Colonoscopic findings from a pilot screening study for colorectal cancer in Catalonia

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ABSTRACT

Objective: to evaluate lesions detected in two screening rounds performed in a pilot screening programme for colorectal cancer in Catalonia, Spain.

Material and methods: a colorectal cancer screening programme was initiated in 2000. The target population included men and women aged 50-69 years. Screening consisted of biennial guaiac-based fecal occult blood testing (FOBT), and colonoscopy for participants with a positive FOBT. Any polyps found were removed, and biopsies were performed for any masses.

Results: colonoscopies were performed in 442 of 495 people with positive FOBT. In 213 (48.2%), 36 invasive cancers, 121 high-risk adenomas, 29 low-risk adenomas, and 27 hyperplastic polyps were diagnosed. Lesion size was smaller than 10 mm in 25.8% of cases. Most detected lesions (37.2%) were located in the distal colon, followed by the proximal colon (5.7%) and both locations (5.2%). Advanced neoplasm was significantly associated with male gender and distal location. The prevalence of advanced proximal neoplasms among patients with no distal polyps was 5.1%.

Conclusions: the most common lesions detected by colonoscopy were high-risk adenomas located in the distal colon. FOBT is a suitable method for detecting small precancer lesions during population screening, and is thus a key factor in reducing the incidence of colorectal cancer.

Key words: Colorectal cancer. Screening programme. Average risk. Fecal occult blood test. Guaiac test. Advanced neoplasm.

RESEÑA

Objetivo: evaluar las lesiones detectadas en las dos rondas ya finalizadas del Programa Piloto de Cribado en Cáncer Colorrectal (CCR) llevado a cabo en L’Hospitalet de Llobregat (Barcelona).

Material y métodos: el programa de cribado de CCR se inició en el año 2000. La población, comprendida entre 50 y 69 años residentes en el área, fue invitada a participar a través de la determinación bienal de sangre oculta en heces mediante el test guaiaco y colonoscopia en los participantes con test positivo. Se realizó polipectomía de las lesiones detectadas o biopsias cuando no era posible la extirpación. Los pólipos se clasificaron según criterios de la Organización Mundial de la Salud.

Resultados: se realizaron 442 colonoscopias de los 495 test positivos. En 213 individuos, se detectaron: 36 cánceres invasivos, 121 adenomas de alto riesgo, 29 adenomas de bajo riesgo y 27 pólipos hiperplásicos. En el 25.8% de los casos, el tamaño de los adenomas fue < 10 mm. La mayoría de las lesiones diagnosticadas (37,2%) estaban localizadas en el colon distal, el 5,7% a nivel proximal y ambas localizaciones en el 5,2%. Las neoplasias avanzadas se asociaron significativamente al sexo masculino y la localización distal. La prevalencia de neoplasias avanzadas a nivel proximal entre los pacientes sin pólipos distales fue del 5,1%.

Conclusión: los adenomas de alto riesgo de localización distal han sido las lesiones detectadas con mayor frecuencia. El cribado poblacional mediante la determinación de sangre oculta en heces es un método factible para detectar pequeñas lesiones precancerosas, factor clave para disminuir la incidencia de CCR.


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INTRODUCTION

Colorectal cancer (CRC) is the third most common neoplasm worldwide after lung and breast cancer (1). In 2006, CRC was the second most common cancer diagnosed in Europe in both sexes combined, and had the second highest mortality rate after lung cancer (2). Recent trends in Spain show a pattern similar to most European countries, not only in the incidence of but also in the mortality rates for CRC (3).

One of the most important advances in recent years is the recognition that most cases of CRC arise as a result of a series of genetic alterations affecting cell replication, differentiation and apoptosis, as well as DNA repair (4). These findings mean that screening for CRC is potentially useful because its natural history is well known, it has high incidence and mortality rates in Western countries (1), the available diagnostic methods enable detection of the disease in its early premalignant stages (5), and its prognosis is favorable when treatment is initiated early (6).

The goals of CRC screening are to reduce colorectal cancer mortality through early detection, and to reduce its incidence by detecting and removing adenomatous polyps (7,8). Numerous organizations worldwide now recommend CRC screening for the population with no risk factors from the age of 50 onwards (5,9). However, published screening guidelines disagree on the best screening method (9,10). The usefulness of detecting occult blood in feces with the guaiac test has been extensively studied in large randomized trials (7,11,12), which have estimated the reduction in CRC mortality to be between 15 and 33%. Follow-up results from one of these trials showed that FOBT also reduced the incidence of CRC (8). The recommendation for flexible sigmoidoscopy as a screening test (13) is based on the Veterans’ Affairs Cooperative Study Group study (14), in which 24% of CRC cases yielded a positive FOBT but only 7% of patients had polyps. The effectiveness of sigmoidoscopy screening in detecting advanced proximal neoplasms depends on the association between proximal and distal adenomas, and the percentage of patients with lesions in the proximal colon only.

In Europe, data available from large screening studies of populations in the United Kingdom (11), Denmark (15), France (16), and Italy (17) led the European Union in 2000 to recommend that its member states implement CRC screening for the 50- to 74-year-old population (18). In response, that same year, the Catalan Government Health Department initiated a pilot study to evaluate the feasibility and acceptability of population screening for CRC by FOB testing. The final objective would be to extend the screening programme to the Catalan population with average-risk of CRC. In this manuscript, we analyze the location and distribution of lesions detected by age and gender in the two screening rounds carried out to date.

METHODS

The CRC pilot screening programme was directed at the 50- to 69-year-old population at L’Hospitalet, a city of 239,000 inhabitants in the metropolitan area of Barcelona (Catalonia), Spain. The protocol has been described in a previous paper (19). The first round, from February 2000 to April 2002, involved 11,011 of the 63,880 people invited to participate. The second round, from February 2003 to March 2005, involved 14,818 of the 66,534 people invited.

The screening test was a guaiac-based FOBT. Participants were asked to collect two stool samples from three bowel movements. No dietary restrictions were required for the initial test, although dietary restriction was indicated when the test had to be repeated (if 1 to 4 samples were positive on initial testing). If 5 or 6 samples were positive on initial testing, or if any of the samples were positive on repetition with dietary restrictions, colonoscopy with sedation was indicated. During colonoscopy, unless medically contraindicated, any polyps found were removed and biopsies performed of any masses. Site and size were documented. If a patient had more than 1 polyp, the most advanced lesion in pathological terms was used for the analysis. Polyps were considered to be located in the right colon (proximal location) when arising in the cecum, ascending colon, hepatic flexure, and transverse colon. Distal location included lesions found in the left colon (splenic flexure, descending colon and sigmoid) and rectum (intestinal portion located no more than 15 cm from the anal verge).

The histological classification of polyps and cancers was based on World Health Organization criteria (20). High-risk adenomas (HRA) were defined as either adenomatous polyps larger than 10 mm, or more than 2 adenomas, any adenoma with a tubulovillous or villous histology, or high-grade dysplasia. Low-risk adenomas (LRA) were smaller lesions showing a tubular histology and low-grade dysplasia. Carcinoma in situ was classified as HRA. Advanced neoplasms were defined as invasive carcinoma or HRA. All detected cases of invasive carcinoma were referred to the multidisciplinary colorectal cancer committee for appropriate oncology treatment. Tumors were staged (S) according to the TNM system (21). Individuals with a diagnosis of hyperplastic polyps or normal colonoscopy will be recalled for screening ten years after the endoscopic examination. The programme included follow-up colonoscopy for subjects in whom one or more adenomas were detected at screening. Time intervals varied depending on the radical nature of the endoscopic procedure and the type of adenoma detected (22).

Differences in categorical variables were compared with the chi-squared test. Differences in the detection of advanced neoplasms were analyzed with logistic regression. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Differences were considered statistically significant when p < 0.05. All
analyses were performed with the Stata® software, version 9.2 (StataCorp, College Station, TX, USA) and SPSS® software (version 13.0 for Windows).

RESULTS

A total of 25,829 screening tests were performed in 18,405 subjects (8,389 men and 10,016 women) with 7,424 persons screened in both rounds. The overall rate of positive FOBT results was 3.4% in the first round and 0.8% in the second.

Colonoscopy was performed in 442 of the 495 participants with a positive FOBT (334 from the first round and 108 from the second). No lesions were found in 229 subjects, 185 (55.4%) from the first screening round and 44 (40.7%) from the second (data not shown). In 213 (48.2%), a total of 410 polyps were diagnosed. Subjects were classified on the basis of the most advanced lesion found: 36 (8.1%) had invasive cancer, 121 (27.4%) had HRA, 29 (6.6%) had LRA, and in 27 (6.1%) participants the most important finding was a hyperplastic polyp.

Table I shows the characteristics of lesions detected in each screening round. The proportion of advanced neoplasms diagnosed was larger in the second round than in the first (p < 0.001). The most common of the histological types considered was tubulovillous adenoma, and 25.8% of removed lesions were less than 10 mm in size.

Table II summarizes the characteristics of detected lesions by gender, age, and location. The number of invasive cancers detected was greater in the 60-69-year age group.

Table III shows the distribution of patients with more than one detected lesion according to age, gender, and location. The prevalence of advanced proximal neoplasms was 5.1% (95% CI, 2.4 to 7.8), increasing among patients

Advanced neoplasms were diagnosed in nearly twice as many men as women. By location, 79.6% of advanced neoplasms were in the distal colon (125 out of 157), 8.3% (13 out of 157) were located in the proximal colon, and 12.1% (19 out of 157) in both. More than one polyp was detected in 42.7% of patients (91 out of 213), with HRA being the most advanced lesion in 67% (61 out of 91). Table III shows the distribution of patients with more than one detected lesion according to age, gender, and location.

Table IV shows the prevalence of advanced proximal neoplasms according to findings in the distal colon. Among individuals with no distal polyps (229 with no lesions on colonoscopy and 25 with proximal polyps only), the prevalence of advanced proximal neoplasms was 5.1% (95% CI, 2.4 to 7.8), increasing among patients

<table>
<thead>
<tr>
<th>Table I. Characteristics of detected lesion by screening round</th>
</tr>
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<tbody>
<tr>
<td><strong>First screening</strong></td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Complete</td>
</tr>
<tr>
<td>Incomplete</td>
</tr>
<tr>
<td>Lesions detected</td>
</tr>
<tr>
<td>Invasive cancer</td>
</tr>
<tr>
<td>High-risk adenoma¹</td>
</tr>
<tr>
<td>Low-risk adenoma</td>
</tr>
<tr>
<td>Non-neoplastic polyp</td>
</tr>
<tr>
<td>Size (mm)</td>
</tr>
<tr>
<td>&lt; 10</td>
</tr>
<tr>
<td>10-20</td>
</tr>
<tr>
<td>&gt; 20</td>
</tr>
<tr>
<td>Not stated</td>
</tr>
<tr>
<td>Histology²</td>
</tr>
<tr>
<td>Tubular</td>
</tr>
<tr>
<td>Villous</td>
</tr>
<tr>
<td>Tubulovillous</td>
</tr>
<tr>
<td>Not stated</td>
</tr>
</tbody>
</table>

¹Includes carcinomas in situ.
²Does not include carcinomas in situ.
with distal advanced neoplasms to 6.9 percent. When we analyzed the risk that an advanced proximal neoplasm would be detected based only on distal colon examination, we found that 45.8% (11 of 24) of patients had at least one adenoma in the distal colon, and that the lesion was an advanced neoplasm in 41.7% (10 of 24 patients).

Advanced neoplasm was significantly associated with male gender (OR: 1.93, 95% CI [1.03-3.60]) and distal location (OR: 2.33, 95% CI [1.05-5.15]) in the bivariate analysis. After a multivariate analysis, only distal location was associated with risk of advanced lesions (OR: 2.48, 95% CI [1.10-1.59]) (Table V).

The distribution of all 36 invasive carcinomas by stage (S) was 15 in S I (41.7%), 7 in S II (19.4%), 10 in S III (27.8%), and 4 in S IV (11.1%). In the second screening round, invasive carcinomas were detected in earlier stages than in the first, with a larger number of S I lesions (53.8 versus 34.8%) and a smaller number of S III lesions (15.4 versus 34.8%) (data not shown).

**DISCUSSION**

The rates of advanced neoplasm detected in our pilot programme do not differ substantially from those observed in published randomized trials (7,11,12). Critical issues relating to the feasibility of CRC screening based on participation and detection rates have recently been analyzed (19).

Although it is generally accepted that the lifetime risk of CRC is similar in men and women, there are important differences in epidemiology according to gender. Age-specific incidence and mortality rates are lower in women than in men (1,23). As in other screening programmes (13,24), the prevalence of advanced neoplasms detected in our study was higher in men than in women. Future results of repeated screening rounds in different groups may show whether these epidemiological differences are relevant for determining the best age for starting CRC screening in women and men.

The larger number of adenomas compared to invasive carcinomas in the 50-to-59-age group was foreseeable in view of the adenoma-carcinoma characteristic of the development of most CRCs (4). As in other screening programmes using FOBT (11,12,25), more HRAs than LRAs were diagnosed. The proportion of colonoscopies detecting these lesions was 27.4% for HRA and only 6.6% for LRA. These findings suggest a higher tendency to bleed in advanced adenoma, so FOBT may select lesions with a higher risk of progressing to carcinoma. Detecting HRA thus plays an unquestionable role in the prevention of future CRC (26).

Several published colonoscopy screening studies have analyzed the association between distal and proximal adenomas (24,27-30), and some studies have estimated the risk of proximal adenomas in patients in whom no distal lesions were detected. There is a clear association between distal and proximal adenomas, although the strength of such association varies depending on whether the distal colon is defined as the portion that can be visualized by sigmoidoscopy or as the segment in which the upper limit is defined by the splenic flexure (28,29). Also, variations in the results can reflect differences in sample size and the inclusion of patients with a family history of colorectal cancer (27). We determined the prevalence of advanced proximal neoplasms in our pa-

### Table IV. Prevalence of proximal colon neoplasm according to the presence of distal lesions

<table>
<thead>
<tr>
<th>Findings</th>
<th>Distal colon</th>
<th>Advanced proximal neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps</td>
<td>254 (57.5)</td>
<td>13 (5.1) (2.4-7.8)</td>
</tr>
<tr>
<td>Advanced neoplasms</td>
<td>144 (32.5)</td>
<td>10 (6.9) (2.7-11.0)</td>
</tr>
<tr>
<td>Low-risk adenomas</td>
<td>22 (5.0)</td>
<td>1</td>
</tr>
<tr>
<td>Hyperplastic polyps</td>
<td>23 (5.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

2. CI: confidence interval.

### Table V. Risk of advanced neoplasm in main lesions (n = 213)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Advanced neoplasm</th>
<th>Bivariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51 (65.4)</td>
<td>1</td>
<td>(1.03-3.60)</td>
</tr>
<tr>
<td>Male</td>
<td>106 (78.5)</td>
<td>1.93</td>
<td>(0.92-3.16)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>66 (68.0)</td>
<td>1</td>
<td>(1.05-5.15)</td>
</tr>
<tr>
<td>60-69</td>
<td>91 (78.4)</td>
<td>1.71</td>
<td>(0.92-3.16)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>18 (58.1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>139 (76.4)</td>
<td>2.33</td>
<td>(1.05-5.15)</td>
</tr>
</tbody>
</table>

OR = Odds ratio; ORj = Adjusted odds ratio; CI = Confidence interval.
patients and the likelihood that they would suffer from adenomas in the distal colon. Our results are similar to those of earlier studies. Thirteen out of twenty-four proximal advanced neoplasms (54.2%) would not have been detected if the distal colon only had been examined. These results should be analyzed with caution because colonoscopies were only performed in patients with positive FOBT tests.

Invasive carcinoma was detected in 8.1% of colonoscopies performed as part of our programme, and was found in earlier stages than might have been expected in our population. Of all the cancers diagnosed by screening, 41.7% were in stage I, as compared to only 11% of all CRC diagnosed in our setting on the basis of the cancer registry compiled by the University Hospital of Bellvitge, the center of reference for our study population (31). The tendency to obtain a diagnosis in earlier stages in the second screening round is consistent with the results of other series (13,32) in which 50% of all invasive carcinomas detected were diagnosed in stage I.

The drawbacks of FOBT with guaiac have led to an increase in colonoscopy screening. US guidelines recognize that, although there are no randomized controlled studies of this option, compelling indirect evidence indicates that colonoscopy screening is the best way to detect most early cancers and enable the resection of most advanced premalignant polyps (5). However, if CRC screening is used as part of a public health prevention programme, it should be an integrated part of existing health care systems (18,33). Issues related to direct colonoscopy, including risk, cost, compliance and capacity, have yet to be adequately addressed. Pending issues notwithstanding, a study conducted by the US Center for Disease Control and Prevention concluded that capacity in the US is sufficient to screen with FOBT followed by colonoscopy for patients with positive findings (34). Although colonoscopy may be a screening option, some information suggests that this method is likely to be unviable for population-based screening and must be reserved for individuals with a higher risk (35). Accordingly, we consider FOBT to be the current method of choice for population-based screening, because it satisfies WHO recommendations (36) as a test for the early detection of disease.

To conclude, our results are not substantially different from other already published. Population screening with FOBT is a suitable method for detecting small precancerous lesions, key factors in reducing the incidence of CRC. In the near future, CRC screening is likely to consider personal risk related to age and gender as highly significant. A FOBT screening programme in Catalonia based on the screening model used in this pilot study is feasible, and may reduce CRC mortality rates to a degree similar to that observed in randomized trials. Colonoscopy after a positive FOBT result was well accepted by patients, and it is feasible for diagnosis and follow-up in our public health system.

**CATALAN COLORECTAL CANCER SCREENING PILOT PROGRAMME GROUP**

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