

Screening for colorectal cancer in Italy: 2004 survey

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Abstract

We present the main results of the first national survey of organised screening programmes, conducted by the Italian Group for Colorectal Cancer Screening (GISCoR). During 2004, 18 programs, adopting faecal occult blood testing (FOBT), sigmoidoscopy (FS), or a combination of both, were active in Italy.

Overall, 331,333 subjects were invited to undergo FOBT and 165,480 were screened; the attendance rate (51.3%) equals the best performances reported in the literature. Positivity rate was 5.4% at first and 3.9% at repeat screening: it increased with age and was higher among men than among women in all age groups.

The average attendance rate at colonoscopy (TC) was 83% (range: 70%-100%; median: 85%). Completion rate of TC was 92%, with higher rates among males.

At first screening, the detection rate (DR) per 1,000 screened subjects was 2.8 and 11.6 for cancer (CRC) and "high-risk" adenomas (HRA) (≥ 3 adenomas, 1 adenoma ≥ 1 cm, or with villous component $>20\%$, or with high grade dysplasia) respectively; the corresponding figures at repeat screening were 1.2 for CRC and 4.9 for HRA. The DR of CRC and adenomas increased with age and it was higher among men than among women; 51% of screen-detected CRCs were at TNM stage I.

The positive predictive value (PPV) was 6.3% for CRC and 25.8% for HRA at first screening, and 3.6% for CRC and 15.1% for HRA at repeat screening. Given this high PPV of positive FOBT, to obtain a high attendance at TC is crucial.

In the three FS programmes 15,688 subjects were invited and 4,884 were screened (attendance rate: 31.9%). TC referral rates ranged between 7.6% and 14.0%, due to different referral criteria. Among subjects referred to colonoscopy the prevalence of HRA and CRC ranged from 7.9 to 9.9%. The overall DR (subjects with at least one advanced lesion) ranged from 5.5 to 7.0%. Comparing the DR at FS and FOBT in the same age range, FS showed a higher sensitivity both for HRA (DR was four times higher) and for CRC.

In conclusion, colorectal cancer screening looks feasible. The reported experiences showed good results in terms of attendance and DR, although some critical aspects need to be carefully addressed when planning and implementing screening activity.

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Keywords: colorectal cancer screening programmes survey, Italy

This paper reports the main data collected by the first survey of the Italian Group for Colorectal Cancer Screening (GISCoR) on the activity of organised screening programmes for the year 2004.

Compared to cervical or breast cancer screening, colorectal screening has some peculiarities that make its evaluation complex, in the collection, interpretation and presentation of the data from active programmes. Programmes employ different screening tests, such as faecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), or a combination of both. Moreover, the type of screening test used implies different strategies as to the age of the target population and to the re-screening interval. Another peculiarity is represented by the fact that this is the first organ-

ised screening programme involving also the male population: analysis stratified by gender is thus necessary for some indicators based on gender related epidemiological variables (positivity rate, detection rate, positive predictive value), and gender may also influence attendance rate to first and repeat screenings.

Organised colorectal screening activities are making their first steps at a national level (with the exception of the longer-standing Toscana and Torino experiences) and at an international level; such a scenario implies lack of stable references for result evaluation, such as an agreed set of indicators and standards. This survey is an important step in this direction, as it provides an essential database to the GISCoR working group, helping to establish indicators and standards.

Extension

During 2004, active programmes increased to 18, from 13 in 2003. Among newly implemented programmes, the introduction of the first screening programme in Southern Italy (ASL Salerno 1) is a significant event.

Table 1 shows the distribution, by region, of active programmes providing 2004 activity data to GISCoR survey: overall, 18 programmes were recorded, mostly from Toscana and Veneto.

Theoretical coverage, commonly used in breast and cervical cancer surveys, indicates the proportion of the regional target population residing in areas where an organised screening programme is active. As shown in Table 1, the number of active programmes is still too small for a projection of coverage on a regional scale to be indicative.

For the present survey we will provide only data on actual coverage, which indicates the proportion of subjects residing in a screening programme area who were actually invited during the surveyed year.

For programmes employing FOBT, which foresee invitation to be completed within two years, the denominator is represented by half of the target population, whereas for programmes employing once in a life FS, the denominator is the total target population. Quantifying coverage is complex, particularly as active programmes have different targets as far as age is concerned: the age of the target population in FOBT screening ranges between 50 and 69-75 years of age, whereas FS screening invites a single cohort (age 58 in Novara and Torino, age 60 in Verona). Moreover, the Torino programme offers FOBT screening to subjects refusing FS screening and subjects in the 59-69 years age range.

Due to marked differences among described screening models, the number of invited and screened subjects is quite different in the FS as opposed to the FOBT screening, with a ratio of about 1:10 for a "once in a lifetime" FS scenario. Overall, 331,333 subjects were invited to the

Region	Nr. of programmes
Campania	1
Lombardia	1
Toscana	7
Piemonte	2
Val d'Aosta	1
Veneto	6
ITALY	18

Table 1: Distribution by Region of active programmes providing 2004 activity data to GISCoR survey.

Invited	331,333	
Screened	165,480	
Adjusted attendance (%)	51.3	
	First screening	Repeat screening
Positivity rate (%)	5.4	3.9
Detection Rate (‰)		
■ carcinomas	2.8	1.2
■ high risk adenomas	11.6	4.9
■ low risk adenomas	6.7	3.2
Positive predictive value (%)		
■ carcinomas	6.3	3.6
■ high risk adenomas	25.8	15.1
High risk adenomas ≥3 adenomas, 1 adenoma ≥1 cm, or with villous component >20%, or with high grade dysplasia		

Table 2: Main figures of FOBT screening programmes activity during 2004.

FOBT screening during 2004, accounting for an actual coverage of 58.4% (Table 2).

Table 3 shows for each Region the age range of the target population, the number of invited subjects, the actual coverage rate, and the number of screened subjects.

It is worth noting that the Campania and Val d'Aosta data are relative to programmes involving only 1-2 municipalities. Even for regions with larger programmes, there is a considerable variability. Since the number of participating

Region	Target age range	Invited during 2004	Actual coverage (%) *	Screened
Campania	44-69	4,857	75.6	718
Lombardia	50-74	57,331	101.3	20,611
Piemonte	59-69	18,387	48.8	5,333
Toscana	50-70	184,033	58.1	94,182
Val d'Aosta	50-74	2,948	100.0	1,836
Veneto	50-69	63,777	48.6	42,800

* fraction of target population invited every year

Table 3: FOBT screening: Actual coverage and screened subjects by Region and age range.

Programme	Invited during 2004	Actual coverage (%)*	Screened
Novara	3,199	50,1	973
Torino	8,633	55,1	2,311
Verona	3,856	69,2	1,600

* fraction of target population invited every year

Table 4: FS screening: Actual coverage and screened subjects by programme.

programmes is limited, regional coverage figures are negatively influenced by programmes which started during 2004, which contributed to the denominator with their whole target population although they were active in some cases for only a few months and therefore did not have the whole year to invite target subjects. This was the case for Salerno, Pistoia, and for two of the Veneto regional programmes. Taking this into account, it is worth noting that even among programmes active for several years, coverage may be inadequate.

Table 4 shows the coverage of FS screening programmes. During 2004, these programmes invited 15,688 subjects (average actual coverage is 56.8%) though only 4,884 subjects were screened. It is worth noting that the Novara programme was implemented in September 2004. Overall, it is not possible to draw average conclusions on coverage, with two established programmes

scoring between 55 and 70%, and the most recent one covering 50% of the target population in a period of four months.

Attendance

A crude attendance rate indicates the ratio of screened to invited subjects. An adjusted attendance rate is more representative of the real attendance of the target population, as subjects reporting that they already had a recent screening test outside the programme are censored from the denominator. However, the difference between crude and adjusted attendance is small, as the magnitude of spontaneous screening by FOBT is negligible; quite a different situation when compared to breast or cervical cancer screening. For this reason, Table 2 and Figure 1 show only adjusted attendance rates, overall (51.3%) and by programme.

Data from Campania and Val d'Aosta, relative to programmes with a limited number of invitations, is subject to statistical fluctuation. Even in the absence of reference standards, it is worth noting that the average national figure equals the best performances reported in the literature.¹ The attendance rate is quite variable among regions; the highest performance being that of Veneto (69.5% regional average), showing high rates for all programmes (range 57-80%).

As currently reported in the literature, and ob-

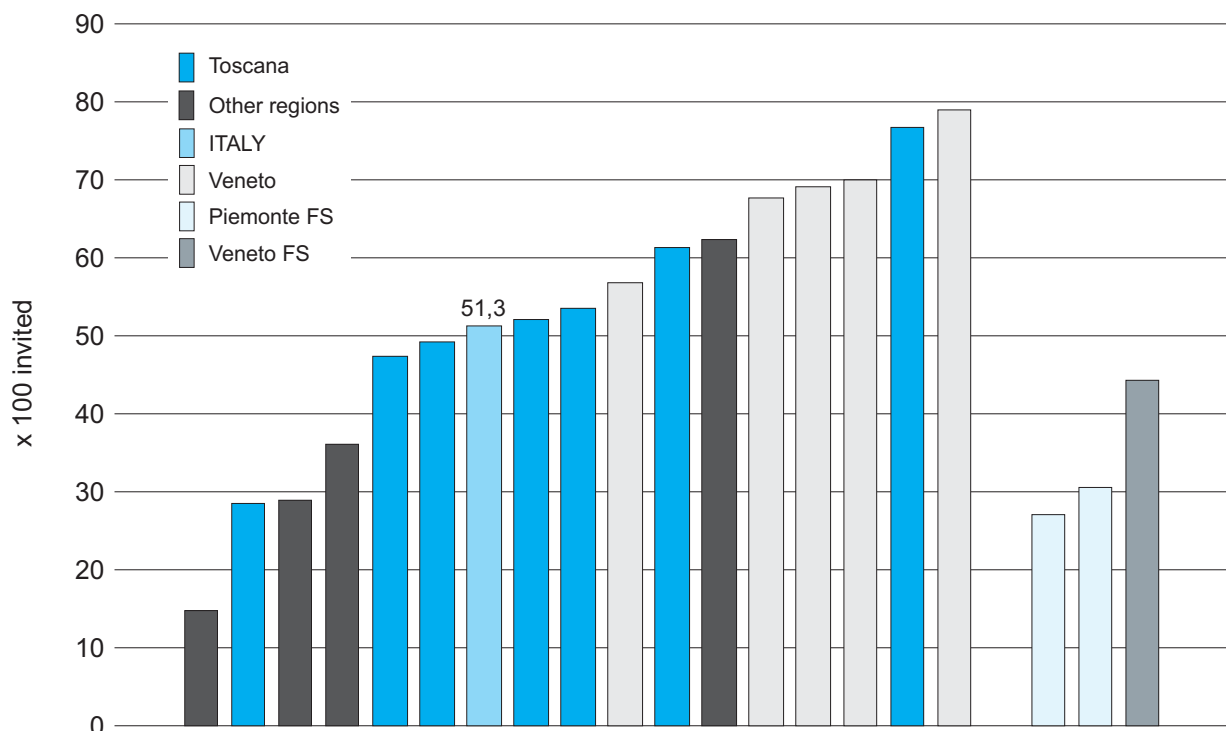


Figure 1: Adjusted attendance rate to invitation.

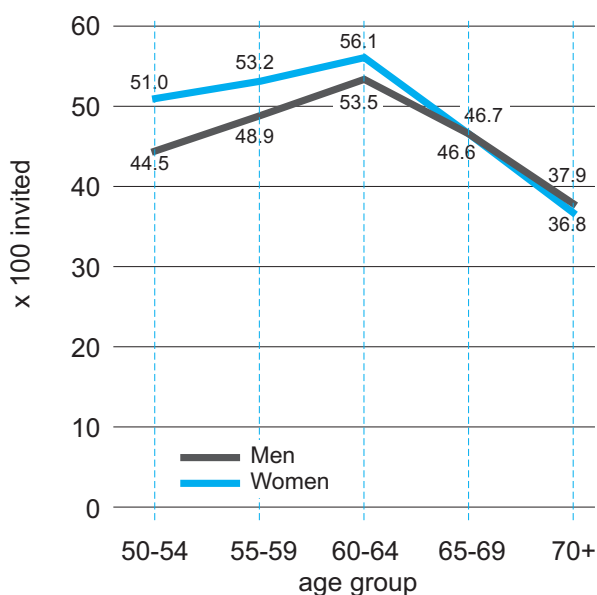


Figure 2: FOBT screening. Adjusted attendance by age and gender.

served in breast and cervical screening, attendance is lower in big urban areas like Torino, as compared to smaller cities, as in Veneto and Toscana, where a more direct connection between people and institutions. In addition, stronger community relations are present in these regions. Attendance to FS screening is substantially lower as compared to FOBT, a less invasive test. FS screening programmes foresee a repeat invitation in two years for non-attendees, which, based on previous experiences, is expected to increase attendance by an absolute 5-8%. Good results were obtained in Verona (44%), most likely due to a capillary information campaign. Attendance to FOBT increases progressively to intermediate age, and then decreases to its lowest values over 70 years of age (Figure 2). A similar trend is reported in the literature, and is consistent to what is observed in breast cancer screening, where attendance is also lowest in the elderly.²

Overall, attendance is slightly higher in women (51.8%) as compared to men (49.0%) in all programmes except Livorno. Differences in attendance by gender decrease with age and disappear in the elderly. On the contrary, FS programmes show higher attendance in men (36%) as compared to women (28%).

Diagnostic indicators

FOBT screening

Among the following indicators, some (positivity rate, detection rate, positive predictive value) are influenced by several variables, partly associated

with the prevalence of lesions in the screened population. Colorectal cancer incidence increases with age and is higher in men than in women.^{3,4} Moreover, a higher detection rate is expected at first (prevalent) screening as compared to repeat screening.

Indicators are thus shown separately by gender, age, and type of screening test in different tables. Data from Empoli was provided without stratification by a screening round; most tests having been performed at a repeat screening.

Positivity rate

The overall positivity rate is 5.4% at the first screening, and 3.9% at a repeat screening (Table 2). As expected, in keeping with the epidemiological situation, the positivity rate increases with age, and men have constant, higher values as compared to women in all age groups (Table 5). The relative decrease in positivity rate between first and repeat screenings ranges from 26 to 40% over age 60, whereas it is more limited (14-25%) in younger subjects. The trend is present in both men and women.

At the first screening, the positivity rate is constantly lower in programmes from Toscana as compared to the overall average, at any age and gender, in programmes from Veneto, which show higher rates than the average. The highest rates are reported in Cremona. In Torino positivity rate for involved age groups is lower than the average in men, and higher in women. At repeat screening, programmes in Toscana show a higher positivity rate at lower ages, and lower in the elderly; an opposite trend is seen in Cremona.

Attendance to colonoscopy assessment

Obtaining high attendance rates at a colonoscopy assessment is of paramount importance, as FOBT has been shown to select subjects at a high risk of having a lesion. In fact, over 30% of all subjects attending the assessment are diagnosed with a carcinoma or high-risk adenoma (see predictive values in Figure 10).

Figure 3 shows attendance rate to diagnostic as-

Age	First screening		Repeat screening	
	men	women	men	women
50-54	4.7	3.3	3.5	2.4
55-59	5.6	3.7	4.1	3.0
60-64	7.0	4.6	4.1	3.4
65-69	8.9	6.0	5.3	3.7
70+	9.8	8.0	7.3	4.5
Total	6.6	4.5	4.6	3.3

Table 5: Positivity rate.

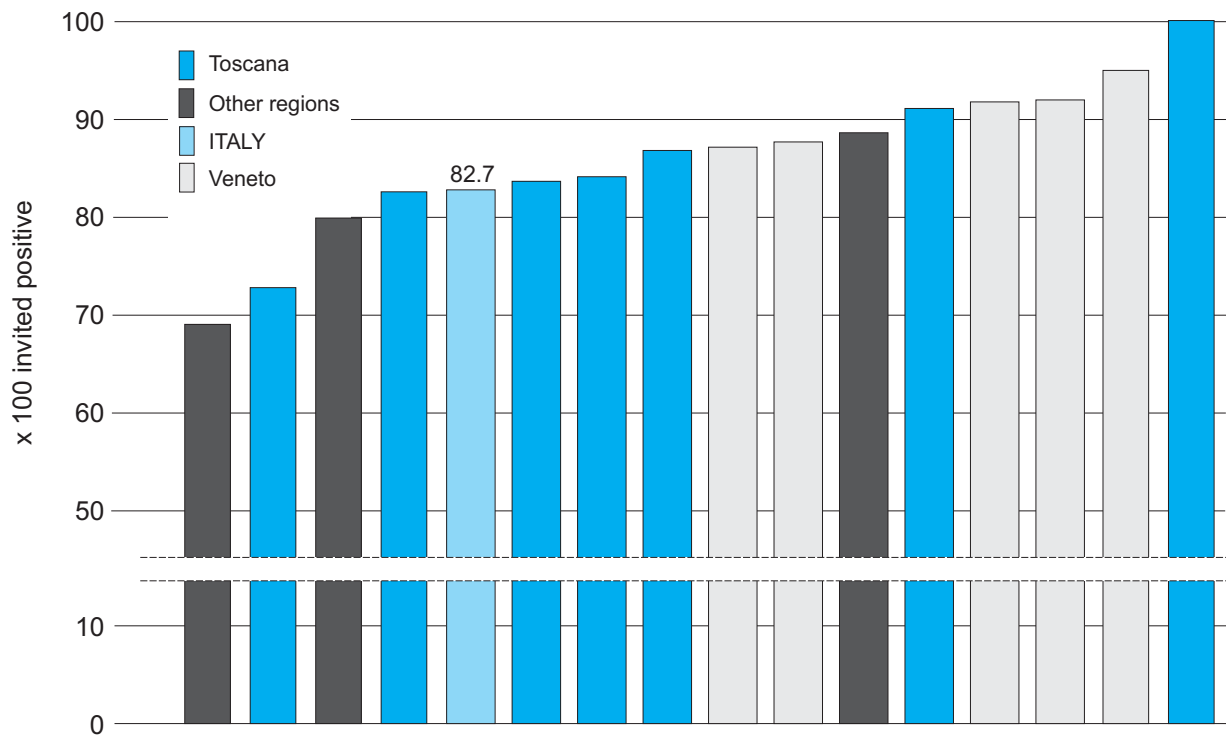


Figure 3: Attendance rate to colonoscopy assessment.

assessment in different programmes. Attendance rate is absolute (100%) in Pistoia in a small series of 36 subjects referred to diagnostic assessment. In more than half of the programmes, attendance exceeds 85%, whereas in two programmes approximately 30% of FOBT+ subjects do not attend recommended assessment. No differences have been observed between men and women, or between first and repeat screening. When comparing Regions, attendance is higher in Veneto, with a regional average rate of 89%.

Proportion of complete colonoscopy

The proportion of complete colonoscopies is another important indicator that needs be monitored when evaluating a screening programme. Differences observed between programmes may be partly due to different criteria in defining completeness. The overall complete colonoscopy rate is 92% (Figure 4). A rate of 100% was observed in Pistoia. Different values are observed according to gender, with higher rates being reported in men as compared to women. This trend is confirmed in the literature.

Detection rates

Carcinoma and high or low risk adenomas are the target lesions of colorectal cancer screening. High-risk adenomas include advanced adenomas (diameters ≥ 1 cm, villous/tubulo-villous type, or high-grade dysplasia) and evidence of three or more adenomas. Low-risk adenomas are those of

smaller size, tubular type, and low grade dysplasia. Screening programmes are assessed for diagnostic performance in terms of detection rate x 1,000 screened subjects (detection rate = DR).

It is worth noting that the presented DR was not adjusted for attendance to colonoscopy: low attendance to assessment reported by some programmes translates into a lower DR. In order to adjust by attendance, it must be assumed that the prevalence of lesions is the same in attendees and non-attendees. Such an assumption may not be valid, as some of the non-attendees reported that they had already undergone a colonoscopy during the previous two years. Preliminary data on motivation for non-attendance to a colonoscopy in FOBT+ subjects indicates that 6% of non-attendees had a negative FOBT the previous year, and 11% had a colonoscopy. Overall, crude DRs are more indicative of the actual diagnostic power of a programme, as they consider all screening phases, including the loss due to low attendance to the assessment. Overall, 2.8 carcinomas and 11.6 high-risk adenomas have been diagnosed for every 1,000 screened subjects at first screening, or 1.2 carcinomas and 4.9 adenomas at repeat screening (Table 2).

The age group of 70+ accounts for a limited number of screened subjects (approximately 1,500 by gender at first screening, slightly more than 2,000 at repeat screening), so significance of the rate for this age group is low.

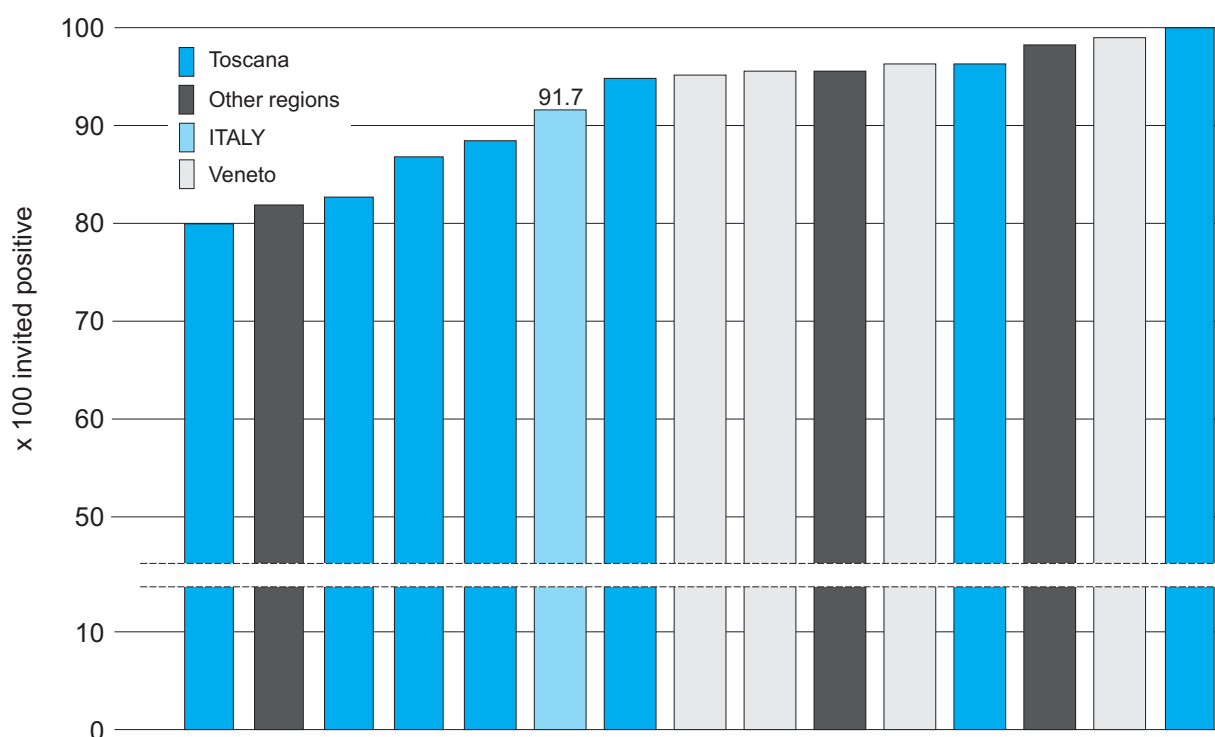


Figure 4: Proportion of complete colonoscopies.

The carcinoma DR increases with age in all considered subgroups; moreover, rates are higher in men than in women, but for few subgroups, and at first screening, compared to repeat screening. High and low-risk adenoma DRs show similar features by age, gender, and screening round.

It is worth noting that the DR is constantly higher for high-risk as compared to low-risk adenoma. Since the prevalence of low-risk adenoma at endoscopy is higher than that of high-risk adenomas, the findings suggest a higher tendency to bleed for advanced adenoma, and FOBT might thus select lesions at higher risk of progression to carcinoma.

Figure 9 compares carcinoma and high-risk

adenoma DR at first screening by region. It must be kept in mind that Piemonte is represented only with the 59-69 years age group. DR in Veneto at first screening is higher than the overall average, to which Veneto strongly contributes in all age and gender subgroups. Higher DRs in Veneto are particularly evident for low-risk adenomas, with 62-79% higher values in different age groups in men and 44-78% higher value in women, and less evident for high-risk adenomas (+20-42% in men, +21-36% in intermediate age groups of women). As recent data does not show a higher incidence of colorectal cancer in Veneto,⁸ the latter finding must be evaluated by also consider-

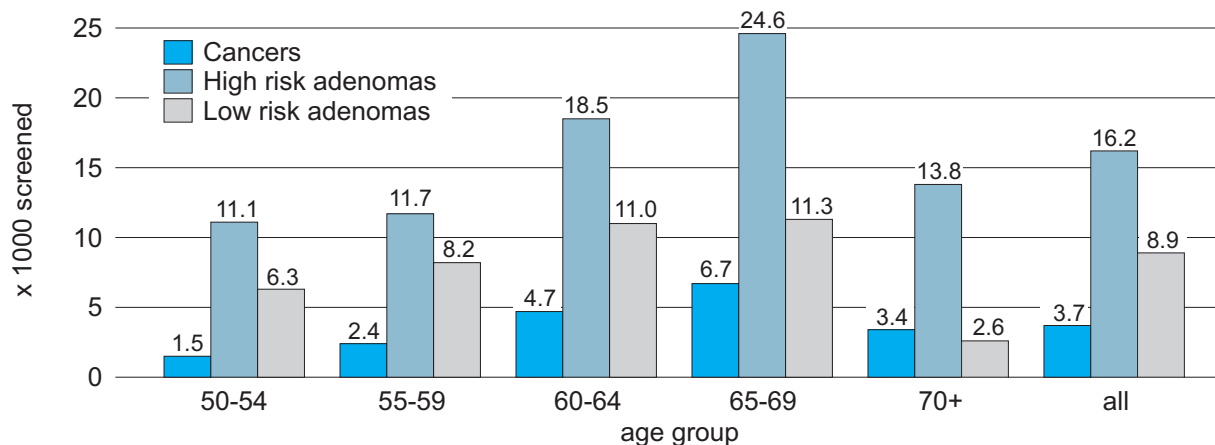


Figure 5: Detection rates x 1,000 screened. Men, first screening.

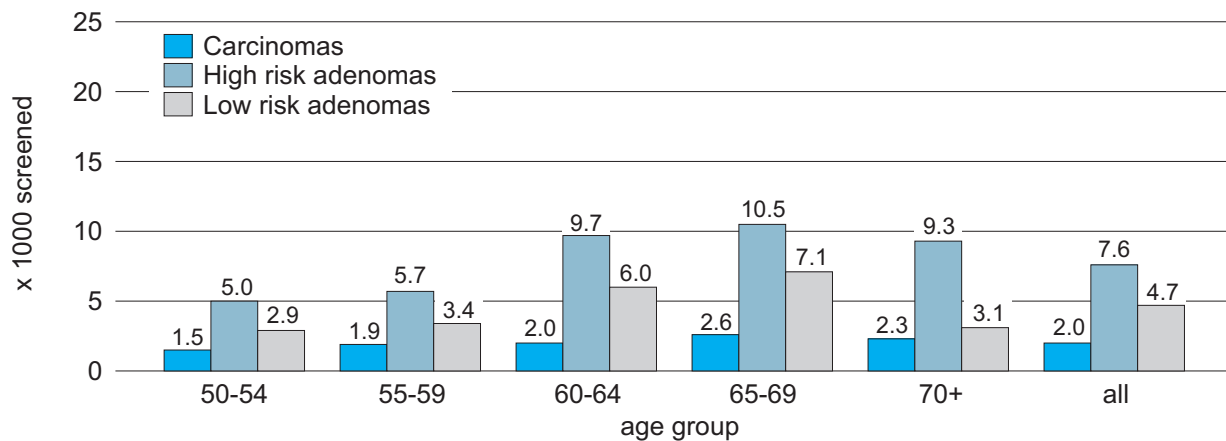


Figure 6: Detection rates x 1,000 screened. Women, first screening.

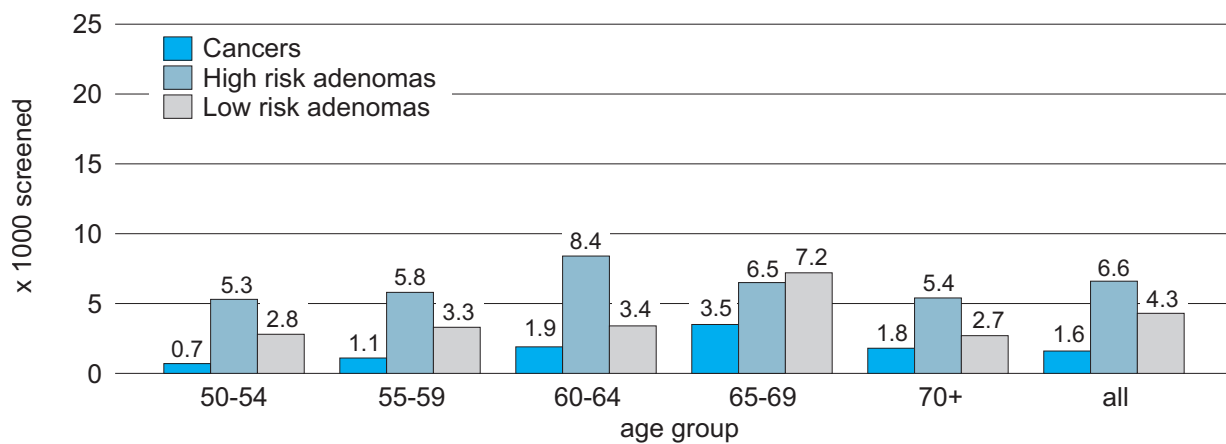


Figure 7: Detection rates x 1,000 screened. Men, repeat screening.

ing the diagnostic criteria used in different regions/programmes. It must be assessed whether definition criteria of diagnosed lesions are common, including histological diagnoses.

Positive predictive value

Positive predictive value (PPV) has been calculated as the proportion of assessed subjects di-

agnosed with carcinoma or high risk adenoma. Overall, 6.3 carcinomas and 25.8 adenomas have been diagnosed for every 100 colonoscopy assessed subjects at first screening round, or 3.6 carcinomas and 15.1 high-risk adenomas at repeat screening (Table 2). Figures 10 and 11 show PPVs for carcinomas and high-risk adenomas by age group, gender, and screening round.

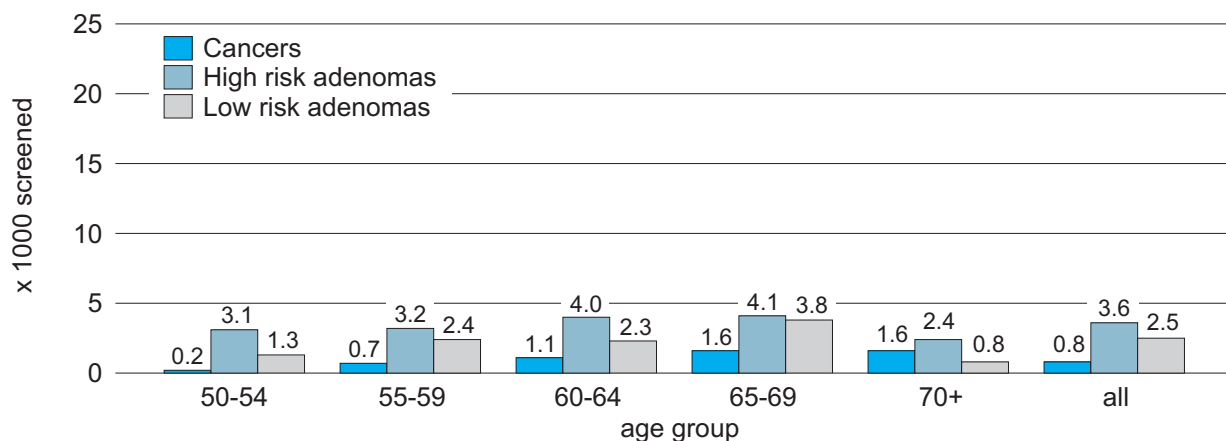


Figure 8: Detection rates x 1,000 screened. Women, repeat screening.

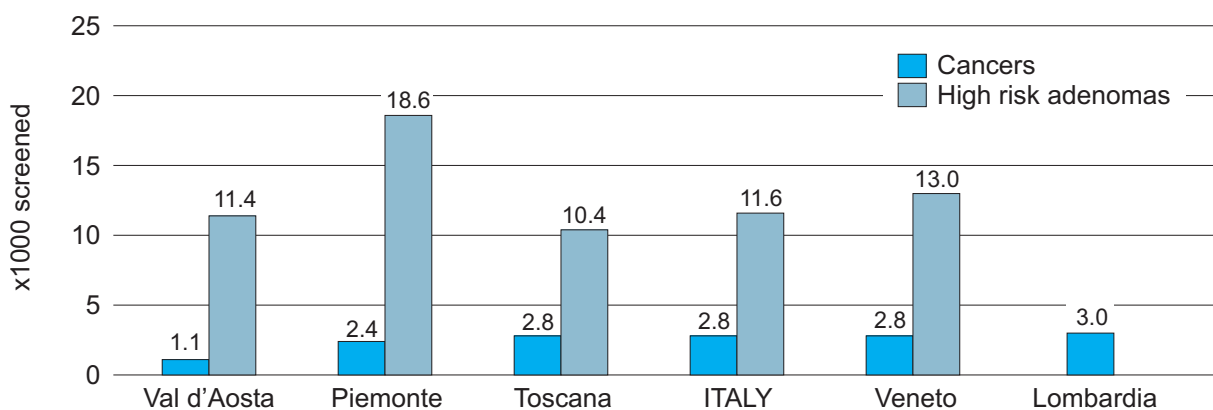


Figure 9: First screening. Detection rates for carcinoma and high risk adenoma, by Region, x 1,000 screened.



Figure 10: First screening. Positive predictive value for carcinoma and high risk adenoma of colonoscopy assessment by age and gender (%).



Figure 11: Repeat screening. Positive predictive value for carcinoma and high risk adenoma of colonoscopy assessment by age and gender (%).

The colonoscopy DR of carcinoma or high-risk adenoma is higher in men than in women, and increases with age (values in the 70+ age group are subject to statistical fluctuation). For both considered lesions, PPVs are substantially reduced at repeat screening.

FS screening programmes

Overall, three programmes referred to colonoscopy assessment in 7.6%, 9.4%, and 14.0% of

screened subjects, respectively. The Verona programme has higher referral rates, as all subjects with at least one adenoma are referred to colonoscopy, irrespective of histological type and size. This choice is more suitable for a clinical, rather than for a screening scenario, particularly considering the level of coverage (Table 4).

The overall attendance rate of the assessment is similar to that observed for the FOBT screening,

Programme	Screened	Reason prompting colonoscopy (%)				Attendance to colonoscopy (%)		Complete colonoscopy (%)	
		advanced adenoma*		other**		men	women	men	women
		men	women	men	women				
Novara	973	7.5	2.7	1.7	3.1	93.8	88.5	93.3	87.0
Torino	2,311	8.8	5.4	2.8	1.5	89.7	84.7	91.6	86.9
Verona	1,600	7.6	3.5	10.3	6.1	94.8	94.4	97.2	98.5

* at least one adenoma ≥ 10 mm; at least one advanced adenoma < 10 mm; 3 or more low risk adenomas < 10 mm; carcinoma
 ** Novara and Torino: inadequate preparation with adenoma; Verona: at least one adenoma or polyp ≥ 5 mm

Table 6: Positive FS, attendance to colonoscopy and colonoscopy completeness.

Programme	Carcinoma		High risk adenoma		Low risk adenoma	
	men	women	men	women	men	women
Novara	7.8	4.5	46.5	15.6	81.4	49.0
Torino	3.3	4.9	61.4	39.5	69.6	55.3
Verona	2.3	4.0	44.3	18.9	122.4	67.4

Table 7: Detection rates of distal lesions by gender (x 1,000 screened).

although it is quite variable among programmes. All centres exceed 90% of colonoscopy completeness rate. Analysis by gender in Piemonte shows a higher attendance and a higher completeness rate for men compared to women. No differences by gender are evident in Verona.

A higher prevalence of high-risk adenomas is evident in men than in women, whereas no differences are evident for colorectal cancer prevalence; however, the latter is based on a limited number of cases and estimates may be affected by statistical fluctuation.

When comparing the DR at FS and FOBT in the same age range, a finding of previous studies is confirmed,⁵ i.e. a higher sensitivity of FS for both high-risk adenomas (the DR is four times higher) and carcinoma.

Among the subjects referred to colonoscopy, the prevalence of proximal advanced lesions (high-risk adenomas and cancers) ranges from 7.9 to 9.9%. Based on this figure, it can be estimated that the overall DR (subjects with at least one advanced lesion) ranges from 5.5% in Novara, to 7.0% in Verona.

Distribution by stage

Stage is available for 243 of 271 (90%) cancers detected in FOBT programmes during 2004.

Stage distribution is evidently better as compared to the clinical series observed in the absence of organised screening programmes, as more than 50% of cases at diagnosis are not infiltrating beyond the muscular layer.

Reporting delay

Providing a prompt report to each screened subject, even if negative, and limiting the waiting time

Stage	2004 Screening (n=271)	Modena 1995-98 (n=779)**	Padova 2000-01 (n=609)
I	33%	18%	12%
I*	18%	–	–
II	17%	36%	32%
III-IV	23%	39%	49%
Unknown	10%	7%	7%
Stage I:	T1 or T2, N0, M0		
Stage I*:	malignant adenomas treated by endoscopy excision only		
Stage II:	T3 or T4, N0, M0		
Stage III-IV:	lymphnode involvement or distant metastases		
** adapted from Ponz de Leon et al, 2001			

Table 8: Stage distribution of screen detected cancers during 2004, compared to two clinical series, observed in absence of organised screening.

for diagnostic assessment are both important. Overall, 89% of negative reports in the FOBT programmes were mailed within 4 weeks from lab processing of faecal samples. In 4% of the cases, the delay exceeded six weeks. Longer delays are seen in Arezzo, where negative reports are mailed within 4 weeks in less than 30% of cases. All other programmes show satisfactory performances.

Delays in diagnostic assessments are more critical, as they are performed within one month from the FOBT only in 55% of cases, and in 15% after more than two months. In two programmes, colonoscopies performed over 2 months after the FOBT occurred in 40% of FOBT+ cases.

Complications of endoscopy and treatment

Information collected on these two aspects is still largely incomplete. Many programmes

have been recently implemented and the procedures necessary to retrieve information on hospitalised cancer cases were not fully operative yet. These aspects will be analysed in detail in the next survey.

Conclusions

A strong progression in the implementation of organised colorectal cancer screening can be observed in Italy. A substantial increase of active programmes was recorded in 2005 compared to 2004, including some programmes activated on a regional scale. This survey is thus an important reference baseline for future surveys.

The coverage average rate is around 50%, with the exception of some programmes active in very limited areas, and may be considered satisfactory, also in consideration of the fact that many programmes were first implemented in the same year as the survey. A high attendance rate is observed in Veneto, even for FS screening. Such experience might be further analysed, in search of useful indications to increase attendance in other regions.

Even though reference standards are not yet available, the DR for high-risk adenomas and cancer averages values that are expected on the basis of the experimental and pilot studies performed thus far. Variations in lesion prevalence were observed, which may be related to age and gender distribution of screened subjects, consistent with the natural history and expected frequency of the disease. Differences observed between regions are probably to be ascribed to differences in the diagnostic criteria employed: the comparison, evaluation and monitoring activity started by GISCoR gives the opportunity to identify and analyse these differences, and to take measures to reduce this variability.

One critical aspect is represented by the relatively large proportion of FOBT+ subjects who do not attend assessment colonoscopy. Effective contact methods need to be defined which may favour a higher attendance to colonoscopy, and at the same time uniform criteria should be defined to manage those cases in which a colonoscopy has already been performed outside the screening programme.

The survey section dedicated to treatment is still

considerably incomplete: programmes need to network with structures providing therapy, in order to extend monitoring also to the treatment of screen-detected lesions.

In conclusion, colorectal cancer screening appears feasible, with good results in terms of both attendance and detection; reported experiences are no doubt encouraging for newly implemented programmes, and highlighted some critical aspects which need to be carefully approached when planning and implementing screening activity.

Data for 2004 GISCoR survey were provided by:

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