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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. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

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

Definitons and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Key References

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

MODEL PURPOSE

SUMMARY

This page summarizes the overall goal of the Simulation Model of Colorectal Cancer (SimCRC) Model.

PURPOSE

The SimCRC Model can be run in one of two ways. It can simulate the US population from birth to death, and track the full US population from 1970 to a future year (e.g. 2020), or it can run a single birth cohort. The type of model run varies depending on the purpose of the model application.

The Model contains:

1. a natural history component that tracks the adenoma–carcinoma sequence as a function of age, sex, race, and risk factors (see Risk Factors CRC);
2. a screening component that allows for the detection and removal of adenomas and possibly an early diagnosis of preclinical CRC; and
3. a treatment component for all persons diagnosed with CRC.

The Model specifically incorporates:

1. population–level trends in risk factors for CRC and the underlying relationship between each risk factor and colorectal disease;
2. population–level trends in CRC screening participation rates and each test's ability to detect and remove adenomas and preclinical cancers; and
3. trends in the use of 5–fluorouracil (5FU) based chemotherapy and projected use of newer chemotherapy agents and their impact on cancer–specific mortality, as well improvements in cancer–specific survival over time not explained by chemotherapy trends.

The primary model outcomes when running a population–based simulation are the predicted number of cases of CRC and the number of deaths from CRC per 100,000 persons, standardized to the 2000 population, which can then be compared with actual incidence data from the Surveillance, Epidemiology, and End Results (SEER) program and mortality data from the US Vital Statistics. The primary model outcomes when running a birth cohort simulation are the number of life years gained with screening compared to without screening per 1000 persons screened. See Model Overview for a more detailed description of the Model.

MODEL OVERVIEW

SUMMARY

This document provides an overview of the structure of the SimCRC Model and its components.

PURPOSE

The SimCRC Model was initially developed to examine the relative contribution of changes in risk factors, screening and treatment on the overall population trends in CRC incidence and mortality. Subsequent uses of the model have targeted policy questions for cancer control. See Model Purpose for more details.

BACKGROUND

Colorectal cancer (CRC) is the second most common cause of cancer–related death in the United States. Although the incidence rate of CRC increased from 1973 through 1985, it has declined steadily since 1985. However, this decline in incidence has been greater for white Americans compared with African Americans. Possible reasons for the decreasing trends in incidence and mortality of CRC include lifestyle changes (e.g., less consumption of red meat),[8] increased screening (resulting in the detection and removal of adenomas and a favorable stage–shift at cancer diagnosis),[15] or new treatment regimens (e.g., new adjuvant therapies).[20]

In addition to examining the relative contributions of risk factors, screening, and treatment on cancer trends, simulation models provide a tool for incorporating multiple sources of data to examine outcomes associated with different screening and treatment policies. Screening rates in the US continue to be lower than that for other cancers and it is not possible to conduct randomized controlled trials of all of the possible screening strategies possible. Models can provide a useful tool for evaluating screening alternatives in the average–risk population. Further, comparing the results of the results from three independently–developed models lends robustness to the model results.

MODEL DESCRIPTION

The model is based on a prior model that was designed as a cohort model to evaluate the cost–effectiveness of screening.[21] The SimCRC Model was originally designed specifically to examine population trends over time in that it simulates the US population from 1970 to 2020. The model can also be used to simulate a single birth cohort, which is typically used to evaluate alternative screening policies. Model components include:

1. population demographics,
2. risk factor trends,
3. screening dissemination,
4. treatment dissemination and other improvements in cancer–specific survival,
5. natural history of colorectal cancer,
6. screening mechanism, and
7. post–CRC diagnosis.

More details on population demographics, natural history of colorectal cancer, the screening mechanism, and post–CRC diagnosis is provided in Assumption Overview.

Variables used to model risk factor trends, screening dissemination, and treatment dissemination are provided in Parameter Overview, with detailed decriptions provided in the Component Overview. The key outcomes of the model are incident CRC cases and CRC deaths each each calendar year, standardized to the 2000 US population.

The SimCRC Model is population–based microsimulation model of the US population that can be used to forecast incidence and mortality associated with CRC. In addition it can simulate the outcomes for a single birth cohort. The model tracks the US population from birth to death. For each simulated person, SimCRC first generates a time of birth and a time of death from causes other than CRC. Next, SimCRC generates adenomas within the individual, with the age of onset for each adenoma drawn from a cumulative probability function that depends on sex, race, age, and an individual risk index that captures whether a person tends to produce more (or fewer) adenomas than average. SimCRC includes an optional risk factor module that allows individual–level risk factors to influence adenoma incidence (i.e., specific values for each of eight CRC risk factors, see Risk Factors CRC). SimCRC simulates three adenoma sizes (1–5mm, 6–9mm, 10+mm) and six locations (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum). All adenomas start small and can transition through larger size categories. The timing of transitions between adenoma size categories depends on age, sex, location (proximal colon, distal colon, rectum) and (optionally) eight modifiable risk factors. Medium and large adenomas may progress to preclinical CRC, although most will not in a person's lifetime. Progression depends on sex, race, and adenoma location. SimCRC can be (optionally) implemented to allow progression to preclinical CRC to depend on eight risk factors and birth year.

Overlaid on this natural history of colorectal disease (no disease to adenoma to preclinical cancer to clinical cancer) is a screening mechanism. If a screening test is performed in a particular year, then a person with an underlying adenoma has a chance of having it detected and removed, or a person with preclinical cancer may have it detected at an earlier stage than clinical detection. When modeling population trends, the chance that a screening test is performed depends on the age, sex, race and birth year of the simulated individual and these screening probabilities are derived to reflect the dissemination of screening (fecal occult blood test, sigmoidoscopy, or both) in the US between 1970 and 2000, with projection to 2020. When modeling screening strategies, the chance that a screening test is performed depends on the screening algorithm and assumptions about adherence. Simulated persons diagnosed with CRC (by symptoms or by screening) are assigned a cancer–specific mortality rate, which depends on age, sex, stage at diagnosis, location of cancer (colon vs. rectum), year of diagnosis and (optionally) race.
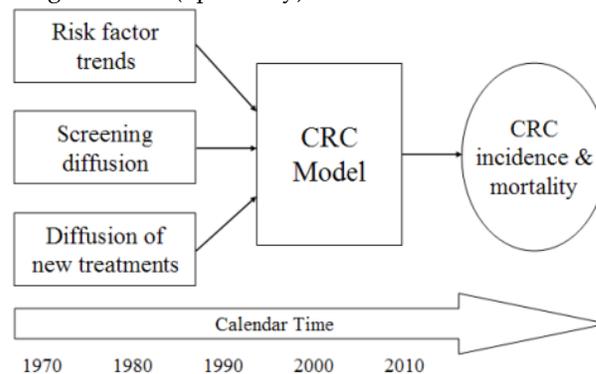
Schematic Diagram of the Population Trends Analysis

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REFERENCES:

[1] Giovannucci, E., Stampfer, MJ., Colditz, GA., Rimm, EB., Trichopoulos, D., Rosner, BA., Speizer, FE., Willett, WC. "Folate, methionine, and alcohol intake and risk of colorectal adenoma" in J Natl Cancer Inst 1993; 85: 875-884

[2] Giovannucci, E., Rimm, EB., Stampfer, MJ., Colditz, GA., Ascherio, A., Willett, WC. "Intake of fat, meat, and fiber in relation to risk of colon cancer in men" in Cancer Research 1994; 54: 2390-2397

[3] Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC "Physical activity, obesity, and risk for colon cancer and adenoma in men" in Ann Intern Med 1995; 122: 327-334

[4] Giovannucci, E., Egan, KM., Hunter, DJ., Stampfer, MJ., Colditz, GA., Willett, WC., Speizer, FE. "Aspirin and the risk of colorectal cancer in women" in N Engl J Med 1995; 333: 609-614

[5] Giovannucci, E., Martinez, ME. "Tobacco, colorectal cancer, and adenomas: a review of the evidence" in J Natl Cancer Inst 1996; 88: 1717-1730

[6] Giovannucci, E., Stampfer, MJ., Colditz, GA., Hunter, DJ., Fuchs, C., Rosner, BA, Speizer, FE., Willett, WC. "Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study" in Intern Med 1998; 129: 517-524

[7] Grodstein, F., Martinez, ME., Platz, EA., Giovannucci, E., Colditz, GA., Kautzky, M., Fuchs, C., Stampfer, M. "Postmenopausal hormone use and risk for colorectal cancer and adenoma" in Ann Intern Med 1998; 128: 705-712

[8] Martinez, ME., Giovannucci, E., Spiegelman, D., Hunter, DJ., Willett, WC., Colditz, GA. "Leisure-time physical activity, body size, and colon cancer in women" in J Natl Cancer Inst 1997; 89: 948

[9] Mandel, J.S., Church, T.R., Bond, J.H., Ederer, F., Geisser, M.S., Mongin, S.J., Schuman, LM. "The effect of fecal occult-blood screening on the incidence of colorectal cancer." in N Engl J Med 2000; 343: 1603-1607

[10] Hardcastle, J.D., Chamberlain, J.O., Robinson, M.H.E., Moss, S.M., Amar, S.S., Balfour, T.W., James, P.D., Mangham, C.M. "Randomised controlled trial of faecal-occult-blood screening for colorectal cancer." in Lancet 1996; 348: : 1472-1477

[11] Jorgensen, O.D., Kronborg, O., Fenger, C. "A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds." in Gut 2002; 20: : 29-32

[12] Atkin, WS., Cuzick, J. , Northover, JM. , Whynes, DK., "Prevention of colorectal cancer by once-only sigmoidoscopy" in Lancet 1993; 341: 736-740

[13] Selby, J., Friedman, G., Quesenberry, C., Weiss, N. "A case-control study of screening sigmoidoscopy and mortality from colorectal cancer." in N Engl J Med 1992; 326: : 653-657

[14] Brenner, H., Arndt, V., Sturmer, T., Stegmaier, C., Ziegler, H., Dhom G. "Long lasting reduction of risk of colorectal cancer following screening endoscopy." in Br J Cancer 2001; 85: : 972-976

[15] Winawer SJ., Zauber AG., Ho MN., O'Brien, MJ., Gottlieb, LS., Sternberg, SS., Waye, JD., Schapiro, M., Bond, JH., Panish, JF. "Prevention of colorectal cancer of colonoscopic polypectomy. The National Polyp Study Workgroup" in N Engl J Med 1993; 329: 1997-1981

[16] Saltz, L.B., Cox, J.V., Blanke, C., et al. "Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group." in N Engl J Med 2000; 343: : 905-914

[17] de Gramont, A., Figer, A., Seymour, M., et al. "Leucovorin and fluorouracil with or without oxaliplatin as first-Line treatment in advanced colorectal cancer." in J Clin Oncol 2000; 18: 2937-2947

[18] Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., Bets, D., Mueser, M., Harstrick, A., Verslype, C., Chau, I., Van Cutsem, E. "Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer." in N Engl J Med 2004; 351: : 337-345

[19] Hurwitz, H., Fehrenbacher, L., Novotny, W., et al. "Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer." in N Engl J Med 2004; 350: 2335-2342

[20] Schrag, D. "The price tag on progress - chemotherapy for colorectal cancer" in N Engl J Med 2004; 351: : 317-319

[21] Frazier, AL., Colditz, GA., Fuchs, CS., Kuntz, KM. "Cost-effectiveness of screening for colorectal cancer in the general population" in JAMA 2000; 284: 1954-1961

ASSUMPTION OVERVIEW

SUMMARY

This section outlines the key assumptions of the SimCRC Model.

BACKGROUND

The structure of SimCRC relies on a number of assumptions. While the natural history component of the model is based on the adenoma–carcinoma sequence,[1][2][3] we need to make several assumptions about how that is operationalized structurally. In addition, we assume that all CRC arises from an adenoma and we do not explicitly model hyperplastic polyps.

ASSUMPTION LISTING

Population Demographics

SimCRC is a compilation of multiple cohorts defined by age, sex, race, and calendar year; the size of each cohort is based on US Census data. Each birth cohort is analyzed one individual at a time as a first–order microsimulation starting at birth, where we assume no adenomas can develop until age 20. Non–cancer–specific mortality rates are based on the US life tables and are a function of age, sex, race, and calendar year. Population migration is not explicitly modeled.

Natural History of Colorectal Disease (prior to diagnosis)

The natural history model describes the progression of underlying disease in an unscreened population. It models the transitions from normal colonic epithelium to low–risk adenomas (defined as 1–5 mm in size), from low–risk to medium–risk adenomas (defined as 6–9mm in size), from medium–risk to high–risk adenomas (defined as ≥ 10 mm in size), from medium– or high–risk adenomas to preclinical cancer (stages I–IV), and from preclinical to symptom–detected CRC. This disease process is allowed to progress separately for three segments of the CRC tract (i.e., the proximal colon, the distal colon, and the rectum) and we allow for up to six lesions in the proximal colon and 3 lesions in the distal colon and the rectum for a maximum of 12 lesions per person. See Parameter Overview for key variables in the natural history model.

The model incorporates (optionally) the effects of eight modifiable risk factors associated with CRC (see Risk Factors CRC). Risk factors are allowed to have an effect on: 1) the development of an adenoma, and/or 2) the progression of an adenoma to preclinical cancer. In addition to these known risk factors we also assign a risk index based on a Truncated Normal distribution with a mean of 1 and variance v. The magnitude of this factor affects the risk of developing an adenoma.

Screening Mechanism

A simulated person who has an underlying adenoma or preclinical cancer has a chance of having it detected during a screening year as a function of his or her adherence rate and the sensitivity of the test.[6] Test sensitivity varies as a function of adenoma size and presence of preclinical cancer. Test specificity is defined as the probability of having a positive test among persons without any adenomas or preclinical CRC.

CRC screening tests vary in terms of their test characteristics, reach, and risk. For example, FOBTs have the ability to detect a lesion in any segment of the colorectal system, but tends to have relatively poorer test characteristics compared with the other screening modalities. We assume that colonoscopy is recommended for all person with a positive FOBT. Sigmoidoscopy can only detect lesions located in the distal colon or rectum, although with better test characteristics within its reach. If any lesion is found the person is then referred to colonoscopy. The test sensitivity of colonoscopy is also lesion–based; however, colonoscopy has the ability to detect lesions throughout the colorectal system. Colonoscopy is also associated with a small mortality risk due to the risk of perforations during the procedure.

We assume that all adenomas that are detected during colonoscopy are removed via polypectomy. All persons who have had a high–risk adenoma (i.e. at least one large adenoma or three or more adenomas of any size) detected and removed are placed on colonoscopic surveillance every 3 years, and those with low–risk adenomas detected and removed are placed on colonoscopic surveillance every 5 years.

Diagnosed CRC
Once a person is diagnosed with CRC, either by symptom detection or by screening, they enter a "diagnosis" submodel. We track diagnosed patients on a monthly basis (as opposed to a yearly basis prior to diagnosis) and do not continue to keep track of risk factors or screening. CRC patients are assigned a cancer–specific mortality rate (in addition to their mortality rate from the life tables), which is a function of age and stage at diagnosis, location of cancer (colon vs. rectum), year of diagnosis, and use of adjuvant chemotherapy. There are two trends that are relevant for CRC patients: (1) cancer–specific mortality has decreased over time independent of known effective therapies and (2) the development of new effective therapies has increased.

REFERENCES:

[1] Morson, B. "The polyp-cancer sequence in the large bowel" in Proc R Soc Med 1974; 67: 451-457

[2] Fenoglio, CM., Lane, N. "The anatomical precursor of colorectal carcinoma" in Cancer 1974;34:819-823. 1974; 34: 819-823

[3] Kronborg, O., Fenger, C. "Clinical evidence for the adenoma-carcinoma sequence." in Eur J Cancer 1999; 8: Suppl 1: S73-86

[4] Allison, J., Ransom, L., Adrain, A. "A comparison of fecal occult-blood tests for colorectal-cancer screening" in N Engl J Med 1996; 334: 155-159

[5] Rex, D.K., Cutler, C.S., Lemmel, G.T., Rahmani, E.Y., Clark, D.W., Helper, D.J., Lehman, G.A., Mark, D.G. "Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies." in Gastroenterology 1997; 112: : 24-28

[6] Hixson, L., Fennerty, M., Sampliner, R., Garewal, H. "Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps" in Gastrointest Endosc 1991; 37: 127-127

PARAMETER OVERVIEW

SUMMARY

This section describes the key parameters in the SimCRC Model.

BACKGROUND

We have several model components that have there own sets of parameters.

1. Parameters that describe the US population dynamics over time.

2. A set of natural history parameters that describe the progression of colorectal disease in a simulated individual. These parameters were estimated through calibration (see Calibration Method).

3. Parameters that describe the risk factor status of a simulated individual (see Risk Factors CRC), the manner in which risk factors can change over time (see Risk Factor Drifts) and parameters that are specific for the risk factor effects on underlying disease progression (see Risk Factor Effect Method).

4. Parameters that describe the test characteristics of the screening tests that are modeled as well as parameters that describe screening dissemination in the US.

5. Parameters relevant for patients diagnosed with CRC, including the dissemination of adjuvent chemotherapy.

PARAMETER LISTING OVERVIEW

Population Parameters (see Population Demographics in Component Overview)

1. number of persons in the US, by age, sex, race and calendar year
2. life table values for each birth cohort

Natural History Parameters (see Natural History)

1. health state descriptors describing the adeno–carcinoma sequence
2. annual probability of transitioning from no disease to low–risk adenoma (function of age, location, risk index, risk factors (optional); see Adenoma Incidence)
3. annual probability of transitioning from low–risk adenoma to medium–risk adenoma (function of location)
4. annual probability of transitioning from low–risk adenoma to medium–risk adenoma (function of location)
5. annual probability of transitioning from medium– or high–risk polyp to stage 1 preclinical cancer (function of age, location, risk factors (optional); see Adenoma Progression)
6. annual probability of transitioning from stage i to stage i+1 preclinical cancer (i=1,2,3; function of stage and location)
7. annual probability of preclinical cancer becoming symptom detected (function of stage and location)

Risk Factor Parameters (see Risk Factor Trends in Component Overview)

1. vector of values for each risk factor
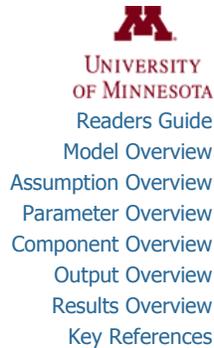
2. multiway distributions of risk factor prevalence in 1970, by age range, sex and race

3. multiway distributions of risk factor prevalence for 25–year–old individuals in 1971 and beyond, by sex and race

4. distributions for each continuous RF category (used to assign risk factor values)

5. menopause status for a simulated woman and time since menopause (linked with hormone replacement therapy use)

6. multipliers for each of the continuous risk factors (body mass index, red meat consumption, fruit and vegetable consumption, physical activity) to reflect cohort–specific changes each year, by age, birth year, sex and race

7. annual probabilities of uptake among non–users or of quitting among users (for smoking, multivitamin use, and aspirin use) to reflect cohort–specific changes each year, by age, birth year, sex and race

8. annual probabilities of uptake among non–users or quitting among users for hormone replacement therapy use to reflect cohort–specific changes each year, by year of menopause, time since menopause and race

Screening Parameters (see Screening Dissemination and Screening Effectiveness in Component Overview)

1. annual probability of getting screened in a year if previously unscreened, by age, birth year, sex and race (for trends analysis)

2. distribution of screening modalities among screened persons (FOBT, sigmoidoscopy, both, colonoscopy) (for trends analysis)

3. distribution of screening behavior among screened persons (low, moderate, high), which influences compliance with a screening strategy

4. probabilities that a person with a low–risk or medium–risk adenoma will be put on surveillance

5. sensitivities and specificities of all screening tests (by disease status)

6. mortality risk associated with colonoscopy

CRC Diagnosis Parameters (see Treatment Dissemination and Diagnosis Model in Component Overview)

1. indicator variable to indicate whether cancer has been diagnosed

2. age, stage, location and year of diagnosis

3. time since diagnosis in months

4. probability that a newly diagnosed CRC patient or a newly metastatic patient receives chemotherapy (function of age, sex, race, stage, location, year) (for trends analysis)

5. monthly cancer–specific mortality rates (function of age at diagnosis, stage, location, treatment, year)

6. hazard ratio associated with treatment (function of age and stage)

Output Parameters (see Output Overview)

1. risk factor categories for a given year, as an external check and Healthy People 2010 website graphs (see Healthy People 2010)

2. incidence CRC cases and CRC deaths

3. adenomas and preclinical cancer

4. screening results and findings

COMPONENT OVERVIEW

SUMMARY

This document outlines the key components of the SimCRC Model.

OVERVIEW

Major inputs into the model include (1) population demographics, (2) changes in risk factors over time for a cohort, (3) changes in CRC screening over time, and (4) changes in CRC treatment over time. The natural history model (see Natural History) tracks the underlying progression of colorectal disease from normal colonic tissue to development of adenomatous polyps to invasive cancer. Cancer incidence is affected by the presence or absence of certain risk factors, and by screening. Cancer–specific mortality is affected by incidence and treatment post–diagnosis. Key model outputs are provided in Output Overview.

COMPONENT LISTING

Population Demographics

The simulated population consists of all persons 25 years or older at some point between 1970 and the last calendar year of a given simulation (e.g., 2000). The simulated population can therefore be broken into two types of cohorts:

1. Prevalent cohorts: all US persons 25–90 years of age in 1970. These cohorts consist of people born in years 1880–1945 (total of 66 birth cohorts per sex and race category).

2. Incident cohorts: new 25–year–old individuals who join the target population every year after 1970 (e.g., 1971–2000). These cohorts are born in years 1946–1975 (total 30 birth cohorts per sex and race category).

Simulated persons face an annual rate of death from non–CRC causes each year based on their age, sex, race and birth year. These rates are based on the US life tables.

Risk Factor Trends

For all birth cohorts, including prevalent and incident ones, individuals are assigned initial risk factor values for each of eight risk factors (see Risk Factors CRC) by random draw from an age (in decades), sex, and race–specific multiway distribution of the eight risk factors (see Risk Factor Distribution). The is done in either 1970 for the prevalent cohorts or the year when the ith incident cohort turns 25 years old (1970+i). A simulated person starts with his/her initial risk factor (RF) profile and then "drifts" with annual changes in each risk factor (see Risk Factor Drifts) that are a function of age, sex, race and birth year and reflect US population trends. The model allows for three basic scenarios to be modeled for 1970–2000:

1. cohort–specific changes; risk factors change with age and year (default)

2. age–specific changes; risk factors change with age but not year (used for Base Case analyses)

3. no changes in risk factors over time (since 1970)

Screening Dissemination

Based on data from the National Health Interview Survey (NHIS) we have incorporated the probability of being screened in any given year, based on age, sex, race and calendar year among persons who have never been screened. Persons who

will undergo screening are then assigned one of four recommended screening strategies: annual FOBT, sigmoidoscopy every five years, annual FOBT and sigmoidoscopy every five years, or colonoscopy every ten years, based on the current recommendations. To account for the fact that screened individuals do not tend to follow recommended screening schedules, we assign a screening behavior to screened persons (i.e., low, moderate, high) that is linked with adherence rates that dictate the probability that he or she will undergo a scheduled screening test. While there are no national data that provide the level of detail necessary for describing screening behavior, we input reasonable assumptions and then calibrate the Model outputs to NHIS data regarding questions asked about a persons history of being screened with FOBT within the past two years or ever screened with endoscopy (by age range, sex and race).

Treatment Dissemination

The probability that a simulated person with a new diagnosis of CRC receives chemotherapy is modeled as a function of stage at diagnosis, age, sex, race and calendar year. These treatment patterns are based on analyses of the SEER–Medicare linked dataset, and are extrapolated for patients aged less than 65 years at diagnosis. We estimated the probability of receiving adjuvant chemotherapy with 5FU for patients who are diagnosed with stage II rectal cancer or stage III colon or rectal cancer. In general, white patients are more likely to get treatment compared with black patients, younger patients are more likely to get treatment compared with older patients, stage III patients are more likely to get treatment compared with stage II patients, and the overall chance of getting treatment increases with time. Starting in the year 2000 we modeled the probability of receiving FOLFOX therapy instead of 5FU. We also estimated the probability of receiving chemotherapy for patients who are diagnosed with metastatic CRC. We modeled the dissemination of irinotecan starting in 1996, oxaliplatin starting in 2001, and the newer therapies (cetuximab and bevacizumab) starting in 2004. Projections of these dissemination probabilities are based on anticipated diffusion patterns into the population on the basis of the 5FU experience.

To account for changes that are not explained by dissemination of chemotherapy regimens we model cancer–specific mortality as a function of the period in which the cancer was diagnosed (1975–1982; 1983–1987; 1988–1990; 1991–1995; 1996–1999). The treatment effects due to the dissemination of chemotherapy are adjusted out of each of the period–specific relative survival curves.

Screening Effectiveness

The ability of a screening test to decrease CRC incidence and mortality is modeled through the removal of adenomas by colonoscopy and the early detection of preclinical cancer. The screening component is run simultaneously with the Natural History Model (see Natural History), which keeps track of the underlying disease status of each simulated individual. The true disease status of the patient, along with the test characteristics, will determine whether or not a test is positive or negative. Ultimately, the adenoma–carcinoma sequence can only be interupted by removal of an adenoma by colonoscopy. For example, a person with a positive sigmoidoscopy finding who fails to be adherent with a follow–up colonoscopy will not benefit from that screening test.

Diagnosis Model

Patients who are diagnosed with CRC in the Model, either by symptom detection or by a positive colonoscopy result, enter the Diagnosis Model. Each month, they face a monthly cancer–specific mortality rate that is a function of sex, the stage at diagnosis, age at diagnosis, year of diagnosis, time since diagnosis, and race (optional). These rates are based on Cox proportional hazards models for relative survival applied to SEER survival data. The SimCRC Model also has a separate post–diagnosis model that simulates the risk of subsequent metastatic recurrence and only allows cancer deaths to occur following an unresectable metastatic recurrence.

OUTPUT OVERVIEW

SUMMARY

This document describes the general outputs of the SimCRC Model.

OVERVIEW

The SimCRC Model provides estimates of the number of incidence cases of diagnosed CRC and cancer–specific deaths per calendar year, as a function of sex and race. These outputs will be reported as age–standardized values.

The model also generates specific Base Case outputs to compare with the model outputs from the other two CISNET models, as well as several outputs that allow for calibration or validation of model inputs (see Results Overview).

OUTPUT LISTING

Base Case I

Base Case I assumes that no screening is performed, that risk factors change only with age and not birth year, and that cancer–specific mortality does not changes with time or treatment. Specific outputs generated are as follows, where age is in five–year age groups and calendar year is 1978–2000:

1. number of incidence cases by age groups, sex, race, stage, location and calendar year (1978–2000)
2. number of CRC deaths by age, sex, race, location and calendar year
3. population size by age, sex, race and calendar year
4. adenoma prevalence by age, sex, race, size, location and calendar year
5. number of preclinical cancers by age, sex, race, stage, location and calendar year
6. number of prevalent cases in 1978, by age, sex, race, stage and location

Base Case II

Base Case II overlays a simple screening assumption onto the assumptions of Base Case I. Specifically, we allow for a single screening event with 100% compliance beginning in Year 1980 for those age 65. We consider 3 tests – colonoscopy, flexible sigmoidoscopy, and fecal occult blood test with and without surveillance (colonoscopy every five years for those with an adenoma found). Specific outputs generated are as follows, where age is in five–year age groups (unless indicated otherwise) and calendar year is 1978–2000:

1. number of screen–detected cases by age, sex, race, stage, location and calendar year
2. number of symptom–detected cases by age, sex, race, stage, location and calendar year
3. number of CRC deaths by age, sex, race, location and calendar year
4. population size by age, sex, race and calendar year
5. number of screenees by result (positive vs. negative), sex, race and calendar year
6. number of persons receiving a surveillance or follow–up test by age (65, 70, 75, ... 95, 100+), sex, race and calendar year
7. number of adenomas detected by age, sex, race, size, location and calendar year

Risk Factor Calibration

For risk factor calibrations, the model outputs the following information for every simulated person for a specified Output Year (e.g., 1991).

1. age group, sex, race, risk factor value of each of eight risk factors, weighting factor (indicates the number of persons in the US population represented by the simulated person)

We compare the 1973, 1978, 1991, and 2001 risk factor distributions (by age, sex, race) outputed by the model with the observed distributions from the four waves of NHANES. We are also generating output of the implied risk factor trends using this output mechanism for Healthy People 2010, and are providing input data for the other modeling groups.

Screen Behavior Calibration

For screen behavior calibrations, the model outputs the following information for every simulated person for specified Output Years between 1987 and 2010 to match NHIS data on screening.

1. number of person who have ever been screened, by age group, sex, race and calendar year
2. number of person who have ever been screened by endoscopy, by age group, sex, race and calendar year
3. number of person who have ever been screened by fecal occult blood test, by age group, sex, race and calendar year
4. number of person who have been screened by fecal occult blood test within the past two years, by age group, sex, race and calendar year

CISNET Runs

For the CISNET analysis (1970–2000) or the Healthy People 2010 analysis (1970–2020) we output the following:

1. number of incident CRC cases by five–year age group, sex, race, stage, location and calendar year
2. number of CRC deaths by five–year age group, sex, race, location and calendar year
3. population size by age, sex, race and calendar year

RESULTS OVERVIEW

SUMMARY

This section summarizes the key analyses done during the development of the SimCRC Model, as well as initial results from the (relatively) completed model.

OVERVIEW

There are five general categories of model results

1. Model Development Results

- We have several analyses that pertain to developing a small piece of the SimCRC modeling puzzle. For example, the methods that we used to determine the effects of the risk factors on the underlying progression of colorectal disease, or the approach that we took for calibrating the natural history model.
- Base Case Results

- There are several Base Case analyses that have been done for purposes of comparing outputs across the three CRC CISNET models.
- Trends Results

- We have initial results that explain the observed CRC trends over the past three decades. These results utilize all aspects of the model to generate results.
- Policy–Relevant Analyses

- Analyses that addresses a particular policy–relevant question.
- Miscellaneous Analyses

- These include analyses that are not relevant to the above four categories.

RESULTS LIST

Model Development

1. Methods used to estimate cohort–specific risk factor drifts using the example of body mass index (see Risk Factor Drift Method)
2. Methods used to estimate risk factor effects on the underlying natural history of colorectal disease (see Risk Factor Effect Method)
3. Calibration methods for natural history model parameters (see Calibration Method)

Trends Analysis

1. Examining CRC trends (see Examining Trends)

Policy–Relevant Analyses

1. Analysis of the degree to which meeting upstream Healthy People 2010 goals for risk factors and screening acheive the downstream goal for CRC mortality (see Healthy People 2010)
2. Projections of the impact in 2015 of optimistic disseminations about the use of computerized tomographic (CT) colonography (see Policy Relevant Analyses)

Miscellaneous Analyses

1. Evaluating the impact of using different estimates of non–cancer–specific mortality on the relative proportion of cancer–specific mortality (see Non Cancer Mortality)

2. Evaluating the impact of the US policy to fortify grains with folate (see Folate Trends)

RISK FACTORS CRC

The model incorporates the effects of eight modifiable risk factors associated with CRC: body mass index (kg/m^2), physical activity level (met–hours per week), fruit and vegetable consumption (servings per day), multivitamin use (yes/no), smoking status (number of cigarettes per day), red meat consumption (servings per day), aspirin use (yes/no), and postmenopausal hormone replacement therapy use (yes/no). Risk factors are categorized as shown below for purposes of estimating multiway distributions of risk factor prevalence (by ten–year age group, sex, race, and calendar year).

Risk Factor	Categories
Body mass index	
Physical activity	0; 0.01–1.9; 2.0–9.9; 10.0+
Fruit and vegetable consumption	0–1.9; 2.0–3.9; 4.0–5.9; 6.0–7.9; 8.0+
Multivitiamin use	non–user; user
Current smoker	non–user; user
Red meat consumption	0–0.104; 0.105–0.43; >0.43
Aspirin use	non–user; user
Hormone replacement therapy	non–user; user

If a person is designated a smoker they are then assigned a number of cigarettes per day on the basis of age–specific population distributions and are assumed to maintain that level of intensity for as long they smoke.

CALIBRATION METHOD

The model is calibrated by simulating the life histories of cohorts of individuals under a given set of parameter values and comparing the model–predicted outcomes with observed data on: (1) the prevalence and number of adenomas by age and sex from a meta–analysis of autopsy studies; (2) the location and size/histology of lesions from two colonoscopy screening studies[1,2]; and (3) the stage– and location–specific incidence of CRC by age, sex, and race from SEER. We assumed that each set of observed data follows a multinomial distribution and calculated two likelihoods for each measure: (1) the likelihood of generating the observed data with a particular set of parameter values (i.e., the observed likelihood) and (2) the likelihood obtained if the model exactly predicted the observed data (i.e., the maximum likelihood). Goodness of fit (GOF) scores were calculated as –2 times the difference between the observed and maximum log likelihoods. An overall GOF score that evaluated the simultaneous fit to the three sets of observed data was calculated by summing the individual GOF scores; a parameter set with a lower overall GOF score provides a better simultaneous fit to the observed data. We used the Nelder and Mead Simplex algorithm to explore the parameter space; this is a direct–search approach to finding the minima of a function. The model with the best fit from the simultaneous optimization underpredicts adenoma prevalence at younger ages and overpredicts at older ages. However, all predictions are very close to falling within one standard error of the observed data. The best–fitting model also provides an excellent fit to the overall risk of developing CRC by age.

REFERENCES:

[1] Imperiale, T.F., Wagner, D.R., Lin, C.Y., Larkin, G.N., Rogge, J.D., Ransohoff, D.F. "Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings." in N Engl J Med 2000; 343: : 169-174

[2] Lieberman, D.A., Weiss, D.G., Bond, J.H., Ahnen, D.J., Garewal, H., Chejfec, G. "Use of colonoscopy to screen asymptomatic adults for colorectal cancer." in N Engl J Med 2000; 343: 162-168

RISK FACTOR DRIFTS

A simulated person starts with his/her initial risk factor (RF) profile and then "drifts" with annual changes in each risk factor. For continuous risk factors: RF(year X+1) = RF(year X)*drift(born Y, age A, sex, race); X=Y+A. Thus, a RF drift value greater than 1 indicates an increase, equal to 1 indicates no change, and less than 1 indicates a decrease. For dichotomous variables, the drift values are either annual probabilities of quitting usage (negative values) among users or annual probabilities of initiating usage (positive values) among non–users.

Estimates of these risk factor drifts were derived from analyses of multiple waves of the National Health and Nutrition Examination Survey (NHANES). We compiled three waves of NHANES (NHANES I, 1971–1975; NHANES II, 1976–1980; NHANES III, 1988–1994) and fit parametric polynomial regression models with age and calendar year as explanatory variables. To estimate risk factor drifts for a particular birth cohort over time, we used our models, increasing age and year simultaneously, to obtain expected RF changes as the cohort ages. (See Risk Factor Drift Method for details.)

Model checks have been done to compare predicted RF cumulative frequency plots for 1978 with those from NHANES II data, predicted RF cumulative frequency plots for 1991 with those from NHANES III data, and predicted RF cumulative frequencey plots for 2001 with those from NHANES 1999–2002. Model predictions tend to be close to the observed data.

RISK FACTOR EFFECT METHOD

We used data from the Nurses' Health Study (NHS)[1] and the Health Professionals' Follow–up Study (HPFS)[2] to derive two stage–specific risk functions that describe the relationship between the CRC risk factors and: 1) the development of an adenoma, and 2) the progression of an adenoma to preclinical cancer. The NHS began in 1976, when 121,700 registered nurses 30 to 55 years of age returned a mailed questionnaire that included details on risk factors for breast and other cancers. Follow–up questionnaires mailed every two years identify incident cancers and collect detailed information on diet, physical activity, smoking history, and other exposures. The HPFS began in 1986 when approximately 51,500 male health professionals 40–75 year of age were recruited to study the dietary etiologies of heart disease and cancer. Risk factors for various cancers were collected at baseline. Incident cancers are identified by follow–up questionnaires, which have response rates of 90% for every two–year cycle. Using data from these two cohort studies, we fit logistic regression models that describe the relationship between CRC risk factors and the diagnosis of CRC, adjusted for screening. Although the data from the NHS and the HPFS provide evidence on the relationship between risk factors and the diagnosis of CRC in an unscreened population of women and men, respectively, the natural history component of the SimCRC Model requires the specification of the influence of risk factors on the underlying progression of disease. To derive the necessary stage–specific risk functions, we use a combination of simulation modeling with epidemiological analysis.

Evidence suggests that three of the risk factors – aspirin use, multivitamin use, and smoking – act primarily on initial adenoma development, since it is the exposure to these risk factors 10 to 15 years prior to CRC diagnosis that is significant. For the stage–specific risk functions we assumed a logistic function for the relationship between adenoma incidence (i.e., risk function 1) and adenoma progression (i.e., risk function 2) and defined all variables in terms of current status (e.g., current aspirin user, current smoker). However, in the logistic regression models that we estimated from the cohort studies, the three risk factors with early effects were defined differently, that is, using the duration of aspirin use, the duration of multivitamin use, and the number of years since smoking was started.

We utilized the basic structure of our natural history model to empirically estimate the effect of CRC risk factors on the unobserved states of colorectal disease. This was accomplished by first specifying starting values for the risk factor effects (via the two stage–specific risk functions), and then generating a hypothetical dataset of women or men with characteristics that mimic the NHS or the HPFS, respectively, in terms of age distribution and risk factor information (e.g., smoking behavior observed during the study). We then analyzed this simulated dataset using regression methods analogous to those used for the cohort study data to estimate the simulated relationship between the risk factors, as defined in the cohort studies (e.g., duration of aspirin use), and diagnosed CRC. The starting values for the risk factor effects were then revised and the simulation process repeated in an iterative fashion until the relationship between the duration of aspirin use and diagnosed colorectal cancer in the simulated dataset matched the analogous relationship observed in the cohort studies.

REFERENCES:

[1] Colditz, GA. "The Nurses' Health Study: a cohort of women followed since 1976" in JAMWA 1995; 50: 40-44, 63

[2] Rimm, E.B., Giovannucci, E., Willett, W.C., Colditz, G.A., Ascherio, A., Rosner, B., Stampfer, M.J. "Prospective study of alcohol consumption and risk of coronary disease in men." in Lancet 1991; 338: 464-468

NATURAL HISTORY

SUMMARY

This document focuses on the natural history component of SimCRC Model. It describes how we model the underying progression of colorectal disease, as well as how we incorporate risk factors.

OVERVIEW

Our natural history model is a microsimulation model that tracks the development of adenomatous polyps and their progression to underlying cancer within the proximal colon, distal colon, and rectum for cohorts of 25–year–old individuals. We calibrate the model by simulating the life histories of cohorts of individuals under multiple sets of parameter values and comparing model–predicted outcomes with observed data on adenomas (prevalence, location, type) and CRC (incidence, location, stage) using a likelihood–based approach (see Calibration Method). This model also includes risk factors and their effects on disease progression (see Risk Factor Effect Method).

Our SimCRC Model tracks multiple cohorts of individuals in order to simulate the US population aged 25 and older starting in 1970 and projecting out to 2020. The parameters that effect the underlying progression of disease are from the calibrated cohort model.

DETAILS

States Tracked by the Model

For each of three locations (proximal colon, distal colon, and rectum) and subsites within each location (6 for proximal colon, 3 for distal colon, 3 for rectum), one of the following disease states is allowed:

1. disease free,
2. adenoma (low–risk, medium–risk, or high–risk),
3. preclinical cancer (by stage), and
4. clinical (diagnosed) cancer (by stage).

Temporal Aspects

Each year we allow a non–diseased colorectal segment to develop a low–risk adenoma, a low–risk adenoma to progress to a medium–risk adenoma, a medium–risk adenoma to progress to a high–risk adenoma, a high–risk adenoma to progress to preclinical stage I cancer, preclinical stage I cancer to preclinical stage II cancer, preclinical stage II cancer to preclinical stage III cancer, and preclinical stage III cancer to preclinical stage IV cancer. Individuals with preclinical cancer can be symptom detected and transition to a clinical (diagnosed) cancer state (of the same stage). In any year and from any state, individuals can die of non–CRC causes (based on age, sex, race, and year). Individuals with cancer can also die from CRC–related causes.

Key Attributes

Variables that affect the transitions among health states are age, sex, race, risk factors (see Risk Factors CRC), a "propensity" factor, and location (proximal colon, distal colon, rectum).

RELEVANT ASSUMPTIONS

There are a number of assumptions that we make.

1. All colorectal cancers arise from adenomas.
2. We do not allow for adenoma regression.
3. Disease progression is independent of calendar year once we adjust for the risk factor effects.
4. We allow for one additional person–specific parameter that affects the chance of developing an adenoma (a propensity factor) in addition to the effects of the risk factors.

RELEVANT PARAMETERS

See Parameter Overview.

RELEVANT COMPONENTS

The Natural History Model forms the basis of the SimCRC Model. The Risk Factor Trends component of the overall model provides information to the Natural History Model about the current risk factor values of each simulated person, thus allowing risk factors and trends in risk factors to have an impact on the underlying progression of disease.

Overlaid on the Natural History Model is a Screening Component, one that represents screening dissemination in the US and thus dictates the chance that a simulated individual will undergo a screening test (as a function of age, sex, race and birth year). The other screening component determines the effectiveness of a screening test by its ability to identify and remove an adenoma (based on the sensitivity of the test or sequence of tests) or to diagnose preclinical cancer.

The Natural History Model endpoint is diagnosed CRC (or death from other causes). Once a person is diagnoses with CRC they enter a Diagnosis Model.

See Component Overview for more details.

DEPENDENT OUTPUTS

The primary outputs from the Natural History Model are Base Case I outputs on adenoma prevalence and cancer incidence (see Output Overview).

RELEVANT RESULTS

See Calibration Method and Output Overview (Base Case I).

ADENOMA INCIDENCE

The annual probability of transitioning from no disease (ND) to low–risk adenoma (LRA) within a subsite of the colorectal track is a function of age, sex, propensity factor and risk factors:

$$Pr(\text{ND} \to \text{LRA}) = \frac{1}{1 + exp(-\alpha - \gamma - \beta_{age} * age - \beta'_{rf} * X)}.$$

α is an intercept term and varies by location (proximal cancer, distal cancer, rectum) and sex. γ is a propensity factor that is randomly drawn for each simulated individual from the same distribution with variance σ. β_{age} dictates the age effect on adenoma incidence and varies by location and sex. α, σ, and β_{age} are estimated via the natural history calibration (see Calibration Method).

β_{rf} is a vector of parameters that describe the effect of a particular risk factor on adenoma incidence and varies by location and sex. These parameters are estimated in a separate calibration exercise in conjuction with analyses of the Nurses' Health Study and Health Professionals' Follow–up Study (see Risk Factor Effect Method). X is the vector of risk factor values for a simulated person for a particular year (see Parameter Overview for risk factor parameters).

ADENOMA PROGRESSION

The annual probability of transitioning from high–risk adenoma (HRA) to stage I preclinical colorectal cancer (PCC) within a subsite of the colorectal track is a function of age, sex, and risk factors:

$$Pr(\text{HRA} \rightarrow \text{PCC}) = \frac{1}{1 + exp(-\alpha - \beta_{age} * age - \beta'_{rf} * X)}.$$

α is an intercept term and varies by location (proximal cancer, distal cancer, rectum) and sex. β_{age} dictates the age effect on adenoma progression and varies by location and sex. α and β_{age} are estimated via the natural history calibration (see Calibration Method).

β_{rf} is a vector of parameters that describe the effect of a particular risk factor on adenoma progression and varies by location and sex. These parameters are estimated in a separate calibration exercise in conjuction with analyses of the Nurses' Health Study and Health Professionals' Follow–up Study (see Risk Factor Effect Method). X is the vector of risk factor values for a simulated person for a particular year (see Parameter Overview for risk factor parameters).

HEALTHY PEOPLE 2010

National health goals currently exist for a number of the health behaviors associated with CRC, and for CRC screening. Healthy People 2010 is a set of health objectives set forth by the US Department of Health and Human Services for the nation to achieve over the first decade of the new century. The objectives aim to increase the quality and length of life, and eliminate health disparities. The Healthy People 2010 goals include targets for obesity, physical activity, smoking, folate intake for women of child–bearing age, fruit and vegetable consumption, CRC screening, and CRC mortality.

Using the SimCRC Model, we conducted a formal analyses to determine the extent to which the Healthy People 2010 cancer mortality goals are achievable. The results of these analyses were presented at the NCI in June, 2004. Two modeling groups focused on the CRC–related goals. Specifically, we used our models to link the Healthy People 2010 risk factor and screening goals with the CRC mortality goal of reducing the CRC mortality rate to 13.9 deaths per 100,000. To do this, we generated model–predicted CRC mortality rates in 2010 assuming that risk factor levels and screening rates do not change from their 2000 values. Then we predicted CRC mortality assuming the Healthy People 2010 risk factor and/or screening targets are met by the year 2010. We found that if risk factors and screening rates do not change from the 2000 values, CRC mortality in 2010 would be 19.4 deaths per 100,000. If the Healthy People 2010 risk factor and screening targets are met by 2010, CRC mortality would fall to 17.7 CRC deaths per 100,000. We found that if the current trends in risk factors and screening continue through 2010, we would achieve 65% of the reduction in CRC mortality needed to reach the Healthy People 2010 goal.

RISK FACTOR DISTRIBUTION

For prevalent cohorts (i.e., persons 25 years of age or older in 1970) we randomly draw from age (in decades), sex, and race–specific multiway distributions of the eight risk factors (categorized). The matrices that represent the multiway distributions contains 4800 cells representing the probability of a US person in each 24 demographic group in 1970 fits into a particular risk factor profile. The number of cells (i.e., 4800) is determined by the number of categories for each risk factor: 5 (body mass index) x 4 (physical activity) x 5 (fruit and vegetable consumption) x 2 (multivitamin use) x 2 (smoking status) x 3 (red meat consumption) x 2 (aspirin use) x 2 (hormone replacement use). Once a particular risk factor category is determined for a simulated individual, an actual value within that category is randomly assigned for continuously–defined risk factors based on the distribution with the category (e.g., a person in the body mass index category defined as 18.5–24.9 may be assigned a value of 22.3).

The multiway distributions were first derived from NHANES III (1988–1994). We then assume that the relative interactions among risk factors from NHANES III are the same in 1970 and implement an iterative proportional fitting algorithm using the marginal distributions estimated for 1970 (e.g., the marginal distribution for body mass index is the proportions of the 1970 population that fall into each of the five body mass index categories) and the multiway distributions from 1988–1994 to obtain multiway distributions for 1970 (one for each of 24 demographic groups).

For incident cohorts we randomly draw from a sex and race–specific multiway distribution that is generated for persons aged 26–34 years during the model simulation from all of the prevalent cohorts and prior incident cohorts. The risk factors that are drawn from these distributions are adjusted backwards using the risk factor drifts to distinguish a 25–year–old individual from a 26–34 year–old group.

RISK FACTOR DRIFT METHOD

Each year, the risk factor values for each simulated person are updated based on age–, sex–, race– and birth year–specific changes over time, or drifts. Estimates of these risk factor drifts were derived from analyses of multiple waves of the National Health and Nutrition Examination Survey (NHANES). We illustrate our basic approach to estimating risk factor drifts with an example using body mass index (BMI). We adopted a similar approach for estimating risk factor drifts for the other risk factors, although each individual risk factor analysis varied somewhat depending upon the availability of the risk factor information in NHANES I.

We compiled three waves of NHANES (NHANES I, 1971–1975; NHANES II, 1976–1980; NHANES III, 1988–1994) to model secular trends in risk factors at the population level. We fit parametric polynomial regression models with age and calendar year as explanatory variables to predict population mean BMI by age and year. These models adjust for the characteristics of the sampling structures of the different waves (i.e., strata, clusters, and unequal probability of sampling). We accounted for the differences in BMI patterns by race and sex by fitting separate models for four demographic subgroups: white men, white women, black men, and black women. The fitted regression models allow for interpolation as well as extrapolation to make projections for any given age and calendar year, allowing for different age effects in different years. We used these models to predict mean BMI values for individuals aged 20 to 90 years in calendar years 1970–2000. To evaluate how well our model projects beyond the three NHANES survey periods, we compared our fitted mean BMI values in year 2000 for each subgroup with the mean BMI values from the recently released NHANES 1999–2000 data. The model predictions for the year 2000 were very close to the actual national estimates from NHANES 1999–2000. In 23 out of 28 age–race–sex groups, the predicted BMI values fell within the 95% confidence limits of the observed BMI means.

To estimate risk factor drifts for a particular birth cohort over time, we used our model, increasing age and year simultaneously, to obtain expected BMI means as the cohort ages. We then derived annual percent changes in mean BMI for each birth cohort. To verify the face validity of these values, we compared them to observed longitudinal BMI changes in two large–scale follow–up studies: Nurses' Health Study (NHS) and Health Professionals' Follow–up Study (HPFS). We compared three birth cohorts of white women from the starting NHS cohort (in 1976) and three birth cohorts of white men from the starting HPFS cohort (in 1986), using our model–based longitudinal projections. Although we do not expect the mean BMI of these two selected groups to be representative of average US persons, we anticipate that the longitudinal weight changes will share similar patterns. As expected, the mean BMI among the NHS cohorts was 2.26–6.21 kg (4.99–13.69 lb) lower than the predicted US population for average white women 1.65 meters (5′ 4″) in height. When we applied the predicted cohort–specific annual changes derived from our models to each cohort using their 1976 baseline BMI means, the projected BMI in 2000 was within 5% of their observed BMI in 1998. Similarly, the mean BMI for the three HPFS cohorts was 3.71 to 8.19 kg (6.69–14.75 lb) lower than the predicted population means for white men 1.75 meters (5′9″) in height for comparable birth years. Applying cohort–specific annual changes to their starting mean BMI, the model–predicted BMI in 2000 was within 4% of the observed values. The above comparisons provide external validity for applying our longitudinal projections to subpopulations.

EXAMINING TRENDS

We have completed an initial analysis of the CRC trends. During the period 1978 to 2000, approximately 2.52 million Americans were diagnosed with CRC and 1.25 million died from the disease. Our model estimates that the observed number of incident cases represents a 4.7% reduction from the estimated number that would have occurred if there had been no secular trends in risk factors and no dissemination of screening over this time period (8.6% reduction in 2000). Changes in risk factors alone account for 31.5% of the overall reduction, and 67.3% is attributable to screening. The number of cancer deaths represents a 13.1% reduction from the estimated number that would have occurred in the absence of changes in risk factors, screening, and treatment (22.0% reduction in 2000). Advancements in treatment alone account for 59.9% of the reduction, while risk factors and screening account for 7.8% and 30.7% of the decline, respectively. From these analyses, we conclude that screening and advancements in treatment have played significant roles in the declines in CRC incidence and mortality. Our results suggest that cancer control policies should focus their efforts on ensuring that patients with CRC receive the best–available care, and on increasing screening dissemination rates. Even with only 34% of the population ages 50 years and older undergoing endoscopy in the past decade, the dissemination of screening has played a significant role in decreasing both CRC incidence and mortality. Widespread adoption of screening could make significant inroads at reducing the burden of CRC.

POLICY RELEVANT ANALYSES

Cost–effectiveness analysis of Stool DNA for the Centers for Medicare and Medicaid Services

In 2007 the Centers for Medicare and Medicaid Services (CMS) requested a cost–effectiveness analysis to assist in a National Coverage Determination for stool DNA screening for CRC. MISCAN and SimCRC modelers performed a cost–effectiveness analysis of stool DNA testing (both version 1.0 and PreGen-PlusTM) among the average–risk Medicare population to determine whether stool DNA testing could be cost–effective compared with CRC screening tests currently reimbursed by CMS[1]. Both models predicted that stool DNA testing every three or five years was both less effective and more costly than the currently recommended CRC screening strategies. Screening with the stool DNA test could be cost–effective at per–test cost $40 to $60 for 3–yearly stool DNA testing, depending on the simulation model used. The findings were consistent across the models and were relatively insensitive to changes in stool DNA test characteristics.

Decision Analysis for age to begin, age to end, intervals of screening, and screening test for the USPSTF

In another policy–relevant analysis, the US Preventive Services Task Force (USPSTF) requested a decision analysis to inform decisions about CRC screening, specifically to determine the age to begin screening, the age to end screening, and screening intervals[2]. This was the first time the USPSTF used a decision analysis in combination with a systematic evidence review to inform their decisions. The CISNET–CRC models provided standardized comparisons of 145 screening strategies using the best available evidence for consideration by USPSTF. Several of these screening strategies gave similar gains in life–years, provided that there is equally high adherence for all aspects of the screening process. Under these conditions, the best screening strategies were high–sensitivity FOBT (Hemoccult SENSA or IFOBT) performed annually, sigmoidoscopy performed every 5 years with Hemoccult SENSA performed every 2 to 3 years, or colonoscopy performed every 10 years. Annual FOBT with a lower–sensitivity test (Hemoccult II) and sigmoidoscopy alone resulted in fewer life–years gained relative to other strategies. These analyses showed that stopping screening at age 75 after consecutive negative screenings since age 50 provides almost the same benefit as stopping at age 85 but with substantially fewer colonoscopy resources and risk of complications.

Evaluation of CT–colonography for the Centers for Medicare and Medicaid Services

In May 2008 CMS requested a cost–effectiveness analysis to assist National Coverage Determination for CT colonography screening for CRC[3]. The three CISNET–CRC modeling groups showed that with perfect adherence to each test type, the predicted life–years gained from screening for CRC with 5–yearly CT colonography were slightly less than predicted life–years gained from 10–yearly colonoscopy, and if reimbursed at approximately the same rate as colonoscopy screening (i.e. 488 USD per scan relative to 498 USD for colonoscopy without polypectomy), CT colonography was predicted to be the most costly of the screening strategies considered. Screening with CT colonography was predicted to be a cost–effective CRC screening option for the Medicare population if the cost per scan were 105–208 USD, or if the availability of CT colonography screening would entice a large fraction of the unscreened population to adopt screening. The predictions were consistent across the models and were relatively insensitive to changes in CT colonography sensitivity and specificity, screening interval, and lesion size threshold for referring an individual for a follow–up

colonoscopy for polypectomy. On May 12, 2009 CMS released its decision not to cover CT colonography screening for Medicare enrollees; this decision was partially informed by our analysis.

Evaluation of CT Colonography for the Institute for Clinical and Economic Review (ICER)

Dr. Knudsen used the SimCRC model to estimate the incremental cost–effectiveness of CT colonography screening for the Institute for Clinical and Economic Review (ICER)[4]. Their analysis showed that compared to no screening, CT colonography every five years from age 50–75 with referral to colonoscopy for individuals with lesions ≥6 mm provides good value for money, with an incremental cost per life year gained of $1500. However, when compared directly with colonoscopy every ten years over this age range, CT colonography every five years was more expensive and only slightly more effective than colonoscopy, with a cost–effectiveness ratio greater than $500,000 per life year gained. An incremental cost per life year saved of $100,000 could be achieved for CT colonography if the exam cost were approximately 47% that of colonoscopy. The results of this analysis were used to inform the Washington State Health Care Authority's decision on coverage of CT colonography for state Medicaid enrollees and state employees.

Evaluation of CT Colonography for ACRIN

The CISNET–CRC team has collaborated with the American College of Radiology Imaging Network (ACRIN) to evaluate the cost–effectiveness of CT colonography as performed in the NCTC trial[5]. The NCTC trial was a large multi–site study to assess the accuracy of CT colonography for CRC screening in the general population and in community–based practices. All three modeling groups collaborated with CISNET–CRC affiliate member Dr. Vanness to conduct the cost–effectiveness analysis. We simulated survival and lifetime costs for screening 50 year–olds in the US with CT colonography every five or ten years and compared them to those from guideline concordant screening using colonoscopy, sigmoidoscopy, Hemoccult SENSA, and IFOBT and to those with no screening. Perfect and reduced screening adherence scenarios were considered. We found screening with CT colonography likely to be net–beneficial compared to no screening but more costly and less effective than other non–CT colonography screening approaches.

Evaluation of CT Colonography for potential radiation exposure

CISNET–CRC modelers also assisted in analyses addressing concerns about risks of radiation–induced cancers that might result from using CT colonography for routine CRC screening[6]. The CISNET–CRC modelers collaborated with Dr. Amy Berrington (NCI) to estimate the ratio of CRCs prevented to cancers induced (benefit–risk ratio) associated with CT colonography screening every five years from age 50–80. Radiation–related cancer risk was estimated using risk projection models based on the National Research Council's BEIR VII committee's report and screening protocols from the ACRIN NCTC trial. The three CISNET–CRC models were used to estimate the potential reduction in CRC cases and deaths from CT colonography screening. The estimated number of radiation–related cancers from 5–yearly CT colonography screening from age 50–80 was 150 cases per 100,000 individuals. The estimated number of CRCs prevented by 5–yearly CT colonography screening from age 50–80 ranged across the three microsimulation models from 3580 to 5190 per 100,000, giving a benefit–risk ratio that varied from 24:1 to 35:1. The benefit–risk ratios for cancer deaths were even higher than the ratios for cancer cases. These models suggest that the benefits from CT colonography screening every five years from age 50–80 clearly

outweigh the radiation risks.

Evaluation of Screening Programs, Including Follow–up

Several industrialized nations recommend the use of FOBT to screen for CRC but guidelines often do not specify whether individuals with a false–positive test result should continue with FOBT screening or switch to 10–yearly colonoscopy screening. The SimCRC group, led by a visiting scholar from the University of Heidelberg, Dr. Ulrike Haug, compared the effectiveness of different strategies for follow–up of patients with a false positive FOBT (Hemoccult II, Hemoccult SENSA or IFOBT), including continued FOBT screening versus switching to screening colonoscopy[7]. A sensitivity analysis was conducted to examine the effect of assuming conditional dependence of sequential testing among people without adenomas or CRC. The preliminary analysis shows that switching to screening colonoscopy is the better strategy for managing patients with a false positive FOBT result, especially in view of the uncertainty regarding conditional independence of sequential testing among people with a previous false positive.

The SimCRC modeling team estimated the comparative effectiveness of different strategies for following individuals with a negative screening colonoscopy[8]. Guidelines recommend that individuals with a negative screening colonoscopy repeat colonoscopy screening in ten years. However, the impact of this versus other follow–up strategies on health and economic outcomes is uncertain. The SimCRC modelers compared four management strategies, starting at age 60, for individuals with a negative colonoscopy at age 50: no further screening; annual IFOBT; 5 yearly CT colonography; and 10–yearly colonoscopy. They found that continuing screening with colonoscopy every 10 years was the most effective strategy for reducing the burden of CRC. In settings with limited resources and/or limited colonoscopy capacity, resuming screening at age 60 with annual IFOBT is also a reasonable approach. If the unit cost of CT colonography were less than $342, CT colonography every 5 years would also be advantageous from a cost–effectiveness standpoint.

The MISCAN and SimCRC modeling teams are evaluating the potential cost implications for Medicare, Medicaid, and private payers from increased CRC screening among pre–Medicare individuals (i.e., individuals aged 50–64 years). Increased screening among this group is likely to result in earlier detection of CRC as well as prevention of CRC from adenoma detection and removal. Both these factors may reduce treatment costs. This work is being performed for the CDC.

The MISCAN and SimCRC modeling groups collaborated with NCI to create a CRC Mortality Projections Website. This site provides a modeling tool that projects future trends in CRC mortality and evaluates how potential increases in prevention, screening, and access to state–of–the–science cancer treatment may affect future mortality trends. It is intended for policy, legislative, and cancer–control planning staff at the federal, state, and local levels, as well as advocacy and professional groups. It features descriptions of and links to the Healthy People 2010 objectives relevant to CRC. Results show that almost half of all CRC mortality can be eliminated by 2020 by more fully utilizing cancer–control opportunities that we know are effective. Lower levels of utilization will substantially reduce those gains. While increased use of state–of–the–art treatment has the most immediate impact on mortality, over the longer term screening has the largest impact. Changing the risk factor profile of the US population to optimistic, but still realistic, levels will take many years to influence CRC mortality trends, but the benefits extend well beyond CRC. Additional information can be found online at cisnet.cancer.gov/projections/colorectal.

Quality of care guidelines

Several additional pieces of work by CISNET–CRC team members focused on clinical guidelines. Drs. Kuntz and Schrag worked with the Cancer Care Quality Measurement Project, an interagency initiative to develop quality–of–care measures for cancer care for evaluation by the National Quality Forum[9]. To assist the National Quality Forum, the diagnostic component of SimCRC was used to assess the relative contribution of four processes of care for improving cancer outcomes. SimCRC predicts that increasing appropriate use of chemotherapy in the adjuvant and metastatic settings is likely to provide a substantial reduction in CRC mortality. Improving CRC care delivery by increasing the intensity of post–treatment surveillance or chemotherapy subsequent to metastectomy will likely have minimal impact on reducing cancer mortality at the population level.

Global screening programs

The SimCRC team is collaborating with Dr. Gabriel Leung to evaluate the cost–effectiveness of population–based screening for CRC in Hong Kong. A version of the SimCRC natural history model was modified to match data from Hong Kong on CRC incidence (lower than the US) and stage distribution (more advanced disease than the US). The modified model also incorporates Hong Kong life tables and reflects clinical practice in Hong Kong. The results show that annual screening with IFOBT is effective and provides good value for money. This research was presented at the International Health Economics Association.

REFERENCES:

[1] Lansdorp–Vogelaar, I., Kuntz, K.M., Knudsen, A.B., Wilschut, J., Zauber, A.G., van Ballegooijen, M. "Stool DNA testing to screen for colorectal cancer in the Medicare population: A cost–effectiveness analysis." in Annals of internal medicine 2010; 153.6: 368-377

[2] Zauber, A.G., Lansdorp-Vogelaar, I., Knudsen, A.B., Wilschut, J., van Ballegooijen, M., Kuntz, K.M. "Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force." in Ann Intern Med 2008; 149: 9: 659-69

[3] Knudsen, A.B., Lansdorp-Vogelaar, I., Rutter, C.M., Savarino, J.E., van Ballegooijen, M., Kuntz, K.M., Zauber, A.G. "Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the Medicare population." in J Nat Cancer Inst 2010; 102: 16: 1238-52

[4] Pearson, S.D., Knudsen, A.B., Scherer, R.W., Weissberg, J., Gazelle, G.S. "Assessing the comparative effectiveness of a diagnostic technology: CT colonography." in Health Affairs 2008; 27: 6: 1503-14

[5] Vanness, D.J., Knudsen, A.B., Lansdorp-Vogelaar, I., Rutter, C.M., Gareen, I.F., Herman, B.A., Kuntz, K.M., Zauber, A.G., van Ballegooijen, M., Feuer, E.J., Chen, M.H., Johnson, C.D. "Comparative Economic Evaluation of the American College of Radiology Imaging Network National CT Colonography Trial with three CISNET Microsimulations." in Radiology 2011; 261: 2: 487-98

[6] Berrington de Gonzalez, A., Kim, K.P., Knudsen, A.B., Lansdorp-Vogelaar, I., Rutter, C.M., Smith-Bindman, R., Yee, J., Kuntz, K.M., van Ballegooijen, M., Zauber, A.G., Berg, C.D. "Radiation-related cancer risks from CT colonography screening: A risk-benefit analysis." in Am J Roentgenol 2011; 196: 4: 816-23

[7] Haug, U., Knudsen, A.B., Kuntz, K.M. "How should individuals with a false-positive fecal occult blood test for colorectal cancer be managed? A decision analysis." in Int J Cancer 2012; 131: : 2094-102

[8] Knudsen, A.B., Hur, C., Gazelle, G.S., Schrag, D., McFarland, B., Kuntz, K.M. "Rescreening of individuals with a negative colonoscopy: A comparative effectiveness analysis." in Ann Intern Med 2012; 157: : 611-20

[9] Kuntz, K.M., Stout, N.K., Schrag, D. "Simulating Clinical Outcomes Associated with Quality Measures in the Treatment of Colorectal Cancer. A Report to the National Cancer Institute." 2006;

NON CANCER MORTALITY

We constructed a simple Markov model to evaluate the impact of the relative proportion of mortality at 5–years attributed to cancer depending on whether we obtained estimates of non–cancer related mortality from: (1) the US general population using life table data from the National Center for Health Statistics, or (2) cause–specific estimates from SEER. For 60–69 year old patients with CRC, overall mortality was 43% at 5 years. Using a life table method to partition mortality, 36% of patients had deaths attributed to cancer and 7% died from other causes. In contrast, the cause–specific method assigned 32% of the cohort to cancer–related and 12% to cancer–unrelated deaths. We concluded that the strategy used to partition mortality may have an impact on the results of decision analyses.

FOLATE TRENDS

The 1998 mandate to fortify enriched grain products with folic acid in the US was aimed to help prevent neural tube defects among pregnant women. To evaluate the increase in folate in the population after fortification, we analyzed food, supplement, and total folate intake by gender, age, and race/ethnicity using data from two waves of the NHANES, one before and one after the policy was adopted. We compared pre– and post–fortification distributions of total folate intake and proportions of the population consuming more than 400 and 1,000 mcg/day of total folate. Overall, daily food and total folate intake increased by approximately 100 mcg/day after fortification. The proportion of younger women consuming greater than 400 mcg/day of folate has increased since fortification, but has not yet reached the 50% target: 28% (pre–fortification) vs. 33% (post–fortification) in white women; 19% vs. 23% in African American women; and 15% vs. 28% of Mexican–American women. Among older populations who may be at risk of B–12 deficiency masking, the percent that are consuming over 1,000 mcg/day (the tolerable upper limit) increased after fortification for whites and African American men, but remained unchanged for African American women and decreased for Mexican–Americans.

We also developed a Markov model to simulate the effect of pre–versus–post fortification changes in folate consumption on incidence of neural tube defects (NTDs), myocardial infarctions (MIs), colon cancers, and B–12 masking. In each one–year cycle, persons face age–, gender–, race/ethnicity–, and folate–specific risks of developing any one of the four health outcomes (multiple events allowed), of staying disease–free, or of dying. We calculated population burden of disease for non–Hispanic whites, non–Hispanic blacks, and Mexican–Americans aged 15 and older among the civilian, non–institutionalized U.S. population. The model predicted that in one year after fortification, the following disease events would be averted: 181 NTDs; 30,541 MIs; and 5,933 colon cancers. On the other hand, fortification was predicted to cause 96 new cases of B–12 masking per year. There were substantial variations by race/ethnicity, with whites showing greater percent reductions in disease risk as compared to blacks and Mexican–Americans, due to the larger changes in folate intake after fortification seen in whites. Whites also experienced the greatest numbers facing increased risk from B–12 masking, again due to their larger increases in folate intake after fortification.

KEY REFERENCES

Allison, J., Ransom, L., Adrain, A. (1996) A comparison of fecal occult–blood tests for colorectal–cancer screening in *N Engl J Med*:334, p 155–159

Atkin, WS., Cuzick, J. , Northover, JM. , Whynes, DK. (1993) Prevention of colorectal cancer by once–only sigmoidoscopy in *Lancet*:341, p 736–740

Berrington de Gonzalez, A., Kim, K.P., Knudsen, A.B, Lansdorp–Vogelaar, I., Rutter, C.M., Smith–Bindman, R., Yee, J., Kuntz, K.M., van Ballegooijen, M., Zauber, A.G., Berg, C.D. (2011) Radiation–related cancer risks from CT colonography screening: A risk–benefit analysis. in *Am J Roentgenol* 196:4, p 816–23

Brenner, H., Arndt, V., Sturmer, T., Stegmaier, C., Ziegler, H., Dhom G. (2001) Long lasting reduction of risk of colorectal cancer following screening endoscopy. in *Br J Cancer* 85, p 972–976

Colditz, GA. (1995) The Nurses' Health Study: a cohort of women followed since 1976 in *JAMWA*:50, p 40–44, 63

Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., Bets, D., Mueser, M., Harstrick, A., Verslype, C., Chau, I., Van Cutsem, E. (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan–refractory metastatic colorectal cancer. in *N Engl J Med* 351, p 337–345

Fenoglio, CM., Lane, N. (1974) The anatomical precursor of colorectal carcinoma in *Cancer 1974;34:819–823.*:34, p 819–823

Frazier, AL., Colditz, GA., Fuchs, CS., Kuntz, KM. (2000) Cost–effectiveness of screening for colorectal cancer in the general population in *JAMA*:284, p 1954–1961

Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC (1995) Physical activity, obesity, and risk for colon cancer and adenoma in men in *Ann Intern Med*:122, p 327–334

Giovannucci, E., Egan, KM., Hunter, DJ., Stampfer, MJ., Colditz, GA., Willett, WC., Speizer, FE. (1995) Aspirin and the risk of colorectal cancer in women in *N Engl J Med*:333, p 609–614

Giovannucci, E., Martinez, ME. (1996) Tobacco, colorectal cancer, and adenomas: a review of the evidence in *J Natl Cancer Inst*:88, p 1717–1730

Giovannucci, E., Rimm, EB., Stampfer, MJ., Colditz, GA., Ascherio, A., Willett, WC. (1994) Intake of fat, meat, and fiber in relation to risk of colon cancer in men in *Cancer Research*:54, p 2390–2397

Giovannucci, E., Stampfer, MJ., Colditz, GA., Hunter, DJ., Fuchs, C., Rosner, BA, Speizer, FE., Willett, WC. (1998) Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study in *Intern Med*:129, p 517–524

Giovannucci, E., Stampfer, MJ., Colditz, GA., Rimm, EB., Trichopoulos, D., Rosner, BA., Speizer, FE., Willett, WC. (1993) Folate, methionine, and alcohol intake and risk of colorectal adenoma in *J Natl Cancer Inst*:85, p 875–884

Grodstein, F., Martinez, ME., Platz, EA., Giovannucci, E., Colditz, GA., Kautzky, M., Fuchs, C., Stampfer, M. (1998) Postmenopausal hormone use and risk for colorectal cancer and adenoma in *Ann Intern Med*:128, p 705–712

Hardcastle, J.D., Chamberlain, J.O., Robinson, M.H.E., Moss, S.M., Amar, S.S., Balfour, T.W., James, P.D., Mangham, C.M. (1996) Randomised controlled trial of faecal–occult–blood screening for colorectal cancer. in *Lancet* 348, p 1472–1477

Haug, U., Knudsen, A.B., Kuntz, K.M. (2012) How should individuals with a false–positive fecal occult blood test for colorectal cancer be managed? A decision analysis. in *Int J Cancer* 131, p 2094–102

Hixson, L., Fennerty, M., Sampliner, R., Garewal, H. (1991) Prospective blinded trial of the colonoscopic miss–rate of large colorectal polyps in *Gastrointest Endosc*:37, p 127–127

Hurwitz, H., Fehrenbacher, L., Novotny, W., et al. (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. in *N Engl J Med* 350:2335–2342,

Imperiale, T.F., Wagner, D.R., Lin, C.Y., Larkin, G.N., Rogge, J.D., Ransohoff, D.F. (2000) Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. in *N Engl J Med* 343, p 169–174

Jorgensen, O.D., Kronborg, O., Fenger, C. (2002) A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. in *Gut* 20, p 29–32

Knudsen, A.B., Hur, C., Gazelle, G.S., Schrag, D., McFarland, B., Kuntz, K.M. (2012) Rescreening of individuals with a negative colonoscopy: A comparative effectiveness analysis. in *Ann Intern Med* 157, p 611–20

Knudsen, A.B., Lansdorp–Vogelaar, I., Rutter, C.M., Savarino, J.E., van Ballegooijen, M., Kuntz, K.M., Zauber, A.G. (2010) Cost–effectiveness of computed tomographic colonography screening for colorectal cancer in the Medicare population. in *J Nat Cancer Inst* 102:16, p 1238–52

Kronborg, O., Fenger, C. (1999) Clinical evidence for the adenoma–carcinoma sequence. in *Eur J Cancer* 8:Suppl 1, p S73–86

Kuntz, K.M., Stout, N.K., Schrag, D. (2006) Simulating Clinical Outcomes Associated with Quality Measures in the Treatment of Colorectal Cancer. A Report to the National Cancer Institute.,

Lansdorp–Vogelaar, I., Kuntz, K.M., Knudsen, A.B., Wilschut, J., Zauber, A.G., van Ballegooijen, M. (2010) Stool DNA testing to screen for colorectal cancer in the Medicare population: A cost–effectiveness analysis. in *Annals of internal medicine*:153.6, p 368–377

Lieberman, D.A., Weiss, D.G., Bond, J.H., Ahnen, D.J., Garewal, H., Chejfec, G. (2000) Use of colonoscopy to screen asymptomatic adults for colorectal cancer. in *N Engl J Med*:343, p 162–168

Mandel, J.S., Church, T.R., Bond, J.H., Ederer, F., Geisser, M.S., Mongin, S.J., Schuman, LM. (2000) The effect of fecal occult–blood screening on the incidence of colorectal cancer. in *N Engl J Med*:343, p 1603–1607

Martinez, ME., Giovannucci, E., Spiegelman, D., Hunter, DJ., Willett, WC., Colditz, GA. (1997) Leisure–time physical activity, body size, and colon cancer in women in *J Natl Cancer Inst*:89, p 948

Morson, B. (1974) The polyp–cancer sequence in the large bowel in *Proc R Soc Med*:67, p 451–457

Pearson, S.D., Knudsen, A.B., Scherer, R.W., Weissberg, J., Gazelle, G.S. (2008) Assessing the comparative effectiveness of a diagnostic technology: CT colonography. in *Health Affairs* 27:6, p 1503–14

Rex, D.K., Cutler, C.S., Lemmel, G.T., Rahmani, E.Y., Clark, D.W., Helper, D.J., Lehman, G.A., Mark, D.G. (1997) Colonoscopic miss rates of adenomas determined by back–to–back colonoscopies. in *Gastroenterology* 112, p 24–28

Rimm, E.B., Giovannucci, E., Willett, W.C., Colditz, G.A., Ascherio, A., Rosner, B., Stampfer, M.J. (1991) Prospective study of alcohol consumption and risk of coronary disease in men. in *Lancet* 338:464–468,

Saltz, L.B., Cox, J.V., Blanke, C., et al. (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. in *N Engl J Med* 343, p 905–914

Schrag, D. (2004) The price tag on progress – chemotherapy for colorectal cancer in *N Engl J Med* 351, p 317–319

Selby, J., Friedman, G., Quesenberry, C., Weiss, N. (1992) A case–control study of screening sigmoidoscopy and mortality from colorectal cancer. in *N Engl J Med* 326, p 653–657

Smith, R.A., Cokkinides, V., Eyre, H.J. (2003) American Cancer Society Guidelines for the early detection of cancer, 2003. in *CA Cancer J Clin* 53, p 27–43

Vanness, D.J., Knudsen, A.B., Lansdorp–Vogelaar, I., Rutter, C.M., Gareen, I.F., Herman, B.A., Kuntz, K.M., Zauber, A.G., van Ballegooijen, M., Feuer, E.J., Chen, M.H., Johnson, C.D. (2011) Comparative Economic Evaluation of the American College of Radiology Imaging Network National CT Colonography Trial with three CISNET Microsimulations. in *Radiology* 261:2, p 487–98

Winawer SJ., Zauber AG., Ho MN., O'Brien, MJ., Gottlieb, LS., Sternberg, SS., Waye, JD., Schapiro, M., Bond, JH., Panish, JF. (1993) Prevention of colorectal cancer of colonoscopic polypectomy. The National Polyp Study Workgroup in *N Engl J Med*:329, p 1997–1981

Winawer, S.J., Fletcher, R., Rex, D., Bond, J., Burt, R., Ferrucci, J., Ganiats, T., Levin, T., Woolf, S., Johnson, D., Kirk, L., Litin, S., Simmang, C. (2003) Colorectal cancer screening and surveillance: clinical guidelines and rationale – update based on new evidence. in *Gastroenterology* 124, p 544–560

Zauber, A.G., Lansdorp–Vogelaar, I., Knudsen, A.B., Wilschut, J., van Ballegooijen, M., Kuntz, K.M. (2008) Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. in *Ann Intern Med* 149:9, p 659–69

de Gramont, A., Figer, A., Seymour, M., et al. (2000) Leucovorin and fluorouracil with or without oxaliplatin as first–Line treatment in advanced colorectal cancer. in *J Clin Oncol* 18:2937–2947,