Ann Ist Super Sanità 2013 | Vol. 49, No. 1: 73-78
DOI: 10.4415/ANN_13_01_12

Advancing the science of cancer cost measurement: challenges and opportunities

Silvia Francisci[a], K. Robin Yabroff[b], Anna Gigli[c], Angela Mariotto[d], Maura Mezzetti[e] and Joseph Lipscomb[f]

[a] Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy
[b] Health Services and Economics Branch, Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD USA
[c] Istituto di Ricerche sulla Popolazione e le Politiche Sociali, Consiglio Nazionale delle Ricerche, Rome, Italy
[d] National Cancer Institute, Bethesda, MD, USA
[e] Università di Roma "Tor Vergata", Rome, Italy
[f] Rollins School of Public Health and Winship Cancer Institute, Emory University, Atlanta, GA

Abstract

Objectives. Cancer accounts for a major proportion of national health expenditures, which are expected to increase in the future. This paper aims to identify major challenges with estimating cancer related costs, and discuss international comparisons, and recommendations for future research.

Methods. It starts from the experience of an international workshop aimed at comparing cancer burden evaluation methods, improving results comparability, discussing strengths and criticisms of different approaches.

Results. Three methodological themes necessary to inform the analysis are identified and discussed: data availability; costs definition; epidemiological measures.

Conclusions. Cost evaluation is applied to cancer control interventions and is relevant for public health planners. Despite their complexity, international comparisons are fundamental to improve, generalize and extend cost evaluation to different contexts.

Key words
- cost-effectiveness
- phase of care
- incidence
- prevalence
- targeted therapy

INTRODUCTION

In most developed countries, cancer accounts for a major proportion of national health expenditures [1]. Although incidence rates have been declining for many cancers due to changes in risk factor prevalence and prevention efforts, the absolute number of newly diagnosed cancer patients is expected to increase due to population growth and aging [2-4]. Further, earlier stage at diagnosis and ongoing improvements in cancer treatments are associated with improved survival following diagnosis [5-7]. As a result of these trends, a large increase in cancer prevalence is expected in the future [8]. Moreover, health care delivery trends, and increasing use of expensive new chemotherapy drugs [9], will likely involve higher overall costs of cancer care. Although anticancer medicines are centrally approved by the European Medicines Agency, access to such therapies might be very heterogeneous across European countries due to different payers' resources and different pricing and reimbursement policies. This is particularly true for targeted therapies, that is approaches that tailor treatments to individual patients or groups based on molecular features of the disease and characteristics of the host. The uptake of these therapeutic approaches is difficult to predict, but it will likely vary across countries, health care delivery settings, and patient groups.

Measuring and projecting cancer-related expenditures is an increasingly important issue for health care policy makers at multiple levels (national, regional or local), as well as for health care payers. Little research has been conducted, however, on methods to assess or estimate cancer expenditures at these multiple levels, or to compare approaches and study findings across countries. International comparison might be especially useful to provide further insight into cancer patient management and best practices to increase efficiency of health care delivery.

On the other hand, differences in health care delivery systems, health care policies, and data availability make international comparisons complex. To begin to address some of these issues, the National

Address for correspondence: Silvia Francisci, Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Via Giano della Bella 34, 00161 Rome, Italy. E-mail: silvia.francisci@iss.it.

Cancer Institute, University of Roma Tor Vergata, Italian National Institute of Health, and Institute of Research on Population and Social Policies (National Research Council) co-sponsored an international and interdisciplinary meeting "Combining Epidemiology and Economics for Measurement of Cancer Costs", held on September 21-24, 2010 in Frascati (Italy). The 29 participants (from Australia, Canada, Finland, France, Germany, Italy, Sweden, the Netherlands, UK, and the USA) were statisticians, epidemiologists and health economists.

The ultimate goal of the workshop was to promote an international and multidisciplinary dialogue on strengths and drawbacks of different methodological approaches to cancer burden evaluation, and ways to improve comparability of data and results.

The workshop was structured in four sessions: "Prevalence and survival estimation"; "Methods to calculate medical care cost"; "Cost-effectiveness, cost-benefit and decision modeling"; "Forecasting, uncertainty"; and a final round table. The detailed agenda and presentations are available from: www.irpps.cnr.it/en/research-activities/population-trends-migration-studies-and-spatial-mobility/methods-and-products-fo-3.

In this commentary we summarize the main issues emerged in the workshop, focusing on major challenges in the estimation of incidence and prevalence cancer related costs, the benefits of international comparisons, and future directions of collaborative research.

MAIN ISSUES

The focus of the workshop was on the review and comparison of analytical approaches to assess current cancer burden and on the prediction of future cancer-related costs across health systems and countries. In order to establish a common background, thus improving the exchange of knowledge between scientists from different research fields, three main topics were afforded: basic information required, data sources available and data-linkage; cost definitions and indicators; epidemiological measures of cancer burden. These items represent the parameters required to inform cancer care costs evaluation at the macro and micro levels.

Data availability

Participants from seven countries provided information on data used to assess cancer burden. Although local features of health care system and health care insurance were associated with different patterns of data collection and availability, the core information is common to all countries.

Prevalence estimates, that is the total number of individuals in a population who have a certain disease during a specified period of time, are mainly derived from population-based cancer registries data, the registries have either nationwide (as in Finland, Sweden, the Netherlands, and the USA with the National Program of Cancer Registries, NCPR), or local coverage (as in France, Italy, UK, and the USA with the SEER Program).

Health care and health insurance databases including individual records are the main sources of information on cancer costs. Examples of such databases are hospital discharge files, physician consultation records, or lists of services provided (*e.g.* outpatient pharmacy, ambulatory surgery, emergency room). In many countries, cancer patients can be identified from population-based cancer registries, while their health service use and related costs or expenditures may be traced through record-linkage (based on individual identifiers) with the above mentioned databases.

In some countries *ad hoc* surveys are valuable sources of information about out-of-pocket costs, disability pensions, sickness absenteeism, days lost from work, and quality of life.

Definition and measurement of costs

Definitions of cost types and related measurement techniques represent the preliminary step in cancer cost descriptive analysis and modeling. There are three categories of costs: *direct health care costs* (related to hospitalizations, outpatient or ambulatory services, chemotherapy and radiation therapy); other *direct non-health care costs* (*e.g.* transportation to and from care centres, time spent by family members in providing home care, and patient time); *productivity or "indirect" costs*, consisting of lost or impaired work or leisure time due to morbidity or early death from the disease, usually estimated either in the societal or employer perspective.

Approaches to valuing time associated with productivity loss include:

a) the *human capital approach* explicitly attaches more value to time lost by individuals who earn more, than to time lost by individuals who earn less, and is based on wages;

b) the *friction cost* is the cost incurred by an employer when a sick worker must be replaced, and it is based on the concept that a productivity loss occurs when a person withdraws from the labor force due to disease or death [10];

c) the *willingness to pay* method estimates the amount individuals would be willing to be compensated for losing time because of a given intervention.

Most studies of patient time cost firstly identify amount of services provided to cancer cases, then assign a specific time duration to each service, and finally apply a time "value" to compute the overall time cost [11, 12].

It is worth noting that the different methods have different meaning, so that each of them is appropriate to answer specific and different questions.

Moreover, none of the approaches reviewed value the quality of time.

Epidemiologic measures of cancer burden

Incidence, mortality, survival and prevalence are the most common epidemiological measures used to quantify the burden of cancer on population health. While incidence, mortality and survival rates are widely reported indicators susceptible of international comparisons [13, 14], prevalence data are far less commonly available, and are usually estimated using

statistical methods. A relevant summary measure of cancer survival is the fraction of patients cured. From a population-level or statistical point of view, cure occurs when the mortality rate in patients reaches the level expected based on the general population experience [15-18]. Cure fraction is a useful measure to disentangle the proportion of patients who will never die of their disease from that of patients who will progress in the illness, require further treatment and will eventually die of the disease; however this definition does not provide information on quality of life.

Cancer survival figures are generally obtained from longitudinal perspective studies, *i.e.* by following-up for vital status a cohort of patients diagnosed within the same time period (usually a calendar year). Notwithstanding its straightforward construct, the main drawback of the cohort approach is the length of the observation period required to obtain survival rates. An alternative method is the period approach [19], which consists of measuring survival by using information from different cohorts of diagnosis within a given recent time period. This approach is well established in other fields, such as demography where it is used to estimate current life expectancy based on cross-sectional information from a mixture of birth cohorts. Period analysis provides survival curves very close to those observed among newly diagnosed patients in the first years after diagnosis, and is particularly useful to capture recent diagnostic or therapeutic improvements affecting short term survival [20].

Prevalence is the most relevant epidemiological measure for cost calculations. National health surveys, even when routinely carried out on representative population samples, are not a suitable source of cancer prevalence data for cost evaluation analyses, due to the quality of information collected (self-reported data lacking details on date of diagnosis and other relevant feature of the disease, such as location, morphology and stage).

Prevalence can be estimated, however, by using information on incidence and vital status provided by cancer registries in different ways: direct methods, which combine the number of newly diagnosed cases recorded by the cancer registry and still alive at a certain period of time (limited duration prevalence) with the unobservable figure of cases diagnosed before the cancer registry started its activity, using statistical modeling [21, 22]; indirect methods, which estimate the total number of prevalent cases (complete prevalence) from mortality statistics and survival modeling, using a back-calculation approach [23], or from incidence and survival modeling based on cancer registry information [24].

Macro-level estimation of expenditures on cancer

The aggregate cancer burden in a given population during a specified period of time is needed to assess the related national or regional expenditure. Macro level estimates of cancer burden are commonly obtained by combining data on prevalence with cost information. Since costs of cancer care vary along the path from diagnosis to clinical recover or death, a typical features of this approach is to split both prevalence estimates and cost indicators into distinct and clinically meaningful phases of care of given duration [25, 26].

Researchers use different definitions of phases of care, all including at least three phases: the initial phase (following the diagnosis), the final phase (before death), and the continuing or intermediate phase (corresponding to the delay in months between the initial and terminal phases). Some studies also include a pre-diagnostic phase and a pre-final phase. In an Italian case study of patterns of care and costs in two regions, using a three-phase disease approach, estimates of phase-specific prevalence and expenditures were obtained by record-linkage of the regional Hospital Discharge Cards database and the cancer registry database [27]. The phase of care approach, when incorporating population projections, can also be used to predict oncology workforce demands [28] or to forecast future trends in cancer-related costs. For example, a recent US study reported that even if cancer incidence, survival and costs remained constant, the national expenditure on cancer care was expected to increase from $ 124.6 billion in 2010 to $ 157.8 billion in 2020, due to population changes only [25]. The prostate cancer costs of care by phase of disease in Ontario is an additional example of macro-level analysis [29].

Micro level cost estimation

Micro level cost estimates are used as inputs in cost-effectiveness analyses of multiple interventions, as well as to predict the impact of future interventions, and are particularly useful in informing the health policy planning process in situations where evidence is lacking [30]. For example, in a study concerning treatment-specific costs of prostate cancer, an individual level approach was combined with a phase of care approach to yield suitable estimates of the parameters required for a model based cost-effectiveness analysis [29].

Another approach to micro-level modeling is micro-simulation, where a population of individuals followed from birth to death is simulated, with individuals' progression through the whole treatment pathway from the disease onset to clinical recovery or death.

Micro-simulation models presented and discussed at the workshop included two analysis of colorectal cancer costs in the general populations of England and the US, respectively, and a US study of prostate cancer costs. The three models shared a common approach consisting in calibrating the modeled natural history of the disease and treatment pathways to national data sources.

Micro-level modeling also allows for the simultaneous evaluation of multiple interventions taking into account the interdependency of services pathways [31, 33].

A drawback of micro-simulation modeling is its heavily dependence on assumptions and input parameters, so that independent modeling studies may yield disparate results, difficult to reconcile.

The comparative modeling approach explores differences between models in a systematic way by setting common input parameters (usually based on strong evidence) across models. For example, two independently developed models of colorectal cancer in the US were used to identify the reimbursement cost at which the stool DNA screening test would be a cost-effective alternative to current screening options

[34]. The use of comparative modeling approaches, by providing a range of results that can be used in sensitivity analysis of the underlying assumptions of the various models, improves the reliability of the study findings.

FUTURE DIRECTIONS: CHALLENGES AND ISSUES FOR IMPROVING ESTIMATION OF CANCER COSTS

The workshop revealed the increasing interest in the assessment of cancer related expenditures in Europe, US, Canada and Australia. Targeted therapies represent a topical research question in the domain of cancer cost evaluation, due to their intrinsic and indirect costs. These therapies require a preliminary molecular biology testing of all potentially eligible patients to identify the subset of likely responders.

Patients and physicians tent to regard targeted therapies as more effective treatments compared to the currently available ones, while payers are concerned with issues such as risk sharing, cost sharing, and budget impact. In this context, managed entry agreements define arrangements between payers or providers and manufacturers that enables access to reimbursement of a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use, or limit their budget impact [35].

International comparisons of data sources and analytical methods are pivotal to check exportability of a given approach to different contexts, and to discuss whether standardization is feasible. The Eurocare study [36] represents a successful example of international collaboration aimed at developing a standardized method of cancer survival analysis across Europe. The implementation of standardized costing methods, however, faces major challenges: between countries, differences in availability of data on disease prevalence, treatment protocols and related costs; within-countries, variability in population coverage of data sources, and their temporal extension and consistency; heterogeneity of cost definitions by country. However, the main obstacle to an international standardization of expenditure on cancer (or other diseases) is represented by differences in the health system structure: while universal public health care systems are adopted by many European countries and Canada, free health care in the US is provided only to the elderly, individuals affected by certain disabilities, and some low-income people. Quality of cancer care and treatment protocols in a given country can benefit from cross-country outcome evaluation. Such comparisons can be complex, however, and are affected by differences in patient characteristics, preventive measures, screening, treatment protocols, and differential coverage of services by health insurance programs and policies. Thus, comparisons across health care systems or countries should firstly focus on documenting and understanding patterns of care. As an example, a joint Italy-US study was planned immediately after the meeting, aimed at comparing patterns of hospitalizations and other care services in cancer patients, using cancer registry data and other administrative sources of information. 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 sub-site were evaluated, and some differences in the use of adjuvant therapies, as well as hospitalization patterns emerged [37]. In a cross-country comparison between US and Ontario (Canada) of end-of-life care and associated costs in elderly lung cancer patients, striking differences in cancer registry data, study population characteristics, and service coverage were observed; moreover, identification and payment for some services are bundled together in one country, but not in the other, so that significant upfront investments were necessary to enroll similar population samples well as to identify comparable service categories and cost components in the two countries [38, 39].

Special rules are implemented in public health care systems, in order to promote efficiency, support patient choice and increasingly incentive best practice models of care, as is the case of the Payment by Results (PbR) system in England, a transparent rules-base payment system under which commissioners pay health care providers for each patient seen or treated, taking into account the complexity of the patient's health care needs. PbR currently covers the majority of acute health care in hospitals, with national tariffs for admitted patient care, outpatient attendances, accident and emergency, and some outpatient procedures. The Government is committed to expanding PbR by introducing currencies and tariffs for mental health, community and other services [40].

In the US there are different payment systems, such as the fee-for-service and the managed care; differences between the two systems, including groupings used to classify services or costs, and incentives to providers in terms of coding procedures, along with the general complexity in payment systems, complicate the comparison of different services [41, 42].

Indirect costs represent a relevant component of the health care total budget, but they are difficult to measure and to compare across countries; as a general recommendation they should be taken into account in cancer burden evaluation and more effort should be devoted to standardized data collection.

Improving the communication of research results to non-scientific audiences is another important research topic to tackle in order to enhance the translation of research findings into policy settings.

Cost evaluation and cost-effectiveness analyses may be applied to a wide range of cancer control interventions: preventive measures, screening programs and related early treatments, diagnostic tests and referral processes, surgical procedures, radiotherapy, chemotherapy, and palliative care. These cost evaluations represent a valuable source of evidence for public health planners and policy makers, provided that the study findings are comprehensibly reported, and the due attention is paid by the investigators to assist the non-technical

users in their correct interpretation. This is a crucial responsibility for authors of studies based on estimates and modeling affected by a high level of uncertainty. For example, benefits of some screening programs for specific population groups are controversial, as increased rates of over-diagnosis and false positives may occur along with modest year-of-life gained. Providing expert panels with suitable analytical techniques to cross-evaluate a range of outcomes would help them in focusing on the most meaningful ones. This is particularly relevant in the US, where guidelines for prostate cancer screening by PSA testing are still subject of debate [43]. A micro-simulation model of prostate cancer in the US population that jointly modeled PSA growth and disease progression was presented at the workshop. A user-friendly interface for this model to be used by policy makers, allowing comparisons costs and benefits of different screening strategies, is being developed [44].

CONCLUSIONS

In summary, a primary goal of the "Combining Epidemiology and Economics for Measurement of Cancer Costs" workshop was to start an international and interdisciplinary dialogue about sharing methodologies for cancer burden evaluation. As illustrated in this commentary, an international network of experts in the field has been established, and strategic research issues along with subjects of collaborative research have been identified. As a first step in this direction, a monograph will be published at the end of this year, including a collection of papers on topics presented at the workshop as well as papers prepared by working groups originated from the workshop. New collaborative research project, aiming to identify relevant data sources and develop standardized analytical methods, will hopefully provide further insights into health care needs of cancer patients, more efficient strategies of resource allocation, and a wide diffusion of best practices in cancer treatment. The ultimate goal is to provide health policy planners with the full evidence needed to face the escalating costs of health care delivery, and to make informed choices on sustainable options.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Received on 27 September 2012.
Accepted on January 2013.

REFERENCES

1. Sullivan R, Peppercorn J, Sikora K, Zalcberg J, Meropol NJ, Amir E, *et al.* Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933-80.
2. Howlander N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, *et al*. SEER Cancer Statistics Review, 1975-2008. Bethesda, MD: National Cancer Institute; 2011.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;2010;127(12)2893-917. DOI: 10.1002/ijc.25516
4. Bray F, Moller B. Predicting the future burden of cancer. *Nat Rev Cancer* 2006;6:63-74.
5. Møller H, Fairley L, Coupland V, Okello C, Green M, Forman D, Møller B, Bray F. The future burden of cancer in England: incidence and numbers of new patients in 2020. *Br J Cancer* 2007;96:1484-8.
6. Verdecchia A, Guzzinati S, Francisci S, De Angelis R, Bray F, Allemani C, Tavilla A, Santaquilani M, Sant M and the EUROCARE Working Group. Survival trends in European cancer patients diagnosed from 1988 to 1999. *Eur J Cancer* 2009;45(6):1042-66.
7. Howard DH, Thorpe KE, Busch SH. Understanding recent increases in chronic disease treatment rates: more disease or more detection? *Health Econ Policy Law* 2010;5:411-35. DOI: 10.1017/S1744133110000149
8. Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer survivors: a booming population. *Cancer Epidemiol Biomarkers Prev* 2011;20(10):1996-2005. DOI: 10.1158/1055-9965.EPI-11-0729
9. Dranitsaris G, Truter I, Lubbe MS, *et al.* Advances in cancer therapeutics and patient access to new drugs. *Pharmacoeconomics* 2011;29:213-4. DOI: 10.2165/11584210-000000000-00000
10. Russell L. Completing costs: patients' time. *Med Care* 2009;47(7 Suppl. 1):S89-93. DOI: 10.1097/MLR.0b013e31819bc077
11. Yabroff KR, Davis WW, Lamont EB, Fahey A, Topor M, Brown ML, *et al*. Patient time costs associated with cancer care. *J Natl Cancer Inst* 2007;99:14-23. DOI: 10.1093/jnci/djk001
12. Jonas DE, Russell LB, Sandler RS, Chou J, Pignone M. Value of patient time invested in the colonoscopy screening process: time requirements for colonoscopy study. *Med Decis Making* 2008;28(1):56-65. DOI: 10.1177/0272989X07309643
13. Coleman M.P, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, Azevedo e Silva G, Francisci S, Santaquilani M, Verdecchia A, Storm H, Young JL, and the EUROCARE-3 Working Group. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9(8):730-56. DOI: 10.1016/S1470-2045(08)70179-7
14. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, Kunkler I, and the Eurocare Working Group. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 Data. *Lancet Oncol* 2007;8:784-96. DOI: 10.1016/S1470-2045(07)70246-2
15. Lambert PC, Dickman PW, Weston CL, Thompson JR. Estimating the cure fraction in population-based cancer studies using finite mixture models. *J R Stat Soc* (Series C) 2010; 59:35-55. DOI: 10.1111/j.1467-9876.2009.00677.x
16. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics,* 2007;8(3):576-94. DOI: 10.1093/biostatistics/kxl030
17. Francisci S, Capocaccia R, Grande E, Santaquilani M, Simonetti A, Allemani C, Gatta G, Sant M, Zigon G, Bray F, Janssen-Heijnend M, the EUROCARE Working Group. The cure of cancer: A European perspective. *Eur J Cancer*

2009;45:1067-79. DOI: 10.1016/j.ejca.2008.11.034
18. De Angelis R, Capocaccia R, Hakulinen T, Soderman B, Verdecchia A. Mixture models for cancer survival analysis: application to population-based data with covariates. *Stat Med* 1999;18:441-54. DOI: 10.1002/(SICI)1097-0258-(19990228)18:4<441::AID-SIM23>3.3.CO;2-D
19. Brenner H, Gefeller O. Deriving more up-to-date estimates of long term patient survival. *J Clin Epidemiol* 1997;50(2):211-6. DOI: 10.1016/S0895-4356-(97)00280-1
20. Brenner H, Hakulinen T. Up-to-date and precise estimates of cancer patient survival: Model-based period analysis. *Am J Epidemiol* 2006;164:689-96.
21. Corazziari I, Mariotto A, Capocaccia R. Correcting the completeness bias of observed prevalence. *Tumori* 1999;85(5):370-81.
22. Merrill RM, Capocaccia R, Feuer EJ, Mariotto A. Cancer prevalence estimates based on tumour registry data in the Surveillance, Epidemiology, and End Results (SEER) Program. *Int J Epidemiol* 2000;29(2):197-207. DOI: 10.1093/ije/29.2.197
23. Verdecchia A, Capocaccia R, Egidi V, Golini A. A method for the estimation of chronic disease morbidity and trends from mortality data. *Stat Med* 1989;8(2):201-16. DOI: 10.1002/sim.4780080207
24. Verdecchia A, De Angelis G, Capocaccia R. Estimation and projections of cancer prevalence from cancer registry data. *Stat Med* 2002;21(22):3511-26. DOI: 10.1002/sim.1304
25. Mariotto A, Yabroff KR, Feuer EJ, De Angelis R, Brown M. Projecting the number of patients with colorectal carcinoma by phases of care in the US: 2000-2020. *Cancer Causes Control* 2006;17:1215-26. DOI: 10.1007/s10552-006-0072-0
26. Yabroff KR, Lamont EB, Mariotto A, Warren JL, Topor M, Meekins A, *et al.* Cost of care for elderly cancer patients in the United States. *J Natl Cancer Inst* 2008;100:630-41. DOI: 10.1093/jnci/djn103
27. Francisci S, Guzzinati S, Mezzetti M, Crocetti E, Giusti F, Miccinesi G, Paci E, Angiolini C, Gigli A. Cost profiles of colorectal cancer patients in Italy based on individual patterns of care. *BMC Cancer* 2013; accepted for publication.
28. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst* 2011;103(2):117-28. DOI: 10.1093/jnci/djq495
29. Krahn MD, Zagorski B, Laporte A, Alibhai SM, Bremner KE, Tomlinson G, *et al*. Healthcare costs associated with prostate cancer: estimates from a population-based study. *BJU Int* 2010;105(3):338-46. DOI: 10.1111/j.1464-410-X.2009.08758.x
30. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. Oxford: Oxford University Press; 1996.
31. Tappenden P, Chilcott JB, Brennan A, Pilgrim H. Systematic review of economic evidence for the detection, diagnosis, treatment, and follow-up of colorectal cancer in the United Kingdom. *Int J Technol Assess* 2009;25(4):470-8. DOI: 10.1017/S0266462309990407
32. Pilgrim H, Tappenden P, Chilcott JB, Bending M, Trueman P. The costs and benefits of bowel cancer service developments using discrete event simulation. *J Oper Res Soc* 2009;60:1305-14. DOI: 10.1057/jors.2008.109
33. Chilcott JB, Tappenden P, Rawdin A, Johnson M, Kaltenthaler E, Papaioannou D, Shippam A. Avoiding and identifying errors in health technology assessment models. *Health Technol* 2010;14(25):iii-iv, ix-xii, 1-107. DOI: 10.3310/hta14250
34. Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, Wilschut JA, Zauber AG, Van Ballegooijen M. Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. *Ann Intern Med* 2010;153(6):368-77.
35. Klemp, M Frønsdal KB, Facey K. What principles should govern the use of managed entry agreements? *Int J Technol Assess* 2011;27(1):77-83. DOI: 10.1017/S0266462310001297
36. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R and the EUROCARE Working Group. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* 2009;45(6):931-91. DOI: 10.1016/j.ejca.2008.11.018
37. Gigli A, Warren JL, Yabroff KR, Francisci S, Stedman M, Guzzinati S, Giusti F, Miccinesi G, Crocetti E, Angiolini C, Mariotto A. Initial treatment for newly diagnosed elderly colorectal cancer patients: patterns of care in Italy and the United States. *J Natl Cancer Inst* 2013; accepted for publication.
38. Warren JL, Yabroff KR, Meekins A, *et al*. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst* 2008;100(12):888-97. DOI: 10.1093/jnci/djn175
39. Warren JL, Barbera L, Bremner KE, Yabroff KR, Hoch JS, Barrett MJ, *et al*. End-of-life care for lung cancer patients in the United States and Ontario. *J Natl Cancer Inst* 2011;103(11):853-62. DOI: 10.1093/jnci/djr145
40. Equality impact assessment of the payment by results national tariff, Department of Health, NHS. October 2012. Available from: http://www.dh.gov.uk/health/2012/02/confirmation-pbr-arrangements/.
41. O'Keeffe Rosetti M, Hornbrook MC, Fishman PA, Ritzwoller DP, Keast EM, Elston Lafata J, Salloum R. A standardized relative resource cost model for medical care: application to cancer control programs. *J Natl Cancer Inst* 2013; accepted for publication.
42. Fishman PA, Hornbrook MC, Ritzwoller DP, O'Keeffe-Rosetti MC, Elston Lafata J, Salloum R. The challenge of conducting comparative effectiveness research in cancer: The impact of a fragmented US health care system. *J Natl Cancer Inst* 2013; accepted for publication.
43. Max W, Rice DP, Sung H-Y, Michel M, Breuer W, Zhang X. The economic burden of prostate cancer, California, 1998. *Cancer* 2002;94(11):2906-13. DOI: 10.1002/cncr.10532
44. Etzioni R, Gulati R, Falcon S, Penson DF. Surveillance modeling approach impact of PSA screening on the incidence of advanced stage prostate cancer in the United States: a surveillance modeling approach. *Med Decis Making* 2008;28:323. DOI: 10.1177/0272989X07312719