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Erasmus/University Of Washington

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at http://cisnet.cancer.gov/profiles. The CISNET model profile topics are not necessarily meant to be read in sequential fashion, so the reader should feel free to skip around as their interests dictate.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

READERS GUIDE

CORE PROFILE DOCUMENTATION

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5–10 minutes. Each contains links to more detailed information if required.

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

Output Overview

Definitions and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Key References

A list of references used in the development of the model.

MODEL PURPOSE

SUMMARY

This part describes the purpose(s) for which the Erasmus/UW model was developed.

PURPOSE

The Erasmus/UW model was constructed for multiple purposes. First, we intend to gain better insight into the natural history of esophagus adenocarcinoma (EAC), especially with regards to the process by which cancer develops from Barrett's esophagus (BE). Second, the model is used to identify the driving factors for the substantial increase in EAC incidence over the last several decades. The model is able to inform investigators which factors might inform plausible explanations for the period or birth cohort efforts observed in the BE and EAC increases. Finally, the model is used in comparative effectiveness studies to calculate consequences of screening, surveillance and treatment strategies.

Model Overview

Summary

The Erasmus/UW model is a semi–Markov microsimulation model and includes three components:

- demography
- natural history
- screening

It uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, BE incidence, and transitions from one state of disease to another. The individual life histories are simulated in the demography component of the model. The natural history component of Erasmus/UW simulates the development of EAC in the population which can be interrupted by screening in the screening component of the model.

Purpose

The Erasmus/UW model was constructed for multiple purposes. See details in Model Purpose.

Background

The Erasmus/UW model is a semi–Markov microsimulation model, which is based on the MIcrosimulation SCreening ANalysis (MISCAN) models also available for prostate, breast, colon and lung cancers. The population is simulated at the individual level with each person evolving through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the Erasmus/UW model generates durations in states. With the assumption of an exponential distribution of the duration in each state, this way of simulating leads to the same results as a Markov model with yearly transition probabilities. The advantage of the Erasmus/UW model approach is that durations in a certain state are not required to be a discrete value (they can be continuous). The model uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, BE incidence, and transitions from one disease state to another.

The basic structure of the Erasmus/UW is separated into three main components:

- demography
- natural history
- screening

Model Description

The basic structure of the Erasmus/UW model is presented in figure 1. the model first simulates the life histories of a large population of individuals from birth to death. After this, the natural history of the disease is modeled according to current knowledge on BE incidence and malignant progression. Depending on age, sex and baseline individual risk, short or long segment BE may develop in an individual, which over time may progress to low–grade dysplasia (LGD) and high–grade dysplasia (HGD). In a minority of patients, malignant cells can arise from HGD, transforming to localized EAC that can progress sequentially into regional and advanced EAC.

In every preclinical cancer stage, there is a probability of the cancer being diagnosed due to the development of symptoms. The cure rate and survival after diagnosis depend on the stage of cancer. Patients may die of other causes at any moment during their lifetime.

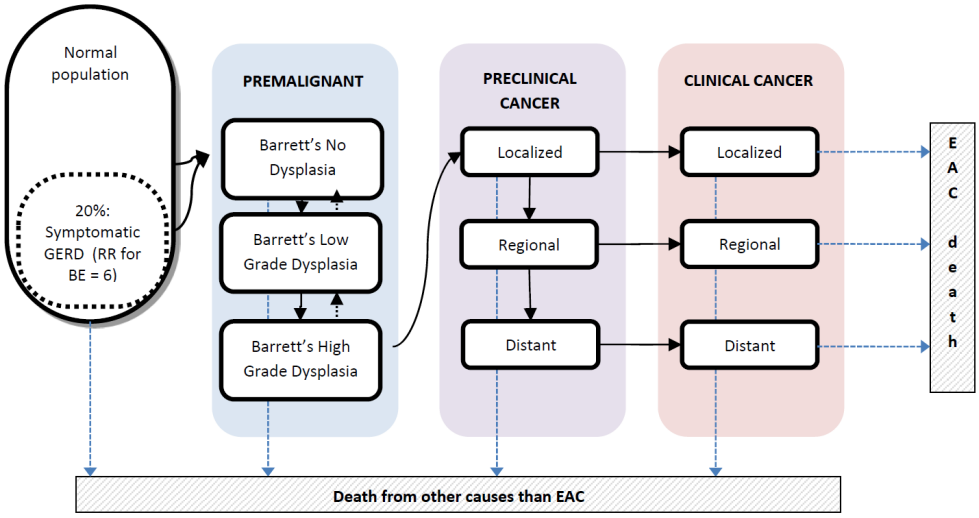

Figure 1. Erasmus/UW-EAC model

Demography component

The individual life histories are simulated in the demography component of the model. For each person, birth date and death date are simulated for causes other than EAC. The distribution of births and deaths can be adjusted to represent the simulated population.

Natural history component

The natural history component of Erasmus/UW simulates the development of EAC in the population. We assume that EAC develops through precursor BE which starts in a phase without dysplasia, thereafter dysplasia can develop. Two stages of dysplasia are defined: low grade and high grade. From HGD, malignant cells can arise that can transform from this stage to preclinical localized EAC, which can sequentially progress into regional and distant preclinical EAC.

Screening component

The development of EAC can be interrupted by screening and related palliative procedures. Screening can detect BE, the dysplasia states and preclinical cancers. BE and dysplasia can be removed using treatment. Usually, the cancers will be found in an earlier stage than with clinical diagnosis. In this way, screening reduces EAC incidence or EAC death.

ASSUMPTION OVERVIEW

SUMMARY

This part provides an overview of the main assumptions used in the Erasmus/UW model.

BACKGROUND

Several assumptions in the different parts of the model are considered to simplify the complex process of the disease progression and the interventions in a population. The assumptions are made in the following components;

- assumptions on demography
- assumptions on natural history
- assumptions on screening

ASSUMPTION LISTING

Demography Assumptions

These assumptions which focus on the demographic characteristics of the population are as follows:

- The life table differs in each cohort based on the birth year.
- Death from EAC cancer and other causes are considered independent from each other.

Natural History Assumptions

Natural history assumptions are related to the onset, progression, and response to treatment of EAC in the model. These assumptions are:

- Gastroesophageal Reflux Disease (GERD) prevalence is considered a fixed percentage of the population.
- BE development: in addition to development from no dysplasia to LGD and then HGD, BE patients could have also regression to the previous states, e. g. from HGD to LGD.
- BE incidence in the population is increasing until age 70.
- Types of BE: Long or short segment BE without dysplasia, with LGD or HGD.
- EAC cancer development: EAC can develop only through BE.
- Transition probabilities depend on the state of the disease.
- State durations depend on the state of the disease, e.g. patients with dysplasia have a shorter duration time than patients without dysplasia.
- Survival rates depend on the stage of cancer. It also depends on the year that they have got to that stage as the treatment modalities have been improved over the last decades which could improve the survival rates.

Screening Assumptions

These assumptions address the screening strategy parts in the model including attendance rate of the population, test characteristics and surveillance or treatment of the precancerous lesions as well. Assumptions are made on:

- Characteristics of screening tests: sensitivity of the screening test depends on the state of the disease.
- Attendance rate of the population is considered 100%.
- Impact of early detection and treatment of EAC which could improve the survival rate.
- Impact of detection of BE and treatment of dysplasia which prevent new EAC cases.
- Surveillance strategies after detection of BE patients are different according to the type of BE.

PARAMETER OVERVIEW

SUMMARY

This part provides an overview of the parameters used to quantify the Erasmus/UW model.

BACKGROUND

We have grouped the parameters in demographic, natural history, screening and output parameters.

PARAMETER LISTING OVERVIEW

Demography Parameters

1. number of birth cohorts
2. proportion of the population in each birth cohort
3. for each birth cohort parameters of its birth table
4. for each birth cohort the parameters of its life table

Natural history parameters

5. prevalence of GERD symptoms in the population
6. BE and EAC sequence states
7. parameters for the age specific distribution of onset of the first screen detectable state
8. parameters for the transition probability in each preclinical state
9. parameters for the duration distribution in each preclinical state
10. parameters for the time from a preclinical state to clinical detection
11. parameters for survival after clinical diagnosis by age at diagnosis, year of diagnosis, stage of disease and localization of the cancer
12. Parameters for proportion of low and high grade dysplasia in the BE population
13. Parameters for progression rate from each non–dysplastic (ND) BE, LGD and HGD to EAC

Screening test parameters

14. parameters for the dissemination of screening
15. the characteristics of screening test
16. parameters for survival after screen detected diagnosis
17. surveillance after screen–detected BE

Main natural history assumptions and results of the Erasmus/UW perfect and realistic model

Model parameter/value	Value in realistic model	Parameter characteristic *
Symptomatic GERD prevalence	20% of the total population	Fixed Input
BE from symptomatic GERD population	60% of total BE is from symptomatic GERD population	Fixed Input
BE prevalence age 60–64	1.4%	Optimized parameter
Percent of LGD in total BE at age 60–65	8.2%	Calibration target: 9.4%

Percent of HGD in total BE at age 60–65	1.2%	Calibration target: 2.2%
Annual progression rate from diagnosed BE (ND+LGD) to clinical EAC	0.07%	Optimized parameter
Annual progression rate from diagnosed BE (ND+LGD) to clinical and detected EAC	0.18%	Calibration target: 0.18% in realistic model
Average sojourn time from preclinical cancer to clinical cancer, given transition	5.0	Calibration target: 4–5 year
Average time in BE to next transition	6.7	Optimized parameter
Average time in LGD to next transition	1.0	
Average time in HGD to next transition	1.1	
Regression transition probability		Optimized parameter
P(LGD to ND BE)	88%	
P(HGD to LGD)	15%	

* Fixed input: the parameter is defined as a fixed input of the model, Optimized parameter: the parameter is relaxed and is optimized during calibration of the model, the value is a result of the model; Calibration target: the model is calibrated to fit the fixed calibration targets as good as possible. Model is furthermore calibrated on the SEER–9 EAC incidence data from 2000–2009 for all males. GERD: Gastro–esophageal reflux disease; BE: Barrett's esophagus; ND: No dysplasia; LGD: Low grade dysplasia; HGD: High grade dysplasia; EAC: Esophageal adenocarcinoma

The following sources were used to define these assumptions: [1,2,3,4,5,6,7,8,9,10,11,12,13,14].

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COMPONENT OVERVIEW

SUMMARY

This part describes the main components of the Erasmus/UW model.

OVERVIEW

As described in the Model overview, Erasmus/UW model includes three components: demography, natural history and screening.

COMPONENT LISTING

Demography Component

The individual life histories are simulated in the demography component of the model. For each person, a birth date and death date is simulated for other causes than EAC. The demography parameters are birth table parameter and life table parameters.

Natural history Component

The Natural History component of Erasmus/UW simulates the development of EAC in the population. We assume that EAC develops through precursor long or short–segment BE. A personal risk index is generated for each individual in the simulated population. Figure 2 shows the modeling natural history with life history.

A minority of the population has symptomatic GERD, giving them a higher risk of developing BE during their lifetime. The development of BE (ND) is generated according to this personal risk index and an age–specific incidence of onset. The sequence from the onset of BE to EAC diagnosis is continued by sojourn times between the different states. BE starts in a phase without dysplasia, thereafter dysplasia can develop. Two stages of dysplasia are defined: LGD and HGD. From HGD, malignant cells can arise that can transform from this stage to preclinical localized EAC, which can sequentially progress into regional and distant preclinical EAC. There is a possibility that regression from HGD to LGD and from LGD to ND occurs. The probability to regress or progress is dependent on a transition matrix and is therefore also influenced by the sojourn time. In each of these three preclinical cancer stages, there is a probability of the cancer being diagnosed. The sojourn times between these described stages are exponentially distributed and in some cases (BE–ND, BE–LGD and BE–HGD) are age–dependent. Because most sojourn times extend beyond the demography–generated age of death from other causes, only a small proportion of the population develop EAC from BE. The survival after clinical diagnosis depends on the cancer stage and the year of diagnosis.

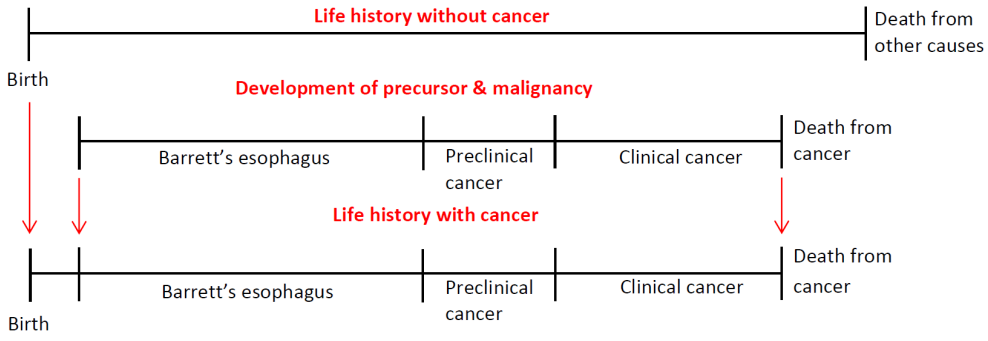

Figure 2. Modeling natural history with life history

Erasmus/UW distinguishes the following states of the disease process:

1. normal, no known disease

Preclinical

2. non–dysplastic short segment BE
3. short segment BE with Low–grade dysplasia
4. short segment BE with High–grade dysplasia
5. non–dysplastic Long segment BE
6. long segment BE with Low–grade dysplasia
7. long segment BE with High–grade dysplasia

Invasive

8. preclinical cancer localized
9. preclinical cancer regional
10. preclinical cancer distant

Clinical

11. clinical cancer localized
12. clinical cancer regional
13. clinical cancer distant

Screening Component

The screening component is simultaneously run with the natural history component. The development of EAC can be interrupted by screening. Screening can detect BE, the dysplasia states and preclinical cancers. Patients with BE and dysplasia could be kept under surveillance or BE and dysplasia can be removed using treatment. In this situation, usually, the cancers will be found in an earlier stage than with clinical diagnosis. See Figure 3 for modeling screening and treatment interventions into life history.

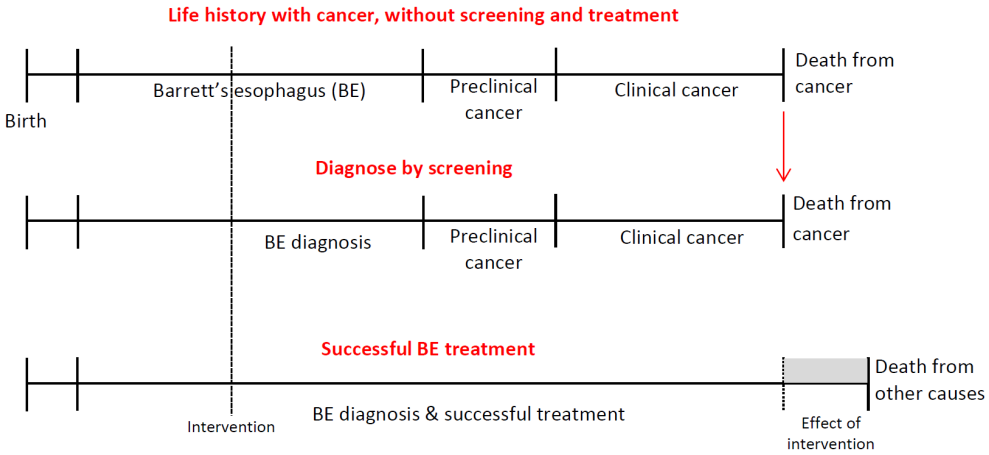

Figure 3. Modeling screening and treatment interventions

OUTPUT OVERVIEW

SUMMARY

This part provides overview of the outputs generated by the Erasmus/UW model.

OUTPUT LISTING

The outputs are generated by Erasmus/UW model include:

1. incidence counts of each disease state by calendar year
2. mean prevalence of each disease state in five year age groups
3. number of invitations for screen tests, and surveillance for each year
4. number of positive and negative test results per disease state and per year
5. number of specific deaths and non–specific deaths
6. total number of life years and life years lost due to cancer
7. number of life years gained due to screening by year of screening
8. total number of life years in surveillance
9. total number of life years with initial therapy after screen–detected or clinical cancer for each state
10. total number of life years with continuous care after screen–detected or clinical cancer for each state
11. total number of life years with terminal care before death from other causes
12. total number of life years with terminal care before death from EAC

RESULTS OVERVIEW

SUMMARY

This part describes the results obtained from the Erasmus/UW model.

OVERVIEW

The Erasmus/UW model has been applied to inform policies with regards to screening of the population, surveillance and management of patients with GERD and BE to prevent EAC. The result part describes the studies which have used Erasmus/UW model.

RESULTS LIST

Estimation of future U.S. EAC incidence

The Erasmus/UW model was calibrated to clinical and epidemiologic data including EAC incidence from the Surveillance, Epidemiology, and End Results (SEER 9) registry from 1975–2010 to project EAC incidence and mortality to year 2030. The results obtained from Erasmus/UW model were compared with two other independently developed models (FHCRC and MGH) as well.

Importantly, all three models identified birth cohort trends affecting cancer progression as a major driver of the observed increases in EAC incidence and mortality. All models predict that incidence and mortality rates will continue to increase until 2030 but with a plateauing trend for recent male cohorts. The predicted ranges of incidence and mortality rates (cases per 100,000 person–years) in 2030 are 8.4–10.1 and 5.4–7.4 respectively for males, and 1.3–1.8 and 0.9–1.2 for females. Figure 4 shows the EAC incidence rates by 10 year birth cohorts for all males. The cohort born in 1959 would be 71 years old in calendar year 2030. The details are described in Kong CY, et al. 2014 paper.[1]

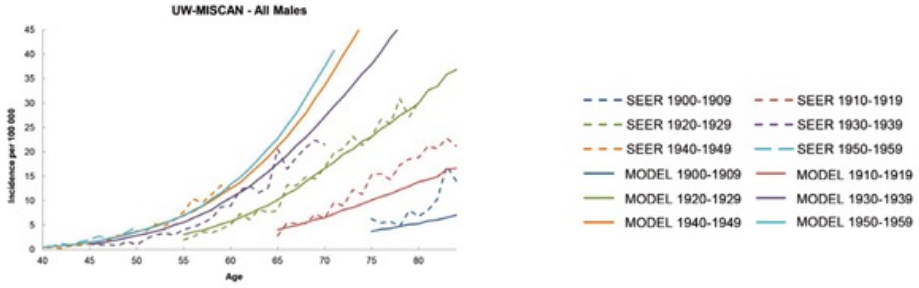

Figure 4. The EAC incidence rates by 10 year birth cohorts for all males

Estimation of the rate of progression from BE to EAC

The Erasmus/UW model was used to reconcile published data and more accurately estimate the incidence of EAC among people with BE. The calibration to the population–based study, including realistic surveillance, resulted in an annual progression rate of 0.19% for BE to EAC with a 5–year follow–up. The same disease model predicted a 0.36% annual rate of progression in studies with a prospective design. Therefore, in the first 5 years after diagnosis, the rate of progression from BE to EAC is likely to more closely approximate the lower estimates reported from population–based studies than the higher estimates reported from prospective studies, in which EAC is detected by surveillance.

The result of this study could be used by clinicians to explain to patients their risk if no

action is taken, and then discuss the risks and benefits of surveillance. You can find details in Kroep S, et al. 2015.[2]

As the previous study showed that estimates for the annual progression rate from BE to EAC vary widely, it was also quantified that how this uncertainty impacts the estimates of effectiveness and efficiency of screening and treatment for EAC. This uncertainty could seriously hamper decision–making regarding the implementation of BE screening and treatment interventions. The details are described in Kroep S, et al. 2015 paper.[3]

Estimation of the impact of endoscopic eradication for BE on EAC incidence and mortality

New techniques for the endoscopic eradication of the EAC precursor BE such as radiofrequency ablation (RFA) is utilized to prevent progression to EAC. The efficacy and durability of endoscopic eradication are reported, but the long–term impact of eradicative treatment and recurrent disease on EAC incidence and overall mortality reduction has not been analyzed with comprehensive and robust simulation models using this recently updated clinical data. The Erasmus/UW model was used to analyze the impact of RFA for the endoscopic eradication of BE with or without dysplasia on EAC incidence and mortality. The results obtained from the Erasmus/UW model were compared with other two aforementioned models as well.

The models showed that a strategy to endoscopically eradicate BE with high–grade dysplasia will decrease EAC incidence by 50% (range 44%–58%) and EAC mortality by 46% (41%–53%). The results indicated that RFA is an effective means of reducing EAC incidence and mortality. The benefit is predicted to be achieved in all patients with BE; however, the efficiency of eradication is substantially reduced if patients with LGD and no dysplasia are treated, and substantially more healthcare resources are required to avert a cancer death in these settings. Figure 5 shows the mortality reduction compared to the total number of treatments per model and strategy.[4]

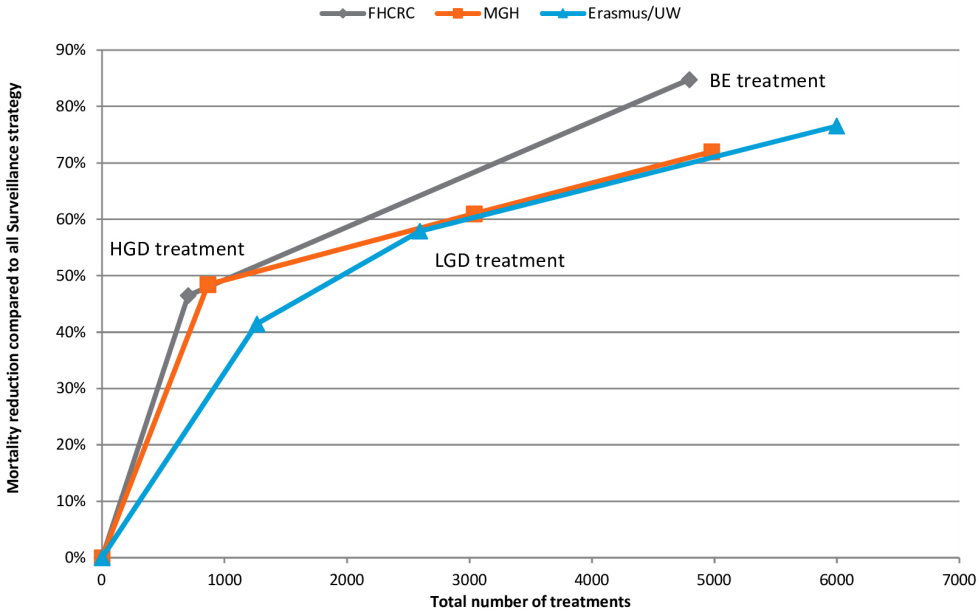

Figure 5. Mortality reduction compared to the total number of treatments per model and strategy. BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, Strategies: HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy.

Analyzing the cost–effectiveness of Cytosponge for screening patients at high risk of developing EAC or BE

The Erasmus/UW and MGH models were used to analyze the cost–effectiveness of Cytosponge as a first–line screening method with endoscopic confirmation for positive results in patients at high risk of developing EAC or BE. The models suggested that initial Cytosponge with endoscopic confirmation would be a cost–effective screening strategy for patients with GERD symptoms. The greatest benefit was achieved by endoscopic screening, but with an unfavorable marginal cost. Figure 6 shows more details regarding cost and QALY gained per strategy and the model.[5]

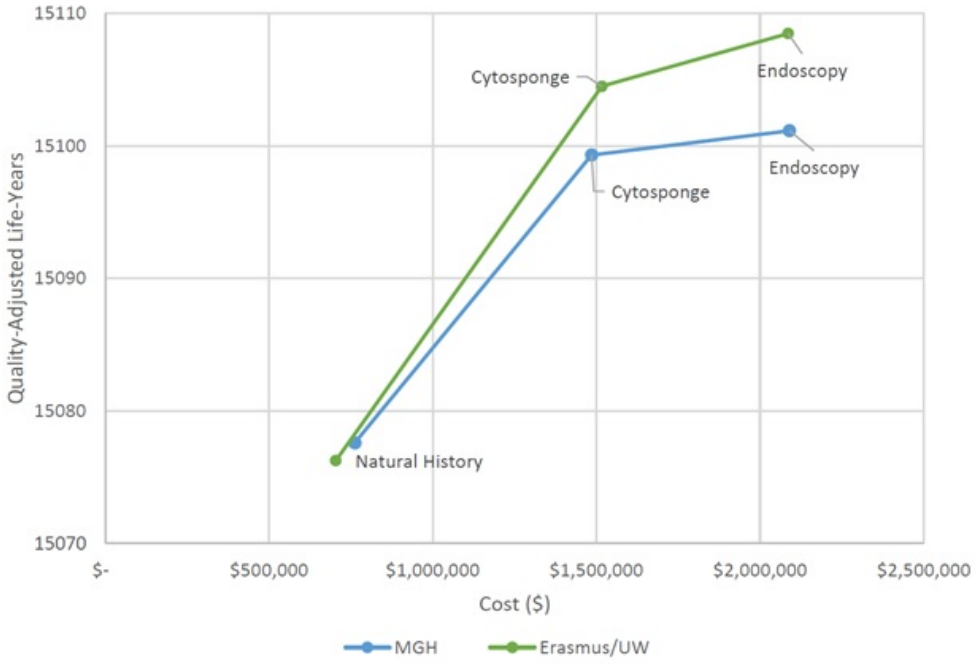

Figure 6. Cost/benefit curves for the MGH (blue) and Erasmus/UW (green) models.

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