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Alimentary Tract

# Colon cancer prevention in Italy: Cost-effectiveness analysis with CT colonography and endoscopy

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**Abstract**

**Background.** Colorectal cancer (CRC) is a major cause of mortality in Italy. Although prevention of CRC is possible, its cost-effectiveness when applied to the Italian population is unknown. Recently, computerized tomographic colonography (CTC) has been proposed for CRC screening.

**Aim.** To compare the efficacy and cost-effectiveness of CTC screening in a simulated Italian population with those of colonoscopy and flexible sigmoidoscopy (FS).

**Methods.** The cost-effectiveness of different screening strategies was compared using a Markov process computer model, in which in a hypothetical population of 100 000 50 year-olds were investigated by CTC, colonoscopy or FS every decade. Outcomes were projected to the Italian national level.

**Results.** CRC incidence reduction was calculated at 40.9%, 38.2%, and 31.8% with colonoscopy, CTC and FS, respectively. As compared to no screening, all screening programs were shown to be cost-saving, allowing a saving of 11€, 17€, and 48€ per person with colonoscopy, FS and CTC, respectively. FS appeared to be less cost-effective than CTC, whilst colonoscopy appeared to be an expensive option as compared to CTC. Undiscounted national expenditure was calculated to be €1042489512, €1093268285, and €1198783428 for FS, CTC and colonoscopy, respectively, as compared to €695818078 without screening.

**Conclusion.** CRC screening is cost-saving in Italy, irrespective of the technique applied. CTC appeared to be more cost-effective than FS, and it may also become a valid alternative to colonoscopy.


*Keywords:* Colon cancer; Colonoscopy; Cost-effectiveness; Flexible sigmoidoscopy; Virtual colonoscopy

## 1. Introduction

Colorectal cancer (CRC) has become the most common malignancy in Europe with an estimated 258 000 new cases in 2000. The high cost of treatment represents a substantial economic burden on European societies [1,2].

Radiological and endoscopic techniques are able to prevent CRC through the removal of pre-malignant adenomas [3,4]. Among radiological procedures, computerized tomographic colonography (CTC) has been defined as an emerging screening test by the American Gastroenterology Association [5,6], with two recent meta-analyses showing a relatively high sensitivity of CTC for the detection of large adenomas and CRC [7,8].

Cost-effectiveness models allow comparison of the main outcomes of different screening tests, which culminate in broad variations in the natural history of a given disease and

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the accurateness of associated procedures as well as on related costs. The importance of these models is obviously emphasised when controlled trials comparing the efficacy and cost of different screening techniques are either lacking or too costly and lengthy to be practicable to perform. This is the case for CRC [9]. The only cost-effectiveness model applied to Italy in this field has shown a clear superiority of efficacy and costing of endoscopy over faecal occult blood testing [10]. However, such analysis was confined to a small Italian population, preventing broader extrapolation of its findings. No study has assessed the potential impact of CTC on CRC prevention in Italy.

The aim of the present study was to compare the efficacy and cost-effectiveness of CTC screening with those of colonoscopy and flexible sigmoidoscopy (FS) in a simulated population at average risk for CRC.

## 2. Methods

A mathematical Markov model was constructed in order to simulate a population of 100 000 Italian subjects at average risk of CRC followed up for 30 years between the ages of 50 and 80 years (see Appendix A). Screening was simulated by assessing the number of subjects diagnosed with an endoscopic or radiological lesion on the basis of the adherence and compliance to the test – colonoscopy, FS or CTC – and the accurateness of each procedure. For those patients diagnosed with an adenomatous polyp, follow-up programs were further simulated on the basis of the severity of the lesion. Screening was simulated with each procedure being performed once per 10 years starting at age 50. Main assumptions on the natural history of colorectal neoplasia and on the accurateness of the screening tests are given in Table 1. Efficacy of a screening test was defined as CRC incidence reduction observed in the screened population as compared to the population in which no prevention was simulated. The cost-effectiveness of a screening program was defined as the amount of additional expenditure necessary in order to save one additional life-year in comparison with no screening or other strategy (incremental cost-effectiveness ratio, ICER). Life-years saved were defined as the difference between the life-years lost in the less effective screening modality and those lost in the more effective program. A strategy was defined dominant when less expensive and more effective than the other. Both future costs and future life-years saved were discounted using an annual rate of 3%. Regarding costing for screening procedures, data were already available for the endoscopic examinations, but not for CTC. As such, an analytic assessment of CTC costing was performed, as shown in Appendix A.

### 2.1. Projections to the general population in Italy

In order to project the outcomes of our simulation on the Italian population, we assumed a steady state for population size and age distribution, represented by the year 2002 Italian census data [11]. Each age-specific model output, calculated by simulating a population at average-risk of CRC, was therefore multiplied by the number of people of that age in the Italian population and this corrected to represent the 75% of Italian adults at average-risk of CRC. Adding results for all ages under each strategy yielded national estimates. As already suggested [12], no discounting was used in these national projections since the model outputs in this scenario reflected all persons aged 50–80 years of age at a given point in time in the steady state as opposed to a cohort aging from 50 to 80 years over 50 years.

### 2.2. Sensitivity analysis

All variables of the model have been broadly varied among plausible ranges (Table 1) in order to compensate for the lack of more exact data on either the natural history of CRC or the accurateness of screening tests. Only those variables able to modify the relationship between the efficacies or cost-effectiveness of the different tests have been extensively reported.

## 3. Results

A total of 2735 CRC were diagnosed in the study population without screening, corresponding to a loss of 13240 cancer-related life years and €51434543 of CRC treatment cost. At baseline conditions with a 65% adherence and a compliance with repeating examinations of 80%, colonoscopy every 10 years appeared to be the most effective technique preventing 40.9% of CRC, whilst CTC resulted to be less effective than colonoscopy (38.2%), but more effective than FS (31.8%), corresponding to 3821, 3589, and 2945 life-years saved with the three techniques, respectively. This corresponds to a reduction of CRC mortality by 43%, 40.5%, and 33.5% with colonoscopy, VC and FS, respectively. As shown in Table 2, CTC and FS appeared to reduce the number of colonoscopies dramatically from 179052 to 63236 and 52048, respectively, corresponding to a 65% and 71% reduction as compared to colonoscopy screening. Fewer colonoscopies translate into fewer complications. Not only do CTC and FS reduce complication rates by 52.6% and 58.1% as compared to colonoscopy, but, more importantly, a similar reduction of 54.0% and 59.8% is achieved in those complications occurring in patients without an advanced lesion (i.e., advanced adenoma or early CRC), as shown in Table 2. Moreover, the number of polypectomies, and consequently patients sent to follow-up, appeared to be nearly two-fold higher in the colonoscopy screening arm when compared to CTC or FS.

The care of unprevented cancer was the only cost calculated in the simulated population without screening (Table 2). In the screening programs, endoscopic or radiological procedures accounted for 32%, 35% and 42.2% of the overall costs

Table 1
Baseline values applied in the model with related references

| Variable | Baseline value (range)[a] | Ref. |
|---|---|---|
| Natural history | | |
| Polyp prevalence at age 50, % | 15 (10–45) | [28,29] |
| New polyp rate, % per year | 1.9 (0.02–5.7) 50–60 years<br>3.3 (0.03–9.9) 60–70 years<br>2.6 (0.03–7.8) 70–80 years | [25] |
| Annual transition rate from ≤5 mm to 6–9 mm, % | 2 (0.02–7.8) | [30–34] |
| Annual transition rate from 6–9 mm to ≥10 mm, % | 2 (0.02–7.8) | [30–34] |
| Annual transition rate from ≥10 mm to early CRC, % | 3 (0.03–13) | [31] |
| Annual transition rate from early CRC to late CRC, % | 30 | [36] |
| Advanced ≥10 mm/advanced <10 mm rate,% | 90 | [18] |
| Polypoid/de novo rate of CRC cancerogenesis, % | 90 (70–100) | [27] |
| Annual transition rate to de novo cancer, % | Age specific-rate, 0.010–0.093 | |
| Mortality rate from early cancer, % for the first 5 years | 4 | [36] |
| Mortality rate from late cancer, % for the first 5 years | 8 | [36] |
| Screening tests | | |
| CTC sensitivity for ≤5 mm polyps, % | 48 (20–96) | [7] |
| CTC sensitivity for 6–9 mm polyps, % | 70 (42–98) | [7] |
| CTC sensitivity for ≥10 mm polyps, % | 85 (51–98) | [7] |
| CTC sensitivity for CRC, % | 95 (47–99) | [7] |
| CTC specificity, % | 86 (50–95) | [7] |
| Colonoscopy sensitivity for ≤5 mm polyps, % | 80 (50–96) | [43,44] |
| Colonoscopy sensitivity for 6–9 mm polyps, % | 85 (50–98) | [43,44] |
| Colonoscopy sensitivity for ≥10 mm polyps, % | 90 (60–98) | [43,44] |
| Colonoscopy sensitivity for CRC, % | 95 (70–99) | [43,44] |
| Colonoscopy specificity, % | 90 (70–100) | [43,44] |
| Sigmoidoscopy sensitivity for ≤5 mm polyps, % | 45 (30–90) | [18,19] |
| Sigmoidoscopy sensitivity for 6–9 mm polyps[b], % | 45 (27–63) | [18,19] |
| Sigmoidoscopy sensitivity for advanced polyps, % | 60–65[c] (36–75) | [18,19] |
| Sigmoidoscopy sensitivity for CRC, % | 60–65 (30–68) | [18,19] |
| Sigmoidoscopy specificity, % | 90 (18–100) | [18,19] |
| Adherence, % | 65 (1–100) | [38] |
| Compliance, % | 80 (1–100) | [15] |
| Colonoscopy bleeding, % | 0.0015 | [40] |
| Colonoscopy perforation, % | 0.002 | [41] |
| Polypectomy bleeding, % | 0.02 | [40] |
| Polypectomy perforation, % | 0.0038 | [41] |
| Sigmoidoscopy perforation, % | 0.00011 | [42] |
| Costs | | |
| Colonoscopy, € | 148.2 (0–500) | [39] |
| Sigmoidoscopy, € | 110 (0–300) | [39] |
| CTC, € | 100.9 (0–500) | Table A.1 Appendix A |
| Colonoscopy with polypectomy, € | 228.6 | [39] |
| Bleeding, € | 3.619 | [15] |
| Perforation, € | 10.790 | [15] |
| Late CRC treatment, € | 24.900 | [10] |
| Early CRC treatment, € | 14.940 | [10] |

[a] Range of values applied in the sensitivity analysis.
[b] Only not advanced adenomas.
[c] Due to the decreasing association between left-side adenomas and right-side neoplasia with aging, sigmoidoscopy sensitivity is supposed to be 65% at age 50 and 60% at age 60.

for FS, CTC and colonoscopy screening, respectively, whilst the cost of managing colorectal cancer decreased from the least to the most effective screening program. The higher cost of screening with colonoscopy as compared to CTC and FS appeared to be mainly related to the overall number of therapeutic procedures and to the higher cost of diagnostic colonoscopy as compared to that of CTC and FS (Table 1). The incremental cost-effectiveness ratio (ICER) allows comparison of each screening strategy with the preceding less effective option. When compared to a strategy of no screening, all the screening programs resulted as being cost-saving at the baseline conditions (negative ICER in Table 2), allowing a saving of €11, €17, and €48 per person with colonoscopy, FS and CTC, respectively. FS appeared to be dominated by CTC, being more costly and less effective, whilst colonoscopy appeared to be only slightly more expen-

Table 2
Main outcomes of the model for each of the baseline screening programs

| Variable | None | FS | CTC | Colonoscopy |
|---|---|---|---|---|
| Prevented cases of CRC, *n* | 0 | 869 | 1.045 | 1.118 |
| Prevented cases of CRC/total cases of CRC, % | 0 | 31.8 | 38.2 | 40.9 |
| Life-years saved | 0 | 2.945 | 3.589 | 3.821 |
| Reduction in mortality, % | 0 | 33.5 | 40.5 | 43 |
| Procedures, *n* | | | | |
| CTC | 0 | | 142.166 | |
| Sigmoidoscopies | 0 | 143.403 | | |
| Colonoscopies | 0 | 52.048 | 63.236 | 179.052 |
| Diagnostic (without polypectomy) | 0 | 31.059 | 39.335 | 136.462 |
| Therapeutic (with polypectomy) | 0 | 20.989 | 23.901 | 42.590 |
| Complications, *n* | 0 | 624 | 706 | 1.491 |
| Bleeding events | 0 | 466 | 537 | 1.056 |
| Perforations | 0 | 142 | 169 | 435 |
| Number of complications in pts. without advanced lesions | 0 | 580 | 658 | 1.443 |
| Costs, € | | | | |
| CTC | 0 | | 16.452.126 | |
| Sigmoidoscopy | 0 | 15.919.675 | | |
| Colonoscopy | 0 | | | 21.265.352 |
| Care for CRC | 51.434.543 | 33.808.734 | 30.410.433 | 29.095.051 |
| Total, € | 51.434.543 | 49.728.410 | 46.862.560 | 50.360.402 |
| ICER versus no screening, € | – | −579[a] | −1274[a] | −281[a] |
| FS, € | – | – | Dominated | 721 |
| CTC, € | – | – | – | 15.091 |

All techniques were considered to be repeated every decade in the simulated population from 50 to 80 years of age.
[a] Negative ICER values mean that these programs are cost-saving when compared to no screening (see text).

sive than FS (€721 per each additional life year saved). On the other hand, at baseline conditions, colonoscopy appeared to be a relatively expensive option as compared to CTC, the ICER being as much as €15091 (Table 2).

### 3.1. Sensitivity analysis

Accurateness for ≥6 mm polyps, initial adherence, costs and time interval appeared to be the main variables affecting the cost-effectiveness of the different screening options.

#### 3.1.1. Sensitivity for polyps ≥6 mm

A drop of baseline CTC sensitivity for ≥6 mm polyps by 39%, corresponding to a sensitivity of 52% for large polyps, was enough to raise the incremental cost-effectiveness, as compared to no screening, of CTC to that of colonoscopy. Regarding the ICER of colonoscopy as compared to CTC, it decreased to €5157€, €1960, and €148, assuming the sensitivity of CTC for large polyps to be 79%, 65%, and 55%, respectively. By reducing CTC diagnostic accurateness for >6 mm polyps, FS no longer appeared to be dominated by CTC after a 28% drop of the baseline CTC accurateness, corresponding to a sensitivity of 61% for large polyps. A drop in CTC sensitivity by 34%, corresponding to a sensitivity for large polyps of 55%, resulted in a dominance of FS over CTC, FS being less expensive (€49728410 vs. €50197256) and more effective (33.5% vs. 32% CRC incidence reduction) under these conditions.

#### 3.1.2. Compliance

Adherence to a screening program proved to be a major determinant of efficacy, although such an effect was equally distributed among the different techniques. Indeed, at 100% adherence, CRC prevention rates of colonoscopy, CTC, and FS rose to 64.3%, 60.2%, and 50.3% – corresponding to a 56% increase as compared to baseline – whilst a decrease of the adherence to 35% resulted in a 49% decrease in the efficacy for all the techniques. This corresponds to CRC prevention rates of 20.8%, 19.3%, and 15.9%, respectively. Interestingly, by only varying adherence to colonoscopy, a reduction of 7.6% – corresponding to an adherence of 60% – was sufficient to reduce the efficacy of this test to that of baseline CTC, whilst a further drop to 51% was needed in order to decrease colonoscopy efficacy to that of FS. At such compliance rates, colonoscopy was dominated by these techniques, being more costly and equally effective. Regarding adherence to CTC, a drop of 17% to an adherence value of 54% was necessary in order for the efficacy of FS to be equalled and no longer dominated by CTC.

#### 3.1.3. Costs

As shown in Table 2, the overall cost for all the CRC screening programs was less than that of CRC care in the simulation without screening. In order to equalise the cost of each of the screening programs to that of no screening, an increase of 10% in the cost of colonoscopy to €163, a rise of 21% in the cost of FS to €133, and an increase in the cost of CTC by as much as 62% to €163 was necessary.

Table 3
Projection of the model output on the Italian population at average risk for CRC

| Strategy | Costs, € | Cases of CRC, *n* | CRC prevention, % |
|---|---|---|---|
| No screening | 695818078 | 15385 | |
| Sigmoidoscopy | 1042489512 | 10556 | 31.4 |
| CTC | 1093268285 | 9551 | 37.9 |
| Colonoscopy | 1198783428 | 9142 | 40.6 |

Undiscounted cost of CRC treatment, number of CRC cases occurring with and without screening, and efficacies of baseline strategies have been reported.

An increase of CTC cost to €148 (+47%) worsened the ICER of CTC as compared to no screening to that of colonoscopy, with colonoscopy dominating CTC under this condition, being more effective and less costly. A rise in CTC cost to €136 (+36%) reduced CTC ICER (as compared to no screening) to that of FS, which was no longer dominated by CTC. Similarly, regarding FS cost, a reduction of 25% to €82 allowed such a technique to no longer be dominated by CTC in our model.

#### *3.1.4. Time interval*

If each test were performed every 5 years, CRC prevention rate would slightly increase to 43%, 41.2%, and 37.3% for colonoscopy, CTC and FS, respectively. Due to the substantial increase in examination-related costs, the ICER as compared to no screening would worsen to €2815, €974, €1735 for colonoscopy, CTC and FS, respectively. Interestingly, FS every 5 years would be dominated by colonoscopy every 10 years, being more costly and less effective, whilst the increased cost-effectiveness of CTC every five years as compared to colonoscopy every 10 years would be €76453.

### *3.2. Italian population projection*

Undiscounted cost of CRC treatment was calculated at €695818078 for the Italian population at average risk for CRC for the 15385 cases diagnosed without applying any screening between 2002 and 2032 (Table 3). Although a program of screening with FS appeared to be less expensive than CTC, it also resulted less effective, missing 1005 CRC at a saving of €50778773 (€50526 per unprevented CRC). On the other hand, CTC allowed a saving of €105515143 as compared to colonoscopy screening to be weighed up against a loss of 409 CRC (€257983 per unprevented CRC).

## 4. Discussion

The present model has shown for the first time that CRC screening in Italy is cost-saving when compared with no screening. Indeed, the overall costs of each of the simulated screening programs was far below that of no screening when discounted at a 3% rate. Such evidence should be regarded as a major breakthrough in Italian health policy, showing

Table 4
Comparison between Italian and US of the screening procedures, assuming a €/$ rate of 0.83

| Cost | CTC (€) | Sigmoidoscopy (€) | Colonoscopy (€) |
|---|---|---|---|
| Italy | 100.90 | 110.00 | 148.20 |
| US [14,15] | 396.70 | 332.50 | 577.60 |

that, irrespective of the CRC prevention screening strategy undertaken, the cost of implementation would be heavily rewarded by the savings made in CRC treatment care. It also means that the feasibility of mass screening depends on political, medical and personal awareness in the Italian society alone, and not related to economic burden. When comparing the data of such an Italian simulation with those applied to the US population [13], a striking difference is noted. Indeed, when the model is applied to US data, most of the screening techniques are cost-effective, but not cost-saving, meaning that any CRC screening implementation will take some resources away from other health investments. The discrepancy between Italian and US data is mainly related to the difference in cost of the screening procedures. In fact, comparing the costs assumed in our simulation with those from two previous US models by Sonnenberg et al. [14,15], it emerges that both endoscopic procedures and CTC are considerably more expensive in the private US system than in the Italian public health service (Table 4). However, it is sadly disappointing to note that, whilst in the US a decrease in CRC incidence has been achieved thanks largely to an increased diffusion of endoscopic screening in the past decade, no reduction has been documented in Italy, presumably due to a very low screening rate among the general population [16,17]. In short, an expensive screening program may turn out to be more cost-effective than a cheaper alternative when a higher compliance is obtained. Furthermore, we should point out that the relatively low reimbursement rates may limit widespread implementation of any screening programme in Italy, particularly in the radiological field, where CRC screening needs to compete with the higher reimbursement rates of other diseases. As previously suggested by Ladabaum for the US [12], we projected the undiscounted costs of the different outcomes of the simulation on the whole Italian population at average-risk for CRC. Such undiscounted evidence may provide an idea of the investment necessary at the present time in order to achieve the future saving. Ladabaum showed that in the US the overall undiscounted cost of screening programs was roughly 80% higher than that of no screening [12], whilst in Italy it resulted in an increase of only 50%. In other words, not only is CRC screening in Italy much less costly when projected and discounted over a long period of time, but it also requires a much smaller initial investment. However, the final cost might be slightly higher since our analysis did not include costs related to an eventual promotional campaign for CRC screening throughout the country, as well as the costs related to the loss of work for the screened patient, which may be of at least two days in the

case of either colonoscopy or CTC and FS requiring a further colonoscopy.

Two recent meta-analyses have shown a very high accuracy for large polyps and carcinomas from CTC [7,8]. Assuming such inputs, CTC appeared to be a very solid competitor to endoscopy in the screening setting. Indeed, if we assume that more than 90% of the advanced neoplasias are larger than 1 cm [18,19], CTC repeated every 10 years resulted similarly as effective as colonoscopy. Avoiding roughly 50% of the costs of the polypectomies for non-advanced adenomas due to the lower accuracy for small lesions, CTC also emerged as a more cost-effective option than endoscopy. However, the variation analysis also showed that even small modifications in the main assumption of the model could radically change the situation in favour of colonoscopy or, less likely, FS. Not surprisingly, with only small differences in our inputs, two previous simulations reached opposite conclusions, showing colonoscopy as a more cost-effective option than CTC [12,14]. However, even when taking these two models into account, CTC emerges as a good competitor to colonoscopy in CRC prevention, and it also demonstrates that the major determinants of such competition are the sensitivity for advanced lesions, the initial adherence, the relative cost of the procedures and the time interval. Sensitivity for large polyps is still a major point muddying the waters of diffuse implementation of CTC screening. Indeed, the high accuracy reported in the two available meta-analyses depends mainly on the dedicated settings in which most of the included studies came from [7,8]. On the other hand, other authorative multicentre studies performed in less dedicated centres have reached disappointing results. For example, if we assume in our model the very low values of CTC sensitivity for advanced polyps as reported by Cotton [20], colonoscopy turns out to be a preferred option over CTC in agreement with Ladabaum's data [12]. Similarly, our model confirms the high importance of adherence ascertained by the two previous models [12,14]. Even a 10–20% gradient in adherence in favour of CTC is sufficient for such a technique to be more effective and dominating over colonoscopy. The introduction of a prepless CTC with faecal tagging could therefore be a major point in favour of CTC [6]. It should also be noted that the baseline assumption of a 65% adherence to screening programs, although similar to previous models [12,14], may appear too optimistic when compared to previous population-based studies [21,22]. Importantly, it has been estimated that unless the population uptake of a screening programme is over 50%, the benefits of screening for the population are likely to be outweighed by the costs of implementing the programme [23]. Unfortunately, screening for bowel cancer may be handicapped by the taboo surrounding anything to do with bowels in general. Moreover, we simulated that all the patients with a polyp detected by CTC or FS will perform a colonoscopy. Any reduction of this compliance would heavily decrease the overall efficacy of these techniques, similarly to what has been reported for a positive faecal occult blood test which is followed up by colonoscopy in less than 80% of cases [24]. Regarding time interval, our analysis clearly confirmed that a screening program with CTC cannot afford to use more frequent scheduling of screening than a similar program based on colonoscopy, in agreement with Sonnenberg's data [14].

A high degree of ethical concern is involved in screening, which mainly relies on the offer of effective medical intervention to apparently healthy people. Since no medical procedure is without risks, screening exposes asymptomatic people to a potential hazard, more often than not affecting subjects who would never actually develop the preventable disease. From an ethical point of view, prevention of major screening-related complications or even death in healthy subjects is at least as critical as the reduction in disease morbidity in those few people actually affected by the disease. Our simulation does not only show that CTC reduces the overall number of complications by more than 50%, but more importantly that most of the latter would occur in those patients with an advanced polyp and not in those with a diminutive lesion as occurring with colonoscopy. In conclusion, our study showed that CRC screening based on cancer prevention is cost-saving in the Italian population, and that, among the less invasive tests, CTC is to be preferred to FS if high accuracy CTC for large polyps can be confirmed.

**Practice Points**

- Colorectal cancer screening in average-risk people is cost-saving in Italy.
- Although colonoscopy screening resulted to be the most effective, that based on CT colonography appeared to be more cost-effective.
- Flexible sigmoidoscopy was shown in our Markov model to be less effective and less cost-effective than CT colonography.
- Colon cancer screening in Italy appeared to be by far less expensive than in the US.

**Research agenda**

- Cost-effectiveness of colon cancer screening in high-risk Italian people is unknown.
- Cost-effectiveness of CT colonography without removal of diminutive polyps should be addressed.
- Identification of psychological barriers preventing a satisfactory compliance to screening programs is needed.

**Conflict of interest statement**
None declared.

## Appendix A

A mathematical Markov model was constructed on Microsoft Excel spreadsheets (Microsoft Corp., Redmond, Washington) in order to simulate a population of 100 000 Italian subjects at average risk of CRC followed up for 30 years between 50 and 80 years of age. In the simulation without any screening, representing the natural history of CRC ("natural history" model), people could abandon the model because of either CRC-related death or the age-specific natural attrition of the Italian population. The simulation of each screening program (colonoscopy, CTC and FS) consisted of a repetition of the "natural history model" in which a screening test was also included ("screening" model). On the basis of the adherence (initial compliance), compliance to repeated examinations, and the accurateness (sensitivity and specificity) for the different polyp type or cancer stage, the number of non-compliant people and of true- and false-positive and -negative patients for each lesion was computed. Non-compliant people were presented in a separate natural history model ("non compliant" model) from which they were not allowed to go back to screening. Patients with an adenomatous polyp were sent to two different follow-up programs according to the severity of the initial lesion. Such follow-up models were similar to the "screening" model, with the exception that the new polyp rates were increased in order to match the results from the National Polyp Study [25], and that the surveillance colonoscopy was planned every 5 years [4]. Those patients with a diminutive adenoma as initial diagnosis were allowed to go back to the "screening" model in the case of a negative surveillance endoscopy, whilst those with an initial ≥6 mm polyp remained in the "intensive follow-up" program until the end of the simulation (Fig. A.1).

Each of the considered models was constructed in order to assess the incidence and mortality for CRC, the number of endoscopic or radiological examinations, the number of the related complications, and the costs related to both CRC treatment, screening tests, and related complications. Moreover, multiplying the cases of CRC-related death for the age-specific life expectancy of the Italian population, the number of life-years lost for CRC was assessed. By comparing the "natural history" model and each of the 3 "screening" models (each of them also including the "non compliant" and 2 "follow-up" models) the main outcomes of the simulation

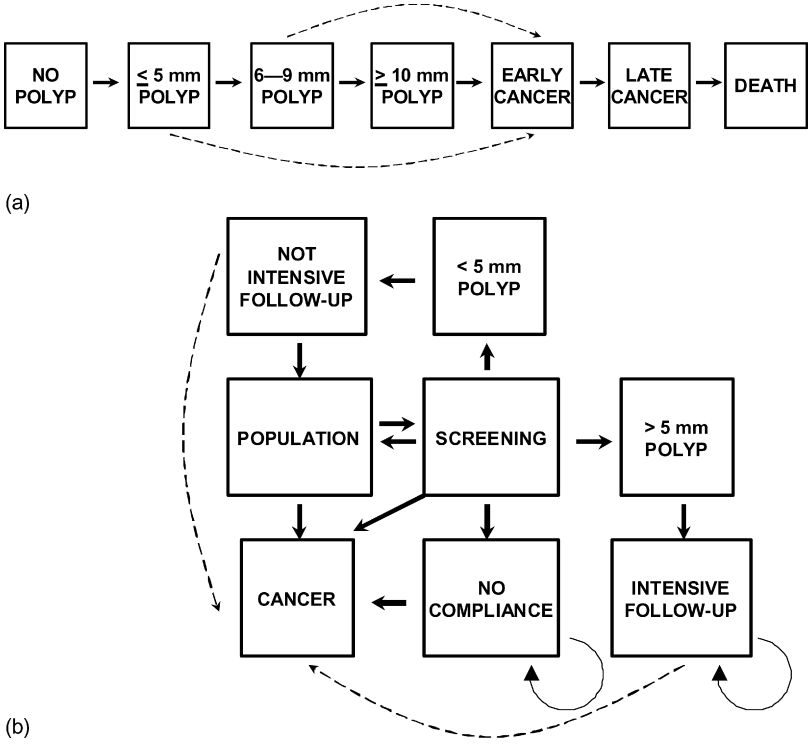


Fig. A.1. (a) The model has been constructed in order to simulate the progression from no lesion to CRC-related death through all the polypoid phases, and through early and late CRC stages. As shown by the bend arrows, it was assumed that early CRC could arise from <10 mm polyps in order to simulate the possibility of advance adenoma in such lesions. (b) The model simulates the transition of the population through consecutive yearly life-time cycles. At the selected timings (one-time, every decade or every 5 years), individuals are sent through the screening process, after which they may go back to the initial compartment if no lesion is detected, or they may enter into a follow-up if an adenoma is detected. Non-compliant people are considered to remain non-compliant until the end of the simulation. Those patients in follow-up for a diminutive polyp are allowed to go back to the initial compartment at the first negative endoscopy. Contrary, those in follow-up for a ≥6 mm polyp remain in the 5-year surveillance program until the end of the simulation.

were calculated. In order to provide the necessary input to the Markov model, several assumptions, mainly derived from the available literature, were needed regarding the natural history of CRC and the efficacy and cost of the screening tests.

We assumed 75% of the general population to be at average risk for CRC, and that 90% of CRC arise from polyps, the remaining 10% being de novo CRC [26,27]. The transition rates through the various stages of the CRC pathway are shown in Table 1. Initial polyp prevalence was available from population studies [28,29]. Regarding the new polyp rate for each decade, the corresponding values were derived from Loeve's paper in which such values had been validated by comparison with autopsy data [25]. Progression from advanced adenoma to early CRC was based on Stryker's study, as similarly reported by Frazier [30,31]. Progression from diminutive to 6–9 mm polyp, and from the latter to advanced adenoma was derived from the few available studies [32–34]. As already suggested [35], all the transition rates were assumed to be progressively higher in the older as compared to the younger ages in order to match the age-specific cancer rates. Cases of CRC diagnosed in an early stage (A-B Dukes' stages) have been supposed to have a two-fold survival rate as compared to those diagnosed in a late stage [36]. The annual age specific incidence rate of colorectal cancer has been derived from the published statistics on CRC mortality of the Italian National Center for Statistics (ISTAT) [37]. In detail, age specific mortality rates have been converted in incidence rates, assuming a CRC mortality of 40%. All the computed age-specific values of CRC incidence were arbitrarily reduced by 25% in order to simulate the CRC incidence of average risk people. The study population also experienced the natural attrition for non-CRC related-death causes [37].

Sensitivity and specificity of each of the tests considered are given in Table 1. A 65% initial compliance (adherence) to each test was assumed on the basis of previous experiences [38], as well as a compliance to repeated examinations of 80%. All those patients who were not compliant to any of the scheduled tests were considered to be non-compliant to all the subsequent tests, as already suggested [15]. It was also assumed that all the patients with an adenoma at FS or a polyp at CTC would undergo a colonoscopy. Each of the three tests has been simulated when performed three (every decade) times in the study population, as well as every 5 years in the sensitivity analysis.

### *A.1. Costs*

Costs of CRC treatment have been adopted from the previous Italian cost-effective model, in which it was calculated as the sum of the costs of surgery, 3 colonoscopies, 2 chest X-rays, 5 physical check-ups, 3 blood check examinations with neoplastic markers, 2 abdominal ultrasound scans, as well as radio/chemotherapy and palliative treatment when necessary [10]. The cost of each procedure was derived by the nominal fees payed by the regional health office to the public hospitals.

Table A.1
Analytical assessment of CTC cost in comparison with those already available for endoscopic procedures

| Variable | CTC | Sigmoidoscopy[a] | Colonoscopy[a] |
|---|---|---|---|
| Employers' cost | €23 | €53.04 | €77.49 |
| Radiology/endoscopy physician | €10.8 | €29.75 | €42.50 |
| No. | 1 | 1 | 1 |
| Minutes | 20 | 35 | 50 |
| Radiology technician | €4.07 | – | – |
| No. | 1 | – | – |
| Minutes | 15 | – | – |
| Nurse | €3.9 | €17.55 | €29.25 |
| No. | 1 | 1.5 | 1.5 |
| Minutes | 15 | 58 | 50 |
| Carrier | €1.91 | €2.24 | €2.24 |
| No. | 1 | 1 | 1 |
| Minutes | 10 | 7 | 7 |
| Administrative | €2.32 | €3.5 | €3.5 |
| No. | 1 | 1 | 1 |
| Minutes | 10 | 10 | 10 |
| Material cost | €10 | €14.88 | €16.35 |
| Depreciation/ manutention | €62.4 | €23.73 | €29.66 |
| General cost | €5.5 | €18.33 | €24.7 |
| Total | €100.9 | €109.98 | €148.21 |

[a] Readapted from Rossi's analysis [39].

As shown in Table A.1, costs of the endoscopic procedures have been adopted from a previous analysis of the Italian Society of Digestive Endoscopy (SIED) [39]. Cost of CTC has been *de novo* computed using the same scheme adopted for the endoscopic tests (Table 1). Cost of endoscopic complications has been adopted from Sonnenberg's paper, assuming a €/$ rate of 0.83. All the costs are expressed in Euro currency and shown in Table 1.

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