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Endoscopic requirements of colorectal cancer screening programs in average-risk population. Estimation according to a Markov model

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ABSTRACT

BACKGROUND: Although colorectal cancer (CRC) screening strategies are quite common in the United States, their systematic introduction in Europe has been delayed until the year 2008. To estimate endoscopic requirements of four different CRC screening strategies (annual and biennial fecal occult blood testing (FOBT), flexible sigmoidoscopy every 5 years, and colonoscopy every 10 years) in an average-risk population.

METHODS: A long-term Markov process model was designed combining three adherence rates for the four above-mentioned screening strategies in individuals aged from 50 to 74. Estimations included endoscopic procedures performed for both screening and surveillance purposes. Models were adjusted for age-related adenoma and CRC incidence rates, life expectancy, and cancer-related survival.

RESULTS: The mean number of annual colonoscopies per 100,000 individuals aged 50-74 ranged from 100 to 271 for annual FOBT, from 75 to 203 for biennial FOBT, from 222 to 601 for sigmoidoscopy, and from 903 to 2449 for colonoscopy-based strategies, depending on the adherence rate. According to these estimations, annual and biennial FOBT strategies would generate a slight decrease of current endoscopic activity (1.4-3.8% and 2.7-7.2%, respectively), whereas sigmoidoscopy and colonoscopy-based strategies would induce a 4.7-12.8% and 32-87% increase, respectively, with respect to a non-screening scenario. The model confirmed a 3-16% mean reduction of CRC incidence depending on the strategy and adherence rate.

CONCLUSION: Whereas endoscopic capacity exists for widespread CRC screening with annual or biennial FOBT, implementation of potentially more effective strategies, such as flexible sigmoidoscopy or colonoscopy, would result in a significant increase of current endoscopic resources.

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REQUERIMIENTOS ENDOSCÓPICOS DE UN PROGRAMA DE CRIBADO DEL CÁNCER COLORRECTAL EN LA POBLACIÓN DE RIESGO INTERMEDIO. ESTIMACIÓN DE ACUERDO A UN MODELO DE MARKOV

INTRODUCCIÓN: Mientras que el cribado de cáncer colorrectal (CCR) es una práctica común en Estados Unidos, su introducción sistemática en Europa se ha ido demorando. El objetivo del presente estudio fue estimar los requerimientos endoscópicos de 4 estrategias de cribado (detección de sangre oculta en heces [SOH] anual y bienal, sigmoidoscopia flexible cada 5 años, y colonoscopia cada 10 años) en una población de riesgo intermedio.

MÉTODOS: Se diseñó un modelo de Markov con 3 tasas de adhesión para cada una de las 4 estrategias, en una población de individuos de edad comprendida entre los 50 y los 74 años. Se estimó el número de procedimientos endoscópicos necesarios para llevar a cabo estas estrategias, considerando tanto las exploraciones de cribado como las de vigilancia de las lesiones detectadas. El modelo se ajustó por la incidencia de adenoma y CCR en función de la edad, la esperanza de vida y la mortalidad relacionada con cáncer.

RESULTADOS: La media anual de colonoscopias por cada 100.000 individuos de 50-74 años de edad fue de 100-271 en la estrategia de SOH anual, 75-203 en la de SOH bienal, 222-601 en la de sigmoidoscopia, y 903-2449 en la de colonoscopia, en función de la tasa de adhesión. De acuerdo con estas estimaciones, las estrategias de detección de SOH anual y bienal generarían un ligero decremento de la actividad endoscópica actual (un 1,4-3,8 y un 2,7-7,2%, respectivamente), mientras que las basadas en la sigmoidoscopia y la colonoscopia la incrementarían en un

4,7-12,8 y un 32-87%, respectivamente, en un posible escenario sin cribado. El modelo confirmó una reducción de la incidencia media de CCR del 3-16% en función de la estrategia y la adhesión al programa evaluado.

CONCLUSIÓN: Mientras que la capacidad de las unidades endoscópicas parece suficiente para realizar un programa de cribado poblacional mediante detección de SOH anual o bienal, la implantación de estrategias potencialmente más efectivas, como la sigmoidoscopia flexible o la colonoscopia, requeriría un incremento significativo de los actuales recursos endoscópicos.

INTRODUCTION

Colorectal cancer (CRC) constitutes a major health care issue since it is the second most common malignant tumor in Europe[1] and also the second leading cause of cancer death[2,3]. Although inherited disorders are responsible for a relevant proportion of these neoplasms[4,5], the overwhelming majority of them cannot be attributed to a known predisposing genetic condition[6]. In this subset of sporadic cases, the only risk factor is the age, with a probability of CRC exponentially increasing after 50 years of age[7].

Screening can lead to decreasing incidences of CRC and death owing to the detection of both precancerous lesions and cancers at early stages[7]. Several strategies, such as fecal occult blood testing (FOBT)[8-13], flexible sigmoidoscopy[14-17] and colonoscopy[18-22], have been demonstrated to accomplish these goals in an average-risk population (i.e. individuals older than 50 without predisposing personal or familial conditions). Moreover, several studies concluded that any modality of CRC screening is cost-effective in the long run[23,24]. Taking into account these considerations, the US Preventive Services Task Force, the American Gastroenterology Association, and the American Cancer Society recommend some type of screening protocol for average-risk individuals older than 50[23-25]. This recommendation rests on the premise that the selection of a particular screening strategy is based on a combination of physician and patient preference, as well as costs and availability.

Whereas CRC screening strategies are largely implemented in the United States, their systematic introduction in Europe has been delayed. This apparent inconsistency reflects the contrast between the «individual-preferences, limitless-resource» attitude and a «population-based, resource-managed» approach[26]. In this latter setting, a model of medical decision-making driven by an appropriate balance among quality, access, and cost parameters is mandatory. To delineate this scenario it is essential to perform a precise estimation of needs and requirements, a circumstance specially noteworthy at present when the European Union Council is pursuing the introduction of population-based screening programs[27].

This study was aimed at establishing the endoscopic requirements of four different CRC screening strategies (annual and biennial FOBT, flexible sigmoidoscopy every 5 years, and colonoscopy every 10 years) in an average-risk population, in order to ascertain their feasibility in a public-based, national health system. Estimations were carried out in the Spanish population for the period 2005-2030, whereas differences in estimations were interpreted in the context of their efficacy, in terms of CRC incidence reduction.

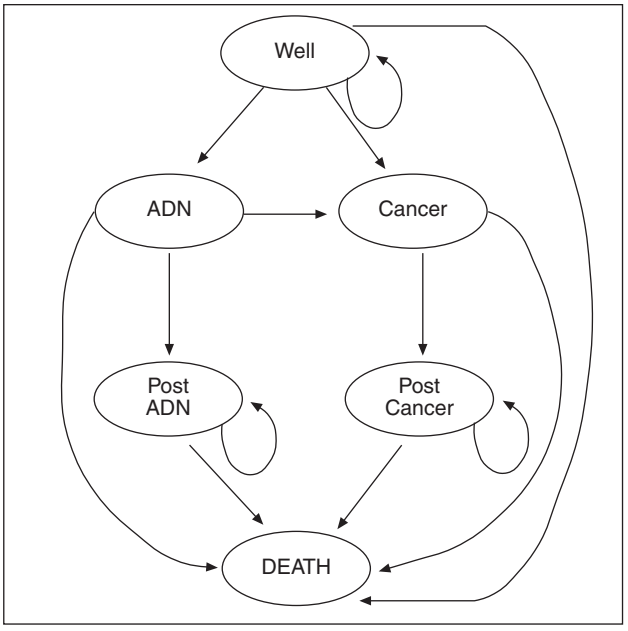

Fig. 1. Schematic diagram of the Markov Model. A Spanish population may acquire different health state within a lifetime based on CRC: no adenona/cancer detection (WELL), adenoma detection (ADN), colorectal cancer detection (CANCER), adenoma surveillance (POST ADN), colorectal cancer surveillance (POST CANCER) and, death from cancer and competing causes of mortality (DEATH)

METHODS

Study population

Estimation of endoscopic requirements for CRC screening strategies was performed in a Spanish population aged between 50 and 74 years. This interval corresponds to the population selected by the European Union Council as the target for CRC screening programs[27], based on the exponential increase of CRC incidence after the age of 50[7] and life expectancy after diagnosis of an early-stage cancer[28]. Baseline data were obtained from the 2005 Spanish National Institute of Statistics census[29], and projections up to year 2030 were established according to the 2004 US Bureau of the Census[30]. In this period, a remarkable increase of individuals amenable to CRC screening in Spain is expected, from 11 million up to 17.9 million in year 2030[29], which parallels the predicted increase in other Western countries[30].

Study population was divided in 5-year interval groups because of differences in incidence of CRC and adenomas according to age[31]. No variation within a particular group was assumed. Population movement was considered, summing up the static movement of the cohort aged 50 to 54 for 25 years and the natural evolution of the whole population according to the overall and cancer-specific mortality. It was expected an initial 'ramp-up' phase during which persons not previously screened undergo testing.

Colorectal cancer screening and surveillance strategies

Evaluation of CRC screening strategies included annual and biennial

TABLE I. **Inputs of the model and sources**

Inputs	Screening strategies[a]				Sources
	Annual FOBT	Biennial FOBT	Flexible sigmoidoscopy	Colonoscopy	
Adenoma incidence	Age-dependent				37-41
Colorectal cancer incidence	Age-dependent				31
Adenomas detection rate	0.0094[b] x age-dependent adenoma incidence	0.007[b] x age-dependent adenoma incidence	10.1-11.6%	Age-dependent adenoma incidence	11,12,36-42
Colorectal cancer detection rate	0.124[c]	0.124[c]	0.006[d]	0.01	11,12,18,36
Colorectal cancer-specific mortality in a non-screening scenario[e]	1st yr, 0.18; 2nd yr, 0.085; 3rd yr, 0.10; 4th yr, 0.073; 5th yr, 0.039				42
Colorectal cancer-specific mortality in an screening scenario[e]	1st yr, 0.075; 2nd yr, 0.054; 3rd yr, 0.057; 4th yr, 0.046; 5th yr, 0.048				42
Overall mortality	Age-dependent				29

FOBT: fecal occult blood testing.
[a]Due to high age-dependency from data, a complete summary table detailing each transition or arrow depicted in the Markov model is available from the authors.
[b]These figures correspond to a ponderate average of all positive rate of annual and biennial FOBT, respectively, during one year.
[c]This figure correspond to the positive predictive value of FOBT for colorectal cancer.
[d]This figure corresponds to colorectal cancer detected in both flexible sigmoidoscopy (0.5%) and sigmoidoscopy-driven colonoscopy (0.1%).
[e]Cumulative mortality rate.

FOBT, flexible sigmoidoscopy every 5 years, and colonoscopy every 10 years, which correspond to the most widely accepted strategies[7,23-25].
A non-rehydrated guaiac test was considered for both annual and biennial FOBT, with colonoscopy examination for those individuals with a positive result[10-13]. Individuals with a positive FOBT result and negative colonoscopy returned to the corresponding FOBT-based screening strategy 10 years after colonoscopy examination. Regarding the flexible sigmoidoscopy strategy, individuals in whom a neoplastic lesion was detected in the distal colon or rectum during this endoscopic procedure were also considered for total colonoscopy.
Individuals found to have a CRC or adenoma in any evaluated screening strategy were excluded from the screening setting and included in a specific surveillance program. Frequency of surveillance colonoscopy was established according to guidelines of the American Gastroenterological Association[7], recently updated[32], and the American Society of Clinical Oncology[33,34]. In order to simplify the model and considering that more than 70% of adenomas correspond to low-risk lesions, patients in whom an adenoma was found underwent a colonoscopy every 5 years. Similarly, patients developing CRC underwent a colonoscopy at 3 years after treatment and every 5 years thereafter. The number of surveillance colonoscopies was estimated until patient death or age 74, when he or she ended the program.

Markov model

Estimation of endoscopic requirements was performed using a discrete-time Markov, 6-state model to describe the experience of CRC and adenomas in the population. The model for CRC screening and surveillance is depicted in figure 1. Hypothetical patients reside for the duration of one cycle length, whereas transition probabilities were assumed to remain constant throughout each cycle. Transition probabilities were derived from published literature and calibrated to Spanish cancer registry data. The 6 health states of the model are: no cancer / adenoma detection, adenoma detection, colorectal cancer detection, adenoma surveillance, colorectal cancer, and death from cancer and competing causes of mortality. Population may remain in the same health state, progress or die.
In addition to the natural history, we implemented the Spanish standard screening and treatment of colorectal cancer into the model. In this model, any evaluated screening strategy was compared with a non-screening scenario corresponding to a theoretical base state in which all colonoscopies performed for any other reason (i.e. diagnostic and surveillance purposes) were considered. Estimation of current endoscopic capacity in Spain was derived from a recent survey performed in digestive endoscopy units of more than 60 public and private hospitals by Campo et al[35].
Basic transitions of the multi-state model included entrance at age 50 and exit at age 74, colorectal neoplasm (both adenoma and cancer) development, and death (fig. 1). Both overall and cancer-specific mortality were considered. The rate of attrition from the program due to any reason was established at 5% annually[10-12]. Adherence with screening strategies was arbitrarily adjusted at three different rates: 20%, 40% and 60% reflecting both the most commonly observed adherence rates seen in European pilot programs (20%)[36], and the maximum rates obtained in a screening study (60%)[10].
In the non-screening scenario, age-dependent adenoma and CRC incidence rates were determined on the basis of previous observational studies[31,37-41]. In the screening scenario, adenoma and CRC detection rates for each particular screening strategy were determined by considering both the probability of positive results test and the age-dependent incidence. Finally, CRC-specific mortality derived from cohorts of patients with CRC diagnosed in non-screening and screening settings were both considered. The parameters of the model and corresponding references are summarized in table I.
The model contemplated the possibility that a FOBT-screened individual underwent a colonoscopy because of presenting symptoms. This possibility was not considered for individuals included in a flexible sigmoidoscopy or colonoscopy-based screening program, or for patients included in the surveillance program.
Primary outcome measures were the number of colonoscopies per 100,000 individuals aged 50-74 years. Results were expressed as mean ± standard deviation of annual requirements (screening, surveillance and both) over the period 2005-2030. For the sigmoidoscopy-based strategy, the number of screening flexible sigmoidoscopies were also estimated. Comparison of overall colonoscopy requirements (for screening, surveillance and other diagnostic purposes) in non-screening and screening scenarios were estimated annually for the period 2005-2030. Finally, efficacy of each CRC screening program was evaluated by estimating its effect on CRC incidence reduction in comparison with a non-screening scenario.
Construction and evaluation of the Markov model was done using DATA 4.0 software (Tree-Age Software, Boston, MA) for Windows.

RESULTS

Endoscopy requirements of colorectal cancer screening programs

Colonoscopy requirements for each specific CRC screening program according to three different adherence rates are shown in table II. For the sigmoidoscopy strategy, endoscopy requirements also include the number of flexible sigmoidoscopies needed for screening purposes, which was estimated at 1,913.0 ± 433.7, 3,655.9 ± 851.7, and 5,178.4 ± 1,241.8 per 100,000 individuals, for a 20%, 40% and 60% adherence rate, respectively. As it is shown, annual colonoscopy needs, estimated for screening, surveillance and both, differ extensively among strategies, the lowest figures

TABLE II. **Annual colonoscopy requirements of each colorectal cancer screening strategy***

Screening strategy		Adherence		
		20%	40%	60%
Screening	Annual FOBT	100.2 ± 17.7	191.44 ± 34.8	271.2 ± 50.8
	Biennial FOBT	75.1 ± 13	143.4 ± 25.6	203.2 ± 37.5
	Flexible sigmoidoscopy	222 ± 50.3	424.1 ± 98.8	600.7 ± 144.0
	Colonoscopy	902.7 ± 225.9	1,728.7 ± 443.2	2,448.6 ± 646.2
Surveillance	Annual FOBT	48.59 ± 28.6	93.19 ± 54.6	132.6 ± 77.4
	Biennial FOBT	36.36 ± 21.4	69.71 ± 40.9	99.2 ± 57.9
	Flexible sigmoidoscopy	275.6 ± 161.3	528.6 ± 308.2	752 ± 436.9
	Colonoscopy	384.5 ± 221.7	737.1 ± 423.5	1,047.7 ± 599.1
Both screening and surveillance	Annual FOBT	148.7 ± 13.4	284.6 ± 24.4	403.8 ± 32.9
	Biennial FOBT	111.4 ± 10.2	213.2 ± 18.5	302.4 ± 25.1
	Flexible sigmoidoscopy	497.6 ± 114	952.7 ± 215.1	1,352.7 ± 301.2
	Colonoscopy	1,287.2 ± 71.3	2,465.8 ± 139	3,496.3 ± 206.6

FOBT: fecal occult blood testing.
*Results expressed as number (mean ± standard deviation) of colonoscopies per 100,000 individuals aged 50-74 years.

corresponding to the biennial FOBT-based program and the highest to the colonoscopy program (table II).

A comparison of overall colonoscopy requirements (for both screening, surveillance and other diagnostic purposes) over the period 2005-2030 for each screening strategy with respect to a non-screening scenario is shown in figure 2. Morphology of the curves reveals a sharp increase after 5 years of starting the screening program, which corresponds to the addition of a significant volume of surveillance colonoscopies, and a steadier rise over the study period reflecting population growth.

According to these estimations (fig. 2), a colonoscopy strategy would increase annual colonoscopy needs by 32.2 ± 3.9%, 61.9 ± 8.2%, and 87.8 ± 12.7% for a 20%, 40% and 60% adherence rate, respectively, whereas the corresponding figures for a sigmoidoscopy-based program would be 4.7 ± 4.0%, 8.9 ± 7.7%, and 12.8% ± 11.3%, respectively. On the other hand, when overall colonoscopy requirements were estimated for strategies based on annual or biennial FOBT, a reduction with respect to a non-screening scenario was observed (annual: 1.4 ± 2.6%, 2.4 ± 5.1%, and 3.8 ± 7.6%; biennial: 2.7 ± 2.6%, 5.2 ± 5.2%, and 7.2 ± 7.6%).

Efficacy of colorectal screening strategies

Efficacy of each CRC screening program was evaluated by estimating its effect on CRC incidence reduction in comparison with a non-screening scenario (fig. 3). According to these estimations, the model predicted a decrease in this parameter for any evaluated screening strategy, which was noticeable in the short run. The uppermost reduction corresponded to the colonoscopy-based program (5.8 ± 1.3%, 10.9 ± 2.3%, and 15.5 ± 3.3% for a 20%, 40% and 60% adherence rate, respectively), whereas the lowest decrease was estimated for the annual FOBT-based strategy (3.1 ± 1.2%, 5.8 ± 2.2%, and 8.1 ± 3.1% for a 20%, 40% and 60% adherence rate).

DISCUSSION

Colorectal cancer screening is effective and cost-effective[23,24,43]. However, these strategies are currently underused in many countries, particularly in Europe. Implementation of any screening program requires an accurate evaluation of its impact on health resources, i.e. endoscopic capacity. This fact is especially important in countries with a public-based health system where population-based, resource-managed strategies are mandatory. To our knowledge, this is the first study to estimate endoscopic needs for CRC prevention in Europe, considering not only current requirements but also projections of population growth over the next 25 years. By using a Markov model, it has been estimated that a CRC screening program based on annual or biennial FOBT seems feasible with the available endoscopic capacity, whereas flexible sigmoidoscopy or colonoscopy-based strategies largely exceed existing resources.

The strength of this study relies on the fact that our mathematical model allows for the comparison of several strategies for both screening and surveillance purposes in a single population, with the simulation of different adherence rates after adjustment for the most relevant clinical parameters influencing screening outcome (i.e. age-dependent adenoma and CRC prevalence, symptomatic presentation of neoplastic lesions, overall and cancer-related mortality, and clinical performance of screening and surveillance tests). More importantly, projections were not limited to the current scenario but they also estimated needs in the near future.

However, we are also aware of the limitations of this analysis. First, estimations pertain exclusively to an average-risk population, whereas endoscopic needs for high-risk people were not evaluated. Considering that these individuals require a more intensive screening and surveillance programs[25,32,44,45], our projections could be somehow underestimated. Nevertheless, since the vast majority of the general population has no predisposing conditions toward the development of CRC, the impact on resource is assumed to be small. Second, although most parameters used in the Markov model derived from studies performed in Spain, data on performance characteristics of evaluated screening strategies came from other countries because of the lack of large Spanish evaluations in this setting. However, the performance of screening tests is

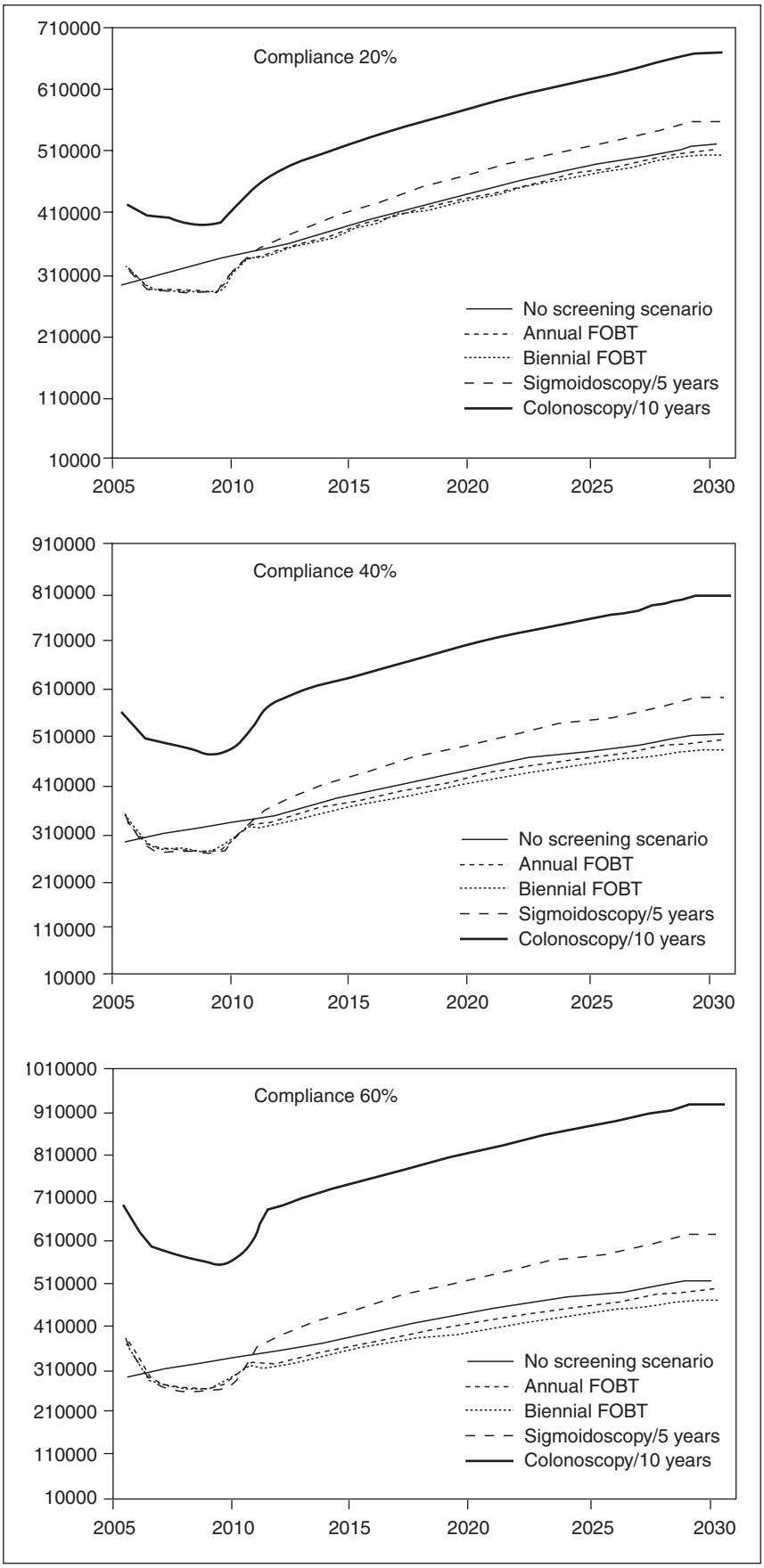

Fig. 2. Annual colonoscopy requirements in Spain over the period 2005-2030 for each screening and non-screening scenario, and according to adherence rate.

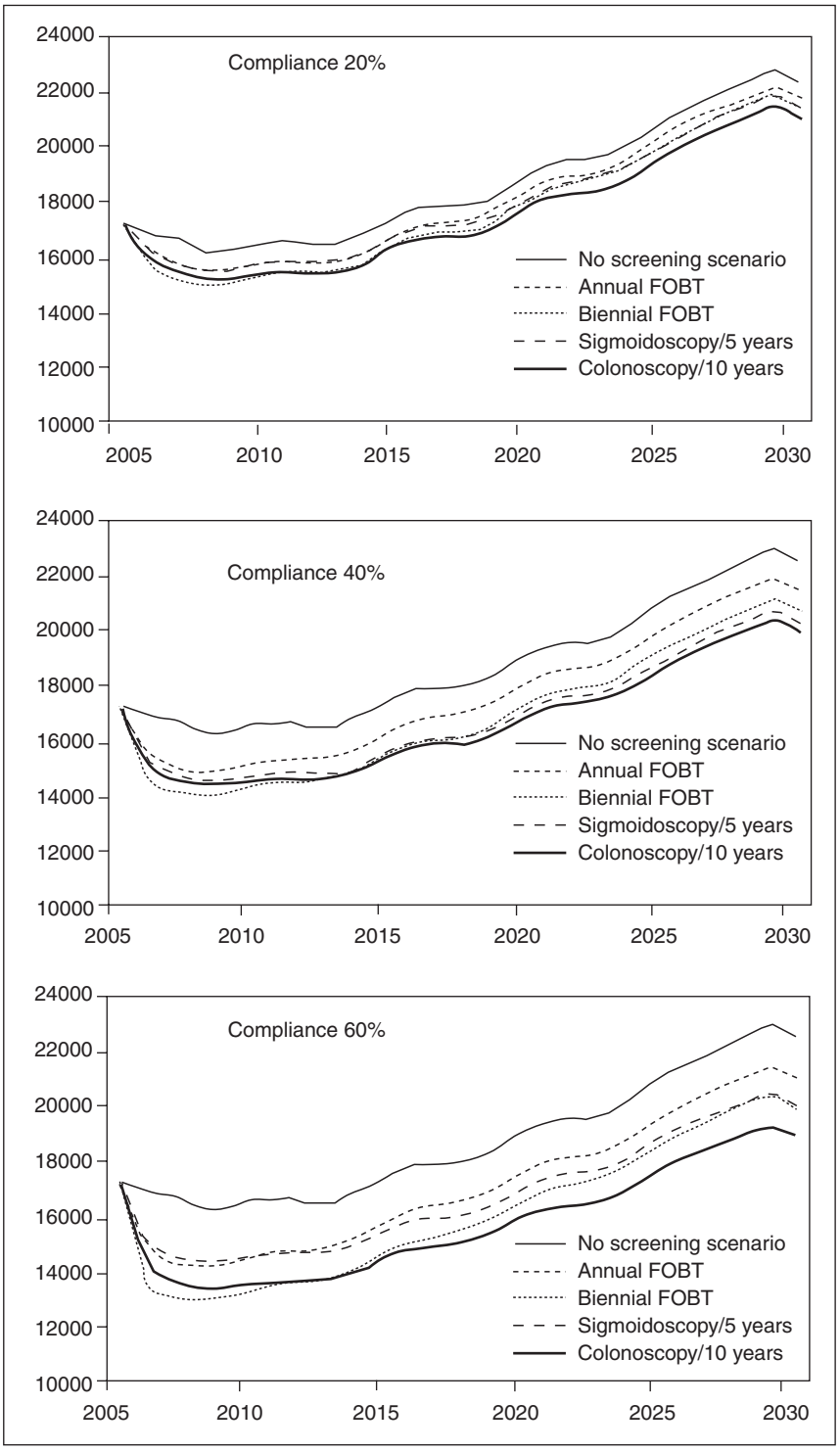

Fig. 3. Colorectal cancer incidence in Spain over the period 2005-2030 in each screening and non-screening scenario, according to adherence rate.

almost identical worldwide and therefore, it is not unreasonable to attempt to extrapolate these results to other geographical areas. Third, a precise estimation of the current endoscopy capacity in Spain is difficult to achieve, as it is in other countries[46]. Following a similar approach as it has been recently employed in the United States[46], we used data from a nation-wide survey performed by Campo et al. in more than 60 public and private hospitals[35]. Although these data represent the most accurate estimates available, we cannot infer from them the proportion of colonoscopies currently being performed for screening purposes. Nevertheless, according to the results obtained in another survey performed by our group, this figure is probably insignificant[47]. Finally, the rojections did not fully

take into account potential deviations from recommended guidelines in clinical practice. Indeed, the model did not consider the possibility that an individual included in sigmoidoscopy or colonoscopy-based screening programs underwent a colonoscopy because of presenting symptoms. This possibility, however, was contemplated for the FOBT-based screening strategies, although estimations of the actual proportion of individuals in whom a negative result was obtained but they still needed a colonoscopy under base conditions is difficult. More important, surveillance strategies for patients found to have a neoplastic lesion did not consider the possibility of undergoing any additional colonoscopy either. This stringent assumption of the model could be responsible for a potential underestimation of endoscopy needs, which may affect all four screening strategies but with a greater impact on the FOBT-based approaches because of their lower base-line requirements. This fact may explain that FOBT strategies resulted in lower colonoscopy use than the base case of no screening.

According to the results of our study, endoscopic capacity seems to be sufficient for widespread screening with FOBT, performed either annually or biennially. Indeed, estimates actually reflected a slight reduction in the number of colonoscopies, thus mirroring a shift from diagnostic indications to screening and surveillance purposes[48]. Besides the influence of the above-mentioned potential bias due to the assumptions in our model, there are few doubts that the introduction of any population-based screening program would contribute to improve the appropriateness of colonoscopy and, consequently, a more rational use of health resources[49].

On the other hand, implementation of screening strategies based on flexible sigmoidoscopy or colonoscopy would require a significant increase of current endoscopic capacity[48]. It is important to note that, although the sigmoidoscopy-based program was associated with a lower increase of colonoscopy needs, from 4.7% to 12.8% with respect to a non-screening scenario, this strategy obviously requires the performance of a large number of screening flexible sigmoidoscopies (estimated in 1,913 to 5,178 per 100,000 individuals, depending on the adherence rate). Whereas flexible sigmoidoscopy is performed by trained endoscopy nurses or general practioners in some countries[50-52], this practice is not common in many others. Hence, this circumstance should be taken into account when endoscopic capacity is locally evaluated.

Although any assessed screening strategy confirmed its efficacy in terms of CRC incidence reduction against a non-screening scenario in our Markov model, noticeable differences were observed among them. In fact, the uppermost reduction corresponded to the colonoscopy-based program, a situation supported by clinical evidence[18-22]. In addition, the potential advantage of colonoscopy also relies on its screening, diagnostic and therapeutic capability. However, implementation of a colonoscopy-based strategy would require the largest increase in endoscopic capacity. The impact of such a program could be somehow mitigated if a once-only colonoscopy approach was demonstrated to be as effective as repeating the examination every 10 years[53].

In conclusion, estimations from this Markov model suggest that endoscopic capacity exists for widespread CRC screening with annual or biennial FOBT. Nevertheless, implementation of potentially more effective strategies, such as flexible sigmoidoscopy or colonoscopy, would result in a significant enlargement of current endoscopic resources. To achieve this final goal, an increase in the government's health budget to cover both human and technical needs as well as improvement on the appropriateness of endoscopy are required. Finally, cost-effectiveness evaluations in the European setting will also contribute to select the most adequate strategy for CRC screening in our setting.

KEY POINTS

– Estimations from this Markov model suggest that endoscopic capacity exists for widespread CRC screening with annual or biennial FOBT.
– Implementation of potentially more effective strategies, such as flexible sigmoidoscopy or colonoscopy, would result in a significant enlargement of current endoscopic resources. To achieve this goal, an increase in the government's health budget to cover both human and technical needs as well as improvement on the appropriateness of endoscopy are required.
– Cost-effectiveness evaluations in the European setting may contribute to select the most adequate strategy for CRC screening in our setting.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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