Indirect costs in patients with breast cancer: protocol for a systematic review

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Protocol

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Abstract

Background:

The rising incidence of breast cancer places a financial burden on national health services and economies. The cost of breast cancer studies is constantly increasing; however, this cost is calculated based on the currency of the country in which the study takes place, therefore limiting national and international comparisons. On the other hand, there is no common method used to conduct such studies. The objective of this review is to contribute to this knowledge pool by examining the indirect costs of breast cancer in order to provide comparable estimates.

Methods and analysis:

This review will consider all relevant cost of illness studies dated from the year 2000 until the year 2018. Relevant papers will be identified through a systematic search in all major medical research databases. Two independent researchers will screen selected articles. Methodological quality of the studies will be assessed using a checklist designed by Stunhldreher et al.

Discussion:

The results will be presented in line with the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) checklist. While the costs of breast cancer studies are helpful in planning health interventions in terms of the severity of the problem and budget priorities, the results could also be of great help to policymakers and decision makers in health systems.

Study registration number: PROSPERO CRD42018108392

Background:

Breast cancer is the most commonly occurring cancer in women, with over 1.3 million new cases reported globally every year, and more than 450,000 related deaths(1, 2). It is considered one of the major health issues in the world today(3). According to the American Cancer Society(4), one in eight women will experience breast cancer during her life. The Organization for Economic Co-operation and Development (OECD) reports that breast cancer is the third leading cause of death in women, after colorectal cancer and lung cancer. The global incidence of breast cancer in women is estimated to reach as many as 3.2 million new cases annually by the year 2050(4). The three cancers with the highest economic burden in the world are lung cancer ($188 billion), colon/rectal cancer ($99 billion) and breast cancer ($88 billion) (5).

Health policymakers and planners are keen to understand the cost-effectiveness of diseases in order to assess the allocation of health resources to various diseases, and examine the potential costs and benefits of public health interventions(6). The cost of illness is investigated using a variety of methods(7). From a social perspective, the cost of a disease consists of three main components: direct

costs, indirect costs, and intangible costs. The monetary value of lost productivity, which results from illness or premature death and recognized as indirect costs, is responsible for a relatively large part of disease costs and significantly affects the results of economic assessments(8-10) .

Indirect costs are an important component of costs of illness studies, especially in the management of chronic diseases that may require lifelong treatment(11).

Breast cancer in many women can cause long-term disability and can significantly affect their financial and social wellbeing(12, 13) . In addition to medical and therapeutic expenses, women must shoulder the costs pertinent to missed work days or loss of productivity in paid employment or at home (14-21) . The risk of job loss among people diagnosed with cancer is 1.3 times higher than those without cancer(12). Even when diagnosed at an early stage, breast cancer can adversely affect an individual's ability to work for up to 5 years after the original diagnosis(22).

Factors associated with impaired productivity include adverse effects and treatments such as progression and exacerbation of disease, cognitive and neurological disorders, poor physical and mental health, chemotherapy, and the time and cost required to receive treatment(23).

In a 2016 American study, nonelderly women with breast cancer, compared with other people, significantly experienced job incapacity (13.6%), including reduced productivity at work (7.2 days) and at home (3.3 days)(24) .

Absenteeism can vary from a few weeks to several months. Many people may return to work, but their hours of work may be decreased due to reduced productivity or employer disagreement. For example, in a 2013 study, reduction in productivity due to adverse effects from breast cancer in the Netherlands and Sweden was 68% and 72% respectively(25). Some patients may never return to work due to disability or premature death.

Lung and female breast are the leading cancers worldwide in terms of the number of new cases diagnosed annually. For each of these cancers, approximately 2.1 million diagnoses were estimated in 2018, or 11.6% of the total cancer incidence burden(26).

A 2008 study in California, USA, showed that on average, a premature death from breast cancer can result in loss of productivity worth $272,000 and the loss of as many as 22.9 years of life(27). Additionally, in 2002 the productivity cost of breast cancer in Sweden was estimated to be 2.1 billion SEK, and over 50% of this (1.1 billion) was due to premature death(28).

In Iran in 2010, the economic burden of breast cancer was estimated to be more than $947 million. More than 70% of this figure is due to productivity lost as a result of death from breast cancer(29).

Despite the simplicity of expressing the components of indirect costs, the proper method of measuring and evaluating the lost productivity of breast cancer can be problematic. There are several methods to measure indirect costs(29). The most accurate estimation of indirect costs requires the use of micro-

costing methods; thus, it requires relatively large sample sizes, well-designed protocols, and well-trained interviewers(7, 30) . In an economic evaluation, the methods used for the measurement and evaluation of lost productivity can affect the results of the studies(29). The use of different methods for calculating the lost productivity may impede the comparison of results between countries. Possible reasons for the differences in indirect costs include methodology, the value of local productivity, disease and patient characteristics, social security systems and epidemiologic environments(31).

Therefore, the primary goal of this study is to systematically review the indirect costs and the monetary value of lost productivity due to breast cancer. The second goal is to examine the methods used in cost of illness studies and economic burden studies to measure and value indirect costs.

Methods:

Eligibility criteria:

Indirect costs are defined as the costs of breast cancer on labor market outcomes (absenteeism, presenteeism, short and long-term disability and premature death). Studies will be selected according to the following criteria.

Type of participants:

Female breast cancer patients

Type of interventions:

There will be no filters for interventions. In the majority of cost of illness studies, intervention is not a primary concern. This protocol will consider all possible treatments for breast cancer.

Types of outcome measures:

Indirect costs due to breast cancer.

Type of studies:

Cost of illness studies which include estimates of indirect costs of breast cancer at a municipal level (for example, city, state, country) or within certain organizations (for example, at employer level, or within health insurance companies).

Exclusion criteria:

- Studies other than cost of illness studies
- Economic evaluation studies
- Reviews, letters, abstracts, conference papers, methodological and general commentary or perspectives
- Studies without English language titles and abstracts

Search strategy:

Mesh term and Emtree:

In order to include all relevant studies, a search of Medline (via PubMed; using Mesh Terms), EMBASE (using Emtree), as well as some full text articles in this field, will be conducted for keywords. Keywords that will be used for building the search strategy include:

Indirect cost: (“Indirect cost” OR “Cost of illness” OR “Illness Cost” OR “Sickness Cost” OR (Costs AND Sickness) OR “Burden of Illness” OR “Illness Burden” OR “Cost of Disease” OR “Economic Burden of Disease” OR “Disease Cost” OR (Cost AND Disease) OR “Disease Costs” OR “Cost of Sickness” OR “Sickness Costs” OR “Costs of Disease” OR “Cost-of-illness” OR “Productivity costs” OR “Productivity lost” OR “Productivity loss” OR “Presenteeism cost” OR “Absenteeism cost” OR “Human capital” OR “Economic burden”)

Breast cancer: ("Breast Neoplasm" OR "Breast Tumors" OR "Breast Tumor" OR "Breast Carcinoma" OR "Breast Carcinoma" OR "Human Mammary Neoplasm" OR "Human Mammary Neoplasms" OR "Breast Cancer" OR "Mammary Cancer" OR "Mammary Cancers" OR "Malignant Neoplasm of Breast" OR "Breast Malignant Neoplasm" OR "Breast Malignant Neoplasms" OR "Malignant Tumor of Breast" OR "Breast Malignant Tumor" OR "Breast Malignant Tumors" OR "Cancer of Breast" OR "Cancer of the Breast" OR "advanced breast cancer" OR "breast cancer recurrence" OR "breast gland cancer" OR "breast gland neoplasm" OR "mamma cancer" OR "mammary gland cancer"

Electronic databases:

The following electronic databases will be searched: (1) The Cochrane Library; (2) PubMed; (3) Web of Science; (4) Scopus; (5) ProQuest; (6) Google scholar; (7) EMBASE.

Date of search:

Searches of electronic databases were carried out by December 31, 2018, with no starting date limitation.

Grey literature:

All conference abstracts and posters written in English will be considered (by handsearching).

Handsearching:

Reference lists of identified studies will be reviewed to include all relevant studies.

Restriction of language:

Study will include all articles in English language.

Contact the authors:

If the full text of articles is not available, the authors will be contacted three times.

Data collection:

Screening of studies for eligibility (selection process):

The first step will be the import of all search results into EndNote and the subsequent removal of duplicates. Screening will then be conducted in two phases. First, title and abstract screening will be undertaken by one of the members of the research team to identify publications that do not meet the inclusion criteria. In doubtful cases, the publications will be included. Next, two reviewers will independently screen the full texts of the selected publications to match the eligibility criteria. Disagreements will be resolved through discussion and the reasons for exclusion will be recorded.

Collection data process:

The following data will be extracted: the author's name, publication year, reference year for cost, region, number of patients, methodology of the study, components of indirect costs, and estimated indirect costs per patient.

Assessment of study quality:

Quality will be assessed using a checklist for cost of illness (COI) designed by Stunhldreher et al (32).

The following items will be assessed: scope, general economic characteristics, and calculation of costs, study design and analysis and presentation of results. Two members of the research team will independently perform the assessment and any discrepancies and uncertainties will be resolved through consensus.

Data synthesis (analysing, interpreting and reporting results):

The data will be analysed using Stata statistical Software 12.0 (Stata Crop, College Station, Texas, The USA).

Dealing with missing data:

If the year of costing is missing an email will be sent to the authors of the COI study.

Assessment of heterogeneity:

Heterogeneity will be tested using Q-statistics with 95% CI. To examine the extent of heterogeneity, I^2 will be computed.

Data synthesis:

The researchers will employ appropriate analytical methods to summarize the results of the study. If applicable, a meta-analysis of resource use or cost data may be considered. In addition to reporting the characteristics of included studies, a summary table of various checklists completed to inform assessments of the methodological quality of cost of illness studies will be presented.

Costs will be presented in real currency (as of the year of study or adjusted to current year), as this will be relevant for readers in the country in which the study takes place. In addition, in order to facilitate comparisons of cost estimates collected from different studies, an international exchange rate based on purchasing power parities (PPPs) will be used to convert cost estimates into a target currency - international dollars. GDP deflators will be used to convert cost estimates into a fixed price year.

Publication bias will be detected by funnel plot.

Subgroup analysis and investigation of heterogeneity:

Subgroup analysis will be used to explore possible sources of heterogeneity, based on the following criteria:

- Patient characteristic (such as age)
- Approach of studies (such as human capital and friction cost)

Sensitivity analysis will be performed to explore the source of heterogeneity as follows:

- Quality components, including full-text publications versus abstracts, published versus unpublished data
- Risk of bias (by omitting studies that are judged to be at high risk of bias)

Summary of findings:

Results of this review will be reported in line with the PRISMA 2009 checklist. The overall quality of evidence on outcomes will be presented using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach, which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The overall quality of evidence will be rated at four levels: high, moderate, low and very low. It is hoped that policymakers will use this document. This protocol describes a systematic review of the indirect costs of breast cancer. Eventual gaps identified in this systematic review could have a significant impact on current public health policies and will highlight areas that need additional research. It will underline challenges that need to be accounted for in future cost of illness studies. The review will also present current data on indirect costs of breast cancer as newer studies have been carried out since the publication of previous reviews.

The findings from this review will be submitted for publication in peer-reviewed journals. They will be shared with decision-makers and health professionals. The researchers will also disseminate the findings through professional conferences, health economists, and public health policymakers. The results of this study will provide policy-relevant recommendations for uptake of cost of illness studies in prioritizing decisions on essential breast cancer care packages.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7-8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7-8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation

and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

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Declarations:

Ethical Approval and Consent to participate:

Iran University of Medical Science approved the study, Ethics code is IR.IUMS.REC 1396.31006

Consent for publication:

Authors agree to publish.

Availability of supporting data:

Not applicable.

Competing interests:

All authors have no conflicts of interest to declare.

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Authors' contributions:

SM, RJ and SS drafted the manuscript. All authors contributed to the conception and design of the protocol and critical review for intellectual content and approved the final version of the manuscript submitted for publication.

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- PRISMAPchecklist.doc