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INCIDENCE-BASED COST-OF-ILLNESS MODEL FOR METASTATIC BREAST CANCER IN THE UNITED STATES

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Objectives: This study aims to estimate the annual U.S. societal costs associated with treatment of metastatic breast cancer (MBC) patients using an incidence-based cost-of-illness (COI) framework.
Methods: An incidence-based COI model was constructed in which MBC patients were simulated from diagnosis through active treatment, palliative care, and death over 5 years. Key model parameters included: annual incidence of breast cancer in the metastatic stage, utilization of cancer therapies and other medical care resources, treatment-related adverse events, unit costs, work days missed by patient and caregiver, and wage rates. Overall survival was based on SEER data and costs were assigned to living patients monthly, according to their disease management phase. The outcomes measures were total discounted societal costs, cost/year, and cost/patient-year.
Results: The annual incidence of MBC in the United States in 2007 was estimated to be 49,674 patients (*de novo* and progressed from earlier stages). The total discounted cost to society attributable to MBC was $12.2 billion for the incident cohort, or $98,571 per patient-year. The 5-year direct medical cost of this incident cohort was $9.3 billion, or $75,415 per patient-year. Treatment-related costs (active treatment, toxicity management, and medical follow-up) contributed 44 percent of MBC expenditure, followed by palliative/best supportive care costs (31 percent). Lost productivity accounted for approximately 21 percent of the total cost ($2.6 billion over 5 years or $21,153 per patient-year).
Conclusions: The societal burden of MBC in the United States is substantial. Earlier detection and effective treatment could lead to a significant decrease in costs while improving overall disease prognosis.

Keywords: Metastatic breast cancer, Cost-of-illness, Lost productivity, Economic model

INTRODUCTION

Breast cancer exacts a staggering toll on patients, payers, and society. In the United States, the annual costs of breast cancer care, was estimated as high as $13.9 billion (USD 2006), greater than all other reported cancers (19). With an estimated 207,090 new invasive cancer cases projected for the year 2010 and approximately 39,840 expected deaths, breast cancer is the second most commonly diagnosed cancer and a leading cause of mortality in U.S. women (19). Disease-related mortality has steadily declined in recent decades, due to earlier detection (primarily through mammography screening) and improved treatments in breast cancer. Despite these medical advancements, a significant portion of breast cancer patients are still diagnosed with metastatic disease, often as a reoccurrence or progression of prior disease. Metastatic breast cancer (MBC) is considered an incurable condition with poor prognosis; however, studies have demonstrated that active cancer treatment and palliative care can help prolong survival, control symptoms, and maintain or improve quality of life (17).

Although there is substantial evidence of the direct medical costs and humanistic burden of breast cancer in the published literature (9;18), only five studies have assessed the economic burden of MBC in the United States and none of these studies have considered indirect costs such as lost productivity due to the illness (1;4;16;23;26). Moreover, none of these studies evaluated resource use data since 2004. Thus the current literature on the economic burden of MBC may reflect outdated treatment patterns that are no longer representative of the current medical environment, which has changed dramatically with the introduction of newer targeted therapies (e.g., trastuzumab, bevacizumab, and lapatinib) (24).

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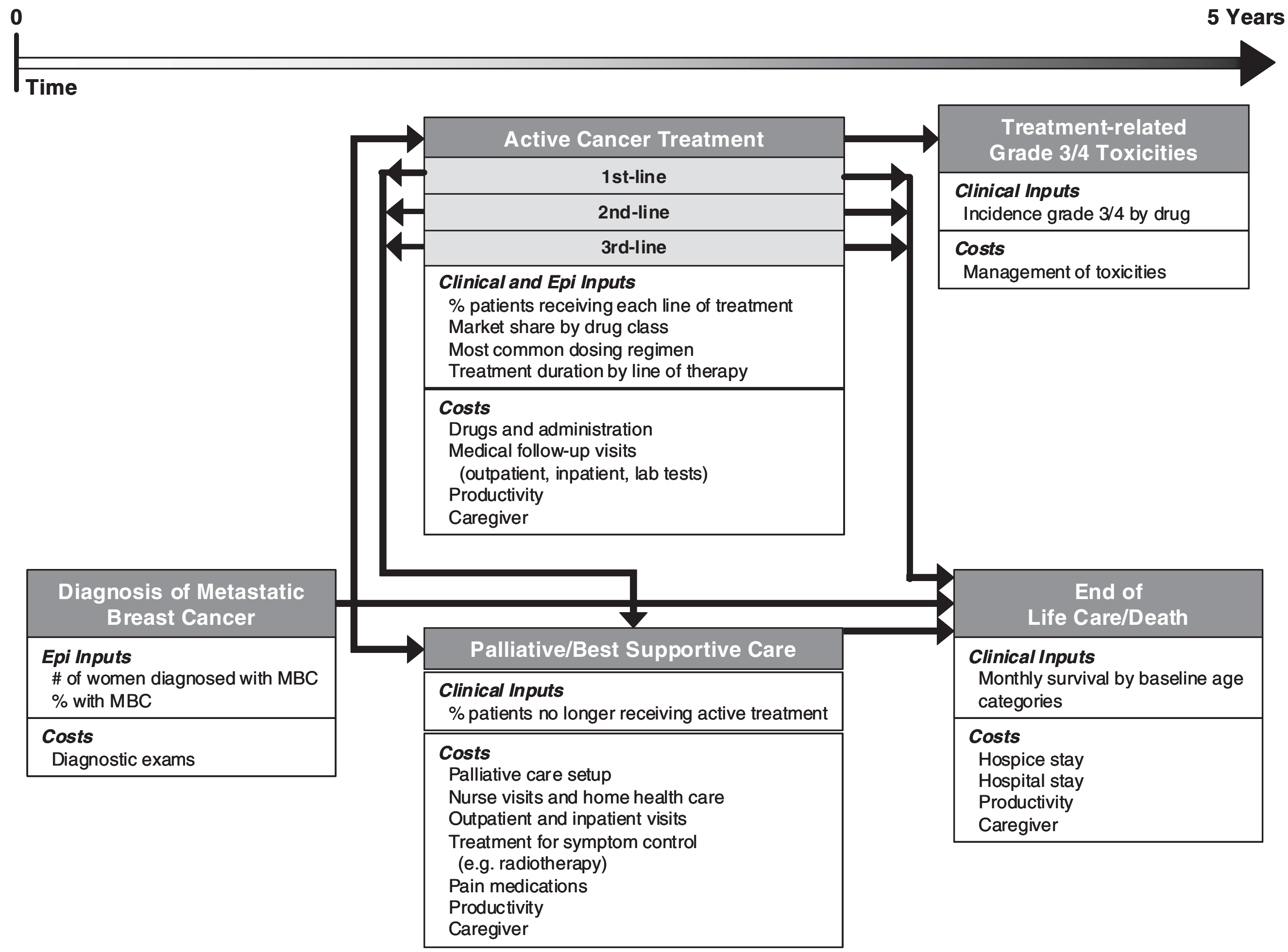

Figure 1. Model flow diagram.

Understanding the societal burden of MBC is challenging but critical for informing decisions and policy makers about the potential cost-effectiveness of preventive or therapeutic measures, which may ameliorate the morbidity and mortality of MBC. The main objective of our analysis was to estimate the societal burden of MBC in the United States using an incidence-based cost-of-illness framework that includes health care costs reflective of current medical practice and lost productivity.

PATIENTS AND METHODS

Model Overview and Design

An incidence based cost-of-illness model was developed in which an incident cohort of MBC patients are followed over 5 years, from diagnosis of metastatic disease and assessment of management course, through active treatment (for eligible patients) and subsequently to terminal care and death (Figure 1). The incident cohort of MBC patients included both *de novo* MBC patients and MBC patients who progressed during that year from earlier stages of breast cancer. To assess the full economic burden, the model framework includes both direct and indirect costs. Direct costs consider the medical expenditures for services and procedures, such as physician visits, hospital stays, diagnostic tests related to MBC. Indirect costs quantify impaired and lost work productivity, measured as lost productivity due to missed days of work, forgone productivity due to premature death in MBC patients of working age, and informal caregiver burden or time spent away from work in the model.

Model Inputs

The cost-of-illness model incorporated four types of inputs: Annual incidence of metastatic breast cancer, survival estimates, resource utilization and related costs, and patient/caregiver work days missed and related wages.

Annual Incident Cases of Metastatic Breast Cancer. Active MBC arises from several sources, *de novo* stage IV disease or disease diagnosed at an earlier stage that has recurred. The number of incident metastatic breast cancer cases in a given year was estimated using (Table 1) the Surveillance Epidemiology and End Results (SEER) data for the years 2000–2007 and published studies (5;20). The number of patients who progress from early stages to MBC in a given year was derived based

Table 1. Estimated Metastatic Breast Cancer Cohort

Incidence and no. of MBC cases		
De novo MBC	Incidence (per 100,000)	No. of patients
20–54 years	2.95[a]	1,862
55–64 years	13.14[a]	3,823
65+years	21.62[a]	4,918
Progression from early stages of BC		39,072[b]
Total number of patients with MBC		49,674

[a]Source: (20).
[b]Sources: (5; 20) (Mathematical model).

on a mathematical equation using the probability rates of progression to MBC from early stages, applied to the prevalence of earlier stages of breast cancer. In the equations, to estimate the prevalence of early stages, the assumption was made that mortality from breast cancer is attributable to advanced cases and equal to the prevalence of MBC.

Survival Estimation. Survival was assessed at monthly intervals. Patient survival was modeled to estimate the proportion of the incident MBC cohort that was alive at each model time point and thus accruing costs. Overall survival was based on SEER estimates of the U.S. newly diagnosed MBC breast cancer population over 10 years (20). Because the survival data was similar across the three age groups defined in the model, a single Weibull function was fitted to the survival data to predict monthly survival. Patients who had progressed from early stages were also assumed to have similar survival. The equation for the Weibull function was: $S(t) = EXP(-0.0778*(t\hat{}0.6924))$, where S(t) is the proportion of patients surviving and t is time in months.

Resource Utilization and Related Costs

In the model, costs were assigned to MBC patients according to their disease management phase (e.g., active cancer treatment, palliative/best supportive care, or end of life care/death). The monthly costs, over 5 years, were summed to estimate the cumulative burden of MBC in the United States. While in the active cancer treatment phase, patients incurred costs for drugs and drug administration, toxicity management, diagnostics, and medical follow-up. The monthly costs for each resource use component were estimated using several sources (Supplementary Material, which can be viewed online at www.journals.cambridge.org/thc2012002).

Among the incident cohort, the proportion receiving active cancer treatment up to four lines of therapy was based on the results of a large physician survey ($n = 100$) (Pfizer, Inc., data on file). To ensure objectivity of responses, only U.S.-based physicians that are not employed by any pharmaceutical company, health care products manufacturer, governmental agency, marketing research firm, or advertising agency were considered for the survey. The recruited physicians must have also spent at least 50 percent of their working time treating patients over the past 3–30 years, and have personally initiated hormonal and chemotherapy and/or trastuzumab treatment in at least 75 breast cancer patients. In the United States, it is estimated that approximately 92 percent of patients still surviving received a first-line treatment, 77 percent received a second-line treatments, 55 percent received a third-line treatment, and only 29 percent of patients alive received a fourth-line treatment. Patients not receiving active anticancer treatment were assumed to receive palliative/best supportive care. The cancer treatments considered in the model were those being prescribed in MBC according to the survey of treating physicians (Pfizer, Inc., data on file) and included drugs with and without an FDA-labeled indication for MBC. Supplementary Table 1, which can be viewed online at www.journals.cambridge.org/thc2012002, presents the treatment interventions considered in the model, along with the market share summarized by drug class. Drug class treatment shares summed to greater than 100 percent for each line of therapy due to treatment combinations across drug classes within the same line of treatment. In the United States, the top three treatment combinations were anthracycline plus a taxane (11 percent), docetaxel plus trastuzumab (7 percent), and paclitaxel plus bevacizumab (6 percent) (Pfizer, Inc., data on file).

For each treatment option, the dosage and administration, associated toxicities, average months of treatment in each line of therapy, and market share of each treatment were considered. The dosage, administration and associated toxicities for MBC drugs were primarily derived from prescribing information. Given that some treatments use several different administration schedules, the model used the most common regimens reported, or the recommended regimens for each treatment (e.g. for paclitaxel the following are considered: 80–90 mg/m^2 every week, 175 mg/m^2 every 3 weeks, 175 mg/m^2 over 3 hours every 3 weeks for 4 courses [in combination with doxorubicin and cyclophosphamide]). Dosing for drugs without an indication for MBC was determined based on the dosage recommended for other cancer indications and confirmed with expert opinion. To estimate drug costs, loading doses, and maintenance doses based on recommended dosing schedule were considered; dosage reductions and wastage were excluded from analysis. Average months of treatment in each line of therapy were informed by prescribing information and a systematic review of the clinical literature. For each line of therapy, a weighted average monthly cost of treatment was estimated. Specifically, the average total monthly costs for each drug and then drug class were weighted by the market share of each to determine the weighted average monthly costs of treatment for each line of therapy (Table 2; Pfizer, Inc., data on file; Supplementary Material).

Table 2. Cost Inputs

Parameter	Costs ($ USD)	Source
Active cancer treatment health state		
Weighted average monthly costs of treatment		
First line	$6,696	(i) Redbook 2010[a] (ii) MAG Mutual, 2010[b] (iii) Pfizer, Inc., data on file
Second line	$7,356	(i) Redbook 2010[a] (ii) MAG Mutual, 2010[b] (iii) Pfizer, Inc., data on file
Third line	$7,061	(i) Redbook 2010[a] (ii) MAG Mutual, 2010[b] (iii) Pfizer, Inc., data on file
Per event treatment-related toxicity (Grade 3/4) management costs		
Prophylactic		
GCSF	$1,529	(i) Physician survey (ii) (14)
Hematologic		
Febrile neutropenia	$22,327	(3)
Thrombocytopenia	$9,728	(11)
Infection	$12,657	(11)
Anemia	$10,251	(11)
Hemorrhage	$8,266	(11)
Non-Hematologic		
Vomiting	$3,629	(11)
Nausea and Vomiting	$3,266	(27)
Diarrhea	$3,257	(11)
Pain	$9,232	(11)
Cardiac toxic effects	$10,466	(i) (15) (ii) Redbook 2010[a] (iii) MAG Mutual, 2010[b] (iv) Lotensin® prescribing information
Stomatitis/mucositis	$5,767	(11)
Ischemic cardio-vascular disease	$75,109	(25)
One-time diagnostic costs		
Laboratory scans and tests	$1,272	MAG Mutual, 2010[b]
Outpatient visits	$272	MAG Mutual, 2010[b]
Hospitalizations	$893	EOHHS 2010[c]
Monthly medical follow-up costs		
Laboratory scans and tests	$1,111	MAG Mutual, 2010[b]
Outpatient visits	$181	MAG Mutual, 2010[b]
Hospitalizations	$595	EOHHS 2010[c]
Bone metastases management	$1,195	(21)
Palliative/best supportive care health state		
Monthly palliative care/best supportive care costs		
Community nurse palliative care set-up	$60	MAG Mutual, 2010[b]
Nurse practitioner/home health aide visits	$19	Genworth 2010[d]
Outpatient visit	$199	MAG Mutual, 2010[b]

Table 2. Continued

Parameter	Costs ($ USD)	Source
Hospitalizations	$1,712	EOHHS 2010[c]
Home care visits	$242	(10)
Radiotherapy treatments	$1,611	(21)
Pain control	$66	(i) (12) (ii) NCI 2010[e] (iii) Redbook 2010[a]
Bone metastases management	$1,195	(21)
Active cancer treatment and palliative/best supportive care		
Monthly indirect costs		
Lost income	$1,766	(8)
Caregiver costs	$185	(8)
End of life care/death health state		
Monthly terminal care costs		
Hospice stay	$1,716	MedPac 2010[f]
Hospital stay	$311	MedPac 2010[f]

[a]Thomson PDR. Red Book for Windows. 057 ed: Thomson PDR; 2010.
[b]MAG Mutual. Physicians Fee & Coding Guide. 21st ed: MAG Mutual Healthcare Solutions Inc., 2010.
[c]Massachusetts Division of Health Care Finance and Policy. Acute Hospital Case Mix Databases: Massachusetts (Fiscal Year 2008). Massachusetts Executive Office of Health and Human Services (EOHHS); 2010.
[d]Genworth Financial. Genworth 2010 Cost of Care Survey. Genworth Financial; 2010.
[e]National Cancer Institute. Basic Principles of Cancer Pain Management; Pharmacologic Management. National Institutes of Health; 2010.
[f]MedPac. Hospice (Section 2E). Report to the Congress: Medicare Payment Policy; March 2010.
For both diagnostic and medical follow-up stages, cost for laboratory scans and tests are derived from the unit costs of selected scans and tests commonly received by MBC patients (e.g., ECG ($20), chest X-ray ($23), chest CT scan ($252), liver CT scan ($242), PET scan ($80), complete blood count ($38) and etc.) and the respective frequencies of these scans and tests in each stage. 90% of MBC patients are assumed to receive treatment in the outpatient setting from medical oncologist ($66 per visit), radiation oncologist ($66 per visit) or other specialists ($66 per visit); while 7.5% of MBC patients undergo cancer care in oncology/general ward ($3,403 per diem) or intensive care unit (ICU) ($4,531 per diem). In the medical follow-up stage, bone metastases management cost is applied as a monthly 4 mg single-dose intravenous infusion of Zometa® ($1,195).

For treatment-related toxicities, only costs associated with the treatment of Grade 3 or 4 toxicities were included in the model as these adverse events were considered most likely to involve significant management costs (Table 2). The frequency of toxicities was based on data for monotherapy and applied in combination therapy where necessary. For each line of therapy, an average toxicity cost per drug class, weighted by market share, was computed (Supplementary Material).

The medical resource use applied for the costing analysis (Table 2) was primarily based on recommendations from clinical guidelines and supplemented by the results of a physician survey (21). Patients in the active cancer treatment health state incurred costs associated with diagnosis and medical follow-up, which included laboratory scans and tests, outpatient visits to medical oncologist, radiation oncologist, and other specialist(s), hospitalizations, as well as bisphosphonate therapy for MBC patients with bone metastases (52 percent of diagnosed MBC patients) (Pfizer, Inc., data on file). While in the palliative/best supportive care health state, patients accrued costs related to community nurse palliative care visits, nurse practitioner/home health aide visits, outpatient visits, hospitalizations, home care visits, radiotherapy treatments, additional medications for pain control (e.g., morphine and NSAIDs) and bone metastases management. Finally, patients entered the end of life/death health state, where they incurred costs of terminal care, which included the cost of hospice stay and hospital stays.

Patient/Caregiver Work Days Missed and Related Wages

Patients aged <65 years were assumed to be of working age and incurred costs representing the value of lost work productivity due to metastatic disease and premature mortality (death before age 65 years). Similarly, indirect costs resulting from lost work productivity for caregivers of patients of all ages were also included. For patients, the total costs associated with lost productivity from work due to metastatic disease were estimated based on the 2010 U.S. average hourly wage and the reported days lost from work per year (8). The latter was estimated at 117 days for short-survival cancer patients by Yabroff et al. 2004 (28). In their analysis, Yabroff and colleagues adjusted the estimated days of lost work to account for patients of working age who are unemployed and unable to work or limited in the amount or type of work performed due to illness. Our decision to use the estimated days lost from work for short-survival cancer patients was driven by the reported survival rate (of less than 25 percent over 5 years) for this subgroup, which is on par with survival estimates for MBC. On the other hand, the indirect costs resulting from premature mortality are estimated by applying the average monthly wage to cumulative premature (<65 years of age) deaths of working MBC patients at each month (6–8;28).

For informal caregivers, value of lost work productivity resulting from providing care to MBC patients was estimated using the following literature based inputs: (i) proportion of cancer patients requiring care (14 percent) (28); and (ii) average number of care giving hours per week (total of 29 hours/week) (13). Caregiver time was valued as equivalent to the wage of a home health aid worker ($10.39 per hour) (8), an approach that was used by Hayman et al. (13).

OUTPUTS

The societal burden of metastatic breast cancer was estimated in terms of total cost and cost per patient year. The calculation based on overall mean survival, instead of total duration of model analyses, represents a more clinically realistic approach of deriving the per-patient costs because it accounts for MBC patients who die mid-way through the follow-up period. All costs are in 2010 USD, with discounting at 3.0 percent per annum. The model was programmed in Microsoft Excel® 2003.

RESULTS

Total Incidence and Survival

The model estimated that the incident cohort of MBC patients per year was approximately 49,674 cases consisting of 10,602 *de novo* cases and 39,072 cases that had progressed from early stages for the year 2007. Mean survival per patient over the 5-year follow-up period was 2.49 years (median, 1.92 years).

Costs

The total discounted cost to society attributable to metastatic breast cancer was $12.2 billion USD accrued over 5 years, or $2.4 billion per year ($98,571 per patient year) for the incident cohort. Of this, the total direct costs, accrued over 5 years for the treatment of MBC, totaled more than $9.3 billion, which translates to approximately $1.9 billion per year ($75,415 per patient year). Table 3 summarizes the overall direct and indirect costs for the incident MBC population and respective costs on a per patient basis, as well as the percentage distributions of direct cost categories. Treatment-related costs (drug and administration, toxicity management, and medical follow-up) incurred during the active cancer treatment phase contributed the largest portion of MBC spending, costing over $1.0 billion per year and representing 57 percent of total costs. Palliative/best supportive care, which is given to MBC patients after active curative therapy has failed, made up the second largest expenditure category, costing $745 million per year (40 percent). Both treatment and continuing palliative care accounted for the majority of lifetime spending in the management of MBC due to the relatively long survival of patients over model time horizon, even after leaving the active treatment phase. Diagnostic and terminal care costs totaled $42.0 million per year and $12.3 million per year, respectively.

Active treatment costs comprised 37 percent of total annual expenditure for MBC. The top three drivers of active treatment costs were non–HER2-targeted therapies, taxanes, and HER2-targeted therapies which accounted for 29 percent, 25 percent, and 21 percent of the expenditures, respectively. Taxane chemotherapy has become the standard of care in the United States for metastatic breast cancer, and targeted therapies are often added to taxanes to improve outcomes. These medical practices, along with the increased price of these therapies, contributed to elevated costs. Correspondingly, management of treatment-related toxicities was the most expensive for taxanes and HER2-targeted therapies. The dominating cost trend of targeted therapies was also supported by the results of sensitivity analysis, where a 10 percent increase in their treatment shares was found to produce an additional $36.5 million per year burden on the incident cohort, or a 2.0 percent impact in total direct costs.

The indirect cost components consisting of lost productivity of MBC patients and care-givers accounted for an additional economic burden of $2.9 billion over 5 years ($23,157 per patient-year) or 23.5 percent of the total costs. Annual indirect cost estimates consist of costs associated with productivity loss due to the metastatic disease ($253 million per year, 10.4 percent total expenditures), premature death ($269.8 million per year, 11.1 percent total expenditures), and caregiving ($49.5 million per year, 2.0 percent total expenditures). Sensitivity analyses findings showed that a 10 percent change in missed days from work in MBC patients was associated with a change in total expenditure of $25.3 million per year or 1.0 percent impact in total annual burden.

DISCUSSION

Increasingly, the economic burden of cancer will be shouldered by all of society. For example, the passing of the Patient

Table 3. Estimated Total Direct and Indirect Costs per Year or per Patient-Year

	Cost/year ($)	Cost per patient ($)/ patient-year	% of total for direct and indirect categories
Direct costs			
Diagnostic	41,961,036	1,698	2
Active treatment (drug and administration)	685,863,844	27,749	37
Treatment-related toxicity management	88,868,780	3,596	5
Medical follow-up	289,871,399	11,728	16
Palliative/best supportive care	745,156,118	30,148	40
Terminal care	12,267,543	496	1
Total direct costs	1,863,988,721	75,415	100
Indirect costs			
Patient lost income due to metastatic disease	253,020,896	10,237	44
Patient lost income due to premature death (death before age 65 years)	269,800,963	10,916	47
Caregiver lost income	49,530,247	2,004	9
Total indirect costs	572,352,106	23,157	100
Total direct and indirect costs	2,436,340,827	98,571	—

Protection and Affordable Care Act may herald a new era in the United States; among more than 160 provisions that impact cancer care, most notable is the elimination of pre-existing condition exclusion and rescission of coverage due to cancer (22). In the face of increasing costs for cancer treatment, a holistic understanding of the societal costs associated with cancer care is needed to contextualize decision and policy making regarding preventive or therapeutic cancer treatments. In the present study, we evaluated the societal burden of metastatic breast cancer in the United States, using an incidence-based cost-of-illness model. The model estimated that a total number of 49,674 incident MBC patients were diagnosed during 2007, including *de novo* MBC patients and patients who progressed from earlier stages of breast cancer. The total 5-year direct medical costs for the management of MBC for this incidence cohort was $9.3 billion (2010 USD), or $75,415 per patient-year. The indirect costs, including costs associated with productivity loss, premature mortality, and informal care-giving, accounted for an additional economic burden of $2.9 billion over 5 years.

The economic burden of MBC has been the subject of a recent review by Allen 2010 and previously evaluated by Berkowitz et al. 2000, Rao et al. 2004, Lamerato et al. 2006, and Stokes et al. 2008 over the last decade (1;4;16;23;26). This study overcomes some of the limitations seen in these earlier studies. First, our model considers more current MBC treatment practices and increased use of targeted therapies in the treatment of MBC, although the trend for the use of targeted therapies is expected to alter in the near future. Second, in addition to evaluating direct costs, our model assesses the indirect costs attributed to lost productivity from work for patients and informal caregivers. When compared with early studies that evaluated the disease burden during 1990s, our study findings show almost a threefold increase in the cost of MBC in the United States (4;23). The burden of illness model developed by Berkowitz and his colleagues estimated a total of $4.2 billion in 1998 over the lifetime of a 1994 SEER cohort. They also reported that the per patient-year burden of MBC was $19,335. Active treatment costs comprised 37 percent of total annual expenditure for metastatic breast cancer in the current study. In contrast, Berkowitz et al. estimated that less than 9 percent of total medical cost was attributable to radiotherapy, chemotherapy, or hormonal therapy in mid-1990s.

While differences in study design and methods hinder direct comparison, older studies of MBC economic burden highlight the increasing costs of metastatic breast cancer care over the last decade. In the study by Rao et al. 2004, the authors presented the findings of a retrospective database analysis using the 1997–99 Medicare data (23). Authors estimated that the mean costs of MBC was $35,164 per patient over a follow-up period averaging 16.2 months, equivalent to $26,000 per patient-year. Lamerato et al. 2006 conducted a retrospective database cohort study, based on charges from health system records. Mean total per patient changes for 6 months post recurrence was $45,855 versus $10,715 before recurrence (16). Mean total monthly per patient charges were $4,965 for metastatic recurrence, which is approximately $59,580 per patient per year. Notably, as Rao and colleagues used Medicare data, these costs are reflective of a subgroup of women who are 65 years and older, while our study considers women 20 years and older. Like Rao and Berkowitz, Stokes et al. 2008 also conducted a retrospective analysis of SEER Medicare data, following patient outcomes, resources use and cost over a 10-year period. Total expected per patient costs were $54,454 with metastatic reoccurrence, $61,601 with loco-regional reoccurrence, and $61,188 with contralateral recurrence as compared to $42,005 with no recurrence (26). The wide discrepancy in MBC burden estimates, even after accounting for cost inflation, can be traced to several reasons, including differences in study methodology, data sources, and most importantly, advances in treatment interventions over the past 10 years, which not only prolonged patient life but also increased the treatment costs dramatically.

Our overall estimates of the direct costs of MBC are consistent with the numbers reported in a more recent study (2). Barron et al. found that an average breast cancer patient in a managed care organization incurred a cost of approximately $4,400 per month in 2004 or approximately $52,800 per year. In this study, as in ours, pharmacotherapy is the biggest cost driver among all treatment-related costs. The Barron study identified intravenous treatments such as cyclophosphamide and doxorubicin as cost drivers but not targeted therapy (trastuzumab was only used in 6.4 percent of patients), whereas in our model, targeted therapies are important cost drivers as over 45 percent of treated patients receive a targeted therapy especially in second and third lines of treatment, along with taxanes. This may reflect the time period during which the studies were performed as the targeted therapies are the most recent additions to healthcare and our study is the most current and up to date reflecting availability of these drugs. Moreover, sensitivity analysis in our cost-of-illness model demonstrated that increase usage of targeted therapies contributes to the total direct costs through additional expenditures in treatment, treatment-related toxicity and medical follow-up cost categories. Another recent study estimated an average lifetime disease-attributable cost of $153,422 among MBC patients using SEER Medicare data (inflated to 2009 U.S. dollars) (10).

A feature of the cost-of-illness model presented here that is not commonly found elsewhere is its flexibility to incorporate indirect costs in model estimation. The level of burden related to lost income attributable to MBC and care-giving of MBC patient is substantial and represents opportunity costs incurred as long as the disease condition persists. Moreover, premature mortality among working MBC patients leads to additional loss in productivity. The impact of productivity loss among MBC patients was substantial. Nevertheless, care-giving was an important element among elderly cancer patients, patients which made up almost half of the incident MBC population in the model (13). Experts in the health research field have long recommended the development of societal-based cost studies that will support U.S.-based cost-effectiveness analyses. However, these studies were rarely presented (9). Our study will be valuable in fulfilling these existing knowledge gaps.

Given the limited cost of illness studies in metastatic breast cancers for other countries, our model structure and approach can be useful for estimating such burden in non-U.S. settings such as Canada and European countries. As the disease burden is largely driven by disease epidemiology, treatment patterns and costs, as well as MBC-attributable productivity losses of patients and informal caregivers, we expect the direct cost of metastatic breast cancer to vary significantly across these countries due to differences in treatment patterns and reimbursement practices (e.g., expensive targeted therapies are not as widely prescribed in European nations compared with the United States) while the indirect cost may be similar given the nature of the disease (similar productivity loss).

It should be noted that the cost-of-illness model is subject to several limitations. First, because an incidence based approach was used, the model does not account for prevalent cases of MBC, therefore, it may underestimate the total economic burden of the metastatic disease. On the other hand, the exclusion of patient adherence to cancer treatment in the costing analysis may lead to an overestimation in MBC treatment costs, though some follow-up medical costs may be expected among discontinued patients. Second, the model study does not consider heterogeneity (e.g., the hormonal receptor status of patients, types of metastases besides bone metastases and etc.) within the MBC population. Additional subgroup analysis may likely yield more informed burden estimates as patients with these characteristics usually require more cancer care.

Third, potential variability and uncertainties are likely to arise in any modeling approach, which relies on the extraction of multiple data sources to generate a burden of illness estimate. However, a modeling approach was warranted as there is no single population or registry database that could represent the entire United States population. The complexity and heterogeneity of the management of metastatic breast cancer posed a significant challenge in modeling, and to produce a functional, comprehensive model, the present study adopted several simplifications and reasonable clinical assumptions; in doing so, some level of precision regarding cost estimates was sacrificed.

Fourth, several of the model inputs relied on the results of physician survey to gain the most updated treatment patterns in light of the challenges and time lag in obtaining medical resource usage from a large prospective study of MBC patients. Physicians who were selected for these surveys specialize in the treatment of breast cancer. Nevertheless, in the absence of properly documented medical resource use behaviors among MBC patients, these clinical insights served as valuable inputs that informed the final model estimates. Finally, the present model, which uses the slightly outdated 2007 survival estimates of MBC patients from SEER, is subject to limitations imposed by the rapidly-changing treatment pattern of metastatic breast cancer and should be updated at periodic intervals.

CONCLUSIONS

The societal burden of metastatic breast cancer in the United States is significant. Early detection, timely intervention, and effective treatment of early stage disease and prevention of recurrence to prevent progression to the metastatic state could contribute to the lowering of costs associated with MBC while improving overall disease prognosis. Given the nature of metastatic disease, our model study can be useful for estimating the indirect cost burden in non-U.S. settings such as Canada and European countries (similar productivity loss), as well as providing a framework to investigate the direct cost attributable to MBC while taking into account the treatment patterns and reimbursement practices specific to the country setting.

SUPPLEMENTARY MATERIAL

Supplementary Material
Supplementary Table 1
www.journals.cambridge.org/thc2012002

CONFLICT OF INTEREST

Sonja Sorensen, Jo Wern Goh, Feng Pan, Kevin Knopf, and Ágnes Benedict report their institutions have received payment for writing the manuscript from United BioSource Corporation. Sonja Sorensen and Ágnes Benedict have also received other funding to their institute from United BioSource Corporation. Connie Chen, Carla Giorgetti, and Shrividya Iyer are employed by Pfizer Inc. and have stock or stock options in this company. Denise Yardley and Miguel Martín report having no potential conflicts of interest.

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REFERENCES

1. Allen JM. Economic/societal burden of metastatic breast cancer: A US perspective. *Am J Manag Care*. 2010;16:697-704.
2. Barron JJ, Quimbo R, Nikam PT, Amonkar MM. Assessing the economic burden of breast cancer in a US managed care population. *Breast Cancer Res Treat*. 2008;109:367-377.
3. Bennett CL, Calhoun EA. Evaluating the total costs of chemotherapy-induced febrile neutropenia: Results from a pilot study with community oncology cancer patients. *Oncologist*. 2007;12:478-483.
4. Berkowitz N, Gupta S, Silberman G. Estimates of the lifetime direct costs of treatment for metastatic breast cancer. *Value Health*. 2000;3:23-30.
5. Brewster AM, Hortobagyi GN, Broglio KR, et al. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst*. 2008;100:1179-1183.
6. Bureau of Labor Statistics. *News release: The employment situation - April 2011*. Washington, DC: U.S. Department of Labor; 2011.
7. Bureau of Labor Statistics. *Table 22: Persons at work in nonagricultural industries by age, sex, race, Hispanic or Latino ethnicity, marital status, and usual full- or part-time status*. U.S. Department of Labor; 2010.
8. Bureau of Labor Statistics & U.S. Census Bureau. *Current Population Survey, Design and Methodology*. Technical Paper TP63RV. Washington, DC: U.S. Department of Labor and U.S. Department of Commerce, Economics and Statistics Administration; 2010.
9. Campbell JD, Ramsey SD. The costs of treating breast cancer in the US: A synthesis of published evidence. *Pharmacoeconomics*. 2009;27:199–209.
10. Davis KL, Iyer S, Candrilli S. Predictors of the direct costs of breast cancer in the United States elderly population. *Value Health*. 2010;13:A260.
11. Elting LS, Shih YC. The economic burden of supportive care of cancer patients. *Support Care Cancer*. 2004;12:219-226.
12. Hartmann LC, Zahasky KM, Grendahl DC. Management of cancer pain. Safe, adequate analgesia to improve quality of life. *Postgrad Med*. 2000;107:267-272, 75-76.
13. Hayman JA, Langa KM, Kabeto MU, et al. Estimating the cost of informal caregiving for elderly patients with cancer. *J Clin Oncol*. 2001;19:3219-3225.
14. Kruse GB, Amonkar MM, Smith G, et al. Analysis of costs associated with administration of intravenous single-drug therapies in metastatic breast cancer in a U.S. population. *J Manag Care Pharm*. 2008;14:844-857.
15. Kurian AW, Thompson RN, Gaw AF, et al. A cost-effectiveness analysis of adjuvant trastuzumab regimens in early HER2/neu-positive breast cancer. *J Clin Oncol*. 2007;25:634-641.
16. Lamerato L, Havstad S, Gandhi S, et al. Economic burden associated with breast cancer recurrence: Findings from a retrospective analysis of health system data. *Cancer*. 2006;106:1875-1882.
17. Mauri D, Polyzos NP, Salanti G, et al. Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer. *J Natl Cancer Inst*. 2008;100:1780-1791.
18. Montazeri A. Health-related quality of life in breast cancer patients: A bibliographic review of the literature from 1974 to 2007. *J Exp Clin Cancer Res*. 2008;27:32.

19. National Cancer Institute. *Cancer trends progress report – 2009/2010 uapdate*. Bethesda, MD: NIH, DHHS; April 2010.
20. National Cancer Institute. *Surveillance Epidemiology and End Results (SEER) - Breast cancer. 2007–2010*. Bethesda, MD: National Cancer Institute.
21. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology. 2011*. Fort Washington, PA: National Comprehensive Cancer Network.
22. Printz C. Healthcare reform affects cancer on many fronts. More coverage for treatment and prevention planned. *Cancer*. 2010;116:3525-3526.
23. Rao S, Kubisiak J, Gilden D. Cost of illness associated with metastatic breast cancer. *Breast Cancer Res Treat*. 2004;83:25-32.
24. Schwartz J. Current combination chemotherapy regimens for metastatic breast cancer. *Am J Health Syst Pharm*. 2009;66(Suppl 6):S3-S8.
25. Sloss EM, Wickstrom SL, McCaffrey DF, et al. Direct medical costs attributable to acute myocardial infarction and ischemic stroke in cohorts with atherosclerotic conditions. *Cerebrovasc Dis*. 2004;18:8-15.
26. Stokes ME, Thompson D, Montoya EL, et al. Ten-year survival and cost following breast cancer recurrence: Estimates from SEER-medicare data. *Value Health*. 2008;11:213-220.
27. Wang SJ, Fuller CD, Choi M, Thomas CR. A cost-effectiveness analysis of adjuvant chemoradiotherapy for resected gastric cancer. *Gastrointest Cancer Res*. 2008;2:57-63.
28. Yabroff KR, Lawrence WF, Clauser S, et al. Burden of illness in cancer survivors: Findings from a population-based national sample. *J Natl Cancer Inst*. 2004;96:1322-1330.