REVIEW ARTICLE

Pharmacoeconomics 2006; 24 (7): 651-659
1170-7690/06/0007-0651/$39.95/0

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Cost of Lung Cancer
A Methodological Review

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Abstract

Cost of illness (COI) studies estimate the overall economic burden of a specific disease, rather than simply treatment-related costs. While having been criticised for not allowing resource prioritisation, COI studies can provide useful guidance, so long as they adhere to accepted methodology. The aim of this review is to analyse the methods used to evaluate the cost of lung cancer. Because of the

increasing incidence and high direct and indirect costs of lung cancer, it is an important disease in terms of economic implications, and therefore provides a relevant example with which to review COI study methodologies.

First, the key points of the methodology relating to COI studies were identified. COI studies relating to lung cancer were then reviewed, focussing on an analysis of the different methods used and an identification of the strengths and weaknesses of each approach.

The COI studies that were analysed confirmed that lung cancer is a costly illness, and that hospitalisation and treatments account for a large part of direct costs, while indirect costs represent a large part of the total costs. The review also showed that COI studies adopted significantly different approaches to estimate the costs of lung cancer, reflecting a lack of consensus on the methodology of COI studies in this area. Hence, to increase the credibility of COI studies, closer agreement among researchers on methodological principles would be desirable.

Cost of illness (COI) studies aim to describe the economic burden of a specific disease to society. They are designed to not only evaluate the costs attributable to the treatment of a particular illness but also evaluate actual illness-related global costs.[1] In principle, they should either inform the most accurate choices in resource allocation or be used in full economic evaluations of healthcare programmes and treatments.[2,3] However, COI studies have been criticised for not really providing useful information or enabling choice of priorities.[1,4] We believe that COI studies can play an important role in informing cost estimates for use in further economic evaluations. Hence, these studies should be carried out in accordance with a clear and widely accepted methodology.[5,6]

Lung cancer is a major public health problem in industrialised countries. Several studies have shown the high cost of this type of cancer for healthcare systems,[7-10] leading to major rethinking in the field of health-cost rationalisation.[11-13] Indeed, the incidence of lung cancer is increasing rapidly, and new costly antimitotic agents are yielding a moderate but significant survival increment.[14] Most of these new drugs are far more expensive than previous reference treatments.

The aim of this review was to analyse the methods used to evaluate the economic implications of lung cancer management. We started by identifying the key methodologies of COI studies. We then reviewed the studies on cost relating to lung cancer, analysing the different methods used and identifying their strengths and weaknesses.

1. Cost of Illness

1.1 Defining the Disease and the Patient

To conduct a COI study, it is necessary to first define the pathological state, the epidemiological approach, the type of costs to be assessed and, thus, the perspective of the study. Subsequently, data on resource consumption and unit costs can be gathered, and results presented and methodically discussed, in conjunction with sensitivity analysis to test their robustness.

Disease definitions are subject to interpretations, so COI studies should precisely define the disease state investigated, including the identification of subgroups of patients according to clinical and economic criteria. This makes the analysis more precise and relevant.

1.2 Epidemiological Approach

In COI studies, prevalence- or incidence-based approaches may be adopted. The prevalence-based approach requires disaggregation of the costs for each stage of the disease before being applied in economic evaluations. On the other hand, incidence-based COI studies generally establish lifetime cost estimates that could be directly incorporated in a cost-effectiveness analysis or a disease model to evaluate future costs. However, as change in the

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healthcare sector is rapid, long-term estimates are not very reliable.

1.3 Perspective of the Analysis and Costs Assessed

Different types of costs (direct, indirect, intangible) are included in economic evaluations, depending on the study's point of view (e.g. the healthcare system perspective only takes the direct healthcare costs incurred by the payer into account whereas the societal perspective also considers indirect costs and costs to be met by the patients and their families).

1.4 Estimating Resource Consumption

Methods for estimating resource consumption vary, depending on available data. Retrospective approaches suit when high-quality data are available, whereas a prospective approach (e.g. from medical records or clinical trials) is required when reliable information is lacking. For the retrospective approach, the activity data can be collected either using aggregate figures from hospital admissions, consultations, mortality, etc. ('top-down' method) or by referring to the records of a sample of patients ('bottom-up' method).

Prospective studies can be considered more reliable than retrospective when relevantly designed and conducted, since they are specifically tailored to the aim of the analysis and, theoretically, should reduce the risks of drawbacks and biases.

1.5 Valuation of Unit Costs

Costs should represent the value of the input in its best alternative use, i.e. the opportunity cost. In a market, this would be the minimum price required to use the input in its current use rather than in an alternative use.[2,15]

1.5.1 Direct Costs

Direct costs can be estimated via per capita expenditure, national tariffs, market prices, data from published studies and specific estimates and other methods, depending on study design. An alternative to using patients' charges and tariffs, which do not accurately estimate underlying costs, is to consider the costs based on accounting principles and estimated by healthcare centres or hospitals, with a clear specification of methodology to account for overhead costs.

1.5.2 Indirect Costs

Estimates of indirect costs mainly use the human capital approach, based on the principle of productive potential. A variation, the friction cost method,[2,3] aims to overcome potential overestimation of indirect costs and assumes that, in the absence of full employment, indirect costs occur only during the period of time necessary to restore the initial level of production (friction period). Since production losses due to mortality are not considered, future lost earnings are neglected.[16,17] This method is seldom applied as it requires a huge amount of information.

1.6 Discounting Costs

Discounting converts future currencies to their present value and is frequently applied when COI studies are considered over several years. The choice of a discount rate originates from the social opportunity cost approach, but it has increasingly been viewed as a general statement about social time preference.[2] Equation 1 is applied to estimate costs:

$$C_0 = \sum_{t=0}^{t=n} \frac{C_t}{(1+r)^t} \quad \text{(Eq. 1)}$$

where C_0 = present value of cost strategy, C_t = value of cost strategy in year t, r = discount rate, t = time period, ranging from 0 to n, n = maximum time period being examined.

1.7 Sensitivity Analysis

Sensitivity analysis of the key variables (e.g. disease incidence, survival probabilities, unit costs) tests the robustness of the results. A sensitivity analysis can take various forms: simple, multi-way and probabilistic.[18] For COI studies, it seems particularly interesting to perform a sensitivity analysis using different methods to estimate the various types of costs.

1.8 Presentation of Results

The presentation of COI results should be consistent with collected data and should break down

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results into as many components as possible with full explanation given for clarity.

2. Review Methodology

COI studies were selected from the MEDLINE database (1986–September 2004) using the keywords 'lung cancer', 'cost of illness' and 'economic evaluation'. Additional publications were identified from the reference list of published articles. All studies assessing the economic burden of lung cancer at a national level and published either in English, French or German were selected. According to these criteria, 12 studies were retained (table I). The major aim of this review was to assess the methods adopted by the authors rather than to compare cost estimates.

Three methodologists among the authors (C. Combescure, A. Vergnenègre and L. Molinier) analysed these studies. In keeping with the key methodological points identified in the first part of the paper, they asked questions based on existing checklists for full economic evaluations.[2,27] An equal weight was given to each item. The final score was a combination of the 11 individual items. The objective was not to establish a hierarchy in the criteria used by allocating them different weights, but to use these criteria to analyse the methods used. Each article was analysed separately by the reviewers. Finally, a meeting of the participants to review the outcome was called and a consensus was formulated by discussion. Then the authors, both clinicians and methodologists, discussed the results.

3. Defining Lung Cancer

The definition of lung cancer is based on histological cell type and the stage of the disease. All but one study reviewed gave a precise definition of lung cancer.[7] Nine studies took into account small-cell lung cancer (SCLC) and non-SCLC (NSCLC).[7-9,19-24] Two studies were limited to stage IV NSCLC.[25,26] One study was in metastatic NSCLC.[11]

4. Epidemiological Approach

All COI studies followed an incidence-based approach.[7-9,11,19-26] Incidence data were mainly estimated from national surveys.[7-9,11,19,21,25,26] Four studies considered a sample of patients and extrapolated results to the entire population.[20,22-24]

5. Perspective of the Analysis and Costs Assessed

One study quantified both direct and indirect costs.[21] In this study, indirect costs accounted for 89% of total costs. All the other studies quantified only direct costs.

Direct costs could be dissociated into two categories: direct costs related to diagnosis and initial investigations, and direct costs related to the treatments. All the studies included treatment-related direct costs.[7-9,11,19-26] One study did not take diagnostic costs into account.[23] Direct costs considered by most studies were initial diagnosis, treatment (with surgery, radiotherapy and chemotherapy) and terminal care.

All but one study specified the viewpoint adopted.[7]

6. Estimating Resource Consumption

All the studies estimated resource consumption retrospectively.[7-9,11,19-26] This appears to be related to the availability of fairly reliable data. Four studies used a bottom-up approach to gather activity data.[20,22-24] In two studies, a full audit of resource-using hospital events was compiled for each patient.[20,22] After exclusions, 253 records of patients diagnosed in Trent (UK) were available for analysis in the English study.[20] Ninety-one records of patients selected in four hospitals, non-representative of institutions treating patients with lung cancer, were available in a French study.[22] Two French studies collected information on resource consumption by the follow-up of a representative nation-wide sample of 428 patients.[23,24] The data collected were then processed by economic modelling (Markov model).

All the other studies used the top-down approach. Thus, resource consumption was mainly estimated using published national indicators, data from national surveys and published studies.[7-9,11,19,21,25,26] The use of top-down approaches to assess resource consumption implies aggregate data processing, which, if not properly performed, could induce errors and unrealistic results. It is not always obvious

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Table I. Review of cost of illness studies in lung cancer

Study	Country	Type of healthcare system	Epidemiological approach	Viewpoint	Currency (year of valuation)	Per capita cost (€)[a]			Total costs (€ [million])	% of total costs		Discounting
						lung cancer	NSCLC	SCLC		indirect	direct	
Koopmanschap et al.[7]	The Netherlands	Public and private insurance	Incidence and prevalence	Not specified	NLG million (1988)	4 597	NA	NA	136.10		100	No
Evans et al.[8]	Canada	PSI	Incidence	Govt as payer in a UHS	$Can (1988)	NA	4 262–12 039	3 189–12 579	NA		100	No
Evans et al.[9]	Canada	PSI	Incidence	Govt as payer in a UHS	$Can million (1988)	14 135	13 313	17 490	221.10		100	No
Berthelot et al.[11]	Canada	PSI	Incidence	Govt as payer in a UHS	$Can million (1995)	NA	16 709–27 713	NA	83.10–138.10		100	No
Evans et al.[19]	Canada	PSI	Incidence	Govt as payer in a UHS	$Can million (1988)	14 135	13 313	17 490	221.10		100	No
Wolstenholme and Whynes[20]	UK	NHS	Incidence	Hospital	£ (1993)	NA	9 280	8 553	NA		100	Yes (6%)
Weissflog et al.[21]	Germany	PSI	Incidence	Sickness funds	DM billion (1996)	150 582	NA	NA	4 246.10	89	11	No
Braud et al.[22]	France	PSI	Incidence	Hospital	€ (2001)	12 518	13 969	7 369	NA		100	No
Chouaid et al.[23]	France	PSI	Incidence	Healthcare payer	$US billion (1999)	NA	17 153–23 041	16 733–26 390	439.10		100	No
Vergnenègre et al.[24]	France	PSI	Incidence	Healthcare payer	€ million (1999)	25 643	19 543–30 424	22 420–27 098	612.10		100	No
Evans and Le Chevalier[25]	Canada	PSI	Incidence	Govt as payer in a UHS	$Can million (1993)	NA	15 949–20 316	NA	70.10–90.10		100	No
Evans[26]	Canada	PSI	Incidence	Govt as payer in a UHS	$Can million (1993)	NA	13 945–16 600	NA	62.10–73.10		100	No

a All costs are in € (NLG1 = 0.454, $Can1 = 0.673, £1 = €1.509, DM1 = € 0.511, $US1 = €0.829; 26 Oct 2005).

DM = deutschmark; **Govt** = government; **NA** = not available; **NLG** = Dutch guilder; **NSCLC** = non-SCLC; **PSI** = public social insurance; **SCLC** = small-cell lung cancer; **UHS** = universal health system.

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to determine how data on resource consumption were processed to obtain more detailed data.[7,9,19,21] Six studies selected the Population Health Model (POHEM) to estimate total direct costs.[8,9,11,19,25,26]

These studies collected information on resource consumption during several periods, ranging from 1 to 5 years.

7. Valuation of Unit Costs

7.1 Direct Costs

Different methods, mainly extrapolations from national sources and published data, were adopted to assess direct costs. Six studies used the fee schedule of the Ontario Health Insurance Plan, data from published studies and national or local hospital indicators.[8,9,11,19,25,26] One study used data from a social insurance plan (AOK).[21] Two studies estimated unit costs from a national unit cost scale and drug purchase prices.[23,24] One study determined unit costs with the UK NHS data;[20] one used a national hospital register and data from published studies;[7] and one estimated unit costs from the accounts of one hospital participating in the project.[22]

7.2 Indirect Costs

Only one study quantified indirect costs,[21] estimated by the human capital approach. Indirect costs due to mortality and morbidity were included. The study estimated lost production distinguishing between the various types of patients according to their sex and age group. Authors extrapolated the results of data on production losses from an average of annual income per capita provided by a local social insurance (AOK). In this study, indirect costs of Deutschmark (DM) 7.40 billion accounted for 89% of total estimated costs. Early death cost, the most significant cost driver of indirect costs, amounted to DM4.85 billion, representing 58% of total estimated costs.

8. Discounting Costs

Costs were discounted in one study.[20] The discount rate chosen was properly explained. Costs were not discounted in any of the other studies. Generally, the time horizon was short (<2 years).

9. Sensitivity Analysis

Only four studies conducted a sensitivity analysis to test the robustness of the results.[11,23-25] Two studies analysed the changes induced in the results by the number of terminal care hospital days.[11,25] Two other studies analysed the effects of percentage variations of actively treated patients, the costs of chemotherapy treatments used in first- and second-line treatments and the cost of palliative care.[23,24]

In the first two studies, the variation of the number of terminal care hospital days had a significant impact on cost estimates.[11,25] For the other studies, mean costs were closely related to changes in the percentage of actively treated patients and less significantly related to changes in the costs of chemotherapy and palliative care.[23,24]

In these studies, the sensitivity analysis was fairly well explained and discussed.

10. Presentation of Results

All the studies presented results quite clearly. Generally, results were well explained and consistently set out in relation to the methods adopted. However, two studies[7,22] did not always fully explain the reasons for certain major assumptions, which often appeared questionable. Furthermore, since the sources were not always clearly specified, it was often difficult to assess the reliability of data from published studies. In addition, two studies did not disaggregate direct costs, thus reducing the strength of the information provided.[7,21]

All but two studies presented results in terms of cost per patient.[7,21] Lastly, only one study predicted costs for the years 2005 and 2020.[7]

According to the key methodological points identified, we have drafted a checklist of questions related to the eight items analysed. For the majority of the studies, the answers to 8 of 11 questions were 'yes', and for the three remaining questions, five studies at the most were scored 'yes' (table II).

All the studies analysed resource consumption retrospectively and only four adopted a bottom-up approach. Also, unit costs were valued mainly through extrapolations from national sources and published data.

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Table II. Answers to the methodological questions by study

Koopmanschap et al.[7]	Evans et al.[8]	Evans et al.[9]	Berthelot et al.[11]	Evans et al.[19]	Wolstenholme and Whynes[20]	Weissflog et al.[21]	Braud et al.[22]	Chouaid et al.[23]	Vergnenègre et al.[24]	Evans and Le Chevalier[25]	Evans[26]
Was a clear definition of the illness given?											
Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were epidemiological sources carefully described?											
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Partial	Yes	Yes
Were direct/indirect costs sufficiently disaggregated?											
No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Were activity data sources carefully described?											
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were activity data appropriately assessed?											
Yes	Yes	Yes	Yes	Yes	Partial	Yes	Partial	Yes	Yes	Yes	Yes
Were the sources of all cost values analytically described?											
Partial	Yes	Partial	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were unit costs appropriately valued?											
Partial	Partial	Partial	Yes	Partial	Yes	Yes	Partial	Yes	Yes	Partial	Partial
Were the methods adopted carefully explained?											
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the major assumptions tested in a sensitivity analysis?											
No	No	No	Yes	No	No	No	No	Yes	Yes	Partial	No
Was the sensitivity analysis carefully explained?											
NA	NA	NA	Yes	NA	NA	NA	NA	Yes	Yes	Yes	NA
Was the presentation of study results consistent with the methodology of the study?											
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NA = not applicable.

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11. Discussion

This study reviewed 12 COI studies on lung cancer with the main goal of analysing the various methodologies. According to the key methodological points identified, 11 of 12 studies scored 'yes' on the majority of the methodological questions, thus showing that the methods had been selected accurately.[8,9,11,19-26]

The COI studies analysed here confirm that lung cancer is a costly illness, and suggest that indirect costs account for a large share of total costs (table I). In all the studies considered, hospitalisation and treatments accounted for a large part of direct costs.

However, commenting on these quantitative results is problematic since significantly different approaches had been adopted to estimate the costs of lung cancer. There were also marked differences in the types of costs included and the sources used to assess activity data. Therefore, the comparison of the results reported in each study is not very useful. This is probably due to the lack of consensus on the methodology. Therefore, the definition of standards, with a large consensus in the methodology selected to conduct these studies should be a major concern for the scientific community.[28,29] Nevertheless, we must bear in mind that, unlike with clinical trial results, it is very difficult to generalise quantitative results of economic studies conducted in different countries. Economic results are difficult to compare on account of monetary issues, such as fluctuating exchange rates and different purchasing powers of currencies. Instead, domestic characteristics also dramatically affect resource consumption and unit costs, including differences in clinical practice and the healthcare system framework.

Many COI studies did not fully explain their methods, and thus were difficult to assess. This might be due to a general lack of economic awareness in the medical journals that support economic studies. Most of the studies reviewed were published in journals that did not demand sufficiently detailed and explicit explanation of the methodologies selected. In 1996, the *British Medical Journal* published guidance information to authors and peer reviewers on economic evaluations, but it did not address COI studies.[30] A detailed description of the methodological choices would improve the credibility of COI studies.

12. Conclusion

COI studies can provide information to support the political process as well as the management functions at different levels of healthcare organisations. These studies must be capable of identifying the actual clinical management of illness and measuring the true cost.

COI study results can serve as a baseline for further economic evaluations. However, an insufficient description of methods may lead to misunderstandings. The COI studies of lung cancer identified in this review highlight the poor consensus of methodological approaches, perhaps reflecting a lack of stringency on the part of medical journals. Hence, journals should encourage researchers to give clear descriptions and discuss limitations, and a further effort should be made to validate methodology.

The viewpoint of the analysis must be consistent with the aims of the study, but the societal viewpoint should be more specifically favoured for COI studies on lung cancer. Resource consumption could be better estimated by the follow-up of a sample of patients, and unit costs of the facilities provided for patients' care could be carefully assessed.

Acknowledgements

We gratefully acknowledge Christiane Saulet and Christine Delbos for their assistance.

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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