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Incidence trends of colorectal cancer in the early 2000s in Italy.

Figures from the IMPATTO study on colorectal cancer screening

Trend di incidenza del tumore del colon retto nei primi anni Duemila in Italia.

Dati dello studio IMPATTO dello screening colorettale

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Abstract

We utilised the IMPATTO study's archives to describe the 2000-2008 colorectal cancer (CRC) incidence rate trends in Italy, once screening programmes based on the faecal immunochemical test were implemented in different areas.

Data on CRCs diagnosed in Italy from 2000 to 2008 in subjects aged 40-79 years were collected by 23 cancer registries. Incidence rate trends were evaluated as a whole and by macro-area (North-Centre and South-Islands), presence of a screening programme, sex, ten-year age class, anatomic site, stage at diagnosis, and pattern of diagnosis (screen-detected, non-screen-detected). The annual percent change (APC) of incidence rate trends, with 95% confidence intervals (95%CI), were computed.

The study included 46,857 CRCs diagnosed in subjects aged 40-79 years, of which 2,806 were screen-detected. The incidence rates in the North-Centre were higher than in the South and on the Islands. During the study period, screening programmes had been implemented only in the North-Centre and had a significant effect on incidence rates, with an initial sharp increase in incidence, followed by a decrease that started in the 3rd-4th years of screening. These incidence rate trends were exclusively due to modifications in the rates of stage I cases. After screening programmes started, incidence increased in all anatomic sites, particularly in the distal colon.

The differential figures introduced by the implementation of screening programmes warrant a continuous surveillance of CRC incidence and mortality trends to monitor the impact of screening at a national level.

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Keywords: colorectal cancer, screening, incidence rates, fecal immunochemical test, Italy

Riassunto

E' stato utilizzato l'archivio dello studio IMPATTO per descrivere i trend di incidenza del tumore del colon retto (CCR) in Italia nel periodo 2000-2008, quando sono stati avviati programmi di screening colorettale basati sul test per la ricerca del sangue occulto fecale in diverse aree.

23 Registri tumori hanno fornito i dati relativi ai CCR diagnosticati nel periodo 2000-2008 in sog-

getti di età compresa fra 40 e 79 anni. Sono stati calcolati i trend di incidenza complessivi e per macroarea (Centro-Nord e Sud-Isole), presenza di un programma di screening, sesso, età, localizzazione anatomica, stadio alla diagnosi e modalità diagnostica (screen-detected, non-screen-detected). Sono riportati gli APC (annual percent change) con intervalli di confidenza al 95%. L'archivio riguarda 46,857 CRC, di cui 2,806 screen-detected. I tassi di incidenza nel Centro-Nord erano maggiori rispetto al Sud-Isole. Nel periodo di studio sono stati avviati programmi di screening solo in aree del Centro-Nord, con un effetto significativo sui tassi di incidenza, con un ripido incremento iniziale seguito da una riduzione a partire dal 3°-4° anno dall'avvio dei programmi. L'effetto degli screening era a carico esclusivamente dei CCR in stadio I alla diagnosi. Dopo l'avvio degli screening, l'incidenza è aumentata per tutte le sottosedi anatomiche del colon, in particolare per il colon distale.
L'avvio dei programmi di screening colorettale in Italia ha avuto un forte impatto portando a un aumento dell'incidenza e delle forme precoci. E' necessario un continuo monitoraggio delle aree italiane per capire gli effetti dello screening su tutta la popolazione.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 115-125)
Parole chiave: tumore del colon retto, screening colorettale, tassi di incidenza, test per la ricerca del sangue occult fecale, Italia

INTRODUCTION

Colorectal cancer (CRC) is a major public health problem. In Italy it represents the most frequent tumour in terms of incidence with more than 50,000 new cases and is the second cause of death among cancers, with about 19,000 deaths per year.[1]
According to estimates by the Italian Association of Cancer Registries (AIRTUM), mortality rates showed a reduction in both genders starting in the early 1990s, while incidence rates increased, particularly in males.[2]
A number of case series from cancer registries in the North of Italy showed that at the end of the 1990s the proportion of cases that were TNM stage III or IV at diagnosis still ranged between 39% and 51% of the total.[3-5] Stage at diagnosis is well known to be closely related to prognosis: a case series from the SEER study showed a 5-year survival of 93% for cases at AJCC stage I, 80% for those at stage II, 58% at stage III, and only 7% at stage IV.[6] The SEER study compared series of cases diagnosed in different periods (from 1973 to 1997) and showed that the increase in stage-specific survival had been very limited.[7]
Therefore, the reported increase in survival, from 51% in 1990-1992 to 64% in 2005-2007,[8] is plausibly associated with a more favourable distribution of stage at diagnosis, which derived from the spread of the uptake of exams for early diagnosis, first spontaneously and then within organized screening programmes (SP). The distribution by stage at diagnosis of screen-detected CRCs is better than that of clinically diagnosed CRCs, with more than 50% of cases at stage I, while those at stage III or IV are about one-fourth of the total.[9-11]
In Italy, CRC SPs were progressively implemented in most regions starting in the early 2000s. By the end of 2010, 66% of the Italian population lived in areas with active CRC screening programmes, but strong geographical differences were present: the corresponding figures were 87% in the North, 79% in the Centre and only 29% in the South and Islands.[9]
Four randomized controlled trials showed that SPs based on the guaiac faecal occult blood test (gFOBT) reduce mortality by 16%,[12,15-19] which rises to 23% in the per-protocol analysis.[12]
Results from a gFOBT population-based SP showed similar figures,[13] while early evidence from faecal immunochemical test (FIT)-based programmes reported a greater reduction in mortality that began earlier compared to the trials, i.e., in the 5th year after screening started.[14]
A population-based SP is expected to initially increase incidence rates, thanks to the diagnostic anticipation of cancers that would otherwise be diagnosed later. In the medium and long term, a progressive reduction of incidence rates is expected, deriving from the prevention of new CRCs as a result of the detection and removal of a large number of precancerous lesions (i.e., advanced adenomas). As a matter of fact, the four trials showed contrasting effects on the incidence rates, with a 17-20% reduction in one of them[15-16] but no effect in the other three.[17-19] The latter reported low compliance with the study by the enrolled subjects (respectively 67%, 60%, and 63%).
A recent paper showed a reduction of incidence rates in the medium term (22% 11 years after screening started).[20] Many studies have shown that FIT sensitivity for advanced adenoma and cancer is higher than that of gFOBT.[21-26] Thus the effect on incidence observed in screening programmes and not in trials could be due to FIT having a higher sensitivity for adenomas than gFOBT.
In Italy, CRC SPs are aimed at residents aged 50-69 or 74 years, who are invited via mail every 2 years to perform a single FIT. Subjects with a positive screening test are contacted to undergo a total colonoscopy performed at an endoscopic referral centre. In only one region (Piemonte) has a different programme been established, with either one sigmoidoscopy at the age of 58, or a FIT invitation every 2 years in the age interval of 59-69 years. The average detection rate of advanced adenomas in organized programmes in Italy is high, compared to that of guaiac trials,[18,27] reaching 13 x 1,000 at the prevalence round and 8 x 1,000 at the incidence round, respectively.[11] Consequently, the impact of screening programmes on incidence is an open question.
To describe the impact that implementing CRC screening programmes has had in Italy, a research project, the IMPATTO study, was financed by the Italian Ministry of Health; the study collects and links information from both screening programme archives and cancer registries.
This paper utilizes the IMPATTO study's archives to describe the CRC incidence rate trends in Italy during 2000-2008, when several SPs were implemented in different areas.

MATERIALS AND METHODS

Data

The IMPATTO study collected data from CRC cases (International Classification of Diseases, 10th revision: C18–C20) in subjects aged 40-79 years that were diagnosed between 2000 and 2008 in the populations covered by 23 population-based cancer registries (CR) in 13 Italian regions (Piemonte, Liguria, Lombardia, Veneto, Trentino, Friuli-Venezia Giulia, Emilia-Romagna, Toscana, Umbria, Lazio, Campania, Sicilia, Sardegna). These areas included about 36%, 17%, and 24% of the resident population in northern, central, and southern Italy, respectively.

Cases based on death certificates only, autopsies without histology, or autopsies with histology and incidence data equal to date of death were excluded. All multiple metachronous cases were included.

Collected data included incidence date, morphology and topography, stage at diagnosis (according to Dukes' classification as modified by Astler and Coller[39]) and grading, surgical intervention, lymph nodes examined and positive lymph nodes. Multiple synchronous cases (incidence date within six months from the index case) were recorded if located in different anatomic sub-sites (fourth digit of the ICD-10 topography code) and only the most advanced were staged. If more cancers were located in the same sub-site, only the most advanced was recorded, maintaining the recording rules of different morphologies.

Vital status was recorded for all cases up to either 31.12.2008 or 31.12.2010, according to the CR. Information about the cause of death was collected for deceased subjects, according to the International Classification of Diseases, 9th revision.

Tumour histological type was recorded according to the International Classification of Diseases for Oncology, 3rd edition.

CRs carried out a record-linkage with the local SPs to retrieve individual data on the screening history of patients before the incidence date by collecting the date of the first invitation and the dates of screening tests. Patients were then classified according to the following screening patterns:

- screen-detected at the first screening episode;
- screen-detected at a repeat screening episode;
- screen-detected at follow-up;
- not compliant with diagnostic work-up after a positive screening test;
- subjects with at least one negative screening test before incidence;
- never compliant (i.e., invited, but not tested within the SP);
- never invited to screening.

Two categories were then created according to the diagnostic modality: screen-detected cases, including the first three classes, and non-screen-detected cases, including the last four.

Finally, age- and sex-specific data on the resident population in the study period for each CR were collected.

Analysis

Cases were classified by geographic macro-area according to the Istat (Italian National Statistics Agency) classification: Northwest, Northeast, Centre, and South and Islands. They were then grouped into two epidemiologically homogeneous areas, North-Centre and South-Islands, apart from Latina, in the southern part of the Lazio region (the centre of Italy), which was included in the South-Islands according to its epidemiological pattern.

During the study period, the CR included in the study only SPs active in the North-Centre. The number of SPs increased particularly in 2006, when the actual extension of invitations rose to 51% of the target population (subjects aged 50-69 years) compared to 16% in 2005.[11] In the IMPATTO study, the proportion of screen-detected cases in subjects aged 50-69 years in the North-Centre rose from 9.1% in 2005 to 30.3% in 2006 and reached 45.9% in 2008. Therefore, two periods were identified, pre-2005 and from 2006 onward. Period-specific indicators were reported for areas where SPs were present.

Incidence rate trends (standardized on the 2001 European population) were evaluated as a whole and by macro-area (North-Centre and South-Islands), sex, ten-year age class, anatomic site (proximal colon: C18.0-C18.4; distal colon: C18.5-C18.8; colon NOS: C18.9; and rectum: C19-C20), stage at diagnosis (according to Dukes' classification), and pattern of diagnosis (screen-detected, non-screen-detected). The annual percent change (APC) of incidence rate trends, with 95% confidence intervals (95%CI), were computed.

RESULTS

We collected data on 47,830 CRCs, of which 973 were excluded (775 anus and anal canal, 129 lymphomas, sarcoma, or melanoma, and 69 for other reasons). The study archives used in this paper are therefore the 46,857 CRCs diagnosed between 2000 and 2008 in subjects aged 40-79 years.

About one-sixth of the cases (15.7%) were from the South and the Islands (**table 1**, p. 118). Most cases were male (58%) and in the upper age class (70-79 years, 44.8%).

There were 3,164 screen-detected cases (6.8% of the total; the proportion increased to 16.6% when considering only cases of 50- to 69-year-olds from areas with an SP).

One third of the cases were in the rectum. The stage was available for 87.6% of the cases.

Overall, the incidence rate was 133.7 and 83 per 100,000 in males and females, respectively.

The incidence in the North-Centre was higher than in the South-Islands: 141 *vs* 103.9 x 100,000 in men and 86.4 *vs* 69.4 x 100,000 in women.

As shown in **table 2** (p. 118), the CRs took part in the study with cases from different periods. Moreover, the SPs were introduced in different years.

Standardized incidence rates of single CRs over the entire study period were between 153.4 in Genova and 99.1 in Sassari in men and between 94.8 in Genova and 65.6 in Sassari in women.

In the North-Centre, incidence rose more steeply from 2006 in both genders, the year that many SPs were implemented in this macro-area (**figure 1**, p. 119). In the South and on the Islands, the figure was stable for both genders.

Table 1. Main characteristics of the study subjects.
Tabella 1. Principali caratteristiche dei soggetti studiati.

	N	%
Total	46,857	100
Macro-area		
North-Centre	39,487	84.3
South-Islands	7,370	15.7
Gender		
male	27,195	58.0
female	19,662	42.0
Age (years)		
40-49	2,180	4.7
50-59	7,741	16.5
60-69	15,927	34.0
70-79	21,009	44.8
Pattern of diagnosis (all areas, age 40-79 years)		
screen-detected at the first screening episode	2,897	6.2
screen-detected at a repeat screening episode	220	0.5
screen-detected at follow-up	47	0.1
not compliant with work-up after a positive screening test	116	0.2
subjects with a negative screening test before incidence	862	1.8
never compliant (i.e., invited but without a screening test)	2,102	4.5
never invited to screening	40,613	86.7
Pattern of diagnosis (areas with a screening programme, age 50-69 years)		
screen-detected	2,805	16.6
non-screen-detected	14,061	83.4
Anatomic site		
proximal colon	13,772	29.4
distal colon	16,278	34.7
rectum	14,278	30.5
colon NOS	2,529	5.4
Stage at diagnosis (Dukes)		
I	8,218	17.5
II	12,051	25.7
III	12,206	26.0
IV	8,577	18.3
unknown	5,805	12.4

Geographic area	Cancer registry	Cases (N)	Incidence rate (x 100,000)								
			2000	2001	2002	2003	2004	2005	2006	2007	2008
Northwest	Genova	2,014				112.1	105.7	102.1			
	Milano	6,019	104.8	108.1	102.0	101.9	102.5	**90.0**	**107.4**		
	Sondrio	875	91.7	88.8	101.1	95.1	89.7	**90.6**	**130.4**	**120.7**	**110.2**
	Biella	893		104.3	88.4	111.6	99.9	**115.3**	**100.5**	**107.3**	
Northeast	Trentino	1,215			91.5	92.2	88.1	90.0	95.8		
	Veneto	1,894	97.9	109.5	**107.7**	**119.5**	**118.8**	**110.8**			
	Friuli-Venezia Giulia	2,336						105.6	104.8	98.9	
	Emilia-Romagna	17,017	120.2	104.1	112.4	108.0	109.5	**117.4**	**139.5**	**117.3**	**113.4**
Centre	Firenze-Prato	3,935	**111.9**	**113.0**	**112.5**	**106.4**	**106.3**	**107.2**			
	Umbria	3,289					111.7	115.6	**111.6**	**142.3**	**128.2**
South/Islands	Latina	932					89.7	86.4	85.3	87.3	
	Napoli	945				83.3	77.2	98.2	84.8	90.5	
	Siracusa	821		81.1	79.7	83.9	83.6	79.1			
	Palermo	1,628				86.3	87.6	86.9			
	Catania-Messina	2,236				78.6	87.3	84.4			
	Sassari	808				87.9	86.8	82.6	79.1		

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

Table 2. Number of colorectal cancer cases and incidence rates (standardized Eu 2001) by cancer registry and year. Males and females aged 40-79 years.
Tabella 2. Casi di tumore del colon retto e tassi standardizzati di incidenza (popolazione europea 2001) per Registro tumori e anno. Uomini e donne, età 40-79 anni.

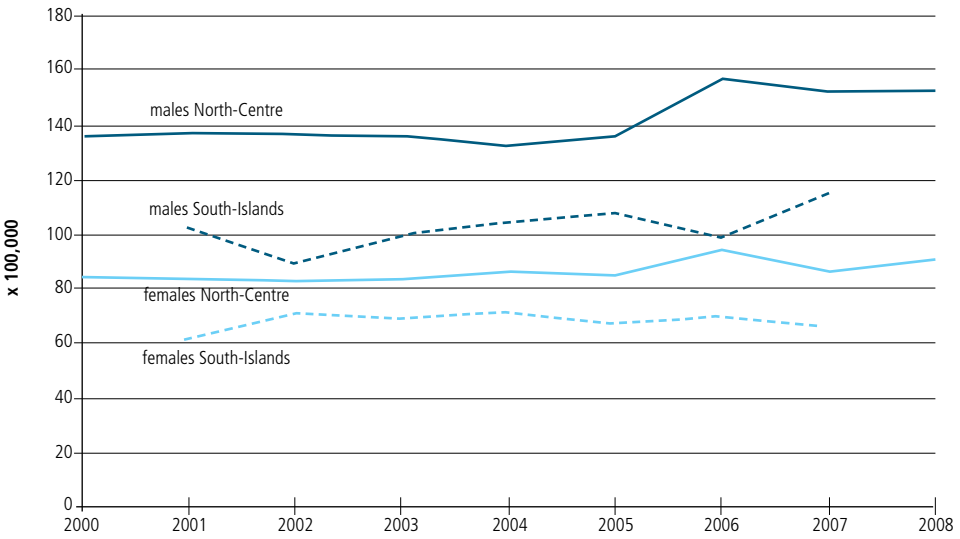

Figure 1. Trends of incidence rates (standardized Eu 2001) by macro-area and gender. Ages 40-79 years.
Figura 1. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per macroarea e genere. Età 40-79 anni.

APC (95%CI)
NORTH-CENTRE
males (2000-2008) 2.1 (0.1 ; 4.1)
females (2000-2008) 1.3 (-0.2 ; 2.7)

SOUTH-ISLANDS
males (2001-2007) 2.5 (-0.6 ; 5.7)
females (2001-2007) -0.4 (-3.0 ; 2.2)

The increase observed in the North-Centre regarded only those areas where SPs were implemented, with the APC in areas without SP being -0.7 (95%CI -4.3 to 3.1) for males and -2.5 (95%CI -5.6 to 0.7) for females (table 3).
The trends in the South and on the Islands showed a non-significant increase in males (APC 2.5; 95%CI -0.6 to 5.7) and a decrease in females (APC -0.4; 95%CI -3.0 to 2.2).
In the North-Centre with an SP present, we recorded a non-significant increase in males 50-69 years old (APC 3.6; 95%CI -0.1 to 7.4) and in females 50-69 years old (APC 2.3; 95%CI -0.8 to 5.4), while the 40-49 and 70-79 year age classes showed small, non-significant decreases.
In the North-Centre without SPs no significant trends were observed in the age class of 50-69 years, while in the South and on the Islands incidence increased in males (APC 4.4; 95%CI 0.4 to 8.5) and overall (APC 3.3; 95%CI 1.3 to 5.3).
Figure 2 (p. 120) shows incidence rates by age in areas with an SP, on a time scale centred on the year of implementation of screening. The pre-screening incidence rates of the four 10-year age classes were stable. During the first two years after screening started, incidence rates increased in all age groups, apart from the youngest, and then decreased. The increase was higher in subjects aged 60-69 years, whose incidence rates shifted from 169 to 249 cases per 100,000 (+47.3%) as opposed to subjects 50-59 years old (+21.7%). The decrease in incidence after year 2 was evident both in subjects aged 60-69 years (APC -5.7; 95%CI -28.3 to 24.2) and in those older than 70 years (APC -7.4; 95%CI -22.7 to 11.0).
In subjects aged 50-69 years, the pre-screening incidence rates were similar to those of areas without SPs in the North-Centre, and became significantly higher after the implementation of SPs (table 4, p. 120). Incidence rates in the South and on the Islands were lower. In particular, pre-screening incidence rates in the North-Centre were generally comparable to North-Centre

	Males		Females		Total	
	APC	95%CI	APC	95%CI	APC	95%CI
North-Centre with SP						
40-79 years	2.5	-0.3 ; 5.4	1.3	-0.8 ; 3.5	2.2	-0.1 ; 4.5
50-69 years	3.6	-0.1 ; 7.4	2.3	-0.8 ; 5.4	3.1	-0.1 ; 6.5
North-Centre with SP pre-screening						
40-79 years	0.2	-1.7 ; 2.2	1.7	-1.9 ; 5.4	1.1	-0.1 ; 2.4
50-69 years	0.4	-2.3 ; 3.1	1.8	-1.9 ; 5.7	1.2	-0.7 ; 3.1
North-Centre with SP post-screening						
40-79 years	2.5	-0.3 ; 5.4	1.3	-0.8 ; 3.5	1.8	-0.8 ; 4.4
50-69 years	3.6	-0.1 ; 7.4	2.3	-0.8 ; 5.4	2.5	-1.1 ; 6.2
North-Centre without SP						
40-79 years	-0.7	-4.3 ; 3.1	-2.5	-5.6 ; 0.7	-1.3	-3.6 ; 1.1
50-69 years	-2.0	-6.4 ; 2.6	-2.7	-9.1 ; 4.2	-2.0	-5.1 ; 1.2
South and the Islands						
40-79 years	2.5	-0.6 ; 5.7	-0.4	-3.0 ; 2.2	1.3	-0.4 ; 3.0
50-69 years	4.4	0.4 ; 8.5	1.5	-2.2 ; 5.3	3.3	1.3 ; 5.3

Table 3. Annual percent change (APC), with 95% confidence intervals, of incidence rates by macro-area, implementation of screening programme (SP), age class, and gender. Years 2000-2008.
Tabella 3. Annual percent change (APC) dei tassi di incidenza (con intervalli di confidenza al 95%) per macroarea, presenza di programmi di screening (SP), classe d'età e genere. Anni 2000-2008.

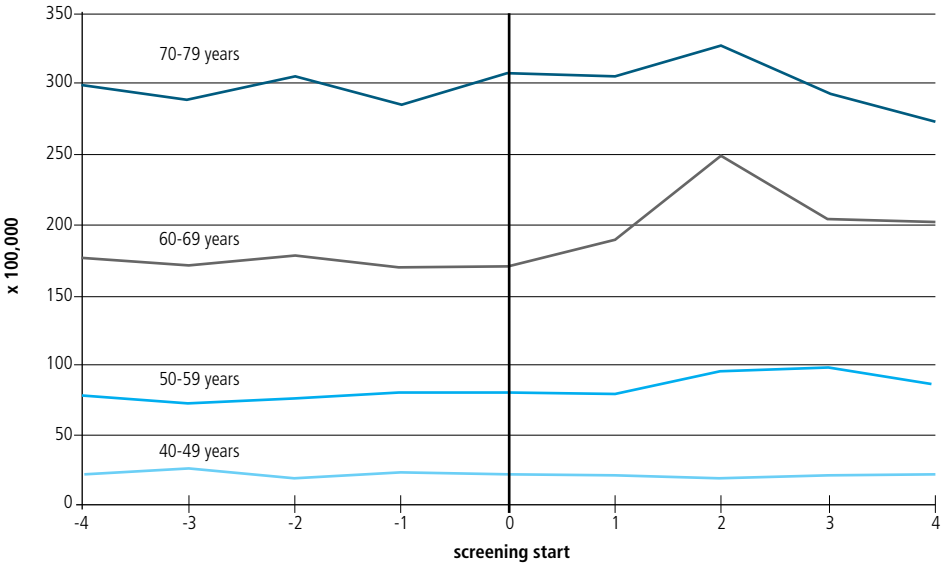

Figure 2. Trends in incidence rates by age class. Cancer registries of areas with screening programme only. The time scale is centred on the year the programme was implemented.
Figura 2. Andamento temporale dei tassi di incidenza per classe d'età. Solo registri tumori di aree dove è attivo un programma di screening. La scala temporale è centrata sull'anno in cui il programma è stato attivato.

Table 4. Incidence rates (standardized Eu 2001) by macro-area, implementation of screening programme and period with respect to different characteristics, x 100,000. Ages 50-69 years.
Tabella 4. Tassi standardizzati di incidenza (popolazione europea 2001) per macroarea, con e senza screening, per periodo, x 100.000. Età 50-69 anni.

	North-Centre without screening programme	North-Centre with screening programme				South-Islands	
		pre-screening		post-screening			
	incidence rates	incidence rates	p-value*	incidence rates	p-value* rates	incidence rates	p-value*
Overall	112.1	116.3	0.10	137.1	<0.001	93.7	<0.001
Gender							
male	142.2	144.0	0.66	170.5	<0.001	112.3	<0.001
female	84.2	91.7	0.02	106.8	<0.001	76.9	<0.001
Age (years)							
50-59	72.9	78.1	0.07	89.7	<0.001	62.2	<0.001
60-69	168.9	171.4	0.59	205.5	<0.001	139.1	<0.001
Pattern of diagnosis							
screen-detected	-	-	-	37.4	-	-	-
non-screen-detected	112.1	116.3	0.10	99.7	<0.001	93.7	<0.001
Stage at diagnosis (Dukes)							
I	18.0	18.6	0.57	32.8	<0.001	11.7	<0.001
II	26.9	29.2	0.08	31.7	<0.001	22.5	<0.001
III	31.4	32.4	0.45	36.6	<0.001	21.4	<0.001
IV	23.2	23.1	0.89	22.0	0.28	21.1	0.18
unknown	12.6	13.1	0.64	13.9	0.14	16.9	<0.001

* compared to reference = North-Centre without screening programme

without screening for all categories of the variables studied, apart from females (+7.5%) and those younger in age (+5.2%). Instead, the respective incidence rates were higher in the North-Centre post-screening and lower in the South and on the Islands for all variables, except for stage IV at diagnosis.
We could not compare the incidence rates by anatomic site of the different areas, because the proportion of colon NOS in the North-Centre without active SPs was too high and unevenly distributed during the years of the study.

Analysis by stage at diagnosis

In the North-Centre without active SPs, and in the South and on the Islands, incidence rates by stage were stable (apart from some fluctuations in the North-Centre during the early years (figures 3 and 4). The APCs for both macro-areas were not significant.
Instead, stage-specific incidence rates in the North-Centre with active SPs showed two different phases (figure 5). Before screening, the incidence rates of stage II, III, and IV cases were stable while those of stage I increased. In fact, during the years before screening the proportion of cases for which the stage was not available decreased. We therefore carried out a sensitivity analysis attributing to such cases the distribution by stage observed among the cases whose stage was known. The pre-screening incidence rates obtained in this way showed a smaller but still significant increase for stage I cases (+5.7 x 100,000 over the entire period).
During the screening period, the incidence rates of stage I cases in-

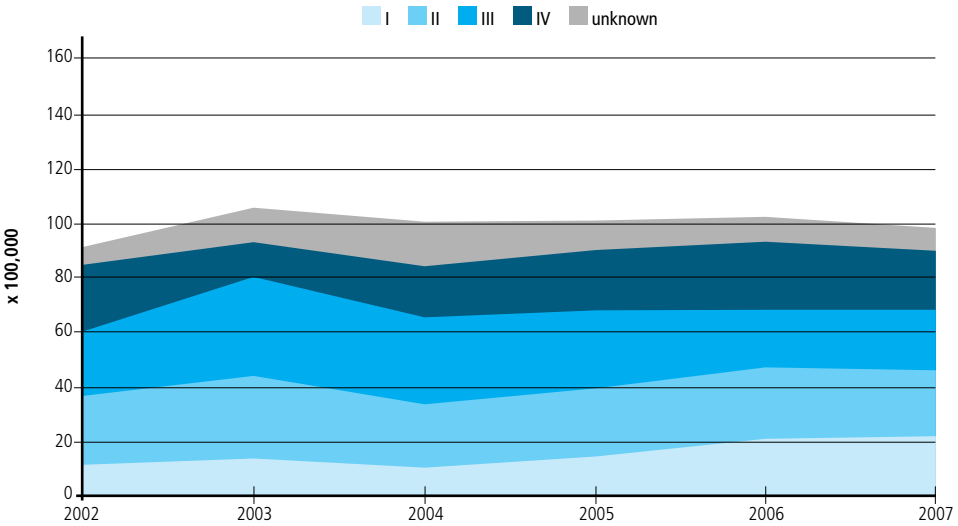

Figure 3. Trends in incidence rates (standardized Eu 2001) by stage at diagnosis. North-Centre with no screening programme. Ages 40-79 years.

Figura 3. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per stadio alla diagnosi. Centro-Nord senza programmi di screening. Età 40-79 anni.

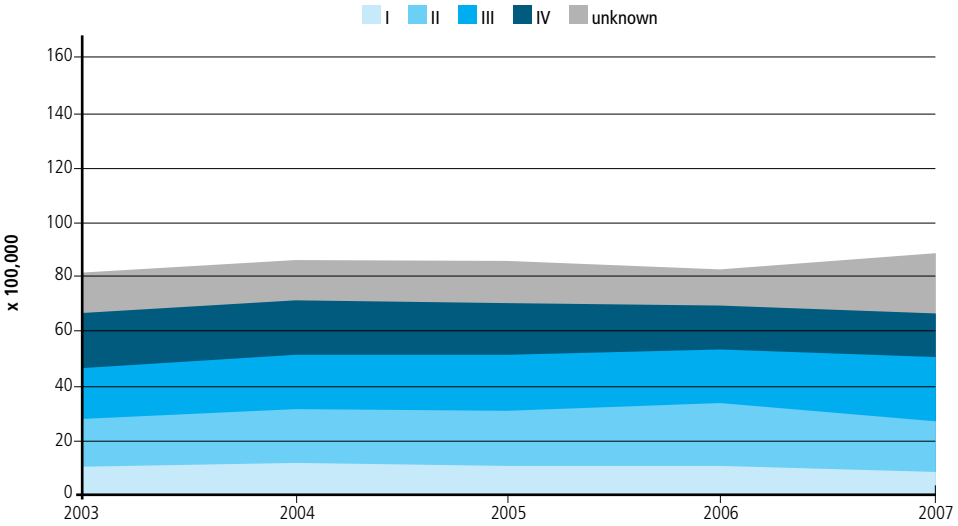

Figure 4. Trends in incidence rates (standardized Eu 2001) by stage at diagnosis. South-Islands. Ages 40-79 years.

Figura 4. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per stadio alla diagnosi. Sud-Isole. Età 40-79 anni.

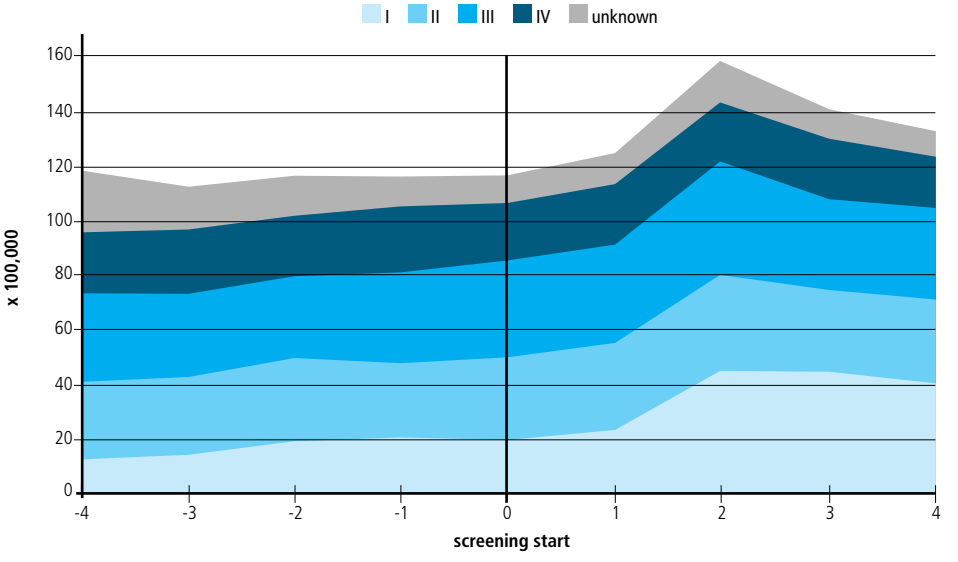

Figure 5. Trends in incidence rates (standardized Eu 2001) by stage at diagnosis. Only areas with a screening programme. Ages 50-69 years. The time scale is centred on the year of implementation of the screening programme.

Figura 5. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per stadio alla diagnosi. Solo aree con programmi di screening attivi. Età 50-69 anni. La scala temporale è centrata sull'anno in cui il programma è stato attivato.

Table 5. Distribution by stage at diagnosis, by macro-area with and without a screening programme, and by period (%).
Tabella 5. Distribuzione per stadio alla diagnosi, per macroarea, con e senza un programma di screnning, per periodo (%).

	North-Centre without screening programme 40-79 years		South/Islands 40-79 years	North-Centre with screening programme 40-69 years	
Stage	**2000-2006 (N=4,488)**	**2006-2008 (N=1,805)**	**2001-2007 (N=7,370)**	**pre-screening (N=6,713)**	**post-screening (N=8,186)**
I	13.7	21.2	12.8	16.0	26.7
II	25.6	25.5	23.9	25.3	23.2
III	29.1	21.7	23.1	27.8	25.8
IV	18.1	22.7	21.3	19.6	15.4
unknown	13.4	8.9	18.8	11.3	8.8

creased from 19.5 to 44.7 x 100,000 in the 2nd year, those of stage II from 30.3 to 35.8 x 100,000, while stage III and IV cases were quite stable, their sum ranging between 68 and 73 cases x 100,000.
In the North-Centre with no active SP during the final years of the study, stage I cases increased by 7.5 percent points and stage IV cases by 4.6 points, while stage III cases decreased by 7.4 points and the proportion of cases with unavailable stage also declined (table 5).
In the South and on the Islands, no variation occurred during the study period. A relevant proportion of cases were stage IV (21.3%), while stage I cases were 12.8%, lower than in the North-Centre. The proportion of cases with an unknown stage was around 20%.
In areas with an SP, the proportion of stage I cases in subjects aged 50-69 years increased from 16% before SP implementation to 26.7% after, while stage III and stage IV cases decreased respectively by 2.0 and 4.2 percent points.

Analysis by anatomic site

The proportion of colon NOS in the North-Centre with no active SP was too high to produce the incidence rates without SP by site for the North-Centre.
In the South-Islands macro-area, incidence rates in the proximal colon decreased, while those in the distal colon were stable and those in the rectum increased (figure 6). Only the latter trend was statistically significant (APC 3.0; 95%CI 0.3 to 5.7).
In areas where SPs were implemented, the pre-screening trend for all sites was stable (figure 7). When the SPs started, we recorded a steep increase of incidence rates in the distal colon (from 43.9 to 69.3 x 100,000 in the 2nd year) and, to a lesser extent, in the proximal colon (from 32.3 to 40.9 x 100,000) and the rectum (from 36.7 to 45.5 x 100,000). This increase ended two years after the implementation of screening and was followed by a reduction in the rates for all three sites.

DISCUSSION

We evaluated CRC incidence rates in Italy from the early 2000s, with particular regard to the effects of the implementation of the SPs introduced during that period in several areas of the country.
Overall, we observed a remarkable difference between the North-Centre and the South and Islands, with the incidence rates in the former macro-area being much higher than in the latter. A different risk of CRC throughout the country, mainly attributed to different exposure to risk factors (e.g., diet), had already been reported.[28]
Of the areas included in the study, SPs had been implemented only in the North-Centre and showed a significant effect on incidence rates. As expected, a sharp increase in incidence was observed in the first years of screening, the prevalence round,[29] followed by a decrease that started quite soon, i.e., within 3-4 years of screening start. For subjects aged 70-79 years, the in-

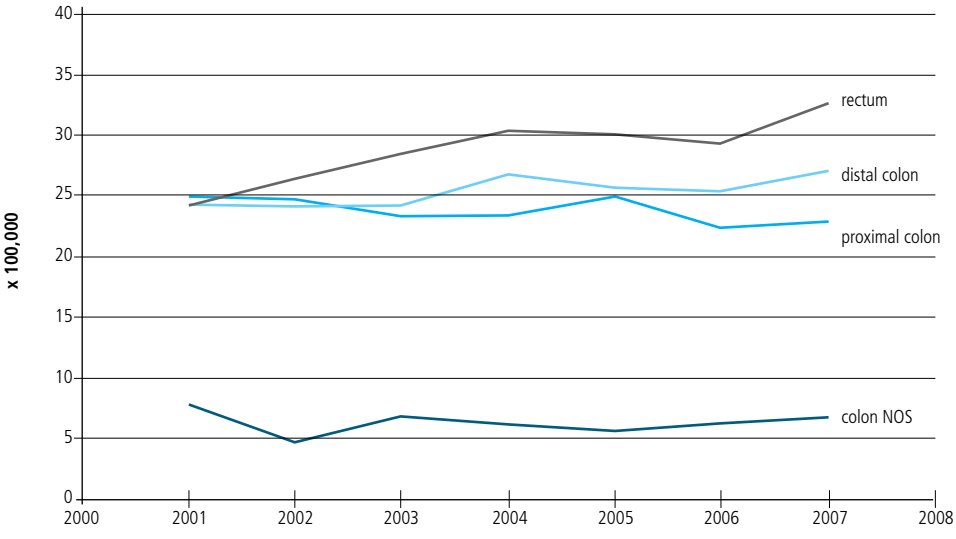

Figure 6. Trends in incidence rates (standardized Eu 2001) by anatomic site. South-Islands. Ages 40-79 years.
Figura 6. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per sede anatomica. Sud-Isole. Età 40-79 anni.

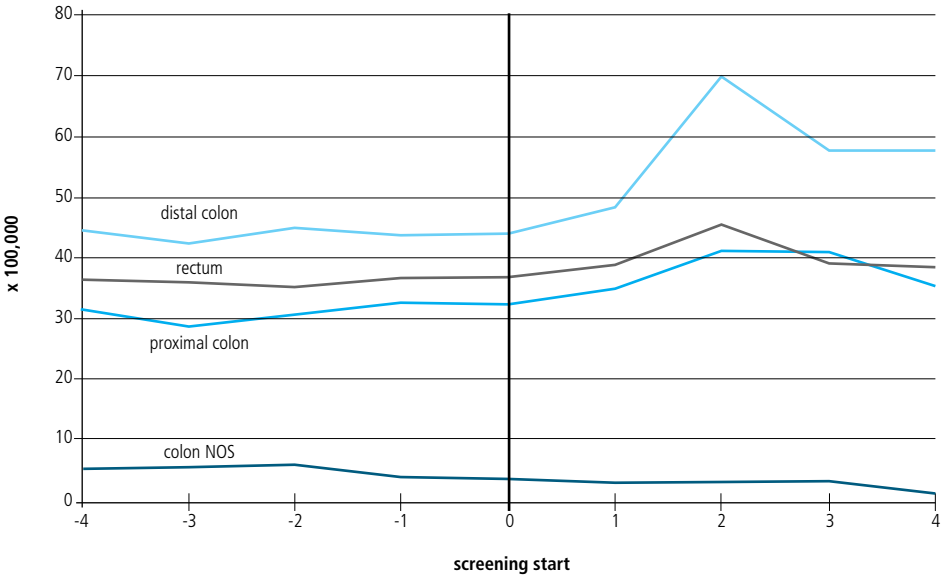

Figure 7. Trends in incidence rates (standardized Eu 2001) by anatomic site. Cancer registries only of areas with a screening programme. Ages 50-69 years. The time scale is centred on the year of implementation of the screening programme.
Figura 7. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per sede anatomica. Solo registri tumori di aree dove è attivo un programma di screening. Età 50-69 anni. La scala temporale è centrata sull'anno in cui il programma è stato attivato.

cidence trend after the prevalence round is suggestive of a decrease to values lower than the pre-screening level.

The overall increase is evident even when considering the whole age range included in the study (40-79 years), which exceeds the specific target population of screening, as well as in the national statistics regarding all ages (0-85+ years).[2] It is of utmost importance that such trends be correctly interpreted in terms of any transient effect related to the implementation of screening and not as an increased risk of CRC in the population.

SPs increased the incidence gap between macro-areas: in the South and on the Islands, no significant trend was observed, in either gender, nor in the pre-screening in those areas where screening was implemented. After the introduction of SPs, the increase in incidence was more evident in the 60-69 year age class than in the 50-59 year one. A differential effect of FIT with age has been described.[30] We also observed a small, non-significant but consistent increase in both genders and across centres, in the age classes above 70 years (probably related to a significant proportion of screen-detected cases in that age group: 15.1% in the 70-74 year class – the SP of Umbria is aimed at residents aged from 50 to 74 years). We do not have enough power to observe even considerably strong trends in the youngest age class because incidence is quite low. Nonetheless, our data suggest a decreasing trend.

These figures are highly suggestive of the expected increase in incidence rates that the introduction of SPs produces through the anticipated diagnosis of cases that otherwise would emerge later and, in part, through a (hard to quantify) number of over-diagnoses.

One relevant aspect analyzed regards the impact of screening on incidence trends by stage at diagnosis. In the areas where an SP was implemented, we recorded a pre-screening trend only for stage I cases. This could be related to a spontaneous (i.e., in the absence of a population-based SP) increased spread of colonoscopies in the population. The implementation of SPs modified exclusively the rates of stage I cases, with the "classic" pattern of initial increase and subsequent reduction in incidence. None of the other stages were affected by screening. This suggests that diagnostic anticipation takes place mainly for cases at an initial stage.

Our data do not allow us to assess the issue of over-diagnosis, mainly because the follow-up period for SPs is too short to determine whether the decrease in incidence observed beginning in the 3rd year will reach the level of pre-screening incidence or drop even lower. However, it has been argued that over-diagnosis of invasive CRC is not a worrisome phenomenon in CRC screening, because the removal of precancerous lesions (i.e., advanced adenomas) determines a relevant incidence reduction.[31-34]

Screening is expected to reduce the incidence rates of advanced stages. We did not notice such an effect, probably because the slow implementation of SPs is still delaying the end of the prevalence round. In fact, only a few programmes have invited the entire target population within the first two years, and all Italian programmes have seen quite low participation rates. Consequently, the proportion of first screening tests is very high even 3 or 4 years after programme start, due to people being invited for the first time or those who did not respond to the first invitation and decided to respond to a second one. Only a longer follow-up period and a more detailed analysis of the cohorts actually invited or participating will make it possible to confirm any effect of screening on the incidence of advanced cancers and incidence as a whole. It is worth underlining that none of the studies evaluating the impact of colorectal screening on incidence rates have found a cumulative reduction of incidence within 5 years of starting to screen,[16,20] including those based on flexible sigmoidoscopy.[35-36]

Differently from areas with SPs, both the North-Centre without SPs and the South and Islands did not record any signifi-

cant trend at any stage of diagnosis. However, notwithstanding the lower overall incidence rates, the specific rates of stage IV in the South and on the Islands were comparable to the other areas of the country. This figure may be attributed to a delay of diagnosis in this macro-area. The lack of any decrease during the study period suggests that no improvements took place to enhance the anticipation of CRC diagnosis. Thus, the widespread implementation of SPs in this macro-area seems particularly relevant.

Unfortunately, we could not evaluate incidence trends by anatomic site in the northern-central areas without SPs, due to a high percentage of missing data. In the South and on the Islands, incidence trends by site showed a significant increase for the rectum.

In areas with SPs, the pre-screening rates in the proximal colon, distal colon, and rectum were stable. After SP started, incidence increased in all anatomic sites, particularly in the distal colon. This figure is in line with the results of many studies that have shown a higher sensitivity for advanced neoplasia in the left versus right colon with faecal occult blood testing[37] and colonoscopy.[38]

The major strength of this study is the large number of cases included in the analysis and the quality of the data collected. The study is based on almost 47,000 CRCs collected by a large number of cancer registries throughout the entire country, and thus offers the best available representation of CRC epidemiology in Italy in relation to SP implementation. On the other hand, the areas included in this study represent a relevant proportion (27% overall) of the national population, but the various macro-areas are unevenly represented. Therefore, projecting our results to the whole country should be done with caution.

This study also has several limits. First, the results of this study do not exclusively reflect the performance of the screening protocols utilised by SPs (first level test and further assessment), but were very much influenced by the spread of screening in the target population, a result associated with the effective extension of invitations and compliance with the invitation to a first-level test, as well as diagnostic workup for subjects with a positive test, etc. These figures are quite different among programmes and make generalizations difficult. This implies that our results should be regarded as purely indicative of what can be expected when implementing an SP, but the figures obtained in a different setting may be very different.

Second, the study only included the few years since screening started. Therefore it could not show how long the decrease in incidence rates, following the initial peak, might last and the size of the reduction that could be achieved.

CONCLUSION

We described the trends of CRC incidence rates in Italy from 2000 to 2008, when several SPs were implemented in different areas. The differential figures introduced by the implementation of SPs warrant a continuous surveillance of CRC incidence and mortality trends to monitor the impact of screening at a national level.

Conflicts of interests: none declared

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