Cost of Oral Cancer: Protocol for a Systematic Review

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Protocol

Keywords: Oral Cancer, Cost of Illness, Systematic Review

Posted Date: June 12th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-34637/v1>

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Abstract

Background: Cancer care is among the costliest in the social sphere. Oral cancer (OC) is a chronic disease whose incidence has been growing worldwide. The lack of economic evaluation studies assessing the economic impact of OC, as well as the need to search for evidence of the economic burden of OC motivated this investigation. This study aims to collect evidence on the cost of OC (lip cancer - LC, oral cavity cancer - OCC and oropharyngeal cancer - OPC) worldwide.

Methods: A systematic review will be conducted take into consideration any perspective. The primary outcome will be the costs related to oral cancer in patients, reported in monetary units. Specific breakdown of costs will be reported (direct hospital costs, rehabilitation care costs, direct non-healthcare costs, indirect costs and productivity loss, and intangible costs). SCOPUS, WEB OF SCIENCE, COCHRANE and BVS databases will be searched. Original studies on cost of OC that assess its cost based on components as: hospital and/or outpatient, promotion and prevention will be included. It will be excluded types of study such as: editorial, letters, reviews, case reports, case series, clinical trials, studies that address specific analysis, such as cost-effectiveness, cost-utility, cost-benefit, cost-minimization. A systematic meta-narrative synthesis will be presented. Data on quantities of health and social resource consumption, currencies used and whether studies show total or incremental costs will be collected.

Discussion: The identification of evidence on the economic burden of LC, OCC and OPC will allow the determination of the contribution share of each sector of society in the total economic burden of oral cancer. Also, this evidence will favour the estimate of the impact that the reduction of the OC burden would have on its associated costs and better guide the choice decision, to optimize the benefits.

Systematic review registration: PROSPERO ID number 172471.

Background

Cost of illness (COI) studies are methods used to estimate the economic and social impact of a disease, the results of which, expressed in monetary value, can assist in decision-making in the health sector [1,2]. In addition, COI can indicate the impact that reducing a disease burden would have on its associated costs. By saving financial resources for preventable disease treatment, the opportunity to invest in the supply of health-promoting goods and services is gained [2].

Oral cancer (OC) is a chronic disease predominantly in those aged over 50 years, the incidence of which has been growing worldwide, as the global population ages [3-5]. Among the regions with the highest incidence of this cancer are South and Southeast Asia, regions of Western and Eastern Europe, parts of Latin America and the Caribbean, and Pacific regions [3]. Brazil is among the Latin American countries with the highest incidence of oral and oropharyngeal cancer [3] and does not have a defined public policy aimed at preventing oral cancer.

Cancer care is among the costliest in the social sphere, as it includes not only direct costs with preventive tests, diagnostic tests and treatments, but indirect costs resulting from the patient's productive disability and cancer-related morbimortality and (or) its treatment [6,7].

From an economic point of view, resources in the health sector are scarce and finite and demand is increasing, a scenario that is being exacerbated by the rising prices of goods and services, incorporation of new technologies, restriction of health resources, restructuring of services, and an increase in the global population and life expectancy. Thus, increasingly, the search for allocative resource efficiency has been paramount. In this context, health economic

assessments are crucial tools for resource use decisions and alternative allocation choices based on comparative cost and consequence analyses with the aim of optimizing health resources [1,8,9].

The lack of economic evaluation studies assessing the economic impact of OC in the context of dentistry, as well as the need to search for evidence of the economic burden of OC [10] motivated this study, which aims to investigate the evidence on the cost of OC worldwide.

Methods

A systematic review of studies revealing the costs of lip cancer (LC), oral cavity cancer (OCC), and oropharyngeal cancer (OPC) will be conducted take into consideration any perspective (societal, third-party players, public systems). The method used will be guided by the concepts of the Joanna Briggs Institute (JBI) [11] and the study description by the PRISMA recommendation [12] and its extension, PRISMA-P [13].

The stage of progress of the review has completed preliminary searches (problem specification, concept mapping) and started piloting of the study selection process. All steps are described below.

Problem specification

What is the cost of oral cancer?

The problem elements of the research question guided the selection of the acronym that best represented them (PEO – Population, Exposure, Outcome), in order to systematically define the subject descriptors for the formulation of the search strategy. The population (P) considered for publication searching was any individual (human) or groups of individuals, without restriction of age, sex, race or socioeconomic status, who were exposed (E) to oral cancer, considered here as LC, OCC or OPC. The outcome (O) required in the publications was information on direct (medical and non-medical) and indirect (lost productivity and death) costs.

Concept mapping

To determine the search strategy, descriptors were selected by building a table (concept mapping). The table rows were allocated for each letter of the acronym PEO and the columns for PubMed controlled vocabulary terms (Medical Subject headings – MeSH), their subcategories (entry terms; see also), and uncontrolled vocabulary (free terms) usually obtained from titles and abstracts of the main publications, books and grey literature on the research theme (Table 1).

As there was no restriction on the population of the studies to be searched, descriptors were not selected for “P”. The definition of exposure descriptors (E) involved the search for MeSH terms and their subcategories related to the disease (OC), its anatomical locations (lip, oral cavity, oropharynx, head and neck) and the main type of neoplasia that occurs in these regions i.e., squamous cell carcinoma. To identify the descriptors of the controlled vocabulary for the outcome (O) we used the terms “cost of illness” and “economics”.

After the PubMed MeSH controlled vocabulary tree was explored for each of the letters of the PEO acronym and the concept mapping was complete, the terms were tested in the PubMed database and the number of publications was verified. The search test for terms defined as MeSH was performed using the “[mesh]” tag in front of them; for the

terms classified as “entry terms” and “see also” the tag was “[tiab]”, which means that the term was searched for in the titles and summaries of database publications. For the “free term” search test no tags were used.

To select the most relevant descriptors, three criteria were used to exclude them from the map:

- Those terms that assessed fewer than 10% of the publications identified by the corresponding MeSH term;
- Terms allocated in the lower level of the hierarchical tree of their respective MeSH;
- If by combining the term with its MeSH, using the Boolean operator “OR”, there was no change in the number of publications assessed, which meant that the publications resulting from the search for that term were already included in the search using the MeSH, the combined term was also deleted from the map.

Literature search

After clearing the concept mapping (Table 1), removing the less relevant terms, we grouped all the terms related to the same letter of the acronym PEO using the Boolean operator “OR”. The intersection of the resulting sets of this grouping of terms was performed with the Boolean operator “AND”, thus defining the search strategy.

Terms related to Population (P)	Terms related to (Exposition - E) oral cancer and connected among themselves by "OR"	Terms related to (Outcomes - O) costs and connected among themselves by "OR"
<p>There was no restriction on the population of the studies to be searched and descriptors were not defined for "P". However, during the search a filter that restricts the search to studies in "humans" will be used.</p>	<ol style="list-style-type: none"> 1. Mouth [MeSH] 2. Lip [MeSH] 3. Tongue [MeSH] 4. Oropharynx [MeSH] 5. Neoplasms [MeSH] 6. Squamous Cell Carcinoma of Head and Neck [MeSH] 7. Mouth Neoplasms [MeSH] 8. Head and Neck Neoplasms [MeSH] 9. Lip Neoplasms [MeSH] 10. Tongue Neoplasms [MeSH] 11. Oropharyngeal Neoplasms [MeSH] 12. Mouth [Tiab] 13. Oral Cavity [Tiab] 14. Lip [Tiab] 15. Lips [Tiab] 16. Tongue [Tiab] 	<ol style="list-style-type: none"> 33. Costs and Cost Analysis [MeSH] 34. Economics [MeSH] 35. Cost of Illness [MeSH] 36. Health Care Costs [MeSH] 37. Hospital Costs [MeSH] 38. Economic Medical [MeSH] 39. Global Burden of Disease [MeSH] 40. Consumption [Tiab] 41. Production [Tiab] 42. Expenditures, Out-of-Pocket [Tiab] 43. Expenditure, Out-of-Pocket [Tiab] 44. Expenditures, Out of Pocket [Tiab] 45. Cost, Out-of-Pocket [Tiab] 46. Costs, Out-of-Pocket [Tiab] 47. Expenditure, Out-of Pocket [Tiab] 48. Expenditures Out-of Pocket [Tiab] 49. Expenditures [Tiab] 50. Expenditure [Tiab] 51. Health care costs [Tiab] 52. Hospital Costs [Tiab]

17. Oropharynx [Tiab]	53. Hospital Cost [Tiab]
18. Tumors [Tiab]	54. Economics Medical [Tiab]
19. Tumor [Tiab]	55. Medical Economics [Tiab]
20. Cancer [Tiab]	56. Management, Office [Tiab]
21. Oral Cancer [Tiab]	57. Global Burden of Disease [Tiab]
22. Neoplasms, Neck [Tiab]	
23. Neoplasm, Lip [Tiab]	
24. Lip Cancer [Tiab]	
25. Neoplasm, Tongue [Tiab]	
26. Neoplasms, Tongue [Tiab]	
27. Tongue Cancer [Tiab]	
28. Neoplasm, Oropharyngeal	
29. Neoplasm, Oropharynx	
30. Neoplasms, Oropharynx	
31. Neoplasms, Oropharyngeal	
32. Oropharyngeal Cancer	

MeSH= Medical Subject Headings; Tiab= Title and abstract

Table 1
Concept mapping after removal of less relevant descriptive terms

Subtitle: Less relevant descriptive terms, identified by searching tests of all terms found in PubMed controlled vocabulary (MeSH terms, entry terms, see also) for each letter of the selected acronym: P (population), E (exposition) and O (outcome). MeSH= Medical Subject Headings; Tiab= Title and abstract

Publications from 2008 to March 2020 were searched in PubMed, using a filter to restrict results to human studies, with no restriction of language or study design.

The search strategy defined for PubMed will be adapted for searches in the following databases: SCOPUS, WEB OF SCIENCE, COCHRANE and BVS (Biblioteca Virtual em Saúde).

The number of publications identified in each database as well as duplicates will be recorded as recommended by the PRISMA standard [12] (Figure 1).

All publications identified in the databases will be exported to the Mendeley Reference Manager (Mendeley®, Elsevier, version 1.19.5/20019) for duplicate removal.

After the duplicates have been removed, all publications will be exported from Mendeley® to Rayyan® software (Rayyan QCRI, Qatar Computing Research Institute – Data Analytics) [14] for the selection process.

Selection process

All publications identified by the search strategy described in this protocol will be analysed using a two-phase process.

In the initial screening phase (Phase I) two reviewers will read the title and abstract of publications using the software Rayyan (Rayyan QCRI) to select those that meet the eligibility criteria.

The inclusion criteria for publications in Phase I are:

- Original studies on cost of oral cancer (lip cancer; oral cavity; oropharyngeal cancer; head and neck cancer)
- Studies that assess cost of oral cancer based on components as: hospital and / or outpatient, promotion and prevention
- No language restriction

On Phase I publications that meet the following criteria will be excluded:

- Types of study such as: editorial, letters to the editor, systematic and non-systematic reviews of the literature, metanalysis, case reports, case series, clinical trials
- Studies that estimate specific item component of oral cancer cost (e.g. only surgery or medication, etc.)
- Studies that address specific analysis, such as cost-effectiveness, cost-utility, cost-benefit, cost-minimization

In the second selection phase (Phase II), confirmation of eligibility will be done by reading eligible publications in full, by two reviewers, independently, and a third will be consulted for consensus in case of disagreement between the first two. Reviewers will undergo training and calibration prior to the publication selection process, which will be performed using 10% of the references found. The agreement between the reviewers will be quantified by Kappa.

To be included in Phase II, in addition to the eligibility criteria from Phase I, publications need to meet the following criteria:

- Studies that provide estimates to the patient or country's health system.

An instrument containing the inclusion and exclusion criteria will be built to guide this step, as well as to record the reasons for the exclusions.

Data collection

Data extracted by means of an instrument containing the variables of interest, built specifically for this study, will be subjected to qualitative and quantitative analysis and synthesis.

If necessary, we will contact authors of included studies in order to ask for unreported information or to clarify possible misunderstandings. Data directly obtained from the authors will be clearly identified.

We will report any assumption resulting from lost or unavailable information.

Information to be obtained from each study [15]:

1. Study identification: first author, journal of publication and year of publication.
2. Main design characteristics: type of study (cost of illness study or another type of study that provides cost of illness information in this field), epidemiological approach (cross-sectional or longitudinal), retrospective or prospective data gathering, perspective of the analysis (hospital, patient, healthcare system or societal); time horizon, use of discount rate, sensitivity analysis (yes/no), presence of a control group (patients not affected by oral cancer), location/setting.
3. Elements of cost considered: direct healthcare costs (hospitalization, intensive care unit, emergency room, physical therapists, speech therapists, medication, laboratory tests, imaging diagnosis, chemotherapy, radiotherapy), direct non-healthcare costs (social services and transportation costs) and indirect costs (loss of productivity, premature death).
4. Data source: primary or secondary database.
5. Study results: the primary outcome will be the costs related to oral cancer in patients reported in monetary units. If the studies provide a specific breakdown of costs, we will report this information (direct hospital costs, rehabilitation care costs, direct non-healthcare costs, indirect costs and productivity loss, and intangible costs). We will also collect data on quantities of health and social resource consumption, currencies used and whether the study shows total or incremental costs.

Quality assessment, risk of bias in individual studies and confidence in cumulative evidence

Methodological quality and risk of bias and meta bias will be evaluated using Larg & Moss's guide [16] for assessing cost-of-illness critical evaluations.

We will give a global score for the quality of each study which will be calculated by dividing the total number of points rated as 'yes' between the total points applicable for each study and record it as a percentage.

Data synthesis

A systematic meta-narrative synthesis will be carried out, so the results will be presented in narrative form. Findings and characteristics of the included studies will be summarised and explained in text and tables. In this section, we will take into account the risk of bias information obtained from each study. No study will be excluded based on its risk of bias, but we will assess how risk of bias may have affected the main results and outcome measures.

Discussion

Diseases always impose costs on society, even if monetary values are not disbursed, since the public health system or some private plan is used, and all production processes imply the use of resources. Even if there are no expenses, there will be costs. However, to our knowledge, no systematic review has been published to date that identifies the evidence of the economic burden of OC worldwide.

Deficiency in early detection of oral cancer has resulted in individuals with costly and mutilating treatments, a reality for most patients who can access treatment at referral hospitals in Brazil and several Latin American countries, a region with a high prevalence of oral cancer.

This systematic review is part of a major research project aiming to evaluate the cost-effectiveness of an oral cancer matrix support and screening program to the public health service in Brazil, and to raise awareness on alternatives to better guide decision-making and optimize benefits.

The identification of evidence on the economic burden of LC, OCC and OPC will allow the determination of the contribution share of each sector of society in the total economic burden of oral cancer. Also, this evidence will favour the estimate of the impact that the reduction of the OC burden would have on its associated costs, assisting in decision-making and implementation of health policies. Savings in the treatment of preventable diseases increase the chances of investing in their prevention.

Cost of illness studies represent the first step towards complete economic analysis (e.g. cost-effectiveness analysis) and can also support economic impact studies, by calculating projections of global cost estimates based on the prevalence or total incidence of the disease.

As additional information, to bring closer health professionals and managers to the field of health economics, Table 2 presents a glossary of terms in health economics.

TERMS	DEFINITIONS
Economic evaluation	The comparative analysis of alternative courses of action, in terms of their costs and consequences [17].
Partial economic evaluation	Measures program or disease costs but does not involve a comparison with alternative options and does not relate costs to outcomes. Partial economic evaluations include cost-of-illness analysis and program cost analysis. Partial evaluations do not provide information on efficiency [18].
Cost-of-illness	Cost of illness (COI) is a summary of the costs of a particular disease to society. This value includes direct costs of treating the disease such as healthcare system costs for diagnosis, treatment and management of disease progression and patients' own costs (travel, over-the-counter medication), as well as indirect costs such as productivity loss resulting from time off employment [19].
Perspective of study	The perspective is the point of view adopted when deciding which types of costs and health benefits are to be included in an economic evaluation. Typical viewpoints are those of the patient, hospital/clinic, healthcare system or society [19].
Time horizon	It is the duration over which health outcomes and costs are calculated. The choice of time horizon is an important decision for economic modelling and depends on the nature of the disease and intervention under consideration and the purpose of the analysis [19].
Discount rate	The interest rate used to determine the present value of future costs and benefits [17].
Direct cost	All the fixed or variable costs of the resources (goods, services, etc.) monopolized in implementing an intervention and managing its consequences [17].
Indirect cost	All costs attributed to the value of economic production lost due to disease, a disabling injury or premature death [17].
Intangible cost	The non-quantifiable cost of pain and suffering caused by a disease, health problem or intervention [17].
Methodological quality assessment	The extent to which the design and conduct of a study are likely to have prevented systematic errors (bias). Variation in quality can explain variation in the results of studies included in a systematic review. More rigorously designed (better 'quality') trials are more likely to yield results that are closer to the 'truth' [17].
Sensitivity analysis	It is used to illustrate and assess the level of confidence that may be associated with the conclusion of an economic evaluation [19].

Table 2
Glossary of terms in health economics

Abbreviations

COI - cost of illness

JB1 - Joanna Briggs Institute

LC - lip cancer

OC- oral cancer

OCC - oral cavity cancer

OPC - oropharyngeal cancer

PEO – population, exposure, outcome

MeSH – Medical Subject Headings

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

Not applicable – protocol manuscript only, no supporting data available.

Competing interests:

The authors declare that they have no competing interests.

Funding:

There are no funding contributions to declare for this study.

Authors' contributions:

RFRR and ALSAZ – are responsible for the study concepts, study design. ENS and DMTPF- contributed to the study design, search strategy and methodological advice. RFRR, ALSAZ, EAR, VM, NRD contributed to manuscript preparation, manuscript editing. All authors read and approved the final manuscript.

Acknowledgements:

Not applicable.

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Figures

Figure 1

PRISMA flowchart.

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