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Characteristics of the colorectal cancers diagnosed in the early 2000s in Italy.

Figures from the IMPATTO study on colorectal cancer screening

Caratteristiche dei tumori del colon retto diagnosticati in Italia nei primi anni Duemila.

Dati dello studio IMPATTO sdelo screening colorettale

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Abstract

The impact of organized screening programmes on colorectal cancer (CRC) can be observed at a population level only several years after the implementation of screening. We compared CRC characteristics by diagnostic modality (screen-detected, non-screen-detected) as an early outcome to monitor screening programme effectiveness.

Data on CRCs diagnosed in Italy from 2000 to 2008 were collected by several cancer registries. Linkage with screening datasets made it possible to divide the cases by geographic area, implementation of screening, and modality of diagnosis (screen-detected, non-screen-detected). We compared the main characteristics of the different subgroups of CRCs through multivariate logistic regression models.

The study included 23,668 CRCs diagnosed in subjects aged 50-69 years, of which 11.9% were screen-detected (N=2,806), all from the North-Centre of Italy. Among screen-detected CRCs, we observed a higher proportion of males, of cases in the distal colon, and a higher mean age of the patients. Compared with pre-screening cases, screen-detected CRCs showed a better distribution by stage at diagnosis (OR for stage III or IV: 0.40, 95%CI: 0.36-0.44) and grading (OR for poorly differentiated CRCs was 0.86, 95%CI: 0.75-1.00).

Screen-detected CRCs have more favourable prognostic characteristics than non-screen-detected cases. A renewed effort to implement screening programmes throughout the entire country is recommended.

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Keywords: colorectal cancer screening, colorectal cancer, Italy

Riassunto

L'impatto dei programmi di screening del tumore del colon retto (CRC) può essere osservato a livello di popolazione solo alcuni anni dopo l'attivazione degli stessi. Abbiamo confrontato le caratteristiche dei CRC, suddivisi per modalità diagnostica (screen-detected, non-screen-detected), come indicatore precoce di efficacia dei programmi di screening.

Sono stati raccolti da diversi Registri tumori i dati sui CRC diagnosticati in Italia dal 2000 al 2008. Tramite linkage con gli archivi di screening è stata raccolta la modalità diagnostica dei casi, oltre al-

l'area geografica e alla presenza di un programma di screening organizzato. Abbiamo confrontato le principali caratteristiche dei diversi sottogruppi di CRC tramite modelli di regressione logistica multivariata.
Lo studio riguarda 23.668 CRC diagnosticati in soggetti di età 50-69 anni, l'11,9% dei quali screen-detected (N=2.806), tutti di aree del Nord o Centro Italia. Tra i casi screen-detected abbiamo osservato una maggiore proporzione di maschi, di casi a carico del colon distale e un'età media più alta. Rispetto ai casi diagnosticati prima dell'attivazione degli screening, i casi screen-detected avevano una migliore distribuzione per stadio alla diagnosi (odds ratio per stadio III o IV: 0,40; IC95%: 0,36-0,44) e grading (OR per grading scarsamente differenziato: 0,88; IC95%: 0,75-1,00).
I casi screen-detected avevano caratteristiche prognostiche migliori anche rispetto ai casi non-screen-detected. Si raccomanda uno sforzo rinnovato per attivare programmi di screening colorettale in tutto il territorio nazionale.

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INTRODUCTION

Colorectal cancer (CRC) survival is strictly related to the stage at diagnosis, with a better prognosis for stage I compared to stage III and IV.[1] CRC screening with a biennial faecal occult blood test (FOBT) has been shown to reduce mortality through the early detection and treatment of cancer in large population-based trials.[2] Routine, organized screening programmes (SPs) based on the faecal immunochemical test (FIT) have been shown to achieve even better outcomes on mortality.[3] Furthermore, there is some evidence that screening can also reduce invasive colorectal cancer through the identification and treatment of adenomas, preventing their transformation into cancer.[4-6]
The effects of screening can be observed at a population level only several years after the implementation of screening and only if SP participation is high. The stage at diagnosis of screen-detected cancers is an interesting early outcome to monitor screening programme effectiveness and predict the impact on mortality, since a necessary condition to achieving a reduction in mortality in the short term is to detect cancer at an earlier stage than clinically detected cancers.
With few exceptions, CRC SPs are aimed at Italian residents aged 50 to 69 or 74 years who receive a mailed invitation to undergo a single FIT every two years. Subjects with positive screening tests are contacted to undergo a total colonoscopy at an endoscopic referral centre. In only one region (Piemonte) has a different programme been established, with either a flexible sigmoidoscopy at the age of 58 or a FIT invitation every 2 years in the 59-69 years age range. The implementation of CRC SPs started gradually in 2005-2006, and has been more rapid in northern and central Italy than in the South. In 2008, theoretical extension, (i.e., the proportion of the resident population aged 50-69 years living in areas covered by an SP), was 73.7% in the North, 56.3% in the Centre, and 21.4% in the South and on the Islands (Sicilia and Sardegna).[7]
In order to describe the impact of implementing the CRC SPs in Italy, the Italian Ministry of Health financed the IMPATTO study, a research project that collected and linked information from both SP archives and cancer registries.
In this paper, we used the IMPATTO study's archives to compare the characteristics of CRCs diagnosed in Italy from 2000 to 2008 by diagnostic modality (screen-detected, non-screen-detected).

MATERIALS AND METHODS

Data

The data collected in the IMPATTO study database have been described in the associated paper of this article.[8] Briefly, for the purpose of this paper, CRCs diagnosed in patients aged 50-69 years were selected and characterized according to the following patterns of diagnosis:

- CRCs diagnosed in areas where an SP has been implemented:
  - pre-screening (i.e., diagnosed before the onset of the SP);
  - screen-detected;
  - not screen-detected, diagnosed after the onset of the SP;
- CRCs diagnosed in areas where no SP has been implemented.

Analysis

The Chi square test was used to compare the distribution of the main CRC characteristics included in the study by pattern of diagnosis: anatomic sub-site, stage at diagnosis, grading, number of lymph nodes examined and positive lymph nodes. The association between pattern of diagnosis and CRC characteristics was evaluated using logistic regression models which included the variables that resulted significantly associated at univariate analysis. In particular, we explored which factors were associated with stage and grading, including the pattern of diagnosis among the explanatory variables.

RESULTS

Overall, the study included 23,668 invasive cases of CRCs diagnosed in subjects aged 50-69 years between 2000 and 2008. The cancer registries took part in the study with cases from different periods. Moreover, the SPs were introduced in different years. In particular, the SPs were implemented in most areas during 2005-2006, as opposed to Veneto (2002) and Firenze-Prato, where SPs were already in place at the beginning of this study. Finally, there were no SPs in the South and on the Islands during the study period.
Table 2 (p. 110) shows the main characteristics by macro-area and period: the North-Centre in 2000-2005 (before the SPs became widespread), the North-Centre with SPs (2006-2008), and the South and the Islands. The cases from the latter macro-area represented about one-sixth of the overall study (15.8%). As expected, the largest proportion of cases was males (59%) from the older age group.

Macro-area	Cancer registry	Number of cases									
		2000	2001	2002	2003	2004	2005	2006	2007	2008	Total
Northwest	Genova				312	294	283				889
	Milano	449	456	415	427	399	**367**	**452**			2,965
	Sondrio	47	41	54	50	48	**54**	**73**	**77**	**67**	511
	Biella		64	54	64	57	**67**	**54**	**63**		423
Northeast	Trentino			120	129	117	138	140			644
	Veneto	138	155	**166**	**188**	**179**	**162**				988
	Friuli-Venezia Giulia						418	395	369		1,182
	Emilia-Romagna	137	240	629	954	**1,334**	**1,519**	**1,994**	**1,565**	**385**	8,757
Centre	Firenze-Prato	**341**	**343**	**319**	**322**	**323**	**319**				1,967
	Umbria					287	296	**266**	**383**	**372**	1,604
South-Islands	Latina					126	129	108	132		495
	Napoli				88	90	111	116	123		528
	Siracusa		78	80	89	88	82				417
	Palermo				268	261	258				787
	Catania-Messina				318	366	368				1,052
	Sassari				114	117	117	111			459

Figures in color represent the years when a screening programme was active

Table 1. Number of colorectal cancer cases by cancer registry and calendar year. Ages 50-69 years.
Tabella 1. Casi di tumore del colon retto per registro tumori e anno. Età 50-69 anni.

	North-Centre 2000-2005		North-Centre 2006-2008			South and the Islands 2000-2008		
	N	%	N	%	p-value[1]	N	%	p-value[1]
Total	13,275	100	6,655	100		3,738	100	
Gender								
male	7,817	58.9	4,075	61.2	0.002	2,151	57.5	0.14
female	5,458	41.1	2,580	38.8		1,587	42.5	
Age (years)								
50-59	4,291	32.3	2,115	31.8	0.44	1335	35.7	<0.001
60-69	8,984	67.7	4,540	68.2		2,403	64.3	
Pattern of diagnosis								
screen-detected	569	4.3	2,237	33.6	<0.001	0	0	-
not screen-detected*	12,706	95.7	4,418	66.4		3,738	100	
Anatomic site								
proximal colon	3,557	26.8	1,776	26.7	<0.001	1,001	26.8	<0.001
distal colon	4,820	36.3	2,631	39.5		1,152	30.8	
rectum	4,276	32.2	1,890	28.4		1,321	35.3	
colon NOS**	622	4.7	358	5.4			7.1	
Stage at diagnosis								
I	2,146	16.2	1,878	28.2	<0.001	471	12.6	<0.001
II	3,299	24.9	1,518	22.8		905	24.2	
III	3,817	28.8	1,598	24.0		852	22.8	
IV	2,461	18.5	1,087	16.3		841	22.5	
not available/missing	1,552	11.7	574	8.6		669	17.9	
Grading								
well-differentiated	1,165	8.8	935	14.0	<0.001	232	6.2	<0.001
moderately differentiated	7,792	58.7	3,740	56.2		2,290	61.3	
poorly differentiated	1,981	15.0	1,178	17.7		531	14.2	
not available/missing	2,337	17.6	802	12.1		685	18.3	

[1] p-value of Chi square test comparing the distribution by each variable in the table with the reference group = North-Centre, 2000-2005
* it includes pre-screening, not screen-detected in areas with screening, diagnosed in areas with no screening
** NOS: not otherwise specified

Table 2. Distribution of colorectal cancer cases according to main characteristics, by macro-area and period.
Tabella 2. Distribuzione dei casi di tumore del colon retto per varie caratteristiche, per macroarea e periodo.

There were 2,806 screen-detected cases, or 11.9% of the whole. This percentage rose to 33.6% in areas with an SP. One-third of the cases (31.6%) were localized in the rectum.

The proportion of stage I cases and of cases with grade I was highest in the North-Centre in 2006-2008 and lowest in the South and on the Islands. Overall, the proportion of cases with a stage missing at diagnosis was 11.8%. This was highest in the South and on the Islands, and lowest in the North-Centre in 2006-2008.

Table 3 shows the characteristics of cases by pattern of diagnosis. Compared to the CRCs diagnosed during the pre-screening period, screen-detected CRCs showed a different distribution for most variables. In particular, the proportion of subjects aged 65-69 years was greater than 40% (41.7%), as compared to 38.3%. Screen-detected cases were more frequently located in the distal colon than pre-screening cancers (50.6% *vs* 36.8%). Grading was more favourable, with 20.1% of screen-detected cases being well-differentiated and only 11% poorly differentiated, compared respectively to 9.6% and 15.6% in the pre-screening period. Also stage at diagnosis was less advanced: 42.8% of screen-detected cases were diagnosed at stage I (*vs* 16.2%) and only 6.2% at stage IV (*vs* 19.8%).

Finally, the number of lymph nodes examined in screen-detected CRCs was similar to pre-screening cases (15.6 in both groups), while the mean number of positive lymph nodes overall and for cases stages III/IV was significantly lower in the former (1.0 *vs* 2.1 and 3.4 *vs* 4.2, respectively).

Both not screen-detected CRCs and CRCs diagnosed in areas without screening showed similar distributions to those of CRC in the pre-screening period, according to major characteristics (except macro-area and number of lymph nodes). Compared with the CRCs diagnosed before implementation of the screening programmes, the probability of stage III or IV at

	Total		Areas with a screening programme			Areas without a screening programme
				period with screening		
	N	%	pre-screening period	screen-detected	not screen-detected	
Total (N)	23,668	100	6,710	2,806	6,759	7,393
Macro-area						
Northwest	4,788	20.2	39.1	6.7	16.1	12.0
Northeast	11,571	48.9	52.2	74.4	47.6	37.4
Centre	4,066	17.2	8.7	18.9	36.4	6.7
South-Islands	3,243	13.7	0.0	0.0	0.0	43.9
Gender						
male	4,043	59.3	58.8	61.7	60.0	158.3
female	9,625	40.7	41.2	38.4	40.0	41.7
Mean age (years) (SD)	61.8 (5.3)		61.8 (5.3)	62.3 (5.2)	61.7 (5.4)	61.7 (5.3)
Mean age (years)						
50-54	2,954	12.5	12.5	9.9	13.6	12.5
55-59	4,787	20.2	19.8	20.2	19.6	21.2
60-64	6,821	28.8	29.4	28.2	28.3	29.0
65-69	9,106	38.5	38.3	41.7	38.5	37.4
Anatomic site						
proximal colon	6,334	26.8	27.2	24.3	27.8	26.4
distal colon	8,603	36.4	37.8	50.6	35.7	30.2
rectum	7,487	31.6	31.2	23.2	32.5	34.5
colon NOS	1,244	5.3	3.9	2.0	4.0	8.9
Grading						
well-differentiated	2,332	9.9	9.6	20.1	9.4	6.5
moderately differentiated	13,822	58.4	57.2	56.9	56.5	61.8
poorly differentiated	3,690	15.6	15.6	11.0	16.7	16.3
not available/missing	3,824	16.2	17.5	12.0	17.4	15.4
Lymph nodes examined						
mean number (SD)	16.1 (9.9)		15.6 (9.3)	15.6 (9.7)	18.0 (11.0)	14.5 (8.7)
Positive lymph nodes						
mean number (SD)	2.0 (4.2)		2.1 (4.0)	1.0 (2.7)	2.4 (4.9)	2.1 (4.2)
Positive lymph nodes in stage III/IV cases						
mean number (SD)	4.3 (5.3)		4.2 (4.9)	3.4 (4.0)	4.6 (6.0)	4.3 (5.0)
Stage at diagnosis						
I	4,495	19.0	16.2	42.8	17.2	14.2
II	5,722	24.2	24.9	19.1	24.4	25.2
III	6,267	26.5	27.5	20.1	28.3	26.3
IV	4,389	18.5	19.8	6.2	20.3	20.5
not available/missing	2,795	11.8	11.6	11.9	9.8	13.8

Table 3. Distribution of colorectal cancer cases according to main characteristics, by pattern of diagnosis.

Tabella 3. Distribuzione dei casi di tumore del colon retto per varie caratteristiche, per modalità di diagnosi.

Table 4. Odds ratios of colorectal cancers diagnosed at stage III or IV (as compared to stage I-II), according to selected variables.
Tabella 4. Odds ratio di stadio avanzato (III o IV), per diverse variabli.

	N stage III-IV*	N stage I-II	Odds ratio**	95%CI
Gender				
male	6,249	6,104	1*	-
female	4,407	4,113	1.02	0.97-1.08
Age (5-year linear increase)			0.91	0.89-0.94
Anatomic site				
proximal colon	3,166	2,770	1*	-
distal colon	3,647	4,019	0.83	0.77-0.88
rectum	3,226	3,026	0.91	0.84-0.97
colon NOS	617	402	1.19	1.04-1.37
N examined lymph nodes			1.002	1.001-1.003
Pattern of diagnosis				
pre-screening	3,182	2,774	1*	-
screen-detected	737	1,734	0.40	0.36-0.44
not screen-detected	3,566	3,090	1.04	0.97-1.12
areas with no screening	3,171	2,619	1.05	0.97-1.13

* reference
** estimated using logistic regression model (response variable stage III-IV vs. stage I-II), adjusted by all the variables in the table

Table 5. Odds ratios of poorly differentiated grading colorectal cancers (as compared to well/moderately differentiated), according to selected variables.
Tabella 5. Odds ratio di grading scarsamente differenziato, per diverse variabli.

	N poorly differentiated*	N well mod. differentiated	Odds ratio**	95%CI
Gender				
male	2,120	9,627	1*	-
female	1,570	6,527	1.07	1.00-1.16
Age (5-year linear increase)			1.00	0.96-1.03
Anatomic site				
proximal colon	1,401	4,114	1*	-
distal colon	1,104	6,411	0.54	0.49-0.59
rectum	980	4,973	0.61	0.56-0.68
colon NOS	205	656	0.93	0.78-1.11
N examined lymph nodes			1.00	0.998-1.00
Pattern of diagnosis				
pre-screening	1,075	4,491	1*	-
screen-detected	308	2,160	0.86	0.75-1.00
not screen-detected	1,298	4,859	1.06	0.96-1.16
areas with no screening	1,009	4,644	0.96	0.87-1.06

* reference
** estimated using logistic regression model (response variable stage III-IV vs. stage I-II), adjusted by all the variables in the table

diagnosis was reduced by 60% among screen-detected cases (table 4, p. 112). Instead, there were no significant differences regarding cases that were not screen-detected and cases diagnosed in areas with no screening. The risk of an advanced stage decreased with age and was lower for cases of cancer located in the distal colon and the rectum.
The probability of a poorly differentiated grading was significantly lower (14%) among screen-detected cases (table 5) as compared to the period prior to screening, even when adjusting for stage at diagnosis (OR not adjusted for stage was 0.62, 95%CI 0.54-0.71), while non-screen-detected cases and cases diagnosed in areas with no screening did not show a different risk from pre-screening CRCs. The risk of poorly differentiated grading was higher in cases with an advanced stage at diagnosis and for cases located in the proximal colon.

DISCUSSION

Using data collected from the large number of CRCs diagnosed from 2000 to 2008, this study found that screen-detected CRCs significantly differ from non-screen-detected ones. In particular, the study confirms what is expected by the diagnostic anticipation of screenings, i.e., more favourable prognostic characteristics of screen-detected CRCs: a better distribution by stage at diagnosis and by grading, and a lower number of positive lymph nodes overall and for stage III/IV cases.
Compared to non-screen-detected cases, the proportion of screen-detected CRCs in males was higher, as was the mean age of the patients.
We also observed a higher proportion of CRCs in the distal colon. This figure could be due to the FIT's higher sensitivity to lesions of the left colon[9-11] and hence to a higher impact on the prevalence round of screening at this anatomic site. Most screen-detected cases included in this study were diagnosed in the first or second screening round, when many of the prevalent pre-clinical lesions are detected, thus producing a transient increase in incidence rates. Another reason why screen-detected CRCs are more frequent in the distal colon could de-

pend on the different biology of these lesions, that have been associated to a slow natural history with a long pre-clinical phase.[12] This would increase the difference in diagnostic yield of the distal versus the proximal colon.

Age was inversely correlated to the probability of stage III or IV at diagnosis. The prevalence round of screening (which occurs at a younger age) could play a role in this effect.

The number of lymph nodes examined was positively associated with a more advanced stage. The interpretation of this effect is controversial: on the one hand, the higher likelihood of a staging upgrade the more lymph nodes are examined; on the other hand, it could be hypothesized that more lymph nodes are examined in more advanced cancers.

In areas with an SP, the proportion of screen-detected cases was about one-third of the total. Besides the diagnostic sensitivity of the first-level test and second-level assessment, this figure depends on the extension of invitations and compliance with invitation to screening. Even though this study monitored the impact of screening in the first years after SP implementation (when the spread of screening over the target population is reasonably lower than expected in well-established programmes), we observed a relevant impact of screening even when evaluating all the CRCs diagnosed in the entire population.

Compared to the North-Centre, cases in the South and Islands showed a worse distribution by stage at diagnosis and by grading. These figures suggest a diagnostic delay in this macro-area that was worsened by the increase in the number of SPs in the North-Centre. This hypothesis is in line with the results from the latest report of the Italian association of cancer registries (AIRTUM) on cancer patient survival. CRCs diagnosed during 2001-2004 in the South and on the Islands showed a lower 5-year survival rate compared to cases diagnosed in other areas of Italy.[13]

Another important result of this study was that, after screening was implemented, the cases diagnosed before the onset of an SP and those not screen-detected in the same areas were very similar in terms of distribution by age and anatomic site, stage at diagnosis, and grading. The only exception was the number of examined and positive lymph nodes, which was higher in the latter group. However, this figure could be due to a period effect.

The cases that were diagnosed outside the SPs were not different from the cases detected before the onset of screening. Therefore, they do not seem to have been significantly affected by SP implementation. This fact has at least three consequences:

- the presence of an SP does not seem to generate a "halo" effect (i.e., an increase in the spontaneous, extra-screening, uptake of FIT and/or total colonoscopy) to produce a visible diagnostic anticipation; this hypothesis needs to be confirmed in areas where SPs have been active for more years;
- non-screen-detected cases are representative of the cases that were diagnosed in the absence of SPs, therefore they can be safely used as a comparison group for screen-detected CRCs;
- the differences that we observed in the screen-detected cases may be entirely attributed to the specific pattern of diagnosis.

The risk of selection bias (i.e., compliance with the screening invitation being higher among healthier subjects, who would have a more favourable pattern of disease even without an SP) seems unlikely. Otherwise, non-screen-detected cases would have shown worse characteristics than cases diagnosed before the onset of screening.

This is in line with data from a national survey on preventive behaviours and service utilization, which showed that in Italy spontaneous screening for CRC is very low and the coverage in regions with well-implemented population-based SPs is higher among subjects with a lower educational level.[14]

However, this picture could be modified as SPs age and following changes in compliance with invitation.

CONCLUSION

Screen-detected CRCs showed a favourable distribution by different prognostic factors, while cases diagnosed in the South and on the Islands reported the worst figures.

A renewed effort to implement screening programmes throughout the entire country, and particularly in the South and on the Islands, is therefore warranted, filling the prognostic gap among geographic areas, to increase the equity of access to a public health programme that is proving to be highly protective of the population.

Conflicts of interests: none declared

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