenberg-West Pomerania	Hospital admission date		√		
	Munich Cancer Registry	Registry	Individuals residing in Munich region, approximately 2.3 million	√	√		√	√
Ireland	National Cancer Registry	Registry	NCR records all cancers diagnosed in Ireland and has 98% completeness of registration	√	√	√	√	√
Italy	University of Milan, San Raffaele Hospital	Hospital data	Single hospital in Milan	Date of treatment	√			
	Oncology centers	Forms completed by treating oncologist	86 Italian oncology centers	NR			√	√
The Netherlands	Netherlands Cancer Registry–National Registry of Hospital Discharges	Cancer registry, national registry of hospital discharge diagnoses, hematology departments and radiotherapy institutions	All malignancies in the Netherlands	√	√	√	√	√
	Eindhoven Cancer Registry	Cancer registry notified by pathology departments, hospital records, and radiotherapy institutes	All malignancies in southern part of the Netherlands, approximately 2.4 million	√	√	√	√	√
	Dutch National Medical Registry	Hospital discharge	All hospitalized patients in the Netherlands	Date of surgery		√		
New Zealand	Christchurch Hospital	Hospital patient notes	Single hospital in Canterbury region	√	√	√	√	

(Table continues)

Table 2 (Continued).

Country	Data source	Type of data	Population coverage	Information about cancer patients		Health services reported		
				Date of diagnosis	Stage at diagnosis	Surgery	Chemotherapy	Radiation
Norway	Aker Hospital linked to registry	Hospital data, registry	Single hospital in Oslo catchment of 180 000	Hospital admission	√	√		√
	Norwegian Rectal Cancer Project	Registry, medical records, patient administrative data	Rectal cancer treated with curative intent in one of 47 hospitals	√	√	√		
Spain	Clinico Universitario of Valencia	Registry	Valencia hospital catchment of 275 000	√	√	√		
Sweden	National Quality Registry for Rectal Adenocarcinoma	Registry	97% of all rectal patients in Sweden since 1995			√		√
	Uppsala/Orebro registries	Registry	Uppsala/Orebro	√		√		
	Multiple hospitals	Medical records	County of Vastmanland, five hospitals	Date of surgery				√
United Kingdom	NHS HES dataset	Hospital discharge	All NHS hospitals	Date of surgery				
	NORCCAG; Newcastle and North Tyneside, Northumberland, Gateshead, South Shields, Sunderland, Teesside, County Durham, Cumbria, and part of North Yorkshire	Hospital data	All hospitals in northern region of England, population 3.1 million			√		
	Hospital	Hospital data	Single hospital, Leeds, England	Date of surgery		√	√	√
	Scottish registry linked to hospital data	Registry, hospital inpatient and day case form data	All hospitals in Scotland	√	√		√	
European collaboration	Cancer registries from the following regions: Genoa and Varese (Italy); Côte-d'Or (France); Granada, Navarra, and Tarragona (Spain); Tampere (Finland); Estonia; Slovenia; Slovakia; and Krakow and Kielce (Poland)	Registry data	Each cancer registry provides detailed information on diagnostic and treatment procedures, obtained from clinical records	√	√	√	√	√

* FRANCIM = French network of cancer registries; NCR = National Cancer Registry; NHS HES = National Health Service Hospital Episode Statistics; NORCCAG = Northern Region Colorectal Cancer Audit Group; NR = not reported; PBS = Pharmaceutical Benefits Scheme.

Table 3. Patterns of care for the initial surgical treatment of colorectal cancer (CRC) in Europe, Australia, and New Zealand by cancer site, publication year, and country (n = 46)*

	First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to initial surgical treatment
Colon	Lepage, 2006 (49)	France	All stages	2000	567	Mean at diagnosis 70	Burgundy Registry of Digestive Cancers	74.4% curative resection, 15% palliative resection; 3.9% exploratory laparotomy or bypass
	Morris, 2007 (44)	Australia	Stage II	1993–2003	812	Mean 64.9	Four hospitals in Western Australia covering 1.8–2 million people; pathology reports	82% of the sample received surgery alone
	Silvera, 2006 (50)	France	All stages	Hospitalized or surgery 2001–2002	1842	18+; mean 68.7	French health insurance database; patients in Paris metropolitan area; surveys of medical advisers	96.6% had surgery; 89.7% laparotomy; LAP used for 5.9% of operated patients, with conversion to laparotomy for 34%
	Phelip, 2005 (63)	France	All stages	1995	1605	75+	FRANCIM and survey given to specialists	Primary tumor resection in 89.6%, ranging from 87.9% to 92.9% by region
	Faivre-Finn, 2002 (79)	France	All stages	1976–1998	3389	NR	Côte d' Or, Burgundy registry; hospital data, physician surveys among specialists and GPs	85.2% had resection, rising from 69.3% (1976–1979) to 91.9% (1988–1991) then stable; rates increased among elderly over time (56.4% vs 90.5%); curative resections rose from 56.6% to 81.0%; in multivariate results, younger age, urban residence, non-MET tumor status, and later diagnosis associated with resection
Rectum	Elferink, 2010 (26)	The Netherlands	Non-MET 77.8%; MET 17.4%; NR 4.8%	2001–2006	16 039	<60: 26.2%; 60–74: 43.4%; 75+: 30.3%	Netherlands Cancer Registry	Patients <75 y and diagnosed with T1-M0 tumors who underwent POL or TEM was 34% vs 43% in 75+; more patients <75 y with an M1 tumor had surgical resection of primary tumor vs 75+ (44% vs 31%)
	Elferink, 2010 (30)	The Netherlands	All stages	1989–2006	40 888	≤44: 4%; 45–59: 22%; 60–74: 43%; ≥75: 32%	Netherlands Cancer Registry	Among patients <75 y with stages I–III, resections remained stable from 1989 to 2006, but decreased in elderly from 91% (1989–1993) to 81% (2004–2006); among stage IV patients, younger patients had metastasectomy more frequently
	Khani, 2010 (27)	Sweden	All stages	Surgery 1993–1996; 1996–1999	277	Period 1 median 70; period 2 median 69	County of Vastmanland; four district hospitals' (period 1) or central county hospital's (period 2) medical records	In period 1, 38% of patients had AR, 8% LAR, 38% APR, and 16% other surgical procedures; in period 2, 3% had AR, 55% LAR, 18% APR, and 24% other procedures
	Marwan, 2010 (25)	Australia	All stages	2005	582	<59: 32.3%; 60–69: 27.3%; 70+:	Victorian Cancer Registry	23.4% had APR; 53.2% AR; 1.2% total proctocolectomy; 0.2% TEM; and 23% ULAR

(Table continues)

Table 3 (Continued).

First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to initial surgical treatment
Raine, 2010 (31)	United Kingdom	NR	Admitted 1998–2006	29 214	≥50	Inpatient treatment HES dataset	71.9% of patients with surgery had AR; in adjusted analyses, AR more common in women, elderly, higher SES, ER admissions, and in more recent years
Ferenschild, 2009 (33)	The Netherlands	All stages	1996–2003	210	Mean 69	Medical charts, including hospital notes, radiotherapy plans, and pathology reports	LAR in 69% and APR in 31%
Martling, 2009 (35)	Sweden	All stages	1995–2002	11 774	Median women 73; men 71	National Quality Registry included patient data, adjuvant treatment, surgery	86.4% had surgical resection; 52.7% AR; 26.9% APR; 10.3% HP; 10.1% other procedures
Sigurdsson, 2009 (37)	Norway	NR	1997–2002	297	Median 77; range 67–84	Norwegian Colorectal Cancer Registry	64% had noncurative surgery, younger patients more likely; in resected patients, 48% major resections, 48% stomas, and 4% local procedures or surgical explorations
Tilney, 2008 (38)	United Kingdom	NR	Admitted 1996–2004	52 643	NR	England; inpatient treatment in HES dataset	24.9% had APR, which decreased from 29.4% to 21.2% over time; in adjusted analyses, APR less likely among older age, female, higher SES, and ER presentation patients
Ptok, 2007 (42)	Germany	Stages I–III	Entered study 2000–2001	1557	Median 66; range 26–92	Multisite observational study, data collected from patients, hospital data	APR rate significantly associated with hospital volume
Phelip, 2004 (66)	France	All stages	1990 and 1995	945	Stratified as <75 and >75	FRANCIM; survey given specialists and GPs	The proportion with resection increased from 84.6% in 1990 to 91.9% in 1995; patients 75+ and with VM less likely to have surgery; the proportion of TE increased over time (3.2% to 13.2%)
Phelip, 2004 (69)	France	All stages	1995	683	≥75: 38.8%	Nine FRANCIM registries; health services data from survey given to gastroenterologists, oncologists, and surgeons	88.4% had resection; age and distant metastases independently associated with resection; 14.2% of patients had resection without laparotomy, which varied across districts; 36.1% of resected patients had a stoma
Wibe, 2004 (72)	Norway	Stages I–III	Surgery 1993–1999	2136	Median 69 (range 18–94)	Norwegian Rectal Cancer Project; hospital databases/ project-specific forms from the Rectal Cancer Registry	62% of patients had AR, 38% APR; younger patients had AR more often than older patients; individuals with T4 tumors more likely to receive APR

(Table continues)

Table 3 (Continued).

First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to initial surgical treatment
Engel, 2003 (76)	The Netherlands	NR	Surgery 1994–1999	15 978	Peripheral mean 64.9; university 56.6	Dutch National Medical Registry	Of all rectal resections, 16% were APRs, 84% were RRs; the proportion of APRs decreased from 0.19 to 0.13; the ratio of APR to total resectional rectal surgery (APR plus RR) declined in peripheral hospitals, but not university
Martijn, 2003 (73)	The Netherlands	All stages	1980–2000	3635	<60: 26.3%; 60–74: 47%; 75+: 26.7%	Eindhoven Cancer Registry	53% had surgery only; treatment with surgery alone decreased from 62% to 42% (1980–2000); surgery + radiotherapy increased (26% vs 40%)
Birbeck, 2002 (80)	United Kingdom	NR	Surgery 1986–1997	586	Median 69.6; range 27.9–96.6	Leeds, United Kingdom; hospital data, case notes from patients with full clinical follow-up	83.3% of surgeries curative resections; 16.7% palliative
Farmer, 2002 (81)	Australia	Dukes A-C	1994	681	NR	Victoria Cancer Registry; physician survey completed for each patient	Restorative AR most common procedure (63.3%); other procedures were APR (23.5%) and local excision (5.0%)
Nesbakken, 2002 (83)	Norway	Dukes A-C	Admitted 1983–1999	312	First period mean 72 (range 27–97); second period mean 73 (range 19–95)	Single institution: Aker Hospital in Oslo, Norway; hospital records, pathology reports, and Cancer Registry	In period 1 (1983–1992), 56.5% had curative resection; 58% LAR, 1% HP, and 42% APR; in period 2 (1993–1999), 55.1% had curative resection using ME 67% LAR, 5% HP, and 28% APR; in period 1, 0 patients had either total or partial ME vs 66% TME and 34% PME in period 2
García-Granero, 2001 (86)	Spain	Dukes A-C; TNM I–III	1986–1995	Total 202	Median 1: 66 (31,88); median 2: 67 (31,85)	Hospital Clinico Universitario of Valencia Health services data from registry (ie, clinical, operative, pathological, and follow-up data)	Period 1 TE was 1.06 vs 2.7 in period 2; radical resectability 67.7 vs. 82.4; APR/overall 25.8 vs 16.7; APR/LAR 54.2 vs 30.5
Marusch, 2001 (85)	Germany	NR	Presented and admitted 1999	1463	NR	Hospital databases/medical records; patients in states of Bradenburg, Saxony, Saxony-Anhalt, Thuringia, and Mecklenberg-West Pomerania	75 hospitals categorized into three annual rectal surgery volume groups: <20 patients/y (n = 44); 20–40 (n = 22); >40 (n = 9); hospitals treating >40 patients/y have lower APR rate vs lower volume hospitals

(Table continues)

Table 3 (Continued).

	First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to initial surgical treatment
	Gatta, 2010 (28)	European collaborative study	NR	1996–1998	6871	≥75: 3.6%; <75: 66.4%	European cancer registries	71% treated with curative intent, ranging from 44% in Kielce to 86% in Genoa; proportion treated decreased with advancing age at diagnosis from 76% in patients under 65 y, 73% in 65 to 74, and 63% in patients of 75 and over ($P < .001$)
CRC	Green, 2009 (32)	United Kingdom	NR	Hospitalizations 1997–2007	182 191	NR	England; inpatient treatment in HES dataset	LAP procedures increased from <1% of all surgeries to approximately 8% over time; in 2000, NICE recommended against LAP surgery, but recommended it in 2006; between 2003–2004 and 2007, LAP surgery increased 2.04% annually
	Kube, 2009 (36)	Germany	All stages	Resections 2000–2005	346 hospitals; 47 436 patients	NR	Hospital data; standardized questionnaire completed at hospital; follow-up survey filled out by patient's doctor or hospital	Rates of curative resection ranged from 80% to 83% for colon and were nearly 85% for rectal cancer
	Carsin, 2008 (90)	Ireland	All stages	1994–2002	15 249	Patients ≥20	National Cancer Registry	78% resection; almost all stage I–III had surgery, 51% of stage IV; among stage IV patients, resection less common in older, unmarried, and male patients in multivariate results
	Borowski, 2007 (45)	United Kingdom	All stages	Admitted 1998 and 2002	8219	<65: 28.8%; 65–74: 35.7%; 75–84: 29.2%; >84: 6.3%	NORCCAG; hospital data, histopathology records	93.8% had resections, including 96.0% of colon and 91.3% rectal tumors; 74·6% had curative resections; older age, comorbidity, ER surgery and rectal cancer associated with nonresection
	Young, 2007 (46)	Australia	All stages	February 2000–January 2001	2984	<60: 22.4%; 60–69: 26.26%; 70–79: 33.3%; ≥80: 17.7%	New South Wales; surgeon questionnaire, cancer registry	Of LAR or ultra-LAR patients, 29.1% had a colonic pouch reconstruction
	Lemmens, 2006 (52)	The Netherlands	NR	2002	308	Colon: mean 70, range 41–91; rectal: mean 64, range 33–86	Eindhoven Cancer Registry	55% had LAR; 37% AR; 5% HP; 95% of colon cancer patients had radical surgical treatment; of those with resectable tumors, 89% had curative resection; 20.6% had urgent surgery

(Table continues)

Table 3 (Continued).

First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to initial surgical treatment
Bouvier, 2005 (57)	France	All stages	1978–1997	2409	80+ at diagnosis	Calvados and Côte-d'Or registries	69% of colon, 54% of rectal cancer patients had curative resection, increasing for all sites over time; patients in urban/periurban areas more likely to have resections
Dejardin, 2005 (59)	France	Non-MET 78%; MET 18%; NR 4%	1995	1413	<65: 30%; 65–74: 35%; 75–84: 25%; >84: 10%; NR: 0.2%	Six FRANCIM registries	22.6% treated for initial surgery in reference center site (ie, university or regional comprehensive cancer centers); women less likely to be treated in reference cancer center and less likely to go reference cancer site for surgery, as travel distance increased
Hall, 2005 (55)	Australia	NR	1982–2001	14 587	<60: 26.6%, ≥60: 73.4%	Western Australia data linkage system; diagnostic codes and registry used to identify patients	85.5% had a surgical procedure; 41% of these had AR and 59% HEM; in adjusted results, surgery receipt associated with private insurance, private hospital status, younger age, female, and less comorbidity
Lemmens, 2005 (60)	The Netherlands	All stages	1995–2001	6931	50+; mean 70	Eindhoven Cancer Registry	TME performed in 20.1% of stage I–II rectal cancer patients and 28.0% of stage III; most patients with stage IV rectal cancer received palliative therapy alone
Robinson, 2005 (64)	New Zealand	All stages; Dukes	1993–1994 and 1998–1999	673	Median 71–90; 51–70	Christchurch Hospital; oncology service or hospital discharge codes, patient notes	Surgery by consultant increased from 44% to 82% over the study period
Barton, 2004 (67)	Australia	All stages	1994–1996	370	Median 68; range 22–98	Cancer registry and hospital databases; Western Sydney and Wentworth Health Areas	80.1% had surgery
Bouhier, 2004 (68)	France	All stages	1990–1999	3135	Mean 70	Calvados Registry	90.9% had resections, including 8.8% endoscopic procedures; rate stable over 10-y study period
Jestin, 2004 (70)	Sweden	All stages	1995–2000 rectal; 1997–2000 colon	3612	Mean: colon 72; rectal 71	Uppsala/Orebro region rectal and colon cancer registries	Colon: 45.2% had rightsided HEM, 10.3% had leftsided HEM, 24.7% sigmoid resection, 6.7% AR, 5.5% HP, 3.3% surgery without resection; rectal: 50.9% had LAR, 24.7% had APR, 1.2% HP, 3.3% surgery without resection

(Table continues)

Table 3 (Continued).

First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to initial surgical treatment
McGrath, 2004 (71)	Australia	All stages	February 1–April 30, 2000	1911	Mean 68; median 70; range 16–100	All newly reported cases to any state cancer registry in Australia; physician survey	All patients had surgery, most with curative intent (81.8%); laparoscopic approach in 2.9%; AR most common procedure (35.7%); among rectal cancer patients, TME in 64.6%
Duxbury, 2003 (74)	United Kingdom	NR	Surgery 1999–2000	211	NR	Derriford Hospital, Plymouth, Devon, United Kingdom; consecutive patients undergoing surgery at single hospital	Initially, CRC surgeons more likely to have guideline-consistent practice vs non-CRC surgeon (rectal 55% vs 3%; colon 42% vs 22%); following audits, guideline consistency improved (rectal 90% vs. 0%; colon 78% vs 38%) and fewer procedures by non-CRC surgeon
McFall, 2003 (75)	United Kingdom	NR	Surgery 1990–1996	892	NR	Worthing Hospital, United Kingdom; hospital data and medical records	88% of patients Dukes stage A–C had resection
Campbell, 2002 (78)	United Kingdom	All stages	1995 and 1996	653	≤59: 121 (19%); 60–69: 159 (24%); 70–79: 216 (33%); ≥80: 157 (24%)	Scotland cancer registry; hospitals in Grampian or Highland with case notes and clinical data abstracted	91% had surgery within 1 y of diagnosis; increased stage and increasing age associated with greater likelihood of surgery
McArdle, 2002 (84)	United Kingdom	Dukes A/B	1974–1979; 1991–1994	3200	75+: 35%	Glasgow Royal Infirmary; data from medical records/audits	70% had curative resection; 30% had palliative surgery; females more likely to have curative resection; ER patients less likely to have resection; overall resection higher in later study period
Chiappa, 2001 (87)	Italy	All stages; modified Dukes	Treated 1992–1999	346	Mean 66 (range 23–92)	Single institution; Department of Emergency Surgery, University of Milan, San Raffaele Hospital	74% of patients had curative resections

* AR = anterior resection; APR = abdominoperineal resection; ER = emergency room; FRANCIM = French network of cancer registries; GP = general practitioner; HEM = hemicolectomy; HES = hospital episode statistics; HP = Hartmann's procedure; LAR = lower anterior resection; LAP = laparoscopy; ME = mesorectal excision; MET = metastatic; NICE = National Institute for Health and Clinical Excellence; NORCCAG = Northern Region Colorectal Cancer Audit Group; NR = not reported; POL = polypectomy; RR = rectal resections; SES = socioeconomic status; TE = transanal excisions; TEM = Transanal Endoscopic Microsurgery; ULAR = ultralow anterior resection; VM = visceral metastasis.

Table 4. Patterns of radiation treatment for colorectal cancer (CRC) in Europe, Australia, and New Zealand by cancer site, publication year, and country (n = 32)*

	First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to radiation treatment
Rectum	Elferink, 2010 (26)	The Netherlands	Non-MET 77.8%;MET 17.4%; Unknown 4.8%	2001–2006	16 039	<60: 26.2%; 60–74: 43.4%; 75+: 30.3%	Netherlands Cancer Registry	In multivariate analyses, female and older patients and those with lower stage treated at teaching/university hospitals and lower-volume hospitals less likely to have preoperative RT; regional variation also observed
	Elferink, 2010 (30)	The Netherlands	All stages	1989– 2006	40 888	≤44: 4%; 45–59: 22%; 60–74: 43%; ≥75: 32%	Netherlands Cancer Registry	Stages II–III patients receiving preoperative RT increased from 1% in 1989–1999 to 68% in 2004–2006 among younger patients and from 1% to 51% among older patients; among stage II–III patients, postoperative RT decreased from 46% to 4% for younger patients and from 23% to 3% for elderly
	Khani, 2010 (27)	Sweden	All stages	Surgery 1993–1996; 1996–1999	277	Period 1: median 70, range 30–93; period 2: median 69, range 40–91	County of Vastmanland; four district hospitals (period 1) or in central county hospital (period 2); medical records	41% of patients in period 1 received preoperative RT and 49% in period 2
	Ferenschild, 2009 (33)	The Netherlands	All stages	1996–2003	210	Mean 69; range 40–91	Medical charts, including hospital, radiotherapy, and operation notes	Almost 25% of patients received preoperative RT
	Martling, 2009 (35)	Sweden	All stages	1995–2002	11 774	Median 73, range 23–99 (women); median 71, range 21–95 (men)	National Quality Registry included patient data, adjuvant treatment, surgery	46.5% received preoperative RT; women were less likely to receive than men (42.5% vs 50.1%)
	Vulto, 2009 (34)	The Netherlands	NR	1988–2006	7767	All ages; distribution; for rectal cancer patients, NR	Eindhoven Cancer Registry	RT receipt increased from 47% to 63% (1998–2002 vs 2003–2006); postoperative RT use decreased; in 2004, 50% of all patients received preoperative RT; patients >75 had lower rates of RT vs middle-aged patients; geographic variation and large interhospital variation present
	Hansen, 2007 (48)	Norway	All stages	Surgery 1993–2001	4113	<50: 3.01%; 50–64: 25.7%; 65–74: 33.4%; 75–84: 30.5%; ≥85: 0.63%	50 hospitals; six of these had RT departments	12.5% received RT (6.9% preoperative and 5.6% postoperative); RT rate with younger age and tumor level; patients who had APR or HP received RT three times more often vs those who had AR; total RT rate increased from 4.6% in 1994 to 23.0% in 2001; preoperative RT use higher for those treated in local hospital with RT department
	Vulto, 2007 (89)	The Netherlands	All stages	1996–2002	—	<70: 55.6%; 70+: 44.4%	Eindhoven Cancer Registry	46% of all newly diagnosed patients received RT; 10% received SRT at least once; multivariate analyses showed patients with stage III had SRT more often and patients in the eastern department received PRT more often

(Table continues)

Table 4 (Continued).

First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to radiation treatment
Ng, 2006 (51)	United Kingdom	All stages	1995–1999	207	All ages	Patients from Royal Berkshire Hospital, Reading, England; data sources NR	36.2% receiving surgery also received RT; preoperative RT more likely among patients treated by CRC surgeon
Engel, 2005 (65)	Germany	All stages	1996–1998	882	<70: 62.5%; 70+: 37.4%	Munich Cancer Registry and Munich Field Study	In both UICC II–III patients, 3.5% received RT alone
Vulto, 2006 (53)	The Netherlands	NR	1988– 2002	2836	NR	Eindhoven Cancer Registry	The proportion with RT increased over time (33% to 43%)
Phelip, 2004 (69)	France	All stages	1995	683	≥75: 38.8%	Nine FRANCIM registries; survey of specialists and GPs	Among resected patients, 46.8% had RT
Phelip, 2004 (66)	France	All stages	1990 and 1995	945	Stratified as <75 and >75	FRANCIM; survey of specialists and GPs	42% of patients in 1990 and 47% in 1995 received adjuvant RT; palliative RT receipt more likely among <75
Wibe, 2004 (72)	Norway	Stages I–III	Surgery 1993– 1999	2136	Median 69, range 18–94	Norwegian Rectal Cancer Project; hospital databases/project-specific forms from the Rectal Cancer Registry	RT given to 10%; 6% preoperatively and 4% postoperatively; RT used more often in APR vs AR group (16% vs 6%)
Martijn, 2003 (73)	The Netherlands	All stages	1980– 2000	3635	<60: 26.3%; 60–74: 47%; 75+: 26.7%	Eindhoven Cancer Registry	Postoperative RT decreased from 2005 to 2010, whereas preoperative RT increased for all tumor stages and all ages; from 1980 to 1989, 25% had postoperative RT and 1% had preoperative RT; by 1995–2000, 4% had postoperative RT vs 35% preoperative RT
Birbeck, 2002 (80)	United Kingdom	NR	Surgery 1986–1997	586	Median 69.6; range 27.9–96.6	Leeds, United Kingdom; hospital data and case notes from patients with full clinical follow-up	4.3% received preoperative RT
Farmer, 2002 (81)	Australia	Dukes A-C	1994	681	NR	Victoria Cancer Registry; physician questionnaire for each patient	Among 153 patients with completed RT survey, 74.5% had RT as adjunct to surgical resection, and of these, 4.4% had preoperative RT vs 95.6% postoperative RT
Nesbakken, 2002 (83)	Norway	Dukes A-C	Admitted 1983–1999	312	Period 1: mean 72, range 27–97; period 2: mean 73, range 19–95	Single institution: Aker Hospital in Oslo, Norway; hospital records, pathology reports, Cancer Registry	2% received pre- or post-RT in period 1, whereas 13% received pre- or post-RT in period 2

(Table continues)

Table 4 (Continued).

	First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to radiation treatment
	Faivre-Finn, 2000 (88)	France	Stage I–III	1976–1996	651	<65: 22.8%; 65–74: 39.4%; 75+: 37.7%	Cancer registry in Côte d'Or, Burgundy; registry provided both patient and health services data	Overall, adjuvant RT given to 37.3% of resected patients; percent of treated patients increased from 14.3% in 1976–1978 to 61.7% in 1994–1996; preoperative RT increased over time, postoperative RT following surgery increased with higher stage; in multivariate results, later period of diagnosis, younger age, surgery type, and hospital type (university vs private) associated with adjuvant RT
CRC	Gatta, 2010 (28)	European Collaborative Study	NR	1996–1998	6871	≥75: 33.6%; <75: 66.4%		Only 12% of stage I–III rectal cancer patients received RT; geographical variation in RT use in multivariate results indicated that patients aged ≥75 were less likely to receive RT than <75 age group
	Carsin, 2008 (90)	Ireland	All stages	1994–2002	15 249	≥20	National Cancer Registry	13% RT (4% colon; 28% rectum); increased by 10% per year; notable increase in preoperative RT after 2000; for all stages, RT decreased with increasing age; women with stage II disease less likely to get RT; tumor extent associated with RT among stage II and unknown stage patients; preoperative RT use less frequent among female patients and decreased with age
	Coriat, 2007 (41)	France	All stages	1998	407	Median 72, range 26–93	Burgundy Registry of GI Cancers	43% with a rectal localization received postoperative RT
	Mahboubi, 2007 (49)	France	All stages	1998	389	<65: 26.5%; 65–74: 34.2%; ≥75: 39.3%	Côte-d'Or and Saone-et-Loire registries, Burgundy; medical records, specialists and GP survey	Overall, 14.9% had RT
	Young, 2007 (46)	Australia	All stages	February 2000–January 2001	2984	<60: 22.4%; 60–69: 26.3%; 70–79: 33.3%, ≥80: 17.7%	New South Wales Cancer registry; treating surgeon surveys	Of high-risk rectal cancer patients, 59.8% were offered RT
	Bouvier, 2005 (57)	France	All stages	1978–1997	2409	80+ at diagnosis	Calvados and Côte-d'Or registries	1% of colon cancer cases and 17% of rectum cases received RT; RT use increased over time
	Drug Utilization Review Team in Oncology, 2005 (54)	Italy	NR	Past/current diagnosis October 2000	434	≤50: 15.2%; 51–60: 25.3%; 61–70: 36.6%; >70: 21.0%	86 Italian oncology centers; forms completed by treating oncologist	Only seven patients with colon cancer received RT; 61% of rectal cancer patients received adjuvant RT

(Table continues)

Table 4 (Continued).

First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to radiation treatment
Gonzalez, 2005 (58)	Spain	All stages	1996–1998	403	Mean 65.4 (men), 63.8 (women)	Hospital Universitario de Bellvitge in Barcelona, Spain	18.8% of men and 20.7% of women had RT
Lemmens, 2005 (60)	The Netherlands	All stages	1995–2001	6931	50+; mean 70	Eindhoven Cancer Registry	Comorbidity influenced adjuvant RT in patients with rectal cancer
Barton, 2004 (67)	Australia	All stages	1994–1996	370	Median 68; range 22–98	Western Sydney and Wentworth Health Areas; cancer registry and hospital databases	6.25% had RT
Bouhier, 2004 (68)	France	All stages	1990–1999	3135	Mean 70	Calvados Registry	53.1% of stage II–III rectal cancers had; preoperative RT given to 90% of these; older patients (≥75 vs <75) less likely to receive RT
McGrath, 2004 (71)	Australia	All stages	All newly reported cases 2000	1911	Mean 68, median 70, range 16–100	All newly reported cases to any state cancer registry in Australia; physician survey	Of 61 rectal cancer surgeries with local invasion, 86.9% offered RT; 65.6% given preoperative RT; among locally advanced patients who did not have surgery, 76.3% offered RT
Campbell, 2002 (78)	United Kingdom	All stages	1995 and 1996	653	≤59: 19%; 60–69: 24%; 70–79: 33%; ≥80: 24%	Scotland cancer registry; hospitals in Grampian or Highland; case notes and clinical data abstracted	13% had RT within 1 y of diagnosis; higher stage and younger stage associated with RT receipt; RT use for colorectal cancer decreased with increasing distance from cancer center

* AR = anterior resection; APR = abdominoperineal resection; ER = emergency room; FRANCIM = French network of cancer registries; GI = gastrointestinal; GP = general practitioner; HP = Hartmann's procedure; MET = metastatic; NR = not reported; PRT = primary radiotherapy; RT = radiotherapy; SRT = secondary radiotherapy; UICC = Union International Cancer Control.

Table 5. Patterns of chemotherapy treatment for colorectal cancer (CRC) in Europe, Australia, and New Zealand by cancer site, publication year, and country (n = 34)*

	First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to chemotherapy treatment
Colon	van Steenbergen, 2010 (29)	The Netherlands	Stage III	NR	1637	<65: 514; 65–74: 539; ≥75: 584	Eindhoven Cancer Registry	Proportion of patients receiving adjuvant chemotherapy decreased with increasing age from 85% among aged <65, 68% for 65–74 y and 17% for ≥75 y; interhospital variation was observed
	Alter, 2007 (40)	France	Stage II	Surgery, 2000	532	Mean 72	81 hospitals; data from medical records	19.5% had adjuvant chemotherapy; older patients, higher tumor stage, and having a bowel obstruction or perforation associated with adjuvant chemotherapy use; hospital procedure volume, multidisciplinary consult, and mode of hospital funding (private vs public) also associated
	Lepage, 2006 (49)	France	All stages	2000	567	Mean 70 at diagnosis	Burgundy Registry of Digestive Cancers	Adjuvant chemotherapy performed in 0.9% of stage I, 17.6% of stage II, and 54% of stage III patients; palliative chemotherapy in 48.1%
	Morris, 2007 (44)	Australia	Stage II	1993–2003	812	Mean 64.9 among patients receiving surgery alone	Four major hospitals in Western Australia; pathology reports used to identify patients	18.0% received chemotherapy; 25% of patients ≤65 received chemotherapy compared with 10% of those between 66 and 75 y; patients receiving chemotherapy had tumors often positive for vascular invasion; adjuvant chemotherapy use peaked at 25–30% in late 1990s but decreased to <15% in 2002–2003
	Silvera, 2006 (50)	France	All stages	Hospitalized or had surgery 2001–2002	1842	18+; mean 68.7	Paris metropolitan area; French health insurance funds administrative database; survey of medical advisers	Chemotherapy given to 53.1%; 5.8% of patients with stage I received chemotherapy; 37.7% of stage II, 76.9% of stage III, 81.4% of stage IV
	Lemmens, 2005 (61)	The Netherlands	Stage III	1995–2001	577	All patients 65–79; 65–69: 31.4%; 70–74: 34%; and 75–79: 34.6%	Eindhoven Cancer Registry	80% of patients 65–69 y received chemotherapy vs 28% among 75–79 y; chemotherapy receipt among elderly increased from 19% to 50% over time, with large interhospital variation; in multivariate analyses, patients of older age, female gender, comorbidity, and lower SES less likely to receive chemotherapy; patients with high-grade tumors and stage IIIB received chemotherapy more often
	Phelip, 2005 (63)	France	All stages	1995	1605	75+	FRANCIM and survey given to specialists	Among nonmetastatic patients <75 y who had complete resection, adjuvant chemotherapy was given to 6.8% of stage I, 49.4% of stage II, and 79.6% of stage III patients; among metastatic patients and those without complete resection, palliative therapy in 61.7%; regional differences observed

(Table continues)

Table 5 (Continued).

	First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to chemotherapy treatment
	Faivre-Finn, 2002 (82)	France	All stages	1989–1998	4093	<65: 24%; 65–74: 30%; 75+: 46%	Côte-d'Or and Saône-et-Loire registries in Burgundy; hospital data from general and specialty practitioners	18.3% treated with adjuvant chemotherapy; over time, chemotherapy use increased from 3.1% to 24.7%; 26% of eligible patients were treated with palliative chemotherapy, with younger patients and males treated more often; in multivariate results, younger patients, later period and stage of diagnosis significantly more likely to receive adjuvant chemotherapy
	Faivre-Finn, 2002 (79)	France	All stages	1976–1998	3389	NR	Côte-d'Or registry, Burgundy; hospital data from general and specialty practitioners	Among stage III patients, adjuvant chemotherapy rose from 4.1% to 45.7%, though increase slower in patients 75+; in multivariate analyses, younger age, later period of diagnosis, and stage II/III disease associated with chemotherapy use; palliative chemotherapy use rose from 4.0% to 34.5% over time and patients <75 more likely to receive palliative therapy
Rectum	Elferink, 2010 (30)	The Netherlands	All stages	1989–2006	40 888	≤44: 4%; 45–59: 22%; 60–74: 43%; ≥75: 32%	Netherlands Cancer Registry	Proportion of stage III patients receiving adjuvant chemotherapy increased sharply, particularly among younger patients; chemotherapy in stage IV patients increased from 21% to 66% for younger patients and from 2% to 25% for elderly patients
	Sigurdsson, 2009 (37)	Norway	NR	1997–2002	297	Median 77, range 67–84	Norwegian Colorectal Cancer Registry	Among patients treated with noncurative intent, 28% of patients received chemotherapy
	Engel, 2005 (65)	Germany	All stages	1996–1998	882	<70: 62.5%; 70+: 37.4%	Munich Cancer Registry and Munich Field Study	In stage II patients, 3.0% received chemotherapy alone compared with 12.8% of stage III patients
	Phelip, 2004 (66)	France	All stages	1990, 1995	945	Stratified as <75 and >75	FRANCIM; survey of specialists and GPs	Adjuvant chemotherapy in patients with resection and no metastasis rose from 8.1% to 19.0%; palliative chemotherapy given to 37.5% of patients <75 with advanced stage and rose to 50.0%; 0 patients >75 received palliative chemotherapy
	Phelip, 2004 (69)	France	All stages	1995	683	≥75: 38.8%	FRANCIM; physician survey	Adjuvant chemotherapy given to 33.2% aged <75 and 4.5% among 75+ with curative surgery
	Martijn, 2003 (73)	The Netherlands	All stages	1980–2000	3635	<60: 26.3%; 60–74: 47%; 75+: 26.7%	Eindhoven Cancer Registry	Chemotherapy increased from 0% to 10% among stage III patients and from 7% to 30% among stage IV patients
	Birbeck, 2002 (80)	United Kingdom	NR	Surgery 1986–1997	586	Median 69.6, range 27.9–96.6	Leeds, United Kingdom; hospital data, patient case notes with full clinical follow-up	11.9% received adjuvant chemotherapy
	Farmer, 2002 (81)	Australia	Dukes A-C	1994	681	NR	Victoria Cancer Registry; physician survey completed for each patient	Data on chemotherapy limited to 144 patients; in 78% of patients, chemotherapy given postoperatively and to 63.9% within 2 mo of surgery

(Table continues)

Table 5 (Continued).

	First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to chemotherapy treatment
CRC	Gatta, 2010 (28)	European Collaborative Study	Stages I–III	1996–1998	6871	≥75: 33.6%; <75: 66.4%	European cancer registries	Among stage II colon cancer patients, 22% received adjuvant chemotherapy; receipt varied by age (38% for <65 vs 5% for 75+) and cancer registry; among stage III colon cancer patients, 46% received adjuvant chemotherapy and varied by age (69% for <65 vs 16% for 75+) and cancer registry; in multivariate results among stage III colon cancer patients, older age decreased the odds of receiving chemotherapy
	Carsin, 2008 (90)	Ireland	All stages	1994–2002	15 249	Patients ≥20	National Cancer Registry	31% had chemotherapy, increased by 10% per year, for all stages; older, unmarried patients less likely to have chemo; among stage III–IV, strong positive effect of year of diagnosis
	Coriat, 2007 (41)	France	All stages	1998	407	Median age 72; range 26–93	Burgundy Registry of GI Cancers	27% of patients received adjuvant chemotherapy
	Damianovich, 2007 (47)	Australia	100% metastatic	Received medication 2002–2003	1465	70+: 23%; 80+: 2%	Health Insurance Commission	For 5-FU refractory patients, oxaliplatin use increased from 48% to 66% and irinotecan use decreased from 52% to 34% between 2002 and 2003; differences greater for younger vs older patients and pattern of use observed across all states; younger patients switched more than older ones; of the 697 patients who started oxaliplatin in 2002–2003, 40% switched to irinotecan
	Mahboubi, 2007 (49)	France	All stages	1998	389	<65: 26.5%; 65–74: 34.2%; ≥75: 39.3%.	Côte-d'Or and Saône-et-Loire registries, Burgundy; medical records and survey of specialists and GPs	Overall, 27.2% had chemotherapy
	Young, 2007 (46)	Australia	All stages	2000–2001	2984	22.4% <60; 26.3% 60–69; 33.3% 70–79; 17.7% ≥80	New South Wales; patients identified through cancer registry and had surgery; physician survey	Of Dukes C colon cancer patients who had surgery with curative intent, 76.0% offered chemotherapy
	Lemmens, 2006 (52)	The Netherlands	NR	Colon 2002; rectal 2002	308	Colon cancer: mean 70, range 41–91; rectal cancer: mean 64, range 33–86	Eindhoven Cancer Registry	95% of patients <70 received chemotherapy vs 48% 70+ years
	Bouvier, 2005 (57)	France	All stages	1978–1997	2409	80+ at diagnosis	Calvados and Côte-d'Or registries	2% colon cancer and 2% rectal cancer patients received chemotherapy; 2.4% stage IV colorectal cancer patients had palliative chemotherapy

(Table continues)

Table 5 (Continued).

First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to chemotherapy treatment
Drug Utilization Review Team in Oncology, 2005 (54)	Italy	NR	October 2000	434	≤50: 15.2%; 51–60: 25.3%; 61–70: 36.6% >70: 21.0%	86 Italian oncology centers; patient, clinical, disease data from treating oncologist forms	Among colon cancer patients, adjuvant chemotherapy given to 42.5%; tumor stage, type of center (hospital vs university), patient age, and number of nodes removed affected decision to give patients chemotherapy
Gonzalez, 2005 (58)	Spain	All stages	1996–1998	403	Mean 65.4 (men), 63.8 (women)	Hospital Universitario de Bellvitge in Barcelona, Spain	42.7% of men and 51.2% of women had chemotherapy
Lemmens, 2005 (60)	The Netherlands	All stages	1995 to 2001	6931	All patients 50+; mean 70.	Eindhoven Cancer Registry	Among stage III patients, surgery and adjuvant chemotherapy given to 82.8% <65, 42.4% of 65–79, 1.2% of 80+; among stage IV patients, chemotherapy decreased from 41.3% among 50–64 to 1.8% among oldest
Robinson, 2005 (64)	New Zealand	All stages	1993–94 and 1998–99	673	Median 71–90; 51–70	Christchurch Hospital; oncology database, hospital discharge codes, patient notes	Adjuvant chemotherapy for Dukes stage C patients increased from 21% to 45%; chemotherapy for metastatic disease rose from 2.4% to 23% of stage D and from 2.5% to 36.5% for patients who developed metastases
Barton, 2004 (67)	Australia	All stages	1994–1996	370	Median 68, range 22–98	Western Sydney and Wentworth Health Areas; cancer registry and hospital databases	5% received adjuvant chemotherapy not same time as radiotherapy, whereas 6% received adjuvant chemotherapy alone; among eligible colon cancer patients, 51% received adjuvant chemotherapy
Bouhier, 2004 (68)	France	All stages	1990–1999	3135	Mean 70	Calvados Registry of GI Tumors	Among colon cancer patients, 21.8% of stage II and 46.9% of stage III patients had chemotherapy; chemotherapy use increased for stage III patients, but remained stable for stage II; among stage IV patients, 45.9% received palliative chemotherapy and this increased over time; older age (75+) associated with decreased chemotherapy use and general hospitals (vs university centers) less likely to treat stage III patients with chemotherapy
McGrath, 2004 (71)	Australia	All stages	2000	1911	Mean 68, median 70, range 16–100	All state cancer registries; survey given to surgeons	Chemotherapy offered to more patients with Dukes A, B and C rectal cancer vs colon cancer patients (49.4% vs 39.4%)
Campbell, 2002 (78)	United Kingdom	All stages	1995–1996	653	≤59: 19%;60–69: 24%; 70–79: 33%; ≥80: 24%	Scotland cancer registry; hospitals in Grampian or Highland; case notes and clinical data	23% received chemotherapy within 1 y of diagnosis; higher stage and younger age associated with increased chemotherapy receipt
Pitchforth, 2002 (77)	United Kingdom	NR	1992–1996	7303	All ages	Scotland cancer registry and services from Scottish morbidity record inpatient and day case form	13.7% received chemotherapy within 6 mo of first admission; ER admissions less likely to receive chemotherapy; noncancer hospital admittees less likely to get chemotherapy

* AR = anterior resection; APR = abdominoperineal resection; ER = emergency room; FU = fluorouracil; GI = gastrointestinal; GP = general practitioner; HP = Hartmann's procedure; LAR = lower anterior resection; MET = metastatic; SES = socioeconomic status; ULAR = ultralow anterior resection.

Table 6. Patterns of multicomponent care for colorectal cancer in Europe, Australia, and New Zealand by cancer site, publication year, and country (n = 11)*

	First author, y (ref.)	Country	Stage	Year of diagnosis	N	Age (y)	Health delivery setting and data sources	Findings related to multicomponent care
Rectum	Elferink, 2010 (30)	The Netherlands	All stages	January 1, 1989–December 31, 2006	40 888	≤44: 4%; 45–59: 22%; 60–74: 43%; ≥75: 32%	Netherlands Cancer Registry	Among younger stage II–III patients, neoadjuvant RT + chemotherapy increased from 1% in 1994–1998 to 9% in 2004–2006; elderly stage II–III patients received neoadjuvant RT + chemotherapy 3% less often in 2004–2006
	Elferink, 2010 (26)	The Netherlands	Non-MET 77.8%; MET 17.4%; unknown 4.8%	January 1, 2001–December 31, 2006	16 039	<60: 26.2%; 60–74: 43.4%; 75+: 30.3%	Netherlands Cancer Registry	Most patients with T2/T3/T4-M0 tumors had either preoperative RT or neoadjuvant chemoradiation; proportion of patients receiving either preoperative RT or neoadjuvant chemoradiation was higher for <75 vs 75+
	Sigurdsson, 2009 (37)	Norway	NR	1997–2002	297	Median 77, range 67–84	Norwegian Colorectal Cancer Registry	Among patients treated noncuratively, 10% had combination of chemotherapy and RT
	Ptok, 2007 (42)	Germany	Stages I–III	Entered study 2000–2001	1557	Median 66, range 26–92	Multisite observational study; data collected from patients, hospital data	Neoadjuvant RT and radiochemotherapy for rectal cancer increased from 6.5% to 25.0% (2000 vs 2005); adjuvant therapy was 53.4% and 49.7%, respectively; higher-volume hospitals had higher rates of neoadjuvant therapy (16.8% vs 9.9%)
	Engel, 2005 (65)	Germany	All stages	1996–1998	882	<70: 551 (62.5%); 70+: 331 (37.4%)	Munich Cancer Registry and Munich Field Study	9.4% received both pre- and postoperative adjuvant treatment
	Martijn, 2003 (73)	The Netherlands	All stages	1980–2000	3635	<60: 26.3%; 60–74: 47%; 75+: 26.7%	Eindhoven Cancer Registry	14% had surgery + preoperative RT, 17% surgery + postoperative RT, 5% surgery + systemic treatment, 5% "other" or missing treatment, 5% no treatment; treatment with surgery and radiotherapy increased in 1980–2000 (26% to 40%)
	Farmer, 2002 (81)	Australia	Dukes A-C	1994	681	NR	Victoria Cancer Registry; physician questionnaire	Chemotherapy was combined with postoperative RT in 65.3%
Colorectal	Kube, 2009 (36)	Germany	All stages	Resections 2000–2005	346 hospitals; 47 436 patients	NR	Hospital data, standardized questionnaire, follow-up physician survey	Neoadjuvant RT and radiochemotherapy for rectal cancer increased from 6.5% in 2000 to 25.0% in 2005
	Drug Utilization Review Team in Oncology, 2005 (54)	Italy	NR	Past or current diagnosis October 2000	434	≤50: 15.2%; 51–60: 25.3%; 61–70: 36.6%; >70: 21.0%; NR: 1.9%	86 Italian oncology centers; forms completed by the treating oncologist	82 patients enrolled were treated with adjuvant therapy; adjuvant RT was administered alongside chemotherapy in 45.8%, sequentially with chemotherapy in 28.8%, alone to 1.7%, and in a nonspecified way in 23.7%
	Lemmens, 2005 (60)	The Netherlands	All stages	1995 to 2001	6931	All patients 50+; mean 70	Eindhoven Cancer Registry	The proportion of patients with stage II/III rectal cancer who received adjuvant chemoradiotherapy increased from 3.9% in 1995–1999 to 15.9 % in 2001
	McArdle, 2002 (84)	United Kingdom	Dukes A/B	1974–1979; 1991–1994	3200	75+: 35%	Glasgow Royal Infirmary; medical records/audits	Of the total, 5% received adjuvant therapy

* APR = abdominoperineal resection; LAR = lower anterior resection; RT = radiotherapy.

time among younger patients and in higher-volume hospitals (26,30,36,42,60).

Post-Diagnostic Surveillance and End-of-Life Care

Seven studies reported information on post-diagnostic surveillance for colorectal cancer, including colonoscopy use, carcinoembryonic antigen testing, chest X-rays, abdominal computed tomography scans or X-rays, and positron emission tomography scans (data not shown) (39,41,49,52,56,62,75). Five studies reported rates of post-diagnostic surveillance in addition to some form of initial care (eg, surgery, chemotherapy), whereas two studies reported exclusively on post-diagnostic surveillance. Studies varied by timeframe for receipt of follow-up care, ranging from 1 year after diagnosis to 3 years post-diagnosis. Notable findings included that patients with advanced-stage cancers and those receiving chemotherapy were more likely to receive follow-up care (39,41). Additionally, variation in post-diagnostic surveillance by physician type (specialist vs general practitioner) and assessment of guideline compliance were also highlighted (39,41,62). The one study conducted in Italy assessing end-of-life care examined patients who died in 2003–2005 and called for guidelines to be created for chemotherapy use among end-of-life patients (data not shown) (43).

Discussion

This systematic review examined patterns of colorectal cancer care in several European countries, Australia, and New Zealand, and was written as a companion to a review on care patterns in the United States and Canada (91). Included studies spanned over 15 countries and focused on initial care for colorectal cancer, including surgery, RT, and chemotherapy. Similar to the United States and Canada review, our analysis revealed limited information on post-diagnostic surveillance and end-of-life care for colorectal cancer (91), representing potential areas where additional research is needed (39,41,43,49,52,56,62,75). Furthermore, existing studies on end-of-life care have included multiple types of cancer patients, and the extent to which colorectal cancer patients have specific end-of-life care needs is not well understood.

In our analyses of study findings for initial care, there were several findings that were common among studies on surgery, chemotherapy, RT, and multicomponent care. These findings included changing trends over time and variation in rates of treatment by patient demographic and health characteristics (ie, age, gender, socioeconomic status, tumor stage, metastatic tumor status, presence of comorbidities), hospital setting and volume, and region (26,28–30,34,36–38,40,42,45,46–48,55,60,61,66,68,69,72,78,79,88). Among these characteristics, patient age was one of the most consistent findings associated with treatment receipt, with older patients being less likely to receive colorectal cancer care compared with younger patients. This finding may be tied to underrepresentation of elder patients in clinical trials, creating challenges for physicians to determine appropriate treatment for older individuals.

Over time, there were also changing trends in specific treatment types. For example, several studies reported lower rates of APR over time and increasing use of sphincter-sparing surgeries, such as total mesorectal excision and lower anterior resection. This change has particular relevance for quality of life among rectal cancer patients. Several studies also noted increasing use of preoperative RT alongside decreasing rates of postoperative RT among rectal cancer patients. Chemotherapy rates also increased over time, especially toward the later part of the 1990s.

Of critical importance, we found wide variation in data sources used across studies both between and within countries, making direct comparisons of patient and health services information for initial care challenging. Because of lack of comparability of data reporting and differences in patient populations, comparing rates of surgery, RT, or chemotherapy for colorectal cancer between countries was difficult, and patterns of care identified were incongruous. In this review, the studies that were more amenable to comparisons had greater similarities in type of treatment assessed and patient demographic and clinical characteristics (eg, stage III colon cancer patients). These factors should be considered in future research and data collection efforts.

Moreover, studies had multiple sources of data, ranging from registries to single or multiple institutions. Although studies from particular countries such as France and the Netherlands relied heavily on registry data, others used medical records and hospital data or a mixture of data sources. However, there were varied degrees of population coverage and representativeness even within countries using registry data (eg, FRANCIM). Studies from several countries also did not appear to use centralized registry information. Furthermore, increased linkages between health insurance systems and cancer registry data to provide more detailed information on service utilization patterns may improve current data collection efforts.

Studies also had variability in reporting clinical characteristics that significantly affect treatment and survival as well as variation in time period that trends were assessed. Strikingly, 20% of studies did not report stage of cancer at diagnosis—a fundamental determinant of appropriate cancer treatment. Another important clinical characteristic that was omitted from nearly one-third of studies was year of diagnosis. Additionally, assessment of comparability was limited by reporting of treatment rates for initial care from distinct, disparate, and wide intervals of time, ranging from 1974 to 2006, across studies (26,84).

Further complicating the ability to make comparisons across countries, few studies assessed care in relation to guidelines or other standards, and those which included this information used disparate guidelines for care receipt. Among the studies that discussed use of guidelines, articles compared trends over time for guideline implementation, but used different sets of guidelines or national consensus conference statements (32,39,41,43,62,74). One study also highlighted better guideline-consistent performance among colorectal cancer surgeons compared with other surgeon types (74). Although the creation of guidelines is challenging given the diversity of patient populations and physician practice patterns, efforts could potentially be made to improve consistency of treatment with guidelines among stage III colon cancer patients or stages II–III rectal cancer patients where greater consensus exists.

Notably, many studies omitted important patient characteristics, which are associated with receipt of treatment, including comorbidities, gender, socioeconomic status, urban/rural residence, and patient race/ethnicity or country of origin. Several countries included in this review (ie, England, France, Australia, Germany)

have significant immigrant populations and racial or ethnic diversity among the general population (92,93). In addition, variables related to care coordination (ie, the process of linking patients to timely care throughout the process of treatment), quality of care, case-mix, and social support were missing from nearly all studies. Each of these factors has a potentially important role in treatment receipt and utilization of services, and may vary by patient clinical and demographic characteristics, geographical region, and hospital setting.

It should also be noted that many studies had important limitations. Selection bias and limited geographical coverage were present in several studies. For instance, single-institution studies within a country limit generalizability of findings to other geographical areas. Among studies using registry data, such as those in France, the Netherlands, and Australia, population coverage varied widely both between and within each country.

Although this systematic review made significant efforts to thoroughly evaluate existing literature on patterns of colorectal cancer care, some limitations should be noted. Our search terms and criteria used could have unintentionally resulted in exclusions of relevant studies. However, as an effort to maximize the inclusion of relevant studies, reference lists of identified papers and published reviews were evaluated to identify additional articles. In addition, articles were limited to those published in English, which may have missed relevant studies published in other languages.

These limitations notwithstanding, this review had several important findings and implications. This synthesis of the literature summarizes a large number of studies focusing on colorectal cancer care in Europe, Australia, and New Zealand, and can be used to identify new directions for future research. For instance, one of the primary gaps in existing literature identified by this review was lack of information on post-diagnostic surveillance and end-of-life care among colorectal cancer patients. Another central finding was significant variation in sources of data for colorectal cancer treatment across studies, which varied by patient demographic and health characteristics, study time period, geographic location, and hospital setting. Therefore, future research and policy efforts should minimize inconsistencies in measurement and emphasize standardization of data reporting for colorectal cancer care.

Additional research is also needed that collects and compares standardized data from multiple European nations, such as EUROCARE, which improve data comparability by using similar standards and quality control measures for registration, data collection, and follow-up of patients within cancer registries (3). Researchers and policy makers from individual countries should further work toward increased representativeness and generalizability of data on colorectal cancer treatment between geographical regions within individual nations. Targeted research and policy efforts in these areas will help to harmonize data sources for comparable analyses and allow for improved assessment of care practices globally.

Appendix

Search #	Limits: English, Journal Article, Humans, Publication Date from 2000 to 2010
1	("Colorectal Neoplasms/drug therapy"[MeSH] OR "Colorectal Neoplasms/radiotherapy"[MeSH] OR "Colorectal Neoplasms/surgery"[MeSH] OR "Colorectal Neoplasms/therapy"[MeSH])
2	"Physician's Practice Patterns"[MeSH]
3	"Guideline Adherence"[MeSH]
4	"Health Services/statistics and numerical data"[Majr] OR "Health Services/trends"[Majr] OR "Health Services/utilization"[Majr])
5	"Quality of Health Care/statistics and numerical data"[Majr] OR "Quality of Health Care/trends"[Majr] OR "Quality of Health Care/utilization"[Majr]
6	"Chemotherapy, Adjuvant/statistics and numerical data"[MeSH] OR "Chemotherapy, Adjuvant/trends"[MeSH] OR "Chemotherapy, Adjuvant/utilization"[MeSH]
7	"Neoadjuvant Therapy/statistics and numerical data"[MeSH] OR "Neoadjuvant Therapy/trends"[MeSH] OR "Neoadjuvant Therapy/utilization"[MeSH]
8	"Radiotherapy, Adjuvant/statistics and numerical data"[MeSH] OR "Radiotherapy, Adjuvant/trends"[MeSH] OR "Radiotherapy, Adjuvant/utilization"[MeSH]
9	"Neoplasm Recurrence, Local/prevention and control"[Majr]
10	"Terminal Care"[MeSH]
11	"Patterns of Care"[Keyword String][Abstract or Title]
12	Search #1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)

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Economic Studies in Colorectal Cancer: Challenges in Measuring and Comparing Costs

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Estimates of the costs associated with cancer care are essential both for assessing burden of disease at the population level and for conducting economic evaluations of interventions to prevent, detect, or treat cancer. Comparisons of cancer costs between health systems and across countries can improve understanding of the economic consequences of different health-care policies and programs. We conducted a structured review of the published literature on colorectal cancer (CRC) costs, including direct medical, direct nonmedical (ie, patient and caregiver time, travel), and productivity losses. We used MEDLINE to identify English language articles published between 2000 and 2010 and found 55 studies. The majority were conducted in the United States (52.7%), followed by France (12.7%), Canada (10.9%), the United Kingdom (9.1%), and other countries (9.1%). Almost 90% of studies estimated direct medical costs, but few studies estimated patient or caregiver time costs or productivity losses associated with CRC. Within a country, we found significant heterogeneity across the studies in populations examined, health-care delivery settings, methods for identifying incident and prevalent patients, types of medical services included, and analyses. Consequently, findings from studies with seemingly the same objective (eg, costs of chemotherapy in year following CRC diagnosis) are difficult to compare. Across countries, aggregate and patient-level estimates vary in so many respects that they are almost impossible to compare. Our findings suggest that valid cost comparisons should be based on studies with explicit standardization of populations, services, measures of costs, and methods with the goal of comparability within or between health systems or countries. Expected increases in CRC prevalence and costs in the future highlight the importance of such studies for informing health-care policy and program planning.

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Estimates of the costs associated with cancer care are essential both for assessing burden of disease at the population level and for conducting economic evaluations of health-care policies and programs to prevent, detect, or treat cancer. Although considerable methodological progress has been made in disease costing (1), significant challenges remain. Importantly, existing data for cost determination in any given study are generally imperfect, sometimes missing, and often collected or analyzed in ways that make cross-study comparisons difficult. An underlying problem is that available data sources were generally created for other purposes (eg, paying bills) and are substantially influenced by features of the health-care system, including the structure of insurance plans and databases for tracking care (2). The alternative approach of collecting precisely the resource use data needed for a given economic evaluation can be expensive and time-consuming in practice, and there is wide variation in these "microcosting" studies (3).

Thus, even within a single health system or country, studies with an identical purpose (eg, estimating the costs of chemotherapy in the year following cancer diagnosis) frequently use different methods, with data sources that vary in scope, population coverage, completeness, and capacity to examine patterns of service use. Internationally there is tremendous diversity in health-care systems, services covered, and availability of existing data sources relevant to health-care costing (4,5)—making comparisons of cancer costs across countries all the more difficult. Despite these challenges, comparisons within and between health systems and countries can enhance understanding of the economic consequences of differences in policies related to cancer care, as well as broader health-care programs, such as a coordinated hospice program for end-of-life care. Understanding the extent to which studies can be compared is also critical for economic evaluations of cancer prevention, screening, or treatment interventions, which may synthesize estimates from multiple sources as inputs to cost-effectiveness models.

In this paper, we investigate the implications of this diversity in methods, health systems, and data sources for cost analyses through a structured review of the published literature on the economic burden associated with colorectal cancer (CRC) care. Worldwide approximately 2.1 million individuals were newly diagnosed with CRC in 2008, and CRC is the second most common cancer in women and the third most common in men (6). CRC prevalence is expected to increase appreciably in most developed countries as a result of population growth and aging, because CRC incidence increases with age (7). Additionally, ongoing efforts to improve early detection and treatment are expected to improve CRC survival and reduce CRC-related mortality, which will also result in increasing disease prevalence.

Consequently, the societal burden of CRC is significant and is likely to increase over time (8,9). Important economic components of this burden include direct medical care costs, direct nonmedical costs (such as patient time involved with receiving medical care),

and productivity losses among patients and caregivers. In this review, we build on and update prior work (10–13) describing the economic burden associated with CRC care. We then categorize the significant challenges in conducting valid, reliable, feasible, and comparable cancer costing analyses, with an emphasis on comparisons across studies, health systems, and countries.

Methods

Study Selection

We used MEDLINE to identify English language articles about the costs of CRC published between 2000 and 2010. The search strategy used the Medical Subject Headings (MeSH) subject term "colorectal neoplasms" combined with MeSH major subject terms "health care costs," or "cost of illness," or "economics," or "cost analysis." The combination yielded 248 studies. Our focus was on CRC care, so we excluded studies of primary prevention and screening. We also excluded simulation models based on hypothetical cohorts with assumed patterns of care, because numerous studies have described patterns of CRC care in population-based samples that are inconsistent with treatment pathways or guidelines (14,15). Studies of costs of specific side effects of treatment (eg, nausea) or symptoms of disease were also excluded, because these studies represented only a small component of cancer care. Also excluded were small studies (with samples of fewer than 100 patients), as well as reviews, editorials, letters, and essays. Economic studies of cancer treatment trials were included only if they were based on primary patient-level data during and possibly after the trial period.

Of the studies identified as potentially eligible for inclusion in our review, 30 met our eligibility criteria (16–43). Because electronic searches may not identify all relevant studies (44), we reviewed the reference lists of the selected studies as well as reviews of the costs of CRC care (10–13,45,46) and identified 25 additional studies (47–73). A total of 55 studies are included in this review.

Data Abstraction

Data were abstracted from each paper using a standardized abstraction format to describe the study characteristics, cancer patient characteristics, and study methods. *Study characteristics* included study publication year, country where study was conducted, geographic setting (single city, single state/province/region, multiple cities and/or states/provinces/regions, national, multiple countries), delivery setting (single institution or clinic, network of institutions or clinics, integrated system/insurance network, other), and the type of cost estimate evaluated (direct medical, direct nonmedical, including patient or caregiver time and travel, and productivity loss). Because health-care delivery in the United States is fragmented, we also abstracted information about the type of health insurance (fee-for-service, managed care, multiple types of insurance) and measurement of cost (insurance payments only, patient out-of-pocket payments, charges). *Cancer patient characteristics* included method of patient identification (medical record review, registry, claims, other), tumor stage (American Joint Committee on Cancer [AJCC] I/II or localized, AJCC III/IV or regional/distant, other, stage not reported), number of cancer patients (100–499, 500–999, 1000–4999, 5000–9999, 10 000+) and patient age groups (<40, 40–64, 65+, mean age <65, mean age 65+, patient age not stated).

Study methods that were abstracted included study design (cross-sectional, cohort, based on a randomized controlled trial), phases of care evaluated (initial treatment, surveillance or continuing, last year of life, long-term/lifetime, all phases together [prevalent], other), use of a comparison group (noncancer controls, other comparison group, no comparison group), and use of price adjusters (time adjusters, other adjusters, not reported).

Medical cost estimates for prevalent CRC patients (both incident and existing patients) were abstracted separately at the per-person and aggregate levels. Medical cost estimates were also abstracted separately for each phase of care. Studies that could not clearly define patients with incident disease, or that identified patients with metastatic disease but did not distinguish newly diagnosed from recurrent disease, or that were based on receipt of specific treatment, were classified as cost estimates of prevalent cancer patients. Studies based on patterns of care observed in clinical trials of cancer treatment were abstracted separately, as were studies of other aspects of the burden of illness, including patient and caregiver time and productivity loss.

Consistent with the diverse approaches found in the literature, we use the term "cost" broadly to reflect either expenditures, insurance payments, charges, actual costs of care, or wages, and we abstracted data as reported in the underlying studies. The "reference year" used to adjust for monetary inflation (eg, in 2000 dollars) was abstracted as reported, or noted as not reported when the reference year was not available in the underlying study. We did not attempt to standardize studies to a single reference year, because it would not be meaningful to do so given the heterogeneity across health systems and countries in cancer care delivery settings, data sources, patient populations, measurement of cost, types of medical services, use of comparison groups, and other methodological differences. Finally, findings are reported as either total costs or cancer-related costs. Total costs reflect the cost of all services received by cancer patients. Cancer-related costs reflect either the cost of services presumed to be related to cancer treatment or else the net cost of all services among cancer patients compared with similar individuals without cancer. Nonmedical costs are also reported as either total or cancer-related based on comparisons with similar individuals without cancer.

Results

Study Characteristics

The number of published studies of the costs of CRC care increased throughout the study period, with almost half being published between 2008 and 2010 (Table 1). The majority of studies were conducted in the United States (52.7%), followed by France (12.7%), Canada (9.1%), and the United Kingdom (9.1%). Studies were also conducted in Brazil, Germany, Greece, Hungary, Italy, Japan, and Norway. Almost 90% of studies estimated direct medical costs, and few estimated patient or caregiver time costs (14.5%), travel costs (7.3%), or productivity losses (7.3%). In the United States, the dominant health insurance type was fee-for-service, with few studies conducted in managed care or across multiple types of payers/providers. The most commonly used data source was the linked SEER–Medicare data, which include only fee-for-service insurance predominantly for patients aged 65 and older. Studies varied in the comprehensiveness of estimates,

Table 1. Study summary (N = 55)*

		No.	Percent
Study characteristics	Study publication year		
	2000–2003	14	25.5
	2004–2007	16	29.1
	2008–2010	25	45.5
	Country		
	Canada	5	9.1
	France	7	12.7
	Italy	2	3.6
	Japan	2	3.6
	United Kingdom	5	9.1
	United States	29	52.7
	Other	5	9.1
	Geographic setting†		
	Single city	4	7.2
	Single state/province/region	9	16.4
	Multiple cities and/or states/provinces/regions	21	38.2
	National	18	32.7
	Multiple countries	3	5.5
	Delivery setting†		
	Single institution or clinic	3	5.5
	Network of institutions or clinics	3	5.5
	Integrated system/insurance network	18	32.7
	National health-care system	12	21.8
	Other	19	34.5
	Cost domain†		
	Direct medical costs	49	89.1
	Direct nonmedical costs	10	18.2
	Patient or caregiver time	8	14.5
	Travel	5	7.3
	Lost productivity	5	7.3
Cancer patient characteristics	Cancer patient identification†		
	Medical record review	6	10.9
	Registry	23	41.8
	Claims	9	16.4
	Other	21	38.2
	Tumor stage†		
	AJCC I/II or localized	24	43.6
	AJCC III/IV or regional/distant	29	52.7
	Other	5	9.1
	Stage not reported	21	38.2
	No. of cancer patients†		
	100–499	17	30.9
	500–999	9	16.4
	1000–4999	10	18.2
	5000–9999	5	9.1
	10 000+	13	23.6
	Patient age groups†		
	<40	18	32.7
	40–64	30	54.5
	65+	42	76.4
	Mean age <65	1	1.8
	Mean age 65+	5	9.1
	Patient ages not stated	7	12.7
Study methods	Study design		
	Cross-sectional	18	32.7
	Cohort	24	43.6
	Based on randomized controlled trial	13	25.5
	Phase of cancer care†		
	Initial treatment of incident disease	19	34.5
	Surveillance, continuing, or monitoring	12	21.8
	Last year of life	10	18.8
	Long-term/lifetime costs	13	23.6
	Prevalence (all patients ever diagnosed)	22	40.0
	Other	5	9.1

(*Table continues*)

Table 1 (Continued).

	No.	Percent
Comparison group†		
Noncancer controls	15	27.3
Other comparison group	22	40.0
No comparison group	18	32.7
Use of price adjusters†		
Time adjusters for inflation	32	58.2
Other adjusters (eg, geographic)	10	18.2
Not reported	15	27.3

* AJCC = American Joint Committee on Cancer.

† Studies may be included in more than one category.

ranging from Medicare payments only, to adjusting also for patient out-of-pocket payments, to using Medicare charges as a proxy for cost. Few studies in the United States included patients without any health insurance at all.

Cancer patients were identified by medical record review (10.9%), tumor registries (41.8%), billing or claims data (16.4%), or other approaches, including clinical trial participation. Many studies included patients with all stages of disease at diagnosis, whereas about 25% included only patients with metastatic disease (recurrent or late-stage disease at diagnosis), and few studies restricted patients to early-stage disease (data not shown). Stage was not reported in 38% of studies. Most studies included patients aged 65 and older, either because they included patients of all ages and CRC incidence was higher in the elderly, or because they were conducted in the United States using SEER–Medicare data. Age was not stated in seven studies.

Of the 55 studies included in the review, 32.7% were cross-sectional, 43.6% were conducted in observational cohorts, and 25.5% were clinical trial–based. The majority of observational studies were conducted in the United States, whereas the majority of clinical trial–based studies were conducted in other countries. Many studies assessed the costs of CRC in prevalent samples of patients (40%), including clinical trial–based studies of treatment for metastatic disease. Many observational studies assessed either costs of initial treatment of incident disease or the initial phase of care (34.5%), or long-term/lifetime costs (23.6%), or both. Fewer observational studies assessed care at the end of life (18.8%). About one-third of the studies did not include a comparison group. Most studies used inflation price adjusters to standardize costs over the study period, but a sizable portion did not report use of any price adjusters (27.3%).

Direct Medical Costs of CRC Care in Observational Studies

National estimates of the direct medical costs of CRC were conducted in France, the United States, Canada, Brazil, and Hungary (20,30,31,34,39,66,69) (Table 2). Estimates were for either the entire population with cancer in a given year or for a subset of newly diagnosed patients in a given year over some defined time period, ranging from the first year following cancer diagnosis up to the patient's lifetime. Although several studies included the entire population of CRC patients, others were restricted to only the elderly. Finally, the scope of care included in these estimates varied widely—one study included only hospitalizations, whereas others included all care following diagnosis.

Ten studies estimated the cost of cancer care in prevalent patients, the combination of newly diagnosed and existing cancer patients (17,19,21,27,36,42,54,57,63,70) (Table 3). These studies were conducted exclusively in the United States, but the number of patients, age distribution, data source, types of costs included, and reference year varied widely. For example, two studies assessed ambulatory care, but one reported cancer-related costs for chemotherapy ranging from $1028 to $38 027 for different regimens (57), and the other reported payments for all care of $946 among individuals with cancer (27). Neither reported the year of dollars, patient age distribution, or period during which costs were accrued.

Fourteen studies assessed the costs of CRC care by phase of cancer care (Table 4), including 10 in the initial phase or initial care period (16,18,31,32,34,39,41,48,55,67), five in the continuing phase (16,24,34,41,66), and five in the last year of life (16,29,34,41,58). The majority of these studies were conducted in the United States, with three in France and one each in Canada and Norway. There was notable variation across studies in the number of patients, age distribution, definition of phase, type of costs, and reference year. For example, even among the US studies using the SEER–Medicare linked data for patients aged 65 and older, estimates ranged from mean cancer-related costs in 12 months of the initial phase of $29 609 in men and $29 930 in women in 2004 dollars (34) to total costs of $41 134 in the first year following diagnosis in 2003 dollars (31). The latter study reported total costs incurred by those diagnosed with CRC, whereas the former estimated cancer-related costs. These studies also differed in the calendar years of observation and definitions of the initial period of treatment (12 months following diagnosis vs initial phase of care).

Eleven studies reported long-term or lifetime costs associated with CRC care (16,22,23,34,38–41,59,62,68) (Table 5). Again, studies were conducted predominantly in the United States, with two in Canada and one each in the United Kingdom and France, and varied substantially in the samples, settings, types of care and costs included, and time periods covered postdiagnosis (eg, 2 years, 6–11 years, 25 years, lifetime). Despite these differences, lifetime cancer-related costs were generally higher in younger patients compared with older patients, as might be expected (16). Additionally, costs were generally higher among patients with more advanced disease at diagnosis (39), although lifetime costs were lower in

Table 2. National estimates of direct medical costs of colorectal cancer (CRC) care*

First author, y (ref.)	Country and setting	Sample characteristics	Components of health care included after patient identification	Findings
Boncz, 2010 (20)	Hungary; National Cancer Registry–National Health Insurance Fund	All patients	Inpatient, outpatient, drugs, and sickness pay	The National Health Insurance Fund Administration spent €32.2 million and €0.8 million on the treatment of malignant and in situ CRC, respectively in 2001
Torres, 2010 (30)	Brazil; Hospital Information Systems of the Brazilian Unified Health System	297 108 hospital admissions 1996–2008 with a primary diagnosis of CRC	Hospitalizations	Overall costs of CRC hospitalizations $16.5 million in 1996 and $33.5 million in 2008; the average cost of each admission, however, decreased from $1283 to $954; estimates in 2007 US dollars
Lejeune, 2009 (66)	France	36 000 patients diagnosed in 2000 with potentially curative surgery	Surveillance up to 3 years	3-year cost of surveillance €42.4 million; year of euros not reported
Yabroff, 2008 (34)	United States; SEER–Medicare	22 935 patients aged 65 and older diagnosed with all stages (including in situ) 1973–2002 with cost data 1999–2003	All care	Aggregate 5-year net costs for patients diagnosed in 2004 to Medicare were estimated to be $3101 million; estimates in 2004 US dollars
Warren, 2008 (31)	United States; SEER–Medicare	64 554 patients aged 65 and older with all stages 1991–2002 with cost data for year following diagnosis 1991–2003	All care	Total 2002 Medicare payments for CRC care in year following diagnosis in the United States was estimated to be $2.04 billion (in 2003 US dollars)
Maroun, 2003 (39)	Canada	16 856 patients diagnosed with colon or rectal cancer in 2000	Diagnosis and staging, surgery, hospital, RT, chemotherapy	Total aggregate lifetime treatment cost for patients in 2000 estimated to be $333 million and $187 million for colon and rectal cancer, respectively (in 1988 Canadian dollars)
Selke, 2003 (69)	France	All patients in 1999	Hospital inpatient and outpatient, physician, and prescription costs	Total direct medical costs of CRC to the health insurance system was €469.7 million

* Total costs reflect all services received by cancer patients. Cancer-related costs reflect either the cost of services presumed to be related to cancer treatment or the net cost of all services among cancer patients compared with similar individuals without cancer. RT = radiation therapy; SEER = Surveillance, Epidemiology, and End Results.

Table 3. Direct medical costs of colorectal cancer (CRC) care among prevalent cancer patients*

First author, y (ref.)	Country and setting	Sample characteristics	Components of health care included after patient identification	Findings
Chu, 2009 (70); Chu, 2010 (17)	United States; Medstat MarketScan	3333 patients identified from diagnosis codes received chemotherapy 2003–2006 and subset of 1396 patients who received chemotherapy within 90 days of surgery	Chemotherapy-related	Monthly cancer-related chemotherapy cost from $6683 to $14 320 for capecitabine and 5-FU/LV/oxaliplatin, respectively; for chemotherapy within 90 days of surgery, monthly costs $8003 and $7263 for 5-FU and capecitabine, respectively (in 2006 US dollars)
Dinan, 2010 (54)	United States; 5% Medicare sample	7039 patients aged 67 and older identified from claims for CRC in 1999, 2003, and 2006	All care	Total costs over 2 years in 1999, 2003, and 2006: $38 724, $51 715, and $56 839, respectively; imaging costs 1999, 2003, and 2006: $1009, $1686, and $1918, respectively (in 2008 US dollars)
Yabroff, 2009 (42)	United States; SEER–Medicare, 5% Medicare sample, MEPS	Patients aged 65 and older; SEER–Medicare: 73 050 diagnosed 1973–2002 with costs 1998–2002; 5% Medicare sample: 3575 patients 1996–2002 with costs 1998–2002; MEPS: 196 patients treated 1996–2004 with costs 1996–2004	All care	Annual cancer-related costs were $5341, $8736, and $11 614 in SEER–Medicare, 5% Medicare sample, and MEPS, respectively (in 2004 US dollars)
Ferro, 2008 (57)	United States; 115 ambulatory centers	421 CRC patients receiving chemotherapy 2002–2005	Ambulatory chemotherapy	Costs of cancer-related chemotherapy ranged from $1028 to $38 027 per regimen; year of dollars not reported
Paramore, 2006 (19)	United States; PharMetrics Database	699 patients with a code for metastases identified from claims, 1998–2004	All care	Cancer-related payments over average of 12.8 months were $97 031 (in 2005 dollars)
Chang, 2004 (21)	United States; Medstat MarketScan	2858 patients identified from claims, 1999–2000	All care	Cancer-related payments were $3742 per month and $30 939 over study; year of dollars not reported
Mullins, 2004 (27)	United States; MD Medicaid	1904 patients identified from claims, 1999–2000; patient age not stated	Ambulatory care	Total mean ambulatory payments were $946; year of dollars not reported
Ray, 2000 (63)	United States; KP–Northern CA	2613 patients of all ages identified from billing 1995–1996	All care	Total annual adjusted and unadjusted cost per capita were $10 506 and $15 253, respectively (in 1996 dollars)
Polednak, 2000 (36)	United States; CT registry and hospitals	11 023 patients all ages diagnosed 1992–1996, with first hospital admission 1992–1996	Hospital care	Total mean charges for first hospital admission after diagnosis were $32 061 for initial emergency department admission and $20 130 for admitted directly to the hospital; year of dollars not reported

* Total costs reflect all services received by cancer patients. Cancer-related costs reflect either the cost of services presumed to be related to cancer treatment or the net cost of all services among cancer patients compared with similar individuals without cancer. CA = California; CT = Connecticut; FU = fluorouracil; KP = Kaiser Permanente, LV = leucovorin; MarketScan = Coordination of Benefits and Health and Productivity Management; MD = Maryland; MEPS = Medical Expenditure Panel Survey; SEER = Surveillance, Epidemiology, and End Results tumor registry.

Table 4. Direct medical costs of colorectal cancer (CRC) care by phase of care and/or care period*

	First author, y (ref.)	Country and setting	Sample characteristics	Components of health care included	Findings
Initial care	Luo, 2010 (55)	United States; MI Registry–Medicare claims	6462 colon cancer patients aged 66 and older diagnosed 1997–2000	All care (including patient and third-party payer)	Mean cost attributable to cancer 1 year after diagnosis was $29 196 (in 2000 dollars), due to higher inpatient costs in cancer patients than controls
	Howard, 2009 (41)	United States; SEER–Medicare	71 397 cancer patients aged 65 and older diagnosed 1991–1999 with claims 1991–2001	All care	Total costs in first year after diagnosis greater for late stage than early stage ($28 500 vs $20 200 in men), and for cancer patients with heart disease or diabetes compared with no comorbid conditions ($33 700, $34 100, and $25 200, respectively, for men with late-stage disease); estimates in 2001 dollars
	Lang, 2009 (16)	United States; SEER–Medicare	56 838 patients in all phases of care aged 66 and older diagnosed 1996–2002	All care (including patient and other insurer)	Mean cancer-related costs in year after diagnosis were $33 294; costs were higher for later compared with earlier stage and younger compared with older age; estimates in 2006 dollars
	Clerc, 2008 (67)	France, two areas in Burgundy	384 patients of all ages diagnosed in 2004 with information from three public health insurance funds	Hospital, outpatient, including drugs and chemotherapy, transportation	Total costs in 12 months after diagnosis were €24 966, of which transportation costs were €623; costs were higher for stage IV (€35 059) than stage I (€17 596) or stage II (€20 472)
	Warren, 2008 (31)	United States; SEER–Medicare	64 554 patients aged 65 and older diagnosed with all stages of invasive CRC 1991–2002 with cost data for year following diagnosis 1991–2003	All care	Average total Medicare payments in the 12 months following diagnosis in 2002 was $41 134 (in 2003 dollars); inflation-adjusted increase of $5345 from 1991; hospitalization accounted for the largest portion of payments
	Yabroff, 2008 (34)	United States; SEER–Medicare	22 935 patients aged 65 and older diagnosed with all stages (including in situ) of CRC 1999–2002 with cost data 1999–2003	All care	Mean cancer-related Medicare costs in 12 months of initial phase of care were $29 609 in men and $29 930 in women; estimates in 2004 dollars
	Wright, 2007 (32)	United States; SEER–Medicare	6108 patients aged 66 and older with stage II–III rectal and stage III colon cancer 1992–1996 with cost data 1992–1998	All care (including patient and other insurer)	Unadjusted charges in 16 months following diagnosis higher for African Americans than whites ($44 199 vs $38 378); adjusted estimates similar in the two groups ($34 588 vs $33 614); estimates in 2000 dollars
	Ramsey, 2003 (18)	United States; SEER–GHC	923 patients aged 50+ diagnosed 1993–1999, with costs 1993–2000	All care year after diagnosis	Total costs for screen and symptom detected were $23 344 and $29 384 in 2002 dollars
	Bouvier, 2003 (48)	France; Caisse Nationale d'Assurance Maladie des Travailleurs Salaries	142 patients of all ages and stages diagnosed 1997–1998 affiliated with health insurance fund	Hospital, outpatient, transportation, medical purchases, and patient assistance (disability)	Mean cost of care was €21 918 in first year after diagnosis; costs were lower in older ages and mean costs per month of survival were higher in higher stages; year of euro estimates not reported
	Maroun, 2003 (39)	Canada	Estimated 16 856 patients with colon or rectal cancer in Canada diagnosed in 2000	Diagnosis and staging, surgery, hospital, RT, chemotherapy	Initial treatment costs were $14 375 and $16 951 for colon and rectal cancers, respectively; estimates in 1988 Canadian dollars

(*Table continues*)

Table 4 (Continued).

	First author, y (ref.)	Country and setting	Sample characteristics	Components of health care included	Findings
Continuing phase of care	Lang, 2009 (16)	United States; SEER–Medicare	56 838 patients in all phases of care aged 66 and older diagnosed 1996–2002	All care (including patient and other insurer)	Mean annual cancer-related cost in 12 months of continuing care was $4280; costs were higher for later compared with earlier stage and younger compared with older age; estimates in 2006 dollars
	Lejeune, 2009 (66)	France, two areas in Burgundy	385 patients diagnosed in 1998 with potentially curative surgery	Surveillance (physician, imaging, tumor markers)	Average surveillance cost per patient €713 over 3 years; year of euros not reported
	Howard, 2009 (41)	United States; SEER–Medicare	71 397 cancer patients in all phases of care aged 65 and older diagnosed 1991–1999 with claims 1991–2001	All care	Total annual costs in continuing phase greater for late than early stage ($3300 vs $3800 in men), but similar for cancer patients with heart disease or diabetes compared with no comorbid conditions; estimates in 2001 dollars
	Yabroff, 2008 (34)	United States; SEER–Medicare	82 559 patients aged 65 and older diagnosed with all stages (including in situ) of CRC 1973–2002 with cost data 1999–2003	All care	Mean net Medicare costs of CRC care $2254 in men and $1595 in women in 12 months of continuing phase; estimates in 2004 dollars
	Körner, 2005 (24)	Norway; single institution	194 patients younger than 76 years with curative surgery for Dukes A-C 1996–1999	Surveillance	The total cost of postoperative surveillance was €20 530 per patient in 2003 euros
Last year of life	Howard, 2009 (41)	United States; SEER–Medicare	71 397 cancer patients in all phases of care aged 65 and older diagnosed 1991–1999 with claims 1991–2001	All care	Total costs in last year of life similar by stage, but higher for patients with heart disease or diabetes compared with no comorbid conditions ($28 900, $28 200, and $20 000, respectively, for men with late-stage disease); estimates in 2001 dollars
	Koroukian, 2009 (58)	United States; OH Medicaid Program	4573 patients with CRC as underlying cause of death 1992–2002, with cost data in 12 months before death 1992–2002	All care	Mean and median per-person month expenditures were $2109 and $1754, respectively, during the 12 months before death; year of dollars not reported
	Lang, 2009 (16)	United States; SEER–Medicare	56 838 patients in all phases of care aged 66 and older diagnosed 1996–2002	All care (including patient and other insurer)	Mean cancer-related cost in final year was $14 538; costs were higher for later compared with earlier stage and younger compared with older age; estimates in 2006 dollars
	Yabroff, 2008 (34)	United States; SEER–Medicare	38 636 patients aged 65 and older diagnosed with all stages (including in situ) 1973–2002 with cost data 1999–2003	All care	Mean net Medicare costs in 12 months of last-year-of-life phase of care were $36 483 in men and $33 610 in women; estimates in 2004 dollars
	Shugarman, 2007 (29)	United States; 5% sample of Medicare beneficiaries	6657 patients aged 68 and older who died 1996–1999 with a diagnosis code for CRC within 3 years of death; costs reported 1995–1999	All care	Total per-person payments were $33 560 in the last year of life (in 1999 dollars); largest portion was inpatient care ($18 832), followed by physician services ($5633); payments for older patients lower than for younger patients

* Total costs reflect all services received by cancer patients. Cancer-related costs reflect either the cost of services presumed to be related to cancer treatment or the net cost of all services among cancer patients compared with similar individuals without cancer. Estimates are in US dollars, unless otherwise noted. GHC = Group Health Cooperative; MI = Michigan; OH = Ohio; RT = radiation therapy; SEER = Surveillance, Epidemiology, and End Results.

Table 5. Lifetime or long-term costs of colorectal cancer (CRC) care*

First author, y (ref.)	Country and setting	Sample characteristics	Components of health care included	Findings
Howard, 2010 (59)	United States; SEER–Medicare	12 473 patients aged 66 and older diagnosed with stage IV CRC 1995–2005	All care	Among patients treated with chemotherapy, lifetime costs increased from $63 200 during 1995–1996 to $100 300 during 2004–2005 in 2006 dollars; life expectancy increased from 16.5 months to 23.4 months; lifetime costs among patents who did not receive chemotherapy were more stable in 1995–1996 and 2004–2005 ($40 500 and $42 300) as was life expectancy (7.6 months and 7.5 months, respectively)
Howard, 2009 (41)	United States; SEER–Medicare	71 397 cancer patients aged 65 and older diagnosed 1991–1999 with claims 1991–2001	All care	Lifetime medical costs lower in patients with detected vs undetected adenomatous polyps and higher in patients with screen-detected vs undetected early-stage cancer across most age groups and types of comorbidities; lifetime costs for screen-detected early-stage cancer ranged from $59 600 to $44 500 in men aged 65 and 85, respectively, and undetected early-stage cancer costs ranged from $57 700 to $42 200 in men aged 65 and 85, respectively (in 2001 dollars)
Lang, 2009 (16)	United States; SEER–Medicare	56 838 patients aged 66 and older diagnosed 1996–2002	All care (including patient and other insurer)	Cancer-related lifetime costs were $28 626 (in 2006 dollars); lifetime costs higher in younger patients aged 66–74 than older patients aged 75–84 and 85+ ($36 401, $21 167, and $23 799, respectively); net lifetime costs were lower in patients with stage IV compared with earlier stage, reflecting lower life expectancy
Macafee, 2009 (68)	United Kingdom; single hospital in Nottingham	227 patients, median age 70.3 diagnosed with all stages 1981–2002 admitted to the hospital for treatment	Cancer-related hospital costs	Median cost up to 2 years following admission was £4479 in 2001 pounds, and higher for Dukes B and C than Dukes A and D
Yabroff, 2008 (34)	United States; SEER–Medicare	22 935 patients aged 65 and older diagnosed with all stages 1973–2002 with cost data 1999–2003	All care	Mean 5-year cancer-related Medicare costs of CRC care in the elderly following diagnosis were $36 621 in men and $35 037 in women; estimates in 2004 dollars
Kerrigan, 2005 (23)	United States; SEER–GHC, SEER–Blue Shield	Patients aged 20–64 with all stages diagnosed 1996–1998, costs 1996–2000; SEER–GHC: 136 patients, SEER–Blue Shield: 201 patients	All care	Mean 2-year cancer-related costs for women and men were $42 837 and $36 673, and $44 208 and $44 376, for SEER–GHC and SEER–Blue Shield, respectively; estimates in 2003 dollars
Borie, 2004 (62)	France; registry: physician records	256 patients diagnosed with Dukes A-C in 1992 undergoing resection	Follow-up tests	Mean cumulative 5-year cost was €842 per patient; reported in 1998 euros
Maroun, 2003 (39)	Canada	Estimated 16 856 patients with colon or rectal cancer in Canada diagnosed in 2000	Diagnosis and staging, surgery, hospital, RT, chemotherapy	Average lifetime costs were $29 110 and $34 475 for colon and rectal cancer, respectively; generally higher lifetime costs for higher stage; hospitalization was the largest component (65% and 61% for colon and rectal); estimates in 1988 Canadian dollars
Ramsey, 2002 (40)	United States; SEER–Medicare	Patients aged 65+ with all stages diagnosed 1984–1994	All care	Mean cancer-related payments years 6–11 in men and women were $13 134 and $9180 for stage I and $3147 and $3731 for stage IV; all in 2000 dollars

(*Table continues*)

Table 5 (Continued).

First author, y (ref.)	Country and setting	Sample characteristics	Components of health care included	Findings
Etzioni, 2001 (22)	United States; SEER–Medicare	71 519 patients aged 65+ with all stages diagnosed 1983–1993	All care	Mean 11-year cancer-related payments in men and women were $29 635 and $25 444 for stage I and $3006 and $3665 for stage IV (in 2000 dollars); discounted costs lower for stage IV lower than controls
O'Brien, 2001 (38)	Nova Scotia, Canada; registry: Department of Health	553 patients of all ages and all stages diagnosed 1990	Hospital care	Total hospital costs were $9.8 million dollars ($1300 per person annually), representing 22 460 hospital days in 3 years following diagnosis; year of dollars not stated

* Total costs reflect all services received by cancer patients. Cancer-related costs reflect either the cost of services presumed to be related to cancer treatment or the net cost of all services among cancer patients compared with similar individuals without cancer. All estimates are in US dollars unless otherwise noted. GHC = Group Health Cooperative; MI = Michigan; RT = radiation therapy; SEER = Surveillance, Epidemiology, and End Results.

patients with stage IV disease than stage I disease, reflecting shorter life expectancy in this group (22,40). One study evaluated trends in lifetime costs and survival in patients treated with chemotherapy and found that, compared with 1995–1996, patients treated in 2005–2006 had greater lifetime costs ($63 200 vs $100 300) as well as greater survival (16.5 months vs 23.4 months) (59).

Medical Costs of CRC Care Among Patients Participating in Clinical Trials

Fourteen studies reported the costs of CRC care among patients participating in clinical trials (26,35,37,43,47,49–53,65,71,72) (Table 6). Studies were conducted mainly outside of the United States, in the United Kingdom, France, Italy, Japan, Germany, and Greece. These studies generally measured patterns of care during the period of the trial and applied standardized cost multipliers to the services and procedures observed to estimate patient-level costs. Several studies were multinational and estimated costs for a single country based on all patients in the trial (across countries), whereas others were single-country trials and yielded cost estimates for that country only. Even though the majority of studies reviewed here assessed chemotherapy, and most evaluated metastatic disease, there was significant variability in the choice of comparators, period of evaluation, types of costs included, and level of detail reported.

Nonmedical Costs of CRC Care

Ten studies estimated patient or caregiver time costs or productivity loss associated with cancer (21,25,28,33,56,60,61,64,69,73) (Table 7). Studies were conducted in the United States, Canada, France, and the United Kingdom. Nine were observational studies and one was conducted among a subset of patients from a clinical trial. As in the studies of medical costs associated with CRC care, there was wide variation in the methods for identifying patients or caregivers, components of time or productivity measured, evaluation periods, and approaches for valuing time or lost productivity. Standard approaches for estimating time costs or productivity loss combine wage rates or other measures of the value of time with measures of time, either as self-reported by patients or caregivers through surveys or else derived empirically from medical care utilization data combined with standard service-specific time estimates or actual sick leave records. There was, however, significant variation observed within this general approach. For example, one study surveyed elderly individuals and asked about the number of hours in a recent week they required informal care and compared estimates for those with and without a self-reported diagnosis of cancer (61). Another study of informal caregiving used registries to identify newly diagnosed cancer patients, who then identified a caregiver who was surveyed about the amount of time they had provided informal care to the patient in the years following cancer diagnosis (56).

Discussion

In this study, we conducted a systematic review of recently published studies of the economic burden associated with CRC care to assess data, methods, scope, and the extent to which estimates from these studies can be used in "head-to-head" comparisons. As might be expected, the economic cost associated with CRC care within study generally varied by stage(s) of disease at diagnosis, patient age, observation time (eg, 12 months following diagnosis vs lifetime), types of medical services included, and the scope of costs considered. Depending on the study, included costs ranged from single components of medical care only (eg, hospitalizations) to more comprehensive economic measures of resource use that might include patient time, travel for care, and productivity losses associated with cancer and its treatment. Even within country, we found great heterogeneity across studies in the settings, data sources, populations, means of patient identification, types of medical services, and study methods. Each of these study characteristics can significantly influence the estimation of cancer costs. When they vary together across studies, as is typically the case, even cost calculations with seemingly the same objective are difficult to compare. Complicating factors include features of the healthcare delivery system, accompanying payer model, and data availability, all of which vary by country. Across countries, published aggregate and patient-level cost estimates vary in so many respects that accurate international comparisons are almost impossible. Our findings suggest that valid cost comparisons must be developed de novo with explicit standardization of patient populations, types of medical services included, measures of cost, and choice of methods,

Table 6. Costs of colorectal cancer (CRC) care among patients in clinical trials*

First author, y (ref.)	Country and setting	Sample characteristics	Components of health-care after identification	Findings
De Portu, 2010 (53)	Italy; multisite trial unit costs from National Health Service tariffs, DRGs, and formulary	231 metastatic patients in trial of capecitabine vs 5-FU-based treatment, 2001–2006	Medical-care use for 6 months	Costs of care for patients receiving capecitabine and 5-FU were €1002 and €3173 per month, respectively; differences reflect aministration and drug cost (in 2007 euros)
Mittman, 2009 (35)	Canada; multicountry trial unit costs from standardized estimates from Ontario and study hospital	557 chemorefractory patients in trial of cetuximab + best supportive care vs best supportive care alone	Medical-care use up to 19 months	Overall, incremental cost with cetuximab compared with best supportive care was $23 969, and ICER was $199 742 per life-year gained; for patients with wild-type *KRAS*, the incremental cost with cetuximab was $33 617, and ICER was $120 061 per life-year gained (in 2007 Canadian dollars)
Shiroiwa, 2009 (43)	Japan; multinational trials	1923 metastatic patients in trial of capecitabine plus oxaliplatin (XELOX) or 5-FU/folinic acid and oxaliplatin (FOLFOX4)	Chemotherapy and other drugs over 1 year	Total costs of first and second line outpatient chemotherapy for FOLFOX4 and XELOX were €21 300 and €18 300 and €14 900 and €12 000, respectively; in 2007 euros
Hisashige, 2008 (65)	Japan; trial with standard costs	274 stage-III rectal patients in trial of uracil-tegafur vs no adjuvant treatment following curative resection	Chemotherapy, tests, imaging, AEs, recurrence for 5.6 years	Costs were $8742 for patients treated with uracil-tegafur and $11 199 for surgery alone; estimates in 2005 dollars
Lopatriello, 2008 (26)	Italy; trial in five oncology centers with Italian Healthcare Service tariffs and market retail prices	202 metastatic patients randomized to first-line infusional 5-FU or oral capecitabine	Chemotherapy, AEs, lab tests, and supportive agents	From the Italian health-care service perspective, mean total costs per patient for 5-FU and oral capecitabine were €12 029 and €5781, respectively; €7338 and €4688 from the hospital perspective; differences in the two perspectives reflect national tariffs and market retail prices and payment for infusion administration; year of euros not reported
Maniadakis, 2007 (37)	Greece; multisite trial with unit costs from the National Health Service	276 patients with advanced CRC randomized to FOLFIRI or FOLFOXIRI	Chemotherapy, radiation therapy, AEs	Total cost of therapy in the FOLFOXIRI was significantly higher than the FOLFIRI group (€18 344 vs €12 201); differences in mean chemotherapy costs, second line drugs, and hospitalizations; estimates reported in 2006 euros
Borget, 2006 (71)	France; multicenter trial with unit costs from National Health System reimbursement, cost accounting systems	294 metastatic patients in trial of HD-LV5-FU2, raltitrexed, LD-LV5-FU2, or weekly infusional 5-FU.	Chemotherapy and toxicity or complications, follow-up and travel until disease progression or death	Total costs were €15 970, €14 888, €13 760, and €10 687 for HD-LV5-FU2, LD-LV5-FU2, weekly 5-FU, and raltitrexed, respectively; estimates in 2001 euros
Cassidy, 2006 (47)	United Kingdom; multinational trial standardized costs applied to service use	1987 patients with Dukes C colon cancer randomized to either oral capecitabine or infusional LV + 5-FU	Chemotherapy, AEs, travel over 6 months	Chemotherapy administration higher for 5-FU/LV vs capecitabine (£5151 vs £419), but mean cost of AEs and travel lower in capecitabine as compared to 5-FU-LV; year not stated
Franks, 2006 (72)	United Kingdom; multicenter trial with unit costs from published sources and single hospital	682 patients in trial of conventional vs laparoscopic-assisted surgery	Hospital, treatment for complications, and outpatient	3-month medical and lost productivity costs for patients treated with laparoscopic vs conventional surgery were £6899 vs £6631; year not stated

(*Table continues*)

Table 6 (Continued).

First author, y (ref.)	Country and setting	Sample characteristics	Components of health-care after identification	Findings
Earle, 2004 (52)	United States; multicenter trial with unit costs from Medicare reimbursement and billing data from a single center	291 CRC patients with metastatic disease refractory to 5-FU randomized to either weekly or every 3-week irinotecan	Hospital, ER, chemotherapy, physician up to 1 year	Major cost drivers were chemotherapy, hospitalization, and chemotherapy administration; every 3-week administration of irinotecan associated with cost–utility ratio of $78 627 per QALY; costs reported in 2001 dollars
Monz, 2003 (49)	Germany; multisite trial, unit costs from the perspective German Social Health Insurance based on fee scale, reports, and Red Book	563 patients with UICC II/III in trial of 5-FU + levamisole vs 5-FU + levamisole + FA following surgery	Chemotherapy and follow-up over 5 years of trial	Cancer-related costs were €4909 and €11 085 for patients without and with progression receiving FU + levamisole and €17 122 and €21 330 for patients without and with progression receiving 5-FU + levamisole + FA; ICER of €51 225 for 5-FU + levamisole + FA vs 5-FU + levamisole; cost reported in 2000 euros
Cunningham, 2002 (51)	United Kingdom; multinational trial with standard costs from formulary and hospital tariffs	385 patients with metastatic disease randomized to 5-FU/FA vs irinotecan and 5-FU/FA	In-study treatment and additional chemotherapy up to 3 years	Mean cumulative costs £3767 vs £4220 for irinotecan and 5-FU/FA vs 5-FU/FA, respectively, with incremental cost per LYG £14 794 reflecting improved survival; year of pounds not stated
Levy-Piedbois, 2000 (50)	France; trial with costs from single hospital in Paris	256 patients in trial of irinotecan vs infusional 5-FU	Chemotherapy, clinic and complications up to 1 year	Total cost of treatment for irinotecan vs infusional 5-FU ($14 135 vs $12 192–$12 344); incorporating survival difference, cost-effectiveness ratios ranged from $9344 to $10 137 per additional year of survival; estimates in 1999 dollars

* All estimates are in US dollars unless otherwise noted. AE = adverse event; DRG = diagnosis-related group; ER = emergency room; FA = folinic acid; FU = fluorouracil; HD = high-dose; ICER = incremental cost-effectiveness ratio; LD = low-dose; LV = leucovorin; LYG = life-year gained; QALY = quality-adjusted life-year; UICC = Union for International Cancer Control.

whether the context is within or between health systems or countries. Further, the design of such studies should reflect a detailed understanding of health-system payment and reimbursement policies and their impact on available data (74,75).

Despite these challenges, improving our understanding of how best to measure and report the economic burden of cancer is critical because the aggregate economic burden of cancer, including direct medical costs, direct nonmedical costs, and productivity losses, is expected to increase in the future (8,9,76). To improve comparability across studies, we need more detailed reporting of patient characteristics, methods, and cost estimates by patient subgroups associated with the cost of care (eg, age, stage at diagnosis), the setting of care (eg, inpatient hospitalizations), and the type of cancer-related service (eg, chemotherapy) in both newly diagnosed and prevalent samples. Additionally, because variation in cancer prevalence and population sizes across countries limits national comparisons, reporting of per-person estimates by age, health-care setting, and components of care will allow better national comparisons.

Expected increases in the burden of cancer highlight the importance of evaluating the transferability and economic consequences of effective care delivery and payment models used in other health-care delivery settings and countries. A key component of this rising cost burden is the growing use of more effective, but dramatically more expensive cancer treatments. Cost-effectiveness analyses of alternative cancer treatment interventions clearly require sound estimates of each intervention's associated costs, as well as its benefits in terms of survival or health-related quality of life. Moreover, when cost-effectiveness analyses are focused on cancer prevention or screening, the cost of *cancer care* is still a pivotal input. Specifically, to prevent or delay the onset of a cancer, or to detect it at an earlier stage, is to alter the expected lifetime cost profile of cancer treatment for the individual. Changes in the costs and benefits of CRC treatments also necessarily affect the cost-effectiveness of cancer prevention and screening strategies (77), such that they may become either more or less cost-effective, or even cost-saving. Updating these analyses to reflect changes in CRC costs and benefits may impact policies in countries that use cost-effectiveness to inform formulary policy decisions. Increased standardization of methods to estimate the economic burden of cancer over time, conditional on choice of intervention, can improve the comparability and consistency of information for setting priorities among competing cancer control interventions (76).

The majority of studies we reviewed included just one component of the burden of cancer—direct medical care costs. Fewer studies assessed costs associated with patient and caregiver time or productivity losses associated with cancer and its treatment,

Table 7. Direct nonmedical costs of colorectal cancer (CRC) care*

First author, y (ref.)	Setting	Sample characteristics	Components included	Findings
Hopkins, 2011 (73)	Canada; Canadian Community Health Survey	929 individuals with cancer aged 19–65 in 2005	Household wage loss	Annual mean cancer-related wage loss of $17 729 and national household cancer-related wage loss of $2.95 billion; wages in 2009 Canadian dollars
Van Houtven, 2010 (60)	United States; CanCORS survey about caregiving and wages	1629 caregivers of patients of all stages and ages surveyed in 2005 either 6 months–1 year or 1–2 years following patient diagnosis	Time caregiving and out-of-pocket costs	Mean cumulative time and out-of-pocket costs were $12 618 and $1442 over periods ranging from 6 months to 2 years since patient diagnosis; costs reported in 2005 dollars
Yabroff, 2009 (56)	United States; survey of caregivers of patients from registries	688 caregivers surveyed about 2-year period following patient diagnosis, 2003–2006	Time providing informal care to the patient since diagnosis	Average of 13.7 months and 8.3 hours per day providing informal care after patient diagnosis; time costs ranged from $28 363 to $50 060 with approach for valuing time
Yabroff, 2007 (64); Yabroff, 2005 (33)	United States; SEER–Medicare, multiple data sources for time	213 278 patients with all stages of disease, diagnosed 1973–1999 aged 65 and older 1995–2001	Service counts, estimates of service time, and wage rates	Cancer-related patient time in initial phase of care was 243.5 hours and time cost ranged from $3432 to $5279 depending on approach to value time; in last year of life, 282.3 hours and time cost ranged from $3986 to $6325
Longo, 2006 (25)	Ontario, Canada; outpatient cancer clinics	261 patients of all ages with breast, colorectal, lung, and prostate cancers 2002–2003	Out-of-pocket costs and days missed from work	The mean monthly out-of-pocket and travel costs were $213 and $372, respectively; in the previous 30 days, caregivers and employed patients lost 7 days and 12.6 days from work, respectively, at $101 per day of work missed
Chang, 2004 (21)	United States; MarketScan	Employed patients with a cancer diagnosis code and workplace absence and short-term disability in 1999	Absenteeism, copays, and deductibles	Cancer patients had more absenteeism ($373 vs $101 per month) and short-term disability days ($698 vs $25 per month); employee caregivers had higher absenteeism ($255 vs $161 costs per month) and copays and deductibles ($302 vs $29 per month); year of wages not stated
Selke, 2003 (69)	France; GAZEL cohort, health insurance payments	All patients in 1999	Disability allowance and work days lost in year after diagnosis	Costs to French social security system were €85.9 million in 1999
Hayman, 2001 (61)	United States; 1993 AHEAD Survey	303 individuals receiving cancer treatment, 718 with cancer history, but not in treatment, and 6422 without cancer; all aged 70+ in 1993	Caregiving hours, valued with wage rates	Adjusted weekly hours of informal caregiving were 6.9, 6.8, and 10.0 for individuals without cancer, with a cancer history, and undergoing cancer treatment, respectively; annual cost of informal caregiving estimated to be $3000, $2900, and $4200, respectively; wages in 1998 dollars
Sculpher, 2000 (28)	United Kingdom; multicountry trial with patient and caregiver travel and time	270 patients with advanced disease in a trial of raltitrexed and 5-FU + LV treatment until progression	Travel and time costs during the trial	Total mean time cost per patient higher for 5-FU + LV vs raltitrexed (£486 vs £378), reflecting greater travel and longer treatment times for patients receiving 5-FU + LV; estimates with 1997 prices

* All estimates in US dollars unless otherwise noted. AHEAD = Asset and Health Dynamics; CanCORS = Cancer Care Outcomes Research and Surveillance Consortium; FU = fluorouracil; GAZEL = GAZ and ELectricité; LV = leucovorin; MarketScan = Coordination of Benefits and Health and Productivity Management; SEER = Surveillance, Epidemiology, and End Results.

but findings in those studies suggest such costs can be substantial and important for understanding the societal burden of cancer (21,25,60,61,64,69,73,76). Additionally, patient time costs are a recommended component of cost-effectiveness analysis of prevention, screening, and treatment interventions (78), but are still rarely included in these studies, in part because these data are not routinely collected. However, their exclusion may bias estimates of cost-effectiveness towards interventions that place a greater time burden on patients and their families (79). As with studies of direct medical costs, reporting of per-person estimates by age, health-care setting, and components of care will allow better comparisons across studies. Further, reporting of intermediate estimates (eg, time, days lost from work) will allow comparisons across studies where the "cost" component is based on different wage structures or different assumptions about the value of time for the underlying populations. Studies conducted in countries with comprehensive data describing cancer incidence and survival and employment and population characteristics (ie, Sweden, Norway) have reported lower incomes for individuals diagnosed with cancer and also their spouses (80) and increased use of sick leave among spouses (81), although these studies did not quantify the impact on employment in economic terms.

Thus, to strengthen the data available for estimating the nonmedical economic burden of cancer, increased attention should be devoted to linking data on cancer incidence and survival with longitudinal information on labor market participation and earnings and the allocation of time to medical care–related activities and, in parallel, to developing additional sources of information on the nonmedical burden of cancer. These could include targeted enhancements to existing population-based surveys, such as the Medical Expenditure Panel Survey Experiences with Cancer Survivorship Supplement in the United States (82). Developing a more comprehensive picture of the economic burden of cancer for the patient and family could inform decisions in the workplace. In particular, these data can be important for employers interested in minimizing the impact of cancer on patient and caregiver employment outcomes, including presenteeism and workplace productivity, absenteeism, and overall retention. Including other components of the burden of cancer, such as patient time costs, caregiver burden, and productivity losses, will improve our understanding of the societal impact of cancer and may inform further development of employment policies.

We observed clearly discernible relationships between the country where a study was performed, study design, and the approaches used for estimating either the prevalence or incidence cost of care. The majority of US studies were observational, whereas the majority of studies in other countries were based on clinical trials focusing on the cost or cost-effectiveness of treatment interventions, presumably to inform coverage decisions by national formularies (ie, NICE) or other purchasers. Other differences in health-care systems, and hence the nature of the data available for cost analyses, influenced the types of studies conducted. For example, the majority of CRC cost studies in the United States were conducted among patients aged 65 and older, using the linked SEER registry–Medicare claims data. By implication, very few studies were conducted in the under-65 population, which leaves an important research gap because cancer care is typically more aggressive in younger compared with older patients within stage at diagnosis (83). In addition, the difference in comorbidity between cancer patients and noncancer controls is greater in the under-65 population compared with the elderly. In the United States, information about health-care use and payments is available primarily from health insurance claims, and the largest population with comprehensive and longitudinal claims and enrollment information currently consists of Medicare enrollees, aged 65 and older. Current efforts to estimate the longitudinal costs of CRC care for patients of all ages in the managed care population and state-based efforts to link population-based cancer registry with multiple public and private claims databases may help address these important data gaps (84–86).

The studies based on clinical trials used service frequencies collected as part of the trial, and actual costs or standardized service-specific costs that were then applied to service use, to estimate CRC treatment costs. An important advantage of this microcosting approach is that it allows country-specific and importantly comparable estimates to be generated from multinational trials. Also, cost estimates are based on actual care received, rather than hypothesized treatment pathways or patterns of care derived from treatment guidelines. Yet, cost studies that capture trial-based service use and apply unit cost multipliers to reflect local circumstances may have other limitations (87–89). Microcosting has also been used in some observational studies, particularly in countries where health coverage is applied centrally (thus, no individual billing). However, the care provided in clinical trials does not reflect typical care in community settings, including "induced costs" for some care that would not occur outside the trial setting. There are, however, processes for defining similar populations of patients, standardizing service and procedure definitions, and taking other steps to promote comparability of cost estimates across observational studies (75,90,91).

Prior reviews have described methodological limitations with descriptive economic studies (12) as well as cost-effectiveness analyses (92). We observed many of the same limitations here. Patient characteristics that influence care and costs, such as age distribution and stage of disease at diagnosis, were frequently not reported, nor were methods used to estimate costs always clearly stated. Many economic studies based on treatment trials did not report the number of patients providing data for the economic study compared with the underlying treatment trial, or reported a smaller sample in the economic study than in the treatment trial, suggesting the potential for bias in the included sample (ie, not conducted in a truly randomized population). Several studies based on multinational trials did not report the number of patients from the country of interest. Reporting of patient characteristics that influence care and costs is critical for evaluation of the study and any comparisons across studies.

We also identified a number of specific methodological concerns in the studies reviewed here, related to sample selection and representativeness, phase of care definitions, and the analysis of cost data over time. Several observational studies used diagnostic or procedure codes from health-care claims to identify patients—an approach that identifies prevalent rather than incident patients, overidentifies individuals without cancer from "rule-out" diagnostic procedures, and underidentifies patients whose cancer care lacks

detailed coding or does not indicate receipt of specific procedures or treatments. Additionally, diagnostic codes may reflect metastatic rather than primary tumor sites.

Finally, we identified concerns with aspects of the cost data analysis and reporting, including omission of inflation price adjusters and inadequate (or inadequately explained) methods for handling missing, censored, or highly skewed cost data. Standards for conducting and reporting cost-effectiveness analyses have been published (78), but we were not able to identify any published standards for conducting and reporting cost analyses in observational studies. Developing standards for observational studies and encouraging adherence to existing standards for cost-effectiveness analyses will be important for future efforts (1,93,94), particularly with expected increases in targeted therapies that are both more effective and more expensive than current regimens. Importantly, the methodological limitations for specific studies also constrain the comparisons that can be made between studies.

We used MEDLINE, one of the largest publications databases devoted to biomedicine and health (ie, more than 5500 journals in 39 languages), to identify studies for inclusion in our review. We then reviewed the reference lists of included studies to identify additional eligible studies. It is possible that we may have missed some other eligible studies by not using additional publications databases (eg, EMBASE), but it is unlikely that our observations of heterogeneity across studies in reporting and methods and concerns about comparability across studies would be altered by missing some studies.

In summary, we found significant heterogeneity across economic studies of CRC care, greatly limiting comparisons across countries and across data sources and patient populations within country. Of particular importance for future research is greater standardization of reporting and costing methods, increased attention to patient and caregiver time costs and lost productivity, and development of data resources that improve the quality, scope, and comparability of studies over time.

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Note

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Variations in Cancer Survival and Patterns of Care Across Europe: Roles of Wealth and Health-Care Organization

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Cancer survival varies markedly across Europe. We analyzed variations in all-cancer 5-year relative survival in relation to macroeconomic and health-care indicators, and 5-year relative survival for three major cancers (colorectal, prostate, breast) in relation to application of standard treatments, to serve as baseline for monitoring the efficacy of new European initiatives to improve cancer survival. Five-year relative survival data were from the European cancer registry–based study of cancer patients' survival and care (EUROCARE-4). Macroeconomic and health system data were from the Organisation for Economic Co-operation and Development, and European Observatory on Health Care Systems. Information on treatments given was from EUROCARE studies. Total national health spending varied widely across Europe and correlated linearly with survival ($R = 0.8$). Countries with high spending had high numbers of diagnostic and radiotherapy units, and 5-year relative survival was good (>50%). The treatments given for major cancers also varied; advanced stage at diagnosis was associated with poor 5-year relative survival and low odds of receiving standard treatment for breast and colorectal cancer.

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Cancer is the second most important cause of death in Europe. According to GLOBOCAN, 2.5 million new cancer cases and 1.3 million cancer deaths occurred in 2008 in the 27 member states of the European Union (population is 497 455 033) (1). Nevertheless, cancer incidence and mortality vary by a factor of two across the continent. Survival also varies markedly: As documented by the European cancer registry–based study of cancer patients' survival and care (EUROCARE-4) (2), survival is generally low in low-income Eastern Europe and high in the high-income countries of Northern and Western Europe (2).

This large variation in cancer burden suggests that much can be done to lessen it by bringing national health-care systems up to or close to the level of the best. Several studies have found correlations between cancer survival and macroeconomic variables such as countries' overall wealth and spending on health (3–6). Health spending depends ultimately on a country's wealth, but also varies widely in relation to social factors and the varying organizational structures of national health systems (7). In some countries, the health service is mainly public; in others, the private sector plays an important role. Methods of financing also vary: In some countries, costs are met almost entirely out of general taxation (national health systems); in others, insurance plays a major role (social insurance systems) and may be mutual (organized by trade or professional associations or government and essentially nonprofit) or private.

The aim of the present study was: 1) to analyze variations in all-cancer survival across European countries in relation to macroeconomic and health-care system indicators; 2) to analyze survival for three major cancers (colorectal, prostate, and breast) in relation to adherence to accepted treatment guidelines.

Materials and Methods

Sources of Information

Relative Survival for All Cancers Combined. Survival data were obtained from EUROCARE-4. The EUROCARE-4 study checked, archived, and analyzed incidence and follow-up information on cancer patients diagnosed from January 1, 1978, to December 31, 2002, collected by European cancer registries (CRs). Here we made use of 2000–2002 period estimates of 5-year relative survival for all cancers combined produced by Verdecchia et al. (2) and based on cases registered in 1996–2002 by 47 of the CRs participating in EUROCARE-4. There were 12 national CRs (100% national coverage) covering 9 countries (Austria, Finland, Iceland, Ireland, Malta, Norway, Slovenia, Sweden, and the United Kingdom) and 36 regional CRs representing 10 countries (Belgium, Czech Republic, France, Germany, Italy, the Netherlands, Poland, Slovakia, Spain, and Switzerland) with national coverage ranging from 1% for Germany and France to 58% for Belgium (2).

Macroeconomic and Health-Care System Indicators. The main macroeconomic indicator we used was total national expenditure on health (TNEH) obtained from the Organisation for Economic Co-operation and Development (OECD) (7,8). TNEH measures current health expenditure (total consumption of health-care goods and services) plus capital investment in health-care infrastructure (7) and includes public and private spending on medical services and goods, public health and prevention programs, and administration. It excludes health-related expenditures such as training, research, and environmental health. To compare the overall consumption of health goods and services across countries at a given point, total health expenditure per capita was converted into

US dollars and adjusted to take account of the varying purchasing power of national currencies (parity purchasing power, US$PPP). Information used to estimate TNEH was obtained from national health accounts (NHAs). NHAs obtain estimates based on expenditure information collected within an internationally recognized framework. The estimates vary in their reliability depending on the availability and quality of national information; however, estimates are sent to the respective Ministries of Health each year for validation. The figures presented in this paper refer to 2002.

We also used information on availability of medical devices or equipment, extracted from the OECD (7). Specifically, we extracted information on computed tomography (CT), magnetic resonance imaging (MRI), and radiotherapy (RT) equipment, including linear accelerators, cobalt-60 units, cesium-137 units, and low orthovoltage X-ray units (brachytherapy units normally excluded). For CT, MRI, and RT devices, numbers per million of population in 2002 are reported. For most countries, the numbers include equipment installed in hospitals and outpatient units. However, coverage is only partial for some countries. In particular, the data for the United Kingdom refer only to devices in the public sector, and in Spain the data refer only to devices in hospitals; thus, for these countries the total numbers of devices are underestimated. Information on RT equipment was also obtained from the Quantification of Radiation Therapy Infrastructure and Staffing Needs (QUARTS) project, which provided estimates of RT infrastructure needs in relation to estimates of actual numbers available in EU countries, based on the best available evidence (9).

We obtained information on European health-care systems from the European Observatory on Health Care Systems and Policies, which classifies such systems into two basic types based on mode of funding: either funded by compulsory health insurance (social insurance systems) or paid for out of general taxation (national health systems) (10,11). The Austrian, Belgian, Czech, Dutch, French, German, Polish, Slovak, Slovenian, and Swiss health systems are funded by insurance, whereas the Finnish, Icelandic, Irish, Italian, Norwegian, Spanish, Swedish, and UK systems are tax-based.

Survival and Standard Care. High-resolution studies make it possible to interpret survival differences between countries by relating those differences to detailed information on stage at diagnosis, staging procedures, and treatments. The latter information was collected for representative samples of cases selected from population-based CR archives. Here we used results from published EUROCARE high-resolution studies on breast, colorectal, and prostate cancer (12–14). Cases to the breast cancer study were contributed by 26 CRs from 12 countries (Denmark, Estonia, Finland, France, Iceland, Italy, Poland, Slovakia, Slovenia, Spain, Sweden, and the Netherlands) (12); 11 CRs from 8 countries (Estonia, Finland, France, Italy, Poland, Slovenia, Slovakia, and Spain) contributed cases to the colorectal cancer study (13); and 12 CRs from 6 countries (France, Italy, Poland, Slovakia, Spain, and the Netherlands) to the prostate cancer study (14).

The range of cancer survival in these studies reflected that documented across the Europe as a whole. Each CR was asked to provide detailed information on diagnostic and treatment procedures, obtained by consulting individual clinical records and abstracted onto a standard form. The studies analyzed 13 485 breast, 6871 colorectal, and 3486 prostate cancer cases diagnosed in 1994–1999, the large majority in 1996–1998.

From these studies, indicators of adherence to "standard care" for the treatment of these cancers were also estimated and related to 5-year relative survival (15). The following indicators of standard care were used:

- **Breast cancer:** 1) Proportion of early-stage cancers receiving breast-conserving surgery plus RT (BCS + RT); 2) proportion of lymph node–positive (N+) patients receiving chemotherapy (12)
- **Colorectal cancer:** 1) Proportion resected with curative intent; 2) proportion of stage III colon cancer cases receiving adjuvant chemotherapy; 3) proportion of stage I–III rectal cancer cases receiving neoadjuvant/adjuvant RT (13)
- **Prostate cancer:** 1) Proportion of patients treated radically (prostatectomy or RT); 2) use of radical therapies in relation to the cancer risk class (high vs low) proposed by Miller et al. (14,16)

The odds of being treated according to the above modalities by country and adjusted by age and sex were estimated by logistic regression (12–14). The CRs providing data for these studies were grouped by country and the countries grouped into regions: Northern Europe (Iceland, Denmark, Sweden, and Finland), Central Europe (France and the Netherlands), Eastern Europe (Estonia, Slovakia, and Poland), and Southern Europe (Italy, Slovenia, and Spain).

Results

Relation of TNEH and Health-Care System Organization to All-Cancer Survival

Figure 1 shows the relationship between TNEH and the age-adjusted 5-year relative survival for all cancers combined. Each dot represents a country, and its color (black or white) identifies the type of health-care system (national health vs social insurance). Countries were grouped into four TNEH classes (<999 US$PPP, 1000–1999 US$PPP, 2000–2999 US$PPP, and >3000 US$PPP). In general, countries with high TNEH had good survival. Sweden and Finland had survival similar to or better than countries with higher TNEH. Ireland and the United Kingdom had lower survival than countries with similar TNEH. Spain had better survival than expected from its moderate health expenditure. TNEH and survival correlated linearly, with TNEH explaining over 50% of the survival variance (R = 0.8). However, after removing the Eastern European countries of Poland, Czech Republic, Slovakia, and Slovenia, which had the lowest expenditure and lowest survival, the TNEH–survival correlation was much weaker (R = 0.4). Many of the countries with national health systems (specifically Iceland, Sweden, Finland, Norway, Italy, and Spain) had better survival than those with social insurance systems (specifically Austria, France, Switzerland, Germany, the Netherlands, the Czech Republic, Slovakia and Slovenia).

Table 1 shows relative survival by country in relation to numbers of CT, MRI, and RT devices available, with countries ranked by decreasing per capita TNEH. From this table, it is evident that

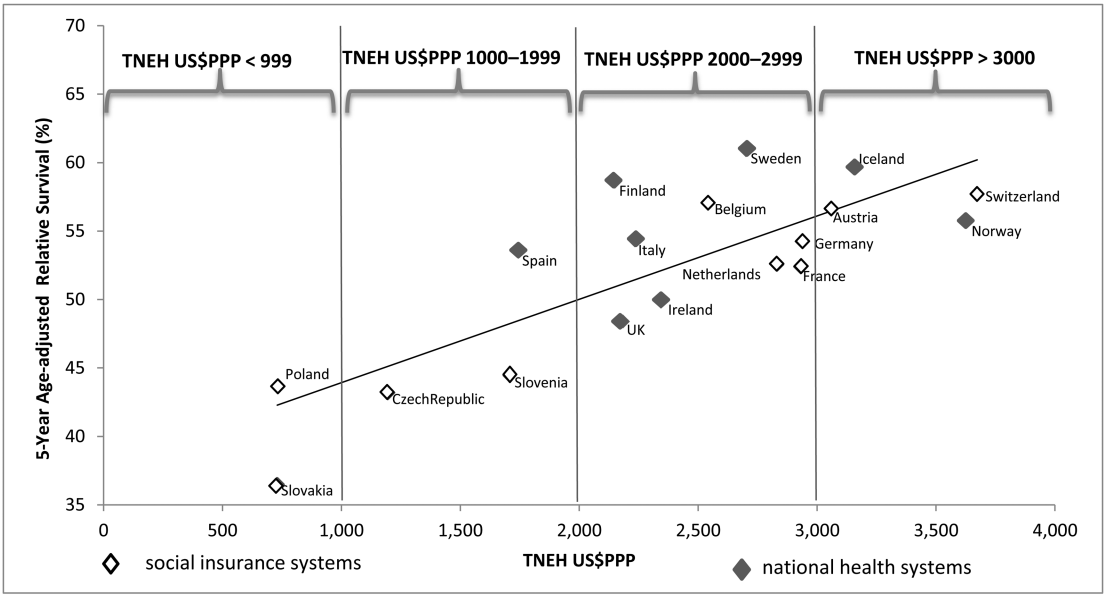

Figure 1. Relationship between total national expenditure on health (TNEH), expressed as US dollar parity purchasing power (US$PPP), and the 5-year age-adjusted relative all-cancer survival (%) by country and national health-care system organization.

Table 1. Medical devices and total national health expenditure (TNEH) expressed as US dollar parity purchasing power (US$PPP) in 2002, in relation to 5-year age-adjusted relative all-cancer survival (period 2000–2002) by country*

	CT per million population	MRI per million population	RT per million population	Actual/ needed RT capacity, %	TNEH, US$PPP	5-year relative survival, %
Switzerland	18	14.1	10.6	NA	3673	58
Norway	NA	NA	NA	NA	3628	56
Iceland	20.9	17.4	13.9	NA	3156	60
Austria	27.2	13.4	4.5	NA	3057	57
Germany	14.2	6	4.6	60–80	2934	54
France	9.7	2.7	6	90	2931	52†
The Netherlands	NA	NA	NA	60–80	2833	53
Sweden	14.2	7.9	NA	90	2702	61
Belgium	28.8	6.6	NA	90	2542	57
Ireland	NA	NA	NA	NA	2344	50
Italy	23.4	10.6	4.3	60–80	2235	54
United Kingdom	5.8‡	5.2‡	3.9‡	50	2184	48
Finland	13.3	12.5	8.8	NA	2150	59
Spain	12.9§	6.2§	3.7§	NA	1745	54
Slovenia	NA	NA	NA	<40	1706	44
Czech Republic	12.1	2.2	6.7	50	1195	43
Poland	5.8	0.9	NA	<40	733	44
Slovakia	8.7	2‖	7.1‖	NA	730	37†
Malta	NA	NA	NA	NA	NA	49

* Countries ranked by TNEH. CT = computed tomography; MRI = magnetic resonance imaging; NA = not available; RT = radiotherapy. Data on CT, MRI, RT, and TNEH from Organisation for Economic Co-operation and Development (7,8). Data on actual/needed RT capacity (%) from Bentzen, et al. (9). Survival data from EUROCARE-4 (2), for France and Slovakia from http://www.eurocare.it.

† Relative survival estimated by cohort approach for diagnostic period 1995–1999.

‡ UK data refer to devices in public sector only.

§ Spanish data pertain only to devices available in hospitals.

‖ MRI and RT data for 2001.

countries with high TNEH (>3000 US$PPP) had the highest numbers of CT, MRI, and RT devices. Countries with TNEH between 2000 and 3000 US$PPP still had relatively high numbers of CT units, ranging from 28 (per million) in Sweden to 14 in Finland, but fewer of the more expensive MRI units. Countries with low TNEH had considerably more CT than MRI units. The correlation between TNEH and MRI was 0.65 and between TNEH and CT was 0.54. Table 1 also shows that all-cancer relative survival

was better in countries with high numbers of CT and MRI units. Relative survival correlated more strongly with availability of diagnostic equipment (particularly MRI; $R = 0.7$) than availability of therapeutic irradiation equipment ($R = 0.3$); however, RT data were missing for many countries. Table 1 also shows QUARTS (9) estimates of the availability of RT equipment as a percentage of that required—estimated from the observed incidence of cancers requiring RT treatment. Slovenia and Poland followed by the Czech Republic and the United Kingdom—all countries with relatively low survival—had the largest gaps between actual and required CT equipment.

At the other end of the range, Sweden, France, and Belgium were the only countries where the availability of megavoltage RT units (in 2003) equaled or exceeded 90% of the QUARTS-estimated need. Sweden and Belgium had high survival. Germany and Italy had relatively good survival in relation to the limited number of RT devices available, even though the actual numbers of RT devices available amounted to 60–80% of requirements.

Survival and Standard Care

Breast Cancer. Overall 55% of the early-stage (T1N0M0) breast cancer patients received BCR + RT (considered standard care) (Figure 2). However, there was marked variation: from 9% in Estonia to 78% in France, and from 20% in Eastern Europe through 47% in Northern Europe, 57% in Southern Europe, to 72% in Central Europe (data not shown). When the data were adjusted by age and tumor size, the odds of receiving BCR + RT (France as reference) were again lowest in Eastern Europe (Estonia, Slovakia, and Poland).

Overall 63% of node-positive breast cancer patients and most (91%) node-positive premenopausal patients received adjuvant chemotherapy (Table 2). Although between-country variation in treatment with adjuvant chemotherapy was marked, especially for the oldest age category, variation was less than for treatment with BCT + RT and showed a different regional pattern: 74% received adjuvant chemotherapy in Eastern Europe, 39% in Northern Europe, 51% in Central Europe, and 70% in Southern Europe. Five-year survival was, as expected, related to stage at diagnosis, in that countries with the lowest survival also had the highest proportion of women with advanced stage at diagnosis (Table 2).

Colorectal Cancer. Overall 71% of colorectal cancer patients were surgically treated with curative intent, ranging from 54% (Poland) to 83% (Italy) (Table 3). Overall 30% of patients had advanced disease at diagnosis. The Eastern European countries had high proportions (>30%) of advanced-stage cases and also lowest proportions of surgically treated cases. High proportions of advanced-stage cases correlated with poorer 5-year survival (Table 3).

Table 4 shows the proportions of stage III colon cancer cases treated with curative intent that also received adjuvant chemotherapy. Overall 46% received adjuvant chemotherapy, with wide variation by country. Adjusting for age, sex, and registry in a multivariable analysis, in four countries (France, Italy, Spain, and Slovakia) stage III cases were significantly more likely to receive adjuvant chemotherapy than Slovenia (reference), and only Polish stage III cases were significantly less likely to receive adjuvant chemotherapy than reference. Adjuvant chemotherapy was less frequently (16%) given to older (>75 years) rather than younger patients (65–74 years, 50%; <65 years, 69%) (Table 4).

Overall only 12% of stage I–III rectal cancers treated with curative intent received neoadjuvant/adjuvant RT (Figure 3). The between-country variation in proportion receiving this standard treatment (1.3% in Slovakia to 51% in France) was greater than the variation in colon cancer cases receiving adjuvant chemotherapy. Multivariable analysis showed that rectal cancer patients in Spain (Navarra), France (Côte-d'Or), Estonia, and Finland (Tampere) had significantly greater odds of receiving RT than those in Slovenia (reference).

Prostate Cancer. About one in three patients received radical treatment (radical prostatectomy or RT), with prostatectomy

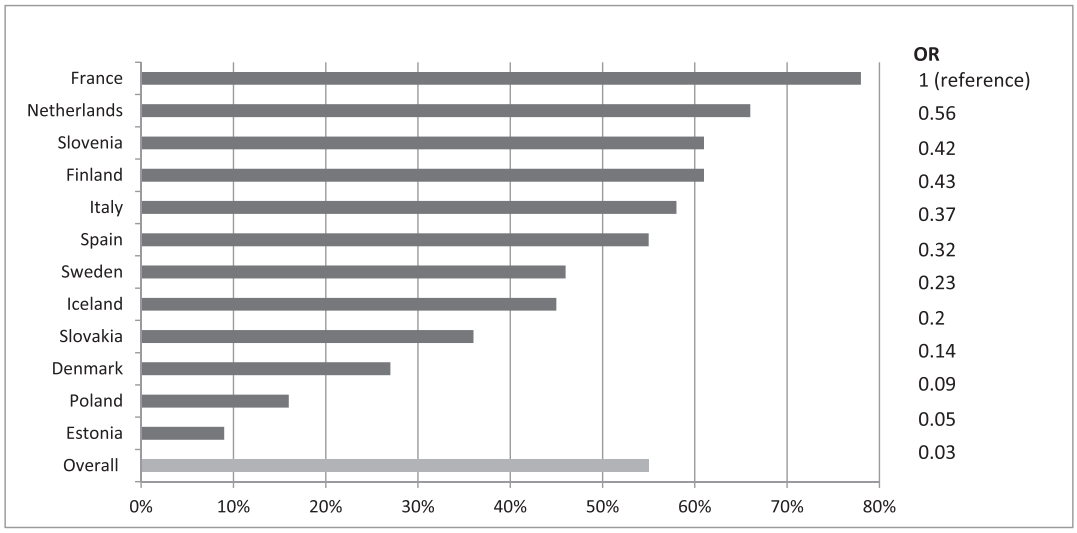

Figure 2. High-resolution study on breast cancer: proportions of T1N0M0 cases that received breast-conserving surgery plus radiotherapy with odds ratios (ORs) by country. Data from EUROCARE high-resolution study (12).

Table 2. High-resolution study on breast cancer: proportions of lymph node–positive (N+) patients who received adjuvant chemotherapy by age, and proportions with advanced stage at diagnosis and 5-year relative survival (cohort 1995–1999) by country and European region*

Country/region	Percentage of N+ breast cancer patients receiving adjuvant chemotherapy by age			Proportion of breast cancer patients with advanced stage, %	5-yr relative survival, %
	All ages	Age 15–49	Age 55–99		
Denmark	21	53	16	54	77.5
Estonia	46	98	77	57	NA
Finland	52	82	23	34	83.5
France	54	90	51	34	77.5
Iceland	56	90	40	40	87.5
Italy	47	84	61	44	82.7
Poland	76	89	46	52	73.9
Slovakia	72	96	73	58	61.6
Slovenia	85	99	67	50	71.9
Spain	71	97	69	42	80.3
Sweden	74	81	16	43	84.7
The Netherlands	66	93	15	34	81.4
Northern Europe	39	83	24	42	80.4
Central Europe	51	85	34	34	79.8
Eastern Europe	74	96	59	55	67.1
Southern Europe	70	92	65	44	81.6
All cases	63	91	52	43	80.5

* Northern Europe includes Iceland, Denmark, Sweden, and Finland; Central Europe includes France and The Netherlands; Eastern Europe includes Estonia, Slovakia, and Poland; Southern Europe includes Italy, Slovenia, and Spain. Data from EUROCARE high-resolution (12) and EUROCARE-4 studies (15), for Slovakia from http://www.eurocare.it. NA = not available (country not included in EUROCARE-4).

Table 3. High-resolution study on colorectal cancer: numbers of cases studied and proportions undergoing surgery with curative intent, with odds (odds ratio [OR], 95% confidence interval [CI]) of receiving curative intent resection, and proportions of advanced cases, by country and European region*

Country/region	N cases	Resected with curative intent, %	OR for resection with 95% CI			Advanced cases, %	5-yr relative survival based on total incident cases, %	Total incident cases, N
Estonia	560	56	0.5	0.4	0.7	33	NA	NA
Finland	523	74	1.3	1.0	1.7	26	58	8737
France	561	77	1.6	1.2	2.0	25	57	1371
Italy	1100	83	2.3	1.9	2.8	26	55	6586
Poland	786	54	0.5	0.4	0.6	36	35	3071
Slovakia	581	63	0.7	0.6	0.9	34	39	10286
Slovenia	940	70	1.0			30	44	4290
Spain	1820	76	1.6	1.4	1.9	31	51	4419
"Western" Europe	4944	76	1.6	1.5	1.8	29	53	25403
Eastern Europe	1927	57	0.6	0.5	0.6	35	38	13357
All cases	6871	71	1.3	1.3	1.4	30	48	38760

* Northern, Central, and Southern Europe comprise "Western Europe," or Finland, France, Italy, Slovenia, and Spain; Eastern Europe includes Estonia, Slovakia, and Poland. Data from EUROCARE high-resolution (13) and EUROCARE-4 studies (15), for Slovakia from http://www.eurocare.it. NA = not available (country not included in the EUROCARE-4).

performed more often than RT (22% vs 14%) (Table 5). Less than 30% of prostate cancer cases were treated radically in Slovakia, Poland, and Spain; 40% or slightly more were radically treated in the Netherlands (55%) and France (40%). Overall, radical treatments were given to 61% of high-risk and to 34% of low-risk cases (Table 5). For all countries, except Slovakia, proportionately more high-risk patients received radical treatment.

Five-year prostate cancer survival was slightly above 80% in the Netherlands, Italy, and France, and the proportion of M+ cases was lowest (<18%) in the same countries. The Polish registry of Krakow with 32% M+ at diagnosis had the lowest (46%) 5-year survival. In fact, overall the proportion of M+ cases was inversely related to the proportion radically treated.

Discussion

This paper has analyzed population-based data. The main outcome considered was 5-year relative survival, estimated using the EUROCARE methodology (2,15). The economic and health indicators used were those estimated by the OECD and are, therefore, authoritative (7,8). The main limitation is that data were not always collected according to uniform criteria. Thus, data on diagnostic

Table 4. High-resolution study: numbers and proportions of stage III colon cancer cases treated by curative intent surgery and adjuvant chemotherapy with odds of receiving that treatment (odds ratio [OR]) with 95% confidence interval (CI), by country and by age*

Country/age	N cases	Resected stage III cases given adjuvant chemotherapy, %	OR	95% CI	
Estonia	37	46	1.2	0.5	2.8
Finland	45	42	1.7	0.8	3.8
France	62	52	2.9	1.4	5.9
Italy	153	40	2.6	1.5	4.4
Poland	46	26	0.4	0.2	0.8
Slovakia	33	73	5.2	1.9	13.8
Slovenia	115	45	1.0		
Spain	228	50	2.5	1.6	3.7
<65 years	240	69	1.0		
65–74 years	261	50	0.4	0.2	0.6
≥75 years	218	16	0.1	0.0	0.1
All cases	719	46			

* Data from EUROCARE high-resolution study (13).

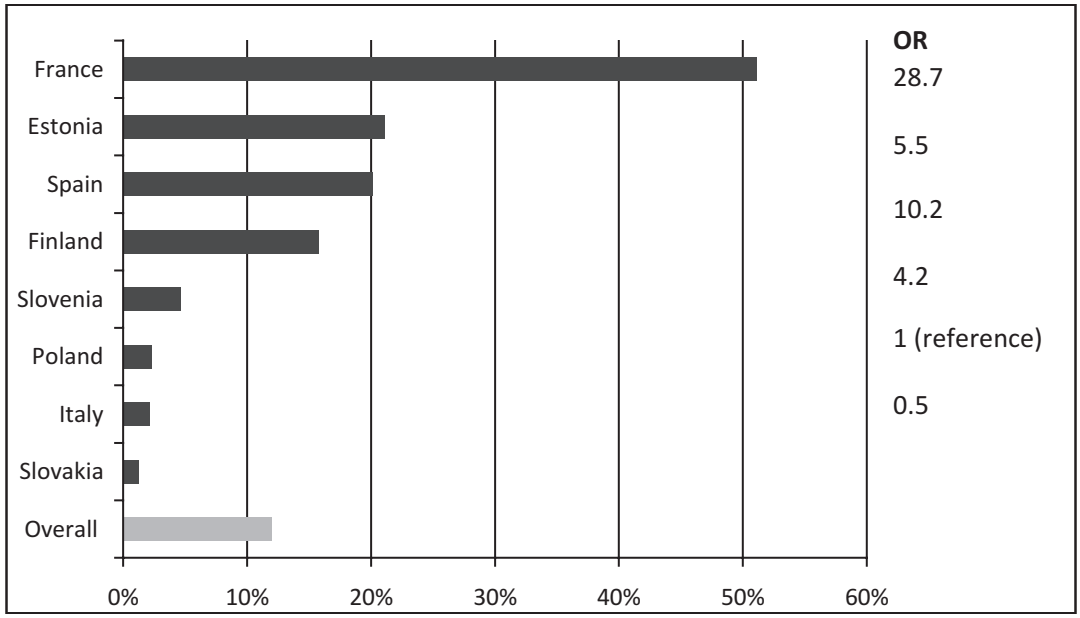

Figure 3. High-resolution study on colorectal cancer: proportions of stage I–III rectal cancer cases treated with curative intent surgery that also received adjuvant radiotherapy by country, with odds ratios (ORs). Data from EUROCARE high-resolution study (13).

or therapeutic device availability were collected in different ways in different countries; survival data were provided by CRs covering entire countries in some cases, but only parts of countries in other cases; adherence to standard treatment was estimated from representative samples of cases provided by CRs participating in high-resolution studies and may not be representative of the case-mix at the national level. However, the survival rates for prostate, breast, and colorectal cancer in the areas covered by CRs included in the high-resolution studies were similar to the national survival estimates. This supports the idea that CRs and the cases reviewed provide a good description of the case population.

We found that both 5-year relative survival for all cancers combined and adherence to standard treatment for major cancers varied markedly between countries. These variations were larger than regional variations documented across the United States, Australia, and Canada (17,18).

Relation of TNEH and Health-Care Organization to All-Cancer Survival

In the last decade, health expenditures grew in real terms by around 3% per year, on average, across OECD countries (including European countries), with similar growth patterns in the European Union and the United States (7). However, considerable variations across countries were observed in health spending growth over time (7). Focusing on 1992–2003, several countries (e.g., Czech Republic, Ireland, and Poland) with lower income and lower health expenditures per capita in the early 1990s experienced exceptionally high growth in health expenditure. By contrast,

Table 5. High-resolution study on prostate cancer: proportions of patients receiving radical treatment by type of treatment and risk group (high risk and low risk), and proportions of metastatic cases (M+) and age-adjusted survival by country and region*

		Radical treatment						
		Type			According to risk			
Country/region	N	RP, %	RRT, %	RP + RRT, %	High, %	Low, %	M+, %	5-year relative survival, %
France	991	21	19	40	67	33	17	80.3
Italy	1166	30	8	38	60	31	11	81.0
Poland	261	13	14	27	44	34	32	46.1
Slovakia	435	19	4	23	29	36	43	47.2
Spain	326	11	12	23	58	22	22	75.0
The Netherlands	307	19	36	55	75	56	12	82.9
Central Europe	1298	21	23	44	69	39	16	81.0
Eastern Europe	696	17	8	25	34	35	39	47.0
Southern Europe	1492	26	9	35	60	29	13	81.0
All cases	3486	22	14	36	61	34	19	72.5

* Central Europe includes France and the Netherlands; Eastern Europe includes Slovakia and Poland; Southern Europe includes Italy and Spain. Data from EUROCARE high-resolution (14) and EUROCARE-4 studies (15), for Slovakia from http://www.eurocare.it. RP = radical prostatectomy, RRT = radical radiotherapy.

some countries (e.g., Finland, Germany, and Italy) experienced slow growth, both in total and public expenditure on health, following the introduction of cost containment measures in the early 1990s (7). Mean European 5-year relative survival for all cancers combined increased significantly from 44% in 1988 to 50% in 1999. The increase was almost linear up to 1994–1996, and then it slowed. Countries with poor relative survival at the beginning (e.g., Poland, Czech Republic, and Slovenia) had larger increases in survival for all cancers combined (6–10%) than countries with high levels (northern European countries and Switzerland). This caused some reduction in between-country survival variation from 1988–1990 to 1997–1999 (19). In 2002, Norway and Switzerland had the highest per capita spending, with almost 4000 US$PPP. At the other end of the scale, Poland and the Czech Republic spent about 1000 US$PPP on health in 2002. A previous study (3) found that, in general, cancer survival increased as health spending increased. This trend was repeated in the present analysis although Sweden and Finland had better survival than Germany, Norway, and the Netherlands—with similar or higher TNEH, whereas Ireland and the United Kingdom had lower survival than several other countries with similar TNEH. Thus, health spending is not the only factor influencing cancer survival differences.

All EU countries have adopted the policy that their citizens should have access to health care (20,21). However, the organization of health-care provision varies markedly between EU countries (22). National health systems are inspired by egalitarian principles and financed through general taxation, and in general, health-care services are publicly owned and managed (23). Social insurance systems are financed mainly through obligatory salary or wage deductions, with rights of access to health services often limited (24) and health-care providers typically a mix of public and private (10).

Visual inspection of Figure 1 tends to support the idea that health-care organization has an effect on all-cancer survival differences across Europe. Many countries with national health systems (specifically Iceland, Sweden, Finland, Italy, and Spain) had better survival than countries with social insurance systems (specifically France, Switzerland, Germany, the Netherlands, the Czech Republic, Slovakia, and Slovenia), although there were notable exceptions: The United Kingdom and Ireland, with national health systems, had worse survival than all countries of comparable TNEH (2000–2999 US$PPP), whereas Belgium with a social insurance system had better survival than many countries of comparable TNEH. Focusing on countries with TNEH of 2000 US$PPP and greater (Figure 1), it is evident that all-cancer survival was similar irrespective of health system organization: 55.2% for countries with national health systems and 55.6% for countries with social insurance systems; however, TNEH was higher for the latter (2518 vs 3008 US$PPP). Previous studies support greater efficiency of national health systems, which tend to have more direct control over expenditures (25,26), more equitable distribution of resources and greater allocative efficiency (27), lower out-of-pocket expenses, and lower administrative costs (28), compared with social insurance systems.

Because cancer survival depends on early diagnosis and effective treatment (3), we also sought to characterize EU countries according to the availability of diagnostic and treatment equipment. The data presented in Table 1 show that countries with TNEH greater than 2000 US$PPP had more CT and MRI scanners per capita than those with TNEH less than 2000 US$PPP. Such scanners are important for the early diagnosis and staging and hence provide vital information for deciding appropriate treatment. MRI scanners are expensive, and it is not surprising that the number per capita was closely related to TNEH. We also found that relative survival correlated directly with MRI units per capita, consistent with the known importance of early and accurate diagnosis in cancer survival. Note, however, that our data indicate the availability of scanners but do not provide information on their actual use (7–9).

The relationship between number of RT devices and relative survival was less clear, probably because information on these devices was unavailable for many countries. The QUARTS project (9) reported that the availability of RT devices varied markedly between EU countries and even regions within EU countries. Governments in several EU countries have recognized, and are trying to rectify, the problem of inadequate RT device availability (9).

Survival and Standard Care

The high-resolution studies reported in this paper show marked differences across Europe in terms of the treatments given for major cancers. By the middle of the 1980s, large multicenter clinical studies had established that, for early breast cancer, conservative surgery reduces side-effects and improves aesthetic outcomes, compared with mastectomy, without adversely affecting survival (29–36). Somewhat later, it was also shown that adjuvant chemotherapy improves prognosis in node-positive breast cancer (37). For stage III colon cancer, trials published in 1989 (38) and 1990 (39) concluded that adjuvant chemotherapy improves prognosis. Neoadjuvant or adjuvant RT also reduces local recurrence rates in rectal cancer (40). It is striking, therefore, that only 55% of European early breast cancer patients received breast-conserving treatment and only 46% of stage III colon cancer patients were given chemotherapy (Table 4) over the study period (late 1990s).

It seems that limited availability of treatment guidelines for breast cancer and colorectal cancer in Europe was the major reason for lack of adherence to what are now standard treatments for these diseases. The first meta-analysis on systemic treatment for early breast cancer was published in 1992 (37), and only in 1998 was a comprehensive series of meta-analyses published (41) after which it became evident that guidelines for breast cancer management were desirable (www.eusoma.org). Adjuvant chemotherapy use for colorectal cancer increased markedly the United States (40,42) following the publication of trial data (38,39), but in Europe, additional chemotherapy trials were conducted (43–45). Furthermore, during the study period, European guidelines for treating colorectal cancer were not available, although some national protocols had been produced (12).

The high-resolution studies also showed that advanced stage at diagnosis was associated with poor 5-year relative survival and low odds of receiving surgical treatment for colorectal cancer and radical treatment for prostate cancer. Although over 70% of colorectal cancers were treated by radical resection (the only treatment that offers a chance of cure), in the eastern European countries of Poland, Slovakia, and Estonia, over one-third of cases presented at advanced stage and much less than 70% received surgery with curative intent (Table 3). For breast cancer, countries with screening programs during the study period (the Netherlands, Finland, and Sweden) had high proportions of T1N0M0 cases and low proportions of M1 cases (46). Conservative surgery is only applicable to relatively early-stage breast cancer.

Thus, stage at diagnosis is a major determinant of whether effective treatments can be applied and long-term disease control achieved; however, it is also important that the facilities to deliver effective treatment are available. Access to RT for treatable rectal cancer and early breast cancer seems to be limited by the availability of RT equipment (9) and is likely to be an additional reason for the low rates of conservative surgery in breast cancer and application of RT in rectal cancers. Thus, countries with highest numbers of RT devices were those with the highest proportions of early-stage breast cancers receiving conservative surgery and RT (12). By contrast, adjuvant chemotherapy appeared to be the foundation of breast cancer treatment in Eastern Europe and was also common for colon cancer (Table 4 and Figure 2), probably because chemotherapy costs less than RT (12).

With regard to prostate cancer, about one in three European patients received radical treatment at the end of the 1990s, with prostatectomy given more often than RT. For high-risk cancers, the odds of receiving radical treatment were about twice as high in the Netherlands, Italy, and France, as in Slovakia (Table 5). The same countries had the lowest proportion of M+ cases (<20%). The odds of receiving radical treatment for prostate cancer also correlated with the incidence rate (14). High incidence is likely to be related to extensive PSA testing, resulting in higher proportions of incident cases being eligible for radical treatment. We also found that a considerable proportion (up to 34%) of patients with apparently low-risk disease was treated radically within a year of diagnosis. This proportion was lower than that estimated in the United States in 2000 (16), although some European regions approached US levels (14). Because prostate cancer incidence is likely to remain high in the foreseeable future due to PSA testing, the proportion of indolent and low-risk cancers diagnosed is not expected to decrease. Expectant management (active surveillance and delayed treatment) should become the main approach to low-risk disease (47). Monitoring the extent of application of expectant management would be a useful way of assessing the appropriateness of treatment for prostate cancer.

We conclude by noting, as this survey illustrates, that the information on which to base policies to increase cancer survival overall and reduce survival differences in Europe is available. In fact, the European Union has been seeking to harmonize public health policies across member states since the beginning of the new millennium. Under the Slovenian presidency of the European Union in 2008 (48), cancer control was prioritized and further actions initiated to improve cancer control. As a result, the European Partnership for Action Against Cancer (EPAAC) was launched in 2009 (49), with the aims of integrating cancer policies across EU member states particularly in the areas of primary prevention, treatment guidelines, and cancer research; a European cancer information system is also being set up. It will be important to monitor the impact of these initiatives on cancer survival in Europe as a whole and individual member states.

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Initial Treatment for Newly Diagnosed Elderly Colorectal Cancer Patients: Patterns of Care in Italy and the United States

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Cancer is a major component of health-care expenditures in most developed countries. The costs of cancer care are expected to increase due to rising incidence (as the population ages) and increasing use of targeted anticancer therapies. However, epidemiological analysis of patterns of care may be required prior to empirically well-grounded cost analyses. Additionally, comparisons of care between health-care delivery systems and countries can identify opportunities to improve practice. They can also increase understanding of patient outcomes and economic consequences of differences in policies related to cancer screening, treatment, and programs of care. In this study, we compared patterns of colorectal cancer treatment during the first year following diagnosis in two cohorts of elderly patients from some areas of Italy and the United States using cancer registry linked to administrative data. We evaluated hospital use, initial treatments (surgery, chemotherapy, and radiation), and timeliness of surgery and adjuvant therapy, taking into account patient characteristics and clinical features, such as stage at diagnosis and the cancer subsite. We observed greater use of adjuvant chemotherapy in stage III and IV colon cancer patients and adjuvant therapy in all stages of rectal cancer patients in the US cohort. We found a higher rate of open surgeries in the Italian cohort, a similar rate of hospitalization, but a higher number of hospital days in the Italian cohort. However, in spite of structural differences between the United States and Italy in health-care organization and delivery as well as in data collection, patterns of care and the timing of care in the year after diagnosis are generally similar among patients within stage of disease at diagnosis. Comparative studies of the costs associated with patterns of cancer care will be important for future research.

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Cancer care is a major component of health-care expenditures in most developed countries. The costs of cancer care are expected to increase, in large part due to rising incidence as the population ages. Additionally, the costs of anticancer therapies have increased dramatically in recent years (1–4). Health-care systems will face the challenge of providing increasingly expensive cancer care to a growing number of patients. In the current climate of constrained resources that is present in most developed countries, policy makers are striving to identify the ways to provide the most efficient and economical care.

Internationally there is tremendous diversity in health-care systems and patterns of cancer care delivery (5,6). These differences offer an opportunity to compare existing patterns of care, patient outcomes, and costs of care between health-care systems or countries. Such comparisons have the potential to inform evaluation, develop policies related to cancer screening and treatment, and identify the need for programs of care delivery (eg, hospice for patients at the end of life). Findings from these comparisons can also be used to establish benchmarks of cancer outcomes for evaluating the introduction of cancer control interventions prospectively.

Several studies have used data from population-based cancer registries for international comparisons of cancer incidence (7,8,9), survival (10,11), and prevalence (12). The European Cancer Registry (EUROCARE)–based Study on Survival and Care of Cancer Patients and the CONCORD Program for a Global Surveillance of Cancer Survival have conducted more detailed systematic international comparisons of cancer site–specific survival, accounting for underlying population characteristics, such as age, gender, and geographical area. As part of the EUROCARE project, high-resolution (HR) studies collected a sample of registered cases with detailed clinical and pathological information for selected cancer sites. The additional information from HR studies is not usually available in population-based cancer registries and represents a way of assessing the overall performance of health-care services and of improving the interpretation of survival differences across countries and over time (13,14). There have been a limited number of international comparisons of patterns or costs of cancer care, in part because of lack of key data elements collected in a systematic way and differences in how the information is reported for common treatments (eg, surgery, radiation therapy, chemotherapy) and biologically targeted therapies and hormonal treatments. To date, the studies that have compared patterns of care internationally have focused on the United States and Canada (5,6,15,16) or in multiple European countries (13). To our knowledge, there has not been a detailed systematic comparison of specific types of cancer treatment between the United States and a European country. Furthermore, this kind of epidemiological analysis of patterns of health-care delivery will provide useful information for empirically grounded cost analyses, and should be carried out prior to any cost analysis.

In this study, we compared patterns of treatment in colorectal cancer patients during the first year following diagnosis in some areas of Italy and the United States, using cancer registry linked to administrative data available in both countries. We chose colorectal cancer for our comparisons because it is a common cancer in men and women, is treated with multiple modalities of cancer therapy (namely surgery, chemotherapy, and radiation), and can be detected early through routine screening. We also explored the time from diagnosis to initial surgery and the time between surgery and adjuvant therapy in cohorts in both countries.

Data and Methods

Health-Care Delivery Systems

Italy and the United States differ substantially in the structure of their health-care systems. In Italy, the public welfare system guarantees universal health care for hospital, ambulatory, and other health-care services. In the United States, health insurance is employment-based for most working age adults and contracted through one of multiple health insurance companies, resulting in separate and generally discontinuous data for the working-age population. However, the Medicare program in the United States provides comprehensive health-care delivery for the population aged 65 and older and persons with select disabilities. Approximately 97% of the population 65 years and older has Medicare. As a result, there is comprehensive data about services for elderly patients in the Medicare program, which can be compared with the comprehensive services provided for elderly patients in Italy.

Data Sources

Both Italy and the United States maintain population-based cancer registries. These registries collect information about all newly diagnosed cancer patients within defined geographical areas. In both countries, the registry data for individual cancer patients have been linked to their health claims. We used these linked data to obtain information on clinical characteristics, receipt of cancer treatment, including surgery, radiation therapy, and chemotherapy, and timing of cancer treatment. We also obtained information about hospitalizations, both before and after the cancer diagnosis.

In Italy, we combined data from two cancer registries: Firenze-Prato, encompassing two provinces of the Tuscany Cancer Registry (17) in Central Italy and covering 1.2 million residents, and Padova, a local health unit of the Veneto Cancer Registry (18) in Northern Italy, which covers 0.4 million residents. Together these areas cover 2.7% of the Italian population. The combined Veneto–Tuscany Cancer Registry (VTCR) database includes information on date of birth, sex, date of diagnosis, date of last follow-up, tumor site, morphology, diagnostic confirmation, and stage at diagnosis. All patients included in the registries are actively followed up to determine vital status. These registries contain information about cancer diagnoses starting in 1990.

In Italy, health claims come from the hospital discharge card (HDC) administrative database, a data system used for reimbursement for services that occur in the hospital setting. Information on outpatient or ambulatory services and physician visits are not included in the database. However, during the period of this study, hospitals were the locus of all open surgical care and infusion chemotherapy; additionally, data for radiation treatments that are performed in outpatient or ambulatory care were added for this study. Claims for hospital-based services reflect information on the HDC completed by the treating physician for each time that the patient goes to the hospital. HDC includes information about inpatient hospital (IH) care and day hospital (DH) care. IH care occurs when a patient is formally admitted to an institution for treatment and/or care and stays for a minimum of one night; any medical treatment provided during the stay is included. DH care comprises medical and paramedical services delivered to patients seen in the clinic for diagnosis, treatment, or other type of health care, without an overnight hospital stay. DH care may last 1 or more days depending on the cycle of treatments. One HDC refers to a single hospital admission or service (IH or DH). It contains demographic information (date of birth, sex, place of birth, place of residence) and clinical information [type of diagnosis, interventions, and procedures coded by the *International Classification of Diseases, Ninth Revision, Clinical Modifications* (ICD-9-CM) (19)]. Different HDCs for the same individual can be linked by a unique personal identification code.

Newly diagnosed colon and rectum cancer patients in 2000–2001 in VTCR database were linked with the corresponding regional HDC databases from 1999 to 2002, in order to obtain all hospital admissions and hospital-based care and corresponding procedures received in the year prior to diagnosis and the first year following diagnosis. The deterministic linkage was based on a unique identification code, with 95% of all colorectal cancer patients linked to one or more HDCs. Less than 1% of cancer patients were diagnosed and treated in private hospitals operating outside the National Health System (20). For these patients, although present in the registry, there is no information on HDC.

In the United States, registry data were from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program of cancer registries. The SEER registries are geographically defined and collect detailed clinical information on the site, pathology, and extent of disease at the time of each cancer diagnosis; stage, month, and year of diagnosis; and patient age and sex. For this study, we included cancer patients from 11 registries—five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and six metropolitan areas (Atlanta, Detroit, Los Angeles, San Francisco–Oakland, San Jose–Monterey, and Seattle–Puget Sound), altogether representing 14% of the total US population. All patients included in the registries are actively followed to determine vital status. Most of these registries contained information on cancer diagnoses from 1975 onward, except Los Angeles and San Jose–Monterey, which joined the SEER program in 1992.

For US patients with fee-for-service coverage, their Medicare claims are contained in different files, depending on the type of service. These include inpatient hospitalizations, outpatient clinic services, and physician visits. Each file includes ICD-9-CM codes for the patient's diagnoses and dates of service. Procedures on inpatient files are billed using ICD-9-CM codes. Procedures billed by outpatient clinics and physicians are coded using the Healthcare Common Procedure Coding System (HCPCS) (available at http://www.cms.gov/MedHCPCSGenInfo/).

All patients in the SEER data have been included in a deterministic match against Medicare's master enrollment file. Approximately

94% of individuals aged 65 or older who have a cancer diagnosis in the SEER data have been linked to Medicare's master enrollment file (21). For SEER patients who were Medicare-eligible, all available Medicare health claims were obtained. For a more detailed description of SEER–Medicare linked data, refer to http://healthservices.cancer.gov/seermedicare/.

Study Populations—VTCR and SEER–Medicare

We selected patients aged 66 and older newly diagnosed with colon cancer (International Classification of Diseases for Oncology [ICD-O] topography codes C18.0, C18.2–9) or rectal cancer (ICD-O topography codes C19.9, C20.9) in the period January 1, 2000, to December 31, 2001 (VTCR = 1844, SEER–Medicare = 46 571). Although Medicare coverage begins at age 65, we selected patients at age 66 and older in order to obtain information on comorbidities in the year period prior to diagnosis. In the SEER–Medicare data, we excluded patients not covered by both Medicare Parts A and B in the year prior and the year after diagnosis (33.7%) to ensure that we had complete claims for all individuals in this study. In both cohorts, we excluded individuals diagnosed through autopsy or death certificate only (0.8% in both databases), patients with a prior cancer diagnosis (VTCR = 6.5% and SEER–Medicare = 12.9%), patients with another cancer diagnosis in the year following colorectal cancer diagnosis (VTCR = 0% and SEER–Medicare = 1.5%), patients with 1 month or less of survival following diagnosis (VTCR = 2.7% and SEER–Medicare = 5%), and unstaged patients (VTCR = 13.2% and SEER–Medicare = 6.1%). The final analysis cohorts consisted of 1396 Italian and 18 438 US patients with a primary diagnosis of invasive colorectal cancer.

Variables Included in the Analysis

Patient Characteristics. Patient characteristics for both cohorts were obtained from the time of diagnosis. Patient age was categorized into five groups (66–69, 70–74, 75–79, 80–84, 85+). The American Joint Committee on Cancer's (AJCC) Cancer Staging Version 3 (22) was used by both registries to classify tumors by their spread and severity of disease. We also used registry data to determine if the tumor was found on the left or right side of the colon or rectum, using ICD-O topography codes (right: C18.0–C18.4; left: C18.5–C20.9). Comorbidity was measured in the year prior to diagnosis using the Charlson Comorbidity Score (23) for inpatient care in both countries. In VTCR, comorbid conditions were identified from the HDC; in SEER–Medicare, from hospital claims. The macro to compute these scores is publicly available at http://healthservices.cancer.gov/seermedicare/program/comorbidity.html.

We compared differences in hospital use between colorectal cancer patients in the two countries, both before cancer diagnosis to assess underlying differences in the two populations and after diagnosis to assess patterns of health-care use. Specifically we assessed the number of admissions, defined by any overnight stay in the HDC or any record of a hospital admission in the Medicare data. We also calculated the total number of inpatient days from the length of stay for each hospitalization, summarized over the course of the year by patient. These were categorized into 0, 1, 2+ weeks in the year before diagnosis, and 0, 1, 2, 3, 4+ weeks in the year after diagnosis.

Initial Treatment. Initial treatment was defined by receipt of open surgery, radiation therapy, or adjuvant chemotherapy during the year following diagnosis. Open surgery for colorectal cancer included colectomy, hemicolectomy, pelvic exenteration, and permanent colostomy. We also assessed the use of chemotherapy, defined as any claim for administration of chemotherapy, and examined use separately for patients who did and did not undergo surgery. We report information for stage I and II colon cancer combined, because guidelines at the time of the study recommend the same therapeutic approach (24): no adjuvant chemotherapy, wide surgical resection, and anastomosis. By contrast, adjuvant chemotherapy was recommended for stage III colon cancer. Rectal cancer surgery is reported separately for all stages, as guidelines for chemotherapy and radiation therapy vary by stage. For rectal cancer patients, we also examined the use of neoadjuvant radiation treatment and chemotherapy, which is intended to allow for sphincter-sparing surgery. These treatments are rarely recommended for colon cancer. See Appendix A for a complete list of ICD-9-CM procedure codes and HCPCS codes used to identify cancer treatments in SEER–Medicare and VTCR–HDC.

Time to Treatment. Time between diagnosis and initial surgery and time between surgery and start of adjuvant chemotherapy was estimated in days because some patients died during the period of observation. Because the SEER registries only collect month and year of diagnosis, we designated the first day of the month as the date of diagnosis in both cohorts. Actual dates for surgery and chemotherapy were available in both countries. For patients with more than one open surgery, we selected the first surgery after diagnosis for the analysis of time from diagnosis to surgery. We used the last surgery date as the starting date for the analysis of time from surgery to adjuvant chemotherapy.

To account for patients who died during the year after diagnosis, we used a person-day approach. For example, if a patient died 40 days after diagnosis and surgery had not occurred, the patient contributed 10 person-days to the time period 31–60 days and zero to the number of surgeries in that time period. If, instead, one surgery occurred at day 40 after diagnosis with death at day 60, the patient contributed 30 days to the time period 31–60 days and 1 to the number of surgeries in that time period. All patients were followed for a maximum of 365 days post-diagnosis.

Results

Sample Characteristics

In the VTCR and SEER–Medicare colorectal cancer cohorts, the majority of patients had colon cancer (VTCR 71%; SEER–Medicare 76%) (Table 1). The SEER–Medicare cohort was older than the VTCR cohort (aged 80 and older: 37% vs 28%) and had more female patients (55% vs 46%). The stage at diagnosis varied in the two colorectal cohorts, with substantially more SEER–Medicare patients diagnosed with stage I or II than the VTCR patients (61% vs 48%). More patients in the SEER–Medicare cohort were diagnosed with rightsided tumors than in the VTCR cohort (46% vs 34%). Additionally, a larger proportion of the SEER–Medicare cohort had higher comorbidity scores than the VTCR cohort (Charlson index 1+; 14% vs 7%).

Table 1. Characteristics of patients aged 66+ diagnosed with colon–rectal cancer in 2000–2001; Surveillance, Epidemiology, and End Results (SEER)–Medicare and Veneto–Tuscany Cancer Registry (VTCR)*

	Colorectal cases				Colon cases				Rectum cases			
	SEER–Medicare (n = 18 438)		VTCR (n = 1396)		SEER–Medicare (n = 13 906)		VTCR (n = 987)		SEER–Medicare (n = 4532)		VTCR (n = 409)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at diagnosis												
66–69	2736	15	247	18	1950	14	150	15	786	17	97	24
70–74	4190	23	367	26	3060	22	274	28	1130	25	93	23
75–79	4673	25	389	28	3524	25	273	28	1149	25	116	28
80–84	3640	20	210	15	2823	20	158	16	817	18	52	13
85+	3199	17	183	13	2549	18	132	13	650	14	51	12
Sex												
Male	8238	45	753	54	5926	43	513	52	2312	51	240	59
Female	10 200	55	643	46	7980	57	474	48	2220	49	169	41
AJCC stage at diagnosis												
I	5430	29	213	15	3672	26	126	13	1758	39	87	21
II	5905	32	463	33	4736	34	349	35	1169	26	114	28
III	4565	25	412	30	3532	25	301	30	1033	23	111	27
IV	2538	14	308	22	1966	14	211	21	572	13	97	24
ICD-O topography												
Right side (C18.0–C18.4)	8443	46	469	34	8443	46	469	34	—	—	—	—
Left side (C18.5–C20.9)	9995	54	927	66	5463	30	518	37	4532	24	409	29
Charlson comorbidity score (hospital claims only)												
0	15 819	86	1291	92	11 942	86	909	92	3877	86	382	93
1	1312	7	71	5	990	7	54	5	322	7	17	4
2+	1307	7	34	2	974	7	24	2	333	7	10	2
Number of hospital admissions in the one year prior to diagnosis												
0	14 491	79	1093	78	10 746	77	767	78	3745	83	326	80
1	2634	14	216	15	2100	15	152	15	534	12	64	16
2	850	5	65	5	675	5	51	5	175	4	14	3
3+	463	3	22	2	385	3	17	2	78	2	5	1
Total number of hospital days in the one year prior to diagnosis												
0	14 491	79	1093	78	10 746	77	767	78	3745	83	326	80
1 week (1–7 days)	2664	14	133	10	2130	15	96	10	534	12	37	9
2+ weeks (8+ days)	1283	7	170	12	1030	7	124	13	253	6	46	11
Mean days in hospital in the one year prior to diagnosis	1.7	—	3.4	—	1.8	—	3.5	—	1.3	—	3.0	—

* AJCC = American Joint Committee on Cancer; ICD-O = International Classification of Diseases for Oncology.

Treatment Patterns for Colon Cancer

Most colon cancer patients underwent open surgery within a year from diagnosis (SEER–Medicare 90%; VTCR 94%), with the highest rates of surgery occurring in patients with stage III cancer (Table 2). Among patients who underwent open surgery, about one-third received adjuvant chemotherapy within a year from diagnosis. However, there was variation between the two cohorts by stage. For patients diagnosed with stage III disease, a group for whom chemotherapy is recommended, 61% of SEER–Medicare cohort received chemotherapy compared with 45% of patients in VTCR. Stage IV patients in the SEER–Medicare data were also more likely to undergo chemotherapy than VTCR patients (57% vs 45%).

The time from diagnosis to surgery was similar between SEER–Medicare and VTCR patients (Figure 1). In general, most patients received treatment within the first 3 months after diagnosis; 67% of stage III SEER–Medicare patients had surgery within the month following diagnosis compared with 54% of VTCR patients. The time from surgery to chemotherapy varied according to stage. For both groups, the percentage receiving chemotherapy rose appreciably between the first and second month following surgery, with the majority of patients in both groups receiving chemotherapy within 3 months of surgery.

Treatment Patterns for Rectal Cancer

The percentage of open surgeries among rectal cancer patients in the year after diagnosis was higher in the VTCR cohort than in SEER–Medicare cohort (93% vs 82%). This difference was largest in stage I patients, where 77% of SEER–Medicare patients underwent open surgery contrasted with 95% of the VTCR patients (Table 3). Neoadjuvant therapy in the year prior to surgery was slightly higher in VTCR, more so for patients with stages III and IV disease. However, adjuvant therapies were generally more frequent

Table 2. Treatment regimen and colostomy information for the first year following colon cancer diagnosis in 2000–2001; Surveillance, Epidemiology, and End Results (SEER)–Medicare and Veneto–Tuscany Cancer Registry (VTCR)

	All cases (stages I–IV)				Stage I and II				Stage III				Stage IV			
	SEER–Medicare (n = 13 906)		VTCR (n = 987)		SEER–Medicare (n = 8408)		VTCR (n = 475)		SEER–Medicare (n = 3532)		VTCR (n = 301)		SEER–Medicare (n = 1966)		VTCR (n = 211)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Patients receiving surgery within a year from diagnosis	12 535	90	925	94	7607	90	466	98	3429	97	300	100	1499	76	159	75
Patients receiving adjuvant chemotherapy after surgery (% of patients with surgery)	4180	33	292	32	1229	16	86	18	2099	61	135	45	852	57	71	45
Patients without surgery (% of total patients)	1371	10	62	6	801	10	9	2	103	3	1	0	467	24	52	25
Chemotherapy only	215	2	9	1	30	1	0	0	17	1	1	0	168	9	8	4
Not treated	1156	8	53	5	771	9	9	2	86	2	0	0	299	15	44	21

in SEER–Medicare patients, particularly the use of chemotherapy and radiation. For stages II and III SEER–Medicare patients, the percent who received chemotherapy and radiation therapy was 23% and 36%, respectively, whereas for VTCR patients, the percent who received chemotherapy and radiation was 4% in stage II patients and 12% in stage III patients. Patterns of colostomies were similar, with VTCR patients generally receiving slightly more colostomies compared with SEER–Medicare patients, except for stage III, where SEER–Medicare patients had more colostomies (37% vs 28%).

The time from diagnosis to surgery was similar in the two cohorts for rectal cancer patients (Figure 2), whereas the time from surgery to chemotherapy (with or without radiotherapy) was generally longer for rectal cancer than for colon cancers, likely a consequence of greater use of neoadjuvant therapies in rectal cancer patients.

Hospitalizations

The distribution of the number of hospital admissions in the year after diagnosis was similar in the two cohorts, across stages, although the mean number of inpatient days in VTCR patients was double that of SEER–Medicare patients (30 vs 15 days) (Table 4). This result is similar to the relative hospitalization pattern in the year prior to diagnosis in VTCR and SEER–Medicare patients (3.4 vs 1.7 days) (Table 2) and is consistent across stages. Furthermore, the distribution of patients by number of weeks in hospital showed a mode of 2 weeks in the SEER–Medicare cohort and 4 or more weeks in the VTCR cohort.

Discussion

In this study, we compared the characteristics of newly diagnosed elderly colorectal cancer patients in two cohorts from Italy and the United States and their patterns of care in the first year after diagnosis. Because of the structural differences in health-care organization and delivery between the United States and Italy, we made great efforts to ensure comparability of results. The major challenges of this study were to ensure that we had comparable cohorts and that we were comparing the same procedures and treatments in both data sources. The HDCs available in the VTCR cohort contained complete information for each hospitalization from a single source. For the SEER–Medicare cohort, treatment information was obtained from SEER data and Medicare claims that included inpatient hospitalizations, outpatient clinic services, and physician visits. Elaborate algorithms were needed for the databases to identify treatments.

More patients in the Italian cohort had advanced disease at diagnosis than did patients in the US cohort. The difference in stage at diagnosis can be explained, in part, by differences in use of colorectal screening between the United States and Italy. Screening programs in 2000–2001 in VTCR area barely reached 10% of the population aged 50 and older (25) and consisted mainly of fecal occult blood testing. A national formal screening program was not introduced in Italy until 2003 (26). In the same year, over 50% of the US population aged 65 and older had undergone colorectal cancer screening (27), reflecting the organized promotion of screening by the Medicare program. We also found more right-sided colon cancers in the US cohort than in the Italian cohort. This difference likely reflects the higher use of colonoscopy in the United States, where it is the predominant form for colorectal cancer screening (27).

We observed greater use of adjuvant therapy in the US cohort, especially in chemotherapy for stage III colon patients and chemotherapy and radiotherapy for stage II and III rectal patients. In 1990, the US National Institutes of Health issued a consensus statement for colorectal cancer treatment. The statement, which was based on evidence from clinical trials, concluded that chemotherapy should be offered as care for stage III colon cancer patients and chemotherapy and radiation therapy should be offered to stage II and III rectal cancer patients (28). The higher use of adjuvant therapy in the US cohort likely reflects a greater acceptance by US clinicians of the potential benefit of adjuvant therapy for elderly patients with cancer (29). This is notwithstanding underrepresentation of elderly cancer patients in clinical trials, thus resulting in uncertainty about whether older patients will benefit from adjuvant treatment (30).

US clinicians also gave more chemotherapy to stage IV colon cancer patients than did Italian clinicians: 57% of stage IV colon cancer patients in the SEER–Medicare cohort received chemotherapy, 12% more than what was reported for the VTCR cohort.

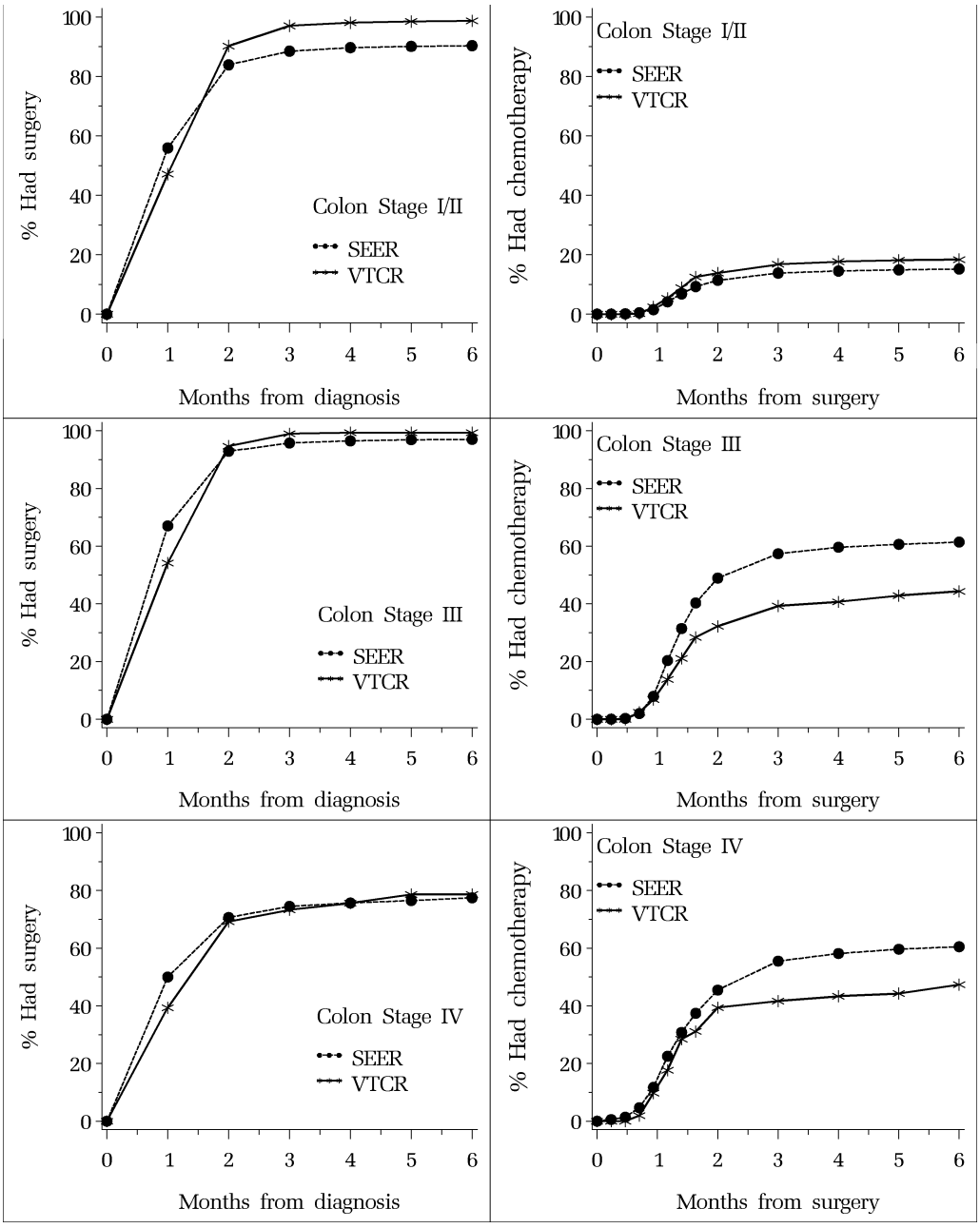

Figure 1. Percent having surgery by time since diagnosis and percent having chemotherapy by time since surgery. Patients diagnosed with colon cancer in Surveillance, Epidemiology, and End Results (SEER)–Medicare and Veneto–Tuscany Cancer Registry (VTCR) by stage.

Whether the higher use of chemotherapy among stage IV SEER–Medicare patients represents overuse of chemotherapy cannot be determined from these data. During the time of this study, oncologists paid by Medicare could profit from the administration of specific chemotherapy agents, potentially resulting in overtreatment, whereas oncologists in Italy did not have a financial incentive to prescribe chemotherapy.

Although use of adjuvant therapy was higher in the US cohort, the percentage of patients undergoing open surgery was higher among VTCR cohort. This was especially true for stage I rectal cancers (95% vs 77%) and stages I and II combined colon cancer (98% vs 90%). To assess if SEER–Medicare patients were more likely to have smaller tumors removed by polypectomy rather than open surgery, we examined SEER data from 2001 to 2002 for persons aged 65 or older who were diagnosed with stage I rectal cancer. We found that 28.5% of these patients had polypectomy reported to the SEER registry as their cancer surgery. Only 3.5% of SEER patients had no cancer surgery reported.

The percentage of IH days in VTCR patients was nearly double that of SEER–Medicare patients, despite the fact that the SEER–Medicare cohort was older and a larger percentage had higher comorbidity scores. The longer length of stay found for the Italian cohort was observed both before and after the cancer diagnosis and may reflect different government policies regarding hospital stays. Both countries adopted the diagnosis-related groups (DRG) system, whereby hospitals receive a lump sum payment for each patient,

Table 3. Treatment regimen and colostomy information for the first year following rectal cancer diagnosis in 2000–2001; Surveillance, Epidemiology, and End Results (SEER)–Medicare and Veneto–Tuscany Cancer Registry (VTCR)*

	All cases (stages I–IV)				Stage I				Stage II				Stage III				Stage IV			
	SEER–Medicare (n = 4532)		VTCR (n = 409)		SEER–Medicare (n = 1758)		VTCR (n = 87)		SEER–Medicare (n = 1169)		VTCR (n = 114)		SEER–Medicare (n = 1033)		VTCR (n = 111)		SEER–Medicare (n = 572)		VTCR (n = 97)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Patients receiving surgery within a year from diagnosis	3717	82	379	93	1348	77	83	95	1055	90	112	98	973	94	110	99	341	60	74	76
Patients receiving neoadjuvant therapy before surgery (% of patients with surgery)	486	13	58	15	149	11	11	13	183	17	20	18	116	12	16	15	38	11	11	15
Chemotherapy only	4	0	1	0	1	0	1	1	1	0	0	0	1	0	0	0	1	0	0	0
Radiation therapy only	74	2	18	5	26	2	2	2	25	2	9	8	17	2	2	2	6	2	5	7
Chemo + radiation therapy	389	11	39	10	116	9	8	10	153	15	11	10	93	10	14	13	27	8	6	8
Patients receiving adjuvant (after surgery) therapy (% of patients with surgery)	1596	43	142	37	227	17	7	9	477	45	33	29	670	69	56	51	222	66	46	62
Chemotherapy only	695	19	98	26	79	6	3	4	165	15	19	17	275	28	40	36	176	52	36	49
Radiation therapy only	197	5	20	5	66	5	4	5	74	7	9	8	44	5	3	3	13	4	4	5
Chemo + radiation therapy	704	19	24	6	82	6	0	0	238	23	5	4	351	36	13	12	33	10	6	8
Patients without surgery (% of total patients)	815	18	33	7	410	23	4	5	114	10	2	2	60	6	1	1	231	40	23	24
Chemotherapy only	49	1	1	0	5	0	0	0	0	0	0	0	2	0	0	0	42	7	1	1
Radiation therapy only	91	2	5	1	28	2	0	0	22	2	0	0	11	1	0	0	30	5	5	5
Chemo + radiation therapy	167	4	4	1	48	3	0	0	38	3	0	0	17	2	0	0	64	11	4	4
None	508	11	20	5	329	18	4	5	54	5	2	2	30	3	1	1	95	17	13	14
Patients receiving a colostomy in the initial surgery (% of patients with surgery)	1285	28	124	30	321	18	21	24	417	36	42	37	387	37	31	28	160	28	30	31

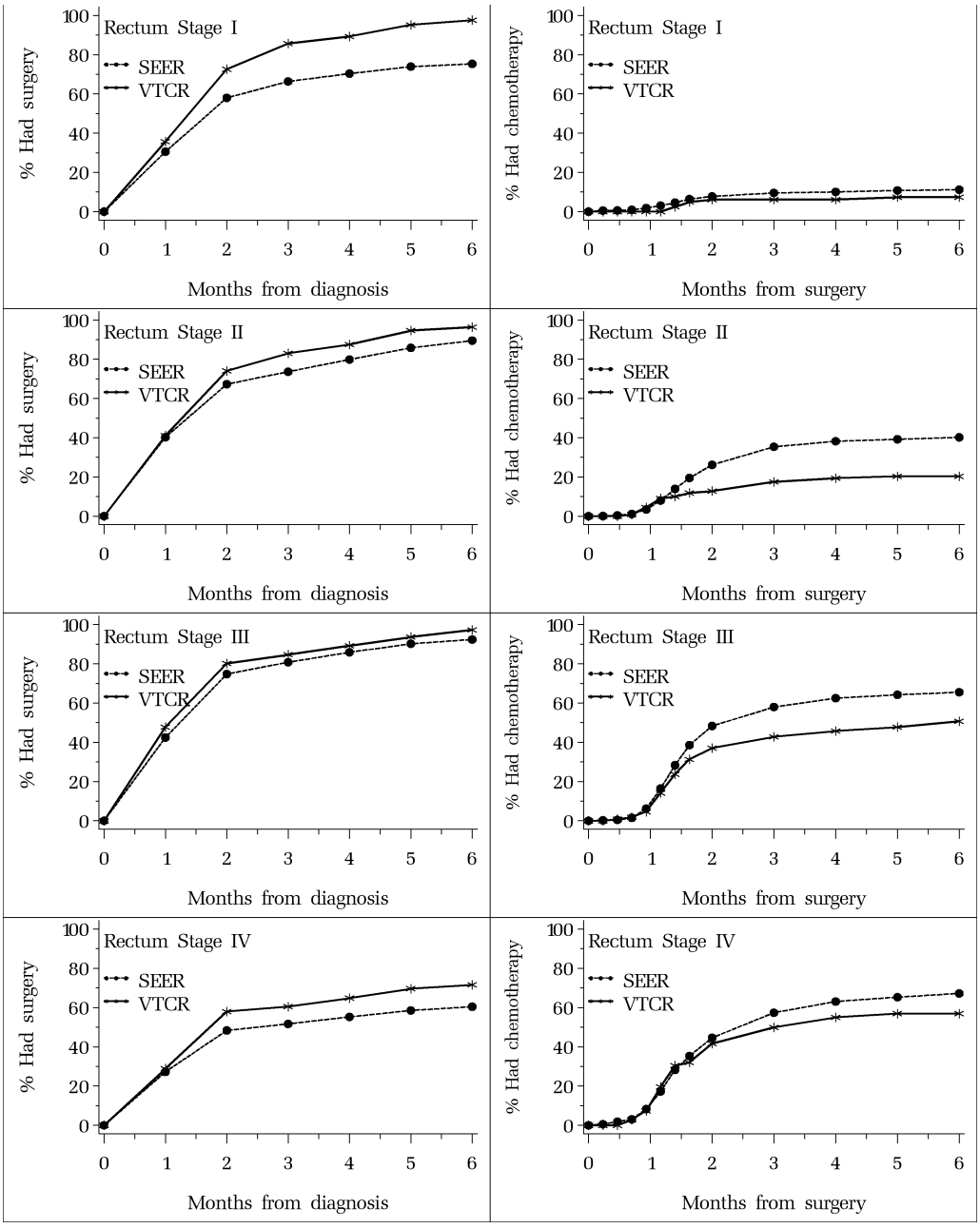

Figure 2. Percent having surgery by time since diagnosis and percent having chemotherapy (with or without radiotherapy) by time since surgery. Patients diagnosed with rectal cancer in Surveillance, Epidemiology, and End Results (SEER)–Medicare and Veneto–Tuscany Cancer Registry (VTCR) by stage.

determined by the patient's diagnosis, health status, and procedures performed during the hospitalization, thus giving hospitals a strong incentive to discharge patients as soon as possible following admission. However, its country-specific implementation has probably been different: At the time of study, in Italy a patient would stay in hospital during the presurgical period for diagnostic tests, whereas in the United States the same patient would have presurgical tests performed in the outpatient setting and be admitted to hospital on the day of their surgery. Differences in hospice programs in the United States and Italy could also have contributed to the observed shorter hospital stays for Medicare patients in our study. In the United States, Medicare hospice services are primarily home-based and allow patients to die at home instead of in hospital. The Medicare program has covered hospice services since 1986. In 2000–2001, a similar service had not yet been established in Italy and a higher proportion of terminal patients might have been hospitalized for end-of-life care.

Within stage of diagnosis, the patterns in both time to surgery after diagnosis and time from surgery to adjuvant therapy were similar in the VTCR and SEER–Medicare cohorts. Evaluation of time-to-care intervals will be important in future studies across health systems or countries as well as for patient subgroups.

Although this study appears to be the first to compare patterns of care between cohorts of cancer patients in the United States and a European country, there were several limitations. The data

Table 4. Hospitalizations in the first year following colorectal cancer diagnosis in 2000–2001; Surveillance, Epidemiology, and End Results (SEER)–Medicare and Veneto–Tuscany Cancer Registry (VTCR)

	All cases (stages I–IV)				Stage I				Stage II				Stage III				Stage IV			
	SEER–Medicare (n = 18 438)		VTCR (n = 1396)		SEER–Medicare (n = 5430)		VTCR (n = 213)		SEER–Medicare (n = 5905)		VTCR (n = 463)		SEER–Medicare (n = 4565)		VTCR (n = 412)		SEER–Medicare (n = 2538)		VTCR (n = 308)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Number of hospital admissions																				
0	1230	7	61	4	726	13	11	5	195	3	21	4	135	3	15	4	174	7	14	5
1	8736	47	679	49	2770	51	121	57	2975	51	250	54	2020	44	199	48	971	38	109	35
2	4678	25	365	26	1053	20	53	25	1537	26	114	25	1321	29	106	26	767	30	92	30
3+	3794	21	291	21	881	16	28	13	1198	20	78	17	1089	24	92	22	626	25	93	30
Number of hospital days																				
0	1230	7	61	4	726	14	11	5	195	3	21	4	135	3	15	4	174	7	14	5
1 week (1–7 days)	4671	25	23	2	1809	33	6	3	1474	25	4	1	967	21	7	2	421	17	6	2
2 weeks (8–14 days)	5838	32	336	24	1538	28	62	29	1969	33	119	26	1514	33	95	23	817	32	60	19
3 weeks (15–21days)	2898	16	235	17	558	10	43	20	997	17	83	18	829	18	65	16	514	20	44	14
4+ weeks (22+ days)	3801	21	741	53	799	15	91	43	1270	22	236	51	1120	25	230	56	612	24	184	60
Total number of hospital days	282 489		41 669		66 474		5620		95 121		13 200		78 692		12 354		42 202		10 495	
Mean number of days in hospital	15		30		12		26		16		29		17		30		17		34	

for this study are over 10 years old. However, 2000–2001 were among the only years that the VCTR data and HDCs were linked. Additionally, during the period of our study, cancer care, including surgery and adjuvant and neoadjuvant treatments, was hospital-based in Italy, allowing complete capture of cancer-related services. Comparisons of more contemporary patterns of care will be important in future studies. Our study was limited to cancer patients aged 66 and older, and although the majority of newly diagnosed cancer patients are in this older age group, we could not compare treatment patterns in the younger population. In both countries, we relied on administrative data to identify treatment receipt. Our study cohorts represented only a portion of colorectal cancer patients in Italy and the United States, and our results are not necessarily representative of the two countries. These data offer no insight into a physician's recommendation regarding therapy or a patient's decision to accept treatment. Finally, information on specific treatments, such as polypectomy, was incomplete and therefore could not be considered in our analysis.

Conclusions and Implications

In spite of structural differences between the United States and Italy in health-care organization and delivery, as well as in data collection, we can conclude that patterns of care and timing of care in the first year after diagnosis are generally similar among patients within stage of disease at diagnosis. The main differences in care were related to hospitalizations and use of adjuvant therapy. In Italy, length of hospital stay has become a major concern in more recent years, as hospitalization is the most costly component of care, and improving its organization represents an opportunity to reduce expenditures without affecting quality of care.

A more challenging question identified from this study relates to the use of chemotherapy for patients with stage IV cancer, where chemotherapy will not cure disease but may increase survival. With the introduction of expensive new agents to treat colorectal cancer, such as bevacizumab and cetuximab, the cost of colorectal cancer treatment has skyrocketed (1,3) and is expected to increase even more in the future. As such, costs of cancer care will put continuing stress on health-care budgets, and new strategies and policies thus become necessary. Presently in the United States under the Medicare program, treatment decisions cannot be made based on costs (2). In Italy since 2006, a national registry for antineoplastic drugs (available at http://antineoplastici.agenziafarmaco.it/) has been activated at the AIFA (Italian Medicines Agency). Assessment of patient eligibility and monitoring of treatment are preconditions for the hospitals to have the approval for use and reimbursement from the National Health System.

Future work with more recent data might include comparisons of biologically targeted therapies and hormonal treatments; different cancer sites, such as prostate cancer, where therapy recommendations are less standardized; and different approaches to end-of-life care. Comparisons between health-care delivery systems and countries, such as this one, can identify opportunities to improve health care and revise practice patterns. These analyses can also increase understanding of patient outcomes and economic consequences of differences in policies related to cancer screening, treatment, and programs of care.

Appendix A. *International Classification of Diseases, Ninth Revision, Clinical Modifications* (ICD-9-CM) and Healthcare Common Procedure Coding System (HCPCS) codes used to define colorectal cancer treatment

Colorectal treatment	ICD-9-CM procedure	HCPCS
Chemotherapy	99.25	J9000–J9999, 36260, 96400, 96405, 96406, 96408, 96410, 96412, 96414, 96420, 96422, 96423, 96425, 96440, 96445, 96450, 96520, 96530, 96542, 96545, 96549, 95990, 95991, A4301, E0782, E0783, E0784, E0785, E0786, G0355, G0357–G0360, C9411, J0207, J0640, J0880, J1190, J1440, J1441, J1950, J9217, J9218, J9219, J2405, J2430, J2505, J2820, J3487, J8520, J8521, J8530, J8560, J8565, J8600, J8610, J8700, J8999, K0415, KO416, Q0083, Q0084, Q0085, Q0136, Q0137, Q0179, S0177, S0181
Pelvic exenteration	68.8	51597
Colectomy/ proctectomy	45.71–45.76, 45.79, 45.8, 48.4, 48.41, 48.49, 48.5, 48.61–48.65, 48.69	44140, 44141, 44143–44147, 44150–44153, 44155, 44156, 44160, 45110–45114, 45116, 45119, 45123, 45160, 45170
Permanent colostomy	46.1, 46.10, 46.13	
Radiation therapy	92.21–92.33, 92.39	76370, 76950, 77261–77263, 77280, 77285, 77290, 77295, 77299, 77300, 77301, 77305,77310, 77315, 77321, 77326, 77327, 77328, 77331–77334, 77336, 77370, 77399, 77401–77404, 77406, 77407–77409, 77411–77414, 77416, 77417, 77427, 77431, 77432, 77470, 77499, 77520, 77523, 77750, 77761–77763, 77776–77778, 77781–77784, 77789, 77790, 77799

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The Challenge of Conducting Comparative Effectiveness Research in Cancer: The Impact of a Fragmented US Health-Care System

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Comparative effectiveness research (CER) can make important contributions to the transformation of US health care by filling gaps left by tightly controlled clinical trials. However, without comprehensive and comparable data that reflect the diversity of the US health-care system, CER's value will be diminished. We document the limits of observational CER by examining the age at diagnosis, disease stage, and select measures of health-care use among individuals diagnosed with incident cancer aged 65 or older from four large health maintenance organizations (HMOs) relative to seniors identified through the linked Surveillance, Epidemiology, and End Results (SEER)–Medicare data for the period 1999–2007. Aged individuals in the HMOs were younger, diagnosed at earlier stages, and more likely to receive care in inpatient settings than individuals in the linked SEER–Medicare data. These differences highlight the need for comprehensive and comparable datasets that reflect the diversity of US health care to support CER that can inform health-care reform in the United States.

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Comparative effectiveness research (CER) provides evidence about the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in "real world" settings (1) and is increasingly seen as a critical component in support of health reform in the United States (1,2). Valid inferences from observational CER depends on high-quality and consistent data on alternative treatments provided to diverse populations, but the variety of ways in which American health care is organized, delivered, financed, and recorded inhibits the availability of comprehensive and comparable necessary data to support this work. We describe the challenges for conducting observational CER for assessing cancer care with data on older adults diagnosed and treated for their cancer in the fee-for-service (FFS) US market compared with seniors treated in a capitated US market. We review the challenges that arise from the fragmented US health-care system and propose a research and a policy agenda for improving the prospects of CER to identify improvements in cancer care.

Background

Cancer is the second leading cause of death in the United States (3,4) and a substantial driver of total health-care costs (5). Therefore, improvements in the detection, treatment, and management of cancer are at the core of efforts to improve population health outcomes and lower total national health-care spending in the United States. However, despite significant resources devoted to cancer research over the past several decades, fundamental questions about effective approaches to care remain along the spectrum from screening (6–11) to palliation (12,13). Further, unexplained variation in rates of prevention, treatment, outcomes, and cost remains across regions and among specific segments of the population, highlighting the potential benefit of identifying and disseminating evidence-based approaches to cancer control and prevention.

CER can identify best practices and provide evidence of the sources of variation in care that affect outcomes; however, the fragmented nature of US health care impacts both the quality and availability of the data upon which CER depends. This fragmentation manifests in several ways:

1. *Health insurance:* Americans' access to insurance and the completeness of covered services differ by age, employment, income, military status, and ethnicity, with almost one-fifth of the US population currently without insurance. These different contact points create parallel but different access to services and thus service utilization and data availability.
2. *Finance:* Most American health-care providers are paid on a FFS basis, reimbursed only when they deliver services, but 22% (14) of Americans are insured through prepaid, capitated insurance that pays providers prospectively regardless of what, if any, services are provided. FFS and capitation create different incentives for care delivery that may impact the type and scope of services used as well as the availability of data, because capitation reduces the incentive to document the provision of every billable service or procedure.
3. *Organization of care:* Most Americans are forced to bundle their care from providers that practice independently of one another, but some Americans receive care from integrated systems that coordinate patient care across providers and care settings. Care integration supports more comprehensive information on health-care use, as electronic information systems can be used to follow patients within and across episodes of care.

4. *Capture of health information:* Although there is increasing use of electronic medical records (EMRs), the majority of US providers continue to rely on paper records. Thus, although EMRs can improve access to patient-level information about personal and environmental risk factors, little is known about how efficiently EMRs from independent providers can be linked.

Coordinated efforts by US federal and state health agencies have led to data resources that document the incidence and prevalence of cancer, addressing many of the challenges created by fragmented US health care. Leading this work are the National Program of Cancer Registries (NPCR) managed by the Centers for Disease Control and Prevention, and the SEER program of the National Cancer Institute (NCI) (15), which together capture cancer incidence data for 96% of the entire country through 45 state, Washington, DC, and territorial cancer registries that report to the NPCR and 17 regional population-based cancer registries that report through SEER. SEER registries provide clinical information (tumor site, morphology and diagnosis stage, first treatment course, and survival), whereas NPCR clinical data are more limited.

Several projects have linked NPCR and SEER with information on health-care use to support CER, with the linkage created and maintained by the NCI between SEER and claims data for Medicare beneficiaries maintained by the Centers for Medicare and Medicaid Services (CMS) being the most widely used (16). The Medicare program insures approximately 50 million Americans (17)—almost all individuals over age 65 and a smaller number of younger adults and children with permanent disabilities. The link between SEER and Medicare allows for cancer-specific CER among Medicare beneficiaries, but two critical gaps remain in its use for comprehensive research. First, because the link is with Medicare, which is primarily an insurance program for persons aged 65 and over, younger adults and children are (for the most part) excluded from the dataset. Although the majority (55.9%) of incident cancers in the United States in the last decade were among individuals aged 65 and over (18), the linked SEER–Medicare data exclude the large minority of Americans with incident cancers younger than age 65. Second, the linked SEER–Medicare data exclude the one-quarter of older Americans enrolled in the Medicare Advantage program (17), an insurance option offered by CMS that allows seniors to receive care from health maintenance organizations (HMOs) that are paid on a capitated, or per-person, basis, rather than FFS. The exclusion of these seniors is an artifact of different data reporting requirements CMS imposes on FFS and capitated providers because HMOs serving seniors are not required to submit detailed, itemized information on health service use similar to the claims submitted by FFS providers.

Methods

We documented the challenge of conducting cancer-specific observational CER using linked SEER–Medicare data by examining differences in cancer incidence and stage of illness and select measures of health service use among seniors in the linked SEER–Medicare data relative to seniors enrolled in four large HMOs. We focused on older adults for two reasons. First, as indicated above, more than half of all individuals diagnosed with incident cancer in the United States are aged 65 or older. Second, the linked SEER–Medicare data provided by the NCI have resulted in this resource being the leading source of information about cancer care and outcomes in the United States.

We examined the differences in populations diagnosed with cancer captured by the linked SEER–Medicare data with seniors diagnosed with cancer in four large nonprofit US HMOs. The four HMOs are Group Health Cooperative, based in Seattle, WA; the Health Alliance Plan (HAP)/Henry Ford Medical Group (HFMG), based in Detroit, MI; and the Northwest and Colorado regions of Kaiser Permanente, based in Portland, OR, and Denver, CO, respectively. Each of these HMOs provides comprehensive health-care services through, primarily, closed-panel delivery models with salaried physicians. The four health plans are members of the HMO Cancer Research Network (CRN), created by the NCI as a population-based laboratory to conduct research on cancer prevention, early detection, treatment, long-term care, and surveillance. The CRN is the largest research effort of the HMO Research Network (HMORN), a consortium of 19 health-care organizations with both defined patient populations and formal, recognized research capabilities.

The four health plans participating in the current study provide health service and capitated health insurance through a wide range of private and public health insurance programs, including employer-sponsored and individual and family plans, Medicaid programs for low-income Americans, as well as the Medicare Advantage for older adults and disabled individuals. Each health plan serves a population that generally represents their local communities (16,17). Group Health and HAP/HFMG are each located within SEER catchment areas and follow SEER protocols to abstract and provide clinical information on all cancer diagnoses among plan members to the local SEER registrars. Individuals diagnosed with cancer at the two Kaiser sites were identified from health plan–specific tumor registries, which follow SEER-compatible protocols. For HMO enrollees, we used enrollment and tumor registry data to identify all incident cancers for individuals whose diagnosis was made as of their 65th birthday and were enrolled in the health plan for at least 30 days prior to their diagnosis. We imposed no requirement for enrollment in the health plan following the cancer diagnosis to allow for individuals who may have died shortly following their diagnoses. Each incident cancer diagnosis was counted independently, so individuals may have multiple primary cancers. Demographic, diagnostic, and stage-of-illness information were obtained from the tumor registries for the years 1999–2007.

Data on patients whose cancer status and health-care use were available from the linked SEER–Medicare data were obtained from Information Management Services Inc (IMS) for the years 1999–2007. The study team obtained the complete set of data for all individuals identified in the 17 participating regional SEER registries for whom a link with CMS files was made, which reflects 93% of all older adults insured through FFS Medicare whose incident cancer is captured in a SEER registry. Demographic, diagnosis, and stage-of-illness information were derived from the Patient Entitlement and Diagnosis Summary File (PEDSF), which contains the relevant data for both SEER and CMS person-level data. All Medicare beneficiaries whose health-care use and cancer status were in the linked SEER–Medicare data during these years were included in

the analysis file with no requirements on pre- or postenrollment in Medicare or survival following the cancer diagnosis.

The stage of disease at diagnosis is based on the SEER Summary Stage, which is available in several variables reported on the PEDSF provided by IMS. The derived SEER Summary Stage 2004 is available for incident cancers diagnosed from 2004; the Summary Stage 2000 captures stage for cancers diagnosed between 2001 and 2003; and the Summary Stage 1977 identifies stage of disease for cancers diagnosed from 1995 to 2000. The SEER Summary Stage reports incident cancers as in situ, localized, regional, or distant/metastasis.

This study was approved by the Institutional Review Boards of the four HMO sites.

Results

There were 16 079 seniors with incident cancer from the HMOs and 405 166 in the linked SEER–Medicare data that met inclusion criteria during the period 1997–2007. Seniors in the HMOs were generally younger than in the linked SEER–Medicare data at time of diagnosis (Figure 1) and were more likely to be diagnosed with localized disease than were seniors whose experience was captured in the SEER-Medicare data (Figure 2). Among HMO enrollees diagnosed with any cancer, 48% had either in situ or localized disease, 19% had regional, and 17% had distant metastasis. Among seniors in SEER–Medicare, 38% had either in situ or localized disease, 36% had regional, and 20% had distant metastatic disease.

Age and stage for individuals with incident cancer for the HMO and linked SEER–Medicare data for colorectal, prostate, breast, and lung cancers are reported in Table 1. Although seniors in the HMOs and linked SEER–Medicare data had similar age distributions for lung and colorectal cancers, women in the HMOs with breast cancer and those diagnosed with colorectal cancer were younger than seniors in the linked SEER–Medicare data. The most notable result regarding stage is the large percentage of men in the HMOs with localized prostate cancer relative to the linked SEER–Medicare data.

Unadjusted rates per 1000 person-months for select measures of health service use for the 6 months before and 6 months after a cancer diagnosis are reported in Figure 3. Inpatient admissions (Figure 3A) and days per admission (Figure 3B) are higher among individuals identified in the linked SEER–Medicare data before and after their diagnosis relative to individuals in the HMOs. The relative gap in use rates is smaller in the post-diagnostic period but still almost twice as great among individuals in FFS settings relative to HMOs for both measures. Outpatient visits (Figure 3C) are higher among individuals in the linked SEER–Medicare data prior to diagnosis but substantially higher among the aged in HMOs in the 6 months following diagnosis.

Discussion

We have demonstrated opportunities for policy-relevant and clinically meaningful CER studies using pooled HMO and SEER–Medicare data that arise from variations in cancer incidence and patterns of care across these systems. Seniors in the HMOs were, on average, younger, diagnosed at earlier stages, and more likely to receive post-diagnosis care in outpatient settings relative to seniors in FFS Medicare. Several factors may explain these differences. HMOs may generally enroll younger seniors and the earlier diagnostic stage may reflect greater emphases on prevention and screening within the HMOs that result in earlier detection. We

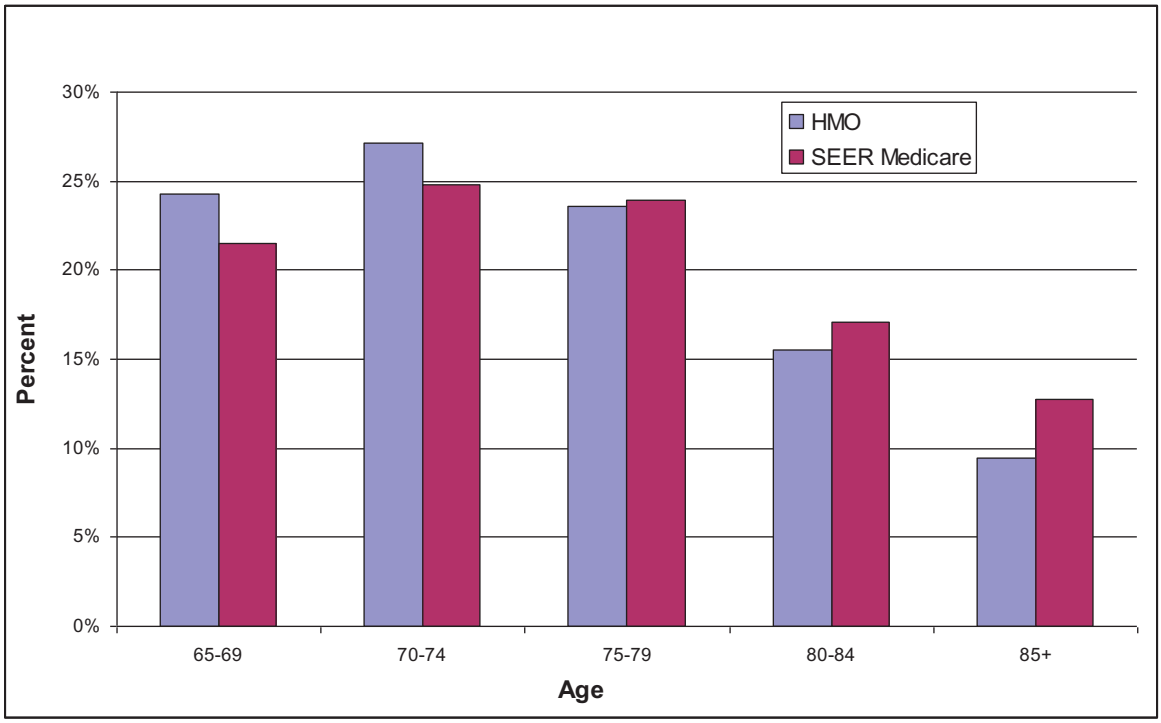

Figure 1. Cancer incidence by age and market segment, all cancers.

Table 1. Age and stage of disease for individuals with incident cancer by cancer site and market segment*

	Cancer site							
	Colorectal		Prostate		Breast		Lung	
	HMO	SEER–Medicare	HMO	SEER–Medicare	HMO	SEER–Medicare	HMO	SEER–Medicare
N	3206	89 993	4210	113 551	4225	90 234	4335	111 388
Age group								
65–69	18.1%	20.4%	29.0%	26.6%	28.1%	22.2%	20.7%	20.1%
70–74	22.6%	23.0%	29.9%	28.6%	26.2%	23.8%	28.9%	25.2%
75–79	25.1%	20.6%	23.3%	23.5%	22.0%	23.4%	24.1%	25.4%
80–84	19.1%	19.8%	12.0%	13.4%	14.3%	17.3%	17.4%	17.8%
85+	15.1%	20.4%	5.9%	8.0%	9.5%	13.3%	8.9%	11.4%
Stage								
In situ	2.1%	5.2%	0.00%	0.03%	17.3%	15.4%	0.1%	0.1%
Localized	30.4%	37.7%	71.45%	27.92%	52.6%	54.7%	17.0%	17.0%
Regional	36.5%	34.6%	6.58%	62.01%	16.2%	22.2%	21.6%	22.4%
Distant metastasis	14.4%	16.1%	6.53%	4.82%	2.6%	4.5%	43.1%	50.6%
Missing/unknown	16.6%	6.4%	15.44%	5.22%	11.4%	3.1%	18.2%	9.9%

* HMO = health maintenance organization; SEER = Surveillance, Epidemiology, and End Results.

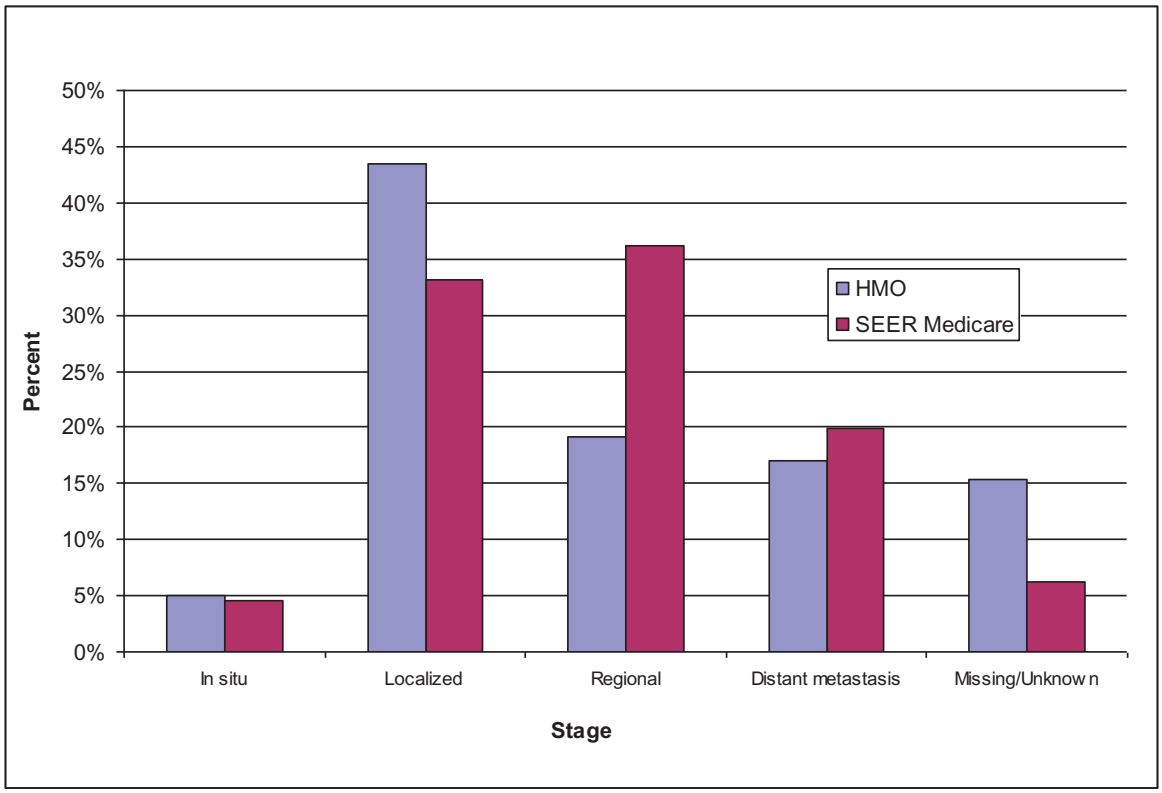

Figure 2. Stage of disease for incident cancers.

note the potentially adverse consequences of this outcome as earlier detection may result in treatment initiation that is premature or perhaps not medically indicated (6,8) and also acknowledge previous research that has examined these factors (19–23). Our results confirm the critical role of observational CER that compares cancer care and outcomes in FFS and HMO Medicare in identifying best practices for older adults in the United States and elsewhere.

Our finding of the different mix and intensity of service use among seniors diagnosed with cancer in the HMOs and FFS Medicare programs has not been previously documented and highlights both the challenge of and opportunity for conducting CER in cancer care in the United States. The evidence we report suggests that the correlated demographic, clinical, and service mix/intensity factors among seniors with cancer in HMOs are a significant methodological challenge to the conduct of comprehensive, integrated, and comparable CER on cancer care for Americans over age 65. The fragmented structure of the US health-care delivery system creates challenges in assessing the impact of variations in financing, sources of care, and patient preferences on observed treatment patterns and outcomes. This fragmentation also makes it

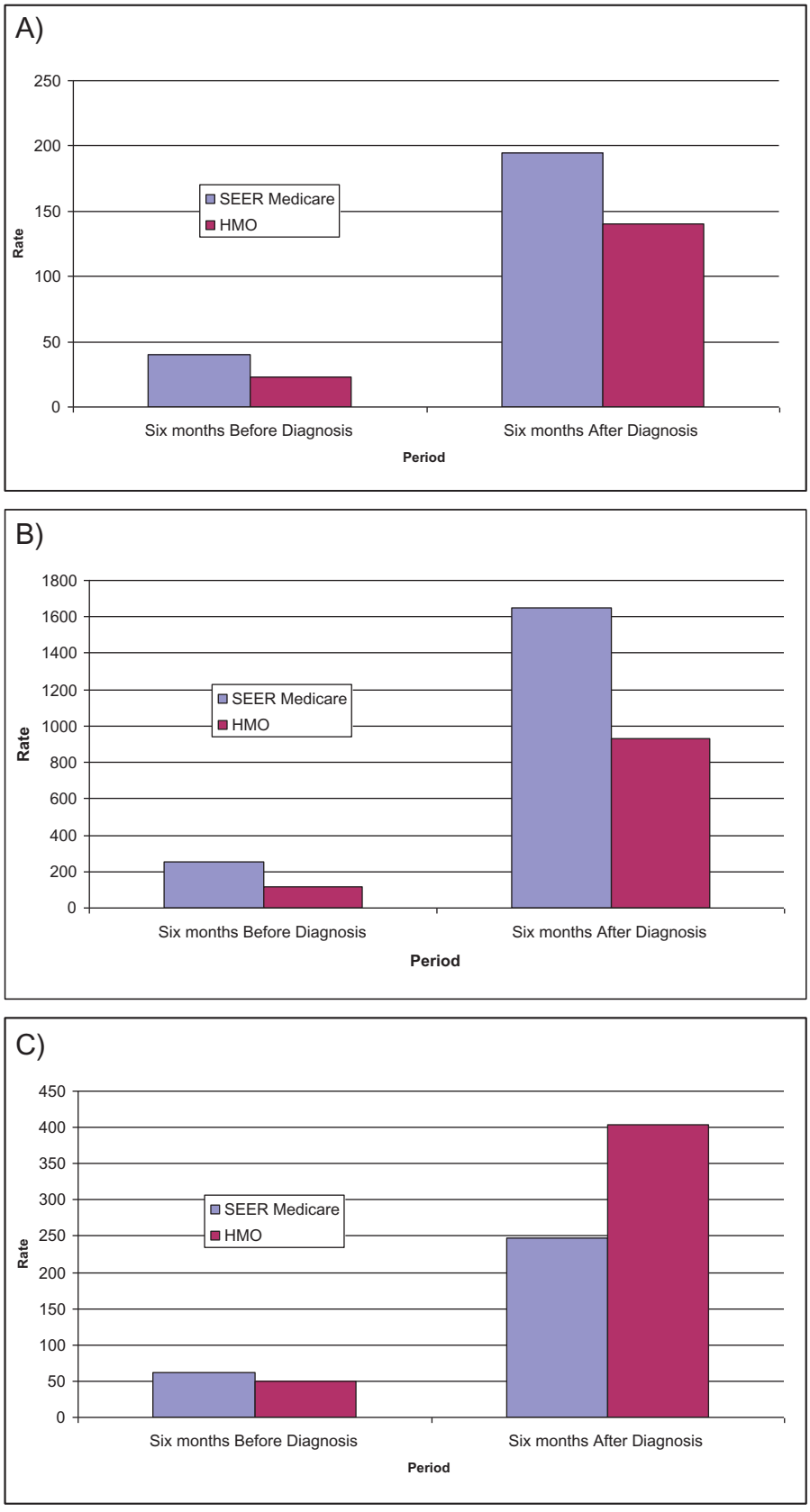

Figure 3. Unadjusted rates per 1000 patients for selected measures of health service use before and after diagnosis by market segment. **A**) Inpatient admissions per 1000 person-months. **B**) Inpatient days per 1000 person-months. **C**) Outpatient visits per 1000 person-months.

difficult to isolate best practices for wider dissemination throughout the United States. Continued efforts to improve data quality and harmonization across the United States, paired with creative multivariable statistical modeling tools, will provide deeper insights and new enigmas. These incremental insights will provide feedback to policy makers, clinicians, and patients on how our health systems are working (and failing), as well as a more rational basis to redirect and/or refine health policy initiatives.

Our study uses the experiences of older Americans to highlight the implications for CER caused by the fragmented US health-care sector (24). The NIH has created programs designed to address some of these gaps and to support collaborative research that bridges differences across geographic regions, care delivery models, and insurance markets. NIH initiatives such as the Roadmap for Medical Research and the Clinical and Translational Science Award program are examples of efforts designed to reduce barriers to conducting collaborative and translational research, but these efforts have yet to produce comprehensive health information resources to support the CER on which health reform depends.

There are examples of successful investments made by federal agencies in coordinated population-based research and health information technology that have the potential to support the type of CER needed to support US health-care reform. One success is the HMORN, of which the four health plans that participated in this study are members, whose research infrastructure has been primarily supported by the NCI. The power of combining HMO datasets across the network creates the opportunity for direct comparisons of the otherwise fragmented elements of US health care (25). The successful investment of the NCI into cancer-specific research within the HMORN has led to subsequent investments into mental health and cardiovascular disease, but each of these efforts is limited to one market segment.

The NIH has invested in several nationally representative panel data series, some of which, such as the Health and Retirement Survey and the observational panel developed for the Women's Health Initiative, also link to Medicare data as the NCI has done with SEER. Although these efforts have the same limitations regarding seniors enrolled in HMOs, they are examples of how CER can be supported through coordinated data collection efforts over time that link detailed primary and clinical data with information on health service use.

An example of an explicit investment in health information technology is the DARTNet program, co-supported by the Agency for Healthcare Research and Quality (AHRQ) and the NIH. DARTNet is a federated network of electronic health record data and other clinical information from typically smaller clinical settings across the county linked through a secure web-based system that can be searched and queried as one large database while maintaining privacy and confidentiality of patient data (http://www.dartnet.info/). AHRQ has also long supported primary care practice–based research networks (PBRNs), which are, as a group of primary care practices, affiliated in their mission to investigate questions related to community-based practice and to improve the quality of primary care (26). PBRNs are often limited by their ability to easily share health records and clinical information but hold promise as a way of conducting CER to reflect actual care settings.

Without data that allow for analyses of the differences in populations, care processes, and outcomes throughout the United States, public and private policy leaders cannot make informed decisions about how to evaluate and implement best practices. The investment made in the data maintained by NPCR and linked SEER–Medicare data is a strong platform on which to build a multisector and multiregional comprehensive dataset that can fully capture the entire population's experience with cancer care and outcomes.

The most effective outcome in support of observational CER in support of improved cancer care and outcomes is the completion of a comprehensive cancer data system, as called for in a 1999 US Institute of Medicine report on improving the quality of cancer care (27). The investments made by the NPCR and NCI to provide comprehensive data on cancer incidence in the United States, and to link this data with health-care use for many older Americans, have supported critical research efforts. The next step is development of a comprehensive data resource that captures health-care use and outcomes for all Americans with cancer.

Conclusion

Health-care reform in the United States requires research that identifies and disseminates evidence of effective care outside of rigorously controlled clinical trials that can reduce the overall cost of providing services. The need for this research has been identified in the most important pieces of federal health legislation passed in recent years, which have created and funded programs of research to support the CER on which health-care reform will depend. What is missing from the current plan for supporting research is the creation of comprehensive data that capture the full diversity of US health-care delivery and finance that will allow researchers to isolate the sources of variations in health-care delivery and determine best practices. We highlighted the need for the creation of such data showing significant differences among those diagnosed with cancer in the FFS Medicare program and those served by HMOs in the Medicare Advantage program.

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A Standardized Relative Resource Cost Model for Medical Care: Application to Cancer Control Programs

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Medicare data represent 75% of aged and permanently disabled Medicare beneficiaries enrolled in the fee-for-service (FFS) indemnity option, but the data omit 25% of beneficiaries enrolled in Medicare Advantage health maintenance organizations (HMOs). Little research has examined how longitudinal patterns of utilization differ between HMOs and FFS. The Burden of Cancer Study developed and implemented an algorithm to assign standardized relative costs to HMO and Medicare FFS data consistently across time and place. Medicare uses 15 payment systems to reimburse FFS providers for covered services. The standardized relative resource cost algorithm (SRRCA) adapts these various payment systems to utilization data. We describe the rationale for modifications to the Medicare payment systems and discuss the implications of these modifications. We applied the SRRCA to data from four HMO sites and the linked Surveillance, Epidemiology, and End Results–Medicare data. Some modifications to Medicare payment systems were required, because data elements needed to categorize utilization were missing from both data sources. For example, data were not available to create episodes for home health services received, so we assigned costs per visit based on visit type (nurse, therapist, and aide). For inpatient utilization, we modified Medicare's payment algorithm by changing it from a flat payment per diagnosis-related group to daily rates for diagnosis-related groups to differentiate shorter versus longer stays. The SRRCA can be used in multiple managed care plans and across multiple FFS delivery systems within the United States to create consistent relative cost data for economic analyses. Prior to international use of the SRRCA, data need to be standardized.

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Measuring the Medical Cost of Cancer

Annually the cost of medical care for cancer accounts for about 5% of national health care expenditures and 10% of Medicare outlays (1–3). Much of what we know about the cost of preventing, diagnosing, and treating cancer in the United States comes from research based on the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) cancer registries, which are linked to Medicare claims from the Centers for Medicare and Medicaid Services (CMS) and known as the SEER–Medicare data (1,2,4,5). This rich data resource provides comprehensive health-care use and claims expense information about Medicare-covered services for persons aged 65 and over, and permanently disabled persons who receive care through the traditional Medicare indemnity program, living in one of the 17 US geographic regions covered by the SEER program. Numerous published studies have used the linked SEER–Medicare data to document the economic consequences of cancer among persons aged 65 and over and permanently disabled persons. The linked SEER–Medicare data serve as the primary information source for much of the health services research on cancer care in the United States (http://healthservices.cancer.gov/seermedicare/overview/publications.html) (6). Nationally Medicare data represent the experience of 75% of aged and disabled Medicare beneficiaries enrolled in the fee-for-service (FFS) indemnity option; unfortunately, this omits the experience of the 25% of aged and disabled beneficiaries enrolled in Medicare Advantage health maintenance organizations (HMOs) (11.8 million beneficiaries in April 2011) (7). FFS is a payment system in which an individual or institution is reimbursed based on the services actually used. This is in contrast to capitated payment systems, in which a set amount per individual is prepaid and is not based on the services used, as in the Medicare Advantage HMOs (8). There is no evidence that the SEER–Medicare data are not reflective of national enrollment patterns in FFS and HMOs. Previous research has found that expense patterns generated from SEER–Medicare and HMO data are roughly consistent (9–11); no studies, however, have systematically examined how cancer-specific and longitudinal patterns of resource and service use and overall expense differ between HMOs and Medicare. Building on the work of the Cancer Research Network [CRN (12–14)], the Burden of Cancer study (BURDEN) has developed a multisite, multipayer database to support analyses extending and complementing the linked SEER–Medicare data. Our study extends the literature on costs of cancer care to include nonaged adult HMO patients (aged 18–64 years) and adds HMO data to the literature that describes the cost experience for those aged 65 and over. To address our research aims, the research team developed a method to compare the costliness of cancer care

across multiple HMOs and between HMOs and Medicare FFS indemnity care on a consistent basis. To ensure that observed differences were not a result of differing costing (or pricing) methods and billing rules (bundling of services), we applied consistent costing weights to standardized Medicare FFS and HMO utilization data.

Here we describe the capture of cancer (and noncancer)-related medical care services as well as how we addressed data issues that arose in developing and implementing our standardized resource cost algorithm. We highlight 15 different Medicare payment systems and describe how our team adapted these systems to calculate relative service intensity of cancer care patterns between Medicare Advantage (capitated HMO contracts) and Medicare FFS (indemnity insurance) systems in the United States. We believe our algorithm can be applied in many different contexts if disease and procedure coding systems are sufficiently aligned. Although this algorithm was developed using Medicare FFS as its basis, it is important to note that the standardized relative resource cost algorithm (SRRCA) can be applied to any FFS data structure. Fishman et al. (15) (another chapter in this monograph) present the case for the importance of developing consistent data from a variety of health systems, both within the United States and internationally. Heterogeneity in health-care delivery systems, payment systems, insurance systems, and medical technologies provide the required practice variation to discover innovative care delivery models as well as relatively less safe delivery models. In this chapter, we show the need for standardized data in calculating a meaningful measure of resource use across health-care systems in the United States and across different countries.

Methods

Data Sources

This research was conducted within four nonprofit integrated healthcare systems: Group Health Cooperative based in Seattle, WA, the Henry Ford Health System of Southeast Michigan, and the Northwest and Colorado regions of Kaiser Permanente. Each system provides comprehensive health services primarily through closed-panel delivery models and places an emphasis on preventive services and cancer screening. All four health systems provide care to enrollees from each key market segment—commercial group, Medicare, Medicaid, and individual/family—and each plan provides services to individuals of all ages. Institutional Review Boards at each site reviewed and approved this research.

Comprehensive utilization data were extracted for the BURDEN population for 2000–2008 from data warehouses maintained by the health plans. Data were standardized across health plans according to specifications established by the CRN's Virtual Data Warehouse (VDW) (12). In any analysis that compares utilization or cost data from multiple organizations or across delivery settings, it is critical that data be standardized to the largest extent possible. Otherwise, one can never be sure that any observed difference is due to differences in the care delivery setting, costing/pricing methodologies, or data structure. Cost data are not included in the VDW, so the development of the standardized resource cost algorithm was a high priority.

Costing Basics

Total expenditures by health-care providers and third-party payers are the sum of the products of units of various inputs and the prices paid for each input. For the purposes of this analysis, we distinguish between production costs and standardized costs. *Production costs* of medical care services are defined as actual expenses incurred by providers in delivering care to individual patients or specified populations. These expenditures usually represent historical accounting costs, if derived from providers' financial management systems, or historical prices, if derived from bills or paid third-party claims. The key attribute of production expenses is that prices of the same input will likely vary across provider and location, and over time. This variation can confound differences in the physical units of medical care services if low-cost services are substituted for high-cost services. *Standardized costs* are computed by applying the same price for each class of inputs across providers and over time, so that the observed variance in expenses is determined only by variations in mix and volumes of the various medical care services delivered to patients. A standardized costing scheme represents a set of relative resource intensity weights, akin to resource-based relative value units (RVUs) (16,17). Relative resource weights derive their face validity from knowing the types, intensity, and complexity of specific medical care services.

Our Model

The foundation for our model is counts of standardized specific services provided to individual patients. Rather than starting from total monetary expenditures, we require that all medical care be defined by standardized procedure and facility classifications across all care sources. We developed relative monetarized resource weights for each service type. The sum of the products of service quantities and monetary weights generates a monetarized relative resource intensity value that can be compared across patients, providers, systems, and time. This approach removes the effects of inflation in input costs and medical care prices, as well as regional differences in input prices. By weighing each service type with fixed monetary values, we can compute an overall index of relative costliness of treatments, episodes of care, and total annual medical care consumption.

Because our primary research aim was to compare Medicare indemnity and capitation systems, we could have selected either HMO-based relative resource weights or Medicare payment schedules. Deriving HMO-based resource weights was not feasible given the scope of our work, as it would have required, for each of our sites, obtaining and mapping the HMO's cost accounting data onto a standardized cost report and then deriving an overall average unit cost estimate for each service. Therefore, we elected to base our algorithm on the 15 different payment systems Medicare uses to reimburse FFS providers of health-care services. Unless specifically noted, all costs have been converted to 2008 dollars. As our focus is on measuring resource intensity versus the effects of geographical payment modifiers, we made no adjustment for geographic input price differences or other adjustments (eg, health professional shortage areas or indirect medical education adjustments).

We applied our algorithm to both Medicare claims and HMO data. This approach meant that we treated a brief physician

office visit with a continuing patient the same in all HMOs in our sample and in the Medicare claims data. Because our HMO data are defined in terms of health-care encounters, rather than health insurance claims, we had to roll up Medicare claims data into relevant encounters to make them comparable to HMO data. Encounter data systems measure bundles of service use defined by facility, clinician, time, and patient. Claims, by contrast, link providers to patients, but individual claims can contain information on multiple encounters, and services provided to patients on a specified date can appear in multiple claims. HMOs represent integrated health-care delivery systems and health insurers. Most group-model HMOs have a predominance of capitation business, and their claims data systems are used mostly for out-of-plan emergency care and outside referrals.

Perspective is an essential element in measuring costs. Possible perspectives include society, payer, health-care system, provider, and family (18). For this analysis, our perspective is that of the health-care system. Hence, we want to capture the relative intensity of the resources used in stays, encounters, dispensings, procedures, etc., rather than the split billing between payers and patients or the revenues actually collected versus bad debt write-offs.

Medicare Payment Systems and HMO Adaptations

Medicare's payment systems are defined by the physical site of care—hospitals, medical offices, ambulatory surgery centers, pharmacies, home health agencies, hospices, skilled nursing facilities, psychiatric and substance abuse hospitals, and rehabilitation hospitals—and by professional service versus facility service. In this section, we describe how we approximate the same types of facility and professional services across prepaid HMOs and FFS practice.

Inpatient Care: Short-Term Stays in General Hospitals

For acute inpatient care, Medicare reimburses hospitals per stay based on diagnosis related groups (DRGs). The payment formula consists of a base DRG-specific payment, an adjusted area wage index, an indirect medical education allowance, a disproportionate share hospital allowance, and an outlier component. The intent of DRG payment is to reimburse institutions for facility-based costs and shift some of the financial risks to hospitals by paying a fixed rate regardless of actual lengths of stay or resources consumed. Professional fees are paid separately via the physician payment system, which uses the Medicare Fee Schedule (MFS) tied to the Healthcare Common Procedure Coding System (HCPCS).

Medicare DRG payments represent risk-adjusted payments for inpatient episodes, a switch from cost-based reimbursement. Payment by DRG shifts the incidence of variations in facility costs per stay within a DRG category from Medicare to the hospital, with allowances for additional marginal payments for cost and day outliers. The intent of the SRRCA is to capture differences in resource intensity of care (rather than risk sharing), so we modified the DRG payment system from a stay-based reimbursement to an average expense per hospital day for each DRG. This allowed us to capture how varying lengths of stay within a DRG affected total resource use. Using Medicare claims data, we first converted all expenses to 2008 dollars and then calculated a daily rate per DRG. In calculating the daily rate, we included only those costs associated with the Medicare Provider Analysis and Review (MEDPAR) DRG price amount ("the amount that would have been paid if no deductible, coinsurance, primary payers or outliers were involved") and any outlier payments ("the amount of additional payment approved due to an outlier situation over the DRG allowance for the stay"). We did not include any additional payments (medical education, organ acquisition, technology, disproportionate share hospitals, critical access hospitals, and sole community hospitals). For each hospital stay, this DRG-specific per diem rate was multiplied by the actual length of stay for each patient's hospitalization to calculate the HMO facility component for inpatient costs.

To calculate the professional services component for inpatient stays, we used the Medicare claims data. Professional bills associated with an inpatient stay were identified based on the overlap between dates of service on hospital (including admission and discharge dates) and physician claims. We then created a professional fee coefficient based on the ratio of total professional costs to total facility costs per DRG. To obtain total inpatient costs (facility and professional), the HMO facility component was multiplied by one plus the professional fee proportion. This approach maintained the resource intensity differences with longer lengths of stay for professional services and also addressed, if present, missing data on professional services in HMOs with internally owned hospitals (19).

In October 2007, Medicare released a new version of the DRGs with major revisions. As there is not a direct correspondence between the two versions, we created two sets of DRG daily facility coefficients and professional fee ratios, one using data from January 2000 to September 2007, and the other using data from October 2007 through December 2007. Ideally we should have a longer time window to calculate the second set of coefficients, but 2007 was the latest year available when we obtained the data.

In calculating both the daily DRG facility rate and the professional service ratio, we examined the data for extreme outliers that could disproportionately affect the cost coefficients. Except for true data errors, outliers can represent actual resource use; hence, an outlier had to be extreme to the point of implausibility and to have a significant influence on the coefficient values before we considered truncation. Surprisingly, even with our high volume of utilization data, we did not need to truncate. Those few records that were identified as erroneous were not used in calculating the ratio.

To the extent possible, we followed Medicare rules for inpatient reimbursement. Emergency room admissions that resulted in hospital admissions were rolled into the ensuing hospital stay. Our day-based inpatient costing algorithm automatically adjusts for interhospital transfers, both in and out of HMO hospitals. We followed the same methodology in costing HMO and Medicare data.

Inpatient Rehabilitation Facilities and Long-Term Care Hospitals

Combined care in inpatient rehabilitation facilities and long-term care hospitals accounts for less than 2% of Medicare expenditures. No such facilities or hospitals were owned by or served as contract service providers for any of the study HMOs. To be eligible for Medicare coverage in an inpatient rehabilitation facility, a patient must be able to participate in and benefit (achieve measurable improvements in functional health status) from 3 or more hours of

therapy per day. This is a relatively restrictive criterion for coverage, so few individuals receive this benefit. Prior to 2002, Medicare reimbursed these facilities based on average incurred cost. After 2002, 385 rehabilitation-based case-mix groups (CMGs) were derived, and predetermined payment rates for each grouping were created (20). Unfortunately, CMGs cannot be calculated from variables contained in the VDW. Therefore, we computed an average daily rate for rehabilitation services from Medicare claims data and multiplied it by lengths of stay at inpatient rehabilitation facilities to compute relative costliness estimates for each inpatient rehabilitation facility patient.

Long-term care hospital stays are assigned a DRG value, but under the Medicare payment system, these DRGs have a different weight than the DRGs from acute care hospitals. Because utilization in such hospitals was relatively rare and difficult to identify in the HMO data, we did not develop a separate algorithm. Costs were assigned using the acute inpatient algorithm.

Psychiatric Hospitals

No psychiatric hospitals were owned by or served as primary contract service providers for any of the study HMOs. Because of this and the low incidence of admission to these facilities, it is difficult to identify and categorize this type of utilization in our HMO data systems. Utilization of this type in the HMO data is most likely classified as either institutional stay or rehabilitation and was assigned the average daily rate for rehabilitation stays.

Ambulatory Care

Physician Services (Including Imaging). For reimbursement under Medicare, physicians' services are classified by HCPCS codes and are paid via the MFS. The MFS summarizes three underlying components into relative resource weights—physician work (time and skill), practice expenses, and professional liability. These three relative weights are added together to obtain an overall RVU. Because medical care is provided across the country in vastly different markets, to calculate the payment for a service, the RVU is multiplied by a dollar conversion factor, and to account for differences in input costs (prices) across geographic regions, one of three geographic indexes is used to adjust the RVU.

Medicare uses two separate fee schedules to pay for physician services depending on the care delivery setting. For physician services provided in a facility setting, such as a hospital, a schedule with lower rates is used. Hospitals receive additional facility payments, so the costs to physicians to practice in this setting are less. If care is provided in noninstitutional settings, such as an ambulatory care clinic or physician's office, then the fee schedule with higher payment rates is used, as this payment covers all practice expenses. Payments to providers can also be adjusted if the care is not provided by a physician, if payment modifiers are present, if the area is identified as a health professional shortage area, or if the provider is not participating in Medicare's physician and supplier program (20).

HMOs are reimbursed on a capitated basis; as a consequence, they do not face the same financial incentive to record procedures performed (HCPCS) as their FFS counterparts (19,21). However, coding practices are improving as a result of increased CMS enforcement of regulations directed at Medicare Advantage plans for accurate coding of diagnoses and procedures. This applies to the data HMOs are required to provide CMS for making risk adjustments to capitation payments. Other incentives for improved data capture include the increased use of computerized physician order entry systems, which require detailed coding, and, in some HMOs, internal incentive payments for physicians. The implications of this for HMOs are an increase, over time, in the number of HCPCS codes recorded per encounter and a reduction, over time, of outpatient encounters with no codes.

Along with the increase in coding, we have seen an increased use of homegrown procedure codes, which are problematic in multisite studies or studies using standardized codes for costing. Often the use of homegrown codes results from a desire to capture a finer level of detail than the corresponding standard code. In these cases, HMOs usually have a crosswalk available to convert codes back to standard HCPCS. If a significant volume of homegrown codes are encountered, they cannot be ignored and need to be either translated back to the most similar standardized code, or assigned costs using a different method.

We assessed our capture of HCPCS codes, and for the majority of outpatient encounters, relied on the fee schedule to estimate costs. For encounters with missing, incomplete, or homegrown procedure codes with no crosswalk, we assigned the evaluation and management code that was used most frequently in that care setting.

Hospital Outpatient Services. Services provided in the hospital outpatient setting are captured using HCPCS codes. Codes representing similar resource use and clinical characteristics are grouped together into 570 ambulatory patient care groups. Medicare reimburses a set amount for each group, which covers the facility portion of the costs (hospital operating and capital costs). The professional component is paid separately under the MFS (20).

HMOs may not always capture both the professional and facility codes associated with hospital outpatient care, particularly if services are provided within HMO-owned and operated facilities by salaried providers. HMO encounter systems identify if a service was provided, typically through a facility code, and often use revenue codes and *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) procedure codes instead of *Current Procedural Terminology*, 4th Edition (CPT-4) codes, which are required in the ambulatory patient care grouper. Therefore, to capture the facility portion, we computed facility to professional fee ratios for hospital outpatient encounters in the SEER–Medicare data and applied these ratios to professional costs based on HCPCS codes for each hospital outpatient encounter.

Ambulatory Surgical Centers. Since 1982, Medicare has covered surgical procedures provided in freestanding or hospital-based ambulatory surgical centers that are designated facilities (22). These surgical facilities are reimbursed for a limited subset of procedures (approximately 2300). Payments to them are based on fee schedules and have both professional and facility components. The professional component is reimbursed according to the physician fee schedule. To calculate the facility portion, procedure codes are grouped and reimbursed at preestablished amounts. Prior to 2008, there were nine surgical facility payment groups; after 2008, the groups were expanded to several hundred and were phased in over a 4-year period. If multiple procedures are performed during

the same encounter, the facility is reimbursed fully for the most expensive procedure and receives 50% of the standard payment for remaining procedures (20).

The procedures performed in surgical facilities can be done in other settings, so not every delivery system has such designated facilities. Therefore, the first step in the costing process is to identify whether there is such a facility in the health-care delivery system. The next step is to assign the procedure codes into payment groups. Given that 8 out of 9 years of our study period occurred prior to 2008, we employed the original nine-group payment system in the SRRCA. Otherwise, we followed Medicare's methodology to derive cost weights for utilization.

Laboratory Services

Medicare reimburses laboratory procedures provided in an outpatient setting based on a HCPCS fee schedule. Laboratory services provided during an inpatient stay are bundled into the DRG payment and not paid using this schedule. In addition, some laboratory services provided as a fixed complement to dialysis treatment are also bundled into monthly dialysis payments.

For laboratory services, the first step in the SRRCA was to convert any local laboratory codes to standard HCPCS codes. The next step was to identify any dialysis laboratory codes that needed to be removed because they were already implicitly included in dialysis payments. Once these steps were completed, we followed the Medicare reimbursement model. For codes that could not be converted, we assigned an overall average payment for a laboratory test.

Post-Acute Care

Skilled Nursing Facilities. To be eligible for skilled nursing facility (SNF) care, Medicare requires at least a 3-day hospital stay prior to admission to an SNF. Medicare reimburses SNFs based on a prospective payment system that uses a set daily rate based on an individual's resource utilization group (RUG). There are 44 RUGs, each of which groups patients who are relatively similar with respect to the intensity of their needs for nursing and rehabilitation care (physical therapy, speech therapy, occupational therapy, etc.) and assistance with "activities of daily living." The daily rate contains a fixed amount for routine care and then a variable amount per RUG for nursing and therapy services (20).

Unfortunately, unlike the DRGs used for inpatient reimbursement, the grouping variables for the RUG system were not commonly available in HMO data systems and they were not included in Medicare claims data. Therefore, the SRRCA could not replicate the Medicare RUG method directly. Using Medicare claims data, we calculated an overall flat daily SNF rate and then multiplied by length of stay to obtain SNF costs for each stay. This method relies on varying lengths of stay to capture differences in resource intensity. Ideally, an additional severity measure to differentiate patients with varying clinical needs would be included in a costing algorithm. However, SNF service use is not a major overall contributor to total health-care costs in the BURDEN study population; therefore, we did not develop a severity measure that could be applied to both Medicare FFS and HMO data consistently.

Home Health Services. For individuals who are homebound due to a medical condition and require skilled nursing care, Medicare provides temporary skilled nursing, therapy, social work, and home health aide services. In 2000, Medicare adopted a prospective payment system for each 60-day episode of home health care. For patients who receive fewer than five visits, Medicare reimburses by visit type. All other patients are classified based on their underlying health condition, level of functioning, and use of services into one of 80 home health resource groups and are reimbursed at a predetermined rate for the episode of care (20). For extremely complicated patients, marginal outlier payments are calculated.

As was the case for the SNF algorithm, lack of adequate data prevented us from adapting the Medicare home health services payment algorithm to HMOs. Classification variables for the home health resource groups are not available in HMO clinical data systems. As a replacement, using Medicare claims data we created average payments per home health service visit by clinical discipline (nursing, physical therapy, occupational therapy, speech therapy, social work, aide services, etc.) and applied them to their respective HMO utilization elements. Although this method does not capture varying patient care intensity within a visit, it will capture the differences in numbers and types of visits received among patients.

Services for Special Populations

Outpatient Dialysis. Medicare covers both hemodialysis and peritoneal dialysis and does not differentiate between the two for reimbursement purposes. Dialysis is covered using a predetermined "composite" rate that bundles reimbursement for the services, supplies, and equipment used for dialysis treatment into one payment. The composite rate is adjusted by age categories and two body measurement variables—body mass index and body surface area. Providers bill separately for physician services and certain medications and laboratory tests that are not included in the composite rate (23).

The SRRCA uses the base composite rate of $132.68 for dialysis costs for freestanding dialysis facilities in 2008. We do not adjust for patient characteristics as body measurement variables were not consistently available from HMO data systems. Provider and laboratory utilization not covered under the composite rate was weighted using the appropriate algorithm.

Hospice Services. Under Medicare, hospice services are authorized for people with a life expectancy of less than 6 months, and enrollment disallows payment for any curative treatment for the underlying terminal condition. Hospice covers a wide variety of services, including physician services and skilled nursing care; physical, occupational, and speech therapy; social work; certain drugs; and home health aide services. Medicare reimburses hospice care based on a fee schedule, which contains a predetermined daily rate for the following four categories: routine home care, continuous home care, inpatient respite care, and general inpatient care. Routine home care accounts for 95% of hospice care days and is the default payment category used by Medicare unless it is demonstrated that services from one of the other categories were provided (24). As long as the patient is enrolled in hospice, Medicare pays the daily rate regardless of the amount of services delivered (20).

Currently the SRRCA uses the 2008 routine home care daily rate of $135.11 as the basis for hospice costs. The vast majority

of hospice care (if not all) provided by the study HMOs falls into this category. In addition, the data required to classify patient days into the payment groups are not available on HMO automated data systems. HMOs vary in how they provide hospice services—some have internal hospice departments and others contract out these services. For HMOs with internal hospice departments, patients enrolled in hospice are given the opportunity to choose an external hospice provider. For some HMOs, data on the patients' duration and use of external hospice services are not available. In these cases, length of hospice enrollment was estimated using death date as a proxy for hospice end date.

Other Services

Ambulance. Prior to 2002, ambulance services were reimbursed by Medicare based on incurred cost. Since 2002, 14 HCPCS codes have been used to establish a base payment, which distinguishes level of service, supplies, and mileage (20). Separate payments are made for mileage for surface and air transport. Ambulance utilization is an incredibly small portion (less than 1%) of Medicare's outlay for medical services. Because of the fact that it is not an important cost driver for our study population, and our inability to obtain mileage estimates, we did not cost this service.

Durable Medical Equipment. Medicare covers certain types of durable equipment needed for medical treatment. Disposable items are not covered under this benefit. Equipment is divided into one of six groups, and is then further classified into about 2000 product groups. Using a fee schedule based on HCPCS codes, Medicare reimburses a fixed amount for each product group (25). As with any of the payment systems relying on HCPCS, homegrown codes must be converted to legal HCPCS codes to be counted. Care should also be taken to ensure durable medical equipment (DME) was captured in the utilization data. For at least one of the study sites, DME utilization was recorded in a database that was not commonly used in the automated clinical data. Once DME codes were located and converted to standard HCPCS, the SRRCA followed the Medicare method closely.

Pharmacy. Relative costs for outpatient prescription drugs are based on the published average wholesale price for a 30-day supply using the National Drug Code classification schema. A few prescription drugs from HMO databases may not have valid codes because of repackaging or other HMO-specific formulations, or drug-specific identifiers may be missing entirely. In the event that drug-specific information is not available, the costing model draws on therapeutic class information and assigns the average cost for all drugs within that class.

A summary of the Medicare payment systems and our HMO modifications is presented in Table 1.

Results

In this section, we provide examples to illustrate how the SRRCA assigns costs to utilization when following Medicare costing and when using novel, standardized approaches, and we briefly summarize the products we have developed.

Comparing Costs: Inpatient Care

At 34%, inpatient care (acute care hospitals) represents the largest component of Medicare spending and is an important driver of overall expenditures (20). Using actual records from the Medicare claims data for three of the most frequent DRGs, Table 2 illustrates how the Medicare payment compares with the results generated from the SRRCA. As was expected, for shorter hospital stays, the SRRCA generates a smaller estimate than the Medicare payment. Average stays generate very similar estimates, and for longer stays, the SRRCA estimate is greater than Medicare's. In each of the examples, we see that the Medicare payment method generates a tighter distribution between stays with a low and high length of stay. For example, in comparing the difference between the low and high payment value for congestive heart failure (DRG 88), when the length of stay is 9 days different, the Medicare payment difference is $6636, whereas the difference from the HMO estimate is $9763.55.

Comparing Costs: Physician Services

The next largest component, at 20% of Medicare spending, is physician services. Table 3 shows cardiology office visits from both HMO and SEER–Medicare data, costed using the SRRCA. As expected, the office visits that coded the same HCPCS procedure receive the same cost, independent of delivery system. Table 4 provides examples of relatively low- and high-cost oncology outpatient visits from both HMO and SEER–Medicare data based on the SRRCA.

Summary of Products Developed

In developing our SRRCA and preparing to answer the questions raised in the BURDEN study, we have created two products. The first is the SRRCA, a comprehensive set of costing algorithms that can be applied to both HMO and FFS data when standardized facility, procedure, service, and product codes are available. SRRCA facilitates the comparison of relative resource intensity within and across delivery systems. The second product is the infrastructure to convert SEER–Medicare claims data into encounter-based data so that they are more directly comparable to HMO data. This second product is important because it can be adapted to convert data from other large, claims-based systems, making even more comparisons possible.

Discussion

Key Considerations

Transforming Medicare claims data to an encounter format is an endeavor. Large numbers of files and variables and a steep learning curve are associated with using these data. Converting claims data to an encounter format requires significant programming and logic infrastructure. For example, in encounter-based systems, all information pertaining to a hospital stay is found in one file. In Medicare data, one must gather information from a facility-based file (MEDPAR) with physician or supplier bills (national claim history and possibly hospital outpatient statistical analysis file) in order to join all the data about an inpatient stay. To further complicate joining these data, there is no variable that directly links data from multiple files together. Therefore, programming rules

Table 1. Summary of Medicare's payment systems and adaptations for use on health maintenance organization (HMO) utilization data (21)*

Care setting	% of Medicare spending†	Medicare method‡	Adaptation for HMOs
Acute care hospitals	34%	• Facility: DRG • Professional: reimbursed independently via HCPCS codes	• Facility: converts Medicare DRG to daily rate multiplied by LOS • Professional: uses Medicare claims data to calculate professional to facility cost ratio per DRG, then multiply facility component
Psychiatric facilities	1%	Prior to 2003, payments based on average incurred operating costs; post-2003 per diem PPS	N/A
Physician services	20%	Fee schedule based on HCPCS codes approximately 7000	Fee schedule based on HCPCS codes when available, otherwise average cost per department
Hospital outpatient	7%	• Facility: fee schedule based on APC approximately 570 groups • Professional: reimbursed under physician system	• Facilty: fee schedule based on APC when available; otherwise, average cost • Professional: uses Medicare claims data to calculate professional to facility cost ratio
Ambulatory surgical centers	1%	• Facility: fee schedule based on procedures classified into nine payment groups; payment groups expanded in 2008 • Professional: physician fee schedule	• Facility: fee schedule based on pre-2008 payment groups when available; otherwise, average cost • Professional: physician fee schedule
Laboratory services	2%	Fee schedule based on HCPCS codes	Fee schedule based on HCPCS codes
Skilled nursing facilities	6.5%	Daily payment rate based on RUG-III group	Average daily rate based on Medicare claims data multiplied by LOS
Home health services	6%	If less than five visits in 60-day period, paid per visit type; otherwise, uses an episode payment method based on 80 HHRGs	Average rate per visit based on Medicare claims data
Inpatient rehabilitation facilities	1%	Prior to 2002, paid on average incurred cost per discharge; post-2002, paid on predetermined rates for 385 CMGs	Average daily rate based on Medicare data
Long-term care hospitals	Lt 1%	Prior to 2002, paid under TEFRA; post-2002, paid by LTC–DRGs	Uses acute inpatient algorithm
Outpatient dialysis	2%	Paid a composite rate per dialysis treatment	Composite rate per dialysis treatment
Hospice services	1%	Per diem rate for each eligible day	Per diem rate
Ambulance		Prior to April 2002, reported costs; April 2002–March 2007, blended method of fee schedule based on HCPCS and reported costs; since April 2007, use only fee schedule	N/A
Durable medical equipment	3%	Fee schedule based on product groups	Fee schedule based on product groups

* APC = ambulatory payment classifications; CMG = case-mix group for intensive rehabilitation products; DRG = diagnosis-related group; HCPCS = Healthcare Common Procedure Coding System; HHRG = home health resource group; LOS = length of stay; LTC = long-term care; N/A = not applicable; PPS = prospective payment system; RUG-III = resource utilization group; TEFRA = Tax Equity and Fiscal Responsibility Act.

† Based on 2003 data, does not sum to 100% because payments to Medicare Advantage programs are excluded.

‡ For complete description, see http://www.medpac.gov/publications%5Ccongressional_reports%5CMar03_AppA.pdf.

and logic must be developed and extensively tested to ensure the correct data are being linked. Another challenge in working with Medicare claims data is the lack of consistency in information or certain variables available across the different types of files. Another requirement is adequate computing capacity to process the extremely large Medicare data files. The BURDEN study obtained utilization data from 1999 to 2007, which involved loading over 1100 text files, containing over 100 million encounters.

The issues involved in measuring the production costs of healthcare services have been well documented (26–28). Cross-national,

Table 2. Comparison of Medicare reimbursement to standardized relative resource cost algorithm (SRRCA) for selected inpatient encounters*

DRG†	LOS, d	SRRCA base facility payment, USD‡	SRRCA professional ratio§	SRRCA total payment, USD‖	Medicare payment, USD¶	Difference#
088	1	$1180.20	0.182	$1394.79	$3362.92	−$1969
088	3	$1180.20	0.182	$4184.38	$4124.49	$60
088	10	$1180.20	0.182	$11 158.34	$9999.17	$1159
127	2	$1344.82	0.194	$3211.42	$6010.64	−$2799.22
127	5	$1344.82	0.194	$8028.55	$8043.01	−$14
127	8	$1344.82	0.194	$12 845.67	$9933.48	$2912.19
209	3	$2665.88	0.207	$9653.16	$13 913.90	−$4261
209	5	$2665.88	0.207	$16 088.59	$16 073.30	$15
209	7	$2665.88	0.207	$22 524.03	$21 540.72	$983

* DRG = diagnosis-related group; HMO = health maintenance organization; LOS = length of stay; MEDPAR = Medicare Provider Analysis and Review; NCH = national claim history; OUTSAF = outpatient statistical analysis file.

† 088 = chronic obstructive pulmonary disease; 127 = heart failure and shock; 209 = major joint and limb reattachment procedures of lower extremity.

‡ (MEDPAR DRG price + Outlier amount)/Total days for DRG.

§ (Allowed noninstitutional professional charges for associated NCH bills + Allowed institutional outpatient charges for associated OUTSAF bills)/(MEDPAR DRG price + Outlier amount).

‖ HMO total payment = HMO facility payment × (1 + HMO professional ratio) × LOS.

¶ Medicare payment = MEDPAR DRG price + Outlier amount + Allowed noninstitutional professional charges for associated NCH bills + Allowed institutional outpatient charges for associated OUTSAF bills.

(SRRCA total payment) – (Medicare payment).

Table 3. Examples of cardiology office visits from health maintenance organization (HMO) and Medicare costed with the standardized relative resource cost algorithm (SRRCA) physician services algorithm*

Data system	ID	HCPCS procedure code	Procedure count	Procedure cost, USD†	Encounter cost
HMO	H1	93325	1	$36.00	$305.83
HMO	H1	93320	1	$83.00	
HMO	H1	93307	1	$186.83	
HMO	H3	J0152	3	$208.05	$252.01
HMO	H3	93018	1	$17.43	
HMO	H3	93016	1	$26.53	
Medicare	S2	80053	1	$14.78	$152.34
Medicare	S2	36415	1	$4.17	
Medicare	S2	99214	1	$72.76	
Medicare	S2	93000	1	$20.46	
Medicare	S2	85025	1	$10.99	
Medicare	S2	80061	1	$29.18	
Medicare	S3	93325	1	$36.00	$305.83
Medicare	S3	93320	1	$83.00	
Medicare	S3	93307	1	$186.83	

* HCPCS = Healthcare Common Procedure Coding.

† Cost per procedure × Procedure count.

multisystem, and multisite economic research can be challenging because of differences in financial incentives and care delivery patterns between national and private health systems, and between HMOs and FFS providers, as well as varying ability to capture key utilization and costing data elements within and across health-care systems and organizations (19,21,29).

An inherent complication of measuring the output of a personal service, such as health care, is that the individual is also an intrinsic input to the production process—that is, no service is produced if the customer does not participate in receiving the service. This unique aspect of personal services presents barriers to output measurement because every individual has unique genomic and behavioral profiles. The practical implication is that we have resorted to measuring services by their inputs, such as medication prescriptions or doctor office visits.

Relative resource intensity schemes allow different utilization types (inpatient, home health, pharmacy, outpatient visits) to be combined into one common metric and provide a measure of overall health-care resource intensity. However, prior to examining these data, care must be taken to be sure the underlying utilization events from each utilization category—such as hospital stays and days, or outpatient visits—are accurately captured, thoroughly examined, and understood. Once service units are converted into monetary values and aggregated, it is difficult to identify inaccurate data points. In

Table 4. Examples of oncology-related visits from health maintenance organization (HMO) and Medicare costed with the standardized relative resource cost algorithm (SRRCA) physician services algorithm*

Data system	ID	HCPCS procedure code	Procedure count	Procedure cost†	Encounter cost
HMO	H4	77295	1	$940.75	$1630.49
HMO		77300	2	$158.44	
HMO		77334	3	$531.30	
HMO	H5	36415	1	$4.95	$282.99
HMO		38221	1	$78.08	
HMO		99245	1	$199.96	
Medicare	S6	76370	1	$163.39	$964.73
Medicare		77290	1	$465.04	
Medicare		77334	1	$177.10	
Medicare		99244	1	$159.20	
Medicare	S7	36415	1	$4.95	$112.74
Medicare		84153	1	$25.52	
Medicare		84403	1	$36.18	
Medicare		99213	1	$46.09	

* HCPCS = Healthcare Common Procedure Coding.

† Cost per procedure × Procedure count.

addition, one must understand the underlying utilization events that are driving costs to derive effective policy implications from cost data.

We have demonstrated that the SRRCA can be used in multiple HMOs and across alternate reimbursement and delivery systems within the US health-care system. The next logical step would be to evaluate how the SRRCA can be used to compare US health-care costs with those of other countries. The Center for Medicare and Medicaid Innovation "encourages widespread adoption of practices that deliver better health care at lower cost (30)." The United States and other countries could benefit tremendously from the ability to evaluate each others' models of care. Using the SRRCA for international comparisons depends on data harmonization issues. Specifically, are physical utilization elements defined consistently so that one can make meaningful comparisons, and are the resource intensity classes reasonably matched to approximately the same utilization events across countries? Currently the answer is no. In an international overview of case-mix classification systems in 25 countries, French and colleagues found that DRG and procedure coding varies by country (31). With respect to utilization, wide variations are observed internationally in average hospital lengths of stay (32), which implies either fundamental differences in the health status of different populations, differences in norms about appropriate lengths of stay, differences in the product of a hospital day, or all of the above.

Anderson and colleagues discuss the potential distortions that can arise in international comparisons of health-care systems when expenditures are compared with the actual resources used for health production (32). They discuss how evaluations change when comparing the use of inputs, suggesting that what is primarily driving differences are large differences in input prices. A standardized costing methodology would help eliminate these distortions. However, care must be taken to ensure that comparable health service products are being evaluated and that the overall context of care is understood. In the case of hospital care, for example, analysis of occupancy rates, hospital admission rates per 1000 population, average lengths of stay, hospital days per 1000 population, and hospital staffing per bed can generate useful insights regarding the magnitude of both crossnational and intracountry variations in resource intensity; for example, which countries achieve shorter stays by intensifying services per day (including using more highly trained staff), and which countries accept longer lengths of stay for lower service intensity per day.

Strengths and Weaknesses

Collaborating to achieve standardized crossnational data and data sharing can be a valuable cancer research and health policy tactic. An important strength of our SRRCA is its ability to make relative cost comparisons within and across systems. Although the application described here is for use within the United States, the fact that the SRRCA is based on comprehensive service-specific utilization profiles means that its application in a crossnational context could facilitate understanding of similarities and differences across health-care systems in terms of patterns of care for diseases and other health problems.

One weakness we acknowledge is an inability to generate absolute cost estimates, especially for subsets of the population. The lack of a severity adjustor in the SNF algorithm is an example of one of the underlying causes of this issue. It also should be noted that by adopting the perspective of the health-care system we are not capturing the full opportunity costs of resources used in receiving health care—for example, patient travel time and transportation costs. Our algorithm also will not detect changes or differences in resource intensity within a specified procedure, inpatient day, or product over time or place. For example, if we are comparing hospitals with predominantly master's degree–prepared nurses to hospitals with predominantly associate's and bachelor's degree–trained nurses, the content of inpatient days will not be homogeneous across these settings.

An additional limitation of our SRRCA is the complexity of the underlying data structure required. This is a direct reflection of the fragmentation of the health-care system in the United States. Current efforts by the federal government to encourage adoption of electronic medical record systems, together with meaningful use requirements that include the ability to transmit harmonized data through secure web portals, augur significant improvements in availability of detailed clinical and utilization data for measuring quality of care and performance of health-care systems. The

challenge to researchers is to keep abreast of this informatics revolution and gain the content knowledge and informatics skills required to extract and analyze these rich datasets. The health-care industry, like the banking industry, will not revert to paper charts and bills once it has adopted electronic information and billing systems.

Although we expect the basic paradigm of the SRRCA to remain unchanged, we are still completing some ongoing work, which may involve some adjustments. For example, we will examine if we are accurately capturing resource intensity for inpatient stays that have a truncated length of stay due to death, especially if it occurs close to admission. We are also examining procedure capture across time in the HMO data to ensure poor coding capture is not artificially lowering costs.

Future enhancements to the SRRCA include improving the algorithms for psychiatric facilities and long-term care hospitals, adding an intensity measure to the SNF algorithm, and further evaluating and updating how to infer resource coefficients for missing data.

Conclusions

We have developed a standardized, comprehensive algorithm to support economic analyses comparing resource intensity within and across different health systems. An understanding of utilization and resource use is essential to policy and research strategies to determine what does and does not work as expected and where potential savings in health-care expenditures may be realized. We must be able to understand these costs regardless of the care setting: in national health systems, community health systems, HMOs, cancer control programs, oncology practices, and alternative cancer treatment settings. Differences in health-care financing and delivery systems and in patterns of cancer treatment can be scrutinized to highlight factors that appear to be related to higher versus lower rates of utilization, expenditures, and outcomes (33). A cross-national perspective can be especially valuable because structural and behavioral factors thought to be immutable by internal clinical and policy leaders may be revealed to be changeable across nations and cultures and, even more importantly, to be binding constraints on reducing health-care outlays in specific types of systems or cultures.

In closing, a quote from Voltaire seems appropriate: "Don't let the perfect be the enemy of the good." This is not to imply we should stop trying to improve our data or methods, but rather to acknowledge that although they are imperfect we must still push forward and use what we have to understand and improve the performance of health-care delivery systems.

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Evaluation of New Technologies for Cancer Control Based on Population Trends in Disease Incidence and Mortality

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Cancer interventions often disseminate in the population before evidence of their effectiveness is available. Population disease trends provide a natural experiment for assessing the characteristics of the disease and the potential impact of the intervention. We review models for extracting information from population data for use in economic evaluations of cancer screening interventions. We focus particularly on prostate-specific antigen (PSA) screening for prostate cancer and describe approaches that can be used to project the likely costs and benefits of competing screening policies. Results indicate that the lifetime probability of biopsy-detectable prostate cancer is 33%, the chance of clinical diagnosis without screening is 13%, and the average time from onset to clinical diagnosis is 14 years. Less aggressive screening policies that screen less often and use more conservative criteria (e.g., higher PSA thresholds) for biopsy referral may dramatically reduce PSA screening costs with modest impact on benefit.

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Cancer interventions often disseminate in the population prematurely, before conclusive evidence of their efficacy has been obtained. For example, prostate-specific antigen (PSA) screening for prostate cancer became widespread in the United States in the early 1990s (1), but clinical trials to evaluate screening efficacy were initiated in 1993 and published results only in 2009 (2,3). Based largely on these results, the US Preventive Services Task Force (USPSTF) recently recommended against routine PSA screening, a reversal which goes against what has become standard practice in this country (4). However, a great deal of uncertainty still remains about the harms and benefits of prostate cancer screening.

In this chapter, we examine the conundrum—and the opportunity—represented by the premature adoption of cancer interventions. By premature we mean the adoption and dissemination of an intervention before conclusive evidence of its efficacy is available from clinical trials. Premature adoption of an intervention may have a negative impact—if the harms of the intervention ultimately turn out to outweigh the benefits. The key characteristic of a premature intervention in the setting of this paper is simply that conclusive evidence about harm–benefit tradeoffs has not yet been obtained. Our primary example is the case of PSA screening in the United States. Although PSA screening began in the late 1980s and became popular in the early 1990s, large clinical trials first published results concerning PSA screening benefit only in 2009.

The conundrum is clear—if an intervention is adopted in the absence of clarity about its benefits, then not only could we end up squandering money and resources for little benefit, but revelation that benefit is not what was expected could indicate that a reversal of contemporary standard practice is warranted. However, the adoption by a population of a novel intervention presents an opportunity as well, namely to assess the effectiveness and costs of the intervention in the population setting as opposed to the artificial setting of a clinical trial.

Because the population represents the ultimate uncontrolled experiment, great caution has to be exercised in making inferences about the comparative effectiveness of novel interventions based solely on population data. Examples of such inferences are provided by studies conducted by the Cancer Intervention and Surveillance Modeling Network (CISNET) (www.cisnet.cancer.gov). For example, CISNET models have been used to quantify the respective contributions of mammography and adjuvant chemotherapy, two major fronts of progress in breast cancer control, to declines in breast cancer mortality (5), and the contribution of colorectal cancer screening, diet, and treatment to declines in colorectal cancer mortality (6).

In this chapter, we show how premature adoption of cancer interventions and their effects on population trends can be used to help inform economic evaluation and policy decisions. We review and synthesize a series of modeling studies specifically focused on extracting the necessary information from population data following the dissemination of the intervention. In some cases, the models we present have been used to make inferences about the contributions of specific inferences to declines in population mortality; in other cases, models have been used to estimate disease progression rates and characteristics of the intervention from population data. This information is then incorporated in a medical decision-making modeling framework that is designed to facilitate inferences about harm–benefit tradeoffs. We focus specifically on questions about the benefits, harms, and likely costs of PSA screening for prostate cancer, but we also discuss how our methods have been used to learn from trends in colorectal cancer, which are a complex product of changes in behaviors over time as well as changes in screening and treatment practices. We show how well-calibrated models can be of value in determining cost–benefit tradeoffs for policy development and demonstrate that there is an important role for modeling to play in determining sound cancer control polices.

PSA Screening Patterns and Prostate Cancer Trends in the United States

The PSA screening era in the United States began in 1986 when the test was approved for monitoring prostate cancer progression but disseminated rapidly for early detection purposes. Different areas of the United States adopted PSA screening at slightly different times (7), but the period of most significant dissemination was the early 1990s when prostate cancer incidence more than doubled relative to historic trends (8). The peak in incidence was followed by a rapid decline as screening use stabilized, and it was at this point that prostate cancer deaths began to fall. The drop in disease-specific mortality has been sustained and impressive; prostate cancer deaths have declined by 44% since their peak in 1991 (9). Among men aged 50–84, the primary group targeted by screening, the fall has been even more substantial, reaching 49% by 2009.

The harms and benefits of PSA screening have been hotly debated, with speculation that PSA explains the mortality declines counterbalanced by skepticism. Until 2009, when results of the two large screening trials were published (2,3), the population data represented the best available evidence about screening benefit. However, interpreting population mortality trends is complex because the population constitutes the ultimate uncontrolled experiment. In the case of PSA and prostate cancer, there have been multiple other changes in disease control and management that have occurred concurrently with the spread of PSA screening. These include changes in primary treatment, with historical treatment trends showing dramatic increase in radical prostatectomy rates during the 1980s (2,3) and similar increases in the use of adjuvant hormone therapy for localized disease during the mid to late 1990s (10). There have also been changes in the detection and treatment of recurrent disease, primarily due to PSA monitoring following primary treatment.

Can we use population prostate cancer trends to learn about the benefits and harms of PSA screening despite these challenges? This has been the mission of the CISNET prostate group, which has used modeling of prostate cancer in the population as its primary approach.

Surveillance Modeling: Learning About Disease Progression From Population Cancer Trends

Surveillance modeling is an approach designed to learn about the process of disease progression from trends in population incidence and mortality. The central idea is that although the events in disease progression are not all observable, they produce an observable process, namely disease incidence trends, that can be used to inform about the underlying natural history. Disease incidence trends that have been recorded before and after the advent of screening in a population are particularly informative, so long as information is available about screening and biopsy referral practice patterns. In the case of prostate cancer, PSA screening became adopted in the late 1980s, so we have used prostate cancer incidence trends, together with retrospectively ascertained screening patterns in the United States, to make inferences about rates of disease onset, metastasis, and clinical detection in the absence of screening (11).

A Model of Prostate Cancer Progression: Parameter Estimation Using Population Incidence Data

Figure 1 summarizes our model, which includes two main components. The first describes how PSA grows in healthy men and cancer cases, and how this growth varies across the population. The second links PSA with disease progression and describes how the risks of disease spread and generation of clinical symptoms change as PSA grows after disease onset. We assume that the risk of disease onset increases with age and that the risks of disease spread and symptoms are proportional to the level of PSA at any given time. This assumption is a mathematical representation of a mechanism that generates the known correlation between the level of PSA and stage of disease at diagnosis, and was found to be most consistent of several models (12,13) with observed data on PSA growth and disease stage from a retrospective series (14). The natural history parameters are, therefore, the PSA growth rates and risks of disease onset, metastasis, and clinical symptoms.

Estimation of the natural history parameters proceeds as follows. PSA growth and its variation are based on serial PSA data from the Prostate Cancer Prevention Trial (PCPT), which screened 18 882 men for up to 7 years (15). Of these, 9459 were in the control group and were used for our analysis. We use the results to simulate a population of men aged 50–84 beginning in 1975 and ending in 2000, of whom a fixed percentage experienced disease onset at a rate proportional to their age. After onset, PSA growth is reset based on the PCPT results, and the events of disease metastasis and clinical diagnosis are set to occur at rates that grow proportionally with the PSA level. We superimpose screening, according to US screening patterns (1), on this simulated population and project the corresponding trends in age- and stage-specific incidence. We then vary the rates of onset, metastasis, and clinical diagnosis so that the projected trends best match the observed trends in incidence. We use a simulated likelihood-based framework (11) to quantify the extent of the mismatch and optimize the simulated likelihood to obtain the best-fitting natural history parameters conditional on the PCPT-based PSA growth curves. Details of our methods and results are provided elsewhere (11,16); we note here that the projected stage-specific incidence curves under the fitted natural history parameters capture both the dramatic peak in local-regional incidence observed in the early 1990s and the steady decline in distant-stage incidence observed after this time. The fitted model suggests that the lifetime probability of biopsy-detectable prostate cancer is 33%, whereas the chance of a clinical diagnosis in the absence of screening is 13% and the average time from onset to clinical diagnosis is 14 years on average (17).

Using the Model to Explain Prostate Cancer Mortality Trends

We used our model to investigate the likely role of PSA screening versus changes in prostate cancer treatment in explaining the dramatic and sustained decline in prostate cancer deaths in the United States through the year 2005. To do so, we first needed to project what mortality rates would have been in the absence of screening. We assumed that in the absence of screening or treatment, stage-specific incidence of prostate cancer would have remained constant at levels observed in 1987, just prior to the PSA era, and

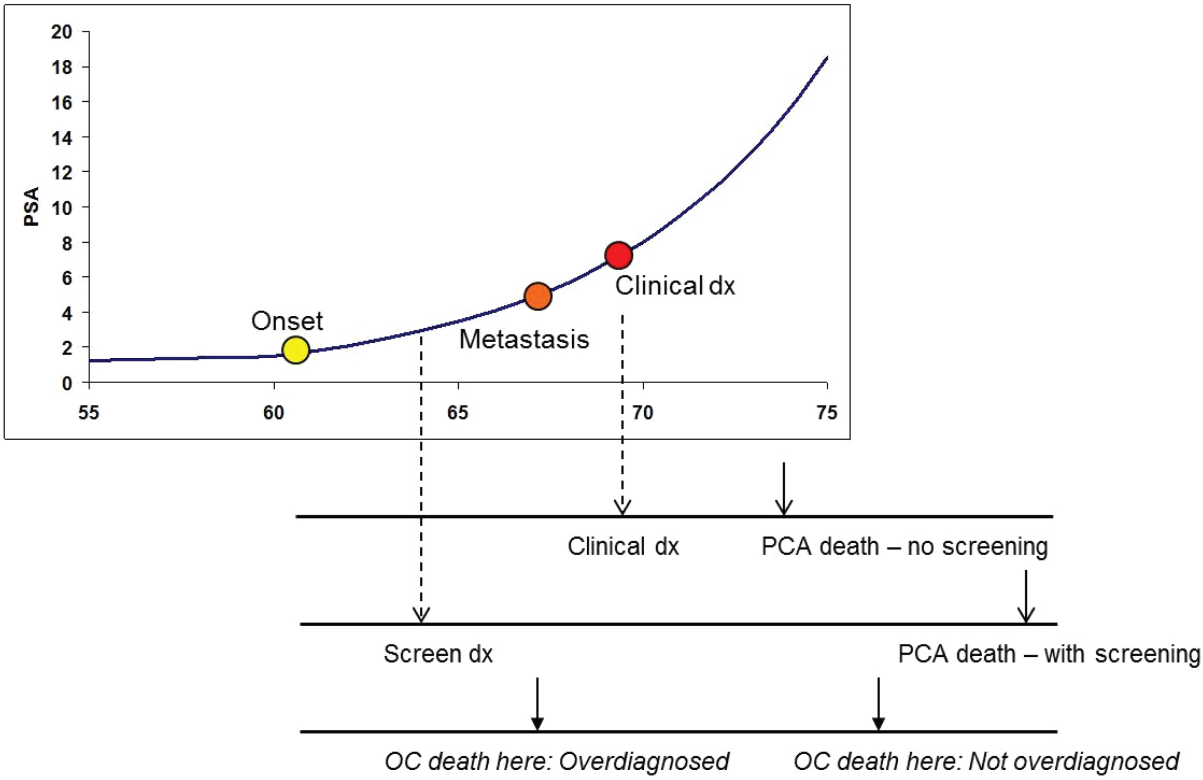

Figure 1. A model of prostate cancer (PCA) natural history, diagnosis, and survival in the absence and presence of screening. Following disease onset, PSA is assumed to grow exponentially. The risks of metastasis and clinical diagnosis (dx) increase proportionally with the PSA level. Without screening, the cancer is diagnosed in distant stage, but with screening, detection occurs while disease is still localized. The figure shows how overdiagnosis depends on the date of other-cause (OC) death relative to the lead time, which is the time from screen diagnosis to clinical diagnosis.

disease-specific survival would have been similar to survival among cases in the Surveillance, Epidemiology, and End Results (SEER) database diagnosed from 1983 to 1986 who did not receive curative primary therapy. We then used information on treatment trends for localized prostate cancer and results from studies comparing primary treatments with each other and with observation (18,19) to project how changes in treatment might have impacted the number of cases dying from prostate cancer. We found that treatment changes explained about one-third of the drop in prostate cancer mortality by 2005 (20). This left two-thirds to be explained by other factors, chief among them being PSA screening.

Adding PSA screening to the model and projecting disease-specific survival under the resulting model-projected stage distribution produced further declines in disease-specific deaths; screening and treatment together accounted for two-thirds of the drop in prostate cancer mortality by 2005 (Figure 2). We concluded that treatment alone could not explain prostate cancer mortality decline in the United States; screening has likely played an important role and could account for as many as 10 000 lives saved per year by 2005.

Estimating Harms of Prostate Cancer Screening

It has become clear that screening for cancer can confer harm as well as benefits. Imperfect diagnostic tests can lead to false positive results, generating anxiety along with unnecessary biopsies. Overdiagnosis, or detection by screening of cancers that would never have presented clinically during a patients' lifetime, can lead to unnecessary treatment with all of its consequences. Screening itself is a costly endeavor because of the sheer number of tests that must be conducted to screen a healthy population.

Overdiagnosis is a particular concern in prostate cancer screening. Because prostate cancer is known to have high latent prevalence relative to its clinical incidence, particularly in older men, there is enormous potential for overdiagnosis and overtreatment. The likelihood of overdiagnosis is closely linked with the lead time, which is the time by which screening advances diagnosis. Lead time, in turn, can be estimated from patterns of disease incidence following the dissemination of a new screening test, so long as information is available on screening patterns in the population. In particular, the height and width of the peak in disease incidence after the introduction of a novel screening test are informative about lead time (21). This is because when a sensitive screening test is adopted in a previously unscreened population where latent disease is prevalent, many cases are identified by the test and their date of diagnosis is correspondingly advanced by the lead time. In later years, these cases are no longer present and there is a consequent drop in disease incidence. The lead time determines when the later incidence drop takes place relative to the initial incidence gain. When the lead time is longer, the incidence drop takes place later and the initial incidence gains are sustained, producing a more pronounced incidence peak.

The likelihood of overdiagnosis can be estimated once the distribution of lead time is known, because overdiagnosis occurs when other-cause death takes place after screen detection but

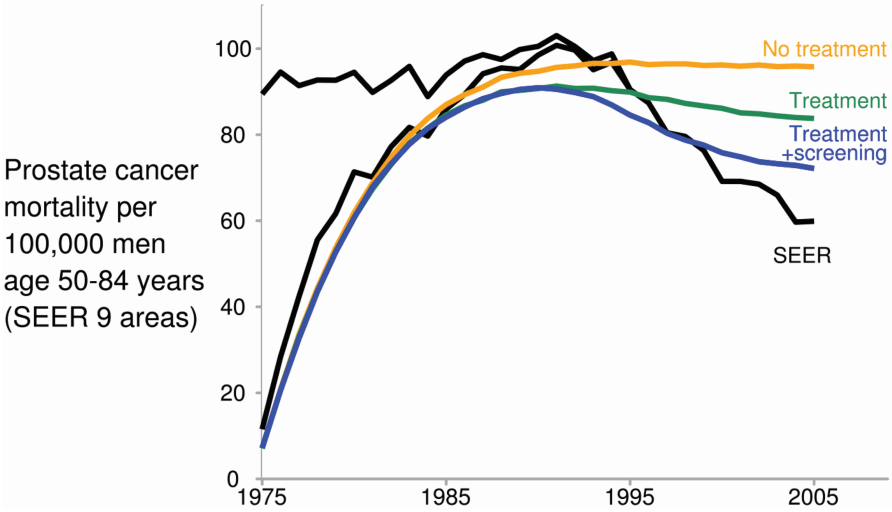

Figure 2. Modeled impact of changes in primary treatment and changes in primary treatment combined with screening on age-adjusted prostate cancer mortality in the United States. The figure shows mortality among men diagnosed after 1975 as observed and then as modeled given changes in treatment and screening. For comparison, the figure also shows total mortality due to prostate cancer in the United States. By 2005, treatment changes account for about one-third of the drop in disease-specific mortality (20), whereas the combination of screening and treatment changes accounts for about two-thirds of the drop in mortality.

before the end of the lead time. Thus, given lead time, the chance of overdiagnosis can be calculated from population life tables.

In the case of PSA screening, the premature dissemination and rapid uptake of the test during the late 1980s and early 1990s have provided an excellent opportunity to estimate the lead time and corresponding overdiagnosis frequency associated with PSA screening. Indeed, our simulated likelihood-based framework for estimating our model parameters produces a virtual population of men in which the times of screen detection and clinical diagnosis in the absence of screening are known. We can use these data to produce empirical estimates of lead time and, given dates of other-cause death, overdiagnosis. We have developed several other algorithms that use data on PSA testing patterns and prostate cancer incidence to estimate lead time and overdiagnosis (17,22–24). Our results consistently point to a frequency of overdiagnosis during the1990s that amounts to approximately one out of every four screen-detected cases in men over age 50. Our results are consistent with another model developed using US data, but are lower than estimates from a model developed partially using data from the European Randomized Study of Screening for Prostate Cancer (24).

Economic Evaluation of Prostate Cancer Screening

The economic implications of cancer screening tests are vast and rest on the drivers of costs that we have already mentioned: the tests themselves, false positive results, and overdiagnosis. Estimation of the costs of prostate cancer screening, therefore, requires an assessment of the costs of testing as well as the costs of prostate biopsies and treatments, including the harms associated with treatment like impotence and incontinence. Given these costs, differences between screening strategies will be determined by how the cost drivers vary across the strategies.

The calibrated model provides a representation for how disease progresses in the absence of screening and, in particular, yields a distribution of age and stage at disease diagnosis without PSA testing. Superimposing a specified screening protocol produces a change in the timing of diagnosis and, consequently, a change in age and stage of disease in the presence of screening. Using stage-specific curves for prostate cancer survival (8), we are able to project the consequences of this earlier detection for disease-specific deaths.

The universe of potential PSA screening strategies is enormous and includes strategies that vary in terms of their starting and stopping ages, interscreening intervals, and criteria for biopsy referral. Each of these screening strategy parameters has been the topic of a great deal of debate and controversy. In the case of criteria for biopsy referral, for example, there is disagreement about the threshold for declaring a test to be abnormal and about whether to base biopsy referral decisions on PSA velocity in addition to absolute PSA (25).

Using our calibrated model, we considered a range of potential strategies and projected a large set of relevant outcomes, including the aforementioned drivers of cost and several measures of benefit. Figure 3 illustrates the results of varying the ages to start and stop screening, the interscreening intervals, and the criteria for biopsy. The results show clearly that less intensive strategies can materially reduce key drivers of cost although only modestly impacting screening benefit.

Modification of Natural History Models for Other Settings and Health Systems

Some aspects of natural history models are dependent on local population practice patterns. An example is the risk of clinical detection in the absence of screening. This depends on the intensity of prostate cancer diagnosis due to other means, and this can differ greatly across population settings. When the same model was calibrated

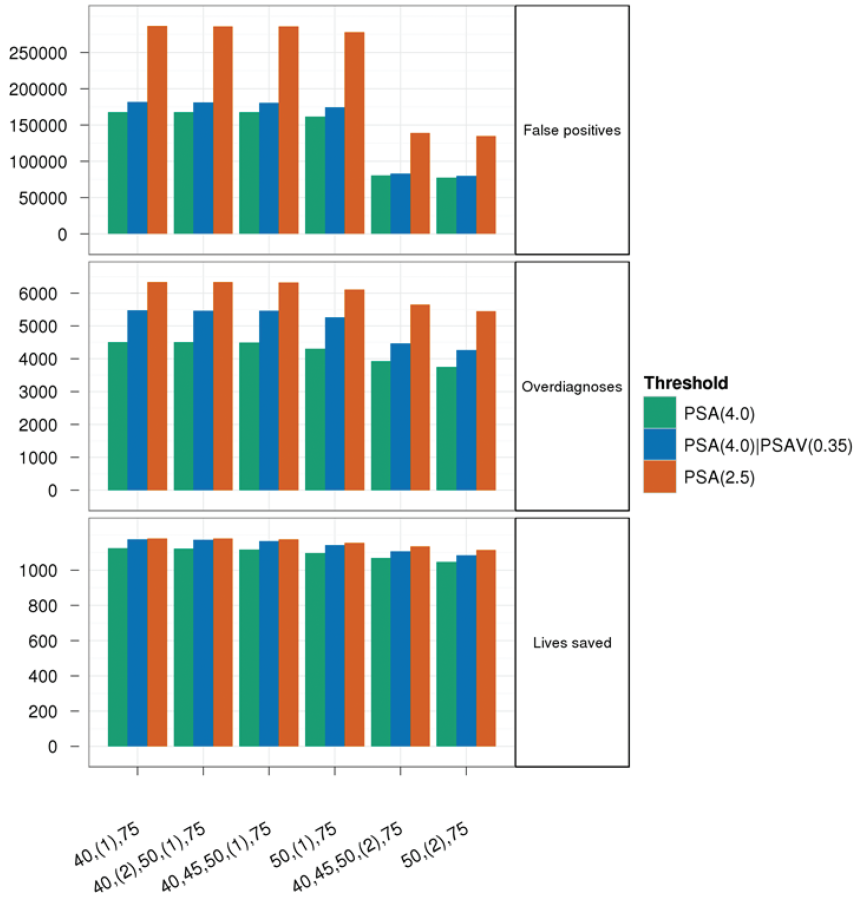

Figure 3. Three outcomes of harm (false positive and overdiagnosis) and benefit (years of life saved) corresponding to six candidate PSA screening policies, varying ages to start and stop screening, and interscreening intervals as well as the criterion or threshold for biopsy referral. Outcomes are numbers of false positives, overdiagnoses, and lives saved per 1 million men screened. The ages to start and stop screening are specified below the figure; upper and lower bounds are provided and the interscreening interval is given in parentheses. As an example, the policy 40, 45, 50, (2), 75 indicates that screens take place at ages 40, 45, 50, and thereafter every 2 years until stopping at age 75. The figure shows that less intensive screening strategies can yield dramatic reductions in screening harms with very modest differences in benefit.

to prostate cancer incidence patterns in the Rotterdam section of the European Randomized Trial of Screening for Prostate Cancer (ERSPC) and then again to data on prostate cancer incidence in the US population after the advent of PSA screening, the clinical incidence hazard rate was higher in the model fit to the US data than in the model fit to the Rotterdam data (24). This example indicates that one important criterion to be applied when selecting data sources as inputs for population-based modeling is that the data should match the setting for which policy is eventually going to be developed. In developing policies for prostate cancer screening in the United States, it will not be appropriate to use models calibrated to ERSPC data.

Discussion

In this chapter, we have shown how dissemination of cancer interventions at the population level can be used to inform about harm and benefit, key inputs for the development of sound public health policies. We have also demonstrated how a well-calibrated model can be adapted and used for economic evaluation of candidate policies that go beyond historic population practices. Our results focused on specific drivers of cost rather than the economic costs themselves, because we were interested in differentiating between harms like false positive tests and overdiagnosis. Unlike costs, which vary across clinical and geographical settings, these measures of harm have consistent absolute interpretations. However, the translations of these measures into economic costs of care will be necessary for cost-effectiveness comparisons. Information on the costs of care is available from a wide variety of sources. For example, Ekwueme et al. (26) reviewed 28 studies (15 US and 13 international) of publicly available data on the resource costs of prostate cancer screening, diagnosing, and staging. They were able to quantify and pool both direct costs—resources used, physician costs, medical supplies, and facility costs—and indirect costs, such as loss of income from time off work, transportation costs, and travel time. Once the costs of different aspects of care have been quantified, they can be incorporated into the models as multipliers of the numbers of corresponding procedures (eg, for screening tests or biopsies) or cases (eg, for treatment costs).

We have focused on the example of PSA screening for prostate cancer, adopted in the United States even before the initiation of the US trial of prostate cancer screening, which began enrollment in 1993. There are many other cases where interventions have been adopted prematurely and, with the subsequent release

of data indicating adverse impact, have been dropped on a wide scale. A classic example is that of female hormone replacement therapy, which was broadly adopted in the United States until publication of results from the Women's Health Initiative in 2002 showed that it adversely impacted cardiovascular and breast cancer risks (27). Examples in cancer chemotherapy abound. In France, for instance, between 2004 and 2010, 31 new cancer drugs obtained market approval, the majority of which were targeted therapies (usually monoclonal antibodies). Although the actual medical benefit from targeted therapies was seldom challenged, the Transparency Commission expressed reservations regarding the survival advantage over existing treatments. In 2009 and 2010, eight targeted drugs were reviewed and received market approval with no improvement in actual benefit and only a few were rated as providing a minor improvement in actual benefit. In the United States, the US Food and Drug Administration actually revoked its accelerated approval of the drug Avastin for advanced breast cancer, noting that the drug "used for metastatic breast cancer has not been shown to provide a benefit, in terms of delay in the growth of tumors, that would justify its serious and potentially life-threatening risks."

We have demonstrated how the surveillance modeling approach allows us to separate the contributions of PSA screening and changes in primary treatment to the declines in prostate cancer mortality. This approach has been similarly used in breast cancer, to separate the contributions of screening and changes in chemotherapy (5), and in colorectal cancer (28), where changes in disease-impacting behaviors over time must also be considered. The MISCAN-colon micro-simulation model used four waves of data from the National Health and Nutrition Examination Survey (NHANES) to estimate the prevalence over time of risk factors, such as physical activity; fruit and vegetable consumption; and use of folate, aspirin, and female hormone replacement therapy. Incorporating estimates of the effects of these risk factors on colorectal cancer incidence from the epidemiological case-control studies allowed the model to separately project the contributions of these factors and the contributions of screening and treatment to mortality (6). The MISCAN-colon model has also been harnessed to compare different potential screening policies, and their results have been used by the USPSTF in determining their most recent recommendations (29). This case of the use of modeling within the policy development process is still unfortunately the exception rather than the rule. The USPSTF has used modeling in defining policy for both breast (30) and colorectal cancer screening (29), but not for prostate cancer screening. And most professional societies do not use models to quantify harm–benefit tradeoffs, but rather rely on literature review and consensus decision making on the basis of observed results. These may not even reflect the likely long-term population costs and benefits of the policies that are being considered. Certainly, economic evaluation on the basis of disease modeling may produce results that are unpopular, particularly if they project that costs of new promising interventions are excessive relative to benefits. However, this type of analysis, on the basis of well-calibrated models, is likely to be a critically important weapon in our battle to manage health-care costs while advancing cancer control in the future.

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Comparing Cancer Care, Outcomes, and Costs Across Health Systems: Charting the Course

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This monograph highlights the multiple payoffs from comparing patterns of cancer care, costs, and outcomes across health systems, both within a single country or across countries, and at a point in time or over time. The focus of comparative studies can be on the relative performance of systems in delivering quality cancer care, in controlling the cost of cancer care, or in improving outcomes, such as reducing mortality rates and improving survival. The focus also can be on comparing the effectiveness, cost, or cost-effectiveness of competing cancer prevention and control interventions within a given system or across systems, while taking into account variations in patient characteristics, disease incidence and severity, resource availability, unit costs, and other factors influencing system performance.

Two recurring themes in this monograph are: 1) the opportunities for cross-system analysis, learning, and improvement are enormous and just beginning to be tapped; and 2) the empirical and methodological challenges in realizing this potential are likewise enormous, but real progress is being made. In this concluding article, we revisit and illustrate both themes, with the aim of suggesting a research agenda for enhancing capacity to conduct strong empirical cross-system analyses in cancer care delivery. To focus the inquiry, we limit consideration to those cancer care systems, whether within or across countries, sufficiently developed to have access to registries that not only can document cancer incidence and mortality but, through linkage to additional data sources, can serve as platforms for patterns-of-care, costing, or other in-depth studies. This necessarily puts the spotlight on developed nations; and among these, we concentrate on those in Europe and North America represented at the September 2010 workshop, "Combining Epidemiology and Economics for Measurement of Cancer Costs," in Frascati, Italy (1).

We distinguish between *population-level* studies, designed to compare the performance of health systems across countries or within a single country along specified dimensions, and *patient-level* studies, designed to investigate the effectiveness, cost, or cost-effectiveness of specific interventions and programs for individual patients (or individuals at risk for cancer) either within a given health-care system or across systems. In population-level studies, the outcome of interest might be summary measures of cancer mortality, survival, or other prominent patient outcome–oriented indexes of performance that are feasible to measure across systems for defined populations. Patient-level studies will often investigate the determinants of variations in patterns of care, costs, or outcomes, or apply economic evaluation methods to examine whether specific interventions offer good value for money. Although most patient-level studies to date are within-country or within-system, we note important examples of cross-country or cross-system analyses.

In the next section, we highlight some examples of population- and patient-level studies. This sets the stage for the subsequent sections discussing a range of options, including some already in progress, for strengthening the data, methods, and organizational infrastructure to support policy-relevant comparative research on cancer outcomes and costs.

Comparisons Across Health Systems: Informative but Difficult

Population-Level Studies

The methods for conducting empirically sound *cross-national* comparisons of cancer incidence, mortality, and survival are relatively well developed. In recent years, important and frequent collaborative contributions have been made by research teams organized by the International Agency for Research on Cancer (IARC) of the World Health Organization and the International Association of Cancer Registries (IACR) (2), as well as by the EUROCARE (European Cancer Registry–based Study on Survival and Care) study group (3,4). Growing out of EUROCARE-3 was the CONCORD study, which provided survival estimates for about 1.9 million adults diagnosed with female breast, colon, rectum, or prostate cancers during 1990–1994, and followed up to 1999 (5). Projects led by EUROCARE and EUROPREVAL have analyzed cancer prevalence within and across European countries (4).

Although these and other prominent studies (6) have compared disease incidence, prevalence, mortality, and survival (singly or jointly), there are evidently no recent cross-national studies on cancer *cost*, whether overall or by disease site. Although Organization for Economic Cooperation and Development (OECD) compiles

and publishes country-specific data on health expenditures and its components, it does not produce cross-national cost estimates by disease class or specific cancer diagnoses (7).

There are noteworthy examples of *within-country* efforts to monitor health system performance on cancer metrics over time. In Canada, Cancer Care Ontario (CCO) supports the Ontario Cancer System Quality Index (8). In the United States, the Agency for Healthcare Research and Quality publishes each year the National Health Care Quality Report (9), and several US cancer agencies and organizations collaborate to produce an annual "report to the nation" on incidence, mortality, survival, and selected special topics (10).

Patient-Level Comparative Studies

The substantial diversity of health-care delivery systems across countries, and indeed within any country, creates significant opportunities for policy-relevant research comparing alternative approaches to care delivery along the cancer continuum: prevention, detection, treatment, survivorship, and end-of-life care (11,12). By observing how seemingly similar individuals either at risk for cancer or with the disease are treated in different systems, we have the opportunity *in principle* of benefitting from what amounts to quasi-natural experiments in care delivery (13). This could allow for benchmarking of "high quality" or "high value" services and identifying best (and less than best) practices.

One cross-national comparison is well illustrated in the study of colorectal cancer treatment patterns in Italy and the United States reported herein by Gigli and colleagues (14), who found clear between-country differences in use of adjuvant therapy, open abdominal surgery and endoscopic procedures, and hospitalization. Similarly, Warren and colleagues (15) compared end-of-life care for non–small cell lung cancer patients aged 65 and over in Ontario and the United States, finding significantly greater use of chemotherapy in the United States, but higher rates of hospitalization in the last 30 days of life in Ontario. Each study was feasible because the participating countries could link high-quality cancer registry data with administrative files to identify similar cancer patients and then track receipt of services over time.

In cross-national settings where insurance or other administrative data files are not available or accessible, alternative strategies for augmenting cancer registry data can be pursued. An instructive case in point is the "high resolution" analyses reported by Gatta and colleagues (16), examining the impact of guideline-recommended care on survival in samples of patients diagnosed with breast, colorectal, or prostate cancer across a number of European countries. Building on earlier EUROCARE studies (17–20), these analyses brought together cancer registry data enhanced with additional clinical detail from multiple participating registries and countries (eg, for breast cancer, data from 26 registries in 12 countries). Included as determinants of cross-country survival differences were such macro-level variables as total spending on health care and the relative availability of such inputs as computed tomography, magnetic resonance imaging, and radiotherapy equipment.

Several implications flow from these cross-system studies. For valid and reliable analyses of cancer care, outcomes, and costs across geographical boundaries, high-quality registry data (or its clinical equivalent) are necessary, but generally not sufficient. Such data must be augmented with either administrative files or additional clinical information to provide an accurate time profile of patient-level diagnoses, services and procedures received, and outcomes, as well as patient, provider, and health system variables. For any given health system comparison, all pertinent variables should be defined and measured in the same way, or at least measure the same construct.

We are far from achieving widespread international "interoperability" in measurement and reporting of cancer care use and costs. The resulting challenges in being able to draw valid cross-country inferences from existing studies are well illustrated in our review here of economic studies in colorectal cancer, as conducted primarily in countries with well-developed networks of cancer registries (21). In the main, studies from different countries yielded estimates of direct medical costs in ways that precluded a sound comparison across studies. Few studies estimated direct nonmedical costs (eg, patient or caregiver time) or the productivity costs associated with disease and treatments. Indeed, aggregate and patient-level cost estimates varied in so many ways across countries that meaningful comparisons now are almost impossible. A broadly similar conclusion emerges from the review of colorectal cancer patterns of care studies from across Europe, Australia, and New Zealand (22) and in comparisons between Canada and the United States (23).

That challenges in conducting micro-level analyses can arise across health-care systems *within* a country is underscored by Fishman and colleagues (24). They describe the data system hurdles in conducting comparative effectiveness research in samples of elderly US cancer patients when some are enrolled in Medicare for-for-service (FFS) plans and others in Medicare-managed care plans that include health maintenance organizations (HMOs). As one direct response to the issue of data comparability within Medicare, Rosetti and colleagues (25) developed a "Standardized Relative Resource Cost Algorithm" (SRRCA) to assign standardized (comparable) relative costs to cancer patients in HMOs and FFS plans.

Such innovative fixes as the SRRCA represent important, yet incremental, steps toward addressing a more fundamental issue in conducting sound comparative effectiveness research within the United States. With its strong cancer registry networks but vast array of administrative data systems and non-interoperable electronic health informatics systems, how does the country advance toward a "national cancer data system," as advocated by the Institute of Medicine in 1999 (26) and echoed by multiple cancer policy makers since then? (27).

Building Capacity for Comparative Studies Across Health Systems

Enhancing the Empirical Base

High-quality sources of data to support scientifically sound population-based studies of cancer care, outcomes, and costs have emerged most often from partnerships involving some combination of government agencies, professional and provider organizations, and researchers. The empirical infrastructure required for comparative analyses will not simply emerge on its own, as the product somehow of "natural market forces" in the health-care arena. Little disagreement arises among payers, providers, and

consumers of cancer care surrounding the contention that decision making about competing interventions should be informed by solid evidence on effectiveness and costs. But only rarely does any single or combination of these private stakeholders have the financial and organizational wherewithal, or indeed an adequate incentive, to take on the full task of building and sustaining a population-level database for cancer research. Now, if by some means the necessary empirical infrastructure does emerge, one would want to encourage its broad and rapid application, not only by the parties that paid for it but by qualified researchers everywhere, and assure that its use by one set of researchers does not diminish its availability or utility to others. In this sense, the data infrastructure needed to support population-level cancer research could well be characterized as a type of *public good*, with the implication that it will be underproduced in the absence of collective action organized and supported by public agencies.

This line of argument (or at least aspects of it) has been well recognized in both the North American and European arenas for population-level cancer research (28). As noted, the EUROCARE project, based in Milan and Rome, has developed the capacity to draw survival and other surveillance data from over 80 publicly supported cancer registries in 21 European nations covering about 36% of their combined populations (16). In Canada, the health services research program jointly sponsored by CCO and the Institute for Clinical Evaluative Sciences (ICES) has developed publicly available datasets linking clinical and administrative information on cancer care, outcomes, and resource utilization in the province of Ontario (29), and now most Canadian provinces have similar linked datasets. Most recently, Ontario and British Columbia researchers teamed up to examine pre- and post-diagnosis cancer-related costs for multiple tumor sites (30). In the United States, the SEER–Medicare linked database represents a partnership involving the National Cancer Institute (NCI), the Centers for Medicare and Medicaid Services (CMS), and the federally supported SEER registries covering roughly 28% of the US population (31,32). The Cancer Research Network has developed standardized tumor, clinical, utilization, and cost data for large HMOs in the United States, all of which have electronic medical record systems (33,34). The Centers for Disease Control and Prevention (CDC), in collaboration with seven state cancer registries and multiple university-based researchers, have supported the Breast and Prostate Cancer Data Quality and Patterns of Care Study, creating large population-based samples to study quality-of-care and survival outcomes (35).

Current collaborative efforts, however, fall short of providing cancer researchers and policy makers with the data platforms required for population-based studies encompassing all geographical regions, all population groups, and the full range of clinical, patient-reported, and cost-related outcomes that can inform decision making. Specific research initiatives such as the NCI-created Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium (36) have rendered proof of concept that primary data collection and multiple datasets linked together can effectively support a range of important innovative studies (37,38). But such initiatives alone are not intended to address the larger matter of how to develop and *sustain* the empirical base for population-based cancer research over time. What are the prospects for building sustainable data platforms that are accessible and affordable to a broad swath of individual researchers and policy makers? A comprehensive pursuit of this mammoth topic would require its own monograph, but we highlight some notable examples.

European Partnership for Action Against Cancer and Other European Confederations. The European Partnership for Action Against Cancer (EPAAC) is a confederation of over 30 public and private sector organizations that seeks to work closely with the European Union, the IARC, the European Network of Cancer Registries (ENCR), the EUROCARE project, the OECD, and others to advance an ambitious agenda for cancer prevention and control research (39). Among EPAAC's objectives is a "European Cancer Information System" that would draw on multiple partnerships to develop harmonized population-based data on cancer incidence, survival, prevalence, mortality, *and* also high-resolution studies to examine the impact of medical resource availability, patient-level variables including lifestyle factors, and specific interventions on outcomes. In a complementary development, IARC and ENCR announced in 2012 the creation of a European Cancer Observatory to provide easier access to basic surveillance data from over 40 European countries (40). Although not disease-focused, the "EUnetHTA" is a network of government-appointed organizations, regional agencies, and nonprofit organizations established in 2008 to harmonize and improve the quality of health technology assessment across Europe (41). As such, its work could eventually inform the evaluation efforts in specific domains, including cancer.

CCO–ICES and Other Provincial Partnerships in Canada. Potentially well positioned to create and sustain data platforms for cancer care, cost, and outcomes research is Canada, at least on a province-by-province basis, as the CCO–ICES health services research initiative in Ontario is beginning to demonstrate (29). A particularly strong feature of this system is the capability of linking cancer registry data with additional clinical information *and* service provision data from the province's publicly funded universal health-care system. As a result, it is possible to track medical services rendered, the corresponding resources consumed, and survival outcomes over time on a population basis.

American College of Surgeons and American Society of Clinical Oncology. In the United States, there are several parallel initiatives underway to strengthen the capability for monitoring and improving the quality of cancer care. These include the American College of Surgeons (ACoS) Commission on Cancer's (CoC) Rapid Quality Reporting System (42), already adopted in over 20% of the CoC's 1500 approved cancer programs, and the new "CancerLinQ" information system under development by the American Society of Clinical Oncology (ASCO) (43). Both of these far-reaching initiatives are aimed at providing near real-time feedback to care providers and eventually at strengthening the basis for comparative effectiveness research of cancer therapies. As currently configured, neither appears readily geared to support population-based cost or cost-effectiveness analyses of care across the cancer continuum.

SEER–Medicare: Building on the Concept. A key to making further progress on the economic analysis front is pursuit of a strategy that is simple in concept but complex in execution: Expand the SEER–Medicare linked dataset "model" to cover virtually 100%

of the US population—in partnership with the CDC's National Program of Cancer Registries—and to include linkages with administrative data from Medicaid and as many major private insurance plans and managed care organizations as possible. If data elements were standardized and harmonized across payers, the result would be linked cancer registry–claims data yielding population-representative samples across all ages, geographical areas, and types of health plans. Clearly, a number of major organizational, financial, and perhaps even legal hurdles would have to be cleared for such an ambitious plan to take flight and become sustainable over time.

Extracting Maximal Value From the Empirical Base: The Essential Role of Modeling

At the core of any epidemiologically based analysis of health outcomes and cost is a model (44) and a number of associated tasks. The tasks can be viewed as falling under two headings: 1) using the available data to assign values (either point estimates or probability distributions) to all the variables deployed in the analysis and then investigating each of the hypothesized causal connections, for example, impact of intervention A on health outcome X, or the impact of Y on cost outcome C, or both, after adjusting for confounding; and 2) combining these estimated variables, and their inferred causal connections, into some form of decision model to investigate the impact of alternative intervention strategies on the outcomes of interest (eg, health outcomes, cost, or cost-effectiveness) for some selected target population. The decision model becomes the analytical platform for posing compelling "what if" questions. For example, how costs are expected to shift if intervention X′ is selected rather than X? At the same time, the decision model is the vehicle for evaluating policy options (X versus X′) to optimize some designated criterion, for example, cost per quality-adjusted life year. The pivotal point is that in studying the impact of X versus X′ in the selected target population, the analyst is not necessarily constrained by data availability or data quality limitations within that population. Rather, the aim is to make the decision model appropriate to the question at hand by bringing to bear the best available data from all feasible sources.

Statistical Inference and Prediction

Whatever the outcome being investigated, the within-country or cross-country context, or the strengths and limitations of the corresponding empirical base, paying close attention to strategies for both statistical inference and decision modeling is foundational. We briefly call attention to three problems of statistical inference (among many) that are especially pertinent: (a) appropriately characterizing the distributional features of the outcome of interest (a particular concern when cost is the dependent variable); (b) adjusting for patient-related and other selection effects that otherwise can lead to biased inferences about the impact of factors on outcomes, costs, or both; and (c) recognizing that cancer care interventions may be complex, multilevel, and delivered in geographical and clinical environments characterized by the statistical phenomenon of "clustering."

Over the past two decades, considerable progress has been made in coping with (a), especially in the area of cost, where robust generalized modeling approaches have been developed (45–47). Regarding (b), the threat of selection bias in the estimation of outcomes, including cost, has long been recognized in the econometrics literature. In recent years, two basic approaches to bias reduction have been pursued, with applications in the health-care arena accelerating over the past decade: propensity score matching or weighting (48) and instrumental variable (IV) methods (49–54), which seek to identify and remove biasing effects arising from observable *or* unobservable influences on the dependent variable of interest. Likewise, developing cost estimation and prediction models that jointly handle problems (a), (b), and (c) by recognizing the frequently hierarchical nature of interventions is a prime area for further work (54–56).

Decision Modeling

Consider the following policy questions:

- What are the relative contributions of screening and adjuvant therapy to achieving reductions in mortality from breast cancer?
- What is the effect of rising chemotherapy costs on the possible cost savings from colorectal cancer screening?
- What is the cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in women older than 30?
- How may one estimate the clinical benefits, harms, and cost implications of a particular cancer screening program *prior* to its widespread adoption so as to inform decision making about optimal screening policy?

These seemingly diverse inquiries in cancer prevention and control have certain important features in common. They are complex, involving many clinical and economic considerations. The time horizon over which clinical benefits, harms, and costs flow at the patient level will not be measured in months but years and, indeed, may span the remainder of the individual's life, from the point of intervention going forward. It is highly unlikely that either experimental or observational data would be available for any one cohort in sufficient detail and duration to include direct observations on all the variables involved in the multiperiod investigation.

There is one more feature in common: Each of these four questions has already been investigated in impressive detail using some form of decision modeling (57–60), most typically a variant of micro-simulation. However strong or deficient the empirical base for population-based cancer research within a health system or across health systems, adopting a decision modeling strategy provides the additional flexibility to bring the best available data to bear (whatever the source) on the problem at hand.

Conclusions

The central challenge in conducting technically sound comparative analyses of cancer care patterns, outcomes, or costs across health-care systems is marshaling the skill, the will, and the fiscal and administrative resources to develop and sustain the necessary data infrastructure that can support strong (and frequently team-based) research. Whether for cross-national studies or within-country studies, the task is made all the more difficult because most of the component building blocks for national, regional, or state cancer data systems—including insurance and other administrative data sources, medical records systems, and even cancer registries—were not originally designed to support research.

Nonetheless, the empirical base needed for a given investigation can frequently be created through some combination of dataset cleaning and updating (eg, re-abstracted registry records); dataset linkages (eg, registry data with claims files, or registry data with medical records); and/or dataset creation (eg, surveys to collect individual-level data on cancer risk-increasing or risk-reducing behaviors, time costs, or patient-reported outcomes, in some cases using the cancer registry to establish the sampling frame). Indeed, some projects have linked both secondary and newly created sources to provide a rich longitudinal picture of the cancer patient experience over time, from diagnosis, through treatment, and into the survivorship period (36).

Population-based cancer registries, whether covering a city, state, province, region, or entire country, are the bedrocks not only of epidemiological investigations of disease trends but also trends in cancer patterns of care and economic cost. As a result of sustained work by tumor registries and their affiliated experts worldwide, a consensus is emerging about the international rules-of-the-road for cancer surveillance data definition, collection, and analysis (2) (pp. 67–71). Over time, disparate registry operations have developed operational definitions and criteria for appraising data completeness, accurate identification of true-positive cancer cases, and approaches to computing and reporting statistics on incidence, prevalence, mortality, and survival (61,62). This standardization supports current and future efforts to foster comparative analyses of cancer care, outcomes, and costs.

Yet to date and to our knowledge, no country-level comparative studies of the cost of cancer have been published, either in the aggregate or by disease site. What is lacking, to be sure, is not the methodological wherewithal, but the data on cancer care resource consumption and prices that have historically been well beyond the scope of registries. Without some systematic, technically feasible, affordable, and sustainable strategy for augmenting registry data on an ongoing basis with additional sources of information on cancer care delivery and resource use, it is difficult to see how country-level comparisons of cancer costs can be estimated directly, that is, from the ground up. As suggested earlier, a viable alternative strategy is to deploy epidemiologically grounded economic modeling, bringing to bear the most appropriate data for cost inferences from multiple information sources.

The policy significance of comparative investigations across health systems has recently been underscored in a report issued by the US National Research Council and the Institute of Medicine finding that US males and females at all ages (up to 75) have greater rates of disease and injury, and shorter life expectancies, than in 16 other wealthy nations (63). The report's recommendations to improve the quality and consistency of data, as well as analytic methods and study designs, highlight a growing consensus about the importance of building capacity for sound comparative analyses. That such comparative analyses can highlight successes, as well as failures, in pursuit of the "triple aim" of better health, better health care, and lower cost is well illustrated in a recently published series of papers (64).

In sum, progress in producing scientifically strong, policy-relevant comparative analyses of cancer care, health outcomes, and costs within and across systems requires continuing investments on three fronts: database development, statistical inference and prediction, and decision modeling. They go hand in hand. What would be the payoffs for such an investment? What are some of the compelling questions and issues that could be more effectively addressed through stronger cancer data systems and research methods? The list is long, but would surely include:

- Assessing the effects on downstream outcomes and costs of specific cancer prevention and screening strategies.
- Investigating the impact of existing high-cost anticancer agents and emerging technologies and interventions (eg, genomics-guided targeted therapies) on outcomes and the costs faced by patients, health-care systems, and governments.
- Evaluating alternative patient management strategies after the initial therapy, including surveillance during the survivorship period and end-of-life care.
- Studying the cost and cost-effectiveness of interventions at any point along the cancer continuum and including the direct medical costs, as incurred typically within health-care systems, direct nonmedical costs (eg, capturing the value of patient and caregiver time), and the cost of disease-related lost productivity.

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