# Impact of Comorbidity on Colorectal Cancer Screening Cost-Effectiveness Study in Diabetic Populations

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## APPENDIX

**Table of Content**

# 1. Introduction and Overview

The Archimedes Model is a large-scale simulation model of physiology, diseases, and healthcare systems that has been described in the literature (1-4). While a number of modeling frameworks exist (e.g. Markov models), the Archimedes Model is relatively distinct. For example, unlike Markov models in which individuals probabilistically transition from one disease state to another at discrete time intervals (e.g. annually), and in which there may be no "memory" of prior disease states, the Archimedes Model is built up from the underlying anatomy, physiology, and biological variables. Diseases and outcomes are defined in terms of these underlying variables and can therefore occur and progress in a continuous fashion. Interventions and treatments act on the underlying variables to modify or prevent disease progression. Validations of the model have appeared in the literature (5-7). Currently, the model includes submodels for diabetes, hypertension, obesity, coronary heart disease, stroke, and cancers of the breast, lung and colon.

The structure and equations of the Archimedes Model pertinent to diabetes and its complications have been discussed in detail in the literature (2, 6, 8). Equations that predict the progression of diabetes over time and cause people to develop diabetes at rates that match observed rates were derived from national surveys (9-10). The risk of developing diabetes depends on many factors including body mass index (BMI), age, gender, and race. The biological variables captured by the diabetes submodel include fasting plasma glucose (FPG), HbA1c, oral glucose tolerance (OGT), random plasma glucose, and blood pressure. The diabetes submodel also tracks symptoms relating to glucose metabolism), diabetes-related events (i.e. ketoacidosis, hypoglycemia), and diabetic complications (i.e. coronary heart disease, stroke, neuropathy, retinopathy and nephropathy). Diabetes patients can either die of the complications of diabetes (e.g. myocardial infarction) or from other causes (e.g. cancers). The model predictions of diabetes-related outcomes have been validated against a large number of epidemiological, basic science, clinical and health service research studies, and controlled clinical trials (5).

The colorectal cancer (CRC) component in the Archimedes Model was developed in collaboration with the American Cancer Society. The CRC component is fully integrated with other diseases in the Archimedes Model. Sections 1-3 of the current appendix provide a detailed description of the CRC submodel within the Archimedes Model. Section 4 summarizes validations of the CRC submodel.

## 1.1 Scope of the colorectal cancer submodel

The CRC component within the Archimedes Model provides a comprehensive description of CRC at the clinical level. It is designed to evaluate the impacts of screening and prevention on health and economic outcomes associated with CRC. More specifically, it is designed to answer questions such as the following:

- What are the effects of perfect and feasible compliance to recommendations regarding cancer screening, smoking, diet/exercise, and weight control, on CRC in terms of incidence, mortality, years of life lost and healthcare cost?
- Is screening for CRC using stool DNA cost effective?
- For people who have had an adenomatous polyp found at colonoscopy, what difference does it make in terms of diagnosed incidence and mortality if the next exam is in three years, five years, or ten years?

## 1.2 Sources of data

The CRC model was built from the following types of data sources:

- ***Summary data of small studies:*** Small studies involving tens to hundreds of individuals were used to estimate parameters for a specific aspect of CRC, such as tumor growth rates or adenoma incidence. These included clinical trials, autopsy studies, colonoscopy screening studies, and retrospective studies. The information in these studies was synthesized through meta-analysis.
- ***Large-scale clinical trials and databases:*** Large-scale trials or databases involving tens of thousands of patients were used to construct and to calibrate several components of the model. For instance, information on polyp location and size were extracted from the Clinical Outcomes Research Initiative (CORI) database(11), which contains data on 220,000 colonoscopies.
- ***National surveys:*** Information from national surveys and databases was used to model various aspects of the general population. The Surveillance Epidemiology and End Results (SEER) database (12) was used to calibrate the rates of malignant transformation and to construct the model for survival of cancer patients following diagnosis. SEER-Medicare data was used to estimate costs of cancer treatments (13).

## 1.4 Structure of the CRC submodel

The model consists of:

- a ***natural history component*** that tracks cancer progression, including adenoma development, tumor growth, and symptoms, as a function of non-modifiable risk factors such as age, gender, ethnicity, and family and personal history, and modifiable risk factors such as obesity (BMI) and exercise;
- a ***screening component*** that allows for detection and removal of adenomas and diagnosis of preclinical CRC;
- a ***treatment component*** that predicts survival following diagnosis of CRC as a function of tumor stage, size, and type; and
- a ***cost component*** that tracks the cost of diagnosis, prevention measures, screening, complications of screening, follow-up in the event of a positive screening, and treatment.

## 1.5 Literature and data search

A systematic literature search was conducted in MEDLINE, Cochrane Database of Systematic Reviews, PUBMED, Web of Science and Google Scholar, supplemented with manual searches of references. We reviewed all the abstracts that indicated quantitative measurements of relevant model parameters. When the abstract did not offer enough information for deciding whether it is relevant to the search, we retrieve the full-text to search for data and measurements that would clarify the matter. When two or more studies used the same data, we only include one study in the meta-analysis. If a study had been superseded, the more recent study was used in the analysis. Table 1 summarizes the keywords used for each search topic.

| **Topic** | **Keywords** |
|---|---|
| Polyp categories | (colorectal OR colon OR rectum) AND (polyp OR neoplasm OR neoplasia) AND (classification OR type) |
| Risk factors for polyps and adenomas | (colorectal OR colon OR rectum) AND (polyp OR neoplasm OR neoplasia) AND (classification OR type) |
| Growth of polyps and adenomas | (colorectal OR colon OR rectum) AND (polyp OR adenoma OR neoplasm) AND (risk factor OR predictor) |
| Size distribution of polyps and adenomas | (colorectal OR colon OR rectum) AND (polyp OR adenoma OR neoplasia) AND (size distribution) |
| Prevalence of polyps and adenomas | (colorectal OR colon OR rectum) AND (polyp OR adenoma OR neoplasia) AND (prevalence OR frequency) |

| | |
|---|---|
| Incidence of polyps and adenomas | (colorectal OR colon OR rectum) AND (polyp OR adenoma OR neoplasia) AND (incidence OR rate) |
| Polyp location | (colorectal OR colon OR rectum) AND (polyp OR adenoma OR neoplasia) AND (location OR distribution) |
| Family history | (colorectal, adenoma, colon, OR rectum) AND (family OR familial OR family history) |
| Physical activity | (colorectal, adenoma, colon, rectum) AND (physical activity OR exercise) |
| Cancer growth | (colorectal OR colon OR rectum) AND (cancer OR tumor OR carcinoma) AND (growth OR doubling time OR natural history) |
| Diabetes and colorectal cancer | (colorectal OR colon OR rectum) AND (cancer OR tumor OR carcinoma) AND (diabetes OR diabetes mellitus) |
| Colonoscopy performance | colonoscopy AND (sensitivity OR performance OR specificity) |
| Colonoscopy complications | colonoscopy AND (complication OR adverse event) |
| Adenoma histology | (colorectal OR colon OR rectum) AND (adenoma) AND histology |
| Delay in diagnosis | (colorectal OR colon OR rectal) AND (cancer) AND (delay diagnosis) |

**Table 1. Summary of literature search algorithm.**

In addition to data from literature, we also have access to individual data from

(i) the Clinical Outcomes Research Initiative (CORI) database (11), which contains data on 220,000 colonoscopies.
(ii) the Surveillance Epidemiology and End Results (SEER) database (12)
(iii) the Cancer Prevention Study-II (CPS-II)

## 1.6 Flow of the model

We model three types of lesions, namely (i) benign polyps, which will never become cancer; (ii) adenomatous polyps (i.e., adenomas), which have the potential to transform into cancer; and (iii) IBD-associated dysplasia, which is a precursor to cancer in patients with inflammatory bowel diseases.

The category “benign polyp” includes hyperplastic, inflammatory, and other non-neoplastic polyps and accounts for one-third of the total number of polyps (21). In the model, polyps arise in the colon and the rectum stochastically through a non-homogenous Poisson process (22). The incidence of polyps increases with age and is a function of several risk factors including gender, BMI, and family history. Polyps can arise at 8 different anatomical sites along the colon-rectum, namely rectum, sigmoid colon, descending colon, splenic fixture, transverse colon, hepatic fixture, ascending colon and ceacum. Polyps can occur at eight different anatomical sites: cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum.

Growth of benign polyps and adenomas is modeled using a log-linear equation. We assume that adenomas and benign polyps are identical in terms of site distribution and growth. The sizes of the polyps increase as function of time according a log-linear growth equation. Polyps have a minimum size of 1 mm and a maximum size of 50 mm. The lower limit comes from what a gastroenterologist may consider to be polyps during an endoscopic section. The upper limit prevents the simulated polyps from attaining unreasonable sizes, given the size of the colon and the rectum. As an adenoma grows in size, its histology and grade of dysplasia worsen. The propensity of an adenoma to become cancerous is a function of age, adenoma size, and adenoma location. The model allows all adenomas to go through the full disease process, such that individuals may develop multiple clinically detectable cancers each of which may result in their death due to cancer.

Once an adenoma becomes a malignant tumor, it will grow exponentially, with a doubling time of ~ 1 year, as derived from a meta-analysis of the literature (23-26). When a tumor reaches a certain size, the patient will experience symptoms of colorectal cancer, and after a delay period, will be diagnosed by the health care system with symptomatic colorectal cancer. The distribution of tumor sizes when a patient is diagnosed with symptomatic colorectal cancer is derived from early SEER data (12) to minimize the effects of screening. If there is screening, malignant tumors are detectable before the symptoms surface. The survival of a patient following diagnosis of colorectal cancer is modeled based on current SEER survival data and is a function of age, gender, stage, and tumor size.

## 1.7 Model validations

The colorectal cancer outcomes predicted by the Archimedes Model have been validated against several studies including the National Polyp Study (14), Minnesota FOBT Screening Trial (15), Cancer Prevention Study II Nutrition Cohort (16), Women Health Study (17), Women Health Initiative (18), the UK Flexible Sigmoidoscopy Trial (19) and the Veterans Affairs Cooperative Study Group (20).

# 2. Natural history of polyps

## 2.1 Overview

In order to correctly capture the progression from adenoma to cancer, we need to be able to accurately predict the arrival time of polyps, their distribution within the colon and the rectum, their growth rate, the histology and the grade of dysplasia of adenomas as they grow in size, and the rate at which adenomas become cancerous. An accurate description of all five of these properties of polyps (i.e., incidence, location, growth, histology, and malignancy) is also necessary in modeling the interactions between the disease and the health care system. For instance, the sensitivity of colonoscopy depends on the size and location of the polyps.

The model for incidence, location and growth of polyp relies heavily on the data from the Clinical Outcomes Research Initiative (CORI) data base (27-29). The CORI database represents a consortium of 580 specialists in GI diseases selected to obtain a cross-section of endoscopic practice in the United States. Participants use a computerized endoscopic report generator to produce all endoscopic reports. Data from a total of 220,000 colonoscopy procedures were recorded in the CORI database. The database recorded demographic information (e.g., age, gender, race/ethnicity, time period, site, type), quality of bowel preparation, size location, and shape (sessile or pedunculated) of polyps. Histopathologic data for most polyps are not consistently retrieved so it is not possible to distinguish between adenomas and benign polyps from the database, at least not at the time that the data was made available to Archimedes.

## 2.2 Polyp categories

***Assumption 1***: We model two classes of polyps, benign polyps and adenomas. Benign polyps are polyps that do not become cancer, while adenomas have the potential to become cancer if left untreated and patients live long enough.

Justifications:

- Polyps are often classified into two categories: benign polyps (also known as non-neoplastic polyps) and adenomatous polyps (adenomas).
- 90-95% of CRC arise from adenomas, so it is reasonable to assume that cancer does not originate from other types of polyps.

- Benign polyps include several distinct categories (e.g., hyperplastic polyps, mucosal polyps, inflammatory polyps, submucosal polyps) (30). From a clinical perspective, it does not make a lot of difference to distinguish between different types of benign polyps.

***Assumption 2***: Sixty-six percent of all colorectal polyps are adenomas (21).

***Assumption 3***: Due to lack of information, benign polyps and adenomas are assumed to have similar anatomical distribution and growth characteristics. The only difference between benign polyps and adenomas in the current model is their propensity to become cancerous.

## 2.3 Polyp incidence

***Assumption 1***: The incidence of polyps depends on the following risk factors: age, gender, BMI, and family history.

Justification:

- Our literature review indicates that age, gender, BMI and family history are strong predictors of incidence of polyps and adenomas. These are also the risk factors that are available in the NHANES database.

***Assumption 2***: The occurrence of polyps follows a non-homogeneous Poisson process (22). The annual risk $\lambda_i$ of developing a new polyp for an individual *i* is given as follows:

$$\lambda_i = \exp\left(\theta_{0i} + \theta_{1i} sex_i + \theta_{2i} age_i\right) RR_{FH} RR_{BMI}$$

where $\theta_{0i}$ is the baseline risk for the individual i, $\theta_{1i}$ and $\theta_{2i}$ account for the influence of gender and age, and $RR_{BMI}$ and $RR_{FH}$ account for the effects of BMI and family history.

Justifications:

- The proposed model of adenoma incidence is inspired by an earlier model developed by Rutter and colleagues who used a meta-analysis to combine information from 14 autopsy studies of adenoma prevalence and counts (22). The occurrence of adenomas was assumed to follow a non-homogeneous Poisson process, with an annual adenoma risk depending on age and gender. Across individuals, the distribution of baseline log-risk follows a normal distribution.

- We extended the Rutter et al. model to include other risk factors such as BMI and family history.

**Parameter estimations**

- Parameters characterizing the dependency on age and gender are estimated from CORI data and Rutter et al.
- To estimate $RR_{BMI}$ and $RR_{FH}$, we conducted meta-analyses of studies quantifying the dependence of adenoma and polyp incidence on BMI (40-45) and family history (31-33, 46).
- $RR_{BMI}$ is modeled as a continuous function of BMI and depends on gender. The relative risks for adenoma by BMI were reported for discrete BMI groups. We believe that the effect of BMI on adenoma incidence is continuous. Therefore, a linear equation is fitted to these data points to model the continuous effects of BMI on adenoma incidence.
- $RR_{FH}$ depends on history of CRC in first-degree relatives and is estimated to be 2.21 (95% CI :2.00 –2.53) (31-33, 46).

## 2.4 Polyp location

***Assumption 1***: Polyp location is represented by a discrete index $l_A$, ranging from 1 to 8, representing the rectum, sigmoid colon, descending colon, splenic fixture, transverse colon, hepatic fixture, ascending colon, and cecum. Multiple polyps can initiate in the same part of the large intestine.

Justifications:

- Ideally, we would like to have data on the location of adenomas as distance from the rectum. However, in literature, the locations of adenomas are often reported in term of their anatomical sites, whether they are at rectum, sigmoid colon, etc (48-49). Furthermore, the length of each part in the intestine may vary considerably between individuals. Thus, we believe the best way to represent adenoma location is to use a discrete position index $l_A$ ranging from 1 to 8. The subscript A represents adenoma. Each position index corresponds to a part of the large intestine (see Table 2). Multiple adenomas can grow from the same site.

| $l_A$ **(Position index)** | **Part of the large intestine** | **Typical length** | **Fraction of polyps (CORI)** |
|---|---|---|---|
| 1 | Rectum | ~12 cm | 0.118 |

| | | | |
|---|---|---|---|
| 2 | Sigmoid colon | ~40 cm | 0.314 |
| 3 | Descending colon | 22-30 cm | 0.114 |
| 4 | Splenic fixture | | 0.023 |
| 5 | Transverse colon | ~45 cm | 0.128 |
| 6 | Hepatic fixture | | 0.051 |
| 7 | Ascending colon | 12-20 cm | 0.149 |
| 8 | Caecum | 5-7 cm | 0.102 |

**Table 2. Anatomical distribution of polyps in the large intestine.**

***Assumption 2***: Based on the CORI dataset, we assume that the probability $p_{AL}(l_A)$ of a new polyp located at site $l_A$ depends linearly on age at polyp initiation as follows:

$$p_{AL}(l_A) = a_l age_{new} + b_l$$

where $age_{new}$ is the age at which the new adenoma initiates. The values of $a_l$ and $b_l$ for each anatomical site were obtained by calibrating the model to CORI data. We assume that adenomas and benign polyps have similar anatomical distributions.

Justifications:

- Analysis of the CORI dataset reveals that the site distribution is a linear function of age and relatively independent of gender and race.
- The anatomical distribution of polyps shifts from the distal colon to the proximal colon at increasing age. In other words, the probability that a new polyp will appear in the proximal colon increases with age. This is consistent with observations reported by other studies (50-51).

**Parameter estimations**

To obtain values of $a_l$ and $b_l$ for each anatomical site, we follow 100,000 individuals from their births to their deaths. The arrival times of new adenomas are predicted by the polyp incidence modeling unit. The location of each new adenoma is given by Assumption 2. We then compute the anatomical distributions of the simulated adenomas for different ages and compare the

predicted distributions with CORI data. The parameters are then adjusted to give the best fits to the data for each gender-race combination.

## 2.5 Polyp size

**Evidence review**

Data from the CORI database provides extensive information on cross-sectional distributions of polyp size. The size distribution appears to approximately log-normal. It appears that gender does not strongly affect polyp size. Overall, ~50% of polyps are smaller than 5 mm, ~40% of polyps are between 5 and 9 mm, and ~8% are larger than 9 mm. This is consistent with the size distribution reported in the past (20, 48, 59-61). Roughly 6%-8% of patients have polyps > 9 mm (62-63).

Overall, CORI data suggest that polyp growth is relatively independent of gender. Black race tends to have larger adenomas as compared to white and Asian. The main factor that affects polyp growth is age. For ages above 50, both the mean and standard deviation of polyp size increase with age. The data also suggest that polyps do not grow exponentially like tumors.

**Modeling approach**

***Assumption 1***: Polyp size increases over time and no regression.

Justifications:

- There is little information available on longitudinal evolution of polyp size. Hofstad and colleagues (52-58) published a series of papers measuring growth rates of adenomas. They purposely left medium-size adenomas ( ≤ 9 mm ) in place and followed them with annual colonoscopies for three years. Within the observational period, adenomas can grow, remain unchanged, or shrink. All three events can occur within the same patient. The growth rates are independent of age, gender, and adenoma location. Interestingly, adenomas in the 5 to 9 mm size range showed a slight net regression in size, while adenomas < 5 mm showed a mean increase in size of 0.5 mm over three years (54). Based on these observations, it was speculated that adenomas grow to a certain size and then spontaneously regress. This hypothesis is not supported by any biological model. A much longer observational period is required to test this hypothesis. In

practice, this is not possible since for ethical reasons polyps that are larger than 10 mm must be removed.

- At this point, there is insufficient robust data to model polyp regression. For the time scale of interest (5 years and longer), it is sufficiently accurate to assume that polyp size continuously increases over time.

***Assumption 2***: We model polyp growth using a log-linear growth equation (64)

$$\ln d_{Aij}(t+1) = \alpha_{ij} + \beta_{ij} \ln d_{Aij}(t)$$

where subscript j denotes the *j*th adenoma in individual *i*, and $\alpha_{ij}$ and $\beta_{ij}$ are the growth parameters, and $d_{Aij}(t)$ is the size of the *j*th adenoma in individual *i* at time *t*. $\alpha_{ij}$ and $\beta_{ij}$ are sampled from normal distributions, whose mean and standard deviation are calibrated to reproduce polyp size distributions derived from the CORI dataset for different race and gender combinations.

Justifications:

- The log-linear equation is selected over other growth equations (e.g., Gompertzian, Janoscheck, or logistic) mostly due to the fact that the polyp size distribution is log-normal. For convenience, we assume that adenomas are spherical.
- We found that model prediction is relatively independent of the growth equation for polyps, as long as it predicts an upper limit of adenoma size.

**Parameter estimation**

The main limitation of the current CORI dataset is that it does not specify whether a polyp is adenomatous or benign. To facilitate analysis of polyp growth, we assume that benign polyps and adenomas behave similarly in terms of growth. This assumption can be relaxed if we have more data that differentiate growth of adenomas and benign polyps.

Both the mean and the standard deviation of polyp size increase with age for ages above 50. Based on this observation, we assume that $\alpha$ and $\sigma_\alpha$ depend linearly on age (see equation 5.7 below) and $\beta$ is a constant, independent of age.

$$\alpha = \overline{\alpha_0} \times \text{age} + \overline{\alpha_1}$$

$$\sigma_\alpha = \overline{\sigma_0} \times \text{age} + \overline{\sigma_1}$$

The algorithm used for calibration of parameters ($\overline{\alpha_0}$, $\overline{\alpha_1}$, $\overline{\sigma_0}$, $\overline{\sigma_1}$, and $\beta$) iteratively minimize the differences between the prediction and data and consists of 5 steps as follows:

- Step 1: Guess the value of $\overline{\alpha_0}$, $\overline{\alpha_1}$, $\overline{\sigma_0}$, $\overline{\sigma_1}$, and $\beta$
- Step 2: Simulate growth of adenomas in 100,000 individuals with for a given race and gender
  - For each person, predict the time of polyp inception, and "grow" his/her polyps from age = 0 to his/her death
  - At age=age of colonoscopy (randomly picked from CORI age distribution for the race and gender combination of interest), send the person to colonoscopy.
  - At colonoscopy, detect polyps with size-dependent sensitivity
  - Record polyp properties (e.g. size, location)
- Step 3: Construct the distribution of polyp size for age groups 50-55, 55-60, and 60-65.
- Step 4: Quantify the error between the predicted distributions and distributions obtained from CORI data for the gender-race combination of interest.
- Step 5: If the error is smaller than the error calculated for the previous parameter set, accept the parameters. If not, make a new guess on the parameters by adding perturbations to the current guess and go back to step 2.
- Step 6: Repeat step 2 through step 5 until the error is smaller than a pre-defined threshold.

## 2.6 Adenoma histology

**Evidence review**

The histology of adenoma is categorized as tubular, tubulovillous, and villous.

- The tubulovillous category contains microscopic areas of both tubular and villous patterns.
- The villous category includes adenomas containing at least 75% or more villous patterns.
- The tubular adenomas contain 25% or less villous patterns.
- Any adenoma that contains from 25% to 75% villous patterns is classified as tubulovillous.

Figure 1 depicts the probability that an adenoma is tubulovillous and villous. The data points are adapted from Shinya and Wolff (49) and Butterly, et al. (65). The bigger the adenoma is, the more likely it contains 25% or more villous patterns.

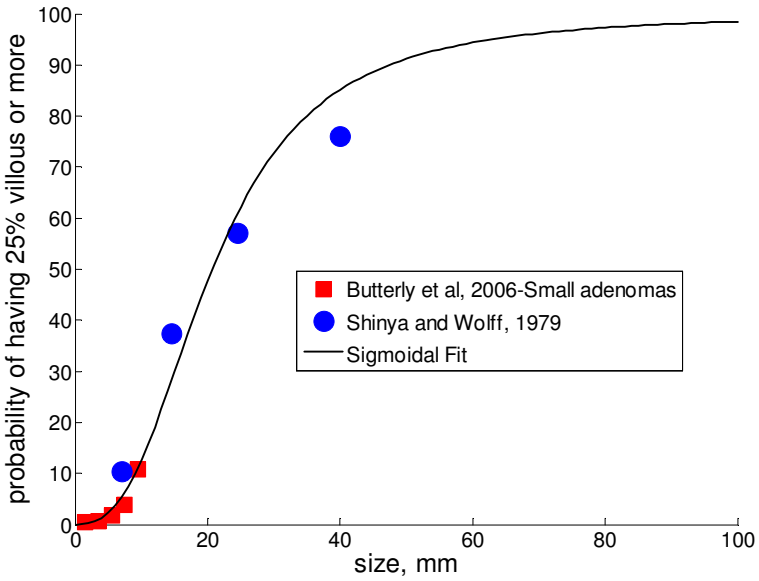


**Figure 1. Probability of having 25% or more villous pattern as function adenoma size (Shinya and Wolff (49); Butterly, Chase, et al. 2006 (65)).**

**Modeling approach**

The probability that an adenoma contains 25% or more villous patterns as a function of adenoma size is fitted to data using a sigmoidal function of the following form

$$P_{>25\%villous}(d_A) = \frac{{d_A}^{n_{tubulovillous}}}{{d_A}^{n_{tubulovillous}} + K_{A,>25\%villous}^{n_{tubulovillous}}}$$

where $d_A$ is the size of the adenoma, $P_{>25\%villous}(d_A)$ is the probably that the adenoma contains 25% villous patterns or more, $n_{tubulovillous}$ and $K_{A,>25\%villous}$ are constants characterizing the sigmoidal function. We use this function to generate for each adenoma the size at which it becomes tubulovillous.

We use a similar approach to construct a function for the probability of having 75% or more villous patterns based on data from Butterly et al. (2006) (65) and Shinya and Wolff (1979) (49) and use this function to predict for each adenoma the size at which it becomes villous.

## 2.7 Adenoma dysplasia

### Evidence review

Dysplasia, or dysplastic changes, are atypical changes in the nuclei of cells, the cytoplasm (the portion of the cell surrounding the nuclei), or in the growth pattern of cells. These changes can be subtle or very pronounced and considered to be pre-cancerous changes (increases the risk of developing cancer). Adenomas with severe or high-grade dysplasia are thought to have a greater likelihood of progressing to cancer. The probability of adenoma containing high grade dysplasia increases with adenoma size (see Figure 2).

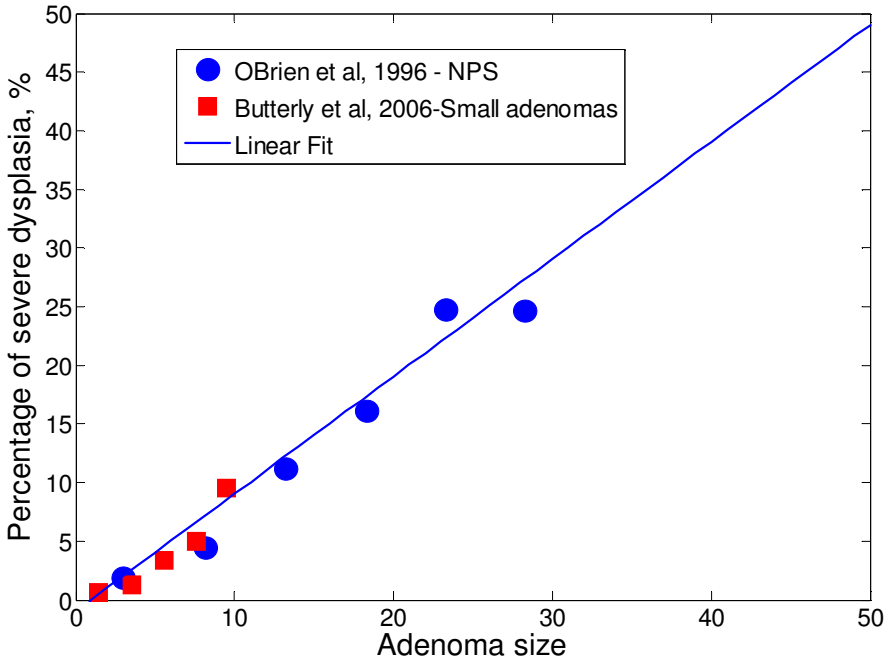


**Figure 2.Probability of severe dysplasia as function of adenoma size in mm (O'Brien, Winawer et al. 1990; Butterly, Chase et al. 2006).**

### Modeling approach

Based on data reported by Butterly et al (2006) and O'Brien et al (1990), we derive a linear equation to predict the probability of an adenoma displaying severe dysplasia as function of adenoma size $d_A$ (in mm).

## 2.8 Malignant transformation

## Evidence review

### Effects of size

The estimates of the rate of transition from adenoma to preclinical invasive cancer vary greatly between publications. Villavicencio and Rex (66) argued that the malignant transformation rate depends on size and estimated the ten-year cumulative incidence of CRC to be 0.35% in persons with adenomas < 5 mm and 0.65% in persons with adenomas > 5 mm. Hofstad et al. (58) and Hermatek and Karrer (1983) reported the dependency of adenoma malignancy on size (see Figure 3).

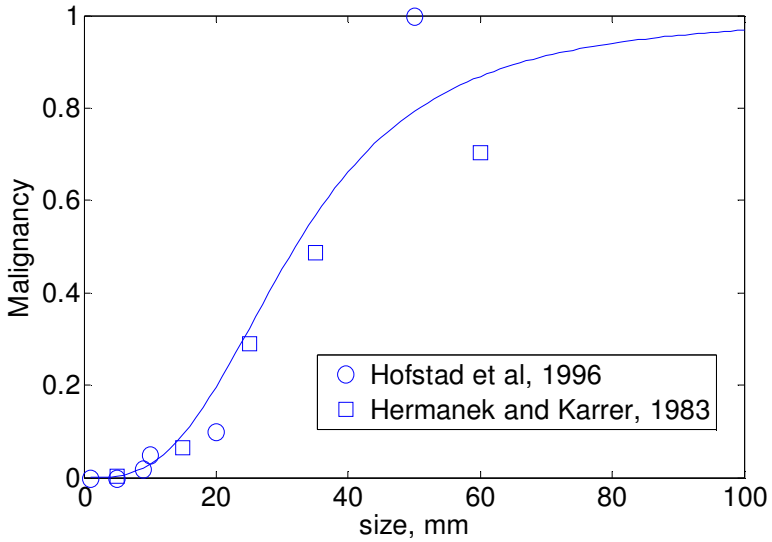


**Figure 3. Likelihood of malignancy as function of adenoma size. The line represents a sigmoidal fit to data.**

### Effects of location

Analysis of the CORI dataset indicates that the anatomical distribution of tumors is different from that of adenomas, suggesting that the rate of malignant transformation might depend on location.

### Effects of age

It is well-established that cancer incidence follows a power-law relationship with age (see Figure 4). However, the dependency of adenoma incidence on age cannot explain such strong dependence of colorectal cancer incidence on age. This suggests that the rate of malignant transformation also varies nonlinearly with age.

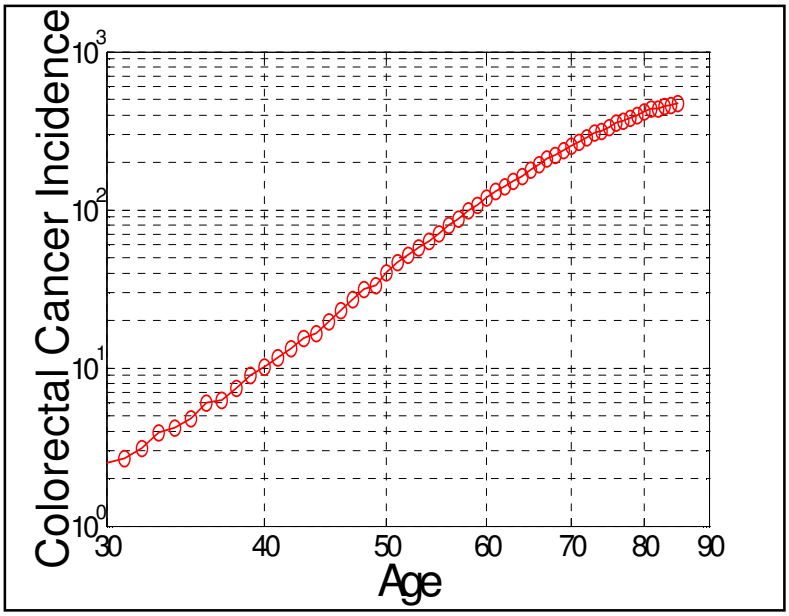


**Figure 4. Colorectal cancer incidence as function of age (SEER), in a log-linear plot.**

**Modeling approach**

Definition of malignant transformation: The objective of the model is to capture the effects of early detection and prevention on incidence and mortality of CRC. The model was not designed to describe the biological processes underlying the transformation of adenoma to cancer. From this rather specific perspective of cancer screening, we use the term "malignant transformation" to refer to a specific event at which an adenoma transforms into "a preclinical cancer", which is detectable by screening but does not yet result in clinical symptoms.

***Assumption 1***: The probability $P_{ij,A\to C}(t)$ that the transition of an adenoma to a malignant tumor has occurred by time t is given by the following propensity function

$$P_{ij,A\to C}(t) = 1 - \mathbf{exp}\left(-\int_{t_0}^{t} h_{ij}^{A} d\tau\right)$$

where the hazard rate, $h_{ij}^{A}$, represents the rate that an adenoma j in an individual i becomes cancerous. The subscript $A \to C$ denotes the transition from adenoma to cancer, and $t_0$ is the time of adenoma inception.

Justifications:

- This is a standard way of capturing transition between disease states.

***Assumption 2***: $h_{ij}^{A}$ depends on adenoma size $d_A$, adenoma location $l_A$, age, and gender and is given in the following form:

$$h_{ij}^{A} = V_{A\to C}\frac{{d_A}^{n_{size}}}{{d_A}^{n_{size}} + {K_{ML,size}}^{n_{size}}} RR(l_A) age^{n_{age}}$$

where

- $V_{A\to C}$ is the maximum transition rate for an adenoma located at site $l_A$ of an individual at a specified age.
- $RR(l_A)$ represents the dependency of the malignant propensity on adenoma location. The values of $RR(l_A)$ are derived from the tumor data in the CORI database.
- The term $\frac{{d_A}^{n_{size}}}{{d_A}^{n_{size}} + {K_{ML,size}}^{n_{size}}}$ is a sigmoidal function fitted to data derived from Hofstad et al. (58) and Hermatek and Karrer (1983) ( Figure 3) to represent the dependency of malignancy likelihood on adenoma size.
- The term $age^{n_{age}}$ represents the dependency of malignant transformation on age.

Justification:

- The form of the equation is motivated by the evidence discussed above.

To predict when the transition occurs, we draw a random number ξ from the uniform distribution U[0,1] and solve the equation $P_{ij,A\to C}(t) = \xi$ for time t.

**Parameter estimation**

The values of $RR(l_A)$ for are derived directly from the CORI data. $n_{size}$ and $K_{ML,size}$ are based on data from Hofstad et al. (58) and Hermatek and Karrer (1983). We use an iterative procedure to estimate $V_{A\to C}$ and $n_{age}$. The target distribution in this case is the CRC incidence by age derived from SEER.

# 3. Natural history of colorectal tumors

## 3.1 Overview

In the current model, a colorectal tumor can arise from either an adenoma or a dysplasia associated with IBD. The tumor will grow inside the colon or the rectum until it is detected either by symptoms or screening. The stage of cancer will be assigned according to the characteristics of tumors at detection.

The algorithm for predicting the natural history of a tumor in an individual consists of 3 steps:

- Step 1: Calculate the growth trajectory of the tumor from inception.
- Step 3: Calculate the time that the tumor will be detected by symptoms.
- Step 4: Assign cancer stage to the patient based on the tumor characteristics at diagnose either by screening or by symptoms..

## 3.2 Tumor growth

**Evidence review**

There have been only a few studies of tumor growth in CRC, because of the difficulty in obtaining follow-up images. Each study only contains information on a limited number of tumors, typically 10 to 30. The growth of the tumor is often characterized by doubling times. The reported average doubling time range from 0.36 to 2.2 years (see Table 3). Many authors distinguish between rapidly and slowly growing tumors. Figure 5 plots the probability distribution of the doubling times obtained from Bolin et al. (1983) and Umetani et al. (2000). These are the only publications that provide access to the doubling time of individual cancer. Figure 5 suggests that the doubling times are log-normally distributed. Similar distributions of doubling times have been observed for tumor growth in breast cancer (Peer et al., 1993).

| Reference | No of Cancers Observed | Doubling time (years) |
|---|---|---|
| Umetani et al. (2000) | 11 | Early 0.78 ± 0.41, Advanced 0.40 ± 0.12, Mean 0.56 ± 0.3 |
| Welin et al. (1960) | 20 | 1.13 (0.25-infinity) |

| | | |
|---|---|---|
| Fiegel et al. (1973) | 18 | 0.22-0.87 |
| Matsui et al. (2000) | 31 | 2.2 ± 1.5 |
| Bolin et al. (1983) | 27 | 0.36 (0.14-4.3) |

**Table 3. Doubling time of colorectal tumors**

Although characterizing tumor growth in term of doubling times implies that the tumors grow exponentially, however, there is no concrete evidence to either support or reject the assumption on exponential growth. Most studies only report two measurements of tumor size. Animal studies seem to suggest tumor growth is Gompertzian. In other words, the growth rate declines as the tumor approaches a maximum size. This could be due to the limited volume available for tumor growth in animals or limited access to nutrients.

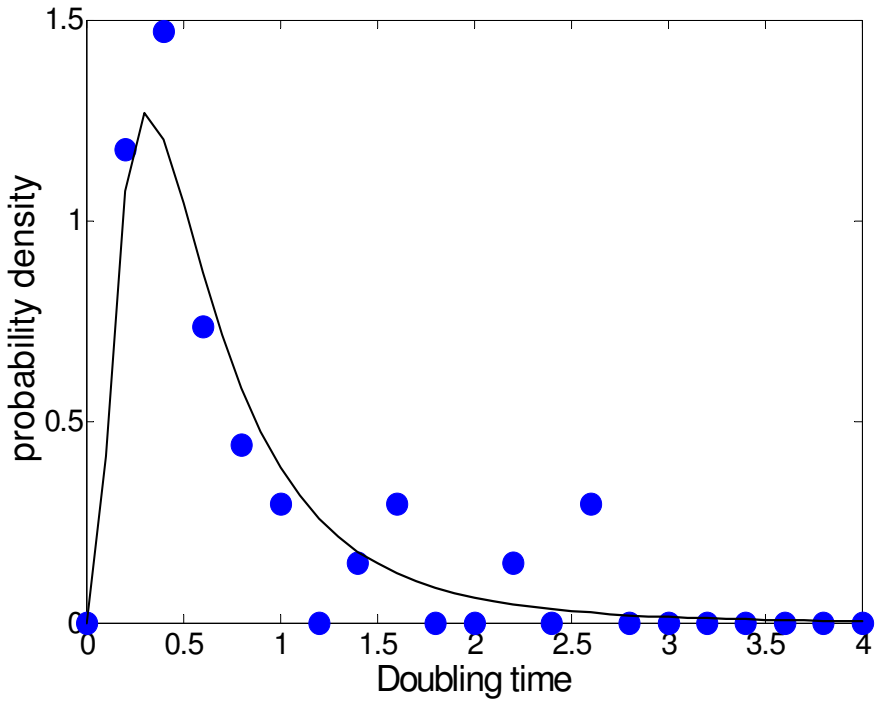


**Figure 5. Distribution of doubling time of colorectal tumors. The symbols represent data from Bolin et al. (1983) and Umetani et al. (2000).**

**Modeling approach**

***Assumption 1***: We assume further that the tumor grows exponentially with a volume doubling time $T_{TG}$, where TG is short for tumor growth. The volume of the tumor (carcinoma) is given by the following equation:

$$\frac{dV_C(t)}{dt} = \frac{\ln 2}{T_{TG}} \cdot V_C(t)$$

where $V_C(t)$ is the volume of the tumor, and the subscript C refers to cancer.

The solution of the above equation is

$$\frac{V_C(t)}{V_C(t_{C,inception})} = \exp(\ln 2 \times \frac{t - t_{C,inception}}{T_{TG}})$$

where $t_{C,inception}$ is the inception time of the carcinoma (i.e. when malignant transformation occurs).

For convenience, we assume that the tumor is spherical and that tumor growth occurs in all three dimensions. In other words, $V_C = \frac{4\pi}{3}\left(\frac{d_C}{2}\right)^3$. Thus, the tumor size $d_C$ can be estimated as follows

$$\frac{d_C(t)}{d_C(t_{C,inception})} = \left[\exp(\ln 2 \times \frac{t - t_{C,inception}}{T_{TG}})\right]^{1/3}$$

where $d_C(t_{C,inception})$ is the tumor size at carcinoma inception.

Justifications:

- There are animal experiments and clinical experiences suggesting that tumor growth is Gompertzian. Unfortunately, there is insufficient longitudinal data of on colorectal carcinoma to construct a robust Gompertzian growth model. We cannot use data from animal experiments, clinical anecdotes or data on other types of tumors to build a reliable growth model of colorectal carcinoma. All available publications on growth of colorectal carcinomas report only 2 measurement points (at the beginning and at the end of the observation, see for instance), while the 3-parameter Gompertzian equation requires at least 3 data points. An exponential growth model with 2 parameters would provide a much more robust representation of tumor growth given the limited

information available. Furthermore, we only use the exponential growth model to describe tumor growth during a short interval between preclinical (screen-detectable) cancer and clinical cancer. We are not interested in tumor growth prior to preclinical cancer and after cancer diagnosis. During this short period, the Gompertz equation can be mathematically approximated by an exponential equation.

- In summary, given the lack of data and the precise measurements of growth of colorectal tumors, we believe that our assumption of exponential growth from preclinical cancers to clinical cancers is reasonable from both modeling and clinical perspectives. In future, we will investigate the model sensitivities to the assumptions on tumor growth.

***Assumption 2***: The doubling time is assumed to follow a log-normal distribution (25). The mean and standard deviation of this distribution are synthesized from the data reported by Bolin et al. (24), Umetani et al. (25), Matsui et al. (26) and Welin et al. (23).

***Assumption 3***: The model does not address the differences in growth rates between advanced and early cancers.
Justification:

- While there is data to suggest that growth rates of advanced and early cancers are different, it is beyond the scope of the current model to capture that level of details.

## 3.3 Symptoms

**Evidence review**

The symptoms of colorectal cancer are

1. Abdominal pain
2. Change in bowel habit
3. Hematochezia or melena
4. Weakness
5. Anemia
6. Weight loss

We do not intend to model each symptom separately. Rather, we are only interested in the characteristics, more specifically, the size of the tumor at the time of detection. Knowing the size at detection will allow us to calculate how long it takes to detect the tumor.

Before 1986, only a small fraction of the general population participated in a CRC screening program, and most cancers were detected by symptoms (e.g. weight loss, abdominal pain etc.). Therefore, SEER data prior to 1986 provides us information on tumor size at the time that the patients are diagnosed by symptoms. Figure 6 plots the probability distribution of tumor size at the time of diagnosis for white males and white females, derived from early SEER. It appears that gender does not strongly affect tumor sizes at detection. Similarly, age at detection does not have much effect on the overall size distribution (see Figure 7). The distribution of tumor size at the time of detection can be fitted using a log-normal distribution (see Figure 8)

Only limited data is available on the delay between symptom onset and diagnosis. Majumdar et al. (1999) reported that the mean and median duration of symptoms, from onset to tissue diagnosis, were 32 weeks and 14 weeks. Fernandez et al. reported a mean duration of 132 days.

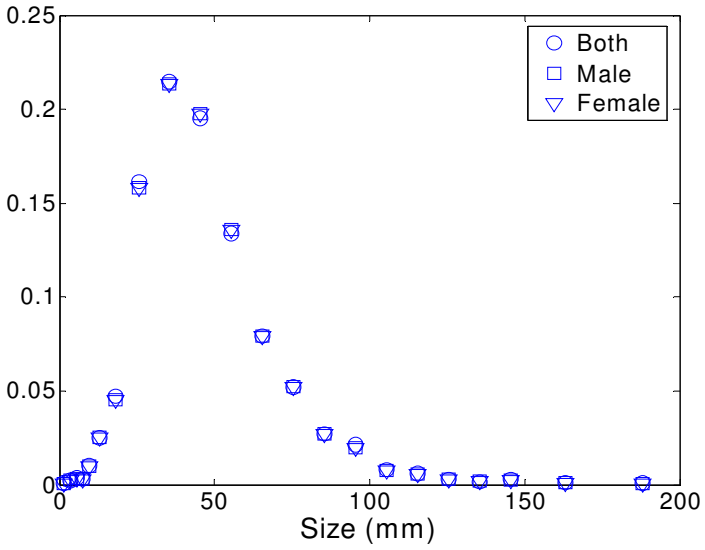


**Figure 6. Probability distribution of tumor size at the time of detection by symptoms for white males and white females (SEER).**

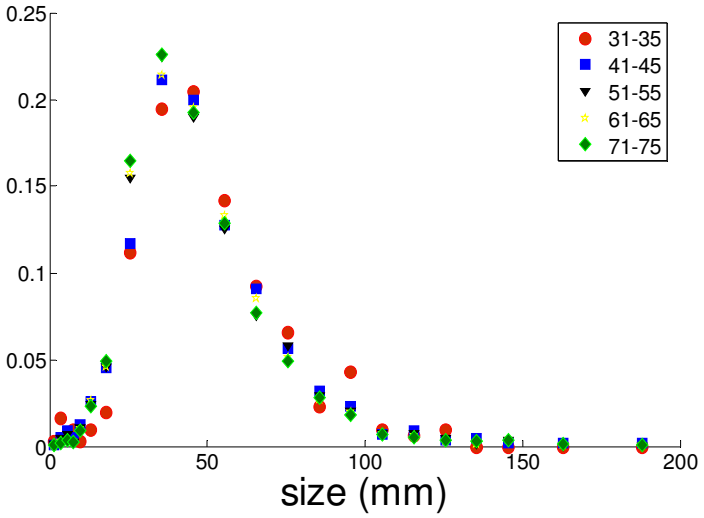


**Figure 7. Distribution of tumor size at detection by symptoms for different age groups.**

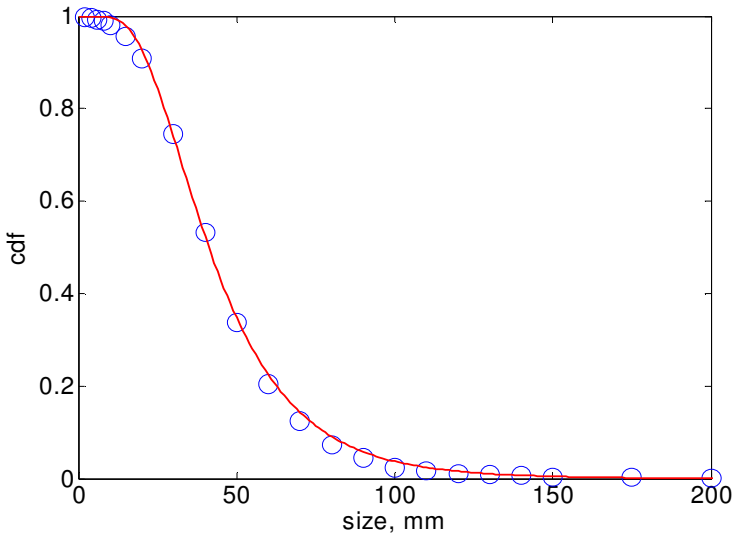


**Figure 8. Cumulative probability distribution of tumor size at detection by symptoms for the white population in the SEER database. The circles represent data and the solid line represents a log-normal fit.**

## Modeling approach

- We use log-normal distributions to fit to the distributions of tumor sizes at the time of diagnosis by symptoms, $d_C(t_{C,symptom})$, for different races. Age and gender do not strongly influence $d_C(t_{C,symptom})$.
- The tumor size at detection for a particular individual is picked randomly from the distributions according to race.
- The time it takes for a tumor to grow from the size at inception $d_C(t_{C,inception})$ to the size at diagnosis by symptoms $d_C(t_{C,symptom})$ is

$$\frac{t_{C,symptom} - t_{C,inception}}{T_{TG}} = \frac{\ln\left(\frac{d_C(t_{C,symptom})}{d_C(t_{C,inception})}\right)^3}{\ln 2}$$

- Delay between symptom onset and diagnosis is modeled using a log-normal distribution. The parameters of the log-normal distribution are estimated based on combining data reported by Barrett et al. (67), Majumdar et al. (68) and Fernandez et al. (69). We use this distribution to predict delay between symptom onset and diagnosis by symptoms for each patient.
- Knowing the delay and the age at which patients are diagnosed by symptoms, we can calculate the age of symptom onset.

## 3.4 Stage

**Evidence review**

Colorectal cancer is often classified using either the Duke or the American Joint Committee on Cancer (AJCC) staging system. The stage of a cancer is usually quoted as a number I, II, III, IV derived from the TNM value grouped by prognosis; a higher number indicates a more advanced cancer and likely a worse outcome.

In the present model, we are only interested in the AJCC stages of cancer. We focus on the primary classification, 0 to IV, but not the sub-stages.

Figure 9 depicts the distribution of stages as function of tumor size. The y-axis represents the fraction of tumors at stage 1 through 4. The symbols are SEER data for all races and ages. The

reason we do not split the data into different races and age groups, because we believe staging should only depend on the properties of the tumor, in this case, the size of the tumor. The lines are our fitted equations to the data. For large tumors, 55% of tumors are diagnosed with stage 3 and stage 4.

**Modeling approach**

Stage of a tumor is set to be a function of tumor size. The relationships between stage of a tumor (T,N, M) and tumor size are derived from SEER. For each tumor, we first use the tumor size at detection to calculate the probabilities of the tumor being stage 0 to 4. We then pick a random number from U(0,1) and assign the stage according to the value of the random number.

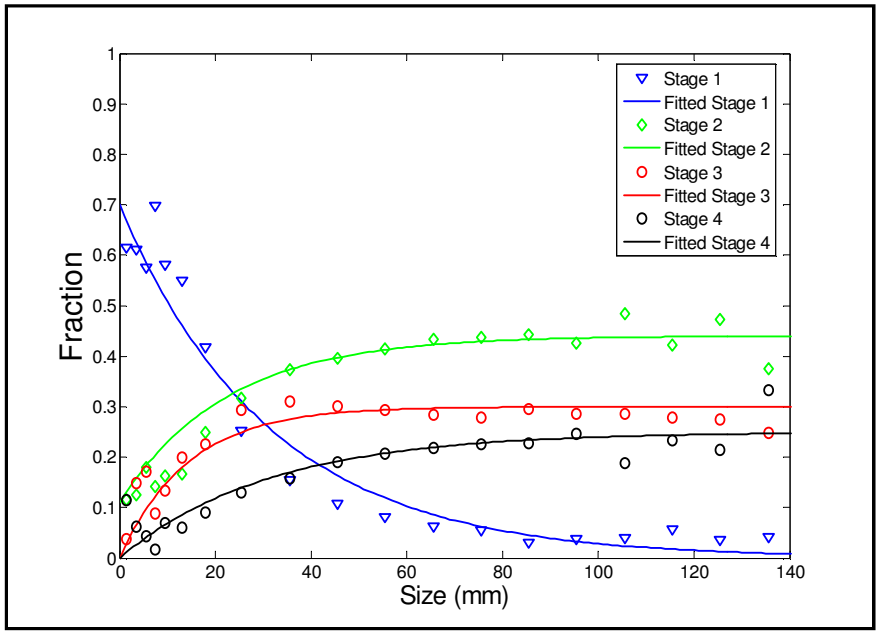


**Figure 9. Cancer stage as function of tumor size at detection (SEER data).**

## 3.5 Survival after diagnosis

**Evidence review**

Survival following diagnosis of CRC is often reported as a function of stage. Most patients will be alive after five years if the tumor has not reached the intestinal wall (stage I). This rate decreases to 60% if the tumor has invaded regional lymph nodes and to only 5–15% if the

neoplasm has metastasized (stage IV). However, stage is a derived variable, based on the tumor characteristics, such as size, number of positive lymph nodes, and state of metastasis.

Analysis of SEER data indicates that both metastasis and the number of positive lymph nodes correlate with tumor size.

**Modeling approach**

***Assumption 1***: Survival is assumed to depend on a patient's age, gender, race, size of primary tumor at diagnosis, and BMI at diagnosis.

Justification: Survival is a function of lymph node status and distant metastasis. In the modeling world, we need to predict these variables from other observable variables such as age, race/ethnicity, and tumor size at diagnosis. In other words, we can choose between two approaches:

- Approach 1: first predict lymph node status and distant metastasis as function of tumor size, age and race/ethnicity and then predict survival as function of lymph node status and distant metastasis or
- Approach 2: predict survival directly as function of tumor size, age and race/ethnicity.

The first approach is better than the second approach as it provides more details. However, mathematically speaking, the two approaches are equivalent in terms of predicting survival for a virtual patient if we only know tumor size. The Archimedes breast cancer model employs the first approach. The current colorectal cancer model employs the second approach.

***Assumption 2***: We use the following form to predict survival,

$$S(t - t_{C,diangosis}) = \exp\left(\frac{c \cdot (t - t_{C,diangosis})}{1 + b \cdot (t - t_{C,diangosis})}\right)$$

where $S(t - t_{C,diangosis})$ is the probability that a patient will survive at least $t - t_{C,diangosis}$ years after diagnosis with CRC at time $t_{C,diangosis}$ . Diagnosis can occur either by symptoms or by screening. $b$ and $c$ are constants, whose values are determined a priori for each individual. The distributions for $b$ and $c$ depend on race, gender, age, BMI, and tumor characteristics at diagnosis. At longer time horizons, $S(t - t_{C,diangosis})$ approaches $\exp\left(\frac{c}{b}\right)$, which represents the cure rate.

To predict the time of death due to CRC, we pick a random number $\xi$ from a uniform distribution U(0,1) and calculate time of CRC death $t_{C,death}$ as follows:

- If $\xi \le \exp(\frac{c}{b})$ then the patient never dies of CRC.
- Otherwise, the time of death is given by solving $S(t - t_{C,diangosis}) = \xi$, i.e.

$$t_{C,death} - t_{C,diangosis} = \frac{\ln \xi}{c - b \ln \xi}$$

We chose the SEER data obtained between 1990 and 2006 to build the survival model. This will provide a good approximation of CRC survival if patients are given treatment according to the current guidelines. It should be noted here that despite changes in cancer treatment in recent years, survival of CRC patients has been only slightly improved.

# 4. Validations

## 4.1 Overview of validation methodology

The complete description of Archimedes validation methodology is described in a separate report titled “Validation Methodology and Performance Report for ARCHes Innovator”, and can be made available upon request.

The purpose of this section is to quantify the accuracy of the colorectal cancer model in predicting the rates of cancer incidence and mortality in a specified population and the benefits of cancer screening. The ultimate objective is to answer the questions: “Is there reason to believe there is a flaw in the Model or code? Is there anything that can be improved? Is there any reasons to change the Model, or should it be left as it is?”

We classify each data source used for validation as “independent” (no information about the study was use to build the Model), “dependent” (the source was the only one to use as part of the model, or the model was calibrated to fit the source), and “partially dependent” (the source was used to build or calibrate part of the Model, but that part by itself does not wholly determine the outcome to be validated). Because the category “partially dependent” is so broad, we identify two subcategories. A validation is considered “largely dependent” if the source was one of very few used to build the parts of the model tested by the validation. A validation is considered “largely independent” if it is only one of a large number of sources used to build the parts of the model tested by the validation. As will be described below, the validations of many of the treatment arms of trials in the validation suite are largely independent. The reason is that the outcome of a treatment arm is determined primarily by the rate of the outcome in the absence of treatment (i.e. the “control arm”) in combination of the effect of the study treatment. If a trial was not used to build the physiology model that determines the outcomes in the control arm, and was only one of many trials used in a meta-analysis to estimate the effect of treatment, then the validation of the control arm is fully independent and the validation of the treatment arm is largely independent.

Validation of the Model against a clinical trial involves several steps. The first step is to use the Archimedes Model to generate a virtual population that matches the study population as closely as possible. The process begins by selecting people randomly from the NHANES 1999-2008 database. The Model then creates simulated people, one-by- one, who match the real people in the database in the sense that when the Model calculates their physiology starting

from the birth of the simulated person (age = 0) up to the current age of the real person, the values of biomarkers, medical history, and other variables for the simulated person closely match the values of the real person.

The second step is to screen the simulated people to see if their medical histories and baseline characteristics meet the inclusion and exclusion criteria for the study, as would happen in a real trial. Call this the “trial-eligible population”.

The third step is to select a subsample of people from the simulated trial-eligible population so that the subsample (call this the “simulated trial population”) has the same baseline characteristics as the real trial population. The Archimedes Model contains automated methods that select simulated people in a way that causes the selected population to converge on any specified targets for biomarkers and other variables, subject to the limitations of the NHANES database. This method achieves the best match possible on each variable, and retains all the correlations present in the US population as represented by NHANES. This is very important: to evaluate the Model, the simulated and real trial populations should be matched as closely as possible with respect to all variables that affect the outcomes of interest. This is necessary to avoid having the comparison of event rates in the simulated and real trials confounded by differences in baseline characteristics. It is also important that these steps be done without using any information about the outcomes of the real trial. Thus in the Archimedes Model these first three steps are done before the start of the trial simulation.

After the simulated population has been created, the fourth step is to set up the treatment protocol. Treatment protocols can be complicated, involving pre-randomization tests and treatments, withdrawing treatments or giving placebos in control groups, and applying complex protocols for treatment groups. The Archimedes Model includes care processes and behaviors that can be set to replicate the processes and behaviors in real trials fairly closely. Any available information about adherence to treatment protocols can also be incorporated in the setup. The success of this part of the setup process can be checked by comparing the trajectories of biomarkers in the simulated and real trials over the course of the trial. If necessary, simulated protocols can be calibrated to improve the match between simulated and real levels of biomarkers.

A related step is the need to replicate the background level of care that was being delivered at the time the trial was conducted. The Archimedes Model includes current guidelines, calibrated to current levels of biomarker control, performance and compliance. For some trials it is necessary to turn off or modify some healthcare care processes in the Model to reflect the level of care patients were receiving at the time the clinical study was conducted.

The steps just described are required for validations that involve clinical trials for which there is information about the trial's design. When any pieces of this information are not available, it is not posible to match the study as closely. In particular, for cohort studies there is no information about tretment protocols or performance/compliance. And for the studies of age-specific incidence rates there may not be good information even about the population. In these cases, the Model is simply run using the NHANES population and current US practices. The importance placed on comparisons of simulated and real results will depend on how well the conditions of the real study could be matched by the setup of the simulation. Specifically, because they it is not possible to replicate the study populations used on studies of age-specific incidence, they can only be used as general checks on the Model.

After the simulated trial has been set up, the next step is to run it. The sample size of the simulated trial is set to be the same as the real trial. Its duration is set for the duration of the real trial. When the simulation is complete, the important biomarker trajectories and the outcomes of interest are recorded, using the same follow-up protocols described for the real trial.

The final step is to interpret the results. This has two parts. The first is to calculate some measures of how well the Model's results match the real results. The second is to examine the measures in light of the potential mismatches identified during the set up of the simulation, as well as other issues that might be identified after the results are examined.

To compare predicted Kaplan Meier curves with data, we introduce a metric called the validation hazard ratio (vHR). It is calculated by fitting a Cox proportional hazard model to the survival data from the simulation and from the study. The vHR is similar to the hazard ratio used in most randomized clinical trials to show the treatment effect, just renamed to emphasize its use for comparing the simulated and the actual event rates in validations. A classical interpretation is that if the 95% confidence interval of vHR contains 1, there is not sufficient evidence to conclude that the Model's result differs from the real result.

It is important to recall that any mismatches in the setup of the simulation could cause the simulated rate to differ from the observed rate. They include: imperfect matching of baseline characteristics or trial protocols, incomplete reporting of performance and/or compliance to a treatment protocol, changes in standard of care over time, differences in definitions of health outcome, placebo effects, and so forth. Assuming that every effort has been made to reduce the effects of these factors, the effects of any that remain can only be addressed subjectively. It is expected that vHR would be larger than 1 in some trials and lower than 1 in other trials.

## 4.2 Overview of validations for the colorectal cancer submodel

Table 4 summarizes the studies that were used to validate the colorectal cancer model. We tested the model predictions against different types of outcomes, including polyp prevalence, size distribution, incidence, and mortality of CRC, as well as the effects of CRC screening by stool test (15) and colonoscopy (14).

The following sections in this chapter provide brief summaries of the key validations for the colorectal cancer model. Full description of each validation with detailed discussion on simulation setup, validation outcomes and sensitivity analyses will be made available in future.

| Data Sets | Type of validation | Outcomes Tested | | | |
|---|---|---|---|---|---|
| | | Polyp outcomes | CRC incidence | CRC mortality | Effects of screening |
| CPS-II Mortality (78) | Independent | | | X | |
| CPS-II Nutrition (79) | Independent | | X | X | |
| Surveillance Epidemiology and End Results (SEER) data (12) | Partially dependent | | X | X | |
| Minnesota FOBT Trial (15) | Independent | | | | X |
| National Polyp Study (14) | Independent | | | | X |

| | | | | | |
|---|---|---|---|---|---|
| Veterans Affairs Cooperative Study Group (20) | Independent | X | | | |
| Women Health Study(80) | Independent | | X | | |
| Women Health Initiative | Independent | | X | | |
| UK Flexible Sigmoidoscopy Study | Independent | | | | X |

**Table 4. Summary of validation exercises of the colorectal cancer model.**

## 4.3 SEER

**Objective**

We want to verify that given our assumptions about colorectal cancer screening behavior in the general population, the model reproduces the incidence by age for CRC diagnoses and deaths in the general population. The validation is considered to be partially dependent since SEER data was used to calibrate the rate of malignant transformation and to construct the survival model.

**Simulation setup**

We created a simulated population that matched the US general population in distributions of age, BMI, race, gender, and family history of CRC. We used NHANES III participants to create our virtual population. Patients diagnosed with cancers prior to the trial start and during the run-in period were excluded.

The simulation ran for 20 years with a run-in period of ten years. The run-in period allowed people full access to the healthcare system before data was collected. Without a run-in period there would be an artificially large number of cancers detected at the beginning of the simulation as people have their first cancer screening.

The simulation assumes that compliance level of colorectal cancer screening does not change with time. Compliance to CRC screening and use of different screening modalities are calibrated to match screening data from the Behavioral Risk Factor Surveillance System (BRFSS) data for 2005.

**Validation results**

Figure 9 show that the model reproduces reasonably well CRC incidence in the general population.

The model over-predicts CRC mortality rate as compared SEER. It should be noted that the survival model was built using data from a long period between 1990 and 2005, over which, the survival rate has improved significantly. Therefore, it is possible our survival model does not reflect the modern rate of survival following diagnosis. In future, we should recalibrate the survival model to modern-day survival data from SEER (e.g. between 2005 and 2011).

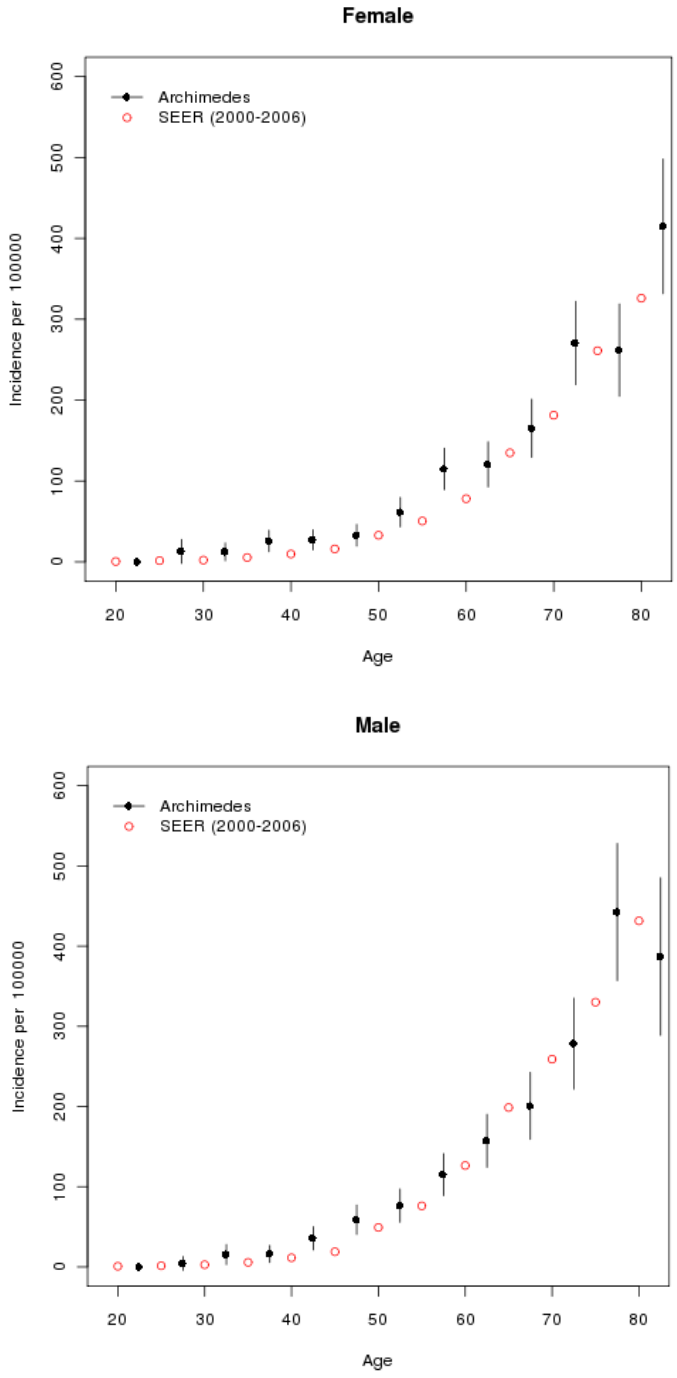


**Figure 12. Colorectal Cancer Incidence-By-Age for Male and Female in the general population.**

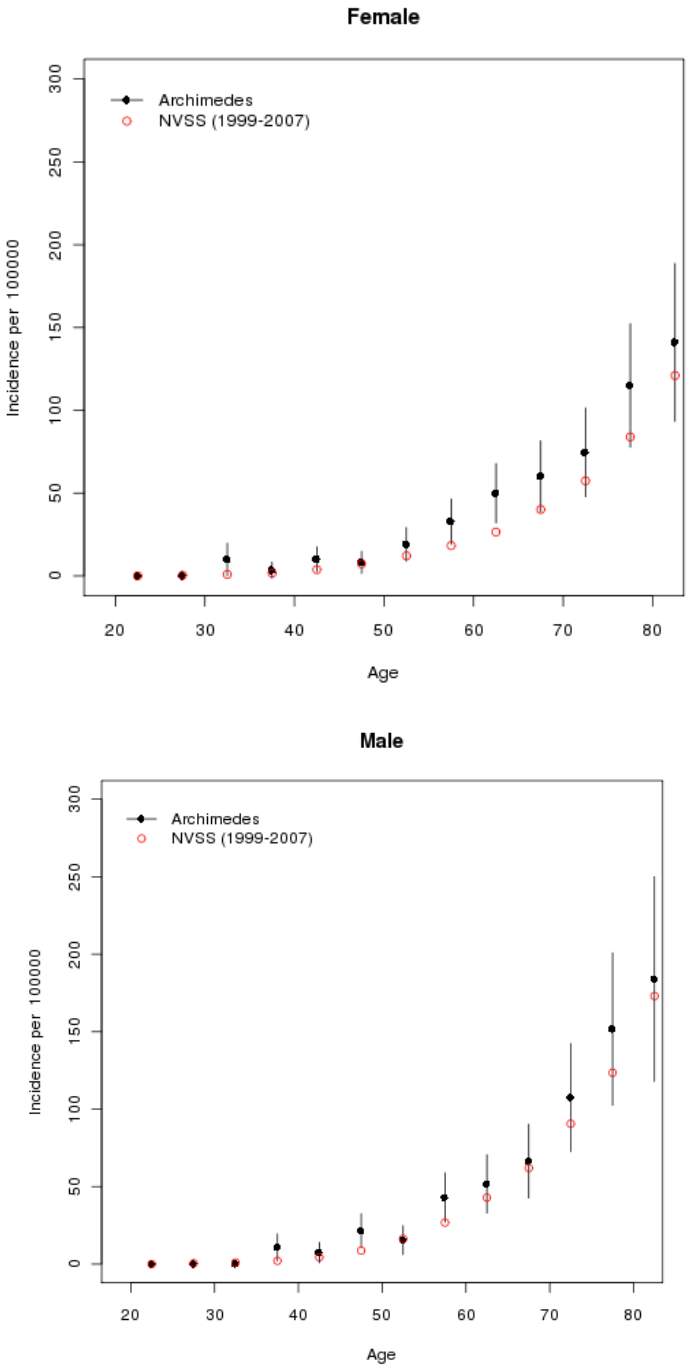


**Figure 13. Colorectal Cancer Death Incidence-By-Age**

## 4.4 Cancer Prevention Study II (CPS-II)

### Objective

The objective of this validation is to confirm that the CRC model can predict with reasonable accuracy the incidence and mortality of CRC in a large-scale population, with a long follow-up. We compare CRC outcomes reported in the Cancer Prevention Study II Nutrition dataset with those observed in Archimedes' virtual populations.

### Study description

The CPS-II Nutrition Cohort was established in 1992–1993; it consists of 86,404 men and 97,786 women recruited from among members of the CPS-II Baseline Cohort (enrolled in 1982 by American Cancer Society (ACS) volunteers in all 50 states, the District of Columbia, and Puerto Rico). CPD-II Nutrition Cohort participants included men and women aged 50–90 years residing in 21 states with population-based cancer registries. The median age at cohort entry in 1992–1993 was 63 years. The CPD-II Nutrition Cohort was re-contacted with self-administered questionnaires in 1997, 1999, 2001, and 2003.

A subset of the CPS-II Nutrition dataset was given to Archimedes by the ACS. This subset consists of 76,275 men and 84,285 women and includes the variables most relevant to breast, colorectal, and lung cancer. All participants had no prior diagnosis of cancer at the time of their 1992 survey.

There were 1152 instances of CRC and 267 CRC deaths among 84,285 females and 1544 incidences of CRC and 367 CRC deaths among 76,275 males. The total follow-up was 7.7x105 person-years for males and 8.9x105 person-years for females.

#### Data analysis

The CPS-II Nutrition Cohort is a high-quality dataset with very little missing data. Fewer than 2% of the samples had missing data. We assume that data was missing at random, and that for each variable, the distribution among respondents with non-missing data for that variable was representative of the distribution among all respondents.

Death records were followed in CPS-II Nutrition, and all deaths were recorded through June 30, 2003. This date is used as the censor date for the mortality data.

Incidence was followed in CPS-II Nutrition in two ways:

- When a person reported cancer on a survey, his/her medical record and/or cancer registry were checked to fill in a diagnosis date and other details.
- If a person was confirmed dead from the death registries and had a cause of death related to cancer, the cancer registries were checked to fill in the diagnosis date and other details.
- If a person did not return surveys and had no record of cancer from a death record, they were not followed for cancer incidence. A small proportion of cancers were self-reported on surveys and not confirmed from medical records or cancer registries.

We use the method suggested by epidemiologists at the American Cancer Society for censoring incidence data. The method, also known as window-of-opportunity censoring method, is briefly described here:

- If a person returned all their surveys, then they are censored on June 30, 2003, which is the day before the 2003 survey was mailed out.
- If a person stopped returning surveys, then we looked up the date on which the last survey was returned and the date on which the next survey was mailed out. (All surveys were sent out on Sept 1, except the 2003 survey, which was sent out on July 1.)
    - If the person died any time between the return date of his last survey and four months past the date on which the next survey was mailed out, then he is censored at his death date or June 30, 2003, whichever comes earlier. This is based on the assumption that people who died before four months after the mailing date of a survey had been too sick to return the survey or dead, and their cancer status can be approximated from their cause of death.
    - If the person did not die in this window, he is censored at the date that his last survey was returned.

If a person had a self-reported cancer (i.e. information on the cancer is not found in the cancer registries), then he was assumed to have cancer and randomly given a diagnosis date between the survey return date on which he reported the cancer and the return date of the previous survey.

**Colorectal cancer screening pattern**

- Survey participants were asked “Have you ever had a sigmoidoscopy or colonoscopy of the bowel?”. Participants who answered “yes” were asked about the number of procedures, year(s), the years and the reason for the most recent procedure. Procedures were categorized into three groups: (1) diagnostic follow-up because of a positive FOBT or symptoms of pain, diarrhea, or visible blood in the stool; (2) diagnostic follow-up because of previous CRC; or (3) CRC screening. The third category of screening endoscopy was further subdivided into (a) follow-up on a personal history of colorectal polyp; (b) follow-up on a family history of CRC; or (c) screening in the absence of symptoms, personal history of colorectal polyp, or family history of CRC (16).
- Chao et al. (16) analyzed the population who returned the survey in 1997 and reported that:
    - 58% of men and 51% of women reported ever having undergone sigmoidoscopy or colonoscopy
    - 40% of men and 32% of women reported endoscopy within the past five years (1992-1997).

**Simulation setup**

We created a simulated population of 80,000 virtual patients that matched the CPS-II population in distributions of age, BMI, race, gender, and family history of CRC. The information on these variables was extracted directly from the CPS-II Nutrition Cohort dataset. We used NHANES III participants to create our virtual population.

As in CPS-II Nutrition, patients diagnosed with cancers prior to the trial start and during the run-in period were excluded. The simulation ran for 20 years with a run-in period of seven years. The run-in period allowed people full access to the healthcare system before data was collected. Without a run-in period there would be an artificially large number of cancers detected at the beginning of the simulation as people have their first cancer screening. The compliance and continuous adherence ratios were selected to match the number of patients ever screened by endoscopy at year 5 of follow-up.

**Validation results**

**Baseline comparisons**

- Table 2 compares the baseline characteristics of the CPS-II Nutrition Cohort to those of the Archimedes simulated population.

| Baseline Demographics | CPS-II Nutrition Men | Archimedes Men | CPS-II Nutrition Women | Archimedes Women |
|---|---|---|---|---|
| Age (y) | 64.5 ± 6.1 | 64.1 ± 6.2 | 62.6 ± 6.7 | 62.9 ± 6.5 |
| White (%) | 98 | 98 | 98 | 98 |
| BMI (kg/m^2) | 26.4 ± 3.7 | 26.2 ± 3.6 | 25.6±4.8 | 25.8±4.8 |
| Age of first live birth | NA | NA | 23.9 | 22.3 |
| Age of menarche | NA | NA | 12.7 | 12.7 |
| Age of menopause | NA | NA | 47.6 | 45.0 |
| Smoking | 9.4% | 9% | 9% | 8.8% |
| Postmenopausal | NA | NA | 94% | 94% |

**Table 5. Comparison of baseline characteristics of the CPS-II Cohort and Archimedes simulated population.**

**Outcome comparisons**

Life-table plots of proportions diagnosed with CRC for females and males are presented in Figure 10 and Figure 11, respectively. Life-table plots for CRC deaths are presented in Figure 12 and

Figure 13. The validation hazard ratios range from 1.03 to 1.09 for CRC incidence and death in female and male populations in the CPS-II study. All 95% CIs cover 1. We can safely conclude that the model performs reasonably well against CPS-II data.

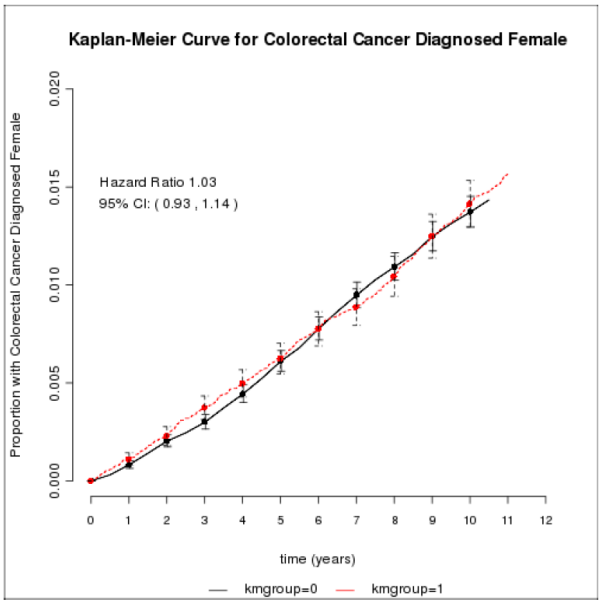

Figure 5: Colorectal Cancer Diagnosed Female (0-published result, 1-simulation)

**Figure 10. Cumulative risk of developing CRC in female population of CPS-II Nutrition: data (black) versus simulation (red).**

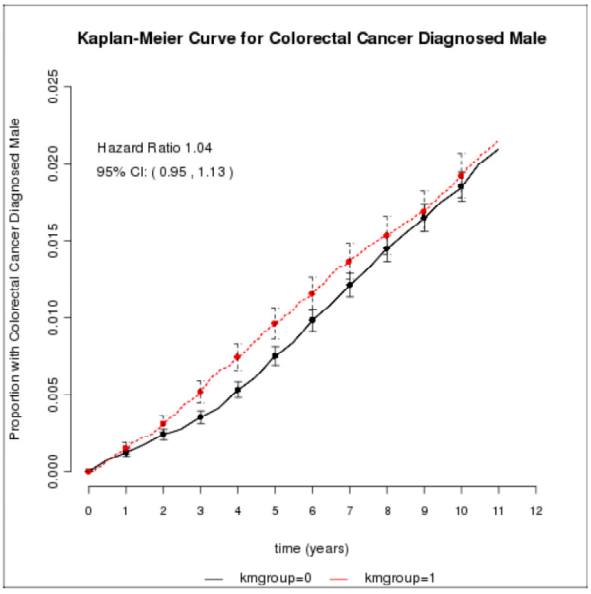

Figure 7: Colorectal Cancer Diagnosed Male (0-published result, 1-simulation)

**Figure 11. Cumulative risk of developing CRC in male population of CPS-II Nutrition: data (black) versus simulation (red).**

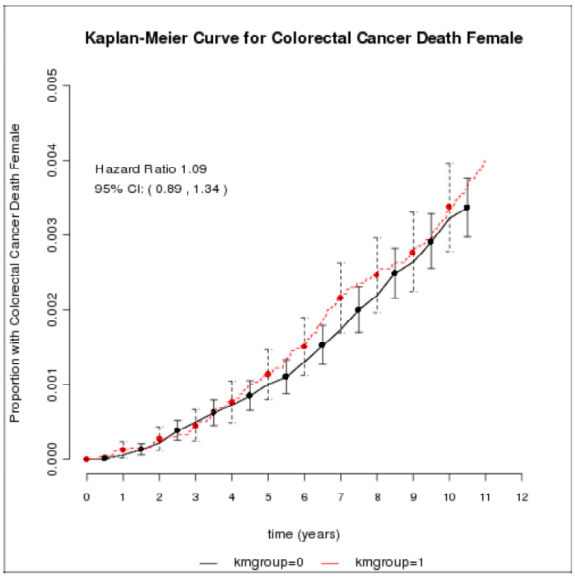

Figure 6: Colorectal Cancer Death Female (0-published result, 1-simulation)

**Figure 12. Cumulative risk of CRC death in female population of CPS-II Nutrition: data (black) versus simulation (red).**

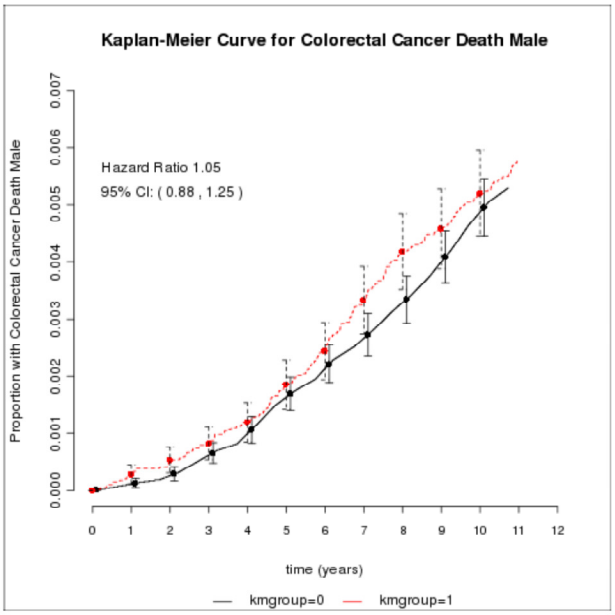

Figure 8: Colorectal Cancer Death Male (0-published result, 1-simulation)

**Figure 13. Cumulative risk of CRC death in male population of CPS-II Nutrition: data (black) versus simulation (red).**

## 4.5 Women's Health Study (WHS)

### Objective

The objective of this validation is to confirm that the CRC model can predict with reasonable accuracy the incidence of CRC in a large population of women, represented by the Women Health Study.

### Study description

The Women's Health Study was established in 1992, enrolling 39,876 female US health professionals (registered nurses, 75 percent) aged 45 years or older and free of cancer and cardiovascular disease at baseline (17). The study was designed as a randomized trial evaluating the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cancers and cardiovascular diseases. Upon enrollment in the study, all participants completed a baseline questionnaire inquiring about their medical history and lifestyle factors, including potential risk factors for cancers.

### Simulation setup

We created a virtual population of 50,000 women that matches the baseline characteristics of the WHS population. We used NHANES III participants to create our virtual population. Based on WHS data on family history of cancer, we inferred that 8% of the population has family history of CRC.

The simulation ran for 20 years with a run-in period of seven years. The run-in period allowed people full access to the healthcare system before data was collected. Without a run-in period there would be an artificially large number of cancers detected at the beginning of the simulation as people have their first cancer screening.

The adherence to colorectal cancer screening is calibrated to match 41.0% of the population undergoing colonoscopy screening and 22.5% undergoing sigmoidoscopy screening in the trial, over a period of 10 years.

## Validation results

### Baseline comparisons

| Baseline Demographics | WHS | Archimedes |
|---|---|---|
| Age (y) | 54.6 ± 7.0 | 54.6 ± 7.1 |
| Age 45-54 | 60% | 61% |
| Age 55-64 | 30% | 29% |
| Age 65-74 | 9% | 9.6% |
| Age > 75 | 0.7% | 0.4% |
| BMI (kg/m^2) | 26.1±4.8 | 25.8±4.8 |
| White | 95% | 95% |
| Current smokers | 13% | 13% |

**Table 6. Comparison of baseline characteristics of the WHS cohort and Archimedes simulated population.**

### Outcome comparisons

The model over-predicts the rate of colorectal cancer incidence in the WHS population by about 21%, see Figure 14. It is possible that the woman population in WHS (consisting of nurses and doctors) is eating healthier diet and exercise more frequently than the general population. This explains that a model built using data from general population might underpredicts the rate of CRC in the WHS population.

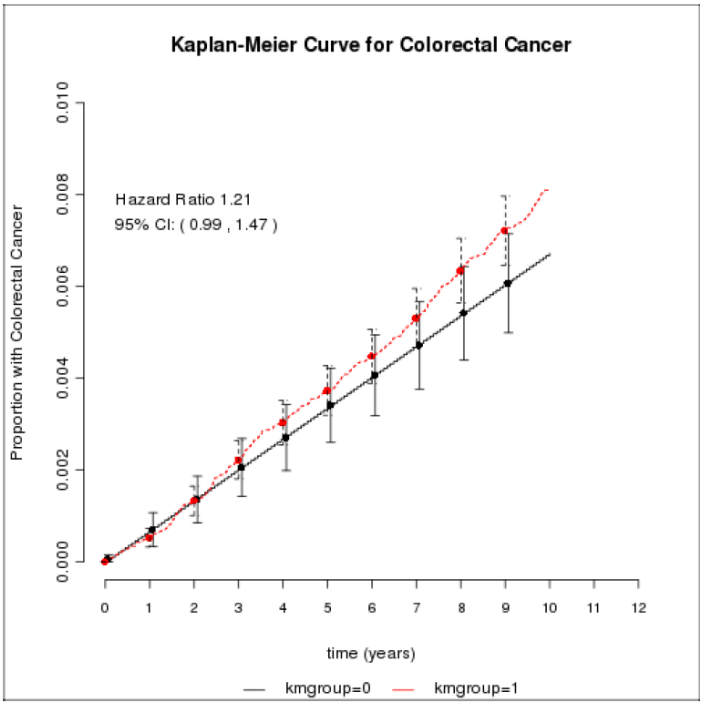

Figure 4: Colorectal Cancer (0-published result, 1-simulation)

**Figure 14. Cumulative risk of CRC incidence in Women's Health Study: data (black) versus simulation (red).**

## 4.6 Women's Health Initiative (WHI)

### Objective

The objective of this validation is to confirm that the CRC model can predict with reasonable accuracy the incidence of CRC in a large population of women, represented by the Women Health Initative.

### Study description

The Women's Health Initiative Dietary Modification Trial, a randomized controlled trial conducted in 48,835 postmenopausal women aged 50 to 79 years. 13% of the population has family history of Colorectal cancer 13.7% (18). Participants were randomly assigned to the dietary modification intervention (n = 19,541; 40%) or the comparison group (n = 29,294; 60%). A total of 480 incident cases of invasive colorectal cancer occurred during a mean follow-up of 8.1 (SD, 1.7) years. There were no difference in incidence of CRC between the two arms: 201 women with invasive colorectal cancer (0.13% per year) in the intervention group and 279 (0.12% per year) in the comparison group (hazard ratio, 1.08; 95% confidence interval, 0.90-1.29).

### Simulation setup

#### Virtual patients

We created a virtual population of 20,000 women that matches the baseline characteristics of the WHS population. We used NHANES III participants to create our virtual population. We also match history of average-risk colonoscopy screening (50%) at baseline.

#### Interventions

Patients have a choice to be screened with either colonoscopy or sigmoidoscopy.The adherence to colorectal cancer screening is calibrated to match 44.0% of the population undergoing colonoscopy or sigmoidoscopy screening in the trial.

### Validation results

#### Baseline comparisons

| Baseline Demographics | WHI | Archimedes |
|---|---|---|
| Age (y) | 62.3±6.9 | 62.3±6.9 |
| Age 50-59 | 37% | 37% |
| Age 60-69 | 47% | 47% |
| Age 70-79 | 16% | 16% |
| White (%) | 82% | 81% |
| BMI (kg/m^2) | 29.1±5.9 | 29.1±5.9 |
| Black | 11% | 11% |

**Table 7. Comparison of baseline characteristics of the WHI cohort and Archimedes simulated population.**

**Outcome comparisons**

The model slightly over-predicts the rate of colorectal cancer incidence in the WHS population by 13%. The 95% confidence interval of the validation hazard ratio is [0.97,1.31] and covers 1. This suggests that the model captures the incidence of CRC in the WHI population with a reasonable accuracy.

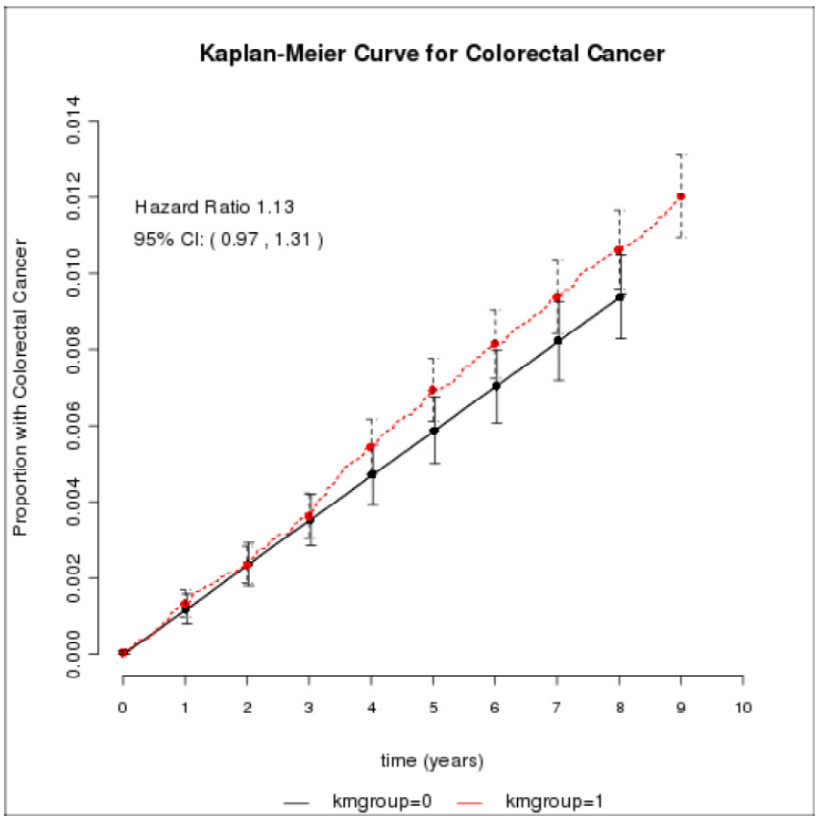

Figure 2: Colorectal Cancer (0-published result, 1-simulation)

**Figure 15. Cumulative risk of CRC incidence in Women Health Initiative: data (black) versus simulation (red).**

## 4.7 UK Flexible Sigmoidoscopy Trial

### Objective

UK Flexible Sigmoidoscopy Trial(19) is a recent landmark trial demonstrating the efficacy of once-only flexible sigmoidoscopy screening between 55 and 64 years of age on colorectal cancer incidence and mortality. We used the study to validate the model predictions of effects of sigmoidoscopy on colorectal cancer outcomes.

### Study description

This randomized controlled trial was conducted in UK. 113 195 people aged 55-64 were assigned to the control group and 57 237 to the intervention group, of whom 112 939 and 57 099, respectively, were included in the final analyses. Exclusion criteria include inability to provide informed consent; history of colorectal cancer, adenomas, or inflamatory bowel disease; severe or terminal disease; or sigmoidoscopy or colonoscopy within the previous 3 years.

In the intervention group, patients were offered flexible sigmoidoscopy screening. In the control group, patients were not contacted. The primary outcomes were the incidence of colorectal cancer, including prevalent cases detected at screening, and mortality from colorectal cancer.

The median follow-up was 11.2 years. 2524 participants were diagnosed with colorectal cancer. In per-protocol analyses, incidence of colorectal cancer in people attending screening was reduced by 33% (0.67, 0.60-0.76) and mortality by 43% (0.57, 0.45-0.72).

### Simulation setup

#### Virtual patients

We could not find sufficiently detailed information on distributions of age, BMI and race in trial publications, except for median age (60.5), male fraction and exclusion criteria regarding prior screening history (sigmoidoscopy or colonoscopy within the previous 3 years). To overcome this lack of information, we adjusted BMI distribution and prior CRC screening history to get the cancer incidence in the control arm to match data. Thus, the validation of the colorectal cancer incidence in the control arm is dependent.

It should be noted that except for the CRC rate in the control arm is calibrated to match data, other aspects of the virtual trial are independent in the sense that they are not modified to match data.

**Interventions**

The virtual patients are subjected to (i) a screening arm, in which patients are screened by sigmoidoscopy at the start of the trial and (ii) a no-screening, in which patients are not offered screening.

In the screened arm, 100% patients received sigmoidoscopy at the start of the trial. A positive sigmoidsocopy will lead to subsequent colonoscopy. Patients, who are diagnosed to have high risk of colorectal cancer based on colonoscopy and sigmoidoscopy results, will be subjected to increased surveillance. The outcomes of this arm will be compared to the data reported for the screened group (Figure 2B in Atkin et al., 2010(19)).

In the no-screening arm, patients only get colonoscopy if they develop symptoms for colorectal cancer. The outcomes reported for the no-screening arm of the virtual trial are compared to data reported for the control group.

**Validation results**

Figure 16 compares the incidence of colorectal cancer predicted by Archimedes to data in the control arm. As discussed above, we calibrated the predicted CRC rate in the control arm to data by manipulating distributions of age and BMI and screening history prior to randomization. The calibration was done at the minimal level. As the result, the predicted CRC incidence curve captures the trend of the data but is not a perfect match to the data.

Figure 17 compares the incidence of colorectal cancer predicted by Archimedes to data in the screened arm. The model predicted a significant jump in colorectal cancer incidence at the start of the simulation due to sigmoidoscopy screening. Such a sudden jump in detection of colorectal cancer was also observed in the trial, however, occurring mostly at years 1 and 2. It is possible that in reality most sigmoidoscopies in the screened arm are scheduled at year 1 or year 2. However, we do not have access to information on timing of sigmoidoscopies.

Figure 18 and Figure 19 compare predicted rates of colorectal cancer death to data for the control arm and the screened arm, respectively. In general, the model captures the trend of the data well but tends to slightly underpredicts the rates of CRC deaths. This could be due to the fact that the survival model was built using US (SEER) data.

Table 8 summarizes the validation results. The model predicts a 27% reduction in CRC incidence and a 47% reduction in CRC mortality by once-only flexible sigmoidoscopy, as compared to 33% and 44% as reported by the trial. Note that the differences in reductions of CRC incidence and mortality between data and model predictions are not statistically significant.

We conducted sensitivity analyses of the validation by varying different degrees of matching of CRC rate in the no-screening arm to data. We found the predicted effects of once-only screening by sigmoidoscopy on CRC outcomes to be relatively independent of the degree of matching. The predicted reduction in CRC incidence ranges from 24% to 30%. Similarly, the predicted reduction in CRC mortality ranges from 41% to 50%.

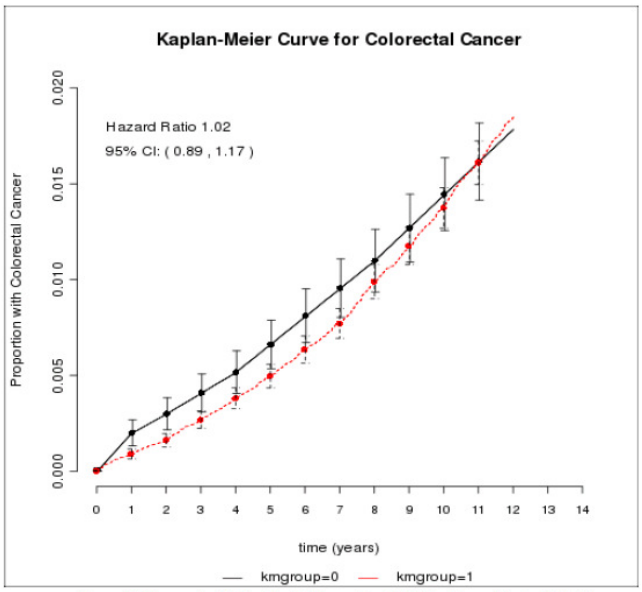

Figure 2: Comparing Data with No Screening, CRC incidence (1-sim, 0-data)

**Figure 16. UK Flexible Sigmoidoscopy Validation. Incidence of colorectal cancer diagnosis in the control arm (black: data; red: Archimedes). The population and prior screening history were calibrated to make the predicted cumulative incidence of colorecancer match data.**

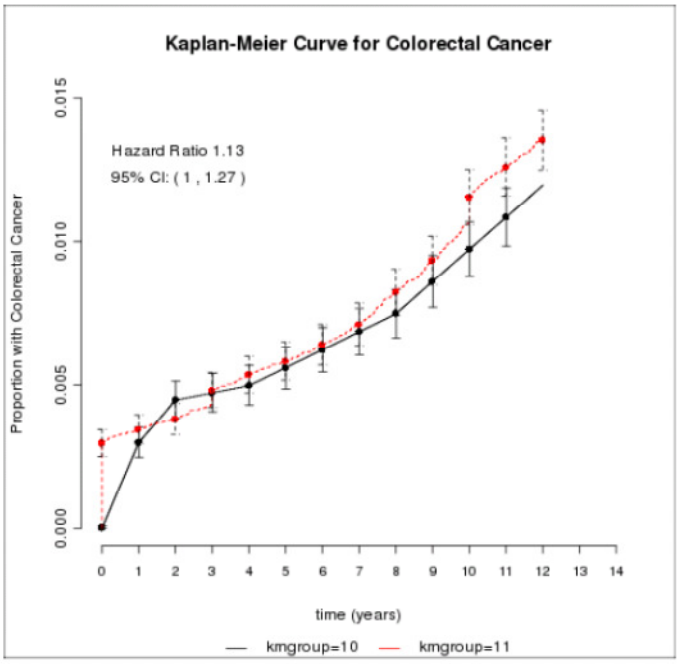

Figure 3: Comparing Data with Screened, CRC incidence (11-sim, 10-data)

**Figure 17. UK Flexible Sigmoidoscopy Validation. Incidence of colorectal cancer diagnosis in the screened arm (black: data; red: Archimedes).**

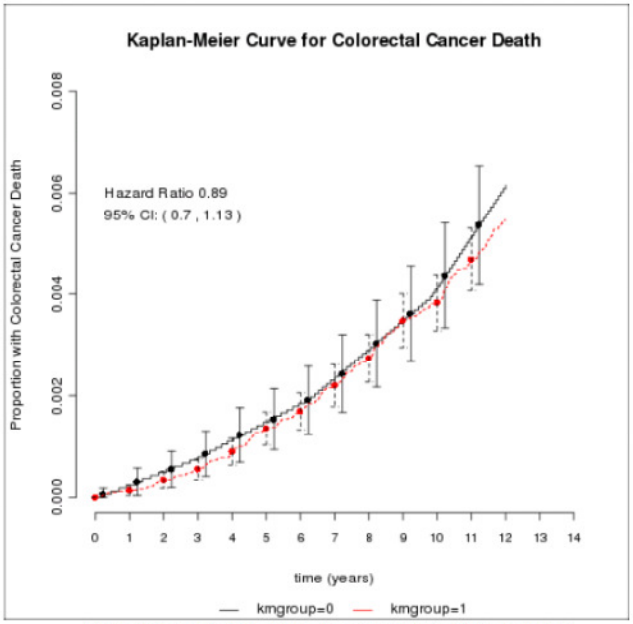

Figure 5: Comparing Data with No Screening, CRC Death (1-sim, 0-data)

**Figure 18. UK Flexible Sigmoidoscopy Validation. Incidence of colorectal cancer death in the control arm (black: data; red: Archimedes).**

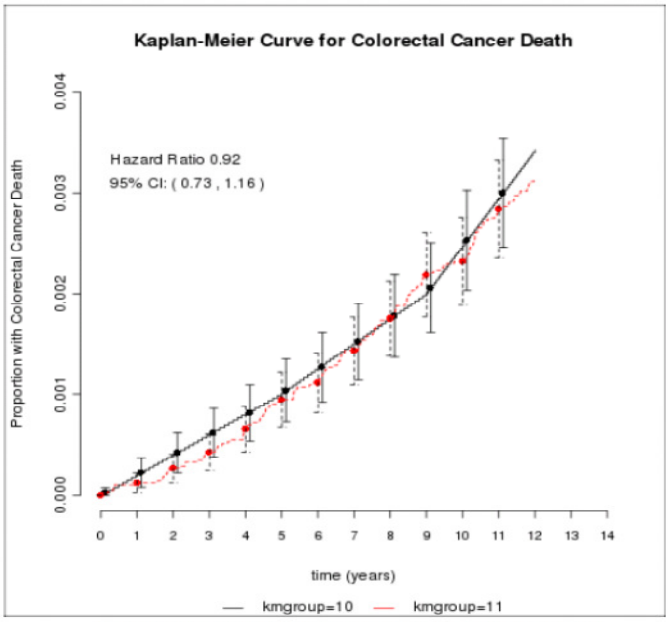

Figure 6: Comparing Data with Screened, CRC Death (11-sim, 10-data)

**Figure 19. UK Flexible Sigmoidoscopy Validation. Incidence of colorectal cancer death in the screened arm (black: data; red: Archimedes).**

| **Cumulative risk at year 12** | **Control** | | **Screened** | | **Hazard ratio** | |
|---|---|---|---|---|---|---|
| | Data | Simulation | Data | Simulation | Data | Simulation |
| Colorectal cancer diagnosis | 1.79% | 1.84%* | 1.20% | 1.35% | 0.67 (0.60-0.76) | 0.73 (0.70-0.76) |
| Colorectal cancer death | 0.62% | 0.60% | 0.34% | 0.32% | 0·56 (0·45–0·69) | 0.53 (0.50-0.56) |

**Table 8. UK Flexible Sigmoidoscopy Tria. Summary of simulation results. Asterisk (*) indicates that the predicted rate is dependent on data that is comapred to.**

# 5. Comparison of Archimedes Model predictions to other models

The table below compares life years gained by colonoscopy screening predicted by the Archimedes Model against those predicted by the CISNET models (MISCAN and SimCRC).

| Screening strategy | Definition | Life years gained per 1000 people aged 50 representative of the general US population. | | |
|---|---|---|---|---|
| | | Archimedes | MISCAN (70) | SimCRC (70) |
| COL 50-75, 10 | Screening starting at age 50, at 10-year intervals, ending at 75 | 269 | 230 | 271 |
| COL 50-85, 10 | Screening starting at age 50, at 10-year intervals, ending at 85 | 276 | 236 | 273 |

**Table 9. Comparisons of predictions of life years gained by Archimedes Model and the MISCAN and SimCRC models.**

It should be also noted that our prediction of reduction in CRC incidence by colonoscopy screening is consistent with a recent large-scale retrospective study by Brenner et al. (81).

The predicted costs are also fairly consistent with other models. For colonoscopy screening of an average risk person between ages 50 and 80, at a 10-year interval, the current model predicts cost of CRC screening/surveillance to be $2,466, while the MISCAN model predicts it to be $2,255 (82).

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