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Cost-effectiveness modeling of colorectal cancer: Computed tomography colonography vs colonoscopy or fecal occult blood tests

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ABSTRACT

Objectives: To assess the cost-effectiveness of three colorectal-cancer (CRC) screening strategies in France: fecal-occult-blood tests (FOBT), computed-tomography-colonography (CTC) and optical-colonoscopy (OC).
Methods: Ten-year simulation modeling was used to assess a virtual asymptomatic, average-risk population 50–74 years old. Negative OC was repeated 10 years later, and OC positive for advanced or non-advanced adenoma 3 or 5 years later, respectively. FOBT was repeated biennially. Negative CTC was repeated 5 years later. Positive CTC and FOBT led to triennial OC. Total cost and CRC rate after 10 years for each screening strategy and 0–100% adherence rates with 10% increments were computed. Transition probabilities were programmed using distribution ranges to account for uncertainty parameters. Direct medical costs were estimated using the French national health insurance prices. Probabilistic sensitivity analyses used 5000 Monte Carlo simulations generating model outcomes and standard deviations.
Results: For a given adherence rate, CTC screening was always the most effective but not the most cost-effective. FOBT was the least effective but most cost-effective strategy. OC was of intermediate efficacy and the least cost-effective strategy. Without screening, treatment of 123 CRC per 10,000 individuals would cost €3,444,000. For 60% adherence, the respective costs of preventing and treating, respectively 49 and 74 FOBT-detected, 73 and 50 CTC-detected and 63 and 60 OC-detected CRC would be €2,810,000, €6,450,000 and €9,340,000.
Conclusion: Simulation modeling helped to identify what would be the most effective (CTC) and cost-effective screening (FOBT) strategy in the setting of mass CRC screening in France.

1. Introduction

Colorectal cancer (CRC) fulfills the recommended criteria for setting up mass screening programs. First, CRC represents a serious public health threat. With >800,000 new cases annually, CRC is the second cause of death by cancer in industrialized countries [1]. Disease is often advanced at diagnosis and, for stage III, the 5-year survival rate does not exceed 50% after surgery alone, and 65–70% after adjuvant chemotherapy. Second, the natural history of CRC includes a long latent period during which normal epithelium is transformed into adenoma and then adenocarcinoma. Colonic adenomas are the precursors of 80–90% of colorectal cancers [2,3]. Fortunately, most of them never progress to cancer, but, when progression occurs, it is thought to take at least 5–15 year [4]. Third, during the latent period, effective treatment consisting of endoscopic removal of all polyps, can be proposed with optical-colonoscopy (OC) follow-up at regular intervals every 3–5 years depending on the polyp type. This strategy decreased the CRC incidence among patients who underwent OC surveillance after the removal of colonic adenomas of 76–90% [5,6].

For patients at high (personal or familial history) and very high (genetic syndrome) risks, OC remains the best screening method that enables polyp detection and removal in one procedure. For the average-risk population, the best screening procedure is still being debated with contrasting US and European approaches. OC is

Abbreviations: CRC, colorectal cancer; CTC, computed tomography colonoscopy; FOBT, fecal occult blood tests; OC, optical colonoscopy; QALY, quality-adjusted life years.

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an invasive approach with high associated cost (anesthesia or sedation) that fails to fulfill the criteria defining a screening test for such a population however OC is proposed as a screening option in USA and in screening programs in Poland and Germany [7,8]. In most of the other European country, the fecal occult blood test (FOBT) every 2 years for 50–74 year olds is proposed to the average-risk population. A positive test leads to OC. Although the effectiveness of this approach has been demonstrated [9–12], it relies on the good programme sensitivity of the accumulated biennial screening rounds and not on the test sensitivity which is quite low. This supposes a good compliance of the screened population during the whole duration of the screening which is not the case in some European countries [9,13–15] probably because psychological barriers to FOBT screening are high.

Computed tomography colonography (CTC), also called virtual colonoscopy, is a now established imaging technique, which has the potential to provide a relatively noninvasive diagnostic evaluation of the colon with good patient acceptability. Moreover, CTC can be performed quickly and without sedation. Recently, numerous clinical and technical advances have enabled CTC to become a potential option for CRC screening. Previous cost-effectiveness analyses using a Markov model comparing CTC using data coming from up-to-date technique studies (fecal tagging, trained readers) with OC found that CTC was the most cost-effective and safest screening option [16,17]. However, considering that the screening programs of most of the European countries concerning the average-risk population are based on FOBT, it is rather studies comparing CTC to FOBT that are necessary. One cost effectiveness study comparing CTC (every 10 years) and biennial FOBT for colorectal cancer screening from the perspective of the United Kingdom National Health System (UK NHS) found that CTC was cost effective [18] however other studies comparing CTC to FOBT are still needed in different health systems and with a CTC performed every 5 years as commonly recommended [19] to evaluate the potential impact of CTC on public health.

The objective of this study was to use a simulation model to assess cost, effectiveness, and cost-effectiveness of 10 years of screening for CRC with CTC vs FOBT and OC in the average-risk population >50 years old in France.

2. Method

2.1. Model framework

In medical decision-making, models synthesize evidence from multiple sources (i.e., the literature, registries, historical databases, expert opinion, etc.) to estimate short, intermediate or long-term costs relative to the outcomes of various diagnostic or therapeutic strategies. Creating a model involves the use of mathematical language to link selected parameters in a mathematical formula. The model currently used is a Markov model but the structure of that model did not consider variations of current medical practices in diagnostic screening over the long term. A more sophisticated approach uses simulation models that are advanced decision-making analytical methods that take into account real-life variability with the use of a random-number generator and various parameter-distribution laws rendering the model highly robust. This type of model becomes especially relevant in the absence of convergent published or unpublished data or when very long-term studies are too difficult to conduct.

Three independent screening strategies were devised and programmed to take into account the entire distribution of costs and test-procedure sensitivity for each predefined parameter according to specific distribution laws [20]. The defined population entered into the three screening strategies was a cohort of subjects >50 years old. The natural incidence of CRC after 50 years of age was applied to the remaining population which was not participating in the screening program. The no-surveillance strategy included also potential incomplete OC.

OC screening strategy simulates 10-year screening for CRC with OC. The model begins by separating between “no screening” and “screening” during the 10 years. If OC is negative, the next OC is planned for 10 years later. If OC detects and removes at least one advanced adenoma, defined as a polyp >10 mm or with villous components (>25% of the adenoma surface) or with high-grade or severe dysplasia [6], OC are then scheduled every 3 years. For non-advanced adenomas, OC are then planned every 5 years. If the first OC was normal no more OC was performed in the studied period.

FOBT screening strategy simulates 10-year screening for CRC with FOBT (processed without rehydratation) as the first-line diagnostic test; hence each individual undergoes five FOBT during the 10 years screening. In case of positive FOBT, OC is performed for confirmation. In accordance with the 2004 screening campaign in Burgundy, France [9], when FOBT is negative, FOBT is scheduled every 2 years. When FOBT is positive, OC is prescribed. In this model, we considered that all patients with positive FOBT would undergo OC. As for the OC screening strategy, when OC is negative, FOBT will no longer be prescribed and another OC will be scheduled 10 years later. When OC detects and removes at least 1 polyp, OC are then planned every 3 years if it was an advanced adenoma or every 5 years for a non-advanced type.

CTC screening strategy simulates 10-year screening for CRC with CTC as the first-line diagnostic test followed by OC for positive test confirmation. When CTC is negative, the next CTC is scheduled 5 years later; hence each individual undergoes two CTC during the 10 years screening. When CTC is positive with detection of fewer than three polyps <6 mm, the next CTC is programmed 3 years later [19,21]. CTC detection of $\geq$3 polyps $\leq$6 mm or $\geq$1 lesion $\geq$10 mm, led to OC. Such a patient was considered to be at high risk for polyp recurrence, making CTC screening no longer justified and reassignment to OC screening mandatory. As for the OC screening strategy, when OC is negative, the next OC is planned 10 years later; when OC detects and removes at least 1 advanced adenoma, the OC are scheduled every 3 years or, for a non-advanced polyp, every 5 years.

Simulation models consuming large amounts of computer-processing time, powerful workstations with parallel-processors and adapted programming languages (DScript language, DecisionPro 4.1 software) were used to develop this model.

2.2. “Effectiveness” end points

To avoid the lack of sensitivity of outcomes, such as “life years saved”, and classical methodological limitations of “utility” indicators often presented in modeling studies generating quality adjusted life years (QALY: “cost-utility analyses”), the “rate of remaining CRC” defined as screened-and-undiagnosed and unscreened-and-undiagnosed CRC, was proposed as a clinically meaningful outcome to provide a real and robust “cost-effectiveness analysis” which is expressed as “cost per CRC avoided” over 10 years. OC, FOBT and CTC screening strategies were simulated 11 times using different adherence rates from 0% (none of the population was screened) to 100% (the entire population was screened) with 10% increments.

2.3. Data sources

Effectiveness data were taken from published sources in French and English (Table 1). When available, data concerning the French population were used preferentially. When the true value of a parameter was uncertain, reported ranges were used. For each uncertain variable (positive-test rate and cost parameters), all

Table 1
Basic costs and transition probabilities used in this simulation model.

Simulation-model parameters	Minimum	Mean	Maximum
Basic costs (€ 2007)			
OC	550	–	650
FOBT	9	–	16
CTC	–	160	–
Biopsy	–	29.10	–
GP consult	–	21	–
CRC	–	28,000	–
Transition probabilities[a]			
Prevalence of adenomatous polyps after positive OC	0.07		0.33
Annual CRC incidence between 50 and 70 years	0.0005		0.002
Positive OC rate for 1st screening[b]	0.034		0.324
Positive FOBT rate for 1st screening round[c]	0.018		0.038
Positive FOBT rate for subsequent screening rounds[d]	0.012		0.015
Positive OC rate (CRC or advanced adenomas) after positive FOBT[d]	0.267		0.319
FOBT false-negative rate for CRC	0.20		0.60
Positive CTC rate	0.079		0.323
Positive OC rate after positive CTC	0.040		0.459
CTC false-negative rate for polyps >10 mm		0.10	

[a] Given the present CRC status, according to the results of the screening strategy used, the next screening-test result is independent of the former, i.e., it can change or stay the same, based on its probability distribution. These changes and the probabilities associated with them, or the probability of being in certain state given the previous one, are referred to as transition probabilities.

[b] Calculated as follows: (CRC incidence + adenomatous polyp prevalence) × true OC-positive rate).

[c] Rate calculated from data obtained from 1,800,000 people included in an FOBT-screening campaign in 12 French departments (http://www.snfge.asso.fr/03-Professionnels/0C-depistage-cancer-colique/pdf/rapport-groupe-tech-sur-depistage-mai-05.pdf).

[d] Data obtained during the 12-year campaign (six screening rounds) in Burgundy, France, that concerned around 40,000 people.

possible values between a reported minimum in one source and a maximum in another were randomly selected, and outcomes were calculated each time using 5000 Monte Carlo simulations. At the end of the simulation iteration process, the model generates three outcomes over the 10 years for each screening strategy: total medical costs, rate of overall remaining CRC and cost per CRC avoided. Distribution parameters, such as standard deviations (SD), are generated for each model outcome, enabling statistical analyses. This approach is considered a robust sensitivity analysis ("probabilistic sensitivity analysis") that takes into account the heterogeneity of published data and medical practices or fees.

Direct medical costs are expressed in Euros from the French national health-insurance perspective and are presented undiscounted using 2006 prices as the reference case scenario, according to French economic evaluation guidelines [22]. CRC medical management costs come from 2006 conducted estimation in the Île de France (region around Paris) [23]. The cost of biopsies was included for each positive OC, including the complication rate and the cost of consulting a general practitioner (GP) for each test prescription (Table 1).

The CRC incidence in France in 2000 was estimated to be 0.0391% for men and 0.0246% for women [24]. However, for the screened population between 50 and 70 years old, the annual cancer incidence ranges from 0.05% at 50 years to 0.20% at 70 years [25] in the USA. Those figures were retained for this study and no difference was made between the sexes. The cumulative incidence over 10 years was calculated using the following formula:

$$\text{Cumulative incidence over 10 years} = 1 - \exp[-10 \times \text{annual incidence}].$$

The prevalence of adenomatous polyps is not well known, but was estimated to be 7% between 45 and 49 years and between 20% and 33% after 65 years [26]. When a polyp is seen, the probability that it is adenomatous is between 50 and 75%. The annual transition rates from small polyp to large polyp and from large polyp to cancer were fixed at 1.5% and 5%, [3,27–32], respectively.

The positive-OC rate, when used as a CRC screening technique, is not known for the French population. In a recent study, Kim et al. [33] found 3.4% positive OC for advanced neoplasia for 3163 patients (mean age, 58.1 ± 7.8 years) who underwent screening for CRC. In addition, assuming no false-positive result, the positive-OC rate corresponds to the prevalence of CRC and adenomatous polyps multiplied by the true-positive rate of the screening technique for CRC and advanced adenomas. These data were not easy to obtain, because OC is considered the gold standard. However, comparison studies with the histological results, with a second OC or with clinical follow-up, suggest that the true OC-positive rate for CRC and advanced adenomas could vary from 94% to 97.7% [34–39].

The positive-FOBT rate was obtained from available data derived from the national screening campaign launched in 22 French departments in 2002 (http://www.snfge.asso.fr/03-Professionnels/0C-depistage-cancer-colique/pdf/rapport-groupe-tech-sur-depistage-mai-05.pdf) and from the preliminary screening campaign conducted in Burgundy from 1989 to 2000 [9]. The range of values obtained was in accordance with the dehydrated-FOBT positivity rate in two large, prospective, randomized studies performed in Nottingham, UK [10] and Fünen, Denmark [11]. False-negative dehydrated-FOBT values were considered to range from 20% to 60% for cancer and 90% for large polyps [40–42]. False-negative values of the subsequent tests conducted after a first false-negative test are not known and were considered in this model as the same as that of the first round.

CTC data were obtained from large studies performed in the USA. Rates of positive CTC, when used as the screening technique in a population over 50 years, ranged from 7.9% [33] to 32.3% [43]. False-negative CTC values for advanced adenoma differed widely from one study to another [33,43–46] and were highly dependent on the quality of the technique used. When radiologists are well trained, when the bowel are correctly prepared with fecal tagging and when modern CT devices are used, the false-negative rate for polyps >10 mm was around 10% and that for polyps >6 mm was around 30% [33,43,47,48].

3. Results

The remaining CRC rates per 10,000 persons after 10 years, according to the screening test and adherence rate are reported in Table 2. In the absence of screening (0% adherence rate), the remaining CRC rate after 10 years corresponds to the cumulative CRC incidence over this period and was calculated to be 123 cancers per 10,000 persons >50 years leading to an outlay of €3,440,000 to treat them. That rate declined for the three screening strategies as the adherence rate increased.

Table 2
Remaining CRC rate for 10,000 persons, total costs (in €) per person and mean cost (in €) per colorectal cancer avoided rate for the three screening strategies over 10 years.

Adherence	Remaining CRC rate			Total costs per person			Mean cost per CRC avoided[a]		
rate (%)	OC	FOBT	CTC	OC	FOBT	CTC	OC	FOBT	CTC
0	123	123	123	344 ± 3074	344 ± 3074	344 ± 3074	–	–	–
10	113	116	111	390 ± 2695	302 ± 2814	444 ± 3130	390 ± 2728	306 ± 2851	449 ± 3170
20	102	108	100	578 ± 2948	349 ± 2948	568 ± 3230	584 ± 2982	353 ± 2982	574 ± 3266
30	91	98	87	661 ± 2716	380 ± 2976	534 ± 2724	668 ± 2747	384 ± 3008	539 ± 2750
40	81	90	75	698 ± 2274	323 ± 2650	555 ± 2373	703 ± 2295	326 ± 2676	560 ± 2394
50	70	82	63	801 ± 2028	328 ± 2563	558 ± 1797	806 ± 2044	330 ± 2585	561 ± 1809
60	60	74	50	934 ± 1985	281 ± 2176	645 ± 1838	939 ± 1998	283 ± 2193	648 ± 1849
70	49	66	38	1046 ± 1803	292 ± 2107	686 ± 1372	1051 ± 1813	294 ± 2124	689 ± 1377
80	38	57	26	1176 ± 1733	260 ± 1792	803 ± 1571	1181 ± 1739	262 ± 1803	805 ± 1576
90	27	49	14	1255 ± 1320	273 ± 1708	857 ± 1239	1259 ± 1324	274 ± 1718	859 ± 1241
100	17	40	2	1375 ± 939	274 ± 1570	931 ± 781	1377 ± 941	275 ± 1578	931 ± 781

[a] Mean cost per CRC avoided rate over 10 years was calculated as follows: Ct/(1 − CRC rate), where Ct is the overall cost of the strategy (including that of CRC occurring in the unscreened population, 1 − P0). The "CRC rate" includes the rate of CRC that occurred in the unscreened population and those corresponding to the cumulative false-negative results of the screening method chosen over 10 years.

The mean total costs and mean cost per CRC avoided (i.e., cost-effectiveness) with corresponding standard deviations, calculated for each screening strategy according to an adherence rate ranging from 0% to 100% are reported in the same table. Except FOBT, the cost of both OC and CTC rose faster than the number of CRC avoided when the compliance increased. However for a given adherence rate, CTC screening was always the most effective but not the most cost-effective. FOBT was the least effective but the most cost-effective strategy because it is very inexpensive. OC achieved intermediate effectiveness but was the least cost-effective strategy. For instance, according to our simulation, without screening, the spontaneous cost would be €3,440,000 to treat 123 CRC in 10,000 persons >50 years. Using a realistic 60% adherence rate it would cost €2,810,000 with the FOBT strategy to prevent 49 CRC and to treat the 74 remaining CRC that occur anyway at the end of the strategy. Expenditure would reach €6,450,000 for the CTC strategy, which would prevent more ($n = 73$) and treat fewer ($n = 50$) remaining CRC. Compared to CTC, adopting the OC strategy would cost more €9,340,000 to prevent fewer ($n = 63$) and treat more ($n = 60$) remaining CRC. OC would be the least effective and the most expensive strategy if its adherence rate was 20% lower than for FOBT and CTC.

4. Discussion

Economic evaluations of healthcare technologies typically use models to make assumptions and generate data based on multiple sources to estimate the long-term costs and outcomes of new therapies [49]. With healthcare providers continuing to struggle with rising costs, sensitivity and specificity alone will no longer be the only criteria to be considered in evaluating the potential contribution of a new diagnostic test. When confronted with limited budgets in the early 1980s, healthcare payers and providers requested evidence of the value of new interventions in terms of economic and clinical benefits. Considering CRC diagnostic management, various current medical practices using specific diagnostic strategies can be identified and modeled. It is recommended that the data used be analogous to real-life benefits and that the clinical pathway selected be consistent with routine practices in the country for which the analysis is being conducted, as for our model, which used French national health-insurance data. For CRC, the screening strategy involves series of diagnostic tests. Our model incorporated variations of published data and medical practices for diagnostic test sequences and costs of sequential diagnostic alternatives over a 10-year period and calculated the overall costs and performance of each strategy. The remaining CRC rate was used as a clinically meaningful outcome to provide a real and robust cost-effectiveness analysis which is expressed as "cost per CRC avoided" over 10 years.

In mass screening for CRC, the size of the detected lesion is the most important criterion. Approximately 10–25% of lesions ≥1 cm are either high-grade dysplasias or carcinomas [28,50,51]. For small and intermediate polyps, the natural history is not entirely known, however the likelihood that polyps ≤5 mm are malignant is estimated to be ≪1% [29,50]. Thirty percent of intermediate polyps, <9 mm in a size are not adenomas [28,45] and, among the 6–9 mm adenomas, only 3–5% exhibit high-grade dysplasia [50,52]. Hence, CRC screening targets the lesion ≥10 mm. However, for screening purposes, it was proposed that 6 mm be retained as the minimum size for reporting polyps [21,53]. Our three screening strategies were based on those considerations. To design the OC screening strategy, we applied the American College of Gastroenterology guidelines [28] and those of the French National Society of Gastroenterology [54]. Concerning the FOBT strategy, when OC was negative after a positive FOBT, we considered that FOBT could remain positive for the next round of screening due to miscellaneous reasons, like hemorrhoids, thereby explaining why we decided, in this situation that FOBT would no longer be prescribed and a second OC would be performed 10 years later.

For this study, the remaining CRC rate was used as outcome criterion to avoid the lack of sensitivity of outcomes, such as "life years saved" or QALY, often used in cost-utility assessment which requires the use of "utility" scores (preference assessment) to generate QALY. Such economic evaluations are regularly published in the medical literature and are often inappropriately presented as cost-effectiveness studies, which may add to the confusion surrounding the two methods that are neither equivalent nor interchangeable. While real cost-effectiveness analyses compare costs with effectiveness criteria expressed in natural units of clinical outcome (e.g., a clinical event avoided), cost-utility analyses compare costs with a QALY indicator derived from patient preferences to construct a "utility" score. However, accumulating evidence suggests that the QALY indicator may yield divergent or inconsistent results depending on the utility assessment method used [55]. Given these limitations, we preferred a real cost-effectiveness analysis for the purpose of this model in which results are expressed in terms of costs per CRC avoided over 10 years. Two kinds of cost-effectiveness ratios could be theoretically calculated: mean cost-effectiveness ratios (mean cost divided by mean effectiveness – for each strategy) and incremental cost-effectiveness ratios (difference of costs between two strategies divided by difference in effectiveness between two strategies). Only mean cost-effectiveness ratios were presented in this analysis as this approach provided one ratio per strategy (mean cost per unit of effectiveness), and allowed a comparison of each strategy

with each other. Incremental cost-effectiveness ratios would have provided one single value for two strategies (mean cost per additional unit of effectiveness), which is usually very difficult to interpret without any reference cases. In addition, smaller the denominator is (very small difference in effectiveness), higher the ratio is, leading to potential large numbers, which remains totally theoretical. Because the linearity assumption between costs and effectiveness is validated in our simulation model, mean cost-effectiveness ratios can be calculated and appear clinically meaningful in this context.

Our simulation results provide useful information concerning public health policy. For a given adherence rate over 10 years, the CTC strategy appeared to be more effective than the other 2, to be more cost-effective than OC as soon as the test adherence was ≥20% and always less cost-effective than FOBT. The lower effectiveness of OC compared with CTC can be explained because we did not consider OC as a perfect test but with a false negative rate ranging from 2.7% to 6% [34–39] and because OC was performed only once during the screening program (10 years) while CTC was performed twice leading to an increase of its overall sensitivity (program sensitivity). In the literature CTC was shown in the US to have a better cost-utility in terms of years of life saved than OC particularly if diminutive polyps (<6 mm) was not reported [17] or when the CTC diagnostic sensitivity for polyps >1 cm was >83% and its costs was less than 60% of those of OC with a test adherence assumed to be 60% [25]. We found comparable results in our study with a test adherence ≥20% probably because the CTC cost is around 26% of OC cost (€160 vs €600) in France. Considering 60% adherence rate, CTC costs could increase by 55% of OC costs for equal cost-effectiveness.

FOBT was the least effective but, because of its extremely low cost in France, the most cost-effective strategy for all adherence rates. These results slightly differs from those obtained in the study of Lee et al. [18] from the perspective of the UK NHS which found like in our study that CTC screening every 10 years yielded greater health benefits (QUALYs and life years) than biennial FOBT but could be also cost saving. Those findings are probably not in contradiction with our observations. Results expressed, in our study, as "cost per CRC avoided" are closer to reality and more robust but they are difficult to compare to those of other studies based on years of life saved. FOBT mainly detects CRC that are more advanced than those seen by CTC, which is able to detect CRC and premalignant adenomatous polyps, probably making a difference in terms of years of life saved. Therefore, a higher FOBT cost-effectiveness compared to CTC in terms of "avoided CRC" might translate into to a lower cost-utility in studies using the number of years of life saved as the effective outcome criterion. The same remarks can be done with the studies based on that criterion which compared FOBT to OC [41,56–58] using Markov simulation models, and which found that FOBT was less effective and less cost-effective than OC.

To date the French health authority chose to introduce a cost-effective mass screening with acceptable, but as shown in our study, not optimal effectiveness based on FOBT. However, retaining the FOBT strategy for mass screening could be discussed if the compliance to FOBT, compared to the 2 other strategies, dramatically decreased with time impairing the program sensitivity that overcomes the low test sensitivity. Herein, we used adherence rates ranging from 10% to 100% to be able to compare the different strategies at different levels. The trial already performed in France showed an FOBT adherence rate around 50% [9], which was considered satisfactory mass screening but its relatively low level may reflect psychological aversion concerning stool manipulation by a large part of the population. However, the adherence rate for OC would perhaps be lower, as shown by Pariente et al. [59] who reported a rate as low as 39% in patients at high risk due to familial history. In addition, studies comparing the adherence rates of FOBT and flexible sigmoidoscopy reported differences ranging from 2% to 26% in favor of FOBT [60,61]. CTC would probably achieve a higher adherence rate than for OC because it has been shown in the Canadian population that the most preferred tests were noninvasive process [62] and because its acceptability appears higher [43]. Nonetheless, this adherence rate remains difficult to predict in the French population. Considering theoretical but realistic rates of 60% for CTC and 50% for FOBT, using the CTC instead of the FOBT strategy, would double the cost of the actual FOBT strategy (€3,170,000 more) to prevent 22 additional CRC in a population of 10,000 persons, given an incremental €144,090 per CRC gained, a figure that is considered expensive relative to most medical interventions [63,64].

Our simulations study has several limitations that must be acknowledged.

First, our study considered only, the sensitivity provided by landmark studies [33,43,47,48] using an up-to-date technique (well-trained radiologist, correct bowel preparation, modern CT scanners) which exceeded 80% and the question remains about the ability of community radiologist to reproduce these results. This point emphasizes performing CTC with an "up-to-date" technique must be taught before launching a mass screening program with this method.

Second, the remaining CRC rate used as clinically outcome did not take into account the stage of the cancer detected. In fact, FOBT is primarily effective at identifying CRC. Some premalignant adenomatous polyps may be detected, providing an opportunity for polypectomy and CRC prevention, but prevention in this setting is both limited and incidental (false-negative rate for polyps is around 90%) and is not the primary goal of CRC screening with FOBT. Hence, FOBT-detected CRC are more advanced than those found by CTC or OC, which are tests that detect CRC and premalignant adenomatous polyps, leading to probable differences in terms of prognosis at an individual level as discussed above.

Third, to simplify the calculation the subsequent adherence rates for OC, once FOBT or CTC was positive, were fixed at 100%. However, the true value seems to be closer to 90% [9,60]. In addition we considered that OC was always complete. Both assertions generated a slight, underestimation of the remaining CRC.

Fourth, for the same reasons the adherence rates for repeated FOBT and CTC were fixed at 100%, after the first test, which lead to an overestimation of program sensitivity for both tests, given the particular advantage of FOBT, which would have had a much poorer program sensitivity with a lower adherence rate due to its poor test sensitivity.

Fifth, we did not take into account in our model the extracolonic findings that may be discovered using CTC. To be exhaustive the cost of the extra workup associated with these findings should have been considered, but also the potential health gain that may result. Because we used the "number of CHC avoided" as final outcome this additional gain could not be considered in this study. Considering life-year as outcome Pickhard et al. [16] recently showed that in an hypothetical cohort of 100,000 adults ≥65 years old, CTC performed every 5 years resulted in 7786 life-year gained compared with 6032 life-year gained with 10-year OC mainly because of the prevention of the Aortic aneurysm rupture.

Sixth, we also neglected the cost generated by the complications that could occur with OC and CTC. The additional costs were not taken into account because they are very rare and their consideration would not have had any impact on the different strategies.

Lastly, we did not consider the recently published data [65–67] concerning the non-polypoid colorectal neoplasms. Using special techniques (chromoendoscopy), Soetikno et al. showed that the overall prevalence of those lesions could reach 9.35%, accounting for 15% of neoplastic lesions [66]. Those lesions are rarely seen with conventional OC and are usually missed by CTC. The use of chromoendoscopy, narrow band imaging or fluorescence endoscopy

could change the efficacy and consequently the cost-effectiveness of OC compared to CTC concerning the number of CRC avoided. New simulations taking into account non-polypoid colorectal neoplasms will have to be undertaken once data on them in western populations will become more available.

In summary, decision analysis using robust simulation models able to embody the range of the published data is a powerful tool that can help identify the most effective and cost-effective screening strategy. When the most effective differs from the most cost-effective strategy, a consensus conference must be organized and public health decisions have to be made. According to our results, FOBT, the current mass screening strategy in France, is the most cost-effective method but CTC is the most effective method designed to detect both early cancer and adenomatous polyps however at a high cost not acceptable today in France.

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