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The MISCAN-COLON Simulation Model for the Evaluation of Colorectal Cancer Screening

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A general model for evaluation of colorectal cancer screening has been implemented in the microsimulation program MISCAN-COLON. A large number of fictitious individual life histories are simulated in each of which several colorectal lesions can emerge. Next, screening for colorectal cancer is simulated, which will change some of the life histories. The demographic characteristics, the epidemiology and natural history of the disease, and the characteristics of screening are defined in the input. All kinds of assumptions on the natural history of colorectal cancer and screening and surveillance strategies can easily be incorporated in the model. MISCAN-COLON gives detailed output of incidence, prevalence and mortality, and the results and effects of screening. It can be used to test hypotheses about the natural history of colorectal cancer, such as the duration of progressive adenomas, and screening characteristics, such as sensitivity of tests, against empirical data. In decision making about screening, the model can be used for evaluation of screening policies, and for choosing between competing policies by comparing their simulated incremental costs and effectiveness outcomes.

1. INTRODUCTION

Colorectal cancer (CRC) is a major cause of cancer-related death in Western countries. About 5% of the population will develop colorectal cancer before 80 years of age, and half of these persons will die of this disease. The presumed natural history of colorectal cancer and the availability of screening tests make colorectal cancer a serious candidate for screening. Theoretically, screening may reduce mortality in two ways. First, detection of an asymptomatic cancer in an early stage may result in an improvement in prognosis. Second, evidence exists that most colorectal cancers develop from adenomas and that this process takes years. Detection and removal of adenomas may thus lead to prevention of cancer. Potentially useful screening tests for colorectal cancer and its precursors are fecal occult blood tests (FOBT), flexible sigmoidoscopy (FSIG), barium enema (BE), and even colonoscopy (CSCPY) (*1*). Randomized controlled trials of fecal occult blood testing have shown that screening can reduce colorectal cancer mortality ((*2–4*)).

Evidence on the effectiveness of BE and endoscopic-based screening strategies,

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however, is still limited, and the size of health benefits and costs is uncertain. The incomplete knowledge of the natural history of the disease makes it difficult to estimate the effectiveness of screening strategies. As has been shown for other cancers, mathematical models can be useful to test hypotheses about the incidence and natural history of disease and screening characteristics and subsequently to make predictions of the (cost-) effectiveness of screening strategies (*5*).

Both Eddy (*6*) and Wagner *et al.* (*7*) have constructed models to estimate the potential benefits and costs of several CRC screening strategies, including FOBT, FSIG, BE, and CSCPY screening. Eddy describes the model as a set of differential equations and developed computer programs in which the equations are solved by numerical integration, while the model of Wagner *et al.*, initially developed at the U.S. Congressional Office of Technology Assessment, is a discrete-time Markov model. Both models make simplifying assumptions about important aspects of the natural history of CRC. For example, in both models the possibility that a person develops more than one polyp in a lifetime is not included. In reality this is common and it will influence the outcomes of screening policies considerably. The single lesion assumption implies that surveillance after screen detection of a polyp is useless because surveillance is intended to discover further polyps. For correct interpretation of data and to make precise estimates on the effect of screening this aspect should be included in an evaluation model. The only model so far that does include this aspect is the model of Geul *et al.* (*8*) which has been designed for the evaluation of sigmoidoscopy screening. However, it concentrates on the multiplicity of lesions and not on the natural history of colorectal lesions, which makes it, for instance, inappropriate for studying the effect of the earlier detection of invasive cancers.

The model presented in this article allows for less simplification and therefore more flexibility in exploring various assumptions and can be used to simulate all candidate screening tests. This model is a version adapted to colorectal cancer of the MISCAN (MIcrosimulation SCreening ANalysis) microsimulation model for the evaluation of screening (*9*), which is being used for breast cancer and cervical cancer screening evaluation (*10–12*). The structure of the model will be explained in Section 2. Next, a formal description will be provided in Section 3. Section 4 deals with the computer program and the input and output of the program. An example of the use of the model will be given in Section 5. In Section 6 special features of the model are emphasized and possible applications of the model are discussed.

2. STRUCTURE OF THE MISCAN-COLON PROGRAM

A general model for evaluation of colorectal cancer screening is implemented in the microsimulation program MISCAN-COLON. Two parts of the program can be distinguished, a natural history part and a screening part. In the natural history part of the program, life histories are generated during which colorectal polyps and cancer may develop and sometimes cause death and in which no screening takes place. In the second part of the program, screening for colorectal cancer is simulated. Screening will change some life histories. The aggregated changes in

life histories constitute the effectiveness of the screening. The effects of different screening policies can be compared by applying them to identical life histories. If one is solely interested in modeling the natural history of the disease, the screening part is not necessary. The stochastic model underlying the simulation is specified in the input of the program. The input relates to demographic characteristics (e.g., the life table), the epidemiology and the natural history of the disease (e.g., the duration of preclinical cancer), and the characteristics of screening (e.g., the sensitivity of the screening test).

2.1. Natural History without Screening

The MISCAN-COLON program simulates a population of fictitious individuals in each of which several colorectal lesions can emerge. Lesions may proceed through three phases, as shown in the upper part of Fig. 1: a preclinical noninvasive polyp phase, a preclinical invasive cancer phase, and a clinical cancer phase. These phases can be further subdivided. More than one lesion can develop in a person and an anatomical site in the bowel is assigned to each lesion. Each lesion can develop into cancer, and it is possible that a person has more than one cancer. The history of a lesion consists of its successive stages and the ages of the individual at which transitions between stages occur. This lesion history is generated for each lesion in a person, and can result in death from colorectal cancer. If none of the lesions is lethal, the person dies from other causes. The life history of a person, consisting of the age and stage at diagnosis and age and cause of death, is based on these lesion histories. Figure 2a gives an example of a person who develops three lesions in his life. The resulting life history is shown at the bottom line.

Life histories are simulated in a number of steps. First, an age at death from other causes is generated from the life table for a person. It is assumed that the age at death from other causes is not affected by colorectal cancer. Subsequently the lesion histories are generated. The moment of onset of a lesion is defined as the moment at which the lesion becomes screen-detectable. In reality, this moment can depend on the screening test used. Usually, the first stage after onset (the initial stage) is a preclinical noninvasive (polyp) stage. Many lesions will still be in the

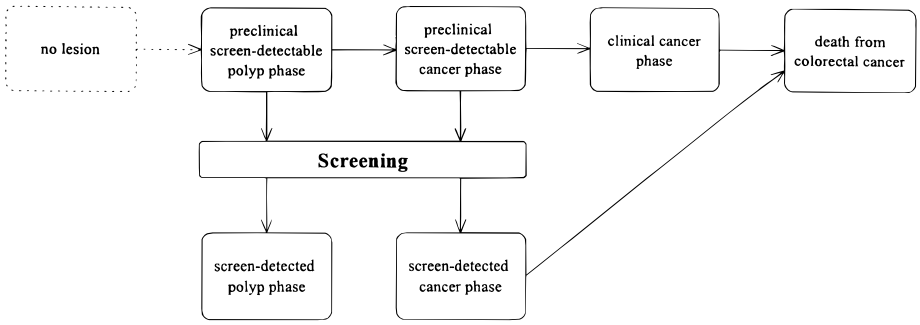

FIG. 1. The phases through which a colorectal lesion can develop in a situation with screening.

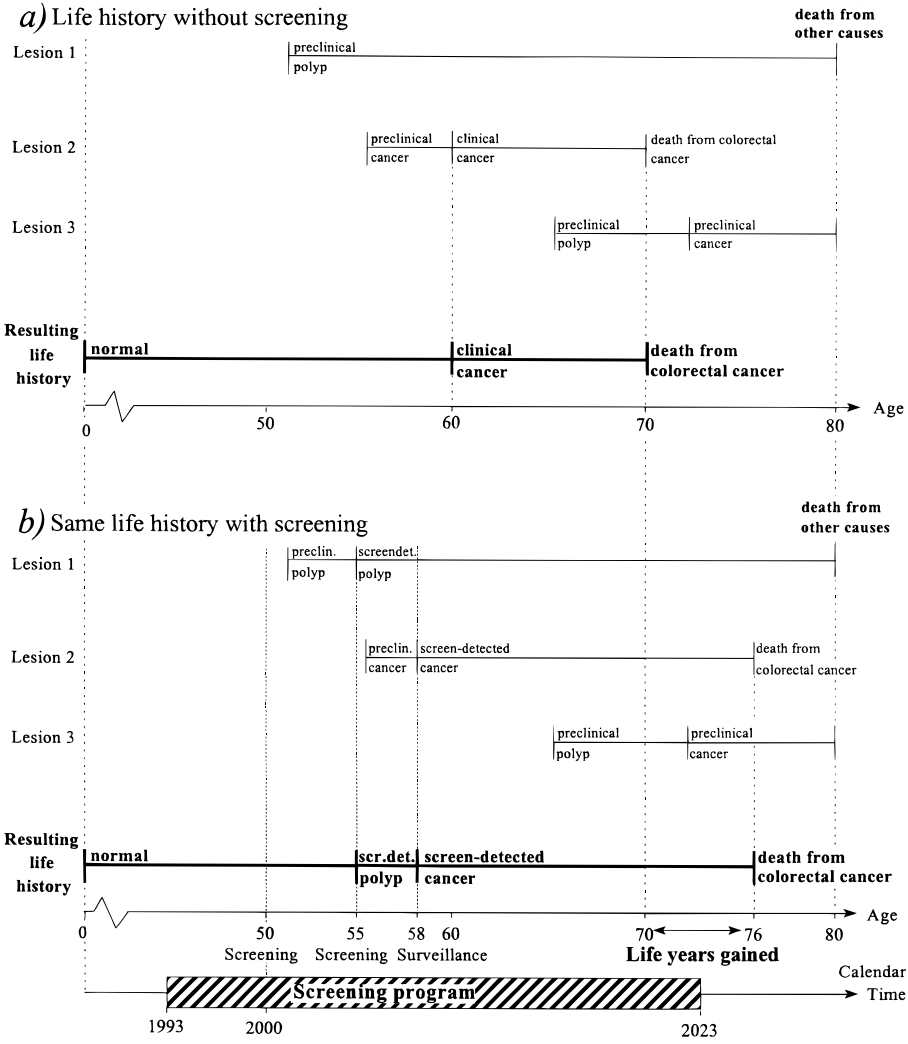

FIG. 2. (a) An example of a life history for a person who develops three lesions over his life in a situation without screening. (b) The life history of (a) in a situation with screening (Scr, screening examination; Surv, surveillance examination).

polyp phase when the person dies from other causes, just as lesion 1 in Fig. 2a. A lesion can transit from a preclinical polyp stage to a preclinical cancer stage. A preclinical cancer stage is a stage in which the lesion is already invasive, but not yet diagnosed. It is possible that a lesion is invasive from the beginning, such as lesion 2 in Fig. 2a, that represents cancer without a preceding polyp. When signs and symptoms lead to diagnosis of a cancer, the lesion enters the corresponding clinical cancer stage and a survival time is generated. The survival of a lesion

after diagnosis depends on the stage of the cancer. In Fig. 2a lesion 2 is diagnosed at age 60. Lesion 2 has a survival time of 10 years, leading to death from disease at age 70.

The life history of a person begins in a stage without disease (see bottom line of Fig. 2a). A person transits to a clinical stage at the first age at which a lesion is diagnosed clinically, i.e., age 60 for the person in Fig. 2a, when lesion 2 is diagnosed. It is assumed that during the diagnostic process, following clinical detection, all other cancers in the bowel will be found as well. Therefore, the person enters the clinical stage of the most developed cancer at the time of diagnosis. The age of death of a person with clinical cancer is the age at death from colorectal cancer or the age at death from other causes, whichever comes first. New lesions that appear after clinical diagnosis of cancer, such as lesion 3 in Fig. 2a, are accounted for in the survival of the clinically diagnosed cancer. In Fig. 2a the person dies at age 70 from colorectal cancer. The person would have died at age 80 from other causes and thus loses 10 life-years due to colorectal cancer.

2.2. Screening

A screening policy consists of the ages at which screening examinations are scheduled, the period of screening, the screening tests used at each examination, and the diagnostic follow-up scheduled after a positive test. The sensitivity of screening and diagnostic tests may differ for lesions in different disease stages. If a lesion in a preclinical detectable stage is missed at a screening, then the result of the screening is false-negative. If a lesion is missed because of a difficult localization (in a fold of the bowel), it is likely that the tumor will be missed again at the next screening. This can be modeled as a systematic negative test result for the lesion.

Figure 1 shows that a screen-detected preclinical lesion transits from the preclinical phase to the corresponding screen-detected phase. A person enters the screen-detected stage of the furthest progressed lesion that was found during screening and diagnostic follow-up. This might be a lesion different from the one that was initially detected by the screening test. For instance, detection of a polyp by sigmoidoscopy screening followed by diagnosis of a proximal cancer at subsequent colonoscopy leads to a transition to screen-detected cancer in the life history. Not all lesions present will necessarily be detected during follow-up tests.

If only noninvasive stages are found, it is assumed that all screen-detected lesions are removed, that their development stops, and that they will not lead to colorectal cancer death. The follow-up after diagnosis of a polyp can be modeled as a surveillance scheme, i.e., a strategy with tests and intervals different from those used in the screening policy. It is assumed that after detection of cancer, further diagnostic and therapeutic management is accounted for in the survival. For each cancer detected at screening, the age at death from disease can be affected in five different ways by screen detection in the model: the death from disease can be prevented, the age at death from disease can be delayed, the age at death from disease can be the same as in the situation without screening, a person can die of

the operation after screen detection, or a new survival after screen detection can be generated independent of the age at death from disease without screening.

In Fig. 2b the life history of Fig. 2a is represented in a situation with screening. At the bottom of the figure a time axis is shown, indicating that screening is performed between 1993 and 2023. At the first screening at age 50 no lesion is found and the test is true-negative. Lesion 1 is detected at the second screening at age 55 as a polyp. The lesion is removed, and the person transits to the corresponding screen-detected polyp stage and is kept under surveillance. At the first surveillance test at age 58 lesion 2 is detected in a cancer stage, and a new age at death from disease is generated for lesion 2. In this example, colorectal cancer death is delayed from 70 to 76 years of age. Again, it is assumed that lesions that appear after diagnosis of a cancer, such as lesion 3 in Fig. 2b, are accounted for in the survival of the detected cancer. Screening tests and surveillance tests after detection of cancer are therefore not simulated explicitly.

The resulting life history is represented at the bottom line. After the second screening the person is in a screen-detected polyp stage. At surveillance detection of lesion 2 the person transits to a screen-detected cancer stage. The person dies from the disease due to lesion 2 at the age of 76 and still loses 4 life-years because of death from colon cancer. Screening resulted in a gain of 6 life-years in this person.

3. FORMAL DESCRIPTION OF THE MODEL

In this section a formal description of the model is presented. The most important parameters of the model are summarized in Tables 1 and 2. Many parameters are optional. This means that, depending on the available knowledge and data and on the purpose of the simulation, the model can, within certain limits, be made as simple or complex as needed.

3.1. Demography

The model simulates an age-structured population, which enables public health evaluation of health benefits and costs of screening during a certain calendar period. Simulating a birth cohort is also possible.

Every person in the simulation has a date of birth and an age of death from other causes. The dates of birth and of death from other causes are generated from a distribution of births over calendar years and from a life table. The population may be divided into several groups (strata), where each stratum can have its own distribution of births and its own life table. Strata can be used to model differences in cancer risk and other characteristics in the population (see the next section). The relative size of each stratum must be specified.

3.2. Epidemiology and Natural History

Development of lesions. Lesions may proceed through three phases: a preclinical noninvasive polyp phase, a preclinical invasive cancer phase, and a clinical cancer phase, as shown in the upper part of Fig. 1. In the situation with screening, screen-detected phases are added. These phases can further be subdivided, to take account

TABLE 1

Summary of Demography and Natural History Parameters in MISCAN-COLON as Described in Section 3 and the Assumptions Used in the Example in Section 5

Parameter (Section 3)	Model specification in example (Section 5)
Population size (3.1)	1,000,000 in 1993
Strata in the model (3.1)	1
Life tables of death from other causes than colorectal cancer (3.1)	Based on age-specific mortality rates in U.S. population in 1989–1991
Distribution of births over calendar years (3.1)	Based on the age distribution in SEER data in 1993 and mortality rates in U.S. population in 1989–1991. No births after 1993.
Types of lesions (3.2)	1 type, with initial stage adenoma $\leq$5 mm
Stages in a lesion (3.2)	See Fig. 3
Parameters of the distribution of the risk index (3.2)	Average risk, 1; variance, 2
Age-specific preclinical incidence rates (3.2)	Based on clinical incidence stage distribution in SEER data in 1978 and a prevalence of adenomas in 15% of the population in age group 50–59 to 33% in age group 70+
Site distribution (3.2)	Site distribution of clinical cancers in SEER data in 1978
Transitions from each stage (3.2)	Based on clinical stage distribution in SEER data in 1978 and size distribution of adenomas in autopsy studies (40% $\leq$5 mm, 40% 6–9 mm, 20% $\geq$10 mm), assumed to be independent of site
Duration in stages (3.2)	*Dwelling time distributions in preclinical stages*: exponential *Mean total duration of preclinical stage of lesions that grow into cancer*: 20 years *Mean duration of preclinical cancer stage*: 3.6 years *Survival in clinical stages*: Based on SEER data
Correlation between durations (3.2)	100% between durations in preclinical stages

Note. Two screening policies are simulated in the example: FSIG: 3-yearly sigmoidoscopy screening; FOBT: biennial unrehydrated FOBT screening.

of differences in prognosis, differences in detectability, and differences in follow-up policy. The stages are ranked in order to determine the "most advanced" lesion found at screening or at clinical diagnosis.

Preclinical incidence. It is possible to define up to three different types of lesions. For example, adenomas and hyperplastic polyps can be distinguished. Each type is defined in the model by a unique initial stage. It is not necessary that subsequent stages are unique as well. For example, lesions of type 1 could start as a small adenoma and then develop into cancer, while lesions of type 2 start immediately as cancer. It is assumed that lesions of different types develop independently in a person. New lesions may start to develop until the age of death from other causes is reached.

TABLE 2

Summary of Screening Parameters in MISCAN-COLON as Described in Section 3 and the Assumptions Used in the Example in Section 5

Parameter (Section 3)	Model specification in example (Section 5)
Screening policy in each stratum (3.3)	First and last year of screening: 1993–2023 FSIG: Screening ages (50, 53, 56, . . . , 74) and FSIG test FOBT: Screening ages (50, 52, . . . , 80) and unrehydrated FOBT test
Specificity and sensitivity of each screening or surveillance test (3.3)	See nested table below
Dependency between tests (3.3)	No dependency
Site-dependent sensitivity (3.3)	No site dependency
Reach of each screening test (3.3)	*FSIG*: 100% of the tests reach the end of the rectum; 75% of the tests reach the end of the transversum (including flexures); 0% reaches farther than 25% of the transversum (including flexures) *FOBT*: Sensitive for lesions in whole colon
Sensitivity of the diagnostic test (3.3)	100% in all preclinical stages
Diagnostic follow-up after a positive result for each test and each preclinical stage (3.3)	Yes
Prognosis after screening (3.3)	*After screen detection of a polyp*: 100% cure *After screen detection of a cancer*: new survival based on stage-specific survival of clinical cancer
Follow-up after screen detection of each noninvasive stage (3.3)	*After a positive screening or surveillance test without lesions detected or only adenomas ≤5 mm detected*: Number of years without screening (surveillance interval): 5 Next test after surveillance interval: screening test *After a positive screening test with adenomas 6–9 mm and/or ≥10 mm detected:* Number of years without screening (surveillance interval): 5 Next test after surveillance interval: surveillance CSCPY
Attendance to screening in each stratum (3.3)	100%

	FSIG (%)	FOBT (%)	Surveillance colonoscopy (%)
Specificity	100	98	100
Sensitivity for adenoma ≤5 mm	75	2	80
Sensitivity for adenoma 6–9 mm	85	2	85
Sensitivity for adenoma ≥10 mm	95	5	85
Sensitivity for cancer	95	60	95

Note. Two screening policies are simulated in the example: FSIG, 3-yearly sigmoidoscopy screening; FOBT, biennial unrehydrated FOBT screening.

The assumption that colorectal lesions are randomly distributed among the human population, with all individuals having the same hazard of obtaining new lesions, would result in a Poisson distribution for the number of lesions in persons of a certain age. However, variation in genetic and environmental factors will result in heterogeneity in preclinical incidence. These risk differences between individuals in a population are modeled by introduction of a risk index for each individual. A high risk index indicates a relatively high probability to develop lesions. For each person a risk value is determined by a random drawing from a gamma distribution, which is a continuous probability distribution ranging between 0 and infinity (*13*). The mean and variance of this gamma distribution can be specified for every stratum and each type of lesion. A high-risk group can be modeled by a stratum with a high mean of the risk index. The risk to develop lesions of a type is proportional to the risk index for that type and the age-specific preclinical incidence rate for that type (see Appendix A).

The gamma distribution for risk in the population results in a negative binomial distribution of colorectal lesions at a given age in the population (*14*). This distribution is widely used in the conceptually similar field of modeling parasite burden in the population (*15*). If the variance of the gamma distribution for risk indices is small, the distribution of colorectal lesions at a certain age will approach a Poisson distribution.

Anatomical site. In the model, each lesion in a person is located at a specific anatomical site. For each type of lesion the distribution of lesions over the anatomical parts of the large bowel can be specified. The anatomical site of a new lesion is assumed to be independent of the anatomical site of previous lesions. The anatomical site of a lesion is indicated by the part of the bowel in which the lesion is situated, e.g., the sigmoid, and a percentage that indicates the localization within this part. Transitions, durations, and the sensitivity of screening tests can but need not depend on anatomical site. Furthermore, the distribution of depth of insertion of a screening test can be specified. The ability to take anatomical site into consideration is important for the evaluation of sigmoidoscopy and colonoscopy screening, where a screening test is characterized by a depth of insertion. For example, a person can have a lesion in the sigmoid at a distance of 60% (of the length of the sigmoid) from the end of the sigmoid. If a sigmoidoscopic examination does not reach the entire sigmoid, but only the last 30% of the sigmoid, this lesion will not be found. In addition, this aspect is important for the evaluation of FOBT screening because there are indications that the sensitivity of FOBT depends on the site (*16*).

Transitions and durations of lesions. After the onset of a lesion in an initial stage, the history of a lesion is simulated by successively generating a subsequent stage and a duration in the present stage. For each stage probabilities to transit to subsequent stages are specified. Transition probabilities can depend on age of the person and anatomical site of a lesion. Each possible transition between two stages has its corresponding probability distribution of the dwelling time in the present stage. Four types of dwelling time distribution functions are currently implemented in the model: a constant duration (parameter: mean), an exponential distribution (parameter: mean), a Weibull distribution (parameters: shape, mean), and a

piecewise uniform distribution (parameters: (a_i, b_i), $i = 1, \ldots, n$, where a_i is a dwelling time and $b_i = P(\text{dwelling time} \leq a_i)$). The mean of exponentially or Weibull distributed dwelling times can depend on age and anatomical site. Simple model specifications will assume independence between the dwelling time in a stage and a dwelling time in a previous stage. However, it is possible to specify that durations in successive stages are correlated. This correlation is characterized by a parameter with values between -1 and 1. Independency of dwelling times is indicated by a value of 0; deterministic dependency is indicated on the previous dwelling time by $\pm$ 1.

3.3. Screening

Screening policy and attendance. In the model, mass screening is offered at predefined ages in a specific calendar period. Individuals without clinical colorectal cancer are invited and a proportion, defined by attendance probabilities, will accept the invitation and attend screening. Screening policies can differ between strata and are defined by the calendar period of mass screening, the ages at which persons are invited to screening, and the screening tests at each age. Up to three screening tests can be used. Attendance probabilities of screening may differ between strata and are specified for each screening age. Attendance probabilities should be given separately for persons who came to the previous screening and for persons who did not.

Characteristics of screening tests. A screening test has a positive or negative result. The probabilities on each outcome depend on the absence or presence of lesions. For each screening test the specificity is defined, i.e., the probability of a negative result in persons without lesions. In persons with lesions, test results are generated for each lesion independently. For each screening test and each preclinical stage the probability of a positive test result due to a lesion in that stage (sensitivity) is specified. A screening result is positive if one or more lesions are detected.

It is possible to specify that the sensitivity of the screening test depends on the anatomical site of a lesion. It is assumed that the site dependency of a test does not differ between preclinical stages. The site dependency relation of a test is specified by a sensitivity multiplication factor for each site. The site-specific sensitivity is obtained by multiplying the sensitivity value of the screening test by the multiplication factor. In addition, it is possible that a screening test reaches only part of the bowel. In that case, the probability to reach sites in the bowel can be specified. For each application of a screening test in a person, the depth of insertion is generated. Only lesions within reach can be found during the screening test.

After a positive screening test, a diagnostic test can be performed. In practice, a diagnostic test is not always performed after a positive screening test. For example, in sigmoidoscopy screening, a finding of a small tubular adenoma does not always lead to diagnostic colonoscopy. Therefore, the stages that lead to a diagnostic test can be specified. Furthermore, it is possible to define the sensitivity of the diagnostic test for each stage separately and to make it site-dependent.

A screening examination may consist of more than one screening test. In case

of complete independency between test results, the probability of a positive test result is independent of the results of the same test in previous screenings, and independent of the results of other tests applied in the same or in previous screening rounds. The assumption of independent test results is only realistic in case false test results occur randomly, e.g., in case of unnoticed and temporary technical or human error. Part of the errors will occur more systematically. The possibility of systematic errors has been implemented in the MISCAN-COLON program via the concept of systematic test results (see Appendix B). In this concept, the result of a test has two components: one random and one systematic. The errors in the random component occur by chance; i.e., the outcome of the test is independent of all other test results. Errors in the systematic component of test results are correlated. Both systematic negative and systematic positive test results may occur.

Systematic test results can occur per:

- person. For example, it is possible that a FOBT is always positive in a person.
- test examination. For example, it is possible that all small polyps within reach are missed at sigmoidoscopy because of bad bowel preparation.
- lesion. For example, a lesion can be missed systematically because of a difficult localization in the bowel.

Screening tests can be specified to share systematic results. For example, rehydrated and unrehydrated FOBT tests may differ in sensitivity level but could have the same systematic results.

Prognosis after screening. In this section screening is defined as the combination of the screening examination and, if applicable, further diagnostics after a positive test result. After a positive screening result all screen-detected polyps are assumed to be removed and cannot lead to further development of the disease. Thus, any cancers that would have eventually developed from these screen-detected polyps are totally cured. The possible prognostic consequences after a positive test result for a cancer are:

- Total cure. The person will not die of the screen-detected cancer.
- Delay in moment of death. The moment of death from disease due to the screen-detected cancer is postponed. The period of delay is drawn from a dwelling time distribution.
- No change in moment of death. It can be specified that although a new (screen-detected) stage is entered at the moment of the positive test result, the moment of death from disease of the lesion does not change.
- Operation mortality. A probability of immediate death after a positive screening can be defined.
- New survival after screen detection, independent of the moment of death in the situation without screening. With this option one can use observed stage-specific survival distributions after screen detection. The prognosis after screen detection of cancer is specified by the probabilities of each consequence. These can differ between cancer stages. If several synchronous cancers are detected at screening, an independent prognostic consequence is generated for each cancer.

Follow-up after screening. Several follow-up strategies are possible in persons who had a positive screening examination, but in whom no cancer was found:

- The person returns to the screening program and is invited to the next screening round as usual. This can, for example, be applied to persons in whom only small adenomas were found.
- The person will not be screened for several years. After this period the person returns to the screening program and is invited for screening at the next screening age. This can be useful to model the screening of persons with a false-positive FOBT test. These persons underwent colonoscopy and no lesions were found, leading to a low risk for cancer in the following years.
- The person will be kept under surveillance. The surveillance interval, i.e., the period between two surveillance tests, can be specified. Surveillance continues until no lesions are found. Subsequently, the person is invited for screening at the next screening age. In this way it is possible to simulate monitoring of persons with large or villous adenomas who are considered to be at high risk for colorectal cancer.

4. THE PROGRAM

The total MISCAN-COLON package consists of two programs: (1) the actual simulation program, and (2) a postprocessing program for processing simulation output. A user interface for preparation of input is available. All programs are written in Delphi (Borland) and require Windows ’95. Simulation of 100,000 individuals that are screened six times takes about 60 s on a 133-MHz Pentium. The average time needed depends on the complexity of the disease process and the number of screenings performed in the population.

The random number generator, based on (*17*), is divided into two disjoint random number subsequences and requires two initial seeds. For each source of randomness the number of the random number subsequence can be specified, which can be used to reduce variance between simulation runs. For each new person in a simulation, the starting points of the random number generators are calculated. In this way, as long as the same initial seeds are used in simulations, in every simulation the same random number sequence is assigned to a life history. This reduces the variance between simulation runs.

The output of the actual simulation program consists of two files, a file for postprocessing and a standard output file. The postprocessing file contains all important outcomes for the evaluation of a screening policy (see Table 3). It contains results per year, useful for detailed analysis, and aggregated totals over time that can be used directly by the postprocessing program. The output in this file can be subdivided into maximally three groups of strata. The preclinical stage assigned to a positive screening or surveillance test is defined by the most advanced stage found by the test or during its diagnostic follow-up. The preclinical stage assigned to a negative test is the most developed stage within reach of the screening test. The age groups into which the output is divided, the reference year for discounting, and the discount percentages can be specified. For any clinical stage, the annual number of entries and the number life-years can be tabulated in the

TABLE 3

Contents of File with MISCAN-COLON Output for Postprocessing

For each risk group[a] by year
Number of first and repeat invitations and screenings, and the number of surveillance tests
Number of prevented and detected cancers by screening and surveillance and number of prevented deaths from colorectal cancer*
Number of life-years gained by the screening program*
Number of positive and negative results of screening and surveillance examinations in each preclinical stage (by age group)
Number of entries to each stage (by age group)
Number of life-years and number of life-years lost by the disease (by age group)
Number of disease-specific deaths and the number of nonspecific deaths (by age group)
Totals over the whole simulated time period, for the situation with and without screening, discounted by three percentages, for example 0, 3, and 5%
Number of first and repeat invitations, number of screening examinations, and number of surveillance tests
Number of positive and negative diagnostic follow-up tests after a positive screening test
Number of entries and life-years in clinical and screen-detected stages
Number of disease-specific deaths
Number of life-years lived
Number of life-years lost by disease

Note. *, optional.

[a] A risk group is a clustering of strata.

output file on demand. The standard output file contains a summary of the input specifications and additional output data if desired, such as incidence and prevalence per age group. Extra output can easily be added to both output files.

The postprocessing program uses the discounted totals over time in the postprocessing output file to calculate the costs and effects of a screening policy. Costs are assigned to screening tests, diagnostic tests, surveillance tests, and cancer treatment. For example, treatment costs are divided into costs for initial therapy in the first 6 months, costs of palliative care in the last 6 months, and yearly costs of continuous care of colorectal cancer patients. The postprocessing program calculates costs per life-year gained and costs per prevented death using three discount percentages.

5. EXAMPLE

As an illustration, the MISCAN-COLON model is used to simulate two screening strategies in the American population from 1993 until 2023. One strategy is 3-yearly FSIG screening between ages 50 and 74; the other strategy is biennial unrehydrated FOBT screening between ages 50 and 80. Preliminary, but in our opinion not implausible, assumptions about the natural history and screening characteristics were implemented. Parameter values are based on literature and expert opinion. Model assumptions were established in two working meetings of experts at the National Cancer Institute (Bethesda, MD). Some aspects, such as the clinical incidence in the situation without screening and survival after clinical detection,

are based on surveillance, epidemiology and end results (SEER) data of the National Cancer Institute in the United States. A summary of the assumptions is given in Tables 1 and 2. In Fig. 3 the assumed natural history of colorectal cancer is presented. The adenoma stages are subdivided according to size, while the cancer stages are based on the AJCC classification.

In Table 4, the simulated totals per 1,000,000 persons in the 1993 U.S. population over the whole simulated time period in this example are shown for 3-yearly sigmoidoscopy screening, biennial unrehydrated FOBT screening, and no screening. Figure 4 displays the annual costs of the screening program for both strategies. Only the costs of the screening tests are taken into account. The costs of the FSIG program are much higher than the costs of the FOBT program. Figure 5 shows the annual mortality reduction due to the screening program. The fluctuations in mortality reduction are due to the stochastic character of the simulation. As an indication, the estimated mortality reduction is based on a simulation with a mean number of 295 colorectal cancer deaths per year. The mortality reduction by the FSIG program is higher than the mortality reduction by the FOBT program. In the first few years of screening the mortality reduction is less than 0 in both programs. This is due to the fact that in the model some people die during their lead time (e.g., by an operation). After these years considerable mortality reduction occurs, and the reduction achieved by FSIG screening is higher than that by FOBT screening under the assumptions. After the end of both screening programs the mortality reduction decreases gradually.

The assumptions in the model can be changed to assess the sensitivity of the

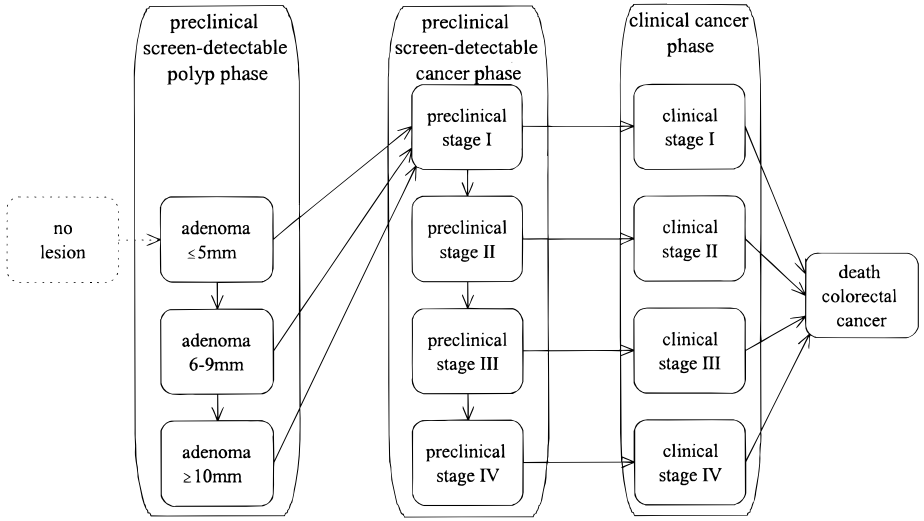

FIG. 3. The subdivision of the phases in Fig. 1 as used in example. The polyp phase is subdivided into size categories. The preclinical and clinical cancer phases are subdivided into AJCC stages.

TABLE 4

Predicted undiscounted Totals in Example per 1,000,000 Persons in the 1993 U.S. Population, Assuming 100% Attendance

	3-yearly FSIG	Biennial unreh. FOBT	No screening
First invitations	645,800	674,100	0
Repeat invitations	2,345,600	4,183,200	0
Screening examinations	2,921,800	4,829,600	0
Surveillance tests	69,600	27,700	0
Positive diagnostic follow-up tests after screening	148,400	40,300	0
Negative diagnostic follow-up tests after screening	127,800	76,700	0
Entries in clinical stages I–IV	50,500	54,500	62,700
Entries in screen-detected stages I–IV	1,100	5,300	0
Life-years in clinical stages I–IV	404,100	443,600	506,200
Life-years in screen-detected stages I–IV	15,700	66,000	0
Colorectal cancer deaths	22,600	25,200	27,900
Total number of life-years	43,729,400	43,689,900	43,655,600
Life-years lost by disease	303,600	343,100	377,500

Note. The screening was performed in 1993 to 2023.

model. For instance, when the dwelling time distribution between preclinical incidence of an adenoma and the clinical diagnosis of the subsequent cancer is assumed to be constant instead of exponentially distributed in this model, the simulated number of colorectal cancer deaths prevented by the screening strategies is doubled.

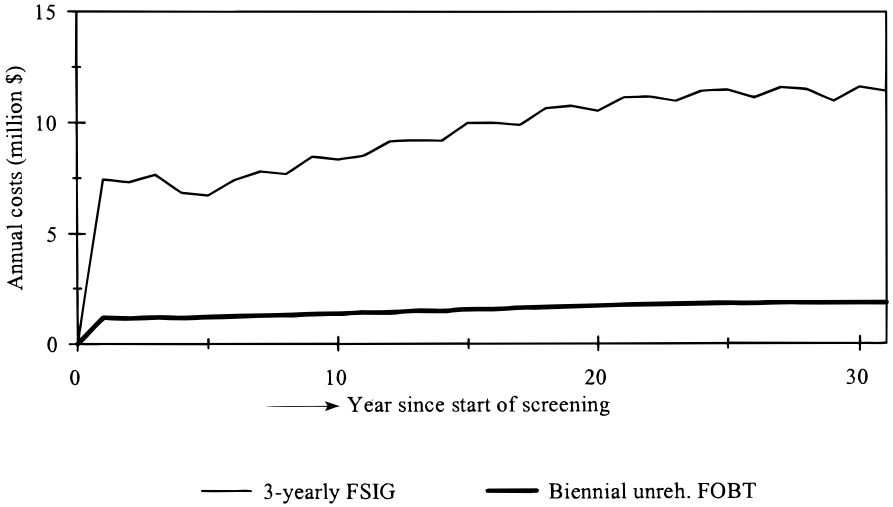

FIG. 4. Predicted annual costs of screening tests of sigmoidoscopy screening and unrehydrated FOBT screening in example per 1,000,000 persons in the 1993 U.S. population, assuming 100% attendance. The screening was performed in 1993 to 2023.

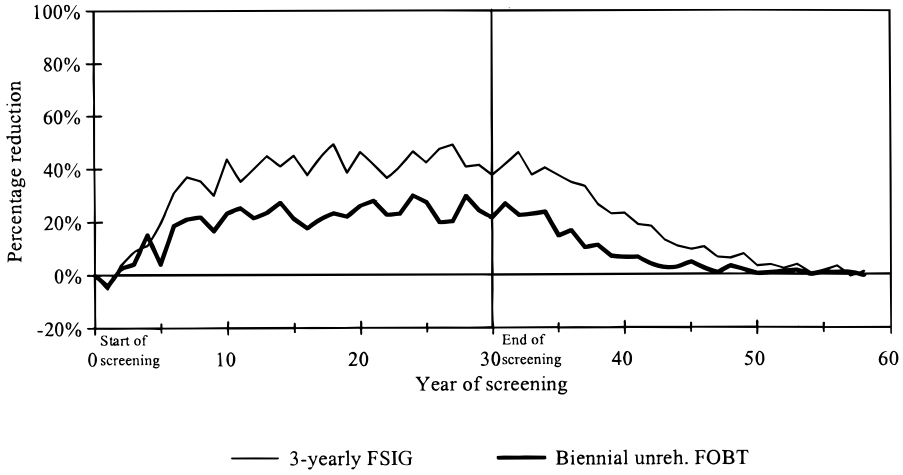

FIG. 5. Predicted annual percentage colorectal cancer mortality reduction by sigmoidoscopy screening and unrehydrated FOBT screening in example in the 1993 U.S. population, assuming 100% attendance. The screening was performed in 1993 to 2023.

6. DISCUSSION

The three main purposes of a screening model are analysis of data, testing of hypotheses, and evaluation of screening policies. Use of the MISCAN-COLON model for colorectal cancer screening will be similar to use of MISCAN models for breast and cervical cancer screening.

First, the model will be used to analyze data from screening studies. Reliable use of a model in prospective evaluation of complex screening policies will be possible when the model is sufficiently validated. For instance, the breast cancer model was used for a model-based analysis of the HIP project for breast cancer screening (*18*), and was checked against the Dutch screening projects in Nijmegen and Utrecht (*19*). In addition, the mortality reductions in five Swedish breast cancer-screening trials were analyzed (*20*). For cervical cancer screening similar analyses were carried out (*21–23*).

For colorectal cancer, the program is being employed to evaluate and possibly improve upon preliminary assumptions by analyzing available data. The MISCAN-COLON program is being used to simulate the Colon Cancer Control Study of FOBT screening in Minnesota and the sigmoidoscopy screening performed by the Kaiser Permanente in northern California. Comparison of simulated and observed results will indicate which combinations of parameter values are, and which ones are not, in agreement with the observed results. Next, data from the National Polyp Study (*24*) will be analyzed. Analysis of these data sets will help to narrow down the uncertainty about model parameters describing the natural history of polyps and colorectal cancer and the characteristics of screening tests. Furthermore, it will indicate the level of complexity required in the model. For instance, analysis of

the Minnesota Colon Cancer Control Study will address the question of whether systematic test results of FOBT screening should be incorporated in the model.

Furthermore, the model can serve to test different hypotheses about the natural history of polyps and colon cancer and about the impact of screening. For example, in a cervical cancer screening model three hypotheses about regression of preinvasive cervical cancer were tested against data from the British Columbia cohort study (*25*). An adequate fit was achieved by assuming that regression of preinvasive lesions is age-dependent.

Finally, a validated model can be used for evaluation of screening strategies. The MISCAN model for breast cancer screening has been employed to predict the impact of breast cancer screening on clinical medicine (*26*) and the impact of breast cancer screening on quality-adjusted life-years (*27*). In addition, cost-effectiveness and quality of life results were calculated for several screening strategies (*10, 11*). The MISCAN model for cervical cancer screening has been used to estimate cost-effectiveness of cervical cancer screening in The Netherlands (*12, 28, 29*) and to explore the potential value of HPV testing for cervical cancer screening (*30*). In the MISCAN-COLON model all kinds of assumptions on the natural history of colorectal cancer and screening and surveillance strategies can easily be incorporated. Therefore, the MISCAN-COLON model can serve to make predictions for the cost-effectiveness outcomes of screening policies, as shown in the example. Furthermore, the model is well suited for performing sensitivity analysis on the outcomes. For example, the effect of possible site dependency of the sensitivity of FOBT (*16*) on the predicted cost-effectiveness can be calculated. After the model has been validated by analysis of data, it will be used for the evaluation of effectiveness and cost-effectiveness of screening policies and of surveillance policies after polyp removal.

APPENDIX

A. Preclinical Incidence of Lesions

For each individual life history and each type of lesion i a risk index R_i is drawn from a gamma distribution denoting the risk to develop lesions of type i. The gamma distribution is based on two parameters α and β, with mean $= \alpha \cdot \beta$ and variance $= \alpha \cdot \beta^2$. The density function of the gamma distribution is:

$$f(x) = \begin{cases} \dfrac{\beta^{-\alpha} x^{\alpha-1} e^{-s/\beta}}{\Gamma(\alpha)} & \text{if } x > 0 \\ 0 & \text{otherwise} \end{cases}$$

Let a_0 denote age 0 or the age at which the last lesion of type i developed. The onset rate $h_i(a)$ is the probability to develop lesions of type i at age a in a person in which the risk index equals 1. The onset rates are assumed to be "piecewise constant," i.e., constant over age intervals denoted by (b_u, b_{u+1}), $u = 1, 2, \ldots$.

The corresponding accumulated preclinical incidence between age a_0 and a in a person with risk index R_i equals:

$$H_i(a, a_0) = R_i \int_{a_0}^{a} h_i(y)dy$$

The probability distribution for the age a_i at which a new lesion of type i develops is:

$$\Pr(a_i \leq a) = 1 - \exp[-H_i(a, a_0)]$$

The age at which a new lesion of type i develops is calculated by solving this equation, where the probability is replaced by random number u, uniformly distributed between 0 and 1.

B. Systematic Test Results

Before simulation of screening in a person, random numbers u_s are generated that will be used to determine whether results of a screening test are systematic. Systematic test results can occur per person. Therefore, a random number u_{st} is drawn for each test t. Systematic test results can also occur per lesion. Therefore, a random number u_{stl} is drawn for each test t and each lesion l. The random numbers u_s for systematic test results per examination are generated when examination is simulated. If two tests v and w have the same systematic results, the random number for the systematic results are equal: $u_{sv} = u_{sw}$ and $u_{svl} = u_{swl}$ for each lesion l.

At each screening and surveillance examination in a person, the test results for each test are generated as follows.

If the person does not carry lesions at the time of the examination: For each test t a tuple (P_{st}, N_{st}, P_t) is given for persons without lesions, denoting the probability of a systematic positive result, the probability of a systematic negative result, and the probability of a nonsystematic positive result if the result is not systematic. If $u_{st} \leq P_{st}$, the random number for systematic test results in this person is lower than the probability of a systematic test result in a person, the test is systematically positive. If $u_{st} \geq 1 - N_{st}$, the generated random number for systematic test results in this person is higher than $1 -$ the probability of a systematic test result in a person, the result is systematically negative. If the result is not systematic, a random number u is generated. If $u \leq P_t$, the result of the test is positive, else the result of the test is negative.

If the person does carry one or more lesions at this age: For each test t and each preclinical stage E a tuple (P_{spEt}, N_{spEt}, P_{seEt}, N_{seEt}, P_{sEt}, N_{sEt}, P_{Et}) is given, where P_{spEt} is the probability of a systematic positive test result in a person in which the most developed lesion within reach of the test is in stage E; N_{spEt} is the probability of a systematic negative result of test t in a person in which the most developed lesion within reach of the test is in stage E; P_{seEt} is the probability of a systematic positive result of test t at a screening examination where the most

developed lesion within reach is in stage E; N_{seEt} is the probability of a systematic negative result of test t at a screening examination where the most developed lesion within reach is in stage E; P_{sEt} is the probability of a systematic positive result of test t for a lesion in stage E; N_{sEt} is the probability of a systematic negative result of test t for a lesion in stage E; and P_{Et} is the probability of a positive result of test t due to a lesion in stage E if no systematic result.

The results are generated separately for each screening or surveillance test t. At each screening in a person, the stage $E_{\max}$ of the most developed lesion within reach of test t is determined. First, it is decided whether the test has a systematic result for this person. Consequently, it is determined whether the test has a systematic result due to the examination moment. Finally, if this does not lead to systematic results, for each lesion separately it is determined whether the test has a systematic result. If the test has no systematic result for the lesion, the random result is generated.

If $u_{st} \leq P_{spEt}$, where $E = E_{\max}$, the result of test t is systematic positive for the person.

If $u_{st} \geq 1 - N_{spEt}$, where $E = E_{\max}$, the result of test t is systematic negative for the person.

If no systematic result of test t for the person, a random number u_t is generated to decide whether the test result is systematic at this test moment.

If $u_t \leq P_{seEt}$, where $E = E_{\max}$, then the result of test t is systematic positive.

If $u_t \geq 1 - N_{seEt}$, where $E = E_{\max}$, then the result of test t is systematic negative.

If still no systematic result for test t, then the test results are evaluated for each lesion l separately. E denotes the stage of lesion l.

If $u_{stl} \leq P_{sEt}$, then the result of test t is systematic positive for lesion l.

If $u_{stl} \geq 1 - N_{sEt}$, then the result of test t is systematic negative for lesion l.

If there is no systematic result of the test, a random number u for lesion l is generated. If $u \leq P_{Et}$, then the test result for lesion l is positive, otherwise the test result for lesion l is negative.

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