Appendix 1: The MISCAN-Colon microsimulation model

OUTLINE

MODEL OVERVIEW

The MISCAN-Colon model is a semi-Markov micro-simulation model. The population is simulated individual by individual, and each person can evolve through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the MISCAN-Colon model generates durations in states. This improves model performance. With the assumption of exponential distribution of the duration in each state, this way of simulating leads to the same results as a Markov model with yearly transition probabilities. The advantage of the MISCAN approach is that durations in a certain state need not necessarily be a discrete value but can be continuous. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, adenoma incidence and transitions from one state of disease to another.

The basic structure of MISCAN-Colon is illustrated in Figure A1.1. Figure A1.1 clearly demonstrates that MISCAN-Colon consists of three parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is useful to consider them separately.

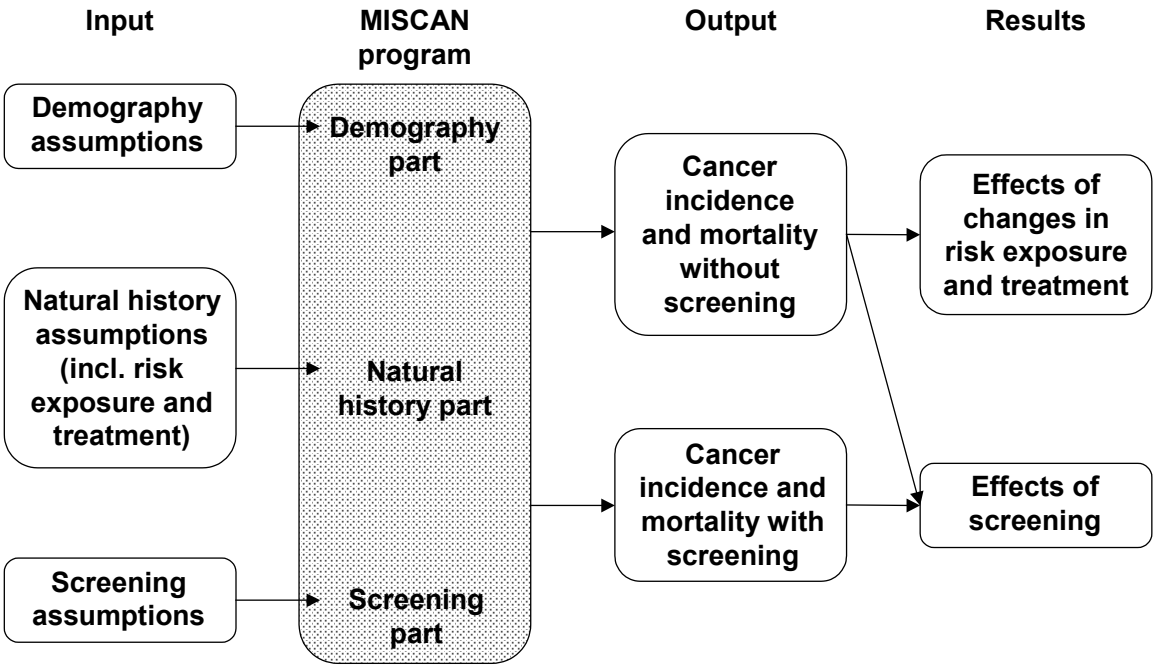

Figure A1.1: Structure of MISCAN-Colon

DEMOGRAPHY PART
The demography part of the model simulates individual life histories without colorectal cancer to form a population. For each person, a date of birth and a date of death of other causes than colorectal cancer are simulated. The distribution of births and deaths can be adjusted to represent the population simulated. For example, a population of Caucasian females will have higher death ages than a population of African American males.

NATURAL HISTORY PART
The Natural History part of MISCAN-Colon simulates the development of colorectal cancer in the population. We assume all colorectal cancers develop according to the adenoma-carcinoma sequence of Morson[1] and Vogelstein[2] (Figure A1.2). For each individual in the simulated population a personal risk index is generated. Subsequently, adenomas are generated in the population according to this personal risk index and an age specific incidence rate of adenomas. This results in no adenomas for most persons and one or more adenomas for others. The distribution of adenomas over the colorectum is simulated according to the observed distribution of colorectal cancer incidence. Each of the adenomas can independently develop into colorectal cancer. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (10+ mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. The survival after clinical diagnosis depends on the stage of the cancer.

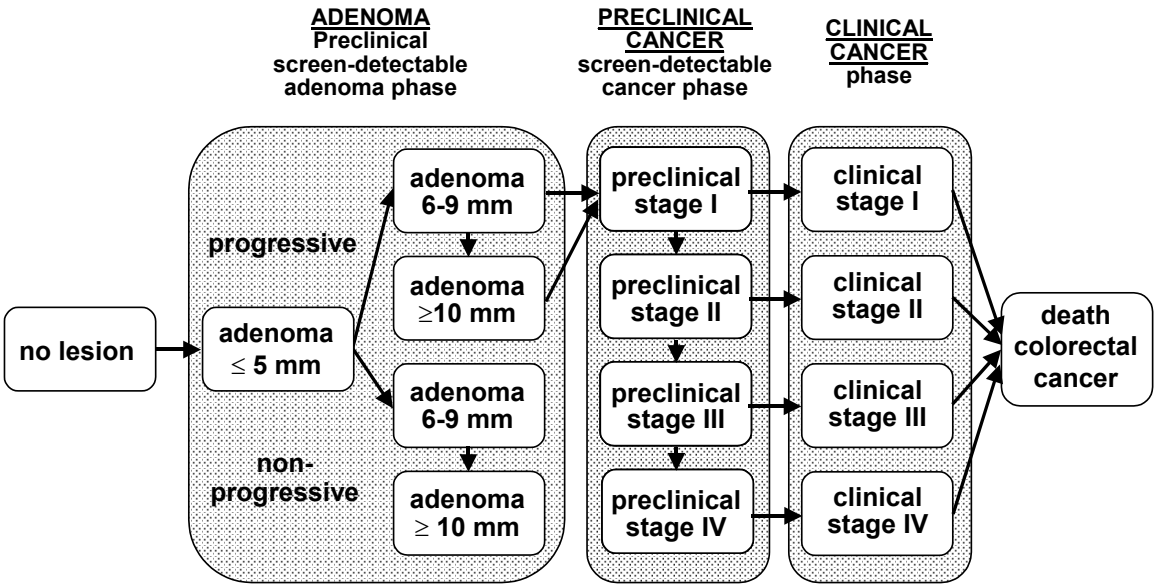

Figure A1.2: Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for colorectal cancer. Adenomas are categorized by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age.

SCREENING PART
Screening interrupts the development of CRC. With screening, adenomas may be detected and removed and cancers may be found, usually in an earlier stage than with clinical diagnosis. In this way screening prevents CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening. The effects of different screening policies can be compared by applying them to identical natural histories.

INTEGRATION OF THE THREE MODEL COMPONENTS
For each individual, the demography part of the model simulates a time of birth and a time of death of other causes than colorectal cancer, creating a life history without colorectal cancer (top line in Figure A1.3a). Subsequently adenomas are simulated for that individual. For most individuals no adenomas are generated, for other multiple. In the example in Figure A1.3, the person gets two adenomas (2nd and 3rd line in Figure A1.3a). The first adenoma arises at a certain age, grows into 6-9 mm and eventually becomes larger than 10 mm. However, this adenoma does not become cancer before the death of the person. The second adenoma is a progressive adenoma. After having grown to 6-9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and diagnosis and eventually resulting in an earlier death from CRC. The life history without CRC and the development of the two adenomas in Figure A1.3 together lead to the combined life history with CRC depicted in the bottom line. Because this person dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly.

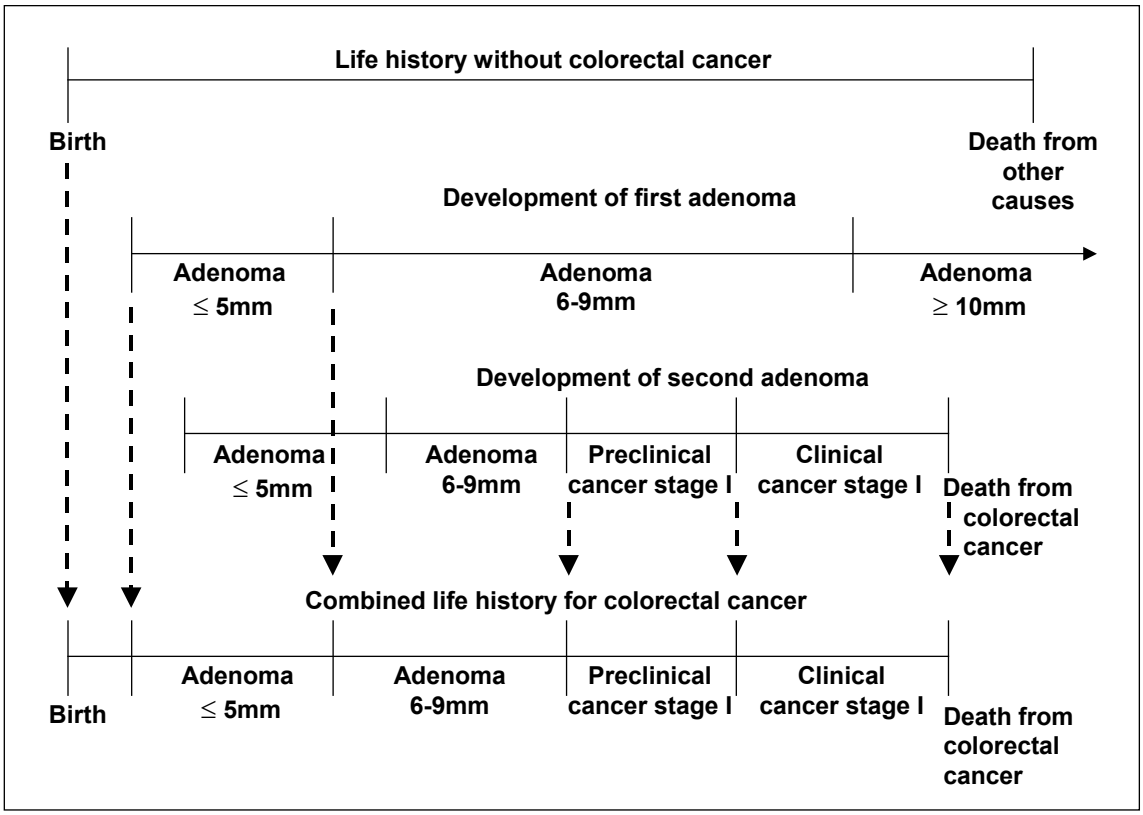

Figure A1.3a: Modeling natural history into life history

After the life history of a person is adjusted for colorectal cancer, the history will now be adjusted for the effects of screening. The effect of screening on life history is explained in Figure A1.3b.The top line in this figure is the combined life history for colorectal cancer from Figure A1.3a. The development of the separate adenomas is repeated in the second and third line. In this picture there is one screening intervention. During the screening both prevalent adenomas are detected and removed. This results in a combined life history for colorectal cancer and screening (bottom line). From the moment of screening the adenomas are removed and this individual becomes adenoma and carcinoma free. He does not develop cancer because the precursor lesion has been removed. Therefore the person dies at the moment of death from other causes and the effect of screening is the difference in life-years in the situation without screening and the situation with screening. Of course many other possibilities could have occurred: a person could have developed new adenomas after the screening moment, or an adenoma could have been missed by the screening test, but in this case this individual really benefited from the screening intervention.

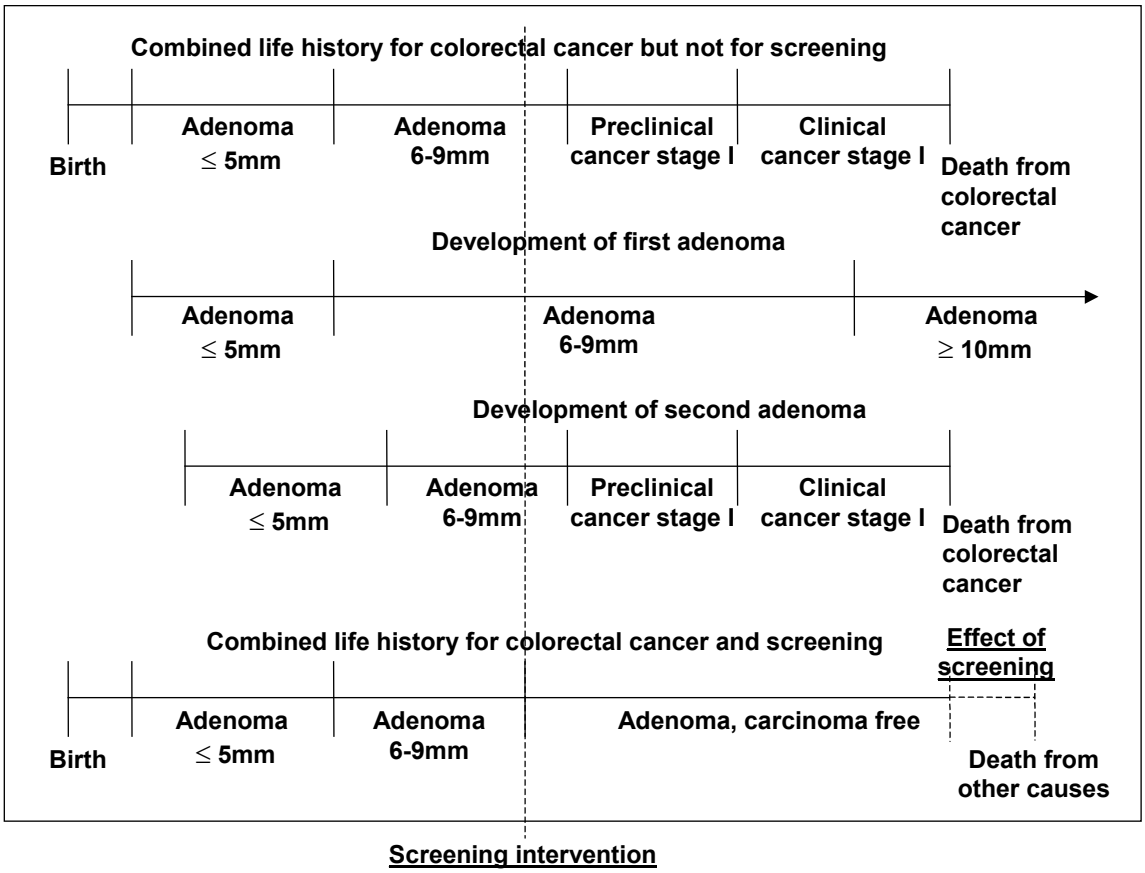

Figure A1.3b: Modeling screening into life history

MODEL QUANTIFICATION
For this analysis we simulated the Dutch population in 2005.

DEMOGRAPHY PARAMETERS
There are two types of demography parameters: birth tables and life tables. Birth tables were constructed such that the age distribution of the Dutch population in 2005 was simulated. Age distribution and life tables were derived from Statistics Netherlands (www.cbs.nl). These life tables include colorectal cancer mortality and the demography part simulates mortality from other causes than colorectal cancer. Therefore, mortality from colorectal cancer was derived from Comprehensive Cancer Centres (CCC, www.ikcnet.nl), and excluded from the life tables.

NATURAL HISTORY PARAMETERS
The parameters for natural history model that could not be directly estimated from data or fit to reference data, were established based on expert opinion. At two expert meetings at the NCI on June 5–7, 1996, and May 12–13, 1997, a model structure was devised in agreement with the currently accepted model of the adenoma–carcinoma sequence. It was assumed that all cancers are preceded by adenomas.

The average duration between onset of a progressive adenoma and the transition to preclinical cancer was assumed 20 years based on expert opinion. The duration of

cancer in preclinical stages was estimated based on the results of three large randomized controlled screening trials [3]. This resulted in an average duration of 2.5 years, 2.5 year, 3.7 years, and 1.5 year, for stages I-IV respectively, with a total average duration of 6.7 years because not every cancer reaches stage IV before clinical diagnosis. All durations were governed by an exponential probability distribution. Durations in each of the invasive cancer stages as well as durations in the stages of the noninvasive adenomas were assumed to be 100% associated with each other, but the durations in invasive stages as a whole were independent of durations in noninvasive adenoma stages that precede cancer. These assumptions resulted in an exponential distribution of the total duration of progressive noninvasive adenomas and of the total duration of preclinical cancer, which has also been used in other cancer screening models [4, 5].

It was assumed that 30% of the cancers arise from adenomas of 6–9 mm and that 70% arise from larger adenomas. Initially, the preclinical incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localization in the Netherlands in 1999-2003 (CCC). The size distribution of adenomas over all ages was assumed to be 56% for stages less than or equal to 5 mm, 24% for stages 6–9 mm, and 20% for stages greater than or equal to 10 mm [6-15]. The preclinical incidence of non-progressive adenomas that will never grow into cancer was varied until the simulated prevalence of all adenomas was in agreement with data from autopsy studies [6-15].

The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of colorectal cancers in the Netherlands in 1999-2003 (CCC). The stage-specific survival after the clinical diagnosis of colorectal cancer before age 75 is taken from the Comprehensive Cancer Centre South from 1989 through 2003, because national data were not available (CCCS, V. Lemmens 2010). The stage-specific survival after age 75 was fitted on the CRC mortality derived from the Comprehensive Cancer Centre from 1999-2003 (CCC). Table A1.1 contains a summary of the model input values and its data-sources.

Table A1.1: Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2.1	Fit to multiplicity distribution of adenomas in autopsy studies [6-13, 15]
Adenoma incidence in general population	Age dependent: 0-19 years: 0.2% per year 20-24 years: 0.4% per year 25-29 years: 0.4% per year 30-34 years: 0.6% per year 35-39 years: 0.6% per year 40-44 years: 2.4% per year 45-49 years: 2.9% per year 50-54 years: 3.0% per year 55-59 years: 3.4% per year 60-64 years: 4.1% per year 65-69 years: 4.7% per year 70-74 years: 5.7% per year 75-79 years: 3.8% per year 80-84 years: 3.6% per year 85-100 years: 1.0% per year	Fit to adenoma prevalence in autopsy studies [6-15] and to cancer incidence in 1999-2003 per 100,000 (CCC) <20 years 0.2 20-24 years 0.5 25-29 years 1.3 30-34 years 2.6 35-39 years 5.6 40-44 years 11.0 45-49 years 23.9 50-54 years 50.7 55-59 years 85.4 60-64 years 142.3 65-69 years 201.4 70-74 years 275.5 75-79 years 347.7 80-84 years 389.3 85+ years 332.4
Probability that a new adenoma is progressive	Dependent on age at onset: 0–45 years: linearly increasing from 0 to 5% 45–65 years: linearly increasing from 5% to 15% 65–100 years: linearly increasing from 15% to 23%	Fit to adenoma prevalence in autopsy studies, [6-15] cancer incidence in 1999-2003 (CCC).
Regression of adenomas	No significant regression of adenomas	Expert opinion
Mean duration of development of progressive adenomas to preclinical cancer	20 years	Expert opinion*
Mean duration of preclinical cancer	6.7 years	Estimated from FOBT trials [3].
Percent of non-progressive adenomas that stay 6-9mm	50%	Fit to size distribution of adenomas in autopsy studies: [6-15] 1-5mm: 56% 6-9 mm: 24% 10+ mm: 20%

Model parameter	Value	Source
Percent of non-progressive adenoma that become 10mm or larger	50%	Fit to size distribution of adenomas in autopsy studies: [6-15] 1-5mm: 56% 6-9 mm: 24% 10+ mm: 20%
Percent of cancers that develops from 6-9mm adenoma and from 10+mm adenoma	30% of cancer develops from 6-9 mm, 70% from 10+mm	Expert opinion
Localization distribution of adenomas and cancer	Rectum: 26% Distal colon: 42% Proximal colon: 32%	Directly estimated from CCC 1999-2003.
10-year survival after clinical diagnosis of CRC	Dependent on age, stage and localization	Directly estimated from CCC South 1989-2003 for diagnosis before age 75 and fitted on mortality from CCC 1999-2003.

* To be estimated from randomized controlled endoscopy trials, data not yet available.

SCREEN PARAMETERS

We assumed a cecal intubation rate of 95% [16-18]. The sensitivity of colonoscopy for each lesion within realized reach was based on back-to-back colonoscopy studies: 75% in adenomas less than or equal to 5 mm, 85% in adenomas 6–9 mm, and 95% in adenomas greater than or equal to 10 mm and cancers (table A1.2)[19]. After a positive test, all lesions are removed within a short time. The percentage of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after colonoscopy has been estimated from Kaiser data:[20] 10%. This percentage was assumed to be independent of the screening round.

The stage-specific survival of patients with screen-detected cancer was based on a previous analysis calibrating on three large randomized FOBT-trials[3], and was more favorable than the survival after diagnosis in the same stage without screen-detecting. Removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma. Risks of complications reported in organized screening programs [21-23] are lower than those reported for general practice colonoscopies [24, 25]. The major complications of colonoscopy are perforations (which can occur with or without polypectomy), serosal burns, bleeds requiring transfusion and bleeds not requiring transfusion [21-25]. We estimated a rate of death of 0.1 per 1,000 colonoscopies [26, 27].

Table A1.2: Colonoscopy characteristics

Parameter	Value	Source
Sensitivity colonoscopy	Dependent on stage of disease Adenoma 1-5mm: 75% Adenoma 6-9mm: 85% Adenoma 10+ mm: 95% Preclinical cancer: 95%	Back-to-back colonoscopy studies [19]
Cecal intubation rate	95%	General practice [16, 17] and guidelines [18]
Complication rate with colonoscopy	2.4 per 1,000 colonoscopies	Organized screening programs[21-23] and general practice [24, 25]
Perforation	0.7 per 1,000	
Serosal burn	0.3 per 1,000	
Bleed with transfusion	0.4 per 1,000	
Bleed without transfusion	1.1 per 1,000	
Fatal complication rate with colonoscopy	0.1 per 1,000 colonoscopies	Prospective endoscopy study [28]
Probability to develop cancer from removed adenoma	0%	Expert opinion
Survival after screen detection of cancer	Same as after clinical diagnosis in the next stage	FOBT trial [3]

MODEL OUTPUTS
The model generates the following output, both undiscounted and discounted:

Demography

1. Life-years lived in the population by calendar year and age
2. Deaths from other causes than colorectal cancer by calendar year and age

Natural history

1. Colorectal cancer cases by calendar year, stage and age
2. Colorectal cancer deaths by calendar year and age
3. Life-years lived with colorectal cancer by calendar year, stage and age
4. Total number of life years with surveillance for adenoma patients
5. Total number of life years with initial therapy after screen-detected or clinical invasive cancer by stage
6. Total number of life years with continuing therapy after screen-detected or clinical invasive cancer by stage
7. Total number of life years with terminal care before death from other causes by stage
8. Total number of life years with terminal care before death from colorectal cancer by stage

Screening

1. Number of invitations for screen-tests, screen-tests, diagnostic tests, surveillance and opportunistic screen tests by calendar year
2. Number of positive and negative test results per preclinical state and per year
3. Total number of life years lived, life years lost due to cancer, number of specific deaths and non specific deaths
4. Number of screenings that prevented cancer by year of screening
5. Number of screenings that detected cancer early by year of screening
6. Number of surveillance tests that prevented cancer by year of surveillance
7. Number of surveillance tests that detected cancer early by year of surveillance
8. Number of life years gained due to screening by year of screening

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