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ORIGINAL PAPER

Incremental net benefit and acceptability of alternative health policies: a case study of mass screening for colorectal cancer

Pauline Chauvin · Jean-Michel Josselin · Denis Heresbach

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Abstract The incremental net benefit (INB) and the related acceptability curves for public health programs provide valuable tools for decision making. We proposed to apply them to the assessment of mass screening of colorectal cancer. The now standard guaiac fecal occult blood test (FOBT) is already implemented in several countries. We considered the innovative immunological FOBT and computed tomography colonography (CTC) as competing screening technologies. Using biennial guaiac FOBT as the reference strategy, we estimated the cost-effectiveness of the following alternatives: biennial immunological FOBT, CTC every 5 years (strategy CTC5), and CTC every 10 years (strategy CTC10). Over a 30-year horizon and from the perspective of a third-party payer, we developed a Markov model on a hypothetical cohort of 100,000 subjects at average risk of colorectal cancer. Close expected net benefits between immunological FOBT and CTC5 induced uncertainty in the choice of the optimal strategy. Probabilistic sensibility analysis then suggested that below a willingness to pay (WTP) per life-years gained (LYG) of 8,587 €/LYG, CTC10 was optimal, while CTC5 would be preferred beyond a WTP of 8,587 €/LYG.

P. Chauvin (✉) · J.-M. Josselin
Faculty of Economics, University of Rennes 1-CREM CNRS UMR6211, 7 place Hoche CS 86514,
35065 Rennes Cedex, France
e-mail: pauline.chauvin@univ-rennes1.fr

D. Heresbach
Gastroenterological Department, University Hospital of Rennes, University of Rennes I, 2, rue Henri Le Guilloux,
35033 Rennes Cedex, France

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Introduction

Colorectal cancer (CRC) is the second cause of cancer-related mortality in France [1] as well as in most of the western countries. Clinical evidence has soon demonstrated that the removal of precancerous lesions (called adenoma) and the detection of early asymptomatic CRC would enable to improve prevention and survival rates [2]. Consequently, several programs of CRC mass screening are already implemented and are regularly assessed. In France, for instance, since 2002, the average risk population for CRC is invited every 2 years for screening with the Hemoccult test, which is a guaiac fecal occult blood test (FOBT) [3]. Often criticized for its lack of accuracy, this test could be soon replaced by an immunological FOBT. This new strategy would enable a better detection of the precancerous and cancerous lesions, but it would also induce a higher rate of positive tests for healthy subjects, hence generating more "useless" and costly control colonoscopies. Recommended by the Council of the European Union [4], these FOBT screening strategies are implemented or at pilot stage in several countries in Europe such as Italy [5] or the Netherlands [6].

Concurrently, an innovative screening method is now receiving growing attention, namely computed tomography colonography (CTC). This new technology uses computed tomography data to generate three-dimensional images of the colon and rectum. Although more expensive than the

previous tests, its promising performances in terms of accuracy make it a realistic competitor. A few cost-effectiveness analyses have already concluded that CTC could be a cost-effective screening strategy only if adenoma greater than 6 mm would be removed [7–9]. However, these studies made the assumption that the reference strategy was the now hypothetical no-screening situation.

Since the biennial guaiac FOBT is now implemented in several countries, the empirical study presented here defined it as the reference strategy. Compared with it, we assessed the cost-effectiveness of the following alternatives: biennial immunological FOBT, CTC every 10 years (CTC10), or CTC every 5 years (CTC5). Only adenomas over 6 mm were removed in both CTC screening strategies. The incremental net benefit (INB) framework was used to describe the results of our modeling. Indeed, the comparison of multiple alternatives is easier with the INB than with the usual incremental cost-effectiveness ratio (ICER) approach [10]. We thus estimated the intervals of values of willingness to pay (WTP) for which successive strategies are the most cost-effective. Uncertainty surrounding our results was then considered.

Materials and method

Modeling

From the perspective of a third-party payer, we compared four screening strategies on a hypothetical cohort of 100,000 average-risk subjects from 50 to 80 years old. Partially observed Markov models were used in order to formalize the competing strategies with 1-year cycles. Simulations were specifically programmed with MATLAB® software. The Markov signal model for the four screening strategies is presented in Fig. 1.

In Fig. 1, single-circled states describe the screening procedure. They are transitional states through which subjects can go during one cycle before stopping over in a bold- or a double-circled state for at least the complete length of a cycle. In order to simplify the framework, the state "death due to natural attrition" is not represented in the figure but is taken into account in the modeling for subjects in bold- or double-circled states. The bold-circled state is an absorbing state. This absorbing state is actually a nested partially observed Markov model. The subset of the cohort entering the latter model comprises patients with either screened (detected by the screening method) or interval (revealed by symptoms) lesions. Patients entering the treatment Markov state can evidence all stages of adenomas (specifically, low-risk and high-risk adenomas) and cancer (from stage 1 to stage 4). The total colonoscopy confirmation test enables such distinctions and allows to identify patients accordingly as they enter the nested treatment Markov model. More details are provided in the description of the model parameters. Except in the case of death (attributable to CRC or to natural attrition), these patients undergo a follow-up colonoscopy every 5 years. This colonoscopic examination is renewed five times or until patients are 80 years old. The model handles patients according to the grade of their colorectal disease with its specific morbidity, mortality, and associated costs. The corresponding Markov model is again specifically programmed with MATLAB® software.

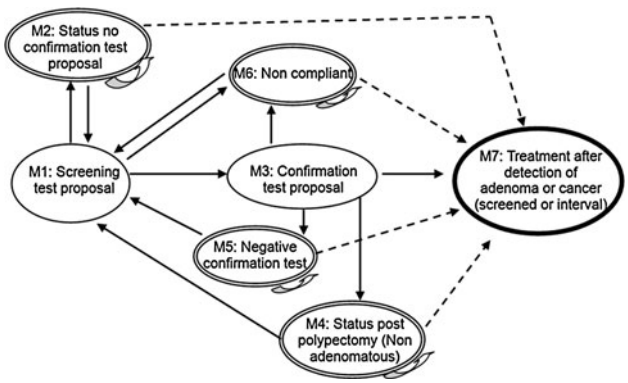

Fig. 1 Markov signal model. *Dotted arrows* refer to interval lesions

For guaiac and immunological FOBT strategies, a total colonoscopy confirmation test is proposed if the screening test is positive. As guaiac and immunological tests are performed every 2 years for patients 50 to 74 years of age, patients with a positive screening test and a negative confirmation test or a simple removal of non-adenomatous polyps are excluded from the next screening procedure. For CTC strategies implemented every 5 or 10 years, patients are invited to undergo a confirmation test when a polyp over 6 mm is detected. Depending on participation and the results of this confirmation test, patients enter states from M4 to M7. Until the next screening procedure, patients in double-circled states remain in their Markov states except in case of transitions due to an interval lesion or to natural attrition. Transition probabilities of the two embedded Markov models are calculated from epidemiological and screening parameters.

Model parameters

Model parameters were obtained from published international data. Key parameters are presented in Tables 1 and 2. The other parameters are available in the appendix. Parameters such as prevalence, incidence, or mortality rate were differentiated according to gender [22, 23]. We thus implemented two simulations (one for each gender) from the same model using the gender proportions in the French

Table 1 Summary of epidemiological and cost parameters used in the base case

Parameter	Value	References
Size distribution of polyps (<6 mm/≥ 6 mm) (%)		
Non-adenomatous polyps	86/14	[11]
Low-risk adenomas	85/15	
High-risk adenomas	9/91	
Annual transition rates (%)		
From <6 mm to ≥6–9 mm	2	[9]
From low-risk adenoma to high-risk adenoma	1.5	[12]
From high-risk adenoma to stage I CRC (male/female)	3.95/4.38	[13]
From stage I CRC to stage II CRC	30	[9]
From stage II CRC to stage III CRC	45	[12]
From stage III CRC to stage IV CRC	50	[12]
Annual CRC symptom detection rates, (stage II/III/IV) (%)	22/60/90	[12]
Five-year survival (stage I/II/III/IV) (%)	94/80/47/5	FRANCIM [31]
Costs (€)		
Guaiac test	16	[14]
Immunological test	23	
Virtual colonoscopy	129	[15]
Optical colonoscopy	789	
Optical colonoscopy with polypectomy of non-adenomatous polyps	920	
Optical colonoscopy with polypectomy of adenomas (50–69/≥70 years old)	1,629/3,598	
Optical colonoscopy with diagnosis of cancer (50–69/≥70 years old)	2,626/4,857	
Complication (bleeding or perforation)	7,223	
Treatment costs of colorectal cancer stage I	17,664	[16]
Treatment costs of colorectal cancer stage II	20,551	
Treatment costs of colorectal cancer stage III	29,125	
Treatment costs of colorectal cancer stage IV	35,195	

Table 2 Key test characteristics used in the base case [reference]

Parameter	Guaiac FOBT [3, 17]	Immunological FOBT [3, 17]	CTC [3, 18]	Optical colonoscopy [19–21]
Sensitivity adenomas 1–5 mm (%)	2	5	48	74
Sensitivity adenomas 6–9 mm (%)	5	10.1	70	87
Sensitivity adenomas ≥10 mm (%)	12	22	85	98
Sensitivity cancers (%)	40	70	85	98
Specificity (%)	98	95	91/93/97 (1–5 mm/ 6–9 mm/≥10 mm)	1
Complication rate (%)	n.a	n.a	n.a	0.22
Screening compliance (%)	42	42	42	n.a
Compliance after positive screening test (%)	n.a	n.a	n.a	90.7

n.a not available

population from 50 to 54 year old (provided by the national statistics office, INSEE, data 2006).

Our model made the usual assumption that all cancers derive from pre-existing adenomas. Adenomas can appear every year according to an age- and gender-specific incidence rate [23]. They can then evolve at annual transition rates estimated in the literature. These rates depend on the size and the type of adenoma (low or high risk) [9, 12, 13]. CRC can go through four stages at an annual rate: carcinoma in situ (stage I), local cancer (stage II),

regional cancer (stage III), and distant cancer (stage IV). We also take into account non-adenomatous polyps. Those polyps never degenerate into cancer, but only biopsies enable to set them apart from adenoma. Patients with a non-adenomatous polyp can also have an adenoma or a cancer.

Characteristics and costs of the screening and confirmation tests are also summed up in Tables 1 and 2. The adherence rate to screening was assumed to be the same for each round of screening, for each strategy and equal to 42%. The latter percentage was observed in a pilot population-based screening program where the average-risk population of twenty-three French districts was invited to undergo a guaiac FOBT [3]. Only patients in FOBT strategies who had a positive screening test and a negative colonoscopy or a removal of non-adenomatous polyps were not invited for the next round. They were thus temporarily associated with a 0% adherence rate.

Finally, since we adopted the perspective of a third-party payer, all costs are direct costs. Costs for colonoscopies and CTC were taken from the 2007 French national cost standard (*Echelle Nationale des Coûts*) [15]. This is the French classification for Diagnosed Related Groups (DRG). Every group has a GHM (*Groupe Homogène de Malades*: Homogenous patients group) code that can be converted into an average cost. Since CTC is not explicitly referenced in the coding, its cost was approximated by the item "abdominal and pelvis CT scan with intravenous contrast agent cost", which amounts to 128.66€. Costs of FOBT tests and treatment of CRC were based on published data [14, 16]. FOBT and treatment costs were inflated to 2007 values using the medical care component of the consumer price index available at INSEE Web site. Calculations are available in the appendix. Finally, effectiveness was measured by life-years gained (LYG). Both effectiveness and costs were discounted at the standard 3% rate.

Incremental net benefit analysis

Cost-effectiveness analysis can be implemented through two analytical frameworks: the INB and the ICER. Both are computed with the differential cost and effectiveness associated with a policy shift from the reference strategy to its alternative. In order to briefly describe those two frameworks, we define variables E_i and C_i, respectively, as the discounted effectiveness and cost for strategy i. For instance, for a policy switch from guaiac strategy (denoted G) to immunological strategy (denoted IM), the differential cost can be written as $(C_{\mathrm{IM}} - C_{\mathrm{G}})$. Differential effectiveness amounts to $(E_{\mathrm{IM}} - E_{\mathrm{G}})$. The ICER is thus $\mathrm{ICER}(\mathrm{G} \rightarrow \mathrm{IM}) = (C_{\mathrm{IM}} - C_{\mathrm{G}})/(E_{\mathrm{IM}} - E_{\mathrm{G}})$ €/LYG and is expressed in monetary units per effectiveness units. Decision making is based on the comparison with WTP. We rather used here the INB because of its easier interpretation in case of multiple alternatives and its statistical properties when analyzing uncertainty [10]. It is expressed in monetary terms and describes the net benefit of investing in an alternative strategy rather than in the reference strategy. Considering again the previous policy switch from guaiac strategy to immunological strategy, the INB can be written as $\mathrm{INB}(\mathrm{G} \rightarrow \mathrm{IM}) = \mathrm{WTP} \times (E_{\mathrm{IM}} - E_{\mathrm{G}}) - (C_{\mathrm{IM}} - C_{\mathrm{G}})$. The INB is thus a function of WTP, but it does not require a priori specifying its value. It puts the third-party payer in a position to compute the INB according to its own WTP or range of WTP. In case of multiple screening alternatives, the optimal strategy maximizes the INB [24].

Probabilistic sensitivity analysis (PSA) with Monte Carlo simulation techniques was then implemented in order to handle parameter uncertainty and consequently output uncertainty. After associating each parameter with a probability distribution, modeling was carried out 10,000 times with a random draw from these distributions for each simulation (Table 5 in the appendix provides information about parameters and their associated probability distribution). The discount rate and the time horizon were excluded from the PSA as they are parameters that cannot be sampled and therefore cannot be associated with a probability distribution [25]. Following [25], we assumed that cost parameters are log-normally distributed and that frequencies are beta-distributed. For each strategy, PSA results are represented by a cost-effectiveness acceptability curve (CEAC). This curve expresses the probability for a strategy to be optimal over a given range of WTP [24].

Results

Model validation

Validation of the model was carried out by comparing simulation results with actual data obtained from an INVS (the French institute for public health surveillance) study [26] and from published clinical trials' data [27, 28].

First, we estimated the mortality due to CRC per 100,000 person-years and compared it with INVS observations [26]. Estimated mortality rates due to CRC were rather close to INVS observations when the no-screening strategy was implemented. Nevertheless, they were slightly underestimated. Figure 4 in the appendix illustrates these mortality curves. However, this underestimation has to be nuanced as INVS built these mortality rates on the average- and the high-risk French population, while our model only regards the average-risk population, i.e., the population considered for mass screening.

In order to further validate the model, we compared positivity rates derived by simulations with those of

published studies [27, 28]. The positivity rate is the percentage of positive screening tests over the total number of screening tests. The model provided positivity rates for FOBT tests that are comparable to those of published clinical trials: with a 2.85% positivity rate for guaiac FOBT, our modeling is consistent with the 2.4% positivity rate observed in a clinical trial based on an average-risk population of 10,673 subjects [27]. The same study found a positivity rate between 2.4 and 6.9% for immunological FOBT, while our model anticipated a 6.28% positivity rate. Similarly, a 13% positivity rate was observed for a CTC screening campaign for average-risk subjects in a clinical trial [28], while our model yields 11% or 12% positivity rates depending on CTC frequency.

Base-case results

Table 3 describes the outcomes of the four simulated strategies for a cohort of 100,000 patients from 50 to 80 years old.

Biennial guaiac FOBT yielded the lowest positivity rate with 2.85% of positive tests, while, at the opposite, CTC10 had the greatest rate with 12.01%. After a positive test, patients were invited to undergo a colonoscopy. Even though CTC10 had the greatest positivity rate and biennial guaiac the lowest, the number of colonoscopies involved by the screening procedure was about the same for these two strategies. The 10-year frequency offset this high positivity rate. As to the total number of colonoscopies, the implementation of CTC10 would keep the total number of confirmation examinations stable, which can be an important argument in the case of a health care system that would not be able to handle a significant increase in the number of procedures. Conversely, CTC5 induced an increase in colonoscopy of 47% and immunological FOBT an increase of 80%.

The distribution of CRC according to their stage was also significantly dependent upon the implemented strategy. CRC are either symptomatic or detected during the screening process or during the follow-up for treated patients. The 10-year interval between each screening proposal for CTC10 seemed to be too long relative to the natural history of the CRC, leading to late CRC detection: 50% of detected CRC were stage III or IV cancers. Conversely, immunological FOBT led to the earliest detection rate with only 32% of detected CRC of stage III or stage IV cancers. CTC5 kept the distribution stable compared with guaiac FOBT (but with fewer cases at each stage). Although immunological FOBT yielded an early detection of CRC, it resulted in the lowest prevention rate (11%) compared with CTC5 (30%) or CTC10 (18%). This relatively poor performance might be due to its lack of accuracy, leading to more missed precancerous lesions than with CTC strategies.

The reference strategy, guaiac FOBT, was the least expensive and the least effective. Then, CTC10 induced the lowest increase in costs and the lowest increase in effectiveness compared with guaiac FOBT. Finally, immunological FOBT was dominated by CTC5, which was both more effective and less expensive.

Table 3 Base-case results

	Guaiac FOBT	Immunological FOBT	CTC10	CTC5
Positivity rate	2.85%	6.28%	12.01%	11.13%
Number of colonoscopy procedures	35,600	64,075	37,090	52,351
Due to the screening procedures	12,390	26,504	12,800	21,579
Due to symptomatic CRC	2,751	1,864	2,681	1,917
Due to the follow-up of treated patients	20,459	35,708	21,608	29,535
Number of diagnosed CRC	3,934	3,494	3,245	2,747
Distribution of CRC[a] according to their stage				
Stage I	21%	34%	13%	22%
Stage II	37%	34%	36%	35%
Stage III	33%	25%	38%	33%
Stage IV	10%	7%	12%	10%
CRC prevention rate (reference Guaiac)[b]	–	11%	18%	30%
Total cost, €[c]	110,555,295	129,881,829	111,074,826	127,905,581
Life-years gained[c]	–	2,744	684	2,771

[a] Either symptomatic or detected during the screening process or during the follow-up for treated patients

[b] Prevention rate of a strategy *j* compared to guaiac = (total number of CRC in guaiac − total number of CRC in *j*)/(total number of CRC in guaiac)

[c] Discounted at 3%

The range of WTP values for which each strategy can be optimal is described in Table 4. Guaiac FOBT was optimal until the WTP of the third-party payer reached 760 €/LYG. This WTP corresponds to the ICER of moving from the reference strategy to CTC10. Below this threshold, no alternative strategy generated health gains that could offset its extra cost. From a WTP of 760 €/LYG to 8,063 €/LYG, CTC10 became the optimal strategy. Finally, CTC5 saved more discounted life-years than CTC10 and yielded the highest INB from a WTP of 8,063 €/LYG.

Univariate sensitivity analysis

Univariate sensitivity analyses were first performed in order to cope with methodological uncertainty about the discount rate and the time horizon. Results are presented in Table 4. Whatever the methodological option, CTC10 was never dominated. At the opposite, depending on these methodological choices, the other three strategies may be either dominated or subject to extended dominance.

Preference for the present was more favorable to FOBT tests. Indeed, for a discount rate of 5%, CTC10 is optimal for a much narrower range of WTP, while CTC5 no longer dominates immunological FOBT. CTC strategies are indeed characterized by high screening costs at 50 years old. For instance, at 50 years old, CTC10 cost 3.5 times more than guaiac FOBT. Discounting thus disadvantages these strategies compared with FOBT strategies, which induce higher treatment costs at a farther horizon.

The time horizon also had a significant impact on results. For a time horizon of 10 and 20 years, CTC10 dominated biennial guaiac FOBT. If we consider for instance a 10-year horizon, CTC10 would be advantaged since only one screening round would be performed for CTC10 relative to five for the guaiac test, thereby inducing higher costs for the latter. Conversely, CTC5 was subject to extended dominance for a short time horizon, providing less expected effectiveness with an ICER higher than that of immunological FOBT. Indeed, its effectiveness, mostly associated with early prevention, requires time to generate significant life expectancy differences. Finally, a long time horizon including patients up to 90 years old brought results where no strategy was either dominated or subject to extended dominance.

Univariate sensitivity analysis was also conducted for participation rates to CTC screening rounds. As no reliable information was available on CTC adherence rate during a mass screening program, screening adherence rate was assumed to be the same for every strategy in the base case. For this univariate sensitivity analysis, one thousand simulations were carried out where the adherence rate of CTC10 and CTC5 could vary from 0 to 100%. The adherence rate of both FOBT tests remained 42% in every simulation as it is an adherence rate obtained from a guaiac FOBT mass screening observations [3]. Variations in CTC adherence rate were positively correlated with both total costs and effectiveness of CTC strategies (see results in Fig. 2). CTC5 was dominated by guaiac FOBT for an adherence rate from 19 to 24%, while it dominated immunological FOBT for a narrow adherence rate from 41 to 45%.

Probabilistic sensitivity analysis

A PSA with 10,000 Monte Carlo simulations was carried out in order to test uncertainty in model parameters. CTC10, CTC5, and immunological FOBT had, respectively, a probability of 86, 100, and 98% to be more effective than the reference strategy. Similarly, they had, respectively, a probability of 53, 97, and 95.5% to be more expensive than guaiac FOBT. Cost-effectiveness results are illustrated by Fig. 3 and Table 4. Diagram (a) plots the

Table 4 Base-case and sensitivity analysis results, optimal strategy according to WTP value (€/LYG)

	Guaiac FOBT	CTC10	CTC5	Immunological FOBT
Base case (BC)	[0; 760]	[760; 8,063]	[8,063; + ∞ [	D
Methodological uncertainty				
Discount rate (BC = 3%)				
0%	D	[0; 4,974]	[4,974; + ∞ [	D
5%	[0; 3,494]	[3,494; 10,971]	[10,971; 20,129]	[20,129; + ∞ [
Time horizon (BC = 30 years)				
10 years	D	[0; 7,746]	SED	[7,746; + ∞ [
20 years	D	[0; 5,957]	[5,957; 38,011]	[38,011; + ∞ [
40 years	[0; 2,497]	[2,497; 7,810]	[12,673; + ∞ [	[7,810; 12,673]
Monte Carlo simulations	D	[0; 8,587]	[8,587; + ∞ [	D

D dominated

SED subject to extended dominance

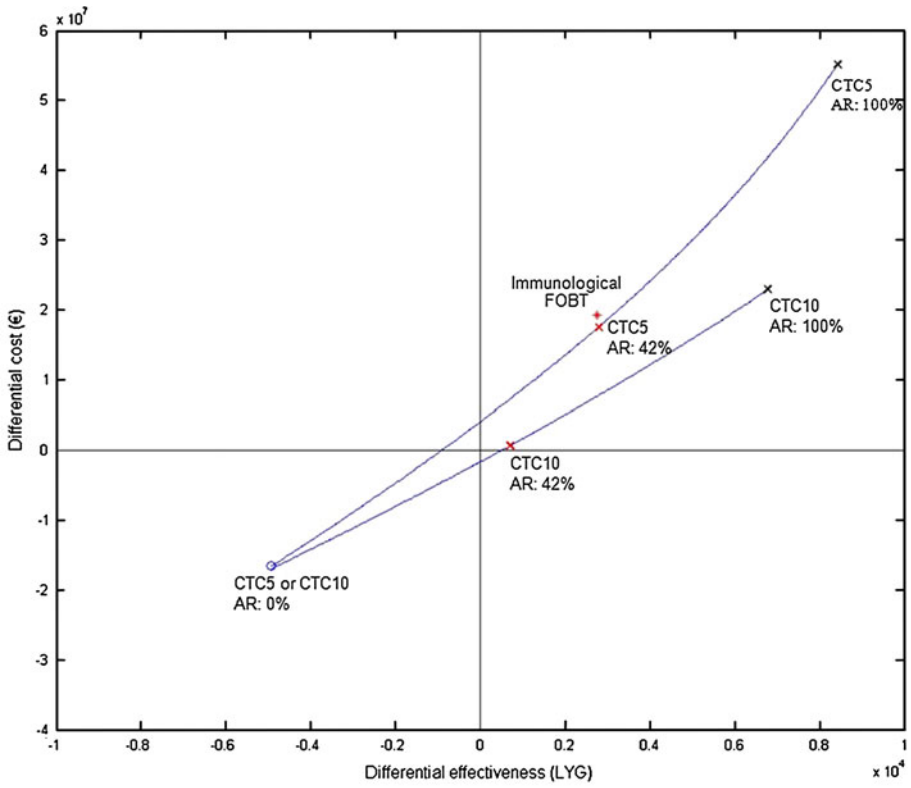

Fig. 2 Univariate sensitivity analysis for CTC adherence rate in CEA plan with guaiac FOBT as reference strategy. Adherence rate is denoted as AR

expected INBs as functions of WTP, while uncertainty is described in a CEAC for each strategy in diagram (b). The optimal strategy is now the strategy with the highest expected INB. Table 4 provides ranges of WTP for which strategies are optimal according to expected costs and expected effectiveness. These optimal strategies can also be determined from diagram (a). The optimal strategy for a given WTP is the one with the uppermost INB curve. Guaiac FOBT was now dominated by CTC10. Until the WTP of the third-party payer attained 8,587 €/LYG, CTC10 was the optimal strategy. Afterward, CTC5 yielded the greatest INB. Immunological FOBT was still dominated by CTC5. Dominations can be observed in diagram (a) of Fig. 3: the INB of guaiac FOBT and immunological FOBT are never the uppermost line.

The PSA also demonstrated that no strategy had a probability to be optimal higher than 70% (see Fig. 3 diagram (b)). This uncertainty was due to the fact that guaiac FOBT and immunological FOBT, although dominated, had a significant probability to be optimal, respectively, for a WTP below 10,000, and between 10,000 and 60,000 €/LYG.

Discussion

Our cost-effectiveness analysis aimed at assessing the potential of alternative mass screening strategies when biennial guaiac FOBT is already implemented in average-risk population. We considered three alternative screening policies: biennial immunological FOBT, CTC every 10 years, and CTC every 5 years.

Our topic has already been investigated notably by [8], who provided a detailed analysis where different frequencies for CTC screening tests were compared. They described CTC5 as a cost-effective alternative to colonoscopy screening. However, FOBT tests were not considered, and no PSA was carried out. Both CTC and FOBT tests were considered by [29] and [30]. The first study concluded that CTC was cost-effective compared with the FOBT strategy. The second study observed that CTC10 was equally likely to be cost-effective versus guaiac FOBT. However, no information was given on the organizational consequences of the competing strategies.

Our own PSA suggested that if a guaiac FOBT national screening program is already implemented, when resources are limited, CTC10 could enhance the effectiveness of the program. Moreover, relatively few additional confirmation tests (i.e., colonoscopies) would be required. However, replacing guaiac FOBT with CTC10 (or CTC5) would generate a significant change in the organization of the screening program since it would involve radiology as well as gastroenterology resources. Feasibility (organizational) studies still have to ensure that there would be no shortage of equipment and qualified staff.

When there is a high level of resources and a corresponding willingness to dedicate it to a CRC screening

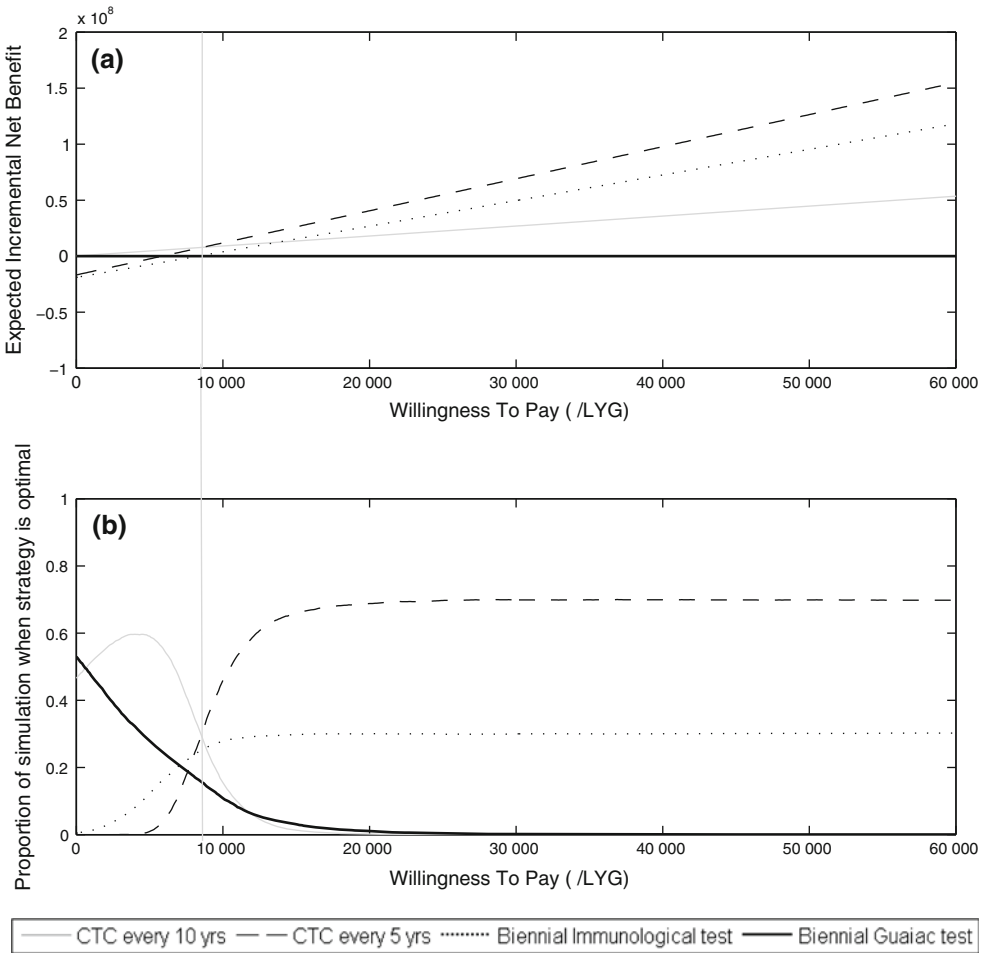

Fig. 3 Results of the PSA presented in terms of **a** expected incremental net benefit as a function of willingness to pay. **b** Cost-effectiveness acceptability curves

program, biennial immunological FOBT and CTC5 strategies are significantly more effective and more expensive than the biennial guaiac test. These two strategies provided very close expected net benefits, which prevents the cost-effectiveness analysis from setting them apart. However, differences remained as these strategies involved very different organizational patterns. On the one hand, CTC5 allowed a better prevention rate and a lower number of colonoscopies than immunological FOBT (such colonoscopies implying heavy care). It would thus put less pressure on the supply of these procedures. On the other hand, immunological FOBT follows the same organizational track as the guaiac strategy, which could facilitate its implementation. In spite of its lack of accuracy, the biennial frequency of FOBT enables an early detection and thus relatively good survival rates.

Another aspect of the organizational dimension of the problem that was not modeled in this study is the waiting time between the screening test and the confirmation test. This waiting time could also have a significant impact on the effectiveness of the competing strategies. For instance, future feasibility studies should verify whether the health care system can handle the 80% increase in the number of colonoscopies induced by the immunological strategy. Otherwise, the organizational effectiveness of immunological FOBT could be hindered, which would give increased relevance to CTC screening techniques.

A further limitation of our study is that we did not include sigmoidoscopy in our analysis even though it is recognized in some European countries as a mass screening strategy for CRC, notably in the United Kingdom. Indeed, in France, this technology is not currently considered by health authorities as a potential replacement of guaiac FOBT in mass screening campaigns.

Modeling constraints obviously imply that our study evidences limits. We shall now try to point out a few of them. One limitation concerns data, which are not obtained from a systematic literature review but rather rest on selected and prominent research published in medical journals. The process of "selection" of relevant data thus implies expertise in the medical field, and even more precisely in gastroenterology. It nevertheless remains that there is indeed a potential bias resulting from this method of data search. Another strong assumption relates to the adherence rate to screening. The base-case model used French data from FOBT screening campaigns. Univariate

sensitivity analysis of compliance to CTC screening demonstrated that this assumption can have significant impact on cost-effectiveness results. Still, both settings assumed constant adherence over time, which is unrealistic to a certain extent. Anyhow, since mass screening is being more and more developed in an increasing number of countries, analysts will probably have a clearer view in a decade or so. Until then, it remains difficult to precisely establish the loss rate from one campaign to the next.

A series of limitations specifically relate to CTC strategies. A first one has to do with the CTC screening techniques which include radiological investigations and thus expose patients to radiations. Since the study object of the model is mass screening, exposure to radiations should be a concern, especially for CTC5, the radiological screening strategy with the highest test frequency. Introducing side effects like this one in the model would require a precise knowledge of the incidence rate of complications due to radiations. Since we still lack data and background on this topic, radiological side effects have not been taken into account, though admittedly they affect both the cost and the effectiveness dimensions of the analysis. A second limitation associated with CTC screening relates to extra-colonic findings during the clinical investigation. They are not considered here. In practice, however, the cost of their follow-up could be significant. Nevertheless, the modeling and measurement of the costs and benefits of following up such findings remain an open question. In particular, one must take into account the possibility that extra-colonic findings would not become clinical during the patient's lifetime. In the absence (to our knowledge) of consensus guidelines on this subject, we were not able to conceive an adequate modeling of extra-colonic findings. If CTC techniques were to be increasingly used, this would become a relevant track for further research.

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Conflict of interest Authors do not report any conflict of interest associated with this paper.

Appendix 1: Parameters of the model

See Table 5.

Table 5 Parameters of the model

Variable	Base case	Min.	Max.	Standard deviation	Probability distribution	Parameters of the distribution[a]		Reference base case
Prevalences (50 year old)								
Males								
Non-adenomatous polyps	38.48%	28.86%	48.10%	4.91%	Beta	37	60	[22]
Low-risk adenomas	11.36%	8.52%	14.20%	1.45%	Beta	54	424	
High-risk adenomas	6.94%	5.21%	8.68%	0.89%	Beta	57	766	
Carcinomas	1.07%	0.80%	1.34%	0.14%	Beta	61	5,621	
Local cancers	0.02%	0.01%	0.02%	0.0024%	Beta	61	323,379	
Regional cancers	0.02%	0.01%	0.02%	0.0023%	Beta	61	341,352	
Distant cancers	0.02%	0.01%	0.02%	0.0019%	Beta	61	409,647	
Females								
Non-adenomatous polyps	40.33%	30.25%	50.41%	5.14%	Beta	36	54	[22]
Low-risk adenomas	7.05%	5.29%	8.81%	0.90%	Beta	57	752	
High-risk adenomas	3.81%	2.86%	4.76%	0.49%	Beta	59	1,492	
Carcinomas	0.49%	0.37%	0.61%	0.06%	Beta	61	12,420	
Local cancers	0.02%	0.01%	0.02%	0.0020%	Beta	61	384,036	
Regional cancers	0.01%	0.01%	0.02%	0.0018%	Beta	61	438,916	
Distant cancers	0.01%	0.01%	0.02%	0.0015%	Beta	61	512,089	
Annual incidence rates (age dependent)								
Low-risk adenoma								
History (males)								

Table 5 continued

Variable	Base case	Min.	Max.	Standard deviation	Probability distribution	Parameters of the distribution[a]		Reference base case
None								[23]
50–59	7.84%	5.88%	9.80%	1.00%	Beta	57	665	
≥60	8.26%	6.20%	10.33%	1.05%	Beta	56	625	
Low-risk adenoma								
50–59	14.06%	10.55%	17.58%	1.79%	Beta	53	322	
≥60	14.29%	10.72%	17.86%	1.82%	Beta	53	315	
High-risk adenomas								
50–59	14.20%	10.65%	17.75%	1.81%	Beta	53	318	
≥60	15.38%	11.54%	19.23%	1.96%	Beta	52	285	
History (females)								
None								[23]
50–59	5.39%	4.04%	6.74%	0.69%	Beta	58	1,020	
≥60	5.34%	4.01%	6.68%	0.68%	Beta	58	1,030	
Low-risk adenoma								
50–59	10.14%	7.61%	12.68%	1.29%	Beta	55	489	
≥60	14.94%	11.21%	18.68%	1.91%	Beta	52	297	
High-risk adenomas								
50–59	10.25%	7.69%	12.81%	1.31%	Beta	55	482	
≥60	6.77%	5.08%	8.46%	0.86%	Beta	57	788	
High-risk adenoma								
History (males)								
None								[23]
50–59	0.25%	0.19%	0.31%	0.03%	Beta	61	24,462	
≥ 60	0.48%	0.36%	0.60%	0.06%	Beta	61	12,682	
Low-risk adenoma								
50–59	0.67%	0.50%	0.84%	0.09%	Beta	61	9,050	
≥60	1.36%	1.02%	1.70%	0.17%	Beta	61	4,396	
High-risk adenomas								
50–59	2.56%	1.92%	3.20%	0.33%	Beta	60	2,279	
≥60	0.96%	0.72%	1.20%	0.12%	Beta	61	6,279	
History (females)								
None								[23]
50–59	0.31%	0.23%	0.39%	0.04%	Beta	61	19,704	
≥60	1.00%	0.75%	1.25%	0.13%	Beta	61	6,023	
Low-risk adenoma								
50–59	0.51%	0.38%	0.64%	0.07%	Beta	61	11,928	
≥60	1.30%	0.98%	1.63%	0.17%	Beta	61	4,605	
High-risk adenomas								
50–59	2.05%	1.54%	2.56%	0.26%	Beta	60	2,876	
≥60	2.26%	1.70%	2.83%	0.29%	Beta	60	2,597	
Size distribution of polyps								
Non-adenomatous Polyps								[11]
<6 mm	86.00%	81.70%	90.30%	4.39%	Beta	53	9	
≥6 mm	14.00%							
Low-risk adenomas								
<6 mm	85.00%	80.75%	89.25%	4.34%	Beta	57	10	
≥6 mm	15.00%							
High-risk adenomas								
<6 mm	9.00%	7.20%	10.80%	1.15%	Beta	56	565	
≥6 mm	91.00%							

Table 5 continued

Variable	Base case	Min.	Max.	Standard deviation	Probability distribution	Parameters of the distribution[a]		Reference base case
Annual transition rates								
From <6 mm to ≥6–9 mm	2.00%	1.50%	2.50%	0.26%	Beta	60	2,951	[9]
From low-risk adenoma to high-risk adenoma	1.50%	1.13%	1.88%	0.19%	Beta	61	3,975	[12]
From high-risk adenoma to localized cancer								
Male	3.95%	2.96%	4.94%	0.50%	Beta	59	1,435	[13]
Female	4.38%	3.29%	5.48%	0.56%	Beta	59	1,282	
From early to late cancer	30.00%	22.50%	37.50%	3.83%	Beta	43	100	[9]
From localized cancer to regional cancer	45.00%	33.75%	56.25%	5.74%	Beta	33	41	[12]
From regional cancer to distant cancer	50.00%	37.50%	62.50%	6.38%	Beta	30	30	[12]
CRC symptom detection rates (annual)								
Localized cancer	22.00%	16.50%	27.50%	2.81%	Beta	48	169	[12]
Regional cancer	60.00%	45.00%	75.00%	7.65%	Beta	24	16	
Distant cancer	90.00%	67.50%	100.00%	8.29%	Beta	11	1	
Five-year survival								
Carcinomas	94.00%	70.50%	1	7.53%	Beta	8	1	FRANCIM [31]
Local cancers	80.00%	60.00%	1	10.20%	Beta	11	3	
Regional cancers	47.00%	35.25%	58.75%	5.99%	Beta	32	36	
Distant cancers	5.00%	3.75%	6.25%	0.64%	Beta	58	1,109	
Guaiac FOBT parameters								
Sensitivity to adenomas <6 mm	2.00%	1.00%	5.00%	1.02%	Beta	–	–	[17]
Sensitivity to adenomas 6–9 mm	5.00%	5.00%	13.70%	2.22%	Beta	5	91	
Sensitivity to adenomas ≥9 mm	12.00%	8.90%	27.50%	4.74%	Beta	6	40	
Sensitivity to cancers	40.00%	25.00%	50.00%	6.38%	Beta	23	35	
Specificity	98.00%	95.00%	99.00%	1.02%	Beta	183	4	
Immunological FOBT								
Sensitivity to adenomas <6 mm	5.00%	2.00%	7.50%	1.40%	Beta	–	–	[17]
Sensitivity to adenomas 6–9 mm	10.10%	7.50%	24.00%	4.21%	Beta	5	45	
Sensitivity to adenomas ≥9 mm	22.00%	16.00%	48.00%	8.16%	Beta	5	19	
Sensitivity to cancers	70.00%	50.00%	87.00%	9.44%	Beta	16	7	
Specificity	95.00%	92.50%	98.00%	1.40%	Beta	228	12	
Virtual colonoscopy parameters								
Sensitivity to polyps <6 mm	48.00%	25.00%	70.00%	11.48%	Beta	9	9	[18]
Sensitivity to polyps 6–9 mm	70.00%	55.00%	84.00%	7.40%	Beta	26	11	
Sensitivity to polyps ≥10 mm or cancer	85.00%	79.00%	91.00%	3.06%	Beta	115	20	
Specificity to polyps <6 mm	91.00%	89.00%	95.00%	1.53%	Beta	317	31	
Specificity to polyps 6–9 mm	93.00%	91.00%	95.00%	1.02%	Beta	581	44	
Specificity to polyps ≥10 mm or cancer	97.00%	96.00%	97.00%	0.26%	Beta	4 337	134	
Optical colonoscopy sensitivity								
Non-adenomatous polyps	73.00%	63.00%	81.00%	4.59%	Beta	68	25	[19]
Polyps 1–5 mm	74.00%	70.00%	79.00%	2.30%	Beta	269	95	
Polyps 5–9 mm	87.00%	80.00%	92.00%	3.06%	Beta	104	16	
Polyps ≥10 mm. or cancer	98.00%	92.00%	99.00%	1.79%	Beta	59	1	
Screening compliance								
Virtual colonoscopy	42.00%	31.10%	54.20%	5.89%	Beta	29	40	[3]
Optical colonoscopy after positive CTC	90.70%	81.63%	1	4.69%	Beta	34	3	[20]
Complication rate of optical colonoscopy	0.22%	0.17%	0.28%	0.03%	Beta	61	27,815	[21]
Costs (€)								

Table 5 continued

Variable	Base case	Min.	Max.	Standard deviation	Probability distribution	Parameters of the distribution[a]		Reference base case
Guaiac FOBT	16.4	12.3	20.45	2.09	Log normal	2.8	0.13	[14]
Immunological FOBT	23.1	17.3	28.85	2.94	Log normal	3.1	0.13	
Virtual colonoscopy	128.7	97.0	161.6	16.49	Log normal	4.9	0.13	[15]
Optical colonoscopy	779.0	591.8	986.25	101	Log normal	6.7	0.13	
Optical colonoscopy with polypectomy of non adenomatous polyps	911.0	690.0	1,150	117	Log Normal	6.8	0.13	
Optical colonoscopy with polypectomy of adenomatous polyps								
50–69 years old	1561.0	1221.8	2036.25	208	Log normal	7.4	0.13	
70 years old	3610.0	2698.5	4497.5	459	Log normal	8.2	0.13	
Optical colonoscopy with diagnosis of cancer								
50–69 years old	2579.0	1969.5	3282.5	335	Log normal	7.9	0.13	
70 years old	4766.0	3642.8	6071.25	620	Log normal	8.5	0.13	
Complication (bleeding or perforation)	7341.0	5417.3	9028.75	921	Log normal	8.9	0.13	
Costs of colorectal cancer care by stage								
Carcinoma	17664.1	14692.7	20635.43	1,516	Log normal	9.8	0.09	[16]
Local cancer	20551.2	17283.9	23818.52	1,667	Log normal	9.9	0.08	
Regional cancer	29125.2	23609.8	34640.68	2,814	Log normal	10.3	0.10	
Distant cancer	35194.6	29346.0	41043.26	2,984	Log normal	10.5	0.08	

[a] For beta distributions, parameters α and β are computed from methodological recommendations of [17]. Likewise, parameters μ and σ for lognormal distributions

Appendix 2: Calculation of inflated costs

See Table 6.

Table 6 Base-case cost and inflated cost from the medical care component of the consumer price index (year of reference: 2007)

Costs parameters	Cost	References	Year of the cost estimation	IPC[b] (medical care component)	Inflated costs (year 2007)
Guaiac test	16.3	[14]	2006	103.42	16.36
Immunological test	23		2006	103.42	23.08
Virtual colonoscopy	128.66	CCAM no. ZCQH002[a]	2007	103.8	128.66
Optical colonoscopy	789	GHM no. 24K28Z[a]	2007	103.8	789.00
Optical colonoscopy with polypectomy of non-adenomatous polyps	920	GHM no. 24K26Z[a]	2007	103.8	920.00

Table 6 continued

Costs parameters	Cost	References	Year of the cost estimation	IPC[b] (medical care component)	Inflated costs (year 2007)
Optical colonoscopy with polypectomy of adenomas (50–69/≥70 years old)	1,629	GHM no. 06M09V[a]	2007	103.8	1,629.00
	3,598	GHM no. 06M09W[a]	2007	103.8	3,598.00
Optical colonoscopy with diagnosis of cancer (50–69/≥70 years old)	2,626	GHM no. 06M05V[a]	2007	103.8	2,626.00
	4,857	GHM no. 06M05W[a]	2007	103.8	4,857.00
Complication (bleeding or perforation)	7,223	GHM no. 06C04V[a]	2007	103.8	7,223.00
Treatment costs of colorectal cancer stage I	17,596	[16]	2004	103.4	17,664.07
Treatment costs of colorectal cancer stage II	20,472		2004	103.4	20,551.20
Treatment costs of colorectal cancer stage III	29,013		2004	103.4	29,125.24
Treatment costs of colorectal cancer stage IV	35,059		2004	103.4	35,194.62

[a] Taken from the 2007 French national cost standard [15]

[b] Available at INSEE website: http://www.indices.insee.fr/bsweb/servlet/bsweb?action=BS_SERIE&BS_IDBANK=000637733&BS_IDARBO=06000000000000

Appendix 3: Model validation

Validation of the model was carried out by comparing simulation results with observed data obtained from INVS (the French institute for public health surveillance) and with published clinical trials.

Mortality due to CRC

Compared with INVS statistics [26], estimations of mortality per 100,000 person-years when no screening is implemented per gender:

Our simulated results were rather close to observed mortality rates due to CRC, but they slightly underestimated this rate. However, this underestimation has to be moderated as INVS built these mortality rates on the average- and the high-risk French population, while our model only regards the average risk population, i.e., the population considered for mass screening (See Fig. 4).

Positivity rate of screening tests

The model provided positivity rates for FOBT tests that are comparable to those of published clinical trials:

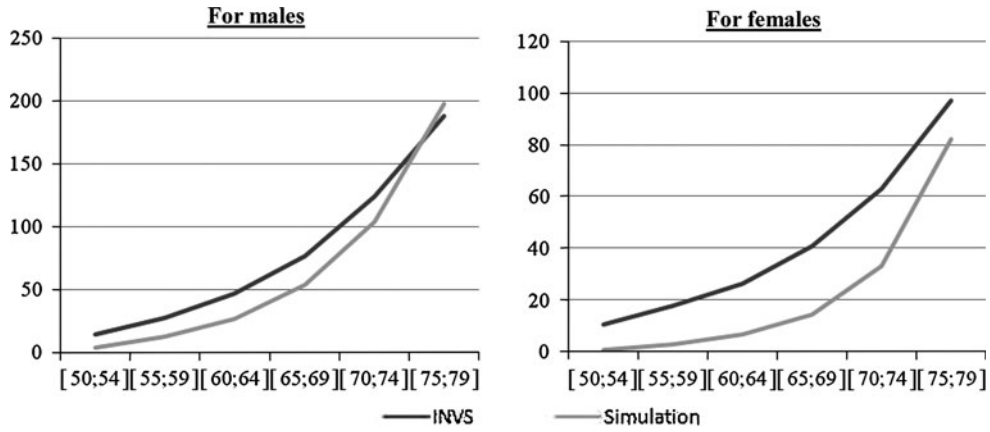

Fig. 4 Mortality due to CRC per 100,000 person-years

- Guaiac FOBT: with a 2.85% positivity rate, our modeling is consistent with the 2.4% positivity rate observed in a clinical trial based on an average-risk population of 10,673 subjects [27].
- Immunological FOBT: the same study [27] found a positivity rate between 2.4 and 6.9%, while our model anticipated a 6.28% positivity rate.
- CTC: a 13% positivity rate was observed for a CTC screening campaign for average-risk subjects in a clinical trial [28], while our model yields 11% or 12% positivity rates depending on CTC frequency.

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