

Screening for colorectal cancer in Italy: 2008 survey

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Abstract

We present the main results from the fifth survey of the Italian screening programmes for colorectal cancer carried out by the National Centre for Screening Monitoring (Osservatorio Nazionale Screening, ONS) on behalf of the Ministry of Health. By the end of 2008, 87 programmes were active (14 had been activated during the year), and 52.9% of Italians aged 50-69 years were residing in areas covered by organised screening programmes (theoretical extension). Ten Regions had their whole population covered. In the South of Italy and Islands, 12 new programmes were activated in 2008, including those of Abruzzo and Molise Regions, with an increase of theoretical extension from 7% to 21%. The majority of programmes employ the faecal occult blood test (FOBT), while some have adopted flexible sigmoidoscopy (FS) once in a lifetime, or a combination of both.

Overall, about 2,593,000 subjects were invited to undergo FOBT, 71% of those to be invited within the year. The adjusted attendance rate was 47.5% and approximately 1,171,000 subjects were screened. Large differences in the attendance rate were observed among Regions, with 10% of programmes reporting values lower than 30%. Positivity rate of FOBT programmes was 5.9% at first screening (range 2.0-11%) and 4% at repeat screening (range 2.9-6.5%). The average attendance rate for total colonoscopy (TC) was 81.3% and in three Regions it was lower than 70%. Completion rate of TC was 92.2%. Among the 665,264 subjects attending screening for the first time, the detection rate (DR) per 1,000 screened subjects was 2.7 for invasive cancer and 13.1 for advanced adenomas (AA, adenomas with a diameter ≥ 1 cm, with villosity/tubulo-villosity type or with high-grade dysplasia). As expected, the corresponding figures in the 552,391 subjects at repeat screening were lower (1.3‰ and 8.3‰ for invasive cancer and AA, respectively). The DR of cancer and adenomas increased with age and was higher among males. Many programmes reported some difficulties in guaranteeing TC in the appropriate time frame to FOBT+ subjects: in 16.0% of cases the waiting time was longer than two months.

Seven programmes employed FS as the screening test: 58.8% of the target population (about 50,000 subjects) were invited and 8,135 subjects were screened, with an attendance rate of 27.2%. Overall, 83% of FS were classified as complete. Overall TC referral rate was 13.5% and the DR per 1,000 screened subjects was 4.7 and 47.5 for invasive cancer and AA, respectively.

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Keywords: colorectal cancer screening programmes survey, Italy

This paper presents the data from the survey carried out by the National Centre for Screening Monitoring (Osservatorio Nazionale Screening, ONS) on behalf of the Ministry of Health, regarding the activities performed by Italian screening programmes for colorectal cancer

during 2008. The previous surveys are available at the ONS website.¹

Important differences prevail among colorectal cancer screening programmes in Italy. The main difference regards the type of screening test performed. While the majority of programmes em-

ploy the faecal occult blood test (FOBT), some have adopted flexible sigmoidoscopy (FS) once in a lifetime, or a combination of both (figure 1). Moreover, FOBT programmes have different targets as far as age is concerned. Invitation to attend screening starts at the age of 50 in all but one programme, however the maximum age is 69 or 70 years in most programmes, or even 74 or 75 years. Most FS programmes invite a single cohort of subjects aged 58 while two invite subjects aged 60 instead.

All FOBT programmes are set to invite their target population by mail every 2 years to undergo a 1-time immunochemical FOBT, without any dietary restriction. Quantitative haemoglobin analysis is performed by automated instruments using the 100 ng Hb/mL threshold to determine positivity (apart from one programme that use 80 ng Hb/mL). People with a negative FOBT are notified of their results by mail and they are advised to repeat screening 2 years later. Non responders to the first invitation are mailed a reminder, usually within 6 months. Subjects with a positive screening test are contacted by phone

to undergo a total colonoscopy (TC) or, when a complete colonoscopy is not possible, a double-contrast barium enema X-ray. Colonoscopies are usually performed at an endoscopic referral centre, during dedicated sessions. Patients with screen-detected neoplasms are referred to surgery or endoscopy, and then enrolled in a follow-up programme.

The GISCoR (Gruppo Italiano per lo Screening Coloretale, Italian Group for Colorectal Cancer Screening) published in 2007 an *Operative report of quality indicators* for the evaluation of colorectal cancer screening programmes.² For each indicator the reference standards (acceptable, desirable) are provided. Table 1 shows the indicators and standards utilised in this paper. The *Operative report* is available at the ONS website.

Data completeness

Only 48 of the 87 programmes that took part in the survey (57%) provided complete data. The items with the lowest level of completeness were screen-detected lesions and surgery: time to surgical treatment, stage at diagnosis, kind of treatment (endoscopic *vs* surgical). However, some programmes were unable to provide baseline data, either.

Programmes activated as of 31-12-2008

In Italy, colorectal cancer screening programmes were mainly activated in 2005 and 2006. After a pause observed in 2007, 14 new programmes were launched during 2008, 12 of which in the South of Italy and Islands, including those of Abruzzo and Molise (figure 2). As of 31st December 2008, 87 programmes were active in 12 Regions (table 2). In particular, programmes on a regional-scale basis were activated in Abruzzo, Basilicata, Emilia-Romagna, Friuli-Venezia Giulia, Lombardia, Molise, Toscana, Umbria, Valle d'Aosta and Trentino. The vast majority of programmes (n=80) employ the faecal occult blood test (FOBT), while three have adopted flexible sigmoidoscopy (FS)

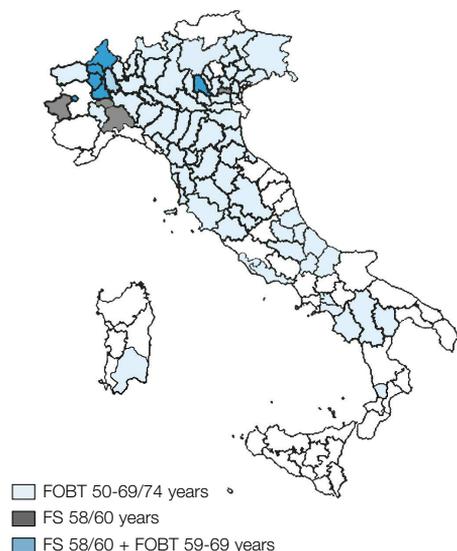


Figure 1. Colorectal cancer screening programmes: first level test and target population.

Indicator	Standard			
	acceptable		desirable	
Actual extension	>80%		>90%	
Compliance to invitation	>45%		>65%	
Positivity rate	FOBT:	first test: <6% repeat tests: <4.5%	FOBT:	first test: <5% repeat tests: <3.5%
	FS:	<8%	FS:	<6%
Inadequate screening tests	FOBT:	<1%	FS:	<5%
	FS:	<10%		
Attendance to further assessment	FOBT:	>85%	FOBT:	>90%
	FS:	>90%	FS:	>95%
Complete FS rate	>85%		>90%	
Complete TC rate	>85%		>90%	
Detection rate	FOBT		FOBT	
	Carcinoma	first test: >2.0‰ repeat tests: >1.0‰	Carcinoma	first test: >2.5‰ repeat tests: >1.5‰
	Adv. adenoma	first test: >7.5‰ repeat tests: >5.0‰	Adv. adenoma	first test: >10‰ repeat tests: >7.5‰
	FS		FS	
	Carcinoma	>3.0‰	Carcinoma	>4.0‰
	Adv. adenoma	>35%	Adv. adenoma	>40%
Detection rate of adenomas at FS	males	>10%	males	>15%
	females	>5%	females	>10%
PPV of FOBT at colonoscopy for advanced adenoma or carcinoma	first test	>25%	first test	>30%
	repeat tests	>15%	repeat tests	>20%
PPV of FS at colonoscopy for proximal advanced adenoma	>7%		>10%	
Delay between FOBT screening and negative result	>90% within 21 calendar days		>90% within 15 calendar days	
Delay between the call for assessment and the assessment procedure	>90% within 30 calendar days		>95% within 30 calendar days	
Proportion of screen-detected cancers in stage III+	<30%		<20%	

FOBT: Faecal Occult Blood test; FS: Flexible Sigmoidoscopy; TC: Total Colonoscopy; PPV: Positive Predictive Value.

Adapted from Zorzi M, et al., 2007.

Table 1. Indicators and reference standards.

once in a lifetime, and four a combination of both. The results of FOBT programmes are reported in the following sections; data of FS programmes are presented in a specific section.

In order to describe the national situation, it is necessary to simplify the variability of the target population among the programmes, by narrowing the analysis to a homogeneous age group. Therefore, we provide the data related only to subjects aged 50-69 years, that are common to all FOBT programmes and constitute the real target population of most of them.

Theoretical extension

Theoretical extension refers to eligible subjects residing in areas covered by organised screening programmes.

According to the National Institute of Statistics (Istat), at the beginning of 2008 approximately 14,381,000 people aged 50-69 years were living in Italy.³ The number of subjects residing in areas where an organised screening programme is active was 7,605,000, with a national theoretical extension of 52.9%, six points higher than that observed in 2007 (46.6%) (table 2).

Region	Programmes	Total resident subjects (N) ¹	Subjects residing in areas covered by a programme (N)	Theoretical extension (%) ²
Abruzzo	6	326,673	326,673	100.0
Basilicata	1*	132,952	132,952	100.0
Calabria	1	451,498	28,471	6.3
Campania	4	1,245,926	314,155	25.2
Emilia-Romagna	11*	1,067,933	1,067,933	100.0
Friuli-Venezia Giulia	1*	325,180	325,180	100.0
Lazio	4	1,355,068	457,057	33.7
Lombardia	15*	2,381,977	2,381,977	100.0
Molise	1*	74,122	74,122	100.0
Piemonte ^o	6	672,515	179,726	26.7
Sardegna	1	417,825	133,525	32.0
Toscana	12*	940,341	940,341	100.0
Trentino	1*	122,618	122,618	100.0
Umbria	4*	231,456	231,456	100.0
Valle d'Aosta	1*	30,109	30,109	100.0
Veneto	18	1,171,715	858,479	73.3
Other Regions	0	3,463,696	0	0.0
ITALY	87	14,381,381	7,604,774	52.9

¹ residents 50-69 years old at 01.01.2008 (source: Istat).

² proportion of eligible subjects residing in areas covered by organised screening programmes.

* regional-based programmes.

^o In the Region Piemonte, programmes screen only subjects aged 59-69 years.

Table 2. Main data of FOBT programmes by Region in 2008: 50-69 year old subjects.

Compared to the previous years, the Northern and Central Regions reported a small increase, while in the South of Italy and Islands the theoretical extension increased from 7 to 21% thanks to the activation of many new programmes and of the reopening of the regional programme of Basilicata (table 3).

Extension of invitations

We define the extension of invitations as the proportion of half the resident population who was sent a screening invitation.

During 2008, about 2,593,000 subjects were invited to attend a screening programme, accounting for 71.3% of the target population to be invited in the year (table 4). Particularly significant results were reached by Emilia-Romagna and Lombardia, which confirmed the full capacity reached in the previous years, and Molise, which reached an extension of 87%. The low levels reported in other Regions are due either to the recent activation of many programmes or to the chronic difficulty of many programmes in ensuring the necessary number of invitations.

	2006		2007		2008	
	N	%	N	%	N	%
North	4,420,000	66.1	4,823,000	71.6	4,966,022	73.3
Centre	1,361,000	48.5	1,487,000	52.1	1,628,854	56.3
South - Islands	460,000	10.0	323,000	7.0	1,009,898	21.4
ITALY	6,240,000	44.3	6,634,000	46.6	7,604,774	52.9

Table 3. Subjects residing in areas covered by FOBT screening programmes and theoretical extension (proportion of eligible subjects residing in areas covered by organised screening programmes) by year and geographical area: 50-69 year old subjects.

Region	Invited subjects (N)	Extension of invitation ¹		Screened subjects (N)	Adjusted compliance ²	
		(%)	10° - 90° percentile		(%)	10° - 90° percentile
Abruzzo	21,850	13.3	3.5 - 29.7	9,644	45.8	40.4 - 70.1
Basilicata	9,734	33.4	-	3,065	33.1	-
Calabria	8,269	55.1	-	2,336	29.9	-
Campania	41,247	53.6	28.2 - 94.2	21,361	53.9	33.3 - 58.9
Emilia-Romagna	518,433	99.8	71.8 - 110.3	271,664	53.7	49.2 - 58.8
Friuli-Venezia Giulia	32,564	24.4	-	11,831	36.8	-
Lazio	35,132	14.9	4.1 - 28.0	11,331	33.3	22.6 - 38.2
Lombardia	1,139,599	93.8	63.1 - 125.3	440,836	42.0	31.9 - 61.3
Molise	32,392	87.1	-	10,847	33.6	-
Piemonte ^o	57,269	63.9	-	16,803	29.3	-
Sardegna	600	0.9	-	144	24.7	-
Toscana	332,884	69.8	18.3 - 95.1	163,885	50.8	33.5 - 58.4
Trentino	17,831	28.8	-	9,255	53.6	-
Umbria	69,538	59.4	38.7 - 80.5	25,660	37.9	35.0 - 43.7
Valle d'Aosta	10,276	68.5	-	6,792	66.1	-
Veneto	265,793	69.0	20.3 - 106.2	165,304	63.7	43.1 - 74.6
ITALY	2,593,411	71.3	9.5 - 108.2	1,170,578	47.5	29.8 - 65.7

¹ proportion of the annual target population that was actually invited.

² subjects attending out of those invited, excluding from denominator those reporting a recent test and those who did not receive the invitation letter.

^o In the Region Piemonte, programmes screen only subjects aged 59-69 years.

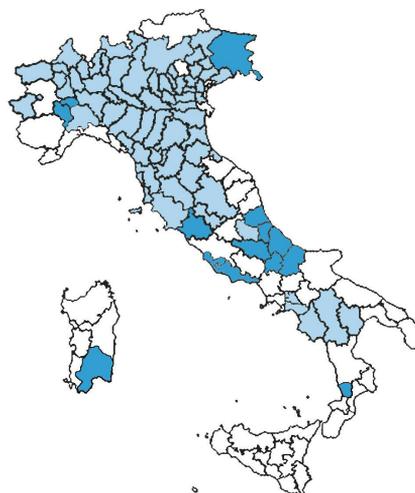
Tabella 4. FOBT programmes: extension of invitations and adjusted compliance by Region: 50-69 year old subjects.

This interpretation is confirmed if we exclude the newly-activated programmes from the analysis: the average extension is 83.7%, however 10% of programmes with the lowest extension (10th percentile) invited less than 30% of the annual target. Overall, in 2008 the 10th percentile was lower than 10% and only 47% of programmes reached the GISCOR acceptable standard (>80%) (54% in 2007).

Intra-regional variability, illustrated in table 4 through the percentiles for the Regions with at least four programmes, is high in all but Emilia-Romagna and Lombardia, where all programmes reached high levels.

Compliance to invitation

We report data on adjusted compliance, calculated as the proportion of subjects invited to attend screening (minus those with a wrong address and those excluded after invitation for a recent test) who underwent a screening test.



■ start before 2008
 ■ start during 2008

Figure 2. Colorectal cancer screening programmes by year of start.

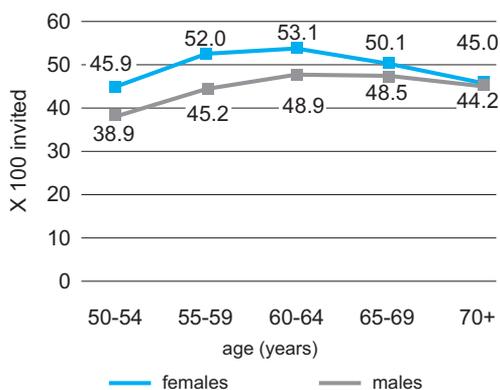


Figure 3. FOBT programmes: adjusted compliance by age and gender.

Overall, about 1,170,578 people were screened with FOBT in 2008. Adjusted compliance (47.5%) slightly increased as compared to 2007 and 2006 (46.3% and 44.6%, respectively) (table 4).

The analysis of compliance by Region shows a high inter-regional variability, with values ranging from 24.7% in Sardegna to 66.1% in Valle d'Aosta (table 4). Moreover, a high intra-regional variability in almost all Regions must be highlighted. The compliance obtained by single programmes ranged from 21% to 79%. The 10th percentile (30%) is clearly insufficient to guarantee suitable coverage of the population and, consequently, efficiency of a screening programme. Overall, 57% of programmes reached the acceptable (>45%) and only 11% the desired GISCOR standard (>65%).

Attendance by age and gender shows higher values in females (49.7% vs 44.8% for males), but only in younger age groups (figure 3). Compliance to FOBT is highest in the central age groups. It is of interest to analyse the attendance by screening history of invited subjects or, more precisely, by their history of attendance to invitation. After the prevalence round, programmes invited essentially three categories of people:

- subjects that had never been invited before (new entries to the target population: essentially 50 years old subjects and immigrants);

- subjects who had already attended a previous invitation (from which a high attendance may be expected);

- subjects who had already been invited, but never attended (who are less likely to comply).

The attendance of subjects invited for the first time was 41.4% with a trend by sex and age similar to the global one. Eighty-one percent of subjects who had already responded attended the new invitation, with lower values in males, particularly at younger ages. It must be pointed out that attendance of the 10% of programmes with the worst value was lower than 66%.

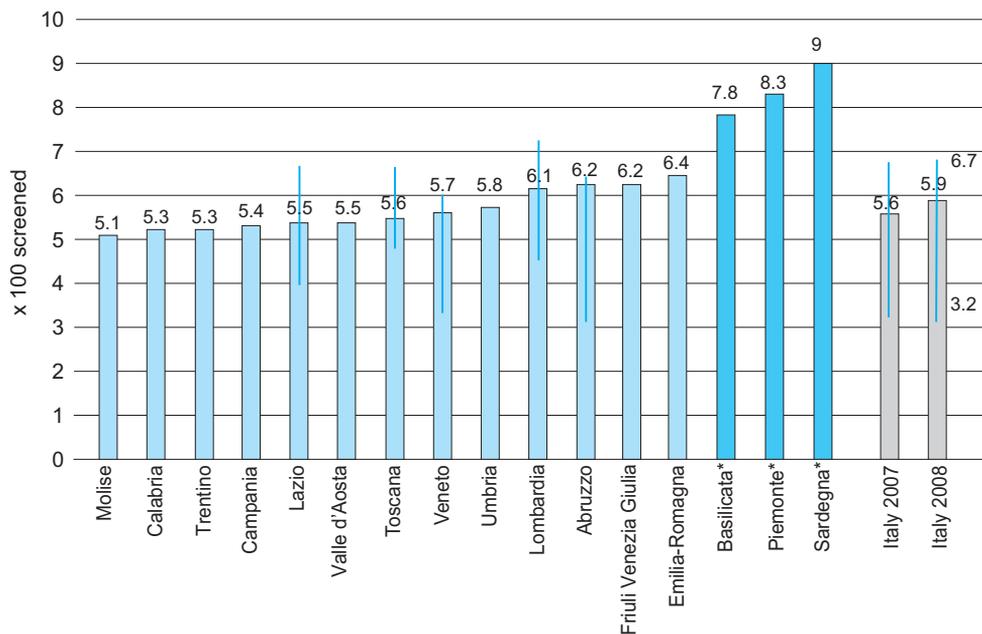
Finally, attendance of subjects who had never responded to previous invitations was 19.6% and decreased from the youngest (21%) to the oldest (14%) age group.

Diagnostic indicators

The most important diagnostic indicators (positivity rates, detection rates, positive predictive values) are strongly influenced by the underlying frequency of the disease in the screened population. Colorectal cancer and pre-cancerous lesions are more frequent in males than females, and tend to increase progressively with age in both genders.⁴ Moreover, the disease is more frequently detected in subjects at first screening test (prevalence round) than in those at repeat tests (incidence round).

Therefore, these indicators are presented separately for subjects at first and repeat screening tests, as well as by gender and five-year age groups.

The mean values of these indicators by Region are standardised by age and gender, using the national mean as standard population. Standardisation was carried out for subjects at first screening test, since a noteworthy variability in the distribution of screened subjects according to age and gender was observed among the programmes. Such variability was essentially due to the newly activated programmes preferentially inviting subjects in older age groups. In subjects at repeat screening, we



* not standardised (screenee aged 60+ only).

Figure 4. Standardised (by age and gender, utilising the national media as standard population) proportion of FOBT+ at first screening by Region, with 10th and 90th percentiles.

observed an elevated homogeneity among programmes and therefore we did not standardise the indicators. The data refer to 1,217,655 subjects screened during 2008 for which data are available; of these, 665,264 (55%) underwent first screening and 552,391 (45%) subsequent examinations.

Positivity rates

In subjects at first screening, the proportion of positive FOBT was 5.9%, with an elevated homogeneity among the mean values of Regions with a large number of screenees (figure 4). The proportion of FOBT+ reported by each programme ranges from 2.0% to 11% (10th-90th percentiles: 3.2-6.8%).

In subjects at repeat screening, the proportion of FOBT+ is 4.5%, with a lower variability between programmes (range: 2.9-6.5%).

Fifty-nine percent of programmes met the accept-

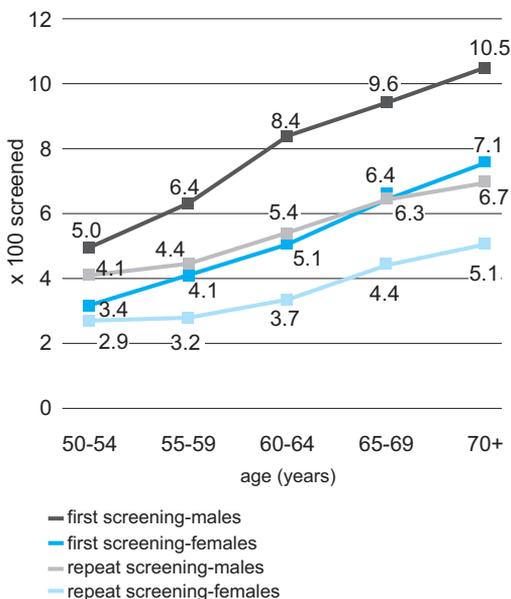


Figure 5. Proportion of FOBT+ by age and gender.

able standard at the first (<6%) exam and 68% at repeat exams (<4.5%).

As shown in figure 5, the proportions of positive results are higher in males at both first and repeat examinations, and they increase progressively with age. The reduction in FOBT+ between first and repeat exams is larger in males, and increases progressively with age.

Inadequate tests

Inadequate tests are essentially due to an incorrect sampling by the subject. During 2008, 88% of programmes reported a proportion of inadequate FOBT lower than 1%, while only five programmes reported a result exceeding 2%. Overall, the national mean value was 0.6%.

Attendance to colonoscopy assessment

Attendance to colonoscopy assessment is essential for screening programmes to achieve colorec-

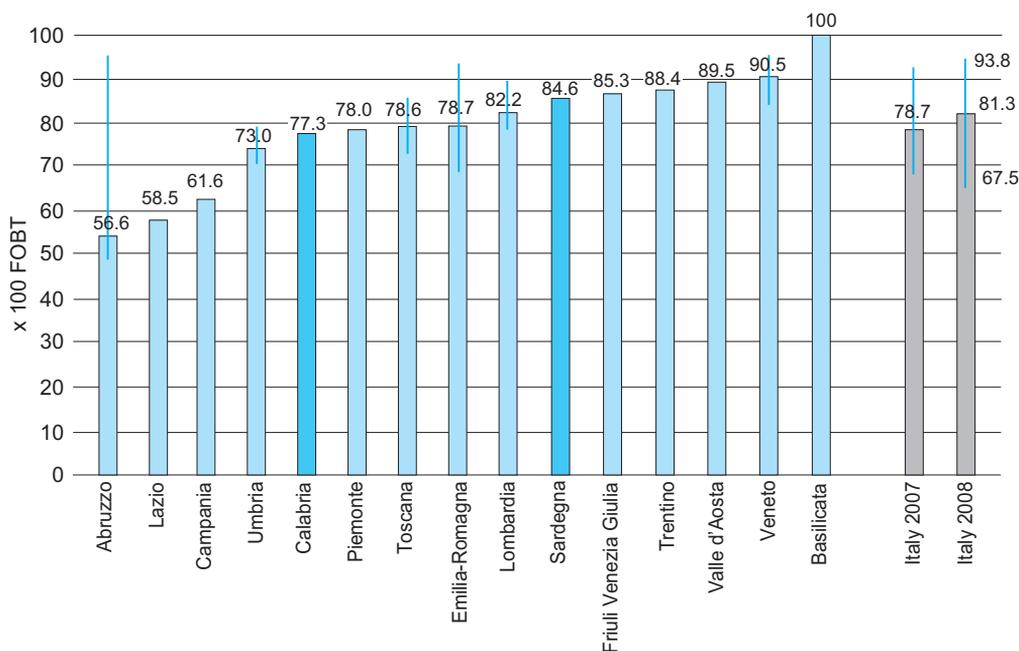
tal cancer mortality reduction. Overall, 81.3% of FOBT+ subjects attended colonoscopy in 2008. This result is lower than that observed in 2007 (78.7%). Only 22% of programmes met the desired standard (>90%).

Attendance was higher in males (82.3%) than in females (80.0%), as described in the literature.⁵ Some studies explored the reasons for non-attendance also in screening settings. One of the most important reasons is a feeling of shame. Women, as a matter of fact, reported some concern about the gender of the endoscopist, who is usually a man.^{6,7}

The lowest values were reported in the Regions of the Centre and South of Italy (Abruzzo, Lazio, Campania), the highest in Basilicata, Valle d'Aosta and Veneto (figure 6).

Complete colonoscopies

Besides compliance to colonoscopy, a cornerstone



Note: deep blu columns refer to Regions whose indicators are based on a limited number of cases.

Figure 6. FOBT programmes: attendance to colonoscopy by Region, with 10th and 90th percentiles.

element in measuring the effectiveness of a screening programme is the completeness of the endoscopic examination. Overall, 92.2% of the colonoscopies carried out in 2008 were classified as complete, a highly satisfactory result. Eighty-two percent of programmes met the acceptable (>85%) and 61% the desired standard (>90%).

Compared to 2007, we observed an increase in variability among Regions, partly due to the worsening of the quality of data. Mean regional values ranged from 63.8% in Basilicata to 96.8% in Trentino. The values of single programmes ranged from 63.8 to 100%, and the lowest values were due to a small number of outliers (10th percentile: 80.1%).

Programmes generally reported higher proportions of complete exams in males compared to females (overall 94.1 % *vs* 91.5%, respectively), as reported in the literature.⁸

Fifty-four programmes reported data about further assessments in case of an incomplete TC, which took place only in 45% of cases.

Complications at colonoscopy

Fifty-five programmes reported the data about complications at TC, relative to 38,764 examinations overall.

Sixty-nine cases of bleeding were reported, 64 of which were during operative TCs, with a rate of 0.03% for non-operative and 0.34% for operative TCs, both in line with the GISCOR standards (<0.5% and <2.5%, respectively). Twenty-three perforations were recorded (21 during operative TCs), with a rate of 0.01% for non-operative and 0.11% for operative TCs, in line with the GISCOR standards (<0.5% and <2.5%, respectively).

Overall these data are very good; however, a high variability in the collection and recording of criteria was observed.

Most programmes do not provide a systematic data collection at a fixed interval after the examination (e.g., 30 days), possibly resulting in an underestimation of complications, including the

most serious ones. On the other hand, the data about bleeding might refer to self-limiting episodes that did not require any intervention such as hospitalisation, blood transfusion, or endoscopic interventions. In that case the indicator would be overestimated.

Detection rates

We describe the detection rates (DR) of invasive carcinomas, advanced adenomas (i.e., adenomas with a diameter ≥ 1 cm, with villous/tubulo-villous type, or with high-grade dysplasia), and non-advanced adenomas (smaller in size, tubular type, and low grade dysplasia). DRs are defined as the number of histologically-confirmed lesions detected per 1,000 screened subjects.

Overall, in subjects screened for the first time 1,796 carcinomas, 8,633 advanced adenomas, and 5,101 non-advanced adenomas were detected. Therefore the DR was 2.7‰ for carcinoma, 13.1‰ for advanced adenomas, and 7.7‰ for non-advanced adenomas (figure 7). Sixty-eight percent of programmes reached the acceptable standard for carcinoma (>2‰), and 77% for advanced adenoma (>7.5‰).

However, the ratio between the DRs of advanced

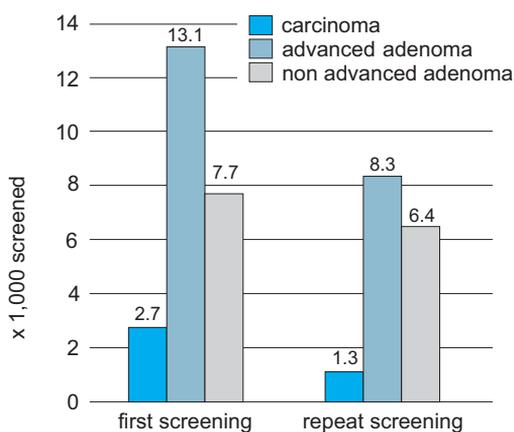


Figure 7. FOBT programmes: detection rates of carcinoma, advanced adenoma and non-advanced adenoma at first and repeat screening.

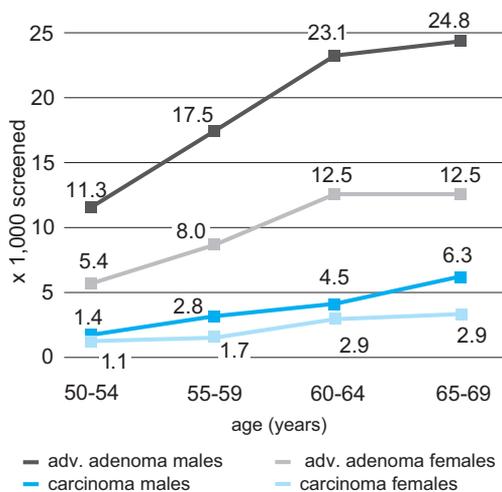


Figure 8. FOBT programmes: detection rates of carcinoma and advanced adenoma by age and sex at first screening.

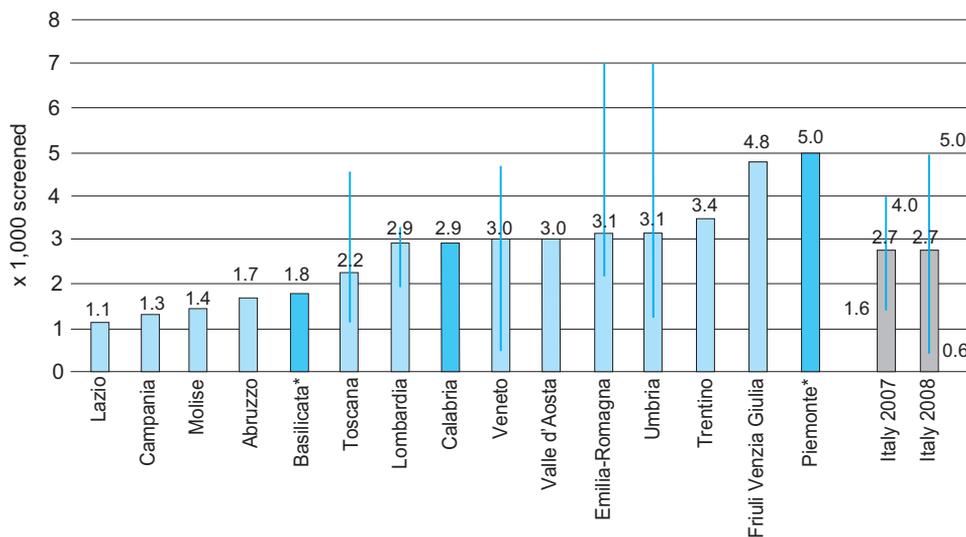
and non-advanced adenomas does not reflect the underlying prevalence of the two groups of lesions in the screened population, the frequency of non-advanced adenomas being higher than that of ad-

vanced adenomas. The DR of advanced adenomas is higher, since FOBT appears to be highly selective for these lesions, which tend to bleed more easily than non-advanced adenomas, as described in the literature.⁹

In subjects undergoing repeat testing, 722 carcinomas, 4,545 advanced adenomas and 3,568 non-advanced adenomas were detected. As expected, the DRs were lower than the corresponding figure at first exams (figure 7). Seventy-four percent of programmes reached the acceptable standard for carcinoma (>1%), and 91% for advanced adenoma (>5%).

As expected on the basis of underlying epidemiological figures, the DRs of the different lesions are higher in males and progressively increase with age in both genders (figure 8). This trend may be observed both in subjects screened for the first time and in those at repeat screening, even if with lower values (data not shown).

With the exception of Regions with unstable data due to the limited number of screened subjects, we

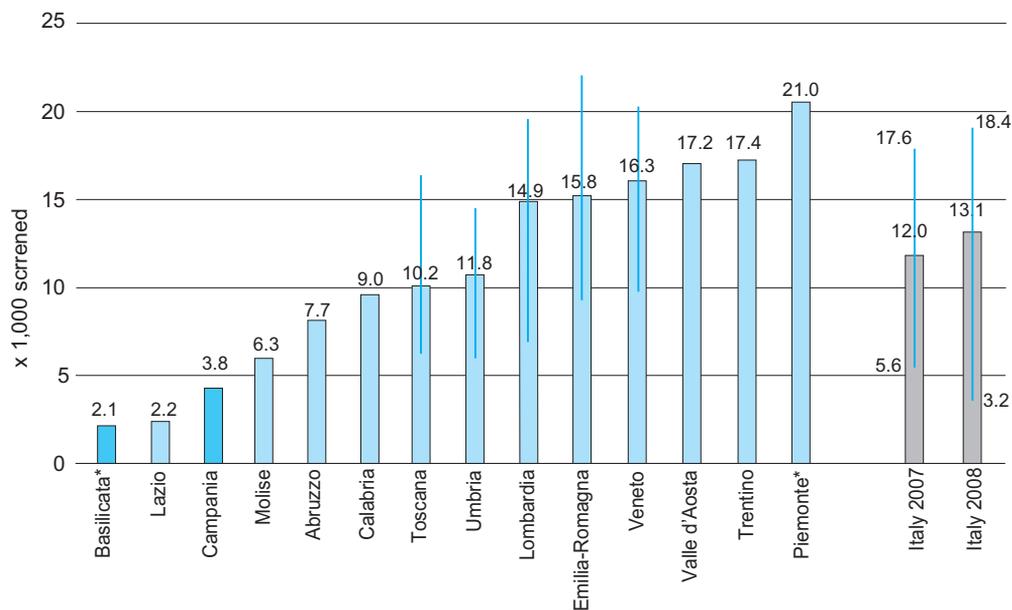


* not standardised (screened aged 60+ only).

Note: deep blu columns refer to Regions whose indicators are based on a limited number of cases.

Figure 9. FOBT programmes: standardised (by age and gender, utilising the national media as standard population) detection rates of carcinoma at first screening, by Region, with 10th and 90th percentiles.

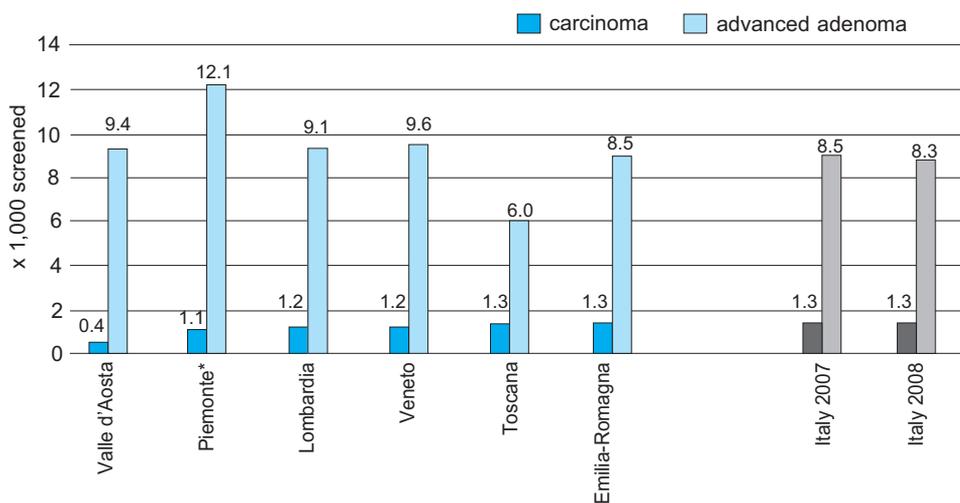
SCREENING FOR COLORECTAL CANCER IN ITALY



* not standardised (screenee aged 60+ only).

Note: deep blu columns refer to Regions whose indicators are based on a limited number of cases.

Figure 10. FOBT programmes: standardised (by age and gender, utilising the national media as standard population) detection rates of advanced adenoma at first screening, by Region, with 10th and 90th percentiles.



* screenee aged 60+ only.

Figure 11. FOBT programmes: detection rates of carcinoma and advanced adenoma at repeat screening, by Region.

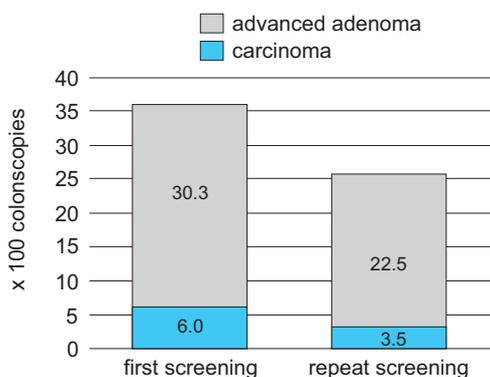


Figure 12. FOBT programmes: positive predictive value (PPV) of colonoscopy for carcinoma and advanced adenoma at first and repeat screening.

observed a high variability among the mean regional values of carcinoma DRs (from 1.1‰ in Lazio to 4.8‰ in Friuli-Venezia Giulia; in Piemonte, programmes screened only subjects aged 60-69 years, figure 9), and advanced adenomas (2.1-2.2‰ in Basilicata and Lazio, 17.4‰ in Trentino, figure 10).

We observed an increasing North-South trend in the detection rates of carcinoma and advanced adenoma, as expected according to the underlying epidemiological figures (carcinoma: North 3.0‰, Centre 2.2‰, South-Islands 1.3‰; advanced adenoma: North 15.0‰, Centre 9.1‰, South-Islands 4.2‰). At repeat examinations, a higher homogeneity was reported among Regions for the DR of carcinoma (Valle d'Aosta: 0.4‰, Emilia-Romagna: 1.3‰) and advanced adenoma (Toscana: 6.0‰, Veneto: 9.6‰) (figure 11).

Positive predictive value

Positive predictive value (PPV) of FOBT+ at colonoscopy is defined as the number of subjects with a diagnosis of carcinoma or advanced adenoma, as a proportion of FOBT+ subjects that underwent colonoscopy.

In 2008, the FOBT showed a noteworthy capability of selecting subjects with a high risk of in-

vasive carcinoma or advanced adenoma, as already reported in the previous years. In fact, among the 29,495 subjects at first screening round who underwent a colonoscopy after a FOBT+, a diagnosis of carcinoma was formulated in 6% and advanced adenoma in a further 30.3% (figure 11). Among the 20,212 subjects at repeat screening, the corresponding values were respectively 3.5% for carcinoma and 22.5% for advanced adenoma.

Eighty-three percent of programmes reached the acceptable standard for subjects at first screening (>25%) and 93% for those at repeat screening (>15%). Similar values had also been observed in the previous years.

Once again, males showed consistently higher values than females and an increasing PPV trend was observed with age, but only for carcinoma (data not shown).

Waiting times

In order to reduce the anxiety of screened subjects, the delay between the test and the mailing of a negative result or the carrying out of a further assessment for those positive must be kept as short as possible. Since FOBT is a laboratory test, it can be carried out quite quickly (as compared to the reading of mammograms and Pap smears), therefore the delay between the test and the mailing of a negative result is generally short. In fact, about 92% of letters after a negative result were mailed within 21 days.

On the contrary, we recorded serious difficulties in guaranteeing a colonoscopy to FOBT+ subjects within a short period of time. Overall, colonoscopy was carried out within 30 days after FOBT only in 44% of cases (41% in 2007) and only three programmes met the acceptable standard (>90% within 30 days). Sixteen percent of subjects had to wait more than two months. The situation was particularly problematic in most Regions, with the exception of Trentino and Basilicata (83% and 80% within 30 days, respectively).

Finally, surgery was performed within 30 days after diagnosis in 64% of cases, and in a further 24% within two months.

FS screening programmes

FS is proposed as a first level test by 5 programmes in Piemonte and 2 in Veneto. Three of these programmes also offer FOBT to subjects refusing FS screening and to those up to 69 years of age. The principal data are presented in [table 5](#).

Overall, during 2008, the 7 programmes invited 20,028 subjects, corresponding to a 58.8% actual extension over their target population (n=49,622): two of these programmes showed values near to 100%, three had very low levels (lower than 33%). Taking all programmes together, 8,135 subjects were screened with FS. Compliance to invitation was 27.2% (range: 12.1-39.6%), slightly lower than that reported in 2007 (27.7%). In all programmes, compliance was higher for males in comparison to females (overall: 29.9% *vs* 24.7%), as currently reported in the literature.

Compliance to FS screening was lower than for FOBT. However, the comparison is related to different geographical areas. Some programmes offer FOBT to subjects refusing FS screening. This strategy makes it possible to increase the overall

coverage and to reduce gender differences. In Torino the proportion of subjects who underwent at least one test was 38% in both sexes.

Since FS is performed on a «once in a lifetime» basis, the proportion of complete exams should be as high as possible. On the other hand, caution must be taken to avoid perforations, bleeding, or other complications. Overall, 83% of FSs were classified as complete, with higher levels in males (88%) than in females (79%). This result is worse than the 88% recorded in 2007 and is below the GISCoR acceptable standard (>85%). Quite a high variability between programmes was recorded (range 75-98%) and the average is strongly influenced by the performance of a single programme (Verona: 75%).

Generally, the programmes referred 17.4% of screened males and 9.0% of females, respectively, to colonoscopy assessment. Only in 40% of the cases was the reason prompting colonoscopy an advanced adenoma, which, according to the literature, is associated with an increased probability of neoplasia in the proximal colon.

The overall attendance rate of the assessment (85%) was higher than that observed for the FOBT screening, probably due to a greater motivation of the subject to undergo further assess-

	Males	Females	Total
Screened (N)	4,346	3,789	8,135
Screened 2007 (N)	4,489	4,189	8,678
Reason prompting colonoscopy (%)			
advanced adenoma*	7.0	2.9	5.1
other**	10.3	6.1	8.4
Detection rate (‰)			
carcinoma	6.8	2.2	4.7
advanced adenoma	65.0	27.5	47.5
non advanced adenoma	114.1	68.1	92.7
PPV (%)**			
carcinoma	0.5	0.0	0.3
advanced adenoma	7.1	1.5	4.1

* at least one advanced adenoma (with a diameter ≥ 1 cm, with villous/tubulo-villous type or with high-grade dysplasia); 3 or more adenomas with diameter <10 mm, with tubular type and low grade dysplasia.

** proximal colon.

Table 5. Main results of FS programmes.

ment following a diagnosis of advanced adenoma. Colonoscopy completeness rate was 90.3%, and all centres reached high levels (range 84.1-100%). Among the subjects referred to colonoscopy, the prevalence of proximal advanced lesions (advanced adenomas plus cancers) ranged between 0% and 14%.

Overall, FS programmes detected 36 carcinomas, of which 34 in the distal tract of the colon, and 366 advanced adenomas, with a DR of 4.7% and 47.5%, respectively. In accordance with the risk of disease, a higher prevalence of colorectal cancer, advanced and non-advanced adenomas is evident in males than in females.

When comparing the DRs of FS and FOBT programmes, we observed a higher sensitivity of FS for adenomas (the DRs are more than 10 times higher for non-advanced adenomas and almost 5 times higher for advanced adenomas), while the difference is much lower for carcinoma.

However, the interpretation of these data is limited by the different age of screened subjects and by the need to consider the cumulative sensitivity of FOBT ensured by repeat screening tests.

Stage at diagnosis

Overall, 1,796 cancers were detected in subjects at first screening and 722 at repeat screening. Seventy-three programmes reported the information about cancerised adenomas, which represented

25.5% of cancers at first screening and 24.2% at repeat screening. FS programmes detected 36 cancers, 11 of which were cancerised adenomas.

As already observed in the previous years, many programmes did not collect any data about stage at diagnosis, while information provided by others is incomplete. Therefore, stage is available only for 1,957 cases (77.7% of the total). The incompleteness of this information is one of the most critical issues of Italian programmes encountered during 2008.

Table 6 shows the distribution by stage at diagnosis of cases screen-detected by FOBT and FS programmes. Overall, 28.9% of cases were in stage III+ at diagnosis, in agreement with the acceptable standard (<30%). As for the proportion of cases in stage III-IV, small differences were reported between cases at first and repeat screening.

Surgery

This survey collects data about the kind of therapy performed on carcinomas, cancerised adenomas and advanced adenomas, and distinguishes between surgical intervention and endoscopic resection alone. Overall, data were provided for 87% of carcinomas and 85% of advanced adenomas.

Seventy-nine percent of carcinomas underwent surgery, while in 19.8% of cases the treatment was limited to endoscopic resection. This percentage increased to 28.4 considering only pT1 cases. As for advanced adenomas, treatment was exclusively endoscopic in 96.6% of cases.

Discussion

After the pause observed in 2007, the theoretical extension of colorectal cancer screening showed a 6% increase in 2008, with 2,554 carcinomas and 13,544 advanced adenomas being detected by screening, which makes the Italian experience one of the most advanced in the world.

By the end of the year, 14 new programmes were started, 12 of which were in the South of Italy and Islands. A positive sign came from the pres-

Stage	FOBT programmes		FS programmes (N=28)
	first screening (N=1,156)	repeat screening (N=585)	
I	38.3	50.3	39.3
I*	10.1	5.1	14.3
II	21.2	18.6	17.9
III-IV	30.4	26.0	28.6

Stage I: T1 or T2, N0, M0

Stage I*: T1, NX

Stage II: T3 or T4, N0, M0

Stage III-IV: lymphnode involvement or distant metastases

Table 6. Stage distribution of screen detected cancers (%). Cases with known stage.

ence of new programmes in otherwise uncovered Regions such as Molise (with a regional programme), Calabria and Sardegna. In the North of Italy, we must point out the start of a regional programme in Friuli-Venezia Giulia. Overall, therefore, we observed a partial reduction in the delay in the South of Italy and Islands, where the theoretical extension was 21%. There are still five Regions without any screening programme.

Compared to 2007, extension of invitations was lower, due to the start of many new programmes that were active only for part of the year. If we consider only the programmes that had been activated before 2008, extension of invitations increases to nearly 83%. The situation varies from Region to Region. In many, all programmes reached the desired level of extension, therefore proving that, with adequate planning and fund raising, it is possible to achieve the desired volumes of activity.

On the other hand, the huge variability in extension between programmes underlines a chronic difficulty of many programmes begun in previous years in reaching and maintaining the two-year invitation rate. This determines a lengthening of the inter-screening interval, with possible effects on the programme's efficacy.

Uptake of invitation increased to 47.5%, the best result observed over the last years. However, the very low values that affect many programmes, particularly when associated with a limited extension of invitations, are of particular concern, as in some cases the combined effect of these two elements makes the proportion of the target population that has been effectively screened marginal.

Intra-regional attendance showed high levels of variability, which suggests the possibility of increasing the performance of many programmes.

The analysis of attendance by the history of compliance to previous invitations allows a deeper insight into this indicator. The average value depends on the specific attendance of subjects that had never been invited before, of subjects who had already attended a previous invitation, and of those that

had already been invited, but never attended, and on the relative weight of these three groups. This specific analysis shows that attendance to the first invitation was lower than the previous years, probably due to the low performance of the new programmes, while the older ones invited a lower number of subjects for the first time (i.e., those entering the target age class of screening during the year). In 2008, more than half of the programmes had already activated a new round and their population, invited for the first time, was mainly made up of 50 year old subjects, a well-known low-attendance class.

In a biennial FOBT screening programme, a salient issue is whether or not the attendance of invited people can be sustained over time. Overall, 81% of the subjects that had attended a screening episode did not respond to the subsequent invitation. We did not observe any differences by age or gender: this suggests that the experience of the previous screening episode becomes the main driver for subsequent attendance, as already described in the literature.¹⁰ Thus, the effect of other factors, which influence response to the first invitation, ceases. It is therefore important for programmes to identify the limitations that may have determined a lack of satisfaction in the screened population.

The low attendance (20%), recorded by subjects that had already been invited but never attended, reflects both the possibility to enrol higher risk subjects (because they had never been screened) and the presence of a group of people wayward to screening. Programmes should evaluate whether to deal with this problem by introducing *ad hoc* invitation strategies, given the scarce efficacy of the traditional invitation by mail.

These data suggest that the screened population changes across the years: overall the test coverage of the target population may be higher than the number of screened subjects, but for the subjects who do not regularly undergo screening the protective effect of screening will be lower than expected.

This aspect should be taken into consideration when comparing the impact of FOBT *vs* FS programmes. If we assume that the highest protection of FOBT screening is given by regular repetition of the test, while the protection of a single FS lasts for some years, we will expect a reduction in the difference in protection between the two strategies.

The evaluation of diagnostic indicators is difficult because many programmes produced incomplete data and this may be misleading when interpreting the results on a regional basis. In fact, many indicators depend on many factors (e.g., DRs are influenced by the distribution of the screened by age and sex, by FOBT positivity and by compliance to colonoscopy) and they should be interpreted according to their intra-regional composition. For each indicator we had to select the programmes that sent complete data, with a possible selection bias. Unfortunately, the less complete questionnaires came from the Regions with the lowest number of programmes, leading to an even greater bias.

Overall, we observed for the first time an equilibrium between first and subsequent screening episodes (n=665,264 - 55%; and n=552,391 - 45%, respectively).

The proportion of FOBT+ is quite homogeneous among programmes, particularly at repeat screening. FOBT positivity is affected by many factors that are mainly related to the prevalence of the disease (geography, distribution by age and sex, first *vs* subsequent test) or to the performance of the test (sensitivity, specificity, positivity threshold). Some studies evaluated the effect of the stability of haemoglobin in the faecal sample on the analytic sensitivity of the test. Van Rossum recently showed that the delay between the sample collection by the subject and the delivery of the sample to the laboratory may negatively affect the test's sensitivity with an increase in the proportion of false negative results.¹¹ The guidelines for lab workers, recently published by GISCoR, recom-

mend a desired maximum delay of 7 days between the sample collection and the performance of the test.¹² However, many programmes are not able to produce the data of the sampling and/or of delivery of the sample by the subject, therefore it is impossible to evaluate the adherence to this recommendation. This is an important aspect, which would be worth studying in the future.

Particular attention should be given to attendance to colonoscopy (81.3% in 2008). The actual proportion of FOBT+ subjects that did not undergo any further assessment is probably lower, since many programmes did not collect data about assessments performed in non-screening settings. However, it must be stressed that the duty of screening programmes is not only that of reaching high levels of attendance to colonoscopy, but also making sure that FOBT+ subjects have undergone assessment, even if outside the programme. The data reported in 2008 suggest that many programmes did not deal with this aspect.

A further issue to analyse in future surveys will be the relationship between attendance to colonoscopy and the use of sedation.

Attendance to colonoscopy may also be negatively affected by a long waiting time for the performance of examinations. During 2008 we observed a generalised difficulty for endoscopic services to deal with the excess workload deriving from screening positives.

Compared to the last years, the DRs of carcinoma and advanced adenoma were stable. However, many programmes showed a reduction in DRs at first screening: this is not worrisome, since for programmes at subsequent rounds, a high proportion of the population that undergoes the screening test for the first time is represented by fifty-year-old subjects, which are at lower risk of disease.

Since DRs are calculated dividing the diagnosed lesions by the screened population, they are inversely associated to the loss of attendance to colonoscopy. In fact, when adjusting the DRs by

attendance to colonoscopy, we observed a leveling off of the differences between regional means. The fluctuations in DRs observed between programmes suggest the presence of factors responsible for this aspect other than the diagnostic sensitivity of the screening programme, such as the quality of endoscopy and the different criteria locally used to classify adenomas as advanced or non-advanced. The detection rate of polyps is one of the indicators for the monitoring of endoscopy quality.¹³ GISCOR and ONS carried out a number of «Train the trainer» courses for endoscopists and pathologists which will hopefully be reproduced at regional level.

Analysis of the PPV of FOBT+ at colonoscopy confirms the high values reported in the previous years. According to these findings, it is essential that screening programmes adopt strategies in order to maximise colonoscopy attendance, or to be sure that subjects with a positive FOBT undergo further diagnostic assessment in non-screening structures.

Moreover, it must be pointed out that most colonoscopies are surgical and should therefore be carried out by expert endoscopists and accurately monitored for quality.

This survey collects little information about the quality of endoscopy. Nevertheless, the data obtained from programmes show a good quality of colonoscopies in terms of completeness and complication rates, both for operative and non-operative TCs.

As for treatment, we collected information about the use of surgical intervention *vs* endoscopic resection alone. Overall, 20% of patients with carcinoma underwent endoscopic resection alone, resulting in improved patient quality of life and cost reduction. However, this percentage increased only to 28% of pT1 cases, which are mostly made up of cancerised adenomas. A possible overtreatment of these subjects should be accounted for.

Overall, 97% of advanced adenomas were treated through endoscopic resection alone. However, we

	UK Pilot study	Italy 2008
Test	guaiac	immunochemical
Participation (%)	56.8	41.4
Positivity rate (%)	1.9	5.9
Detection rate (‰)		
cancer	1.6	2.7
neoplasia*	6.9	23.5
PPV (%)		
cancer	10	6
neoplasia*	46	54
Attendance to colonoscopy (%)	82.2	81.3

* carcinoma or advanced adenoma or non-advanced adenoma.

Table 7. UK Pilot study (first round) and Italian FOBT screening programmes (first exams): comparison of the main results.

underline the high variability among programmes: surgical intervention was used for 5-10% of adenomas by nine programmes and for more than 10% of cases by two.

We did not notice any difference between cases at first and repeat screening with respect to the proportion of cases in stage III-IV. This might be due to the sub-optimal sensitivity of FOBT, which fails to identify all tumours present at first screening. Monitoring this indicator over time should clarify this aspect, because as the number of screening rounds increases, the proportion of cancers at an advanced stage detected at subsequent episodes should decrease thanks to the cumulative protection offered by repeat negative episodes. Finally, these data will need to be compared with the frequency and distribution by stage of interval cancers.

Stage distribution, instead, was clearly better for screen-detected cases than the clinical series observed in the absence of organised programmes, since about 40 to 50% were at stage III or IV at diagnosis.

Concerning FOBT screening, the performance of the diagnostic phase was consistent with other international experiences. Nevertheless, comparing Italian results with data emerging from the first round of the UK Pilot study (table 7), important

Programmes participating in the survey

Programme	Head of the programme	Programme	Head of the programme
Abruzzo		Molise	P. Mescia, G. Cecere
Avezzano Sulmona	A. Sedici	Piemonte	
Chieti	S. Martinotti	Alessandria	G. Faragli
L'Aquila	A. Agnifili	Asti	T. Miroglio
Lanciano Vasto	G. Ferrini	Biella Vercelli	N. Lorenzini
Pescara	E. Liberatore	Collegno Pinerolo	M. Sartori
Teramo	S. Prospero	Novara	C. Magnani, A. Cipelletti
Basilicata	A. Sigillito	Torino	C. Senore
Calabria		Sardegna	
Lamezia Terme	M.P. Montesi	Cagliari	S. Tilocca
Campania		Toscana	
Avellino 2	V. Landolfi	Arezzo	F. Mirri, P. Ceccatelli
Salerno 1	V. Gallo, A. Caiazzo, G. Storti	Empoli	L. Rossi, M. Biagini
Salerno 2	A. Rossi, MG. Panico	Firenze	G. Grazzini, C. Visioli, N. Ianniciello
Salerno 3	A. Giuliano, G. Della Greca	Grosseto	R. Rosati, P. Piacentini, S. Quaranta, A. Rechichi
Emilia-Romagna		Livorno	P. Lopane, C. Maffei, G. Niccoli
Regione Emilia-Romagna	A.C. Finarelli, C. Naldoni, P. Landi	Lucca	G. Finucci, S. Cocciolo, G. Gujana
Piacenza	F. Fornari, E. Borciani	Massa Carrara	C. Nicolai, P. Vivani, F. Pincione
Parma	A. Franzè, C. Zurlini	Pisa	G. Venturini, M. Perco, V. Calvaruso
Reggio Emilia	L. Paterlini, R. Sassatelli	Pistoia	A. Natali, M. Rapanà
Modena	R. Corradini	Prato	A. Battaglia, C. Epifani, A. Candidi Tommasi
Bologna	N. Collina, M. Manfredi, N. D'Imperio, F. Bazzoli	Siena	A. Ciarrocchi, R. Turillazzi, P. Galgani
Imola	R. Nannini	Viareggio	C. Ciabattoni, U. Ferro
Ferrara	G. Zoli, M.C. Carpanelli, V. Matarese,	Trentino	S. Piffer
Ravenna	O. Triossi	Umbria	
Forlì	F. Falcini	Città di Castello	D. Felicioni
Cesena	P. Pazzi, M. Palazzi	Foligno	A. Di Marco
Rimini	M. Giovanardi, D. Canuti	Perugia	B. Passamonti, M. Malaspina
Friuli-Venezia Giulia	L. Zanier	Terni	R. Corvetti
Lazio		Valle d'Aosta	S. Crotta
Viterbo	M. Anti, S. Brezzi	Veneto	
Rieti	G. Baldi, F. Barberani	Alta Padovana	P. Coin
Roma D	P. Grammatico, A. Sorce	Alto Vicentino	F. Banovich
Roma H	A. Scozzarro, A. Vella	Asolo	G. Lustrò
Lombardia		Belluno	F. Soppelsa
Bergamo	R. Paginoni, G. Rocca, L. Tessandri	Bussolengo	A. Bortoli
Brescia	C. Scotti, F. Speziani	Chioggia	M.L. Polo
Como	M. Gramegna, G. Gola	Dolo Mirano	A. Montaguti
Cremona	L. Boldori, M. Dal Soldà	Este Monselice	M. Penon
Lecco	A. Ilardo	Feltre	L. Cazzola
Lodi	A. Belloni, G. Marazza	Legnago	F. Vaccari
Mantova	E. Anghinoni	Ovest Vicentino	M. Lestani
Milano città	L. Bisanti	Padova	I. Simoncello
Provincia Milano 1	M.E. Pirola, P. Ceresa	Pieve di Soligo	T. Menegon
Provincia Milano 2	L. Fantini	Rovigo	L. Gallo
Monza	M. Ignone	Treviso	G. Gallo
Pavia	L. Camana, G. Magenes	Veneto Orientale	A. Favaretto
Sondrio	L. Ceconami	Verona	P. Costa, A. Ederle
Vallecarnonica	L. Pasquale	Vicenza	M. Merzari
Varese	F. Sambo		

differences were evident.¹⁴ Positivity rates were much higher in Italian programmes but, on the other hand, detection rates for cancer and for adenoma in the UK study were lower than those observed in Italy. In addition, although the Italian positivity rate was higher, the positive predictive values for neoplasia of a positive test result were similar to those registered in the UK study, given the large number of lesions detected by a more sensitive test.

Collection of interval cancers and evaluation of the follow-up of advanced adenomas are two further important aspects in the assessment of colorectal cancer screening programmes; both require *ad hoc* surveillance systems that are beyond the objectives of the present survey.

Some programmes have already started to monitor interval cancers: it will be important to share these experiences in order to identify the most efficient and feasible method for data collection, analysis, and interpretation.

GISCoR recently proposed a surveillance system for the follow-up of advanced adenomas in order to evaluate locally adopted protocols and to collect data about compliance, detection rates, and workload for the Endoscopy Units.

Data providers for the year 2008:

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BASILICATA: A. Sigillito

CALABRIA: M.P. Montesi

CAMPANIA: R. Pizzuti

EMILIA-ROMAGNA: C. Naldoni, P. Sassoli de' Bianchi (Regione Emilia-Romagna);

F. Fornari, G. Gatti (Piacenza); C. Zurlini (Parma);

A. Franzè, M. Zatelli, F. Maradini (AOSP Parma);

L. Paterlini, C. Campari (Reggio Emilia);

R. Sassatelli (AOSP Reggio Emilia); R. Corradini,

C. Goldoni (Modena); N. Collina, M. Manfredi,

P. Baldazzi (Bologna); R. Nannini, L. Caprara

(Imola); M.C. Carpanelli, O. Buriani (Ferrara);

O. Triossi, M. Serafini, B. Vitali (Ravenna); F. Falcini,

A. Colamartini, O. Giuliani, R. Vattiato (Forlì);

M. Palazzi, C. Imolesi (Cesena);

D. Canuti, C. Casale, C. Fava (Rimini)

FRIULI-VENEZIA GIULIA: S. Di Bartolomeo,

S. Tillati

LAZIO: A. Barca, D. Baiocchi, F. Quadrino

LOMBARDIA: R. Galli (Bergamo); C. Scotti

(Brescia); L. Zerbi (Como); M. Dal Soldà

(Cremona); A. Ilardo (Lecco); G. Marazza (Lodi);

E. Anghinoni (Mantova); E. Tidone, N. Leonardo

(Milano città); P. Ceresa (Milano 1);

L. Fantini (Milano 2); M. Ignone (Monza);

G. Magenes (Pavia); L. Cecconami (Sondrio);

F. Sambo (Varese); L. Pasquale (Vallecambonica)

MOLISE: A. Di Credico

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C.B. Visioli, P. Falini, P. Piccini (Firenze);

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C. Fedato (Alto Vicentino); G. Diacono (Asolo);

S. Di Camillo, R. Mel (Belluno); A. Ganassini,

C. Fedato (Bussolengo); M.L. Polo (Chioggia);

C. Fedato (Dolo); M. Gennaro,

F. Talpo (Este Monselice); C. Fedato (Feltre);

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