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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

The primary purpose of the esophageal adenocarcinoma model (EACMo) is to advance our understanding of esophageal adenocarcinoma (EAC), including its natural history in order to positively impact cancer control. A particular interest is the management of Barrett's esophagus, a pre–malignant condition associated with high risk of developing EAC, which has become a significant clinical management issue with increasing upper endoscopy utilization.

Purpose

Since 1975 the incidence of EAC in the United States has seen a more than six–fold increase. In light of this alarming trend, EACMo was developed to advance our understanding of this disease. The model includes a natural history component, as well as screening and intervention components.

The purpose of the natural history component is to systematically integrate and synthesize all available information about the progression of the disease. EACMo includes a calibrated Markov state transition model of EAC, including precursor health states such as GERD, Barrett's esophagus (BE), and dysplasia; this model agrees well with available data on EAC incidence and mortality, as well as with published rates of BE and GERD prevalence. The natural history model includes age, period, and cohort effects, and can be used to explore and analyze different hypotheses as to the cause of the rise in EAC incidence. It has been used to produce projections of EAC incidence into the future.[1] Finally, the natural history model serves as a foundation upon which we can overlay and assess the impact of screening or other interventions.

In addition to the natural history of the disease, EACMo seeks to evaluate the effectiveness of current practice in screening for EAC and managing precursor states such as BE. To accomplish this, EACMo's design includes screening and treatment components which can be tailored for each specific analysis. Specific questions which EACMo has been used to address or may be used to address in the future include:

1. What is the effectiveness of current endoscopic practice in terms of surveillance of BE patients?
2. What is the practicality of targeted screening based on biomarkers or other identifiable risk factors?
3. What is the impact and effectiveness of radiofrequency ablation as a treatment for non–dysplastic or dysplastic BE?
4. What are the chemopreventive effects of asprin or other medications?
5. What is the impact of early detection of EAC with new endoscopic technologies?

Future plans for EACMo include its use in the development of decision aids.

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[1] Kong CY, Kroep S, Curtius K, Hazelton WD, Jeon J, Meza R, Heberle CR, Miller MC, Choi SE, Lansdorp-Vogelaar I, van Ballegooijen M, Feuer EJ, Inadomi JM, Hur C, Luebeck EG "Exploring the recent trend in esophageal adenocarcinoma incidence and mortality using comparative simulation modeling." in Cancer Epidemiol Biomarkers Prev. 2014; 23: 6: 997-1006

Model Overview

Summary

This document provides a broad overview of EACMo, including information about its basic structure and the kinds of problems it was designed to solve.

Purpose

The purpose of the model is to inform our understanding of esophageal cancer, its natural history, and the efficacy of screening and other interventions.

Background

Since 1975 there has been a rapid (more than six–fold) rise in EAC incidence in the United States. Given this increase, and the high mortality associated with advanced stages of the disease, it is imperative to explore approaches to prevention or early detection to reduce the burden of the disease.

Even with this dramatic increase, the absolute number of EAC cases per year remains too low to screen the general population,[1] although targeted endoscopic screening may be appropriate. Heartburn, the primary symptom of gastroesophageal reflux disease (GERD), affects 60 million Americans[2] and can lead to Barrett's esophagus (BE), a pre–malignant condition associated with the greatest risk (30–125x) of developing EAC.[3] Because of the significant number of individuals affected by GERD and BE, the management of these patients has become a public health issue, recently underscored by an Institute of Medicine report that prioritized crucial areas for comparative effectiveness research.[4] However, the relatively low rate of progression to cancer[5] has made clinical trials with cancer endpoints challenging because of the number of subjects and follow–up period required. These difficulties have contributed to the lack of an accepted screening and management strategy.

EACMo has numerous precursor model versions including clinical or patient–centered models of Barrett's esophagus that focused on specific clinical issues such as the management of high–grade dysplasia and chemoprevention with aspirin as examples. However, EACMo is different and more comprehensive as it is a population model that fully leverages the US SEER cancer data registry. Thus, the model is now equipped to assess screening, surveillance and prevention strategies for population cancer control.

Model Description

EACMo represents the natural history of esophageal adenocarcinoma as a state–transition model. It models the progression of a population through health states including normal health, BE, dysplasia, preclinical cancer, clinical cancer, and death. Screening and treatment can be imposed on top of this natural history model to estimate their potential impact.

The natural history component of EACMo is a Markov model with a cycle length of one month. Transition rates depend on age, and may also depend on birth cohort and/or calendar year. Transition rates which cannot be determined directly from empirical data are calibrated. Model parameters are calibrated separately for white male, all male, white female, and all female versions of the model. Given the large number of

parameters, a simulated annealing algorithm is used to efficiently search the parameter space and determine the optimum values in an automated fashion.

EACMo's natural history component supports simulation at both the population and individual levels of analysis. When simulating individuals during screening and treatment components, the model transitions from a semi–Markov population model to a microsimulation model to account for transitions that depend on an individual patient's history beyond the most recent health state. This allows us to conduct analyses with a high degree of clinical realism while keeping the core of EACMo as simple as possible.

Primary calibration inputs are SEER EAC incidence and mortality data, by age, gender, and calendar year. Additional inputs for calibration include estimates of GERD prevalence and of BE prevalence.

Inputs for the calibrated model are primarily the calibrated transition parameters, which include parameters for age–dependent transition functions as well as functions of birth year and of calendar year. Other inputs include initial values for BE and GERD prevalence, population tables, and life tables for including all source mortality.

Primary outputs are incidence and incidence–based mortality of EAC, including future projections. Secondary outputs include prevalence of GERD, BE, including dysplasia. Other outputs which have been or can be computed from the model include life years/ expectancy, cancer progression/dwell time, progression rates, costs, and measures of the impact of screening and medical efficiency such as the number of endoscopies needed to prevent one cancer in a given population.

We have sought to attain a high degree of transparency via a simple model design; consequently, some aspects of the model may be oversimplified relative to clinical reality. (See Assumption Overview for more details.) Additionally, data pertaining to the natural history of EAC, particularly precursor states, remain sparse, making it difficult to estimate needed calibration targets such as the prevalence of BE as a function of calendar year stratified by age and gender.

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ASSUMPTION OVERVIEW

SUMMARY

This document provides an overview of the major assumptions made in constructing EACMo.

BACKGROUND

Although SEER provides extensive data on EAC incidence and mortality, data on EAC's precursor health states, including GERD, BE, and dysplasia, are relatively sparse. Thus, any model of EAC will involve significant assumptions about the natural history of the disease. In developing EACMo, assumptions were chosen with two goals in mind: keep the model structure as simple as possible, and maximize the utility of the high quality data that does exist.

ASSUMPTION LISTING

No Regression

We assume that there is no 'regression' between health states. In particular, patients with dysplasia cannot return to BE with no dysplasia (or to a lower grade of dysplasia) without treatment, and likewise patients with Barrett's esophagus do not spontaneously regress to normal health. The extent to which regression from these states occurs in the real world is unclear as there are reports in the clinical literature. Omitting regression is an example of prioritizing model simplicity in the lack of definitive evidence.

Markov Property

In the natural history model we assume that a patient's health state depends only on their state in the previous cycle. Thus, for example, a patient who has been in the BE health state for one year has the same probability of transitioning to cancer as a patient who has had BE for 10 years (provided they are the same age, gender, etc.). This is a key simplifying assumption that makes automatic calibration feasible. It is important to note that this assumption applies only to the natural history of the disease in the model; screening and treatment strategies can take into account details of the patient's full history.

Calibration Constraints

Calibration to SEER data is the process used to systematically fill in the gaps in our knowledge of the disease natural history. Several assumptions based on the published literature were made to constrain the parameter space for the calibration process. These include constraints on the relative transition rates from normal to BE vs GERD to BE, the ratio of short vs long segment BE, and the progression rates out of short vs long segment BE. More detail on these assumptions can be found in the component overview document under the calibration component.

PARAMETER OVERVIEW

SUMMARY

This document provides a high level description of the parameters used in EACMo.

BACKGROUND

Data pertaining to the natural history of EAC is generally quite limited, due to the rarity of the disease and the low progression rate from identifiable precancerous states. However, the Surveillance Epidemiology and End Results (SEER) registry provides data on the incidence and mortality of EAC (including stage distribution) in the U.S. population, stratified by age, year of diagnosis, gender, and race, from ages 20 to 84 and calendar years 1975 to 2010. EACMo is designed to leverage this high–quality data as much as possible. Additionally, estimates of GERD prevalence and BE prevalence over time are drawn from the literature. The actual parameters are determined by calibration to produce outputs matching the known values, with an emphasis on agreement with SEER data.

Analyses of screening or treatment require additional parameters to realistically model the strategies being tested. Examples are provided in the parameter listing below. These parameters are estimated as needed from clinical studies in the published literature, including additional patient–level data when available directly from researchers when possible. When such clinical study is not available, we may rely on estimates based on both expert opinion and biologic plausibility. Sensitivity analyses can be conducted to incorporate the uncertainty in these parameters and assess potential impact on model results.

PARAMETER LISTING OVERVIEW

Natural History Parameters

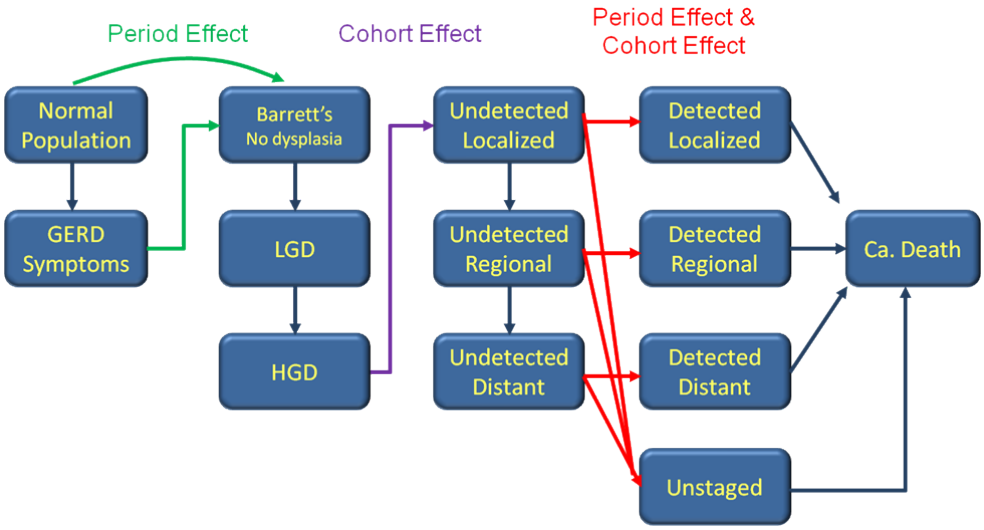
Most parameters in the natural history model are used to determine the probability of transitioning from one state to another. For a few transitions, this probability can be computed directly from available data. For example, the transition probability from any state to non–cancer–related death can be taken directly from available life tables, and the transition probabilities from detected cancer states to cancer mortality can be inferred from SEER survival data.

All other transition rates are determined by parameter calibration. In general multiple parameters may be needed to compute a single transition rate. Parameters may be logically divided into those pertaining to age, calendar year, and birth cohort. Age is assumed to be the predominant effect; in the current model, all transition rates increase as a linear function (determined by two calibrated parameters) of the patient's age. Period and cohort effects are secondary and are only applied to certain transitions. Currently all period and cohort effects are modeled as logistic functions, requiring four parameters each to fit, although other functions are possible. Further understanding of the underlying causes of the rise in EAC will allow us to better inform the period and cohort effects in our model, providing for more confident projections of EAC incidence and mortality.

The current model includes a period effect on the rate of transition from Normal and GERD to BE, a cohort effect on the transition from high grade dysplasia to undetected localized EAC, and both period and cohort effects on the transitions from undetected

to detected cancer, with the cohort effect from HGD to undetected localized EAC having the largest impact on the increase in EAC incidence over time. This is summarized in the diagram below.

The choice of where to apply period and cohort effects represents important assumptions about the natural history of EAC and the potential causes of its recent rise in incidence. These assumptions merit careful consideration as additional data become available and during the development of the model.



Model Schematic

Parameters for Screening and Other Interventions

When overlaying screening or other interventions on the natural history model it is necessary to obtain estimates of many other parameters. These are generally not determined by calibration but rather taken directly from the literature or estimated by expert opinion. The parameters needed vary widely with the strategy being tested. An incomplete list of examples includes test performance characteristics, recurrence rates after treatment, complication (and mortality) rates for a particular treatment or screening method, costs of treatment or screening, quality of life adjustments, and efficacy of treatment.

COMPONENT OVERVIEW

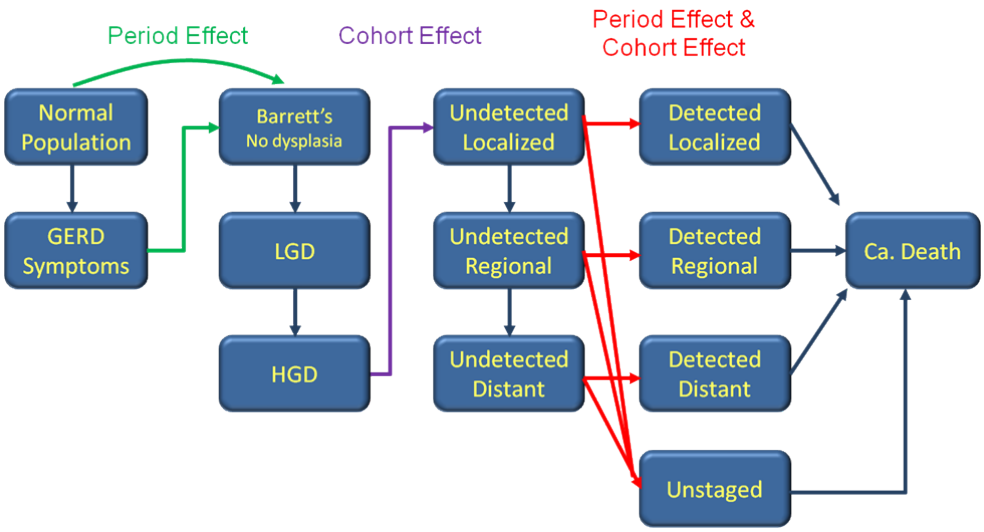
SUMMARY

This document describes the components of EACMo.

OVERVIEW

Natural History Component

Simulated populations enter the model in the Normal Population state and may pass through up to five additional health states. Fractions of the population can progress from the Normal State to the GERD symptomatic state (or directly to the BE state) and fractions of this second state can further progress to the BE state. Increasingly smaller populations then progress from BE to Undetected Cancer and Detected Cancer, and finally Death. A simplified schematic of the natural history model is shown below. The natural history component supports both population–level and individual–level simulation.



Model Schematic

Calibration Component

The calibration component is responsible for determining the optimum parameters for the Natural History Component. It uses a simulated annealing algorithm to efficiently and automatically find the natural history transition rates that produce output best aligned or optimally calibrated to SEER data.

Screening/Intervention Components

These components interact with the calibrated natural history model, overlaying the strategy to be tested and allowing its health impact to be measured. These simulate patients at the individual level, allowing for a high degree of clinical realism. They can be customized for each individual analysis.

COMPONENT LISTING

Natural History Component

This is the core component of EACMo; it simulates the natural history of EAC from normal health through GERD, BE, Undetected Cancer, Detected Cancer, and Death. Transition rates between states are determined by the calibration component, which

automatically chooses the values which optimize the model fit to SEER data.

Patients enter the model in the Normal state at age 20 and may progress directly to BE, or may progress to the GERD state and then to BE.

The BE state consists of six subdivisions (clinical factors) by length and dysplasia status: Short segment BE (SSBE) with no dysplasia (ND), with low grade dysplasia (LGD), and with high grade dysplasia (HGD), and long segment BE (LSBE) with the same dysplasia classifications. These subdivisions are important because dysplasia status and BE segment length are known predictors of risk of progression to cancer; a patient with high grade dysplasia warrants a different management strategy for their condition than a patient with BE alone. Patients in the no dysplasia states may progress to either LGD or directly to HGD. From the HGD subcomponents patients may progress to undetected localized cancer.

From undetected localized cancer patients may progress to regional cancer, and from there to distant. At each stage there is a probability of progressing to detected cancer.

We assume that all cancer patients must first pass through BE (both non dysplasia and HGD), that there are no transitions from short segment BE subcomponents to long segment BE subcomponents or vice versa, and that there is no regression among health states. We assume that all transition rates increase with age, while a few transition rates are assumed to depend on calendar year or birth cohort.

Recently, the natural history component has been used – in conjunction with the other CISNET EAC models – to explore the rise in EAC and provide projections of future incidence and mortality.[1]

Calibration Component

This component is responsible for setting all transition rates in the natural history component, with the exceptions of all–cause mortality and cancer–specific mortality for patients with detected cancer (which are derived directly from available data). Calibration is necessary because the transition rates can vary by calendar year, age, and birth cohort and there is insufficient data in the literature to estimate these values directly. Therefore, this component uses a simulated annealing approach to efficiently search the parameter space and automatically select an optimum set of transition rates that maximize model fit to clinical targets. The optimum calibrated parameter set can be used to inform estimates of quantities that cannot be measured in a clinical setting, such as mean sojourn times and estimated transition rates between preclinical states.

The search space for this process was constrained by several assumptions. The age–dependent transition rates from normal to no dysplasia were fixed as 1/6 the corresponding rates from GERD to no dysplasia. Likewise, the transition rates from short segment HGD to cancer were fixed as 1/2 the corresponding rates from long segment HGD to cancer. The transitions into long segment and short segment no dysplasia were constrained such that the total ratio of short segment BE to long segment BE is approximately 3:1.

Screening/Intervention Components

These components overlay screening, treatment, or other disease management strategies on top of the natural history model. EACMo uses a 'parallel universe' approach; the impact of an intervention is measured by simulating the disease history

in the presence of that intervention, then comparing the outcomes to a simulation of the natural history alone. The specifics of the intervention components vary with each analysis. Costs and health–related quality of life adjustments are common to each CISNET model of esophageal adenocarcinoma, and are therefore handled external to the core of EACMo.

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Output Overview

Summary

This document provides an overview of the outputs produced by EACMo.

Overview

EACMo outputs can be broadly divided into natural history outputs and intervention assessment outputs.

Natural history outputs include incidence and mortality of EAC, prevalence of BE and GERD, progression rates, and dwell time (the time from onset of BE to development of cancer). Outputs in this category can be used for calibration and validation of the model. Additionally, the model can be extrapolated into the future to provide projections of these outputs.

Intervention assessment outputs or clinical endpoints can include number of treatments or endoscopies needed, reduction in cancer mortality, life years gained, and total costs. These outputs relate directly to decisions about treatment/prevention of EAC and management of precursor health states such as BE.

Output Listing

EAC Incidence & Mortality

A primary output of the model is the incidence and mortality of EAC, stratified by age, race, gender, and calendar year. The model is calibrated so that the natural history model output agrees with SEER data for the years where such data are available. This output is also available in future projections. When intervention strategies are overlaid on the natural history model, the change in this output is a key endpoint.

BE/Dysplasia Prevalence

An early version of EACMo was used to estimate the prevalence of BE in the U.S. population. In the current model, overall BE prevalence as estimated from the available literature is used as a calibration target. The breakdown of low grade and high grade dysplasia within BE is also constrained during calibration. Estimates of BE and dysplasia prevalence within different subpopulations are important when evaluating the overall costs and benefits of screening, surveillance, and treatment.

Progression Rates/Dwell Time

EACMo can produce various estimates of the time of progression from one health state to another. For example, the 'dwell time' between onsets of BE and development of EAC can be estimated. These timings are of clinical significance, and are useful for model validation and comparison to other models.

Costs/Efficiency Estimates

The cost of an intervention is of obvious importance to health policy planning. These costs can be aggregated as dollars, or measured directly by the needed number of endoscopies, treatments, etc., as estimated by the model. Numbers of complications and of treatment–related deaths can also be computed directly from these outputs, provided estimates of per–procedure complication rates are available.

Results Overview

Summary

This document provides an overview of the results produced by EACMo.

Results List

Cytosponge Screening for Barrett's Esophagus
The Cytosponge is a noninvasive cell–sampling device that can identify Barrett's esophagus, a precursor to esophageal adenocarcinoma, in patients with GERD. In this analysis, done with the current version of EACMo and the UW–MISCAN model, it was found that first–line screening of patients with GERD with the Cytosponge is cost–effective.[1]

Cost effectiveness of radiofrequency ablation for Barrett's esophagus
This analysis assessed effectiveness and cost–effectiveness of radiofrequency ablation (RFA) using a simple precursor to the current version of EACMo. It was found that RFA was cost–effective (compared to endoscopic surveillance) for patients with high grade dysplasia, might be cost–effective for low grade dysplasia, and might not be cost–effective for Barrett's with no dysplasia.[2]

In a later joint analysis with the FHCRC and UW–MISCAN modeling groups, it was found that all three models confirmed current guidelines endorsing RFA for patients with high grade dysplasia. The models diverged on low grade dysplasia eradication conclusions, highlighting the need to better understand the health state.[3]

Projections of esophageal cancer incidence and mortality
Calibrated natural history models were used to provide future projections of esophageal cancer incidence and mortality. This was a collaborative modeling exercise performed in conjunction with the FHCRC and UW–MISCAN modeling groups.[4]

The impact of obesity on the rise in esophageal adenocarcinoma incidence
Understanding the rise in EAC incidence is a critical goal of EACMo. This analysis used an early version of the model to measure the extent to which this rise could be attributed to the concurrent rise in obesity rates. It was found that obesity could account for only a small percentage of the increase.[5]

The prevalence of Barrett's esophagus in the US
Barrett's esophagus is a precursor to and risk factor for EAC. It's prevalence in the population is difficult to estimate, but has public health significance. This analysis used an early version of EACMo to estimate the true prevalence of BE at 5.6%, based on model fit to SEER incidence data.[6]

Development, calibration, and validation of a U.S. white male population–based simulation model of esophageal adenocarcinoma
Contains details on an early version of EACMo, and an analysis of aspirin chemoprevention.[7]

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