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## Original article

## Results of a study on populational colorectal cancer screening

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## A B S T R A C T

**Introduction:** As colorectal cancer (CRC) screening based on occult blood detection has been shown to be effective in reducing mortality due to this disease, it is now important to decide on the best methods to obtain the maximum numbers of participants. The aim of the study was to analyse the results from a pilot CRC screening programme in a general population sample in Barcelona. A follow-up of false positive cases was made after 5 years.

**Patients and method:** A cross section of the population aged 50–74 years in one primary health care centre was studied. The creening test consisted of an immunological method for the detection of faecal occult blood which was sent to the homes of the target population.

**Results:** Participation was 46.6%, 11.7% of the tests were positive, and 79.3% agreed to have a colonoscopy. Eight adenocarcinomas and 32 patients with adenomas >0.4 cm were diagnosed.

**Conclusions:** The results obtained on the initial participation and the follow-up at 5 years suggest the viability of a CCR screening programme in our country.

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## Resultados de un estudio de cribado poblacional de neoplasia colorrectal

## R E S U M E N

**Introducción:** El cribado poblacional de cáncer colorrectal (CCR) basado en la detección de sangre oculta en heces se ha demostrado efectivo en disminuir la mortalidad por esta enfermedad, si bien es importante encontrar los métodos adecuados para obtener una participación suficiente. El objetivo del estudio fue analizar los resultados clínicos de un programa piloto de cribado de CCR y las causas de rechazo. También se realizó el seguimiento de los casos falsos positivos a los 5 años.

## Palabras clave:

Cribado de cáncer colorrectal

Diagnóstico precoz

Sangre oculta en heces

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**Pacientes y método:** Se diseñó un estudio de corte transversal en una población diana de 2.105 personas de 50 a 74 años atendidas en un centro de asistencia primaria. La prueba de cribado fue un método inmunológico, que se remitió al domicilio de la población diana.

**Resultados:** La participación fue del 46,6%, el porcentaje de positividad de la prueba fue del 11,7% y la aceptación de la colonoscopia fue del 79,3%. Se diagnosticó en total a 32 pacientes con adenomas 40,4 cm y a 8 con CCR.

**Conclusiones:** Los resultados obtenidos en nuestro estudio, tanto en participación como el seguimiento a los 5 años, permiten creer en la factibilidad de un programa de cribado poblacional de la neoplasia colorrectal en nuestro país.

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## Introduction

Colorectal cancer (CRC) is an illness that could ideally be a candidate for screening due to its biological characteristics and socio-economic impact. The high prevalence of this type of tumour and the existence of its precursor, the adenoma (whose diagnosis and treatment [endoscopic polypectomy] could alter the natural history of the illness and improve its prognosis), broadly justify the efforts in the implementation of populational screening programs.<sup>1</sup>

At present, the usefulness of screening in the population older than 50 and with a medium risk of suffering CRC is not doubted, due to the scientific evidence provided by randomized prospective studies<sup>2-4</sup> as well as by cases and controls.<sup>5</sup> Type A scientific evidence,<sup>6</sup> reached with the results of different controlled studies, has marked its progressive recommendation by the majority of scientific societies.<sup>7-12</sup>

Furthermore, studies that analyzed the cost-effective relationship of the CRC screening programs are also available. A clear benefit has been demonstrated in said studies involving a cost of 10 000-25 000 dollars per gained year of life.<sup>13,14</sup> In addition to this, other benefits have been demonstrated after the implementation of CRC screening programs, that include not only the early diagnosis of CRC (secondary prevention), but also a decrease in the incidence of the illness (primary prevention), which, depending on the screening method used, may oscillate between 20<sup>15</sup> and 58%.<sup>16</sup> Because of this, the prestigious National Polyp Study Group has estimated that, after a screening program and an adequate endoscopic control, up to 90% of the CRC cases could be avoided.<sup>17</sup>

In the United States, 46% of people older than 50 years are included in a CRC screening program with adequate follow-up,<sup>18</sup> whereas in Spain the use of CRC screening in the medium risk population is scarce and limited to studies and pilot programs with diverse strategies.<sup>19-27</sup> In this respect, our group published the results that corresponded to a prospective and randomized study in order to demonstrate that it was possible to achieve a greater participation in a CRC screening program according to the invitation strategy to which the target population was subject to.<sup>23</sup>

The goal of the current study is to present the clinical results obtained from the participating population in the abovementioned study, including the follow-up of the false positives after 5 years. The results of a telephone survey

about the reasons of not participating in the screening are also presented.

## Patients and method

The design of the study was a transversal cut carried out in the Hospital Universitario del Mar setting. The recruitment period took place from October 1998 to January 1999. The population pertaining to a primary healthcare centre in Barcelona was selected for this study. The only inclusion criteria was an age between 50 and 74 years.

The target population included 2105 people. Seventy-nine people were excluded because of a personal history of CRC or census errors.

The screening test consisted of the use of the Hexagon Obti Test®, an immunological method to detect occult blood in faeces that has been used in other studies of this type as an alternative to more traditional chemical methods.<sup>28,29</sup> This method, based on the detection of human haemoglobin, does not require any previous diet and is specific for the detection of colorectal originated blood.<sup>30</sup> The test was carried out in 2 consecutive days.<sup>30</sup> The samples collected from each patient had to be delivered to the primary healthcare centre of which the participants belonged.

The target population received a letter of invitation to the study at their home address, as well as the screening test together with the necessary information. A self-administered questionnaire was also included to obtain information about colorectal symptoms in the last 12 months. Fifteen days later a reinforcing telephone call was made to those that had not responded.

A telephone survey was carried out for those that decided not to participate, in order to find out the possible causes of their rejection. The open answers were grouped in one of the following sections:

1. I am not interested in having more information about my health.
2. The subject could not carry out the test. In this section, the responses of people that had expressed said impossibility for different reasons were grouped, such as serious or limiting illness, personal problems that they did not want to clarify, temporary absence because of travel, not understanding the characteristics of the study and/or the instructions, and other responses which generally belonged to this section.

### 3. Previous knowledge of the existence of symptoms and adequate medical control already in course.

The people in which the presence of occult blood in faeces was detected were scheduled for a medical appointment and all were encouraged to undergo a complete colonoscopy with sedation. The detection of any irregularities initiated the adequate therapeutic mechanisms for each case according to the healthcare protocol of the Colorectal Surgery Unit of the Hospital del Mar. The staging of the detected CRC is presented with TNM classification.<sup>31</sup>

Those patients that presented a positive faecal occult blood test, with no cause found in the colonoscopy performed, were considered false positives and they were proposed another colonoscopy 5 years later. As in previous studies, a polyp must be at least 0.4 cm to be considered the origin of faecal occult blood.<sup>32</sup> These cases were considered to be true positives as well as those in which CRC was diagnosed.

The study was approved by the Clinical Ethics Committee at the Hospital Universitario del Mar.

## Results

### Participation results and clinical findings

The total participating population included 945 of the 2026 people that were included in the study, which meant a participation of 46.6% (Figure); and of those who participated, 881 (93.2%) belonged to the first group and 64 (6.8%), after a reinforcing telephone call.

Twenty-three point four percent of the people that participated claimed to have observed in some occasion blood in their faeces, 44.5% had suffered from haemorrhoids, 11.3% had anal fissures, and 3.5% noticed the presence of mucus.

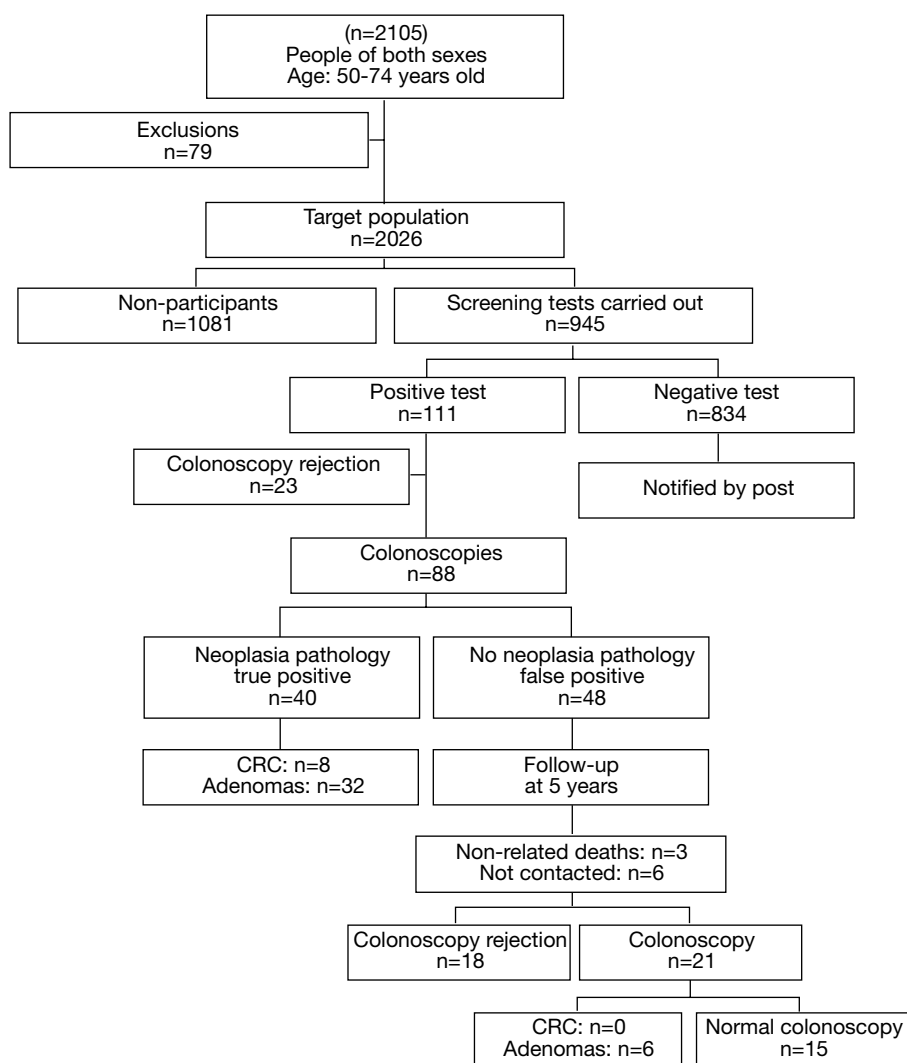


Figure - Diagram of the intervention in the colorectal screening programme and results.

In 111 (11.7%) of the 945 cases, the screening test was positive for occult blood in faeces. All were recommended to undergo a colonoscopy, and 23 refused it. The colonoscopy acceptance rate was 79.3%.

Of the 88 colonoscopies performed, 87 (98.9%) were complete and only 1 case was incomplete and thus required a double contrast barium enema study.

One or more polyps >0.4 cm were detected in 32 people. The total number of polyps in all 32 patients was 90, and thus the number of lesions per patient oscillated from 1 to 14. An endoscopic polypectomy was performed in all 32 patients.

Eight patients were diagnosed with colorectal adenocarcinoma, which is 9.1% of the colonoscopies performed and 8.5% of the participants of the study. The treatments carried out on these patients and the histopathological results were: 3 endoscopic polypectomies (pTis pN<sub>0</sub> pM<sub>0</sub>), 2 sigmoidectomies (pT<sub>1</sub> pN<sub>0</sub> pM<sub>0</sub> and pT<sub>2</sub> pN<sub>0</sub> pM<sub>0</sub>), 2 right hemicolectomies (pT<sub>1</sub> pN<sub>0</sub> pM<sub>0</sub> in both cases), and 1 right hemicolectomy extended to a right hepatectomy associated by synchronic hepatic metastases (pT<sub>3</sub> pN<sub>2</sub> pM<sub>1</sub>). There were no important postoperative complications in any case and the patients were discharged with the appropriate controls depending on their pathological staging.

#### *Results of the telephone survey about reasons of non participation*

Calls were made to 1081 (53%) people that did not participate, (40% males and 60% females). Fifty-one percent of males and 55% of females did not participate. According to age, 54% of the 50-64 years old group and 52% of the 65-74 years old group did not participate. Contact with 476 (44%) of the cases was impossible after calling at 2 different timeframes of normal hours to be found at home.

Six hundred five people (56% of the total) were contacted and their responses were grouped into one of the abovementioned sections in "Patients and method." The results found are expressed in Table.

#### *Follow-up of the false positives after 5 years*

Five years later, contact was sought with the 48 people that had resulted as false positives for colorectal neoplasia as well as for other illnesses that justified the presence of blood in faeces.

The person had died in 3 of the cases from causes not related to CRC. The individuals could not be contacted in 6

cases and 18 did not accept the repetition of the colonoscopy. Of the 21 people that accepted a new colonoscopy, 15 turned out normal and 6 had adenomas of 0.2 to 1 cm removed. No cases of CRC were detected.

## **Discussion**

The first point that should be covered in a screening programme to be effective in its objectives is to reach certain rates of adequate participation. It has been stated that the necessary rates of participation are greater than 50% to achieve a reduction in the secondary mortality of CRC.<sup>33</sup> There are clear differences between the participation rates in the screening programs that take into account not only the country where they are carried out, but also the screening test itself, the level of prior knowledge of the population and the strategy used.<sup>34</sup>

Cancer screening tests for cervical and breast cancer are well known and highly accepted in our country.<sup>35</sup> Without doubt, this is motivated by the fact that the health authorities and professionals have elaborated programs and designed strategies for years that facilitate the execution of the screening tests of these illnesses as well as the knowledge and transcendence that it has for the general population. However, the situation has not been the same with CRC, which implies a first obstacle to be overcome by any program of this type.

In our study, the participation achieved was 46.6%, a rate that we believe is hopeful if we keep in mind the abovementioned lack of prior knowledge of the early diagnosis of colorectal neoplasia. In addition to this, we must keep in mind that we have few prior references because of the lack of screening programs for colorectal cancer in our country.<sup>35</sup> The preliminary results of the pilot program implemented in the area of Hospitalet de Llobregat and carried out by the Catalan Institute of Oncology have recently been published. In the first round they had a participation of 17.2% and 22.3% in the second round.<sup>36</sup>

This difference of rates is demonstrative of the multiple factors that can condition participation in these screening tests as well as the possibility to intervene. Indeed, in the majority of the studies where actions have been taken to increase participation, positive results have been obtained independent of the method chosen, and it is usual that simple publicity and knowing the advantages of the method can increase participation, as seen when comparing the participation in groups with and without receiving informative brochures by mail.<sup>34</sup> Furthermore, knowing the level of participation is essential to predict the number of colonoscopies to be performed and to confirm if the health system can adequately take them on.

We also believe it is important to evaluate the reasons for not participating in screening to correct them if possible. When analysing the results obtained, we observed a high percentage of cases where it was impossible to get in contact with the invited person by telephone (44%). The availability of a current and updated census is essential when sending a personalised invitation letter.

**Table – Results of the survey about reasons of non participation**

	No. (%)
Total of non participants	1081
Total of surveys carried out	605 (100)
Not interested in the test	361 (59.7)
Impossibility to undergo the test	233 (38.5)
Low active medical control	11 (1.8)

Among the other reasons for not participating, 56% of the surveyed people stand out by giving diverse reasons that can be grouped into fear about the test or lack of interest. These are precisely the people that can be influenced to change their minds with adequate information about this topic. Less than 2% report being controlled by their family physician or specialist.

In our study, the screening test was positive in 11.75% (111/945). This number should be considered as high if we compare it to that obtained in the majority of studies where chemical methods without rehydration were used (less sensitivity), but very similar to that obtained with rehydration<sup>2</sup> or with immunological methods like the one we have used, with which a greater rate of positives is obtained, and although a greater number of FOBT must be proposed, it has demonstrated its efficacy, especially for the detection of adenomas, as seen in studies where both methods have been compared.<sup>37</sup> Another fact to keep in mind is that almost a fourth of the studied population had a history of rectal bleeding, which makes it not strictly asymptomatic.

The most important clinical point is obviously the result of the colonoscopies performed and what type of abnormalities were detected. The detection of 8 cases of CRC is greater than expected, from prevalence data in Spain as well as from similar studies.<sup>2,10,22</sup> Indeed, an incidence of 2-3 cases/1000 would be expected, yet the detected cases were 3 times greater (8,4%). The sample is insufficient to make conclusions in this sense, although an increase in the incidence of CRC cases in our country in the last few years was evident.<sup>38</sup>

The staging of the detected CRC cases has been earlier than the norm in clinical practice. Three cases were at stage 0; 4 cases, at stage I; and only 1 at stage IV, which coincides with the data obtained in the totality of the studies or programs of CRC screening and thus justifies them. However, in CRC screening, the number of cancer cases is not the only important fact, but also the number of detected adenomas, since, as the adenoma-cancer sequence is well known,<sup>39</sup> the detection of adenomas during screening and the corresponding polypectomy make it clear that we are also carrying out primary prevention of CRC. Indeed, in recent years, in the United States, where the prevalence of CRC screening is close to 50% of the population older than 50 years, the incidence of this illness has started to decrease.<sup>15</sup>

Regarding the follow-up that was carried out after 5 years for the cases labelled as false positives, we must point out that no cancer was detected and that only small-sized adenomas were found, which demonstrates the reliability of the first examination. If 18 people refuse the test, we think that it is important that 21 of them did accept, which represents an acceptance of 54%; we believe this is not a bad fact if we keep in mind that we are dealing with healthy people whose first colonoscopy showed no signs of any abnormalities.

To conclude, we believe that the published evidence about the effectiveness of CRC screening requires its immediate implementation, while, firstly, an adequate participation must be ensured and, secondly, the necessary resources for the colonoscopies and other procedures that the detected illness could require must be available. The results obtained in our study advocate for the possibility to initiate a program of these characteristics in Spain.

## REFERENCES

- Viñes JJ, Ardanaz E, Arrazola A, Gaminde I. Epidemiología clínica del cáncer colorrectal: la detección precoz. *Cir Esp*. 2003;73:2-8.
- Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med*. 1993;328:1365-71.
- Hardcastle JD, Chamberlain JO, Robinson MHE, Moss SM, Amar SS, Balfour TW. Randomised controlled trial of faecal occult-blood screening for colorectal cancer. *Lancet*. 1996;348:1472-7.
- Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet*. 1996;348:1467-71.
- Selby JV, Frieman GD, Quesenberry Jr CP, Weiss NS. A Case control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med*. 1992;326:653-7.
- Smith RA, von Eschenbach AC, Wender R, Levin B, Byers T, Rothenberger D, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal and endometrial cancers. Also: update 2001-testing for earlylung cancer detection. *CA Cancer J Clin*. 2001;51:38-75.
- US Preventive Service Task Force. Screening for colorectal cancer: recommendation and rationale. *Ann Intern Med*. 2002;137:129-31.
- Rex DK, Johnson DA, Lieberman DA, Burt RW, Sonnenberg A. Colorectal cancer prevention 2000: screening recommendations of the American College of Gastroenterology. *Am J Gastroenterol*. 2000;95:868-77.
- Sinmang CL, Senatore P, Lowry A, Hicks T, Burnstein M, Dentsman F, et al. Practice parameters for detection of colorectal neoplasms. The Standards Committee, The American Society of Colon and Rectal Surgeons. *Dis Colon Rectum*. 1999;42:1123-9.
- Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-update based on new evidence. *Gastroenterology*. 2003;124:544-60.
- Ransohoff DF. Colon cancer screening in 2005: Status and challenges. *Gastroenterology*. 2005;128:1685-95.
- Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. *CA Cancer J Clin*. 2001;51:38-75.
- Wagner JL, Tunis S, Brown M, Chaing A, Almeida R. Cost-effectiveness of colorectal cancer screening in average-risk adults. In: Young G, Levin B, editors. *Prevention and early detection of colorectal cancer*. London: Saunders; 1996.
- Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the US Preventive Services Task Force. *Ann Intern Med*. 2002;137:96-104.
- Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med*. 2000;343:1603-7.
- Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA*. 2000;284:1954-61.
- Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med*. 1993;329:1977-81.

18. Levy BT, Dawson J, Hartz AJ, James PA. Colorectal cancer testing among patients cared for by Iowa family physicians. *Am J Prev Med* Sep. 2006;31:193-201.
19. Tárraga P, Garcia-Olmo D, Celada A, Garcia-Molinero MJ, Divison JA, Casado C. Cribado del cáncer colorrectal por detección de sangre oculta en heces en una zona de salud controlada. *Rev Esp Enferm Dig*. 1999;91:335-9.
20. Maldonado-Tiestos J, Méndez M, Ginovés-Sosa A, Andújar P, González F. Resultados preliminares de una estrategia de búsqueda de casos mediante test de sangre oculta en heces para detectar pólipos y cáncer colorrectal. In: Libro de ponencias y comunicaciones de las VII Jornadas de la Sociedad Canaria de Medicina de Familia y Comunitaria. Tenerife; 1994.
21. Maldonado-Tiestos J, González F, Bellas-Beceiro B, Nuñez-Díaz V, Alfonso-Rodríguez JJ, Pérez-Palma J. Detección precoz del cáncer colorrectal mediante sigmoidoscopia en una población voluntaria y asintomática. *Cir Esp*. 1999;66:534-8.
22. Espinás JA. Detección precoz del cáncer colorrectal. Experiencia del cribado en Catalunya. Bilbao: Reunión de programas de detección precoz del cáncer de mama (ámbito Ibérico); 2001.
23. Courtier R, Casamitjana M, Macia F, Panadés A, Castells X, Gil MJ, et al. Participation in a colorectal cancer screening programme: Influence of the method of contacting the target population. *Eur J Cancer Prev*. 2002;11:209-13.
24. Cortés UF, Artal MF, Garcés TA, Izcarra DJ, Lacasa SE, Zubiri SF. Cáncer colorrectal: detección mediante la prueba del guayaco en un centro de atención primaria. *Med Clin (Barc)*. 1992;98:325-8.
25. García A, Carballo F, de la Morena F. Aplicabilidad de programas de screening para el cáncer colorrectal basados en el test de hemorragias ocultas en heces. *Rev ACAD*. 1993;IX:40-1.
26. Herreras JMG, Caunedo AA, Herreras EJM. Detección de sangre oculta en heces y cáncer colorrectal. *Rev Esp Enferm Dig*. 1999;91:331-5.
27. Lledó-Matosés S, Roig-Vila JV, Garcia-Garcia A, Villanueva-García P, Alvarez-Pernia I, Ferri-Romero J, et al. Detección de las neoplasias colorrectales mediante encuesta clínica y test Hemoccult. *Cir Esp*. 1988;43:40-1.
28. Greenber PD, Bertario L, Gnauck R, Kronborg O, Hardcastle JD, Epstein MS, et al. A prospective multicenter evaluation of new fecal occult blood test in patients undergoing colonoscopy. *Am J Gastroenterol*. 2000;95:1331-8.
29. Saito H, Soma Y, Nakajima M, Koeda J, Kawaguchi H, Kakaizaki R, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. *Oncol Rep*. 2000;7:815-9.
30. Nakayama H, Kamijo N, Fujimori K, Fattah AA, Zhang B. Relationship between fecal sampling times and sensitivity and specificity of immunochemical fecal occult blood test for colorectal cancer. *Dis Colon Rectum*. 1997; 40:781-4.
31. Colon and rectum. En: American Joint Committee on Cancer: AJCC Cancer Staging Manual. 5th ed. Philadelphia: Lippincott-Raven; 1997. p. 83.
32. Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. *Ann Intern Med*. 2007;146:244-55.
33. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev*. 2007;(1).
34. Ferreira MR, Dolan NC, Fitzgibbon ML, Davis TC, Gorby N, Ladewski L, et al. Health care provider-directed intervention to increase colorectal cancer screening among veterans: Results of a randomized controlled trial. *J Clin Oncol*. 2005;23:1548-54.
35. Castells X, Sala M, Ascunce N, Salas D, Zubizarreta R, Casamitjana M. Descripción del cribado del Cáncer en España. Proyecto DESCRIC. Madrid: Plan Nacional para el SNS del MSC. Agència d'Avaluació de Tecnologia i Recerca Mèdiques. Informes de Evaluación de Tecnologías Sanitarias; 2007.
36. Peris M, Espinas JA, Muñoz L, Navarro M, Binefa G, Borrás JM. Lessons learnt from a population-based pilot programme for colorectal cancer screening in Catalonia (Spain). *J Med Screen*. 2007;14:81-6.
37. Guitet L, Bouvier V, Mariotte N, Vallee JP, Arsène D, Bouteaux J, et al. Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. *Gut*. 2007;56:210-4.
38. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. Ministerio de Sanidad y Consumo. Available from: <http://193.146.50.130/morta/consulta.php>.
39. Mutto T, Bussey HJR, Morson B. The evolution of cancer of the colon and rectum. *Cancer*. 1975;36:2251-70.