#02/2021
ISSN 2299-1247

JHPOR | Journal of Health Policy & Outcomes Research

The economic burden of advanced breast cancer

DOI:10.7365/JHPOR.2021.2.6

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Keywords:

Advanced breast cancer; burden; cost of illness

How to cite this article?
Tabor B., Jakubczyk M., Bojanic L., Zawodnik S., Bojkow S., Chahoud L., Sweeney N., Benkovic V., Christodoulou C., Dimitrova M., Liepina E., Ondrušová M., Pana A., Petrova G., Petrovica M., Ulici A., Niewada M., The economic burden of advanced breast cancer J Health Policy Outcomes Res [Internet]. 2021 [cited YYYY Mon DD];2. Available from: https://www.jhpor.com/article/2270-the-economic-burden-of-advanced-breast-cancer

contributed: 2021-07-15 final review: 2021-12-06 published: 2021-12-30

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Abstract

Background
Breast cancer is the most frequently diagnosed and leading cause of death amongst cancers in women. Understanding its burden is important in healthcare management. We assessed direct medical and indirect costs of advanced breast cancer (ABC) in selected countries: Bulgaria, Croatia, Czech Republic, Estonia, Greece, Israel, Latvia, Poland, Romania, and Slovak Republic.

Methods
The data were collected in individual countries with a unified questionnaire (covering epidemiology, mortality, treatment patterns, and economic aspects) based on databases/registries, published studies, or experts' opinions in the absence of published data. International scope allowed for consistency checks and missing data imputing.

Results
The total annual costs of ABC per 100,000 women varied from 1 million EUR in Romania to 3.4 million EUR in Slovak Republic with the differences partially related to data availability. The direct costs resulted mainly from the costs of treatment (covering surgery, breast reconstruction, external breast prosthesis, chemotherapy, radiation, hormonal and targeted therapy). The indirect costs (lost productivity due to premature mortality and reduced employment rate) constitute a large part (>50%) of the total costs. The average (for all countries) total annual costs per 100,000 women amounts to 1.8 million EUR.

Conclusion
ABC is associated with substantial healthcare costs and imposes a significant societal burden, as indicated by high indirect costs. Early detection, timely intervention, and effective treatment of early stage BC hold potential to decrease burden of ABC. Our findings may be used in informing decisions on resource allocation, improving cancer policies and supporting national cancer plans.

Highlights

- Advanced breast cancer costs between 1 and 3.4 million euro per 100,000 women in studied countries; lost productivity (from societal perspective) accounts for most of the cost
- The data availability is still limited; comparisons between countries reveal some gaps, but collecting more information, e.g. in registries, is crucial for improved decision making.
- The results of our study may be used in cost-effectiveness modelling of diagnostic or treatment technologies.

Introduction

Cancer incidence is increasing globally.[1] Among all cancers diagnosed in women, breast cancer (BC) is the most frequent, representing the leading cause of death. In 2018, there were over 2 million new BC cases worldwide.[2] World Health Organization (WHO) estimates that almost 627,000 women died in 2018 because of BC, which constitutes approximately 15% of all cancer deaths amongst women.[3]

BC is also responsible for a large part of the cost of oncological treatment. For example, in the United States in 2014, approximately $18.1 billion can be attributed to female BC, out of $137.4 billion of the national expenditures for cancer care (i.e. 13%).[4] The total costs of cancer not only vary by tumour type but also depend on the stage of disease: treatment of the advanced stages of cancer is often more intensive or invasive, most costly, and less successful.[5,6] Sun[6] showed that the mean treatment costs of stage II, III and IV (at diagnosis) exceeded those of stage I by 32%, 95%, and 109%, respectively. As can be seen, the increase is substantial for stages III (locally advanced breast cancer) and stage IV (metastatic breast cancer), referred to as an advanced breast cancer (ABC), i.e. BC that has spread to another part of the body.[3] These stages are also most costly among all stages due to intensive treatment and associated indirect costs.

BC affects relatively young patients. WHO estimates that approximately 30% of new cases of BC in 2018 affected women under 50 years.[2] For example, in females aged 25-49 in the United Kingdom, BC is the most common cancer, accounting for more than 4 out of 10 (44%) of all cancer cases.[7] Therefore, working population may be largely affected and BC may generate substantial in-

direct cost (i.e. opportunity cost of foregone product)8. Even though indirect costs are not associated with actual cash flows, they measure the disruption to the economy caused by the illness and are considered as an important element from the societal perspective. Estimating the magnitude of ABC costs can help to determine its economic significance (not undermining the clinical importance). Understanding the components of these costs can help to optimize healthcare spending, e.g., by informing the cost-effectiveness analyses of a treatment or diagnostic technologies or deciding on investment in a particular health care setting (primary or hospital care) or type of care (prevention, curation, palliation).

We aimed to assess the direct medical costs and the indirect costs of ABC in selected European countries: Bulgaria, Croatia, Czech Republic, Estonia, Greece, Israel, Latvia, Poland, Romania, and Slovak Republic. The international scope of the analysis has at least two benefits. First, the results can be juxtaposed and the credibility of final estimates can be concluded. Second, in case of missing information for particular country, if the same estimation methodology is used throughout the study, the missing data can sometimes be imputed based on available values in other countries.

Methods

A unified questionnaire was used for all countries, enabling comparison of intermediary results and allowing for filling missing data based on average values reported in other countries, if needed. The questionnaire encompassed sections on epidemiology, mortality, treatment patterns (which intrinsically differ depending on the moment of diagnosis) using various types of resources, also the end-of-life treatment, unit cost information, and other economic data (e.g. economic activity) (questionnaire template is given in Online Resource 1). The questionnaires were filled based on available registers and databases, literature, published data, and local clinical experts' experience, etc. (see Online Resource 2)..

2.1 Epidemiology and mortality

The data were collected split by the stage of disease; if split data were not available, the data for stages III and IV jointly or for the whole BC population were collected. As treatment patterns may evolve with time, and considering an average patient may be cumbersome in cases where experts' opinion was used, we separately considered the newly diagnosed (more recently than 12 months) and the remaining patients (i.e. after progression or diagnosed >12 months ago), expecting that it is easier to estimate the costs separately in two clinically distinct groups.

To understand the resource consumption, we collected data on the percentage of patients in whom the procedure was used and the average number of procedures used per year (among patients who used it at least once).

2.2 Direct cost estimation

In cost estimation, we used the prevalence-based approach, i.e. we multiplied the number of patients (as measured at a given moment) by the average annual cost9. The number of patients was defined irrespectively of the disease onset, except the split for the newly and previously diagnosed, as described above. To calculate the average annual cost, the product of the percentage of patients receiving a given procedure, the average number of units of the procedure received per year, and the unit cost was used. The study encompasses three categories of direct medical costs: diagnostics, treatment, and other medical services. The treatment costs were divided into: surgery, breast reconstruction, external breast prosthesis, radiation therapy, chemotherapy, hormonal therapy, and targeted therapy.

Due to data availability, a modified approach was used in Croatia and the Czech Republic. In Croatia, we used the incidence-based approach, i.e. we multiplied the number of new patients per year by the average number of procedures in life-long horizon. In the Czech Republic, we directly multiplied the total annual resource consumption for patients with ABC identified in Czech National Cancer Registry by the unit cost (information extracted from the National Registry of Reimbursed Health Services).

2.3 Indirect cost estimation

In the indirect cost estimation, the deaths from a single calendar year were assigned the stream of lost future productivity (i.e. the fact that the deceased person does not generate the product in the future). In a sense, this way has some incidence-based approach elements (where death is the event the number of which per year we measure). A purely prevalence-based approach would rather artificially require estimating the total number of people who would be alive in a given moment if they had not died because of ABC.

We used the human capital approach, i.e. accounted for the whole period of illness-related absence from workforce, and not the friction cost method (FCM), in which it is assumed that market adjustments (e.g. new people being hired) will make up for an absent person after some friction time (see, e.g., van den Hout 201010 for a more detailed comparison of the two). Firstly, we believe it is more suitable approach of obtaining a single number that expresses the overall disruption to the economy: for example, under FCM the death of a 20-year old would generate the same cost as the death of a 60-year old (ig-

noring differences in salaries, as both deaths impact the economy only within a short friction period). Secondly, using FCM would require additional assumptions in the multi-country setting: e.g., how the job markets function, how quickly replacements can be found, what is the degree of complementarity/substitution between the employees, country specific friction time, etc.

To estimate the indirect costs of ABC, the country-specific information on the economic activity (like employment rate, sick leaves, average monthly gross salary) was necessary. We used two sources of indirect costs: the productivity lost due to premature mortality (i.e. before the expected death of a general population, restricted to pre-retirement age) and the productivity lost due to reduced employment rate (because of morbidity). We have collected data on mortality (yearly number of deaths) and age structure (at death; for the age ranges: ≤20 years, 21-30 years, 31-40 years, …, ≥81 years). Based on these data, the annual number of deaths for age ranges was calculated (assuming that all deaths occurred in the middle of the analysed age ranges). The number of potential years of work lost were estimated as follows: restricted mean survival time ranges multiplied by the annual number of deaths in the age ranges and by the employment rate. Finally, indirect costs of premature mortality were calculated as potential years of work lost multiplied by average annual gross salaries.

Productivity lost due to the reduced employment was calculated as follows. Based on the number of ABC patients and age structure (for prevalence; for the age ranges: 21-30 years, 31-40 years, 41-50 years, and 51-60 years) we estimated the size of the ABC population in the working age. The indirect costs of productivity lost due to reduced employment rate was calculated based on these data, as the number of working age population multiplied by decrease in employment rate (i.e. the difference between the general population employment rate and the sick population employment rate) and by the average annual gross salaries.

2.4 Data collection and analysis

Calculating both the direct and indirect cost a two-stage approach was used. First, data from countries were validated and answers for all parts of the questionnaire were analysed separately and compared between the countries. In case of missing data for epidemiology and mortality, this allowed the use of average values from the other countries. This method was not used for the other elements of questionnaire. Analysed countries differ in terms of economic development, price levels, and the scope of public payer health care coverage (i.e. which procedures, drugs etc. are covered by the public payer and which need to be covered by patients by out-of-pocket payments). The costs vary across countries, also due to the differences in general prices levels, clinical practice, and available treatment methods. Therefore, we believe that transferring such data cannot be performed credibly. Second, the direct and indirect costs were estimated based on the available data. All costs were converted to Euro (using standard exchange rate from European Central Bank of 30.05.2019)11 for comparability. We assumed that unit costs from the patient perspective are zero, if not explicitly reported otherwise.

Tab. 1. The number and structure of BC patients (split by stage).

Stage	Bulgaria[a]	Croatia[a]	Czech Republic	Estonia[a]	Greece[a]	Israela	Latvia	Polanda	Romania	Slovak Republic[a]
0	119	871	6 322	308	2 100	802	291	6 257	2 413	908
I	13 914	7 855	40 200	2 780	18 938	7 230	4 847	56 430	10 463	8 185
II	19 861	10 001	32 701	3 540	24 113	9 205	6 008	71 849	22 420	10 422
III	9 038	4 239	7 895	1 501	10 222	3 902	2 158	30 458	13 773	4 418
IV	8 682	1 459	1 485	516	3 517	1 342	270	10 478	1 729	1 520
women population[b]	3 651 881	2 149 003	5 378 133	698 097	5 546 916	4 357 025	1 054 433	19 595 127	10 041 772	2 783 659
BC prevalence per 100,000 women	1 413	1 137	1 647	1 238	1 062	516	1 287	895	506	914
ABC prevalence per 100,000 women	485	265	174	289	248	120	230	209	154	213
total number of BC patients	51 614	24 424	88 603	8 646	58 890[c]	22 481	13 574	175 472	50 798	25 452
total number of ABC patients	17 720	5 698	9 380	2 017	13 739	5 244	2 428	40 936	15 502	5 938
the share of ABC patients in total BC patients	34.3%	23.3%	10.6%	23.3%	23.3%	23.3%	17.9%	23.3%	30.5%	23.3%

[a] the split-by-stage data were not available, this is result of our calculation.
[b] women population on 1 January 2017 from EUROSTAT.[12]
[c] the primary data were not available, this is result of our calculation.
ABC — advanced breast cancer; BC — breast cancer.

Results

3.1 Epidemiology and mortality

As shown in Tab. 1, the average BC prevalence in women for studied countries amounts to 1.06% (approx. 1,060/100,000 women). The prevalence is highest in the Czech Republic (1,647/100,000 women), and lowest in Romania (506/100,000 women). ABC constitutes on average 20% of total BC patient population.

The annual disease specific mortality rate was calculated as the number of deaths per year divided by total number of patients with BC in an individual country. The highest annual disease specific mortality rate of BC was observed in Romania (approx. 7%). For other countries, the annual BC mortality rate ranges from 2.2% (the Czech Republic) to 4.6% (Israel) (see Online Resource 3). The data on the age structure for mortality are given in Online Resource 4. In the age range 41-50 years (this range was selected as it matters for indirect costs due to large prevalence and non-negligible number of remaining life years before retirement), the highest mortality is in Romania (8.9%), while in other countries it ranges from 5.3% to 6.4%. Other data seem to be consistent between countries. In countries where prevalence was higher for early disease stage (BC stage I and II), the mortality rate tends to be lower. For example, in the Czech Republic, almost 45% of patients are in the stage I of BC and the mortality rate is low; in Romania, almost 25% of patients are in the stage III of BC, and the mortality rate is the highest of all participating countries.

3.2 Cost

Our results show that the annual direct cost of ABC per 100,000 women is the highest in Slovak Republic (2.7 million EUR) and the lowest in the Czech Republic (0.4 million EUR). The direct costs are not presented for Estonia because of the limited information.

In all the countries, except for Greece, the direct costs resulted mainly from the costs of treatment (Fig. 1, as reported in available data).

The employment rate (full-time and part-time jointly) in ABC population was only available for Latvia, and it amounts to 39% there. Based on this information, we estimated the employment rate in ABC population in other countries assuming the same relation of employment rate in ABC and general populations (see Online Resource 5 for results).

The results cvering years of potential life lost and of the productive lost are summarized in Tab. 2. The number of years of potential life lost ranges between approx. 2,000 (Estonia) and 55,000 (Poland), also leading to the productive years loss: between 250 (Estonia) and 4,000 (Poland). The high annual disease specific mortality in Poland and Romania results in a high number of years of potential life lost in these countries.

In absolute terms, the indirect cost was estimated as approx. 6 million EUR in Latvia and 121 million EUR in Poland (see Tab. 3). The indirect cost of lost productivity due to premature mortality is related to the number of potential years of work lost (see Tab. 2), which is the highest in Poland and the lowest in Estonia and Latvia. The indirect cost of lost productivity due to reduced employment rate is closely related to the number of the women working age population with ABC in individual countries. In Estonia and Latvia there are about 2,000 women with

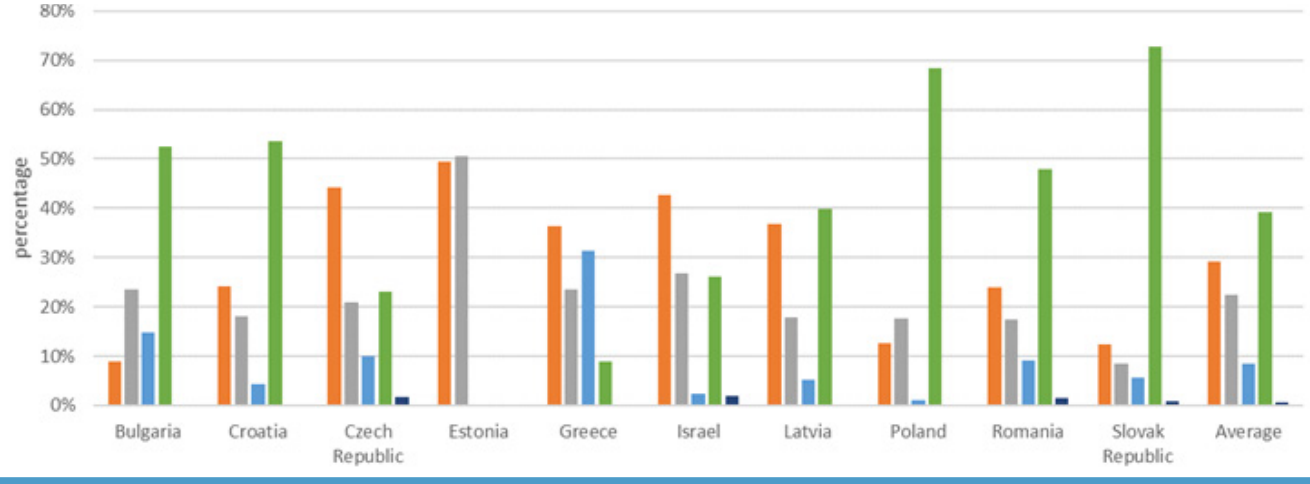

Figure 1. The cost structure.

Tab. 2. The years of potential life lost and potential years of work lost in the specific country.

Country	Years of potential life lost	Productive years loss
Bulgaria	9 538	1 430
Croatia	6 284	856
Czech Republic	12 369	1 616
Estonia	1 919	257
Greece	16 464	2 044
Israel	8 728	954
Latvia	3 235	385
Poland	55 139	4 467
Romania	30 116	2 850
Slovak Republic	7 977	1 014

Tab. 3. Main components and total annual cost of ABC (EUR).

Country	Indirect costs	Indirect costs due to premature mortality	Indirect costs due to reduced employment rate	Direct costs	Diagnostic costs	Treatment costs	Other medical services costs	Total costs
total, per country								
Bulgaria	36 247 351	10 058 380	26 188 971	75 332 511	16 515 505	58 655 659	161 346	111 579 862
Croatia	19 431 302	11 150 667	8 280 634	26 644 421	1 997 835	24 646 585	n/a	46 075 722
Czech Republic	43 589 054	29 655 940	13 933 114	23 400 978	6 701 647	15 524 855	1 174 476	66 990 033
Estonia	7 619 306	3 769 235	3 850 071	n/a	n/a	n/a	n/a	7 619 306
Greece	47 673 616	29 015 574	18 658 042	31 987 029	24 948 292	7 038 738	n/a	79 660 645
Israel	48 996 217	30 080 682	18 915 535	21 517 018	1 730 768	18 445 279	1 340 971	70 513 235
Latvia	6 350 869	4 278 848	2 072 021	5 252 157	614 710	4 613 636	23 810	11 603 026
Poland	121 314 585	50 650 944	70 663 641	277 792 765	4 635 974	273 156 791	n/a	399 107 350
Romania	39 249 523	22 722 445	16 527 079	55 784 103	8 758 435	45 570 783	1 454 885	95 033 626
Slovak Republic	19 608 305	11 606 102	8 002 203	74 288 049	5 286 769	68 227 706	773 574	93 896 354
per 100,000 women								
Bulgaria	992 567	275 430	717 136	2 062 841	452 247	1 606 177	4 418	3 055 408
Croatia	904 201	518 876	385 324	1 239 850	92 966	1 146 885	n/a	2 144 051
Czech Republic	810 487	551 417	259 070	435 113	124 609	288 666	21 838	1 245 600
Estonia	1 091 439	539 930	551 509	n/a	n/a	n/a	n/a	1 091 439
Greece	859 462	523 094	336 368	576 663	449 769	126 895	n/a	1 436 125
Israel	1 124 534	690 395	434 139	493 847	39 724	423 346	30 777	1 618 380
Latvia	602 302	405 796	196 506	498 102	58 298	437 547	2 258	1 100 404
Poland	619 106	258 487	360 618	1 417 662	23 659	1 394 004	n/a	2 036 768
Romania	390 863	226 279	164 583	555 521	87 220	453 812	14 488	946 383
Slovak Republic	704 408	416 937	287 471	2 668 719	189 922	2 451 008	27 790	3 373 127
Average	809 937	440 664	369 272	994 832	151 841	832 834	10 157	1 804 769

ABC — advanced breast cancer; EUR — euro; n/a — not available.

ABC, while in Poland almost 41,000 (see Tab. 1). In Bulgaria, Poland, and Romania, the percentage of patients in working age (20-60 years) is higher than in the other countries (more than 50%), while in the Czech Republic and Latvia less than 30% women with ABC are aged 20 to 60. Based on the data above, the working age population with ABC is the largest in Poland (about 24,000 women) and the smallest in Latvia (700 women). All indirect costs are linked to average monthly gross salary, which is the highest in Israel (2 628 EUR), and the lowest in Bulgaria and Romania (about 600 EUR). In other countries, the average monthly gross salary is quite similar and ranges between 926 EUR (Latvia) to 1 530 EUR (the Czech Republic).

The estimates of the indirect costs per 100,000 women is rather consistent between countries and ranges between 0.4 million EUR (Romania) to 1 million EUR (Estonia and Israel) (see Tab. 3). To a significant extent, ABC occurs in young patients of working age. Hence, premature deaths prevent patients from contributing to the economy and incur economic burden on society. As a result, the indirect costs weigh heavily up to 55% of the total costs of ABC (see Fig. 1).

Finally, the average (for all countries) total costs per 100,000 women amounts to 1.8 million EUR. This finding complements the fact that BC among all the cancers has one of the highest economic costs per country in the European Union13. Luengo-Fernandez13 showed that lung cancer had the highest economic cost (18.8 billion EUR, 15% of overall cancer costs in the European Union in 2009), followed by breast cancer (15 billion EUR, 12%), colorectal cancer (13.1 billion EUR, 10%), and prostate cancer (8.43 billion EUR, 7%). The results of estimation of total annual cost of ABC are summarized in Tab. 3.

Discussion

In this study we estimated the economic burden of ABC: the direct medical costs (defined from the public-payer and patient perspectives) and the indirect costs (societal perspective). This multitude of perspectives sheds more light on the overall economic burden of the illness and demonstrates how various components weigh overall. On the other hand, the multinational context of our analysis allowed us to detect potential problems with data (where values differed substantially between the countries) or replace the missing data (in case of epidemiology, where we believed the transferring data can be done rather credibly). Although we have included quite many countries, we managed to maintain a unified approach to data collection and analysis, with a few exceptions as indicated above.

As in some cases data of sufficient quality were inaccessible (e.g. information about the treatment related to AE or other complications), some cost categories may be inaccurately estimated. The differences in the level of total costs of ABC between countries do not necessarily mean that the costs differ so much, but rather that the access to reliable data or the nature of this data differs. Only for Bulgaria, the Czech Republic, Israel, Latvia, Romania, and Slovak Republic all components of direct costs are known. As missing categories were typically omitted, we tend to treat our results as a lower bound of the actual economic burden.

Still, our results show that the estimated total cost of ABC is rather consistent among the countries. The total costs of ABC per 100,000 women ranges between approx. 1 million EUR (Romania) to 3.4 million EUR (Slovak Republic). As the data were consistent, we believe that these numbers are one of the major findings of our research. Because of the possible downward bias due to data unavailability, in future analyses it may be worth considering a country result but also an average result (for every 100,000 women in the general population, ABC generates approximately 1.8 million EUR annually).

Regarding the cost structure, even though ABC occurs frequently in the elderly (almost 60% of patients are over 60 years old), the indirect costs constitute a large part of the total: on average, they are responsible for 55% of the cost. The earlier assessments confirm our estimate: in a Swedish study the indirect cost was assessed to be 50%14, while in the Netherlands the total cost of BC was estimated at 1.27 billion EUR, of which 768 million EUR (60%) is the healthcare expenditure, 260 million EUR (20%) is the indirect cost of morbidity, and 243 million EUR (19%) is the indirect mortality cost15. Owing to this high share, omitting indirect costs in burden of illness studies may not reveal the complete picture. We also conclude that these findings confirm the importance and additional benefits of early diagnosis.

Importantly, our indirect cost estimates are conservative, as they do not include the cost of sick leaves or of presenteeism (reduced productivity while present at work).
Regarding the direct cost component, in all the countries (except for Greece) the direct costs resulted mainly from the costs of treatment.

Early detection of BC is also financially beneficial in terms of direct cost. The cost of treatment is much smaller in the early stages of disease. This finding seems to be in line with other analyses presented in the literature: it was found that treating advanced- versus early-stage BC is associated with increases in costs (costs increased with increased stage of cancer).[16]

Obviously, our study is subject to several limitations. Burden of disease studies bear lot of limitations due to data collection as well as inherent differences among countries (related to delivery, financing and organization of health care as well as cultural differences). Chronic diseases, including cancer, are highly country-specific, thus comprehensive and uniform approach to resource use and costing are challenging. With study pilot we could identify but not fully adjust for these diversities. Especially the coverage and funding methods are very specific, as different care items could be contracted separately, pooled, or financed within various budgets.

Due to the wide scope of the requested data, the collection proceeded in an iterative way, with data being scrutinized, compared across countries, and amended, if needed. As mentioned above, we find this to be a difficulty but also an advantage of multinational studies. As mentioned, the variety of available format of data as well as the data quality differs among the countries. Therefore, the comparability of the individual cost components between the countries is rather limited. Fortunately, the final aggregated results are fairly consistent. We conclude that using these total cost estimates is rather well-grounded and safe. This is especially the case for indirect costs, where there are fewer parameters used in the estimation. Apart from the estimates, the present study indicates there are still issues with data availability or quality. For example, in most of the countries the number of patients with BC split by the stage of disease, the information about employment rate in ABC/BC population or data on sick leaves were not available. In all the countries, the information about treatment related to AE or other complications were limited and insufficient to calculate related costs. In Estonia and Greece, information on unit cost of diagnostic and other medical services was limited. The cost of other medical services was omitted in three counties (Croatia, Greece, and Poland) because it was not possible to either obtain data from existing databases or get reliable data through the interviews with experts. For example, implementing national registers would allow for more accurate estimates to be obtained in the future, which could result in more informed decisions on resource allocation. Finally, the retrospective, bottom-up like design, input data driven by the quality of specific epidemiological data justify careful consideration of our research findings. We were also unable to project future burden, which is likely to double in the next 15 years.[17]

Conclusions

ABC is associated with substantial healthcare costs and imposes a significant societal burden, as indicated by the high indirect costs. Early detection, timely intervention, and effective treatment of early stage BC can lead to the decrease of costs associated with ABC while improving the overall disease prognosis. Our findings may be used in informing decisions on resource allocation, improving cancer policies, and supporting national cancer plans. Better data availability would improve the quality of estimates and lead to more informed decision making.

Funding

The study was funded by Novartis.

Supplement

Online Resource 1

Introduction

Thank you for agreeing to participate in the study; we appreciate your time and expertise! We ask for information to assess the cost of advanced breast cancer (ABC) in several European countries, including yours, in order to increase the awareness of this disease. By ABC, we understand stages III (locally advanced breast cancer) and IV (metastatic breast cancer). We aim to estimate the ABC cost split by the stage of the disease; thus, we will be grateful for filling the data separately for each stage. If relevant data are not publicly available, please try to estimate them (e.g. using experts' opinions). If split is unavailable, provide answers for ABC jointly or, at worst, data for the overall BC population. In case of mortality, we ask for similar information in various ways, not knowing what kind of data may be available in your country. Based on data availability and quality we will choose the analytical strategy.

Once again, thank you for your valuable time!

Contact information

Name and e-mail of the contact person	
Name and Affiliation of Expert #1	
Name and Affiliation of Expert #2	
(add rows for more experts, if needed)	
Name of the country	

Epidemiology

Prevalence

Please provide 2017 data, if available; if using older data, provide info on the year. If relevant data are available, do fill all fields; we may use your data to fill in the gaps in other countries.

Stage	Number of patients with BC (at a given point in time, e.g. 1st January)	Proportion of patients actively treated	% of patients diagnosed at this stage ≤12 months ago	Data source	Comments (e.g. is exactly the required population estimated, any important assumptions, possible biases)
0					
I					
II					
III					
IV					
unknown*					
All**					
*use, if needed **If split data not available, provide the overall value					

Annual disease specific mortality

Please provide 2017 data, if available; if using older data, provide info on the year. If relevant data are available, do fill all fields; we may use your data to fill in the gaps in other countries.

Stage	# of deaths yearly (for disease specific reasons)	Data source	Comments (e.g. is exactly the required population estimated, any important assumptions, possible biases)
0			
I			
II			
III			
IV			
unknown*			
All**			
* use, if needed ** If split data not available, provide the overall value			

Age

Please provide data on the age structure for the age ranges below. If needed, use your own ranges. Provide the most recent data with info about the year.

Age	Prevalence (at a given point in time, e.g. 1st January)			Age structure for mortality (at death)		
	% of patients (should add to 100%)	Data source	Comments	% of patients (should add to 100%)	Data source	Comments
≤20 y						
21-30 y						
31-40 y						
41-50 y						
51-60 y						
61-70 y						
71-80 y						
≥81 y						

Please provide the mean age at death, per stage. If not available, provide values for the III and IV jointly or for the whole BC population.

	Stage				Data source	Comments
	III	IV	ABC jointly	Overall BC		
Mean age of patients being at given stage*						
Mean age at death**						
* if not available, please provide average duration of remaining in a given stage ** if not available, please provide a 1 and a 5-year survival rate or mean survival years or life expectancy						

Economic activity

In order to estimate the indirect costs of ABC, we ask for info on the economic activity.

What is the employment rate (full-time and part-time jointly) in ABC population (in working-age)?	Data source
If not available, provide data for the overall BC population.	Data source
If not available, provide data for the general population.	Data source
Are data on sick leaves in the ABC population available? If yes, provide the average number of days per year.	Data source
If not available, provide data for the overall BC population.	Data source
What is the average monthly gross salary including all taxes (also paid by the employer) (in national currency)? Provide data for year 2017 - if not available, then earlier (please specify).	Data source

Instructions for the remaining part of the questionnaire

The remaining part consists of four sections: diagnostics, treatment, other medical services, and end of life management; in which we ask for different kind of resources. As treatment patterns may evolve in time, in each section, we separately ask for data for newly (≤12 months before) diagnosed patients and other patients (i.e. patients after progression to a given stage or having been diagnosed >12 months ago). We believe averaging values for so different patients could be cumbersome. To understand the resource consumption, we ask about the percentage of patients in whom the procedure is used and the average number of procedures used per year (amongst patients who use it at least once). We also ask about the unit cost (both from public payer and patient perspective). Please follow the suggestions below.

1. Please try to provide data split by stage. If not possible, stages III and IV jointly. In some cases, we ask for overall BC population.
2. Several medical procedures may be financed jointly within some broad category (e.g. a DRG) – in such cases please provide data on this broadest category only. Report all the procedures which are financed separately (e.g. are not included in hospitalization tariff) and ignore procedures which are included in hospitalization tariff etc., i.e. avoid double counting.
3. In the diagnostics section, some procedures are used only in newly diagnosed (e.g. biopsy), while others are also used during monitoring of the disease. Please note that we ask for these groups separately (i.e. newly diagnosed vs other patients).
4. In the treatment section, for some procedures (e.g. surgery) we need only data for stage III and IV BC (if split data are not available, then for ABC population jointly). However, for drug therapies we need data for each stage, ABC jointly, as well as the overall BC population. This will allow us to estimate relationship between cost in BC and ABC (split by stage) and will be further used for countries where detailed data are not available.
5. If you have a publication with costs (e.g. hormonal therapy) calculated, please provide the average cost (with the information about the data source and year for which it was calculated). However, try also to provide the detailed data: the method of cost estimation used in the publication may differ from the method used in other countries and may not include all currently available drugs.
6. Use your national currency. Whenever data are outdated and inflation should be accounted for, report this and provide details.
7. Please provide references. This will be needed, e.g. when preparing publication.
8. Add new rows if needed.

Diagnostics

Newly diagnosed patients

Proportion of patients

		% of patients receiving			Data source	Comments
		Stage III	Stage IV	ABC jointly (if split not available)		
Imaging tests	Mammography					
	Ultrasound					
	Magnetic resonance imaging					
Biopsy	Fine needle aspiration biopsy					
	Core needle biopsy					
	Image-guided biopsy					
	Surgical biopsy					
Diagnostic testing	ER and PR status					
	HER2 status					
Laboratory tests	Histology					
	Cytology					
	Other*					
Radiological investigation	Chest X-ray					
	CT scan					
	PET scan					
	Other*					
* please name						

Resource consumption

		Resource usage (#/year)			Data source	Comments
		Stage III	Stage IV	ABC jointly (if split not available)		
Imaging tests	Mammography					
	Ultrasound					
	Magnetic resonance imaging					
Biopsy	Fine needle aspiration biopsy					
	Core needle biopsy					
	Image-guided biopsy					
	Surgical biopsy					
Diagnostic testing	ER and PR status					
	HER2 status					
Laboratory tests	Histology					
	Cytology					
	Other*					
Radiological investigation	Chest X-ray					
	CT scan					
	PET scan					
	Other*					
* please name						

Patients after progression or >12 months after the diagnosis

Proportion of patients

		% of patients receiving			Data source	Comments
		Stage III	Stage IV	ABC jointly (if split not available)		
Imaging tests	Mammography					
	Ultrasound					
	Magnetic resonance imaging					
Diagnostic testing	ER and PR status					
	HER2 status					
Laboratory tests	Histology					
	cytology					
	Other*					
Radiological investigation	Chest X-ray					
	CT scan					
	PET scan					
	Other*					
* please name						

Resource consumption

		Resource usage (#/year)			Data source	Comments
		Stage III	Stage IV	ABC jointly (if split not available)		
Imaging tests	Mammography					
	Ultrasound					
	Magnetic resonance imaging					
Diagnostic testing	ER and PR status					
	HER2 status					
Laboratory tests	Histology					
	cytology					
	Other*					
Radiological investigation	Chest X-ray					
	CT scan					
	PET scan					
	Other*					
* please name						

Unit costs

		Unit cost		Data source	Comments (e.g. year)
		Public payer	Patient		
Imaging tests	Diagnostic mammography				
	Ultrasound				
	Magnetic resonance imaging				
Biopsy	Fine needle aspiration biopsy				
	Core needle biopsy				
	Image-guided biopsy				
	Surgical biopsy				
Diagnostic testing	ER and PR status				
	HER2 status				
Laboratory tests	Histology				
	cytology				
	Other*				
Radiological investigation	Chest X-ray				
	CT scan				
	PET scan				
	Other*				
* please name					

Treatment

Newly diagnosed patients

Proportion of patients

		% of patients receiving				Data source	Comments
		Stage III	Stage IV	ABC jointly	BC overall		
Surgery (%)	Lumpectomy*				X		
	Mastectomy				X		
	Sentinel lymph node biopsy				X		
	Axillary lymph node dissection				X		
Breast reconstruction				X			
External breast prosthesis				X			
Radiation therapy				X			
Chemotherapy				X			
Hormonal therapy	Fulvestrant						
	Tamoxifen						
	Aromatase inhibitors						
	Ovarian suppression						
	Other**						
	Overall#						
Targeted therapy	Ado-trastuzumab emtansine						
	Trastuzumab						
	Pertuzumab						
	Lapatinib						
	Everolimus						
	CDK4/6 inhibitors						
	Other**						
	Overall#						
Treatment related to AE drugs or other treatment complications^	Please name and add rows if needed						
Other treatment services**							

* a lumpectomy may also be called breast-conserving surgery (BCS), a partial mastectomy, quadrantectomy, or a segmental mastectomy
** please name
# if detailed data are not available, provide overall data
^ please consider e.g. analgesics (ATC group N02), antineoplastics (ATC group L01), antiemetics (ATC group A04)

Resource consumption

		Resource usage (#/year)				Data source	Comments
		Stage III	Stage IV	ABC jointly	BC overall		
Surgery (%)	Lumpectomy*				X		
	Mastectomy				X		
	Sentinel lymph node biopsy				X		
	Axillary lymph node dissection				X		
Breast reconstruction				X			
External breast prosthesis				X			
Radiation therapy				X			
Chemotherapy				X			
Hormonal therapy	Fulvestrant						
	Tamoxifen						
	Aromatase inhibitors						
	Ovarian suppression						
	Other**						
	Overall#						
Targeted therapy	Ado-trastuzumab emtansine						
	Trastuzumab						
	Pertuzumab						
	Lapatinib						
	Everolimus						
	CDK4/6 inhibitors						
	Other**						
	Overall #						
Treatment related to AE drugs or other treatment complications^	Please name and add rows if needed						
Other treatment services**							

* a lumpectomy may also be called breast-conserving surgery (BCS), a partial mastectomy, quadrantectomy, or a segmental mastectomy
** please name
# if detailed data are not available, provide overall data
^ please consider e.g. analgesics (ATC group N02), antineoplastics (ATC group L01), antiemetics (ATC group A04)

Patients after progression or >12 months after the diagnosis

Proportion of patients

		% of patients receiving				Data source	Comments
		Stage III	Stage IV	ABC jointly	BC overall		
Surgery (%)	Lumpectomy*				X		
	Mastectomy				X		
	Sentinel lymph node biopsy				X		
	Axillary lymph node dissection				X		
Breast reconstruction				X			
External breast prosthesis				X			
Radiation therapy				X			
Chemotherapy				X			
Hormonal therapy	Fulvestrant						
	Tamoxifen						
	Aromatase inhibitors						
	Ovarian suppression						
	Other**						
	Overall#						
Targeted therapy	Ado-trastuzumab emtansine						
	Trastuzumab						
	Pertuzumab						
	Lapatinib						
	Everolimus						
	CDK4/6 inhibitors						
	Other**						
	Overall#						
Treatment related to AE drugs or other treatment complications^	Please name and add rows if needed						
Other treatment services**							

* a lumpectomy may also be called breast-conserving surgery (BCS), a partial mastectomy, quadrantectomy, or a segmental mastectomy
** please name
# if detailed data are not available, provide overall data
^ please consider e.g. analgesics (ATC group N02), antineoplastics (ATC group L01), antiemetics (ATC group A04)

Resource consumption

		Resource usage (#/year)				Data source	Comments
		Stage III	Stage IV	ABC jointly	BC overall		
Surgery (%)	Lumpectomy*				X		
	Mastectomy				X		
	Sentinel lymph node biopsy				X		
	Axillary lymph node dissection				X		
Breast reconstruction				X			
External breast prosthesis				X			
Radiation therapy				X			
Chemotherapy				X			
Hormonal therapy	Fulvestrant						
	Tamoxifen						
	Aromatase inhibitors						
	Ovarian suppression						
	Other**						
	Overall #						
Targeted therapy	Ado-trastuzumab emtansine						
	Trastuzumab						
	Pertuzumab						
	Lapatinib						
	Everolimus						
	CDK4/6 inhibitors						
	Other**						
	Overall #						
Treatment related to AE drugs or other treatment complications^	Please name and add rows if needed						
Other treatment services**							

* a lumpectomy may also be called breast-conserving surgery (BCS), a partial mastectomy, quadrantectomy, or a segmental mastectomy
** please name
# if detailed data are not available, provide overall data
^ please consider e.g. analgesics (ATC group N02), antineoplastics (ATC group L01), antiemetics (ATC group A04)

Unit costs

		Unit cost		Data source	Comments (e.g. year)
		Public payer	Patient		
Surgery (%)	Lumpectomy*				
	Mastectomy				
	Sentinel lymph node biopsy				
	Axillary lymph node dissection				
Breast reconstruction					
External breast prosthesis					
Radiation therapy					
Chemotherapy					
Hormonal therapy	Fulvestrant				
	Tamoxifen				
	Aromatase inhibitors				
	Ovarian suppression				
	Other**				
	Average cost#				
Targeted therapy	Ado-trastuzumab emtansine				
	Trastuzumab				
	Pertuzumab				
	Lapatinib				
	Everolimus				
	CDK4/6 inhibitors				
	Other**				
	Average cost#				
Treatment related to AE drugs or other treatment complications^	Please name and add rows if needed				
Other treatment services**					

* A lumpectomy may also be called breast-conserving surgery (BCS), a partial mastectomy, quadrantectomy, or a segmental mastectomy
** please name
^ please consider e.g. analgesics (ATC group N02), antineoplastics (ATC group L01), antiemetics (ATC group A04)

Other medical services

Proportion of patients

		% of patients receiving			Data source	Comments
		Stage III	Stage IV	ABC jointly (if split not available)		
INPATIENT SERVICES						
Acute hospital admissions						
OUTPATIENT SERVICES						
Physician offices	Primary care doctor					
	Oncologist					
	Radiation oncologist					
	Breast surgeon					
	Psychologist					
	Other*					
Emergency room						
Other outpatient services*						

* please name

Resource consumption

		Resource usage (#/year)			Data source	Comments
		Stage III	Stage IV	ABC jointly (if split not available)		
INPATIENT SERVICES						
Acute hospital admissions						
Average # of days in hospital						
OUTPATIENT SERVICES						
Physician offices	Primary care doctor					
	Oncologist					
	Radiation oncologist					
	Breast surgeon					
	Psychologist					
	Other*					
Emergency room						
Other outpatient services*						
* please name						

Unit costs

		Unit costs		Data source	Comments (e.g. year)
		Public payer	Patient		
INPATIENT SERVICES					
Acute hospital admissions					
OUTPATIENT SERVICES					
Physician offices	Primary care doctor				
	Oncologist				
	Radiation oncologist				
	Breast surgeon				
	Psychologist				
	Other*				
Emergency room					
Other outpatient services*					
* please name					

End of life

How many patients with stage III or IV BC are given end-of-life treatment? Please provide the proportion of patients (among those who died), preferably split by stage.	Data source

What is the proportion of patients treated in hospitals, palliative centres, etc.?	Data source
Are there any specific therapies these patients (treated in hospitals, palliative centres, etc.) receive during this period (not included previously as to avoid double counting)? If yes, please name them and provide data regarding resource consumption and unit costs (both from public payer and patient perspective).	Data source

What is the proportion of patients treated at home?	Data source
Are there any specific therapies these patients (treated at home) receive during this period (not included previously as to avoid double counting)? If yes, please name them and provide data regarding resource consumption and unit costs (both from public payer and patient perspective).	Data source

What is the proportion of patients treated in other places, e.g. hospice, nursery/residential (please name)?	Data source
Are there any specific therapies these patients (treated in other places) receive during this period (not included previously as to avoid double counting)? If yes, please name them and provide data regarding resource consumption and unit costs (both from public payer and patient perspective).	Data source

Online Resource 2

Tab. 1. Data sources.

Country	Data source					
	Epidemiology	Economic activity	Proportion of patientsa	Resource consumptiona	Unit costsa	End of life
Bulgaria	Squilline virtual database, National Cancer Registry	National statistical institute, Expert opinion	Squilline virtual database, NHIF, Bulgarian standards for treatment of oncology diseases	Bulgarian standards for treatment of oncology diseases, NCPR	NHIF, NCPR	—
Croatia	Croatia Cancer registry	Croatian Bureau of Statistic	Clinical Hospital Center "Sisters of Mercy" – Clinic for tumors	Clinical Hospital Center "Sisters of Mercy" – Clinic for tumors	DTS list of CHIF, CHIF – list of reimbursed products	—
Czech Republic	IHIS, NRRHS	Czech Statistical Office, Information system - Incapacity for Work	NRRHS, IHIS	NRRHS, IHIS	NRRHS	National Registry of Hospitalized
Estonia	Health Statistics and Health Research Database, National Institute for Health Development	Statistics Estonia	NHIF	NHIF	NHIF	—
Greece	Global cancer observatory, Expert opinion, ELSTAT (Hellenic Statistical Authority)	ELSTAT, Single social security entity (EFKA)	Kotsakis 2019, Expert opinion	Expert opinion	Government Gazzette, Price Bulletin	—
Israel	MoH website	OECD website, Central Bureau of statistics	Expert opinion	Expert opinion	MoH Price list, Yarpa – update price list for Prescription Medicines	Expert opinion
Latvia	Centre for Disease Prevention and Control of Latvia	Latvian oncology centre clinical data base, Central Statistical Bureau of Latvia	Latvian oncology centre clinical data base, HCP opinion	Latvian oncology centre clinical data base, HCP opinion	MK regulation (Regulations of the Cabinet of Ministers)	—
Poland	Polish National Cancer Registry, Hospital database, Expert opinion	Central Statistical Office	Expert opinion	Expert opinion	Minister of Health - list of reimbursed drugs	—
Romania	North Western Cancer Registry, National Institute of Public Health CNSISP Mortality Database	National Institute of Statistics, Expert opinion	Cluj Napoca Regional Oncologic Institute	Cluj Napoca Regional Oncologic Institute	Cluj Napoca Regional Oncologic Institute, Methodological Norms National Health Programs, Reimbursed Drug List, Methodological Norms Framework Contract Health Benefit Package	Cluj Napoca Regional Oncologic Institute
Slovak Republic	NHIC	Statistical Office of the Slovak Republic, Social Insurance Agency in Slovakia	Expert opinion	Expert opinion	No information	—

a for three categories of direct medical costs: diagnostics, treatment, and other medical services
CHIF — Croatian Health Insurance Fund; IHIS — Czech National Cancer Registry; MoH — Ministry of Health; NRRHS — National Registry of Reimbursed Health Services; NCPR — National Council on pricing and reimbursement of medicinal products; NHIC — National health information center; NHIF — National Health Insurance Fund.

Online Resource 3

Tab. 2. Annual disease specific mortality.		
Country	Number of BC deaths yearly	Annual disease specific mortality rate
Bulgaria	1 344	2.6%
Croatia	853	3.5%
Czech Republic	1 937	2.2%
Estonia	241	2.8%
Greece	2 163	3.7%
Israel	1 026	4.6%
Latvia	426	3.1%
Poland	6 493	3.7%
Romania	3 558	7.0%
Slovak Republic	1 054	4.1%
BC — breast cancer		

Online Resource 4

Tab. 3. The age structure for mortality per country (totals to 100% in each column).									
Age	Croatia	Czech Republic	Estonia	Greece	Latvia	Poland	Romania	Slovak Republic	Mean
≤20 years	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
21-30 years		0.3%	0.0%	0.1%	0.0%	0.1%	0.1%	0.2%	0.1%
31-40 years	1.8%	2.3%	2.1%	2.1%	1.2%	2.2%	2.0%	2.8%	2.1%
41-50 years	5.5%	6.0%	6.2%	6.4%	6.3%	6.2%	8.9%	5.3%	6.4%
51-60 years	13.6%	10.4%	13.7%	11.9%	14.6%	15.8%	14.7%	14.3%	13.6%
61-70 years	21.8%	22.1%	20.3%	17.7%	23.5%	26.5%	26.1%	26.1%	23.0%
71-80 years	29.3%	27.5%	27.8%	22.1%	27.0%	21.5%	26.0%	23.8%	25.6%
≥81 years	27.8%	31.5%	29.9%	39.7%	27.5%	27.7%	22.2%	27.5%	29.2%

Online Resource 5

Tab. 4. Employment rate in the specific country.		
Country	Employment rate	
	ABC populationa	General population
Bulgaria	40.0%	66.9%
Croatia	52.5%	87.9%
Czech Republic	46.9%	78.5%
Estonia	47.0%	78.7%
Greece	34.5%	57.8%
Israel	41.3%	69.1%
Latvia	39.0%	65.3%
Poland	38.5%	64.5%
Romania	33.3%	55.8%
Slovak Republic	42.5%	71.1%
a the primary data were available only for Latvia, this is results of our calculation. ABC — advanced breast cancer.		

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