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What is the best screening strategy to detect advanced colorectal adenomas? Simulation from ongoing Italian screening experiences

Leonardo Ventura, Marco Zappa, Giulia Carreras, Stefano Ciatto, and Grazia Grazzini

ISPO Cancer Research and Prevention Institute, Florence, Italy

ABSTRACT

Aims and background. The best screening strategy for colorectal cancer is still debated. We simulated two screening strategies, namely flexible sigmoidoscopy (single episode) and immunological fecal occult blood test (FOBT) (five biennial rounds) and comparing their results as regards advanced adenomas and colorectal cancer detection.

Methods. A Markov model was developed to estimate the number of advanced adenomas and colorectal cancer detected with the two compared screening strategies. Two different scenarios, namely a) where the same compliance (50%) at both flexible sigmoidoscopy and immunological FOBT invitation is applied, and b) where the actual compliance observed at a national level (immunological FOBT, 45%; flexible sigmoidoscopy, 30%) is applied.

Results. In scenario a), immunological FOBT would detect a total of 20,573 adenomas and 3,952 colorectal cancers, performing 74,507 total colonoscopies compared to 20,939 and 2,511, respectively, detected by flexible sigmoidoscopy, with 17,985 total colonoscopies. In scenario b), immunological FOBT would detect 17,845 advanced adenomas with 65,215 colonoscopies performed compared to 12,672 detected by flexible sigmoidoscopy with 10,796 colonoscopies. The probability of having a colonoscopy for a subject attending all the five immunological FOBT rounds was 15.9%.

Conclusions. The simulation suggests that also immunological FOBT screening may achieve a substantial detection of advanced adenomas and therefore may have an impact on colorectal cancer incidence.

Key words: colorectal cancer, Markov model, screening.

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Correspondence to: Leonardo Ventura, via delle Oblate, Pal. 28/a, 50100 Florence, Italy.
Tel +039-055-7972502;
fax +039-055-7972535;
e-mail l.ventura@ispo.toscana.it

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Introduction

Colorectal cancer (CRC) is one of the five most frequent cancers in Italy among males and females[1]. Screening for CRC has a high potential to reduce morbidity and mortality from the disease, but a debate is ongoing as to the best and most effective screening policy. Recently, the American Cancer Society[2] made a distinction between screening tests aimed at early detection of both CRC and adenomas (e.g., endoscopic examination) and tests mainly aimed at early cancer detection (e.g., fecal occult blood testing, FOBT). Such a distinction may be acceptable when a single screening examination is considered, not when a screening program is considered. Current protocols foresee FOBT being repeated every two years from age 50 to 70, and the resulting cumulative detection rate of adenomas, particularly of advanced adenomas, is substantially high. Mathematical modeling is increasingly used in health-care programs to assist in decision-making processes.

We simulated two screening strategies, namely flexible sigmoidoscopy (FS) and immunological FOBT (iFOBT) and compared their results as regards advanced adenomas and CRC detection rates. The model was implemented using figures available

from ongoing screening experiences of screening in the Province of Florence.

Materials and methods

Description of the model

A Markov model[3] was developed to estimate the number of advanced adenomas and CRC detected with the two compared screening strategies. A Markov model is defined by a finite number of discrete, mutually exclusive states. Progression and regression through the model is based on a set of transition probabilities of moving among states. States and transition probabilities are defined for each model in accord with the literature and data. The model was evaluated with microsimulations.

In order to take into account uncertainty on model parameters, a probabilistic sensitivity analysis approach was used. Transition probabilities were therefore sampled for each individual from a logistic-normal distribution with mean and variance estimated from available data[4,5]. In the present model, we assumed that each subject can only move one state further in a given round. Two different models were developed for FS and iFOBT screening scenarios. The FS scenario consisted of a single screening episode at age 60. We assumed a cohort of 1,000,000 subjects (50% women, 50% men) being invited, non-responders being re-invited twice. The iFOBT screening scenario consisted of an identical cohort of 1,000,000 subjects invited to five consecutive biennial screening rounds from age 60 to age 68. Subjects entering the model were followed for a period of 10 years.

As consequence of a positive iFOBT test, subject are invited to undergo a colonoscopy. Individuals complying to colonoscopy may have an adenoma (or a cancer) detected. In the case of the FS test, most adenomas or cancers are detected directly during the primary sigmoidoscopy, whereas others are detected during the following assessment test (colonoscopy). The screening detection rate of advanced adenoma (adenomas larger than 10 mm in diameter, with severe dysplasia, or with a villous component) as well of CRC were thus estimated.

Possible transitions from one state to another are described in Table 1. An adsorbent state was defined as a state from which there is no escape. Once entered, no other states are possible.

Epidemiological sources for transition probability estimates

To estimate transition probabilities, the most reliable local sources were used. For the FS scenario, CRC and adenoma detection rates were drawn from the Florence arm of SCORE2 and SCORE3 studies[6,7]. For the iFOBT screening scenario, reference CRC and adenoma detection rates were drawn from online archives of screening performances in the district of Florence. For the iFOBT scenario, transition probabilities were stratified in two age classes (60-64 and 65-69). Transition probabilities were different for sex and for first or repeat screening examination (iFOBT).

Table 1 - Transition state of the model

State no.	Initial Markov state	Next Markov state
1	Invitation to the FOBT test	Compliance No compliance Death for all causes
2	Compliance at the FOBT	Positive test Negative test
3	Positive at the test	Compliance at colonoscopy No compliance at colonoscopy
4	Compliance at colonoscopy	Negative Advanced adenomas, CRC
5	Advanced adenoma, CRC	Absorbent state
6	Death for all causes	Absorbent state

CRC, colorectal cancer.

In a first simulation, compliance to screening invitation at first round was assumed to be the same (50%) for both FS and iFOBT scenarios. In a second simulation, the actual compliance observed for each policy at a national level (45% for iFOBT, 30% for FS) was used[8]. Compliance at subsequent iFOBT screening rounds was modeled differently according to three different probabilities, namely a) never responders, b) responders at least once in previous rounds, and c) regular responders. Probabilities were based on those observed in three consecutive screening rounds in a large municipality in the district of Florence (data available from ISPO CRC screening archive). Compliance to total colonoscopy for iFOBT or FS positive subjects was obtained from data available from the ISPO CRC screening archive and from Italian multicenter randomized trial[6-7], respectively.

For the iFOBT scenario, the probability of CRC or advanced adenoma detection was based on positive predictive value observed in 21 municipalities of the Florence District where at least three screening rounds had been performed since 2000 (data available from ISPO CRC screening archive). A total of 55,000 screening tests were considered.

Age-specific mortality rates (all causes) were obtained from the mortality registry of the Florence and Prato districts for the year 2006. The model assumes that death may occur between one round and the other. Resulting transition probabilities are reported in Table 2 for iFOBT and in Table 3 for FS.

Results

Results are reported in Table 4. Under the assumption of a fixed 50% compliance at both screening modalities,

Table 2 - Reference transition probabilities from one model state to another (iFOBT)

Variable	Value			
	Males		Females	
	60-64 yr	65-69 yr	60-64 yr	65-69 yr
FOBT positive (%)				
First screening	5.4	6.5	4.0	4.7
Repeat screening	4.2	4.7	2.7	3.6
Compliance at the colonoscopy (%)				
First screening	78.0	77.0	76.0	78.0
Repeat screening	88.0	84.0	87.0	84.0
PPV high-risk adenomas (%)				
First screening	37.0	37.0	29.0	31.0
Repeat screening	29.0	29.0	17.0	20.0
PPV cancer (%)				
First screening	9.0	14.0	6.0	6.0
Repeat screening	6.0	8.0	7.0	7.0

PPV, positive predictive value; iFOBT, immunological fecal occult blood test.

Table 3 - Reference transition probabilities from one model state to another (flexible sigmoidoscopy)

Variable	Value	
	Males age 60	Females age 60
FS positive (%)	5.0	2.7
Compliance at colonoscopy (%)	95.0	95.0
DR advanced adenomas (‰)	62.0	24.0
DR cancer (‰)	7.0	3.0

FS, flexible sigmoidoscopy; DR, detection rate.

Table 4 - Number of adenomas and cancers detected by two different screening policies, assuming different compliance to invitation

			50% iFBOT and FS scenario		Real compliance scenario (45% iFOBT, 30% FS)	
Type of test	Round	Sex	Adenoma	Cancer	Adenoma	Cancer
iFOBT	1	M + F	5,500	836	5,469	796
iFOBT	2	M + F	3,732	738	3,661	694
iFOBT	3	M + F	3,525	644	3,370	667
iFOBT	4	M + F	3,969	869	2,439	521
IFOBT	5	M + F	3,847	865	2,906	675
Total iFOBT			20,573	3,952	17,845	3,353
Total FS			20,939	2,511	12,672	1,455

iFOBT, immunological fecal occult blood test; FS, flexible sigmoidoscopy.

5,500 advanced adenomas were detected at first iFOBT screening round and 4,000 at each of the following four rounds, for a total of 20,573 adenomas compared to 20,939 detected at the only FS screening round. It is noteworthy that under the aforementioned assumption of compliance, whereas we observed almost 50% compliance at each round, during five rounds 65.4% of the initial population performed at least one iFOBT and 31.7% performed all five rounds. As regards the CRC detection rate, iFOBT would detect 3,952 CRC in five rounds compared to 2,511 detected by FS.

The total number of colonoscopies to be performed would be 74,507 and 17,985 for iFOBT and FS screening, respectively.

When actual compliance data are assumed, iFOBT would detect 17,845 advanced adenomas compared to 12,672 with FS. As regards CRC detection rate, iFOBT would detect 3,353 CRC compared to 1,455 with FS. In this case, the number of colonoscopies to be performed would be 65,215 and 10,796 for iFOBT and FS, respectively.

The probability of having a colonoscopy for a subject attending all five iFOBT rounds was 15.9%.

Discussion

The aim of the present paper was to compare two different screening policies, presently used in our Country, as regards advanced adenoma and CRC detection rate. The advanced adenoma detection rate is relevant as the removal of these lesions could be considered as a proxy of invasive cancer prevention.

The present comparison was performed via mathematical modeling. A peculiarity of our modeling compared to other studies is that transition probabilities were based or real figures drawn from several rounds of a population-based iFOBT screening program and from a pilot study of FS screening within the SCORE trial, all carried out in our District. The main limitation of our methodological approach is that the natural history process of the colorectal disease was not modeled at all. Given that our primary interest in the study was focused on detection rates, in our opinion this simplified model seemed sufficiently appropriate.

Considering the scenario of current observed compliance, (45% iFOBT and 30% rectal sigmoidoscopy, RSS), the number of persons needed to invite (NNI) for detecting one important lesion (advanced adenomas or cancer) is 230 and 71 for iFOBT and RSS, respectively. In the scenario of the same compliance (50%) for both the policies, the NNI is 198 and 43 for iFOBT and RSS, respectively. The number of people needed to screen (NNS) is 93 and 21 for iFOBT and RSS, respectively, under the scenario of current compliance. In the scenario of the same compliance (50%) for both the policies, the NNS is 91 and 21 for iFOBT and RSS, respectively.

When the same compliance is assumed for both iFOBT and FS screening, a comparable number of advanced adenomas is detected by both policies, and a higher number of CRC is detected by iFOBT.

This does not necessarily mean that the effect on invasive cancer prevention will be the same, as in the FS scenario advanced adenomas are detected at an earlier age (at an average of 3.70 years before) than with iFOBT, which might imply a better control of adenoma progression to CRC. However, the higher number of CRC detected at an early stage by iFOBT than by FS (in particular, in the right colon) might imply a higher efficacy of iFOBT screening in reducing mortality from CRC cancer.

A similar result was evidenced by a recent paper[9] where a simulation model was used: an annual immunochemical FOBT strategy and a five-year FS was compared. Over a 30-year period, both strategies were associated to a comparable reduction of CRC compared with no screening, thus suggesting that the same number of advanced adenomas were detected.

As regards the cumulative number of high-risk adenomas, we can see that under the hypothesis of 50% compliance for both the examinations, after five rounds the iFOBT policy will detect about the same number of lesions as the RSS (about 20,500 high-risk adenomas).

When real compliance rates are introduced in the model, iFOBT detects the same number of advanced adenomas as FS within three rounds (i.e., with a shorter delay, 3.29 years on the average), whereas in five rounds iFOBT will detect 41% more advanced adenomas than FS.

From a public health point of view, different screening policies should be compared as regards their health outcome (lives saved, years of life gained), considering the involved resources (costs). This is a more complex issue and was not the aim of the present analysis. Nevertheless, the present simulation model seems to indicate that iFOBT screening may also achieve a substantial detection of advanced adenomas and therefore may have an impact on CRC cancer incidence.

We think that the issue of cost should be a key point in decision analysis. The present paper provides some elements (i.e., the number of invitations, the number of screened persons, the number of colonoscopies) to carry out a formal cost-outcome analysis. However, is it evident that the cost of a single RSS is much higher than the cost of an iFOBT. In the near future, we will provide such an analysis.

In the present paper, we have based our estimates on the best evidence of compliance to screening invitation available at the Italian level. In fact, from 2004-2005, five surveys have been carried out at the Italian level on CRC screening (www.osservatorionazionalescreening.it), and the average results are in line with adopted parameters (45% for iFOBT and 30% for RSS). Furthermore, we have carried out a simulation adopting the same compliance to invitation (50%) for both the policies. Of course, if in the future the compliance of RRS exceeds the compliance to iFOBT, we should revise our conclusions.

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