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Retrospective Study

Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain)

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Author contributions: All authors have contributed as qualified researchers in the article: Portillo I in the design and writing of the paper with Arana-Arri E, who also wrote the discussion with Gutierrez-Ibarluzea I and the statistical methodology in coordination with Martínez-Indart L, who analyzed the data and drew up the results; Idigoras I and Bilbao I registered every cancer case and reviewed all items related to quality control; Bujanda L reviewed all clinical features and contrasted the data against published articles; Gutierrez-Ibarluzea I offered feedback on all drafts in order to include an appropriate bibliography and analyze the relevance of the results to health systems to write the discussion.

Supported by The Basque Health Service, BioCruces and BioDonostia Research Institutes supported this study, since the evaluation of screening programmes such as Colorectal Cancer is a strategy included in the Health plan. Osteba (Basque Office for Health Technology Assessment of the Ministry for Health) offered the methodological support to ensure that data were aligned with the quality requirements and needs of the local health system.

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Abstract

AIM

To assess proportions, related conditions and survival of interval cancer (IC).

METHODS

The programme has a linkage with different clinical databases and cancer registers to allow suitable evaluation. This evaluation involves the detection of ICs after a negative faecal immunochemical test (FIT), interval cancer FIT (IC-FIT) prior to a subsequent invitation, and the detection of ICs after a positive FIT and confirmatory diagnosis without colorectal cancer (CRC) detected and before the following recommended colonoscopy, IC-colonoscopy. We conducted a retrospective observational study analyzing from January 2009 to December 2015 1193602 invited people onto the Programme (participation rate of 68.6%).

RESULTS

Two thousand five hundred and eighteen cancers were diagnosed through the programme, 18 cases of IC-colonoscopy were found before the recommended follow-up (43542 colonoscopies performed) and 186 IC-FIT were identified before the following invitation of the 769200 negative FITs. There was no statistically significant relation between the predictor variables of ICs with sex, age and deprivation index, but there was relation between location and stage. Additionally, it was observed that there was less risk when the location was distal rather than proximal (OR = 0.28, 95%CI: 0.20-0.40, $P < 0.0001$), with no statistical significance when the location was in the rectum as opposed to proximal. When comparing the screen-detected cancers (SCs) with ICs, significant differences in survival were found ($P < 0.001$); being the 5-years survival for SCs 91.6% and IC-FIT 77.8%.

CONCLUSION

These findings in a Population Based CRC Screening Programme indicate the need of population-based studies that continue analyzing related factors to improve their detection and reducing harm.

Key words: Colorectal cancer; Population Screening Programme; Interval cancer; Faecal immunochemical test; Colonoscopy; Diagnosis; Mortality; Survival

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Core tip: Population based screening programmes are implemented when benefits are superior to harms and risks are acceptable to healthy population. However, programmes should continuously improve their quality and efficiency. This study shows by means of a well-accepted screening strategy that there is room for improvement and those programmes could be personalized or at least, stratified. Main results show

that instead of a reduction in the cut-off points of faecal immunochemical test, other strategies such as different follow up periods for sex, stage and previous location could be more effective and minimize risks at the same time that they increase benefits.

Portillo I, Arana-Arri E, Idigoras I, Bilbao I, Martínez-Indart L, Bujanda L, Gutierrez-Ibarluzea I. Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain). *World J Gastroenterol* 2017; 23(15): 2731-2742 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i15/2731.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i15.2731>

INTRODUCTION

The Basque Country is one of the 17 autonomous regions of Spain and has a population of approximately 2200000 inhabitants. Colorectal cancer (CRC) is the most common type of cancer when taking both sexes into account and is the most frequent in men^[1]. The number of cases has increased since 1990 and there has been certain stability in mortality rate. In 2008, the year before the screening programme was implemented, there were 1869 new cases and 798 deaths were registered due to this type of cancer^[2].

Following the 2003 European Guidelines^[3] and the National Strategy against Cancer of 2006, validated in 2009^[4,5], population based screening of CRC was approved by the Basque Autonomous Government and implemented in 2009. The screening is based on the detection of occult blood in faeces (FOB) using a biennial quantitative faecal immunochemical test (FIT), targeting women and men between 50 and 69 years of age (approximately 586700 inhabitants) and a colonoscopy under sedation for FIT positive cases. With the first invitation, almost 100% of the target population was reached at the beginning of 2014; by the end of 2015, 85% of the population had been invited at least twice and 56% a third time.

The characteristics of the programme and the main results of the first invitation were published in 2013, obtaining an average participation rate of (64.3%, 95%CI: 64.1%-64.5%) higher in women^[6], finding significant differences in the rate of detection of Advanced Adenomas (AA) between women and men (OR = 0.45, 95%CI: 0.41-0.49) and CRC (OR = 0.80, 95%CI: 0.66-0.96), more frequent in men as well as the positive predictive value (PPV) for any type of adenoma which was significantly higher in men (72.4%, 95%CI: 71.2%-73.5%) than in women (48.8; 95%CI: 47.2%-50.5%), with differences depending on the age group and type of adenoma^[7]. Likewise, there were differences in participation and detection of lesions according to the index of deprivation: men on the most deprived index, having a lower participation rate (60.2%) although a higher rate in the

identification of lesions (55.7/1000) compared to the least deprived (41.0/1000)^[8].

The characteristics of CRC detected by the programme in the first and second rounds after a negative result were observed by Bujanda *et al.*^[9]; significant differences being found in location, most frequently in the second round in the right-sided colon and in a less advanced stage.

Participation and the detection rate of advanced lesions and CRC were found to be within the parameters defined by the European Guidelines of Quality (2010)^[10], which recommend 65% participation and an Adenoma detection rate between 13.3‰–22.3‰ and of CRC between 1.8‰–9.5‰. However, one aspect to bear in mind is the possible losses of the programme, which are interval cancers (ICs), and which are one of the biggest concerns of the screening programme as not only the capacity for detection is measured, but also the quality of the confirmatory diagnostic test, in this case a colonoscopy. As was pointed out by Robinson *et al.*^[11], in the Randomized Controlled Trial in Nottingham, both the positive effects (reduction of mortality because of screening) as well as the negative effects (false negatives among others) should be monitored and taken into account.

In fact, for a correct detection, it is necessary to have an organized Screening Programme and the possibility of individualized linkage with clinical databases (diagnostic procedures, pathological confirmation, hospital discharges and cancer registers), in such a way as to allow a suitable evaluation of the impact of the programmes^[12].

A standardized methodology like the proposal for GISCOR 2013^[13] is also required.

The aim of this study is to compare CRC detected by the Programme or screened cancers (SCs) and ICs detected from 2009–2015 both after a negative FIT and before the following invitation (IC-FIT), such as post-confirmatory colonoscopy cancers following a positive FIT and before a follow-up colonoscopy, depending on the lesion found (IC-colonoscopy).

MATERIALS AND METHODS

The Basque Country's Population Based Screening Programme has the support of a Coordinating Centre which plans, organizes, monitors and evaluates the individualized invitation process as well as the test results and follow-up of all positive cases. This is possible thanks to the interaction of software, specially designed for the programme, with clinical databases and cancer registries. The software contains a system of encryption and access in accordance with the current data protection laws as it is all systematically anonymized for analysis and subsequent publication. Participants in the programme are informed and consent to the use of their data. The FIT tests used were FOB Gold in 2009 and 2010 (Sentinel Diagnosis SpA, Milan Italy) and OC-Sensor from 2010 onwards

(Eiken Chemical Co. Tokyo, Japan). Only one sample was collected, as the haemoglobin concentration cut-off (f-Hb) 100 ng Hb/mL of buffer, which is equivalent to 17 µg Hb/g faeces in Sentinel and to 20 µg Hb/g faeces in OC-Sensor, as the comparison of both tests showed^[14].

The screening is based on the detection of occult blood in faeces (FOB) using a biennial quantitative FIT, targeting women and men between 50 and 69 years of age (approximately 586700 inhabitants) and a colonoscopy under sedation for FIT positive cases.

The tests were analyzed in the laboratories of the publicly-funded hospital system under strict internal and external quality control. The colonoscopies were also performed in publicly-funded hospitals by qualified and trained specialists in the digestive system; sedation was also provided by the same endoscopy team, although 20% included the presence of an anaesthetist. The recommendations of the European Guidelines (2010) and Spanish Guide for Quality Control (2011)^[15] were followed in all cases. The resected polyps and CRC with biopsy and/or endoscopic or surgical resection were analyzed in laboratories of Pathological Anatomy by staff skilled in histopathology of gastrointestinal disease with specific emphasis on CRC. CRC was diagnosed when the neoplastic cells pass through the muscularis mucosae, invading the submucosae (\geq pT1). All CRCs were registered according to the criteria of the American Joint Committee on Cancer (AJCC)^[16].

Methodology of interval cancer detection

Detection of ICs after a negative FIT (IC-FIT): prior to a subsequent invitation, all negative cases from a previous round are linked to the register of hospital discharges with ICD-9 1530–1548, in primary and secondary diagnosis, ICDO-10 C18–C21 of hospital registers and population-based Cancer registries as well as codes of Pathology. In all coinciding cases, the qualified staff from the Programme's Coordinating Centre checked the clinical history, including the cases as ICs which complied with the criteria of having a negative FIT result in the previous invitation (0–24 mo or more in case of a delay in the invitation to the screening programme). To ensure against any possible losses, this process was repeated on an annual basis with all negative FITs from the previous 24 mo.

Detection of ICs after a positive FIT and confirmatory diagnosis without CRC detected and before the following recommended colonoscopy (IC-colonoscopy): these data were annually cross-referenced with all the colonoscopies with a different result to detected CRC by the Programme or Screen-detected Colonoscopies (SCs), following the same methodology as the previous section. It was considered to be IC if a CRC was detected prior to the scheduled follow-up: 10 years with an invitation for a FIT in the case of a normal result/non-neoplastic polyps; 5 years with an invitation for a FIT in the case of a Low-Risk Adenoma (1–2 tubular

adenomas and/or ≤ 10 mm and/or without high grade dysplasia); a colonoscopy after 3 years in the case of an Intermediate Risk Adenoma (3-4 adenomas and/or ≥ 10 mm and < 20 mm and/or a vellos component and/or a high grade dysplasia; colonoscopy in < 1 year in the case of a detected High-Risk Adenoma (≥ 5 adenomas and/or ≥ 20 mm). Given that the follow-up period is longer, cases detected up to May 2016 were taken into consideration, which means that the number could increase in the next five years.

In all the cases of SCs and ICs, the following variables were taken into account when analyzing: (1) type of participant (first invitation, regular - participated in the last two invitations, irregular - participated in at least one previous invitation), ICs were not considered in the case of not participating or refusing a colonoscopy after a positive FIT; (2) round of invitations; (3) sex and age; (4) deprivation index assigned to each patient - socioeconomic deprivation index (DI) of their area of residence, using the methodology of the MEDEA project^[17]; (5) quantitative result of the test in μg Hemoglobin/g of faeces in invitations prior to a negative FIT; result of a confirmatory colonoscopy and date; diagnostic method in ICs and date; (6) details of CRC: location, size, morphology, TNM, degree of differentiation, state and type of first treatment; and (7) survival with a link to the Population Death Register until 1st December 2016.

For the description of qualitative variables frequency tables and percentages were used, for quantitative variables means and standard deviation or median and interquartile range (IQR). For comparison between two groups contrast of exploratory hypotheses have been made using exact test of Fisher or χ^2 for categorical variables. To compare quantitative variables and categorical variables with 2 categories *t*-test or the non-parametric Mann Whitney *U* test was used. Logistic regression analysis was performed with interval vs screening detected CRC as the outcome variable. Overall survival after CRC diagnosis for the patients with interval CRC was compared, by Kaplan-Meier estimation, long-rank test and Cox proportional hazard ratios. The survival time was measured from the date of CRC diagnosis to date of death or censoring resulting from the end of the study period (December 1, 2016). Significance was set at the 5% level. The analysis was performed by a biomedical statistician using IBM SPSS Statistics 23.0.

RESULTS

From January 2009 to December 2015, 1193602 people were invited to the CRC Screening Programme, with a participation rate of 68.6%. Of the participants, 49687 obtained a positive result, with 2518 cancers diagnosed, with a 92.7% acceptance rate for screening colonoscopies. The global adenoma detection rate by the Programme for the period studied was 57.25%.

Seven point five percent (204/2722) of the diagnosed

cancers were IC. Of the colonoscopies performed, 18 cases of IC-colonoscopy were found before the recommended follow-up and of the 769200 negative FITs, 186 IC-FIT were identified before the following invitation. Table 1 shows the characteristics associated with the three types of cancers analyzed in this study. Significant statistical differences were observed by age, round of invitations and characteristics of the tumour such as: location, stage, morphology, degree of differentiation and size of the tumour.

Table 2 shows the medians of f-Hb and their corresponding IQR in the invitation, just before the diagnosis of IC. No differences between the variables analyzed were observed: sex, age, deprivation index, time to diagnosis; neither was there differences found in the characteristics of the tumour: location, state, morphology, degree of differentiation and size. What was observed in both the analysis of variables as well as in the global (Median: 2.8 μg Hb/faeces; IQR: 0.4-9.9) was that the values of the f-Hb of the FIT with a negative result prior to the diagnosis of IC-FIT were found to be very distant from the cut-off point established as positive (20 μg Hb/g faeces). Patients diagnosed after two rounds with a negative result, also presented low values in the first round (Median: 0.8 μg Hb/g faeces; IQR: 0.0-4.5).

In Table 3 the characteristics of negative colonoscopies are shown for CRC prior to the diagnosis of an interval cancer (IC-colonoscopy) and after a positive FIT result. More than a third of the diagnosed cancers were seen to be in the sigma location and 27.8% in the caecum. In 55.5% of colonoscopy cases prior to screening, polyps were detected and removed, although in two cases their removal was in the same location as the diagnosed cancer, in sigma. In 83.3% of the colonoscopies, the caecum was reached and the rate of colonic preparation was adequate in the majority of cases (66.7%). It should be clarified that out of the 18 IC-colonoscopies, 12 had an adequate preparation, 2 had a bad quality of colonic cleansing and 4 were not described in the report.

On the other hand, consultations were made about 85% of these interval cancers for suspected symptomatology - rectal bleeding (30.1%) and abdominal pain (29.6%) being the most frequent causes, respectively. On the other hand, in those cases where there were no symptoms, anaemia was the diagnostic sign in 5.4% of the cases.

Figure 1 shows the distribution of the different types of colorectal cancer by stages at the time of diagnosis and its link to their location. A larger proportion of advanced stages were observed, firstly in the rectum and then in the proximal colon, in both the IC-FIT and IC-colonoscopy.

Table 4 shows that there was no statistically significant relation between the possible predictor variables of interval cancer by sex, age and deprivation index, but there was a relation between location and stage. However, it was observed that there was less risk

Table 1 Characteristic of interval cancers and screen-detected colorectal cancers *n* (%)

	Interval cancers		Screen-detected (SCs)	<i>P</i> value
	FIT	Post-colonoscopy		
Total	186 (6.8)	18 (0.7)	2518 (92.5)	-
Patient characteristics				
Sex				
Male	125 (67.2)	10 (55.6)	1651 (65.6)	0.601
Female	61 (32.8)	8 (44.4)	867 (34.4)	
Age (yr)				
Mean (SC)	60.2 (4.9)	62.0 (3.5)	61.7 (3.4)	0.042
50-54	28 (15.1)	0 (0)	375 (14.9)	0.001
55-59	53 (28.5)	5 (27.8)	539 (21.4)	
60-64	61 (32.8)	10 (55.6)	709 (28.2)	
65-69	44 (23.7)	3 (16.7)	895 (35.5)	
Round of invitation				0.001
1	143 (76.9)	16 (88.9)	1615 (64.1)	0.086
2	40 (21.5)	2 (11.1)	680 (27.0)	
3	3 (1.6)	0 (0)	223 (8.9)	
Type participation				
Initial	149 (80.1)	17 (94.4)	1863 (74.0)	0.192
Regular	35 (18.8)	1 (5.6)	639 (25.4)	
Irregular	2 (1.1)	0 (0)	16 (0.6)	
Deprivation Index				
1 (least deprived)	42 (23.9)	3 (16.7)	521 (21.4)	0.0001
2	43 (24.4)	1 (5.5)	503 (20.6)	
3	29 (16.5)	6 (33.4)	539 (22.1)	
4	38 (21.6)	2 (11.1)	461 (18.9)	
5 (most deprived)	24 (13.6)	5 (27.8)	414 (17.0)	
Unknown	0 (0)	1 (5.5)	0 (0)	
Time to diagnosis (months)			-	< 0.0001
Median (IQR)	13.5 (8.5-18.9)	28.1 (16.5-40.1)		
Range	1.5-39.4	5.6-61.2		
Cancer characteristics				
Location				< 0.0001
Proximal ¹	68 (36.6)	7 (38.9)	478 (19.0)	< 0.0001
Distal ²	58 (31.2)	9 (50.0)	1529 (60.7)	
Rectum	58 (31.2)	2 (11.1)	404 (16.0)	
Unknown	2 (1.1)	0 (0)	107 (4.2)	
Stage				< 0.0001
I	43 (23.1)	4 (22.2)	1376 (54.6)	0.002
II	36 (19.4)	2 (11.1)	408 (16.2)	
III	57 (30.6)	7 (38.9)	566 (22.5)	
IV	50 (26.9)	5 (27.8)	152 (6.0)	
Unknown	0 (0)	0 (0)	16 (0.6)	
Morphology				
ADC, NOS	139 (74.7)	15 (83.3)	1823 (72.4)	0.002
ADC in adenomatous polyp	4 (2.2)	0 (0)	121 (4.8)	
Carcinoid tumor	0 (0)	0 (0)	7 (0.3)	
ADC in villous adenoma	6 (3.2)	0 (0)	154 (6.1)	
ADC in tubulovillous adenoma	10 (5.4)	0 (0)	174 (6.9)	
Mucinous ADC	5 (2.7)	2 (11.1)	42 (1.7)	
Mucin-producing ADC	3 (1.6)	0 (0)	23 (0.9)	
Signet ring cell carcinoma	0 (0)	0 (0)	4 (0.2)	
Other	15 (8.1)	0 (0)	64 (2.5)	
Unknown	4 (2.2)	1 (5.6)	106 (4.2)	
Degree of differentiation				< 0.0001
Well differentiated	76 (41.1)	7 (38.9)	988 (39.2)	0.022
Moderately differentiated	59 (31.9)	7 (38.9)	1061 (42.2)	
Poorly differentiated	14 (7.6)	1 (5.5)	86 (3.4)	
Undifferentiated/anaplastic	33 (17.8)	2 (11.1)	320 (12.7)	
Unknown	3 (1.6)	1 (5.5)	63 (2.5)	
Size (mm)				
Median (IQR)	20 (8.0-40.0)	38.0 (30.0-60.0)	26.0 (19.7-40.0)	
Range	2.0-90.0	9.0-80.0	2.0-95.0	

Treatment				< 0.0001
Endoscopic resection	5 (2.7)	0 (0)	733 (29.1)	
Surgery	56 (30.1)	9 (50.0)	182 (7.2)	
Surgery and neoadjuvant therapy	106 (57.0)	7 (38.9)	1332 (52.9)	
Palliative procedure	18 (9.7)	2 (11.1)	164 (6.6)	
Unknown	1 (0.5)	0 (0)	107 (4.2)	

¹Cecum, Ascending, Hepatic Flexure, and Transverse; ²Splenic Flexure, Descending, Sigmoid. ADC: Adenocarcinoma; FIT: Faecal immunochemical test.

Table 2 f-Hb values of previous negative screening test in interval cancer cases

	Median f-Hb (µg Hb/g faeces)	IQR	P value
All	2.8	0.4-9.9	-
Sex			
Male	3.4	0.2-10.0	0.409
Female	1.9	0.4-9.8	
Age (yr)			0.380
50-54	1.9	0.2-6.9	
55-59	3.0	0.6-13.0	
60-64	2.8	0.2-8.6	
65-69	4.0	0.4-12.5	
Deprivation Index			0.887
1 (least deprived)	3.0	0.6-11.9	
2	2.6	0.0-10.2	
3	4.2	1.1-12.4	
4	4.0	0.4-11.2	
5 (most deprived)	2.6	0.0-8.7	
Time to diagnosis (mo)			0.795
Within 1 yr	3.4	0.2-10.6	
1-2 yr	2.5	0.5-9.6	
Location			0.171
Proximal ¹	1.9	0.0-9.3	
Distal ²	3.8	0.3-13.7	
Rectum	3.9	0.7-9.1	
Unknown	1.0	0.0-...	
Stage			0.927
I	2.0	0.0-9.7	
II	2.6	0.2-10.6	
III	3.2	0.7-9.8	
IV	4.0	0.2-9.9	
Unknown			
Morphology			0.550
ADC, NOS	3.0	0.6-10.0	
ADC in adenomatous polyp	10.0	2.0-17.2	
ADC in villous adenoma	0.5	0.0-9.8	
ADC in tubulovillous adenoma	2.4	0.0-9.3	
Mucinous ADC	0.4	0.0-12.5	
Mucin-producing ADC	14.0	0.0-...	
Other	1.7	0.0-6.0	
Unknown	1.0	0.0-6.9	
Degree of differentiation			0.600
Well differentiated	2.8	1.0-9.0	
Moderately differentiated	4.4	0.6-13.0	
Poorly differentiated	0.6	0.0-5.6	
Undifferentiated/anaplastic	4.0	0.0-9.4	
Unknown	2.0	0.0-...	
Size (mm)			0.586
< 10	1.4	0.4-12.4	
10-19.99	1.0	0.0-7.9	
≥ 20	2.9		

¹Caecum, ascending, hepatic flexure, transverse; ²Splenic flexure, descending. ADC: Adenocarcinoma; IQR: Interquartile range.

when the location was distal rather than proximal (OR = 0.28, 95%CI: 0.20-0.40, $P < 0.001$), with no statistical significance when the location was in the rectum as opposed to proximal. The risk of having an advanced

stage at the time of diagnosis was significantly higher in relation to the stage of the cancers detected out the programme said relation in Stage II: 2.73 (1.75-4.24); in Stage III 3.31 (2.24-4.88) and in Stage IV: 10.6

Table 3 Characteristics of post colonoscopy colorectal cancers at the time of diagnosis

	<i>n</i> (%)
Interval CRC tumor site	
Appendix and caecum	5 (27.8)
Ascending	0 (0)
Hepatic flexure	1 (5.6)
Transverse	1 (5.6)
Splenic flexure	0 (0)
Descending	2 (11.1)
Sigmoid	7 (38.8)
Rectum	2 (11.1)
Unknown	0 (0)
Polyp found on the Screening colonoscopy	
Yes	10 (61.1)
No	8 (38.9)
Polyp frequency	
Median (IQR)	2.0 (1.0-3.5)
Range	1-6
Previous resection in the same location	
Yes	2 (11.0)
No	16 (89.0)
Report of incomplete Screening colonoscopy	
Yes ²	3 (16.7)
No	15 (83.3)
Polyp size on the Screening colonoscopy	
≥ 10 mm	
Yes	2 (11.1)
No	16 (88.9)
Polyp histology (<i>n</i> = 10)	
Hyperplastic polyp	0 (0)
LRA	6 (60.0)
AA	4 (40.0)
Bowel preparation	
Inadequate	2 (11.1)
Adequate ¹	12 (66.7)
Unknown	4 (22.2)
Diverticulosis	
Yes	5 (27.8)
No	13 (72.2)

¹Boston scale ≥ 7; ²Complementary radiological test (Barium Enema or Computerized Tomography) was performed after colonoscopy. AA: Advanced adenoma; LRA: Low risk adenoma; CRC: Colorectal cancer; IQR: Interquartile range.

(6.93-16.18), respectively.

With regard to the analysis of survival rate, an average follow-up time was 3.6 ± 1.6 years (Range: 0.46-7.7 years). Significant differences in survival were found between groups ($P < 0.0001$), when comparing the screening-detected group (SCs) with the ICs. Figure 2 shows the survival graph and the percentages for groups at 1, 3 and 5 years, SCs having a better prognosis. It was also observed that for women, a distal rather than a rectal location, stages I - II has a significantly better survival prognosis as do SCs, as the risk of death is 3 times lower in relation to interval cancers (ICs).

DISCUSSION

Screening programmes are implemented into health systems to detect early and cure or improve the

Table 4 Multivariate analysis of patients and tumors predictors of interval cancers compared with screen-detected cancers

	% with CI	OR (95%CI)	<i>P</i> value
Sex			
Female	69 (33.8)	1 (ref.)	
Male	135 (66.2)	1.03 (0.76-1.39)	0.860
Age (yr)			
50-54	28 (13.7)	1 (ref.)	
55-59	58 (28.4)	1.44 (0.90-2.31)	0.127
60-64	71 (34.8)	1.34 (0.84-2.11)	0.206
65-69	47 (23.0)	0.70 (0.43-1.14)	0.153
Deprivation			
1 (least deprived)	45 (23.3)	1 (ref.)	
2	44 (22.8)	1.01 (0.66-1.56)	0.954
3	35 (18.1)	0.75 (0.48-1.19)	0.222
4	40 (20.7)	1.00 (0.64-1.57)	0.984
5 (most deprived)	29 (15.0)	0.81 (0.50-1.32)	0.396
Location			
Proximal ¹	74 (36.8)	1 (ref.)	
Distal ²	67 (33.3)	0.28 (0.20-0.40)	< 0.0001
Rectum	60 (29.9)	0.96 (0.67-1.38)	0.824
Stage			
I	47 (23.0)	1 (ref.)	
II	38 (18.6)	2.73 (1.75-4.24)	< 0.0001
III	64 (31.4)	3.31 (2.24-4.88)	< 0.0001
IV	55 (27.0)	10.59 (6.93-16.18)	< 0.0001

¹Caecum, ascending, hepatic flexure, transverse; ²Splenic flexure, descending.

prognosis of the pathologies which they are aiming to address. There are two main aims in the case of early detection of cancer programmes: detecting the cancer at early stages to be able to cure it and, in the later stages, to begin the treatment to improve the chances of survival and the quality of life of the individuals concerned. There are a series of factors which determine the value and quality of the programmes. On the one hand, the cases which are not identified (false negatives) and the cases which are "wrongly identified" (false positives) and, on the other hand, the time periods in which there is no diagnosis and new premalignant or malignant lesions may occur. There are various screening methods and it is necessary to determine which is the most effective and which are the periods or typology of lesion (location, size...) to guarantee the best result for them to be effective and efficient. This study on the basis of the Population Based CCR screening Programme in the Basque Country, following a rigorous methodology in the diagnosis of both SCs and ICs, presents relevant data regarding both the methodology used as well as results of interest. The validity of these results is based on a programme with a high participation rate and acceptance of the diagnostic tests including colonoscopy, an effective cross-referencing between databases and adequate follow up in a public health system with universal coverage.

Various limitations can be found in the study's findings. One of these is that when comparing FIT ICs to post-colonoscopy Interval Cancers, the latter are

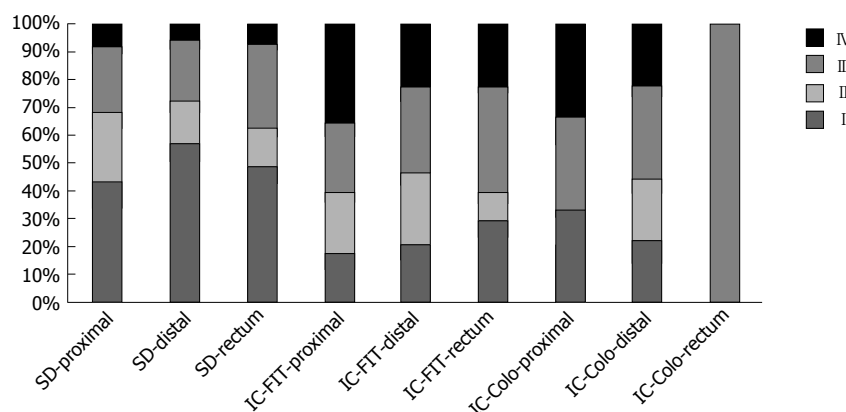
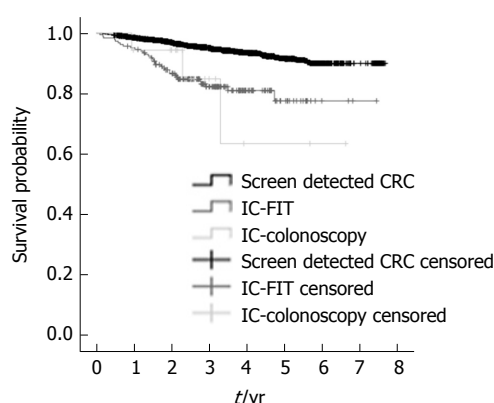


Figure 1 Distribution of colorectal cancer stages by location and type.



	1-yr survival	3-yr survival	5-yr survival
Screen detected CRC	98.5%	95.0%	91.6%
IC FIT	95.2%	82.4%	77.8%
IC colonoscopy	94.4%	85.0%	63.8%

Figure 2 Kaplan-Meier survival curve by different colorectal cancer types.

underestimated as they require a longer follow-up time and therefore the number of cases could increase in the next few years, hence the figures for post-colonoscopy ICs should be considered with caution. The same is not true regarding the data related to each individual case and their characteristics which justify the importance of this study.

Another limitation of this study is not having taken other risk factors of patient-related ICs into account, such as habits or other biochemical or genetic markers in order to provide a more detailed analysis. These factors are to be explored in prospective future studies. Advanced Adenomas were not analyzed either, as they were in the study by Stegeman *et al.*^[18]. In the FIT arm (OC Sensor) of the clinical trial, with a cut off of 50 ng/100 mL, defined a person with an advanced neoplasia (AA + CRC) found in a colonoscopy as a false negative. In Stegeman *et al.*^[18] study, of 1112 participants, 65 (64%) had a false negative result, age (OR = 1.04 per additional year) and smoking (OR = 2.02) were found to be risk factors and sensitivity

in women was lower. However, these results coincide with our programme's regarding age and sex. The classification and definition used by Sanduleanu *et al.*^[19] was also employed in this study, using a modified Delphi methodology defining Interval Cancer as a "colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended exam" (Table 5). Classification was established based on the systematic revision from January 2004 to January 2014, checking the time of diagnosis, location, stage and histology as well as the etiology (missed, incompletely resected polyps or biological factors associated with a more rapid progression). In the aforementioned revision, people with hereditary CRC syndromes or inflammatory bowel diseases were excluded. This classification used in our study will allow a more standardized comparison of the results, which has not happened in previous studies.

Our results show similarities to those found by Zorzi *et al.*^[20] in Italian CRC screening programmes. In these studies, ICs which had had a negative result with only a FIT (OC-Sensor in 4 programmes and FOB Gold in one of them with a cut-off of 100 ng/100 mL) were analyzed. The follow-up period was from 2002-2007 in 267789 invitations *via* linkage with hospital discharges and an active search in clinical histories and pathological anatomy reports. Of the 126 ICs identified, compared with the expected 572 cases, 15.3% and 31.0% were found in the first and second period (interval-years), respectively. Of the total number of cases identified, in 86 cases with known stages, 21.2% were stage I, 22.3% stage II and 56.5% stages III/IV. The most advanced stage was found in the proximal colon (76.6% as opposed to 46.8% in the distal colon above the splenic flexure). The sensitivity for the proximal colon was 68.3% (95%IC: 57.7%-76.8%). Even though cases of those not invited and not participants were not analyzed, the most frequent cases in men with ICs and in the left-sided colon (distal colon and rectum) coincided exactly with those shown by Gill *et al.*^[21] in their comparative study of SCs (322 cases), ICs (192 cases), controls

Table 5 Hazard ratios and 95%CI for interval cancer vs screen-detected cancers

	Hazard ratio	95% CI	P value
Sex			
Female (ref)			
Male	1.39	1.01-1.93	0.049
Age (yr)			
50-54 (ref)			0.451
55-59	1.37	0.79-2.36	0.258
60-64	1.22	0.72-2.07	0.463
65-69	1.47	0.89-2.44	0.137
Deprivation Index			
1 (least deprived) (ref)			0.839
2	0.89	0.54-1.46	0.639
3	1.01	0.63-1.62	0.956
4	0.90	0.54-1.51	0.696
5 (most deprived)	1.16	0.72-1.88	0.537
Location			
Rectum (ref)			< 0.001
Proximal ¹	1.17	0.78-1.77	0.456
Distal ²	0.56	0.39-0.82	0.003
Stage			
I (ref)			< 0.001
II	1.99	1.11-3.54	0.020
III	3.67	2.31-5.83	< 0.001
IV	26.54	17.37-40.56	< 0.001
CRC type			
Screen detected CRC (ref)			< 0.0001
IC FIT	3.31	2.25-4.85	< 0.0001
IC colonoscopy	3.49	1.11-10.97	0.032

¹Caecum, ascending, hepatic flexure, transverse; ²Splenic flexure, descending.

never invited (511) and non-participants (311) in the National Health Service. Although these were done with gFOBT, in which ICs were found to be more frequent in men (60.4%, $P = 0.003$), in the left-sided colon (66.7%, $P = 0.003$). However, the study undertaken by Steel *et al.*^[22], points out that where location is concerned, screening cancers are diagnosed in earlier stages than interval cancers in the colon (I - II: 62.2% vs 21.5%) but not in the rectum (I / II: 54.3% vs 49.9%); unlike in our study in which all screening cancers were diagnosed in earlier stages than those of interval cancers.

There was a significant reduction in the detection rate of SCs in subsequent rounds, which was also seen in ICs. When comparing the three rounds of screening with gFOBT of 48500 invitations with an average participation rate of 61.8%, 57.0% and 58.7% respectively, Moss *et al.*^[23] found a sensitivity of 71% and 50% in men and women, respectively, in the first round and 65% and 51%, respectively, in the second round, observing the same pattern of reduction. In our study, the detection rates of ICs were found to have the same trend, which points to the fact that screening is a protective factor, corroborated in our study by the high participation rate. In this sense, no significant differences were found regarding participation in SCs and ICs, unlike those found by Steele *et al.*^[24], who

categorized the cancers detected in Scotland with the gFOBT Programme according to the pattern of participation, finding that of the 1927 CRC detected, 405 were SCs, 529 were ICs and 993 CRC in people who had not participated in over 2 years, and of which 658 had never participated. The stage was similar in those who had participated one, two or three times, indicating that it was not likely that the prognosis of SCs would be worse if it had not been detected in the first invitation. Similarly, differences were found between SCs and ICs in the pattern of participation.

Regarding the study by Garcia *et al.*^[25], differences were found in the detection rate of ICs in rounds. An increase was observed, even though different tests were used in four invitations with gFOBT and FIT, and a shorter follow-up period than in our case, 30 mo of monitoring (30480 tests carried out), finding 97 SCs, 74 ICs after a negative test result, 17 after an inconclusive result and 2 in post-colonoscopy follow-up. The rate of ICs increased in the rounds (32.4%-46.0%). In their study, they also found that the ICs were found predominantly in the rectum (OR = 3.66, 95%CI: 1.51-8.88), as opposed to our study in which they were more commonly found in a proximal location in the case of IC-FIT and distal in IC-colonoscopy. However, very similar data were found regarding the most advanced stages of ICs ($P = 0.025$) and there were no significant differences regarding sex or location.

Many studies published over the last few years have tried to study the impact of ICs in screening programmes as well as the factors associated with its appearance. Robertson *et al.*^[26] study, which monitored 9167 patients who had had a colonoscopy with adenomas diagnosed after a follow-up of an average of 47.2 mo, identified 58 ICs, 0.6%, similar to our findings of IC-colonoscopy (0.7%). Fifty-two percent of the CRC were classified as possible missed lesions, 24% as probable new lesions and 19% possibly related to a previous and incomplete resection of polyp. One of the risk factors associated with an IC-colonoscopy could therefore be an incomplete resection, which was shown in 11% of the cases in our study, which is an important fact in the quality of the programme and its possible consequences. le Clercq *et al.*^[27], in their follow-up of people diagnosed with CRC (5107 patients) five years after an index colonoscopy, where 147 ICs were identified or postcolonoscopy CRCs (PCCRCs) found that 8.8% were seen to have had an incomplete resection in the previous colonoscopy. Location could also be another risk factor to be taken into account. In this study as well as others which have been published in recent years [Brenner *et al.*^[28], Samadder *et al.*^[29] and Richter *et al.*^[30], a proximal location or right-sided colon seem to be a risk factor when developing an IC; similar to our study in which a proximal location was significantly more frequent than distal]. These locations would benefit from further

targeted research.

Moreover, the study by Samadder *et al*^[29], carried out on 26851 patients who had had a colonoscopy, found 159 ICs which developed between 6-60 mo after the colonoscopy. In 57.2% of the cases, previous adenomas had been identified, which is a similar percentage to our study (61.1%). As in other studies, another factor associated with IC is the stage. In the study by Samadder *et al*^[29], as well as that by Brenner *et al*^[28], ICs are diagnosed in more advanced stages than screening cancers, which also coincides with our study.

Neither sex nor age seem to play an important part in the diagnosis of an IC. Samadder *et al*^[29], like our study, did not find any relation between these two factors. On the other hand, Richter *et al*^[30] identify being over the age of 60 as a risk factor. These differences could be due to the context of implementation of the programmes, but new studies should corroborate or reject this hypothesis.

Another key point in screening programmes is the f-Hb cut-off. In a study carried out by Digby *et al*^[31] with FIT analyzing interval cancers, they concluded that the average value of f-Hb just before the round prior to the diagnosis of interval cancer (2.8 µgr f-Hb/g faeces) is much lower than the cut-off used most frequently in screening programmes (20 µgr f-Hb/g Faeces). In this study, by reducing the cut-off to 10 µgr f-Hb/g Faeces, the rate of positives would increase from 2.4% to 9.4%, with an important increase in the need for colonoscopies (increasing the number of false positives), which would increase the proportion of interval cancers by 38.3%. In this study, a similar average of f-Hb to this study was observed, so interval cancers do not seem to have f-Hb levels close to positive in previous rounds. This fact could reduce both cut-off and sensitivity without an important increase in the number of colonoscopies needed. Moreover, it is considered that an increase in false negatives would affect the balance risks/benefits of the programmes, increasing the risk for healthy people unnecessarily and reducing the number needed to harm (NNH).

In our study, a survival pattern was seen to be greater in SCs and also in women, even though significant differences were not found in the deprivation index. These data are in keeping with those analyzed by Gill *et al*^[32], although a different classification of the stage was used in our study. In their study, 322 SCs were compared with 192 ICs with gFOBT, according to their stage, and differences were found in survival in stages Dukes C and D, higher in SCs than in ICs ($P = 0.014$ and $P = 0.04$, respectively). In fact, Cox's proportional hazards regression showed that Dukes' stage, location of tumour and diagnostic group ($HR = 0.45$, 95%CI: 0.29-0.69, $P < 0.0001$) as SCs were all found to have a significant impact on patients' survival.

These data also coincide with the study carried out by Morris *et al*^[33], in which a better prognosis is

estimated, with earlier stages in screening cancers (95.9% one-year survival rate) and interval cancers (78.4% one-year survival rate), which is the greatest difference when compared to our study. Patients with screening cancers were offered a higher percentage of treatments with curative intent than those with interval cancers, which is the same as in our study.

On the basis of our results, there are a wealth of options, among which a comparison of CRCs in people who were not invited (in fact, total coverage was not achieved until the beginning of 2014), people who have not participated in any of the rounds of the programme, people who refused a colonoscopy after a positive test and CRC detected during the scheduled follow-up stand out. These comparisons would help us to know the programme's outcomes and quality? more precisely and the impact of early detection by screening as opposed to other strategies, as developed by Morris *et al*^[33].

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COMMENTS

Background

Colorectal cancer (CRC) is one of the main leading causes of death in the world. There is a consensus that population based screening programmes help improving life expectancy and quality of life of those suffering from CRC by early detecting CRCs and early management of patients. Interval Cancers in CRC screening programmes could be seen as failures of detection and they are due to the inexistence of diagnostic tools that ensure 100% sensitivity without harming healthy people (false positives).

Research frontiers

Except for those well-known genetic disorders that are directly linked to CRC (5% of the CRC) to whom personalised strategies are proposed, the rest of the population are managed equally in CRC population based CRC screening programmes. In this sense, there is a need to know the characteristics of interval cancer (ICs), in order to achieve a better understanding of CRC development and thus, propose context and patients' tailored strategies that could improve the efficiency of CRC screening programmes while innovators are trying to find more accurate diagnostic tools.

Innovations and breakthroughs

This research has studied the differences among ICs and Screening-detected cancers (SCs) on the basis of a high rate participation and population based screening programme (100% coverage and more than 70% participation rate). When studying ICs and SCs we have found that the survival rate of SCs is higher than ICs. Furthermore, we observed relation between ICs, lesion location and stage.

Applications

These findings help designing more efficient and tailored strategies that reduce

unnecessary harm and improve current achievements regarding quality of life and overall life expectancy. Under current diagnostic paradigm, these findings can define a less harmful and more efficient alternative to those that propose an increase of diagnostic cut-off points to improve detection while increasing harms (false positives) and costs (increasing number of unnecessary colonoscopies).

Terminology

Interval cancer refers to lesions that are detected within the periods in which no diagnostic strategies are performed. Interval Cancers FIT (IC-FIT) refers to interval cancers that are detected after a negative FIT and before the following invitation inside a CRC screening programme. In the case, the period among invitations is two years. Interval cancers colonoscopy (IC-colonoscopy) refers to interval cancers that are post-confirmatory colonoscopy cancers following a positive FIT and before a follow-up colonoscopy. SCs refer to lesions that have been detected within the programme in each round.

Peer-review

It's an interesting and informative manuscript, although the manuscript has a little complicated design to understand, especially in terms of data presentation.

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