REVIEW ARTICLE

Received: June 2017
Accepted: August 2017

Comparing Health Economic Models to Answer Public Health Problems: A Review

Fereydoon Jariri[1], Maryam Hadji[2], Azin Nahvijou[2]*

1. School of Engineering, Industrial Engineering Group, Mahdasht branch, Payame Noor University
2. Cancer Research Center, Cancer Institute, Tehran University of Medical Sciences

***Corresponding Author:**
Azin Nahvijou
Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, Iran.
Tel: (+98)9123846953
Email: azin.nahvijou@gmail.com

BCCR
2017; 9(1): 26-39
www.bccrjournal.com

ABSTRACT

Nowadays, decision analysis models are extensively used in solving healthcare problems. Considering the limited resources, the results of these studies will greatly assist policymakers with resource allocation. The purpose of this study is to provide a review of different decision analysis models in healthcare systems and to compare the components used in developing these models in studies addressing cervical cancer prevention. In this comprehensive review on decision analysis models used for cervical cancer prevention, we determined that the major components of the models included costs, outcomes, cycle lengths, discount rate, and perspective. The most commonly used model found in our review was the Markov model; nevertheless, it appears that dynamic models are gaining popularity over recent years. Conclusion: Using decision analysis models and encouraging healthcare policymakers to apply the results of modeling studies will result in saving time and costs, and will facilitate decision making in healthcare issues.

Keywords: Health Economic Models, Cervical Cancer, Mathematical Models

INTRODUCTION

The ever-growing advancements in technology in the field of healthcare, as well as the limitations of resources mandate policymakers to seek the tools and science of decision making. Nowadays, economic studies are extensively applied to answer questions in healthcare. These studies are mostly based on mathematical models and provide the policymaker with powerful tools to make decisions regarding choice of healthcare interventions. Such studies compare the costs and the outcomes of a certain intervention with the costs and outcomes of another. Quantitative models use different techniques, as outlined in **Table 1**[1]. Numerous variables are involved in development of a model, including the course of the disease, time horizon, data availability, and perspective of analysis[2]. Simulation models are extensively used due to their flexible techniques, ability to use variables and uncertainty, and the ability to prepare graphic displays[3, 4]. Nowadays, decision analysis models have an established position in the field of healthcare. Simulation models are commonly used for cancer due to its chronic nature, high costs, and presence of diverse treatments[4]. Considering the fact that certain cancers may be preventable, these models enable the policymakers to make better decisions[5]. In 2012, annually 14.1 million new cases of cancer were diagnosed worldwide. The mortality rate of cancer is 8.2 million cases, and 32.6 million people are living with more than 5 years since their cancer was diagnosed. In less developed countries, cancers amount to 57% (8 million) new cases, with 65% (5.3 million) mortality and 48% (15.6 million) 5-year prevalence[6]. According to the latest GLOBOCAN report in 2012, cervical cancer is the fourth leading cancer in women worldwide, and ranks 7th as the most common malignancy in both sexes[6]. Overall, 528,000 new cases of cervical cancer were diagnosed in 2012. The long course of this malignancy provides an opportunity for effective screening to identify the patient at a pre-invasive stage, and thus initiate therapy in a timely manner[7]. The Papanicolau test was first introduced in 1930 by George Papanicolau. Later on, Ernest Ayre, an American gynecologist, devised a technique to isolate cells in the transitional zone. In 1940, Pap smear found its place as the screening method with widespread application and still remains the first line of screening in most countries[8]. In England, the National Health Service Cervical Cancer Programme (NHSCCP) was launched in 1988 and managed to reduce incidence by 42%[9]. In the United States, the Surveillance, Epidemiology, and End-Results (SEER) program demonstrated that the incidence and mortality of cervical cancer have reduced to 43% and 46%, respectively, from 1973 to 1995[10]. In addition, reports from 13 European countries with organized screening programs indicated a reduction in cervical cancer[10]. Identification of the main causative agent for cervical cancer, i.e. the Human Papilloma Virus (HPV), has resulted in modifications in screening methods[11, 12]. This highlights the importance of decision making techniques in selecting the screening method for this malignancy[4]. Simulation models are a type of multivariate decision-making method to help policymakers to select the most efficient policy through the decision analysis approach[4]. In the field of cancer studies and prevention, decision

analysis models are extensively applied[13-16]. Previous studies indicate that the outcomes of cancer are closely related to income and wealth. For instance, better outcomes in breast and colorectal cancer have been substantially associated with growth domestic product per capita (GDP) of countries[17]. Therefore, another crucial feature of decision making models is their contribution to resource allocation for healthcare plans.

In this review, we provided a definition of each model and compare the various models of decision analysis. Subsequently, we explored the application of these models in economic studies of cervical cancer screening as a healthcare problem. The models addressed in this study include the decision tree, Markov model, dynamic systems, Monte-Carlo simulation model, and discrete event simulation.

TYPES OF MODELS

Decision Tree

A Decision tree is one of the simplest models of decision making. In this method, the patients' prognosis is modeled according to the type of treatment chosen[18]. The considered interventions for a problem are investigated in pathways and ramifications. Each pathway shows the procedures of one intervention to the end. At the end of each pathway, variables such as costs, years of life, and QALY are assigned.

Decision trees are widely used due to their simplicity and clarity. These models are easily developed and their interpretation is relatively simple, and thus applicable to cohort and individual studies. However, their time-independent nature precludes their use in models which take time into account.

Table 1. Comparison of different methods of quantitative models

Deterministic	**vs.**	**Stochastic**
- Used for constant and predictable events		- Combination of random events and behaviors - Used in specific and long-term patterns
Dynamic	**vs.**	**Static**
- Stage of variables change over time. -The components of the model allow for the change in the system. - Prediction is made with high precision.		- Provides an instantaneous image of the system in a specific time point. - Prediction is made based on inference. - These models are limited in precision. - Easily developed.
Continuous	**vs.**	**Discrete**
Continuous variables are used with linear real numbers, so that between every two values, a third value may exist.		Variables belong to a series of possible and available values on lists of time restraints or integers.

Another weakness of these models is that addition of disease stage causes them complicated and thus inapplicable to complicated scenarios. Moreover, they cannot be looped[19-21].

Markov Model

These models allow for a simple and flexible sequence of events that occur throughout the course of the disease over a specific time period. They are usually applied when the risk of the disease occur over time. It is assumed that at a given time, the patients are one of the health states and they may transition between the states. The number of the states and the duration of each state (named the cycle) depend on the question requiring a decision. In acute and infection diseases, the cycles are quite short, spanning a few days to a month. In chronic diseases, such as cancers, the cycles last six months to a year. These studies are usually conducted on hypothetical cohorts. All considered conditions must be demonstrated in different stages. If the time horizon spans longer than a year, the costs and outcomes need to be discounted[19, 20, 22]. In the hypothetical cohort of Markov models, transition probability helps to alter the distribution of patients in each state over the cycle[22].

Markov models assume that the transition occurs at the end of each cycle. In fact, this event may occur at any time point. For this reason, these models use half cycle corrections, which are important for evaluation health-related outcomes in long-lasting diseases such as cancer[23].

This model may be applied to the individual as well as the population. Also, the interaction between individuals or populations is allowed. One challenge of these models is that with addition of disease stage, the models become rapidly complicated[24].

Dynamic Systems

Dynamic systems are deterministic in nature and consist of qualitative and quantitative aspects. For this reason, these models are used for improving the understanding of an identified problem, as well as enhancing the structure of the problem and the relationship between variables[3]. Dynamic decision making models are applied to problems that have high uncertainty and require time. These models are recommended when continuous information of different perspectives is required[24].

One strength of these models is that they allow for the interaction between the population and the environment. Moreover, the recurrence feedback may be considered in these models. However, they are more oriented toward the population rather than the individual[21].

Monte-Carlo Stimulation Model

Monte-Carlo models are also known as individual simulation. In these models, a large population enters the model, but only few are randomly selected to transition from one stage to another[23]. Similar to Markov models, Monte-Carlo models constitute a form of cohort, but they simulate more clinical complications compared to Markov models[22, 25]. Usually in Markov models, the individuals of the presumptive cohort go through a given path, while in Monte-Carlo models, the individual undergoes transition in a stochastic fashion. In addition, the outcomes are calculated differently in these two models[23].

Monte-Carlo models are also known as micro-simulation models. They are sometimes used as a decision analysis method and not a decision analysis model because they may be combined with other models such as the decision tree or Markov models. In particular, in the case of heterogeneous

populations or diseases with numerous stages, this method will facilitate modeling. The problem with this type of modeling is that in complicated models, the required data and simulation may be challenging and the model is limited to the main model[21, 22].

Discrete Event Simulation (DES)

DESs are a network of queues and activities with transition occurring at a discrete point of time[3]. In a DES model, the patient's transition through the model and it is possible that at any discrete time interval, the next event occurs after the previous event. Model analysis is based on the occurrence of the event at that time, inquiring about the subsequent event, whereas in Markov models, the events occur at regular intervals[26]. These models are better in demonstrating the disease history and future events. In these models, the interactions between individuals or between the individual and the environment are well defined. Unlike Markov models, these models are applicable when the disease has numerous risks. The lengths of cycles are constant in Markov models, while the interval between events may vary in these models. Nevertheless, the structure of these models is very difficult for establishing relationships and interpretation; furthermore, the calculations for developing and implementing these models are very difficult and challenging[21, 27].

Methodology in Economic Studies

Economic studies mandate the knowledge of variables required for simulation. Therefore, selection of key issues is of great importance. The components of decision analysis models include perspectives, interventions, outcome, costs, and discounting, which will be discussed in the following.

Perspectives

The perspective of a study depends on the objective which requires a decision. When the costs and health effects are integrated, without considering who bears the costs and who benefits, the perspective will be of societal type. In this perspective, all costs and benefits are calculated for all groups of the society. Although the societal perspective is the most comprehensive and preferred approach, there are other perspectives such as service providers and hospitals, insurers and payers[4, 28, 29]. Many studies are based on the hospital perspective, but mention having taken societal perspective into account, as well[29].

Cycle Length

Selecting this variable in models depends on the disease course. The length of the cycle must reflect the shortest interval in which the patient will manifest signs and symptoms of the disease, and may vary from days to a year depending on the acute or chronic nature of the disease. For instance, in viral diseases, the length may be days, while in chronic diseases, the occurrence of events through the course of the disease takes one year on the average[30-32].

Interventions

Interventions may be associated with a specific service, such as a hospital or a clinic, or they may depend to a population, such as screening or vaccination. The interventions may vary based on the complexity of the service, demand, or settings[4].

Health Outcome

Using health outcomes is much more challenging compared to the costs. One problem is that the results reported by a study are comparable to only other studies addressing the same outcome[4]. In all cost-effectiveness studies, researchers looking for the optimal cost-effectiveness and benefits in such studies usually require clinical outcomes[33]. A broad spectrum of outcomes may be used based on the type of the disease and its acute or chronic nature, such as overall survival, quality-adjusted survival,

progression-free survival, tumor response, adverse events avoided, QALY, DALY, and YLL[4, 34].

Costs

Costs constitute one of the most important components of the cost-effectiveness models. The major costs calculated include direct medical costs, direct non-medical costs, patient, and indirect costs[4].

Direct costs refer to those directly associated with spending one or several resources for the purpose of intervention. These costs include direct medical and direct non-medical costs. Direct medical costs are those used for disease management, such as diagnosis, treatment, and patient care. Direct non-medical costs result from the disease or its treatment, such as transportation costs[28, 35].

Costs are calculated based on the currency of the target country. The calculated costs are usually converted to US dollars for universality and comparability[4].

Discounting

For chronic diseases requiring cost and benefits calculations for periods longer than one year, discounting is necessary. More researchers agree on cost discounting, but there is controversy regarding benefit discounting[4, 28]. Many studies consider an annual 5% discount; however, 3%-10% is usually implemented for the purpose of robustness[28].

Sensitivity Analysis

Sensitivity Analysis is used in decision models to choose the optimal strategies based on changes in parameters value in different scenarios. The potential impact of these changes are investigated in order to find the cost effective strategies[36, 37].

METHODS

The present study is a comprehensive review. We identified and reviewed articles addressing various strategies for cervical cancer prevention based on economic modeling, and compared their findings. The studies were searched for in Medline through Pub Med, Web of Science, Embase and HTA via Ovid databases.

The major keywords used for search included modeling, decision analysis models, decision tree, Markov model, Monte-Carlo model, dynamic model, screening, and cervical cancer.

The variables extracted from the studies included author's name, year of publication, country, type of model, time horizon, perspectives, discount rate, cycle length, type of cost, type of sensitivity analysis and outcome.

RESULTS

A total of 43 articles published from 1998 to 2017 were reviewed. The countries where the studies had been conducted included 13 (30.2%) developing and 29 (67.4%) developed countries. One study (2.3%) was conducted on 179 countries, including developed and developing nations.

Totally, 25 studies (58.1%) used Markov models, 6 studies (13.9%) used Markov models followed by Monte-Carlo simulation, 4 studies (9.3%) used dynamic models, and 2 studies (4.6%) used MISCAN simulation. Also, six studies (13.9%) did not specify the simulation model used.

The discount rate of costs and outcomes was 3% in 23 studies (53.4%). Five studies (11.6%) used 5% discount rate, and five studies (11.6%) did not discount the costs and outcomes, most of which (four studies) used Markov models. Only four studies (9.3%) did not mention discounting and six studies (13.9%) used various discount rates.

The most common perspective used in the studies was societal (16 studies, 37.2%). Service provider, payer, and lack of mentioning the perspective were found in 13 (30.2%), 3 (6.9%) and 11 (25.5%) studies, respectively. **Table 2** compares the major components of different models in the studies.

Table 2. Review of model components

No	Author	Published year	Country	Name of model	Perspective	Discounting	Cycle length	Outcome	Cost	Sensitivity Analysis
1	van Ballegooijen M[38]	1997	The Netherlands	Stochastic micro simulation model	Not declared	0	Not declared	Mortality reduction, LYG	DMC	Not specified
2	Brown A D et al[39]	1999	USA	Time-varying transition state model	Societal	3%	Not declared	LYG	DMC marginal cost	Not specified
3	Goldie[40]	2001	South Africa	Markov model	Societal	3%	Monthly	Life expectancy	DMC & D N M C	Multi Way S A
4	Mandelblatt J S et al[41]	2002	Thailand	Markov / Mont Carlo model	Societal	3%	Annual	LYG	DMC & D N M C	Multi Way S A
5	Elske van den Akker-van Marle M et al[42]	2002	In the high income countries of Western Europe, North America, and Australia	The MISCAN simulation	societal	3%	Not declared	LYG	DMC & D N M C	1way SA
6	Mandelblat[43]	2002	USA	Markov / Mont Carlo model	Not declared	3%	Annual	QALY	DMC & D N M C	1way SA
7	Maxwell[44]	2002	USA	Markov model	Health care provider	3%	Annual	LYG	DMC	Not specified
8	Goldie[45]	2004	USA	Markov model	Societal	3%	Monthly	Life expectancy	DMC	Not specified
9	K Canfell et al[46]	2004	UK	Markov model	not declared	not declared	Annual	Annual age-specific incidence	Not declared	Not specified
10	Goldie[47]	2005	South Africa, India, Peru, Thailand, Kenya	Markov model	Not declared	3%	Monthly	LYG	DMC & D N M C	Not specified
11	Kim[48]	2005	UK, The Netherlands, France, Italy,	Markov model	Societal	3%	Monthly	LYG	DMC & D N M C	Extensive S A
12	Berkhof J et al[49]	2005	The Netherlands	Markov model	Societal	1.5 & 4%	6 months	QALY	DMC & D N M C	1way SA
13	Bidus[50]	2006	USA	Markov model	Not declared	3%	18months	LYG	DMC & D N M C & I C	Not specified

Table 2. Continued

No	Author	Published year	Country	Name of model	Perspective	Discounting	Cycle length	Outcome	Cost	Sensitivity Analysis
14	Shin- Ian Koong et al[51]	2006	Taiwan	Markov / Mont Carlo model	not declared	not declared	not declared	Mortality and Prevented ICC	Not specified	Not specified
15	Uwe Siebert et al[52]	2006	Germany	Markov model	not declared	not declared	Annual	Incidence, Mortality and Life expectancy	not declared	1way SA
16	Kim J et al[53]	2007	USA	Markov / Mont Carlo model	not declared	not declared	Monthly	age-specific prevalence of HPV, CIN 1, and CIN 2,3;cancer; age-specific incidence of ICC	DMC	Not specified
17	Kohli M et al[54]	2007	UK	Markov model	not declared	0	6 months	CIN2,3 prevalence, Incidence, Mortality	not declared	Not specified
18	Bistoletti P et al[55]	2008	Sweden	Markov / Mont Carlo model	Health care provider	3-5%	not declared	LYG	DMC	Multi Way SA
19	Goldhaber-Fiebert et al[56]	2008	USA	Individual-based stochastic micro simulation model	Societal	3%	Monthly	QALY, lifetime costs	DMC & DNMC	1,2 way SA
20	Anderson R et al[57]	2008	Australia	Markov model	Health care provider	5%	12 months/ 18 months	cancer prevented / death avoided, LYG	DMC	1,2 way SA
21	Andres-Gamboa[58]	2008	Colombia	Markov model	Payer	3%	Annual	LYG, life time cost, Mortality	DMC	Not specified
22	Vijayaraghavan[59]	2008	South Africa	Markov model	Societal	3%	Not available	QALY	DMC, DNMC& IC	1way SA
23	Goldie[60]	2008	33 countries in Latin America	Markov model	Not declared	3%	Monthly	LYG	DMC & DNMC	Not specified
24	Kulasimgam[60]	2009	Canada	Markov model	Health care provider	3%	Annual	Life Expectancy	DMC	1way SA

Table 2. Continued

No	Author	Published year	Country	Name of model	Perspective	Discounting	Cycle length	Outcome	Cost	Sensitivity Analysis
25	Levin[62]	2010	China	Markov model	Societal	3%	Not available	LYG	DMC & D N M C	Not specified
26	Gaby Sroczynski et al[63]	2010	Germany	Markov model	Third party payer	3%	Annual	LYG	DMC	Extensive S A
27	Creighton et al[64]	2010	Australia	Markov model	Health care provider	5%	0	Age-specific predicted rates of Screening, Incidence & Mortality	DMC	Multi Way S A
28	Anderson huck[65]	2010	Canada	Markov model	Health care provider	5%	Annual	QALY	DMC	SA
29	Obradovic M et al[66]	2010	Slovenia	Markov model	Health care provider	5%	Annual	LYG, QALY	DMC	1way SA
30	Chow[67]	2010	Taiwan	Markov model	Health care provider	3%	Annual	life expectancy, QALY	DMC	SA
31	Vijayaraghava[68]	2010	USA	Markov model/ Monte Carlo model	Payer	0	Monthly	QALY	DMC	Extensive S A
32	Shi J et al[69]	2011	Rural china	Dynamic simulation/Markov model	societal	3%	not declared	LYG, QALY	D M C , D N M C & I C	1way SA
33	Demarteau N et al[70]	2011	France	Markov model	societal	3% for cost and 1.5% for outcome	6 months	LYG, ICC Incidence, Mortalityand QALY	DMC	1way SA
34	Yamamoto N et al[71]	2011	Japan	Markov model	societal	3%	Monthly	QALY, ICC incidence	DMC & D N M C	2way SA
35	Burger[72]	2012	Norway	The individual-based stochastic model	Societal	4%	Monthly	lifetime risk of cancer, life expectancy, and	DMC & D N M C	Extensive S A
36	De Kok[72]	2012	Europe	MISCAN Model	Societal	3%	Not declared	QALY	DMC & D N M C	2way SA
37	Kulasingum et al[74]	2013	USA	Markov model	Not declared	0	Annual	LYG	Not declared	1way SA

Table 2. Continued

No	Author	Published year	Country	Name of model	Perspective	Discounting	Cycle length	Outcome	Cost	Sensitivity Analysis
38	Demarteau et al[75]	2014	Nigeria	Markov model	Health care provider	0	6months/ 12months	incidence ICC	DMC	1way SA
39	Laprise et al[76]	2014	Canada	Dynamic model	Health care provider	3%	Not declared	QALY	DMC	1way SA
40	Jit et al[77]	2014	179 countries	Not specified	Not declared	6%	Not declared	DALY	DMC	1way SA
41	Jit et al[78]	2015	United Kingdom	Dynamic model	Health care provider	1.5-3.5%	Not declared	QALY	DMC	PSA

Not Declared: The variable is not explicitly mentioned.
Not Specified: The variable exists, but its type is not specified.
DMC= Direct Medical Cost, DNMC= Direct Non-Medical Cost, IC= Indirect Medical Cost, LYG= Life Years Gained, QALY= Quality Adjusted Life Years, ICC= Invasive Cervical Cancer, PSA=Probabilistic Sensitivity Analysis, SA=Sensitivity Analysis

DISCUSSION

This study attempts to provide a definition of decision analysis models and their application in healthcare systems. Furthermore, we compared the models and their major components, focusing on those used for preventing cervical cancer. Our review demonstrates that in all the economic models studied, the most important components include costs, effectiveness, length of the disease, and perspective. As our findings showed, Markov models are more commonly used for preventing cervical cancer, although it appears that dynamic models are being extensively applied over the recent years. Similarly in other healthcare fields, Markov models have been more popular[21]. In our review, we observed that the decision tree was not used alone in any of the studies, and it was usually applied following modeling in the second section where scenarios of different strategies are conducted[54, 57, 64]. As explained before, the reason why decision tree is not used alone in studies addressing cervical cancer prevention may be the natural course of the disease and its sophistications, alongside the fact that it is time-dependent[19, 20]. Moreover, DES models were not used, as HPV is the only risk factor addressed for occurrence of cervical cancer and other risk factors were not taken into account; as mentioned above, DES models are used for addressing multiple risk factors[27]. Decision models are more important for chronic diseases which impose greater financial burdens on nations. In a review on decision models dealing with cervical cancer, Cantor reported that using these models may reduce discrepancy and thus there are good reasons to recommend health policymakers to apply such models[33]. Despite the recommendations of some priority setting studies regarding the implementation of cost-effectiveness studies before running healthcare programs in many countries, there are disparities in the results of the implemented programs compared to the findings of such studies[81, 82]. In a systematic review on Markov models used for cervical cancer screening, very few countries where these studies had been conducted actually incorporated the findings of these studies in their screening program[82]. One reason for this is the establishment of the program prior to conducting these studies[83]. For this reason, the World Health Organization recommends that novel technologies, if cost-effective, must be utilized in settings where a screening program is not already in place[84].

Our study has certain limitations. First, our review was not systematic; therefore, it is possible that some studies may have remained unidentified. In addition, since our scope was limited to cervical cancer screening, the findings cannot be generalized to cases other than screening.

CONCLUSION

Using decision analysis models in healthcare systems will save costs and time. It is recommended to encourage policymakers to use the findings of these studies for making decisions and solving health-related challenges.

REFERENCES

1. (CSMG) CSMG. Modelling in Healthcare2009.
2. Chelimo C, Wouldes TA, Cameron LD, Elwood JM. Risk factors for and prevention of human papillomaviruses (HPV), genital warts and cervical cancer. Journal of Infection. 2013;66(3):207-17.
3. Brailsford S, Hilton N. A comparison of discrete event simulation and system dynamics for modelling health care systems. 2001.
4. Goldie SJ, Goldhaber-Fiebert JD, Garnett GP. Public health policy for cervical cancer prevention: The role of decision science, economic evaluation, and mathematical modeling. Vaccine. 2006;24:S155-S63.
5. Weinstein MC, Toy EL, Sandberg EA, Neumann PJ, Evans JS, Kuntz KM, et al. Modeling for health care and other policy decisions: uses, roles, and validity. Value in Health. 2001;4(5):348-61.
6. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase Lyon, France: International Agency for Research on Cancer. 2013(No. 11).

7. Schiffman M, Castle PE. The promise of global cervical-cancer prevention. New England Journal of Medicine. 2005;353(20):2101-4.
8. Chang A. The cervical smear test in the next millennium. HKMJ. 1999;5:294-302.
9. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. The Lancet. 2004;364(9430):249-56.
10. Altekruse S, Kosary C, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER cancer statistics review, 1975–2007, National Cancer Institute. Bethesda (MD)(based on November 2009 SEER data submission, posted to the SEER web site, 2010). seer cancer gov/csr. 2012.
11. Munoz N. Human papillomavirus and cancer: the epidemiological evidence. Journal of clinical virology. 2000;19(1):1-5.
12. Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human papillomavirus testing in the prevention of cervical cancer. Journal of the National cancer institute. 2011;103(5):368-83.
13. Parsonnet J, Harris RA, Hack HM, Owens DK. Modelling cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer: a mandate for clinical trials. The Lancet. 1996;348(9021):150-4.
14. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. Jama. 2000;284(15):1954-61.
15. Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. Jama. 2003;289(3):313-22.
16. Hillner BE, Smith TJ. Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer: a decision-analysis model. New England Journal of Medicine. 1991;324(3):160-8.
17. Chahoud J, Rieber AG, Semaan A. Wealth, health expenditure, and cancer: A national perspective. American Society of Clinical Oncology; 2015.
18. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation: Handbooks in Health Economic E; 2006.
19. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. Bmj. 2011;342:d1548.
20. Sonnenberg FA, Beck JR. Markov models in medical decision making a practical guide. Medical Decision Making. 1993;13(4):322-38.
21. Briggs AD, Wolstenholme J, Blakely T, Scarborough P. Choosing an epidemiological model structure for the economic evaluation of non-communicable disease public health interventions. Population health metrics. 2016;14(1):17.
22. Kreke JE, Schaefer AJ, Roberts MS. Simulation and critical care modeling. Current opinion in critical care. 2004;10(5):395-8.
23. Sun X, Faunce T. Decision-analytical modelling in healthcare economic evaluations. The European Journal of Health Economics. 2008;9(4):313-23.
24. Leong TY. Multiple perspective dynamic decision making. Artificial Intelligence. 1998;105(1):209-61.
25. Harrison RL, editor Introduction to Monte Carlo simulation. AIP conference proceedings; 2010: NIH Public Access.
26. Karnon J. Alternative decision modelling techniques for the evaluation of health care technologies: Markov processes versus discrete event simulation. Health economics. 2003;12(10):837-48.
27. Standfield L, Comans T, Scuffham P. MARKOV MODELING AND DISCRETE EVENT SIMULATION IN HEALTH CARE: A SYSTEMATIC COMPARISON.
28. Walter E, Zehetmayr S. Guidelines on health economic evaluation–Consensus paper. Inst Pharmaeconomic Res. 2006.
29. Uyl-de Groot CA. Economic evaluation of cancer therapies: more and better studies will lead to better choices in cancer care. European Journal of Cancer. 2006;42(17):2862-6.
30. Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. Annals of Internal Medicine. 1990;113(2):147-54.
31. Sculpher M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models. Pharmacoeconomics. 2000;17(5):461-77.
32. Kim S-Y, Goldie SJ, Salomon JA. Cost-effectiveness of Rotavirus vaccination in Vietnam. BMC Public Health. 2009;9(1):29.
33. Cantor SB, Fahs MC, Mandelblatt JS, Myers ER, Sanders GD. Decision science and cervical cancer. Cancer. 2003;98(S9).
34. Tappenden P, Chilcott J, Ward S, Eggington S, Hind D, Hummel S. Methodological issues in the economic analysis of cancer treatments. European journal of cancer. 2006;42(17):2867-75.
35. Slothuus U. An Evaluation of Selected Literature on the Measurement of Costs in Health Economic Evaluations. 2000.
36. Pannell DJ. Sensitivity analysis of normative economic models: theoretical framework and practical strategies. Agricultural economics. 1997;16(2):139-52.
37. Pannell DJ. Sensitivity analysis: strategies, methods, concepts, examples. Agric Econ. 1997;16:139-52.
38. Van Ballegooijen M, Van Den Akker-Van Marle M, Warmerdam P, Meijer C, Walboomers J, Habbema J. Present evidence on the value of HPV testing for cervical cancer screening: a model-based exploration of the (cost-) effectiveness.

British journal of cancer. 1997;76(5):651.
39. Brown AD, Garber AM. Cost-effectiveness of 3 methods to enhance the sensitivity of Papanicolaou testing. JAMA: the journal of the American Medical Association. 1999;281(4):347-53.
40. Goldie SJ, Kuhn L, Denny L, Pollack A, Wright TC. Policy analysis of cervical cancer screening strategies in low-resource settings. JAMA: the journal of the American Medical Association. 2001;285(24):3107-15.
41. Mandelblatt JS, Lawrence WF, Gaffikin L, Limpahayom KK, Lumbiganon P, Warakamin S, et al. Costs and benefits of different strategies to screen for cervical cancer in less-developed countries. Journal of the National Cancer Institute. 2002;94(19):1469-83.
42. van den Akker-van ME, van Ballegooijen M, van Oortmarssen GJ, Boer R, Habbema JDF. Cost-effectiveness of cervical cancer screening: comparison of screening policies. Journal of the National cancer institute. 2002;94(3):193-204.
43. Mandelblatt JS, Lawrence WF, Womack SM, Jacobson D, Yi B, Hwang Y, et al. Benefits and costs of using HPV testing to screen for cervical cancer. JAMA: the journal of the American Medical Association. 2002;287(18):2372-81.
44. Maxwell GL, Carlson JW, Ochoa M, Krivak T, Rose GS, Myers ER. Costs and effectiveness of alternative strategies for cervical cancer screening in military beneficiaries. Obstetrics & Gynecology. 2002;100(4):740-8.
45. Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. Obstetrics & Gynecology. 2004;103(4):619-31.
46. Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. British Journal of Cancer. 2004;91(3):530-6.
47. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, Gordillo-Tobar A, Levin C, Mahé C, et al. Cost-effectiveness of cervical-cancer screening in five developing countries. New England Journal of Medicine. 2005;353(20):2158-68.
48. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. Journal of the National Cancer Institute. 2005;97(12):888-95.
49. Berkhof J, Coupé VM, Bogaards JA, van Kemenade FJ, Helmerhorst TJ, Snijders PJ, et al. The health and economic effects of HPV DNA screening in The Netherlands. International Journal of Cancer. 2010;127(9):2147-58.
50. Bidus MA, Maxwell GL, Kulasingam S, Rose GS, Elkas JC, Chernofsky M, et al. Cost-effectiveness analysis of liquid-based cytology and human papillomavirus testing in cervical cancer screening. Obstetrics & Gynecology. 2006;107(5):997-1005.
51. Koong S-L, Yen AM-F, Chen TH-H. Efficacy and cost-effectiveness of nationwide cervical cancer screening in Taiwan. Journal of medical screening. 2006;13(suppl 1):44-7.
52. Siebert U, Sroczynski G, Hillemanns P, Engel J, Stabenow R, Stegmaier C, et al. The German cervical cancer screening model: development and validation of a decision-analytic model for cervical cancer screening in Germany. The European Journal of Public Health. 2006;16(2):185-92.
53. Kim JJ, Kuntz KM, Stout NK, Mahmud S, Villa LL, Franco EL, et al. Multiparameter calibration of a natural history model of cervical cancer. American journal of epidemiology. 2007;166(2):137-50.
54. Kohli M, Ferko N, Martin A, Franco E, Jenkins D, Gallivan S, et al. Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK. British journal of cancer. 2007;96(1):143-50.
55. Bistoletti P, Sennfält K, Dillner J. Cost-effectiveness of primary cytology and HPV DNA cervical screening. International Journal of Cancer. 2008;122(2):372-6.
56. Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16, 18 vaccination. Journal of the National Cancer Institute. 2008;100(5):308-20.
57. Anderson R, Haas M, Shanahan M. The cost-effectiveness of cervical screening in Australia: what is the impact of screening at different intervals or over a different age range? Australian and New Zealand journal of public health. 2008;32(1):43-52.
58. Andrés-Gamboa O, Chicaíza L, García-Molina M, Díaz J, González M, Murillo R, et al. Cost-effectiveness of conventional cytology and HPV DNA testing for cervical cancer screening in Colombia. salud pública de méxico. 2008;50(4):276-85.
59. Vijayaraghavan A, Efrusy M, Lindeque G, Dreyer G, Santas C. Cost effectiveness of high-risk HPV DNA testing for cervical cancer screening in South Africa. Gynecol Oncol. 2009;112(2):377-83.
60. Goldie SJ, Diaz M, Constenla D, Alvis N, Andrus JK, Kim S-Y. Mathematical models of cervical cancer prevention in Latin America and the Caribbean. Vaccine. 2008;26:L59-L72.
61. Kulasingam S, Rajan R, Yvan St Pierre C, Myers E, Franco E. Human papillomavirus testing with Pap triage for cervical cancer prevention in Canada: a cost-effectiveness analysis. BMC medicine. 2009;7(1):69.
62. Levin CE, Sellors J, Shi JF, Ma L, Qiao Y, Ortendahl J, et al. Cost-effectiveness analysis of cervical cancer prevention based on a rapid human papillomavirus screening test in a high-risk region of China. International Journal of Cancer. 2010;127(6):1404-11.

63.Sroczynski G, Schnell-Inderst P, Mühlberger N, Lang K, Aidelsburger P, Wasem J, et al. Decision-analytic modeling to evaluate the long-term effectiveness and cost-effectiveness of HPV-DNA testing in primary cervical cancer screening in Germany. GMS health technology assessment. 2010;6.
64. Creighton P, Lew J-B, Clements M, Smith M, Howard K, Dyer S, et al. Cervical cancer screening in Australia: modelled evaluation of the impact of changing the recommended interval from two to three years. BMC public health. 2010;10(1):734.
65. Chuck A. Cost-Effectiveness of 21 Alternative Cervical Cancer Screening Strategies. Value in Health. 2010;13(2):169-79.
66. Obradovic M, Mrhar A, Kos M. Cost-effectiveness analysis of HPV vaccination alongside cervical cancer screening programme in Slovenia. The European Journal of Public Health. 2010;20(4):415-21.
67. Chow IH, Tang C, You S, Liao C, Chu T, Chen C, et al. Cost-effectiveness analysis of human papillomavirus DNA testing and Pap smear for cervical cancer screening in a publicly financed health-care system. British journal of cancer. 2010;103(12):1773-82.
68. Vijayaraghavan A, Efrusy MB, Goodman KA, Santas CC, Huh WK. Cost-effectiveness of using human papillomavirus 16/18 genotype triage in cervical cancer screening. Gynecologic oncology. 2010;119(2):237-42.
69. Shi J-F, Canfell K, Lew J-B, Zhao F-H, Legood R, Ning Y, et al. Evaluation of primary HPV-DNA testing in relation to visual inspection methods for cervical cancer screening in rural China: an epidemiologic and cost-effectiveness modelling study. BMC Cancer. 2011;11(1):239.
70. Demarteau N, Detournay B, Tehard B, El Hasnaoui A, Standaert B. A generally applicable cost-effectiveness model for the evaluation of vaccines against cervical cancer. International journal of public health. 2011;56(2):153-62.
71. Yamamoto N, Mori R, Jacklin P, Osuga Y, Kawana K, Shibuya K, et al. Introducing HPV vaccine and scaling up screening procedures to prevent deaths from cervical cancer in Japan: a cost-effectiveness analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 2012;119(2):177-86.
72. Burger E, Ortendahl J, Sy S, Kristiansen I, Kim J. Cost-effectiveness of cervical cancer screening with primary human papillomavirus testing in Norway. British journal of cancer. 2012.
73. de Kok IM, van Rosmalen J, Dillner J, Arbyn M, Sasieni P, Iftner T, et al. Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: cost effectiveness analysis based on a Dutch microsimulation model. Bmj. 2012;344.
74. Kulasingam SL, Havrilesky LJ, Ghebre R, Myers ER. Screening for cervical cancer: a modeling study for the US Preventive Services Task Force. Journal of lower genital tract disease. 2013;17(2):193.
75. Demarteau N, Morhason-Bello IO, Akinwunmi B, Adewole IF. Modeling optimal cervical cancer prevention strategies in Nigeria. BMC cancer. 2014;14(1):365.
76. Laprise J-F, Drolet M, Boily M-C, Jit M, Sauvageau C, Franco EL, et al. Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: a transmission-dynamic modelling study. Vaccine. 2014;32(44):5845-53.
77. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. The Lancet Global health. 2014;2(7):e406-e14.
78. Jit M, Brisson M, Laprise J-F, Choi YH. Comparison of two dose and three dose human papillomavirus vaccine schedules: cost effectiveness analysis based on transmission model. Bmj. 2015;350:g7584.
79. Nahvijou A, Daroudi R, Tahmasebi M, Hashemi FA, Hemami MR, Sari AA, et al. Cost-Effectiveness of Different Cervical Screening Strategies in Islamic Republic of Iran: A Middle-Income Country with a Low Incidence Rate of Cervical Cancer. PloS one. 2016;11(6):e0156705.
80. Lew J-B, Simms KT, Smith MA, Hall M, Kang Y-J, Xu XM, et al. Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic assessment for the National Cervical Screening Program. The Lancet Public Health. 2017;2(2):e96-e107.
81. Majidi A, Ghiasvand R, Hadji M, Nahvijou A, Mousavi A-S, Pakgohar M, et al. Priority Setting for Improvement of Cervical Cancer Prevention in Iran. International Journal of Health Policy and Management. 2015.
82. Nahvijou A, Hadji M, BaratiMarnani A, Tourang F, NedaBayat E, Daroudi R, et al. A Systematic Review of Economic Aspects of Cervical Cancer Screening Strategies Worldwide: Discrepancy between Economic Analysis and Policymaking. Asian Pacific Journal of Cancer Prevention. 2014;15(19):8229-37.
83. Farnsworth A. Screening for the prevention of cervical cancer in the era of human papillomavirus vaccination: an Australian perspective. Acta Cytol. 2011;55(4):307-12.
84.Organization WH. Cervical cancer screening in developing countries: report of a WHO consultation: World Health Organization; 2002.