ANTICANCER RESEARCH *39*: 353-359 (2019)
doi:10.21873/anticanres.13119

Costs in Different States of Breast Cancer

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Abstract. *Background/Aim: This cross-sectional study estimated direct cancer-related health care, productivity and informal care costs for a six-month period for different states of breast cancer (BC). Patients and Methods: A total of 827 BC patients answered a questionnaire enquiring about informal care, work capacity, and demographic factors. Direct health care resource use and productivity costs were obtained from registries. Mutually exclusive groups were formed based on disease state and time from diagnosis: primary treatment (first six months after diagnosis), rehabilitation (>six months after diagnosis), remission (>1.5 years after diagnosis), and metastatic. Results: Mean total costs were: primary treatment €22,876, rehabilitation €3,456, remission €1,728, and metastatic €24,320. Mean direct health care costs were: primary treatment €11,798, rehabilitation €2,398, remission €1,147, and metastatic €13,923. Mean productivity costs varied between 18-39% and indirect costs (productivity and informal care costs) between 31-48% of the total costs. Conclusion: Direct medical costs were highest, but indirect costs constituted up to half of the total costs and are essential when estimating the total cost burden, as many patients are of working age.*

Breast cancer (BC) is the most common cancer in women with 1.67 million new cases diagnosed in 2012 worldwide, accounting for 25% of all cancers (1). In Finland, the incidence of BC was 4984 and the prevalence 69,790 in 2016, and the incidence has been rising. More than half of the new cases in Finland are diagnosed in women under the age of 65 years (2). In addition to the rising incidence, the more advanced and often more expensive new treatments lead to prolonged survival, and consequently to an increased prevalence. To implement new treatments, cost-effectiveness data are needed, *i.e.*, cost data of the new treatment and data on the real-life effectiveness of treatments.

BC was estimated to be the most expensive cancer per citizen in the Nordic countries in 2007, and the cancer-related treatment costs were predicted to rise by 28 percent until 2025 due to the increasing cancer prevalence alone (3). In Canada, the mean lifetime costs for BC were estimated as one of the highest when compared to 18 other prevalent cancers (4). When evaluating the total costs of a disease, both direct and indirect costs need to be assessed. Disregarding productivity losses could result in an underestimation of the true cost of a disease. Informal care provided by family members or friends should also be included, as it is an important element of care for many cancer patients.

The aim of this study was to provide results for health economic analyses of new treatments and to deepen the understanding of BC-related costs in different states of the disease. Costs and resource use were analyzed as direct cancer-related health care costs, productivity costs, *i.e.*, the costs related to absence from work because of cancer, and costs of informal care provided free of charge by family or friends.

Patients and Methods

Study design and patients. This cross-sectional registry and survey study is part of a project investigating the health-related quality of life (HRQoL) and economic impact of breast, colorectal and prostate cancers in Finland (5-9). The study is registered in the Helsinki and Uusimaa Hospital District (HUS) Register with the unique trial number 233895 and was approved by the HUS Ethics Committee. Patients were identified from hospital records by date of diagnosis and recruited between September 2009 and December

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Key Words: Burden of disease, costs, direct costs, indirect costs, resource use, breast cancer.

2010. All patients aged 18 years and over and diagnosed with BC were eligible for the study. Questionnaires and consent letters were sent to the patients, and those signing a written informed consent were enrolled. The response rate was 59%. The questionnaire enquired about informal care, work capacity, and demographic factors. The patient survey included HRQoL questionnaires of which the 15D was used in this study (10).

For every study patient, two control subjects were extracted from the Social Insurance Institution's (SII) electronic records. The control group subjects were standardized for age, gender and place of residence. The data extracted from SII registries covered outpatient medication, sickness allowances and use of private health care. To assess cancer-related private health care usage, sickness allowances and outpatient medication, costs were compared against the control group and are reported as incremental costs related to BC for a six-month period. All costs are presented at the 2010 price level.

The patients' clinical background information regarding the disease state and the treatments given were collected from hospital records. Four mutually exclusive groups were formed based on the disease state: less than six months from diagnosis (primary treatment), 6–18 months from diagnosis (rehabilitation), subsequent years of remission (remission), and metastatic disease (metastatic). The costs were calculated for a six-month period based on clinical relevance and to be applicable in health economic analyses.

Direct health care costs. Specialist care: Data include inpatient episodes and outpatient visits to secondary health care. These retrospective data included the duration of the hospital stay, diagnosis and procedure code, and patient-level costs, including overheads, equipment, hospitalization, and drugs administered at the hospital. Specialist care visits not related to cancer were excluded. All resource use and cost data came from the hospital's electronic records. The costs of travel to the place of treatment and the number of journeys were available from the SII records when they exceeded the maximum co-payment for the patient, €14 per visit.

Primary health care: Primary health care in Finland is funded and organized by municipalities. The services are free for patients except for some user fees. Data were collected from the patient records of the three largest cities in the catchment area of the hospital, Helsinki, Espoo and Vantaa, covering more than 80% of the total population of the hospital district. Data included information on general practitioner and nurse visits, home hospital care and primary health care hospitalization. Data concerning the reasons for the visits, however, remained unavailable. To estimate the proportion of visits related to BC, we used the background questionnaire to identify the share of primary health care visits that were cancer-related. For patients whose home municipality differed from those mentioned (n=255; 30% of the patients), missing primary health care costs were imputed by using the average cost from the same disease state. Travelling costs related to BC visits were also included.

Private health care: Data on the use of private health care services were available from SII's registries. The costs of visits related to BC were estimated as those that exceeded the control population's private health care usage and travel costs. Resource use and unit cost data from the local private hospice care unit were also included.

Medicines: The usage and costs of outpatient medicines related to BC were extracted from the SII's electronic records and compared to those of the control population. The cost of medication dispensed in the hospital was extracted from the hospital records.

Productivity costs. The work status of the patients and the potential retirement from work due to BC were obtained from the patient survey (Table I). The number of days the patients were on sick leave and absent from work due to BC during the six-month observation period were calculated from the SII's electronic records. The human capital approach was used to value the loss of productivity (11). To assess the loss of productivity, wages were translated to average labor costs by including employer's social security payments, on average 38.6%, in addition to the pre-tax salary (12). Actual annual wages were used when calculating productivity losses due to early retirement. The valuation of productivity losses due to sick leave followed the same approach, however, we used the average daily cost of labor based on actual wages. Daily average labor cost was €127.70.

Informal care. Informal care was defined as care received free of charge from family and friends. The patients were asked to estimate the number of weekly hours of informal care received during the previous three months. These estimates were then extrapolated for the whole six-month observation period. The maximum amount of daily support and care was limited to 16 hours. To be able to calculate the total costs, we imputed missing values with the average values from the same disease state. We used the proxy good method in which the value of informal care is calculated by multiplying the number of hours of informal care by the value per hour for each care task performed (13). To value informal care, a practical nurse's mean hourly pre-tax salary of €13.63 for the year 2010 was used (14). The hourly labour cost was calculated by adding side costs on top of pre-tax salary, resulting in an hourly labour cost of €18.89.

Data analysis. The main objective was to estimate the mean six-month costs in different states of BC. The costs and resource use are reported as means and their confidence intervals. Stepwise log linear multivariate models were built to analyze how background factors are associated with total costs. Due to skewed distribution of cost variables, we used the natural logarithm of total costs as the dependent variable. Age, cohabitation, educational level, 15D utility score, and estrogen-, progesterone- and HER2- receptor status were used as independent variables. Three models were built: one for primary treatment, one combining remission and rehabilitation, and one for metastatic disease. A risk level of 5% was used for type 1 error in all analyses. Analyses were performed with SPSS 22 (15).

Results

The study population consisted of 827 BC patients. Of them, 650 had local and 177 advanced disease (Table I).

The mean total costs for the six-month period were €22,876 in the primary treatment, €3,456 in the rehabilitation, €1,728 in the remission, and €24,320 in the metastatic state (Figure 1).

Direct health care costs. The mean direct health care costs were highest in metastatic (€13,923) and primary treatment (€11,798), and mean specialist care costs were highest in the metastatic state (Table II, Figure 2). The mean cancer-related primary and private health care costs were low in all disease states. Of the patients, 28% (n=228) reported usage of primary health care and sixteen percent (n=136) usage of private health

Table I. *Patient characteristics*.

	Primary treatment	Rehabilitation	Remission	Metastatic disease	All patients
Respondents (%)	117 (14)	151 (18)	382 (46)	177 (21)	827 (100)
Demographic factors					
Age, mean (range)	57.0 (26-78)	60.6 (32-84)	63.1 (37-90)	62.7 (32-87)	61.7 (26-90)
Female (%)	116 (99.1)	149 (98.7)	380 (99.5)	177 (100)	822 (99.4)
Higher education (%)	72 (62)	92 (63)	207 (54)	104 (60)	475 (58)
Work status (%)					
Employed	69 (59)	70 (47)	149 (39)	36 (21)	324 (40)
Unemployed/not working	9 (8)	8 (5)	23 (6)	10 (6)	50 (6)
Retired	39 (33)	70 (47)	209 (55)	128 (74)	446 (54)
• of them due to cancer	2 (1.7)	1 (0.7)	5 (1.3)	43 (24.7)	51 (6.2)
White-collar employment (%)	62 (53)	72 (50)	200 (53)	89 (52)	423 (52)
Married/cohabiting (%)	81 (69)	99 (69)	231 (61)	103 (60)	514 (63)
Tumour characteristics					
ER positive (%)	73 (62)	119 (79)	313 (82)	136 (77)	641 (78)
PR positive (%)	54 (46)	90 (60)	248 (65)	90 (51)	482 (58)
HER2 positive (%)	13 (11)	17 (11)	48 (13)	51 (29)	129 (16)
Treatment					
Endocrine treatment (%)	38 (32)	106 (70)	294 (77)	76 (43)	514 (62)
Chemotherapy (%)	69 (59)	14 (9)	4 (1)	120 (68)	207 (25)
Radiotherapy (%)	31 (26)	7 (5)	0	27 (15)	65 (8)

care because of their cancer during the preceding three months. Private health care costs were minimally higher than those observed in the control group (Table II). The mean costs of medicines, including inpatient and outpatient medicines, were by far the highest in metastatic (€8862) and second highest (€3112) in primary treatment (Table II, Figure 2). The mean travel costs were highest in metastatic (€441), second highest in primary treatment (€179) and low in the rehabilitation and remission states (Table II).

Productivity costs. At the time of the study, 324 (40%) of the patients were working: In primary treatment 59% of the patients were working and 33% were retired, and in metastatic 21% and 74%, respectively (Table I). Mean estimated productivity losses were highest in primary treatment (€8887) and in metastatic states (€7412) (Table III). In primary treatment most of the costs (€8490) came from sick leave days (mean 62 days) as in metastatic the costs were predominantly due to early retirement (€5646). In the other states the productivity costs were rather low (Table III).

Informal care. Less than a third (n=243, 30%) of the patients received informal care due to BC. The estimated mean cost of informal care was highest in metastatic (€2985) where 58% (n=102) of the patients reported having received informal care, and second highest in primary treatment (€2191). In the rehabilitation and remission states the utilization of informal care was low (Table III).

Factors associated with total direct health care costs. Background factors were able to explain only around 7-22% of the variance of the total costs of BC in the different disease states (Table IV). Positive HER-2 receptor status was associated with higher total costs in all treatment states. Higher 15D utility scores, indicating better HRQoL, were associated with lower costs only in the rehabilitation/remission state, but the explanatory power (adjusted R2) of the analysis was lowest in this state. Higher age was associated with less cost burden in the primary treatment and metastatic states. Cohabitation was associated with lower costs only in the primary treatment state.

Discussion

This study evaluated the real-life costs which incur when patients are treated for BC. Only costs related to BC were assessed, while other possible health care costs were not considered, which makes it possible to establish a reasonably reliable estimate of the costs related to the disease beyond other health care utilization. When evaluating the total cost burden of a disease from a societal viewpoint, all the costs associated with the condition should be included regardless of who pays them. Our analysis included health care resource utilization and direct costs that had accrued both in the primary and specialist care settings. Productivity costs and the value of informal care provided by family members, relatives, or friends were also assessed.

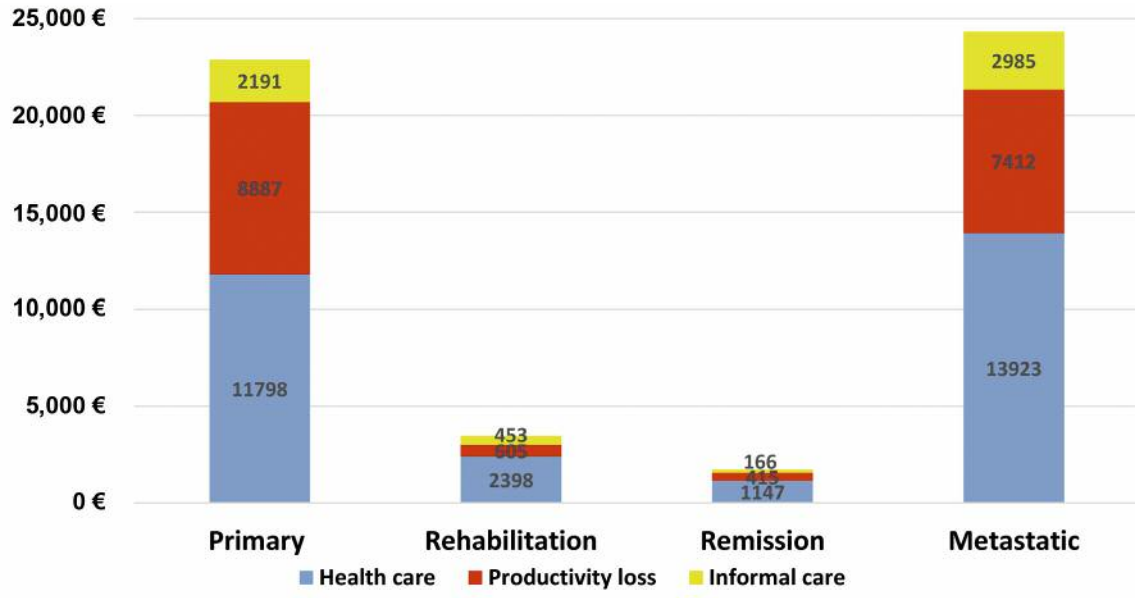

Figure 1. *Total costs for a six-month period in different states of breast cancer, €.*

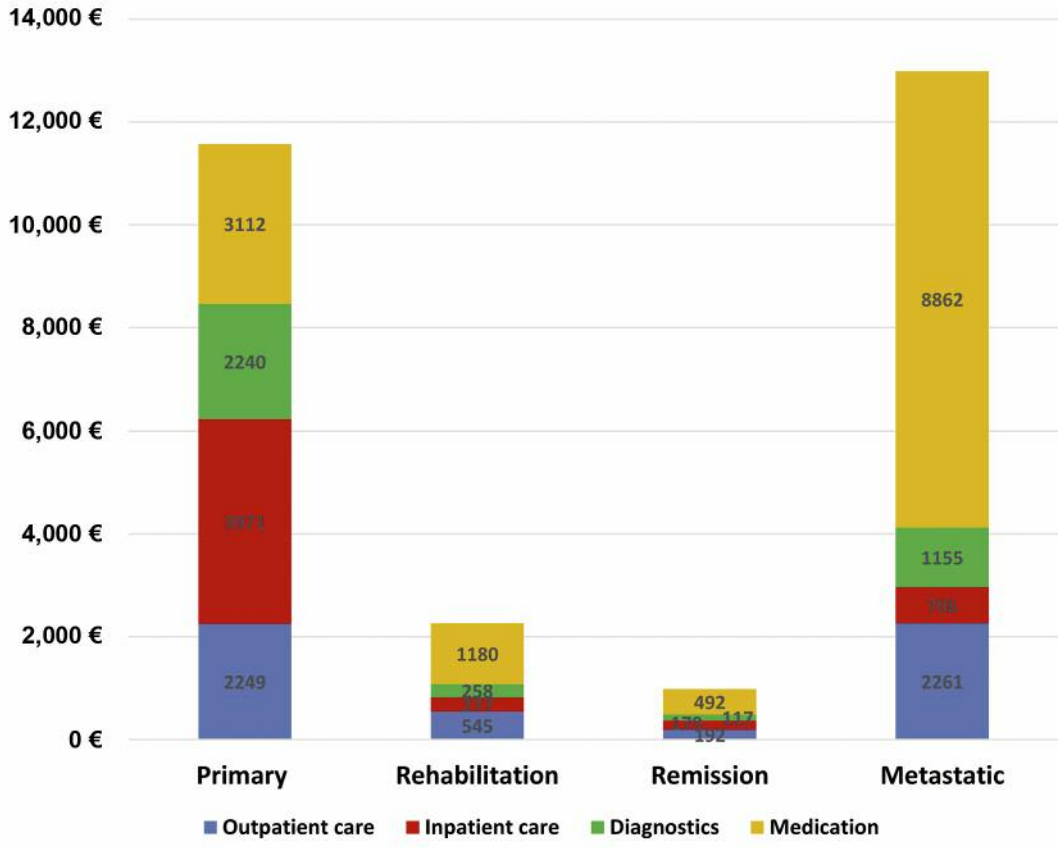

Figure 2. *Direct health care costs of specialist care for a six-month period in different disease states, €.*

Table II. *Direct healthcare costs for a six-month period in different states of breast cancer, €.*

Cost item	Primary treatment	Rehabilitation	Remission	Metastatic disease
Specialist care, total	11,572	2,260	980	12,984
(95%CI)	(10,746;12,398)	(1,566;2,954)	(768;1,191)	(11,799;14,170)
Outpatient care	2,249	545	192	2,261
(95%CI)	(2,071;2,427)	(412;678)	(158;226)	(2,046;2,475)
Inpatient care	3,971	277	179	706
(95%CI)	(3,568;4,374)	(54;500)	(88;270)	(451;962)
Diagnostics	2,240	258	117	1,155
(95%CI)	(2,104;2,377)	(186;330)	(93;141)	(1,051;1,260)
Inpatient medication[1]	2,092	799	143	5,578
(95%CI)	(1,660;2,523)	(349;1,248)	(10;276)	(4,653;6,504)
Outpatient medication[2]	1,020	381	349	3,284
(95%CI)	(672;1,369)	(226;536)	(256;442)	(2,720;3,848)
Medication, total	3,112	1,180	492	8,862
(95%CI)	(2,518;3,706)	(684;1675)	(333;651)	(7,844;9,881)
Primary Health Care	41	80	147	490
(95%CI)	(29;55)	(60;99)	(90;204)	(147;833)
Private Health Care[3]	6	10	6	7
(95%CI)	(0.5;12)	(2;18)	(1;10)	(2;13)
Travelling	179	48	15	441
(95%CI)	(98;259)	(21;76)	(–0.05;30)	(302;581)
Total health care cost	11,798	2,398	1147	13,923
(95%CI)	(10,950;12,646)	(1,699;3,096)	(922;1,372)	(12,690;15,157)

[1]Medications administered at the hospital during cancer-related inpatient and outpatient visits; [2]Medications related to BC extracted from SII's electronic records and compared to that of the control population; [3]Private health care costs were compared against the control group and are reported as incremental costs related to BC.

Table III. *Productivity loss and informal care for a six-month period in different states of breast cancer.*

	Days absent from work		Productivity loss, € (95%CI)		
	Sick leave	Early retirement	Sick leave	Early retirement	Total
Primary treatments	62	3	8,490 (6477;10503)	397 (–157;951)	8,887 (6855;10920)
Rehabilitation	4	1	449 (123;774)	156 (–148;460)	605 (51;1159)
Remission	1	2	111 (30;191)	304 (38;570)	415 (138;692)
Metastatic disease	14	44	1,766 (890;2641)	5,646 (4163;7129)	7,412 (5684;9140)
	Informal Care (IC)		Informal Care (IC)		
	% of patients receiving IC (n)	Mean hours of IC/week in patients receiving IC	Mean hours of IC/week in all patients	Mean cost (€) of IC (95% CI)	
Primary treatments	33 (39)	13.4	4.5	2,191 (775;3607)	
Rehabilitation	17 (26)	5.4	0.9	453 (95;811)	
Remission	20 (76)	1.7	0.3	166 (68;265)	
Metastatic disease	58 (102)	10.5	6.1	2,985 (1719;4250)	

The mean total costs of BC for the six-month period were remarkable and differed substantially between the disease states. Our results support previous findings that BC is an expensive cancer to treat (3-4). Treatment of metastatic BC accounts for a considerable share of the total cost burden, as the costs in this state are the highest and all the costs expand over a long time. During the primary treatment phase, the most intensive period of resource use and costs is the first year after diagnosis, after which the costs remain relatively low if the disease does not recur or progress.

Table IV. *Multivariate analysis of cost drivers with the natural logarithm of total costs (€) as the dependent variable (stepwise).*

Variable	Primary treatments		Remission/Rehabilitation		Metastatic	
	Coefficient	*p*-Value	Coefficient	*p*-Value	Coefficient	*p*-Value
	R^2=0.127		R^2=0.063		R^2=0.215	
(Constant)	10.246		9.398		10.186	
Age, years	–0.007	0.001			–0.008	0.008
Higher education			0.105	0.001		
Co-habitation	–0.105	0.033				
15D SCORE			–0.630	0.000		
HER2 receptor	0.161	0.017	0.197	0.000	0.388	0.000
Estrogen receptor						
Progesteron receptor						

The breakdown of the direct health care costs varied between the disease states. In primary treatment the costs are driven by inpatient care, as operation is usually the first treatment in newly-diagnosed BC, often followed by adjuvant chemo- and/or radiotherapy causing high specialist care costs. The adjuvant endocrine therapy extends in time over the rehabilitation and the remission states causing quite substantial medication costs in these states. In metastatic the medication costs are by far the highest constituting up to 64% of the total health care costs.

The mean direct health care costs (€11,798) for the first six months after diagnosis (primary treatment) were slightly higher than the mean incremental health care costs reported in a Canadian study ($12,219 Canadian dollars, around €8,099 in 2009) (4). In the Canadian study, costs for outpatient prescription drugs for patients under the age of 65 years and out-of-pocket healthcare costs were lacking. The mean total costs for the first six months after diagnosis in our study were €22,876 which is high compared to a Swedish study from 2005 reporting total costs of 280,000 SEK (€30,435) for the first year after diagnosis in patients under the age of 65 (16). The mean total costs of metastatic disease for the six-month period (€24,320) in our study were also high compared to the Swedish study reporting total annual costs of 334,000 SEK (€36,304). The cost assessment in our study was more comprehensive, containing also primary and private health care costs and costs related to traveling. There were also quite substantial differences in chemotherapy agents used in these two studies, with more expensive treatment agents being used at the time of our study. To value the costs of informal care, we used the proxy good method whereas in the Swedish study the value of leisure time lost was applied. The number of hours per week of informal care received reported by the patients was nearly double in our study amounting to informal care costs of €2,985 whereas the Swedish study found the costs to be approximately €454 (16).

Informal care constituted 10-13% of the total costs in the different disease states. The percentage of patients receiving informal care was modest, except for in the metastatic state where 58% of the patients needed informal care. The share of productivity costs of the total costs varied between 18-39% in different states of the disease. In primary treatment high sick leave costs and in metastatic the costs of early retirement were dominating. In the rehabilitation and remission states the productivity losses were low as patients usually return to normal routines and working life. When adding informal care costs to the productivity costs, the share of indirect costs (productivity and informal care costs) increased to 31-48% of the total costs.

In the Swedish study, indirect costs accounted for more than 50% of the total costs in patients under 65 years of age (16). In a study from Australia, the indirect costs amounted up to 62% of the total costs and were even higher in younger women (17). In a Belgian study, the productivity costs due to morbidity and premature mortality were evaluated to be up to 89% of the total costs and in a recent study from the Netherlands up to 40% of the total economic burden caused by BC (18-19). The share of indirect costs varies according to the methods used and differences in health care systems and income loss compensation payments between countries. As in many studies the indirect costs constitute up to half of the total costs, these costs are essential when evaluating the total costs of BC.

The strength of this study is that the costs are real costs that accrue when patients are treated or followed-up for BC. The productivity costs, which are based on the SII's register's payments and are compared to the controls without cancer, are more reliable than productivity cost assessments based on patient recall or patient diaries. We also included costs of primary health care, which make our assessment of the total cost burden of the disease comprehensive. Likewise, all the medicines related to BC were included, regardless of whether they were dispensed at the hospital or delivered by a pharmacy.

The cross-sectional approach that did not permit the follow-up of patients throughout the disease course could be seen as a limitation. As we did not have access to all patients' primary health care costs, the missing costs were imputed with the mean costs from the same disease states to be able to calculate the total costs. The same was used for missing informal care costs. Since we only had the patients' questionnaire answers for the reasons of primary health care visits and usage of informal care for the past three months, we used extrapolation to six months to be able to calculate the costs for the whole study period.

The time between data collection and reporting was approximately seven years. This should not have had a major impact on the relevance of our findings, however, since the general price level has remained relatively stable during this time in the Organisation for Economic Co-operation and Development (OECD) countries including Finland (20).

Conclusion

The direct health care costs accounted for about half the total costs. The indirect costs amounted up to one third to a half of the total costs depending on the disease state. The indirect costs are essential when evaluating the costs of BC as many patients are of working age. The treatment of metastatic BC takes up a great share of the total costs of BC for the society, as the high total costs extend over a long period of time.

Acknowledgements

This work was supported by the Cancer Foundation Finland and GlaxoSmithKline Oy, Finland. The writing of this article was supported by research grants from the Cancer Foundation Finland and The Finnish Medical Foundation. The study sponsors were not involved in the study design, or the collection, analysis and interpretation of data nor in the writing of the manuscript, or in the decision to submit the manuscript for publication.

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Received November 30, 2018
Revised December 11, 2018
Accepted December 12, 2018