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Colorectal cancer screening: The surgery rates they are a-changing. A nationwide study on surgical resections in Italy

Manuel Zorzi[a,*], Nicola Gennaro[b], Giulia Capodaglio[b], Emanuele Damiano Luca Urso[c], Salvatore Pucciarelli[c], Laura Memo[a], Eva Carpin[a], Mariachiara Corti[b], Massimo Rugge[a], Ugo Fedeli[b]

[a] Veneto Tumour Registry, Azienda Zero, Padua, Italy
[b] Regional Epidemiology Service, Azienda Zero, Padua, Italy
[c] Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua, Padua, Italy

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ABSTRACT

Background: Growing evidence suggests that colorectal cancer (CRC) screening based on the fecal immunochemical test (FIT) reduces CRC incidence and surgical resection rates.
Aims: To compare trends in surgery for proximal and distal CRC among Italian regions at different stages of screening implementation.
Methods: From the National Hospital Discharge Database we selected hospitalizations with CRC resection of residents aged 50–74 years during 2002–2014, and computed surgery rates for the 8 most populous Italian regions with/without a screening program.
Results: In regions with screening, implemented around 2006–2007, the annual percent change (APC) of distal CRC resection was +1.7 (95% confidence interval −1.0, 4.4) during 2002–2007 and −9.1 (−10.6, −7.7) during 2007–2014. No significant change was observed in regions without screening. The APC for proximal colon resection in regions with screening was +5.8 (2.5, 9.0) during 2002–2007 and −4.1 (−5.8, −2.4) during 2007–2014, while in regions without screening surgical rates increased through the whole study period. Compared to 2002, in 2014 distal CRC resection rates were greatly reduced in regions with screening, reaching values similar to proximal CRC resection.
Conclusion: Following the implementation of screening programs surgery rates steeply decreased, confirming the deep impact of FIT-based screening on the burden of CRC.

1. Introduction

Colorectal cancer (CRC) screening programs based on the fecal immunochemical test (FIT) in single Italian regions have been demonstrated to reduce cause-specific mortality [1], CRC incidence [2], and surgical resection rates [1,3]. The introduction of screening has a two-step effect on CRC incidence: an immediate increase due to the diagnostic anticipation of new cases that otherwise would be diagnosed later, and a long-term reduction derived from the detection and removal of precancerous lesions [4]. CRC surgical resection rates have been shown to mirror such complex effect, with a differential impact on proximal and distal CRC possibly explained by a different sensitivity of screening by cancer sub-site and by pre-existing diverging incidence trends [3,5]. Namely, in northeastern Italy within 5 years after the introduction of screening programs, distal CRC resection rates declined significantly and the previous increasing trend in proximal CRC surgery rates was reversed [3].

However, population-based data on the overall impact of CRC screening on resection rates at the national level are lacking in Italy. The Italian National Health System is organized at central and regional level: at the national level, the Ministry of Health allocates national funds to the Regions which are responsible for organizing and delivering health care, including cancer screening. CRC incidence in the early 2000s displayed a geographical gradient across Italian regions, with higher rates in Northern and Central with respect to Southern Italy [6]. Meanwhile, population-based screening programs for CRC were generally established in Northern Regions about one decade ago, while they are still being implemented in Southern Italy. Such variability in the baseline epidemiological scenario and in screening programs provides the opportunity to compare changes over time in surgical resection

* Corresponding author.
E-mail address: manuel.zorzi@azero.veneto.it (M. Zorzi).

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Table 1
Study population, coverage of colorectal cancer screening at the end of the study period, and first year with at least 30% of the target population screened: eight major Italian regions.

Region	Population aged 50–74 years (2014)	Screening coverage (2014)	First year with coverage >30%
Lombardy	3,050,107	52.4%	2006
Veneto	1,520,805	58.3%	2007
Emilia Romagna	1,369,596	64.4%	2006
Tuscany	1,195,918	45.2%	2007
Lazio	1,775,238	11.2%	–
Campania	1,654,211	8.4%	–
Puglia	1,216,429	0.6%	–
Sicily	1,490,974	10.5%	–

rates between Italian regions at different stages of CRC screening implementation.

2. Methods

The analysis included all hospitalizations in the country for the period 2001–2014. Data were obtained from the National Italian Hospital Discharge Database, provided by the Ministry of Health (Banca Dati SDO, Ministero della Salute, Direzione Generale della Programmazione Sanitaria). Among variables listed are age, date of hospital admission and discharge, main and up to 5 secondary discharge diagnoses, and up to 6 procedures/interventions, based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The Health Ministry removed potential patient identifiers from the database in order to respect national rules on confidentiality; a consecutive identification number for each patient was the only identification data allowed in order to track repeated hospital admissions.

All discharges between January 1, 2002, and December 31, 2014 of residents in Italy aged 50–74 years with a diagnosis of CRC (ICD-9-CM codes 153–154, 230.3, 230.4) and with colorectal resection intervention codes (45.7–45.8, 48.35–48.36, 48.49, 48.5–48.6) were extracted. In the case of the same subject being repeatedly admitted with the selected codes, only the first hospitalization was considered; subjects already hospitalized for CRC surgery in the year 2001 were excluded. Surgeries were broken down into proximal colon resection (from caecum to transverse colon included: codes 45.72–45.74), and distal colon (from splenic flexure to sigmoid colon) or rectal resection (codes 45.75, 45.76, 48.35–48.36, 48.49, 48.5–48.6). Since the first admission with both colorectal cancer diagnosis codes and colorectal resection intervention codes was considered, also surgery after neo-adjuvant therapy of rectal lesions was included.

Through a methodology similar to that applied in the United States by Myer et al. [5], and already adopted in the analysis of Italian hospitalization data [3], when the procedure did not specify the anatomic site, the latter was defined by the primary discharge diagnosis (proximal 153.0–153.1, 153.4–153.6; distal 153.2–153.3, 153.7, 154).

Age-standardized national surgery rates (European standard population) by proximal and distal CRC were computed with population data from the Italian National Institute for Statistics. Further analyses at the regional level were carried out limited to the most populous Italian regions, classified by stage of screening implementation. In most Italian Regions, screening involves 50- to 69-year-old residents who are invited via mail every 2 years to perform a single FIT; subjects with a positive test (the cut-off for test positivity being 20 μg Hb/g faeces (100 ng Hb/mL buffer)) are contacted by telephone to undergo a total colonoscopy performed at an endoscopic referral centre. Based on available data on CRC screening population coverage, we individuated the four largest Regions where screening was implemented in the period 2006–2007 (>30% target population screened in the year) [7], and the four largest Regions which lacked sufficient coverage (<30% target population screened) still in 2014 (Table 1) [8]. The eight selected areas in 2014 accounted for 72% of the national population.

In each of the study Region and separately by proximal and distal CRC cancer, time trends expressed as annual percent change in rates (APC) with 95% confidence intervals (95%CI) were assessed by log-linear models; significant changes in time trends were investigated by the permutation test carried out using the Joinpoint Regression Program [9]. The impact of screening implementation was further investigated in the two groups of Regions separately, with and without an established screening program, by segmented Poisson regression models with a first-order autoregressive correlation structure. The predictive variables included were gender, age (5-year classes), pre-intervention trend (years since the start of the study period), immediate effect of screening implementation (variable equal to 0 until screening implementation, 1 thereafter), change in trend after the intervention (variable equal to years after screening implementation, 0 before screening). The latter two intervention-related variables were always equal to 0 in Regions without established CRC screening. Regression models were carried out by means of the xtgee function of the statistical package Stata13.

3. Results

CRC screening programs were implemented around 2006–2007 in three major regions in Northern Italy (Lombardy, Veneto, Emilia-Romagna) and one in Central Italy (Tuscany), with coverage of the target population ranging from 45 to 64% in 2014. For one region in Central (Lazio) and three in Southern Italy (Campania, Puglia, Sicily), coverage in 2014 was still about 10% or less (Table 1).

Out of 262,219 subjects who underwent resection for CRC during the study period, 88,247 were proximal and 170,213 distal colon or rectal resections; 4159 hospitalizations with unspecified sub-site (1.6%) were excluded from the analyses. The number of patients aged 50–74 years undergoing proximal or distal CRC resection was 18,564 in 2002, peaked to 22,148 in 2007, and decreased to 17,936 in 2014; resections of the proximal colon accounted for 30% of total surgeries in 2002 and for 39% in 2014. In the whole country, after a peak reached in 2007, resection rates decreased through all the second part of the study period, with distinct trends by cancer sub-site. Resection rates for cancer of the distal colon and rectum sharply declined after a peak in 2007; in 2014 rates were reduced by about 25% with respect to 2002–2003 (Table 2). Resection rates of proximal colon showed a steep increase in the first study years, thereafter leveling-off and only slightly declining; still in 2014 observed rates were higher than those at the baseline.

Fig. 1 and Table 3 show trends observed in each of the eight investigated areas. Distal CRC resection rates remained unchanged or slightly increased in three regions without screening (Campania, Puglia, Sicily); only in Lazio a moderate, continuous decline could be observed. On the whole, no significant

Table 2
Number of proximal and distal colorectal cancer resection, with corresponding age-standardized rates (European standard population). Italy, 2002–2014.

	Proximal		Distal	
	n	Rate × 100,000	n	Rate × 100,000
2002	5566	34.1	12,998	79.8
2003	5646	34.4	13,132	80.3
2004	6290	38.1	13,921	84.5
2005	6485	38.9	13,792	83.0
2006	7110	42.4	14,536	87.1
2007	7274	43.0	14,874	88.3
2008	7339	43.0	14,023	82.4
2009	7297	42.3	13,337	77.8
2010	7263	41.7	12,868	74.3
2011	7060	40.1	12,306	70.4
2012	6896	39.4	12,056	69.1
2013	7068	39.7	11,387	64.5
2014	6953	38.0	10,983	60.6

change in rates could be observed in areas without screening (APC −0.2, 95%CI −0.7 to 0.4). Three regions with established CRC screening programs (Lombardy, Veneto, Emilia-Romagna) showed a similar pattern, with a clear peak at screening implementation and a fast decrease thereafter. In Tuscany, a steep decline could be observed through the whole study period. In the whole area with screening, APC was 1.7 (95%CI −1.0 to 4.4) during 2002–2007 and −9.1 (−10.6 to −7.7) during 2007–2014; resection rates in 2014 were greatly reduced with respect to 2002.

Surgical rates for cancer of the proximal colon significantly increased in all regions without CRC screening through the whole study period (APC 7.4, 95%CI 3.6–11.2 during 2002–2005 and 1.0, 95%CI 0.4–1.7 during 2005–2014). In regions with established screening programs, such tendency was briefly amplified by screening implementation, but the trend was reversed in subsequent years and rates returned to levels registered in the first study years; the estimated APC was 5.8 (95%CI 2.5–9.0) during 2002–2007 and −4.1 (95%CI −5.8 to −2.4) during 2007–2014. As a consequence of the above trends, in all regions with established screening programs surgical rates for proximal and distal CRC tended to converge; by contrast in all regions without screening resection rates remained much higher for distal than for proximal cancer through the analyzed period.

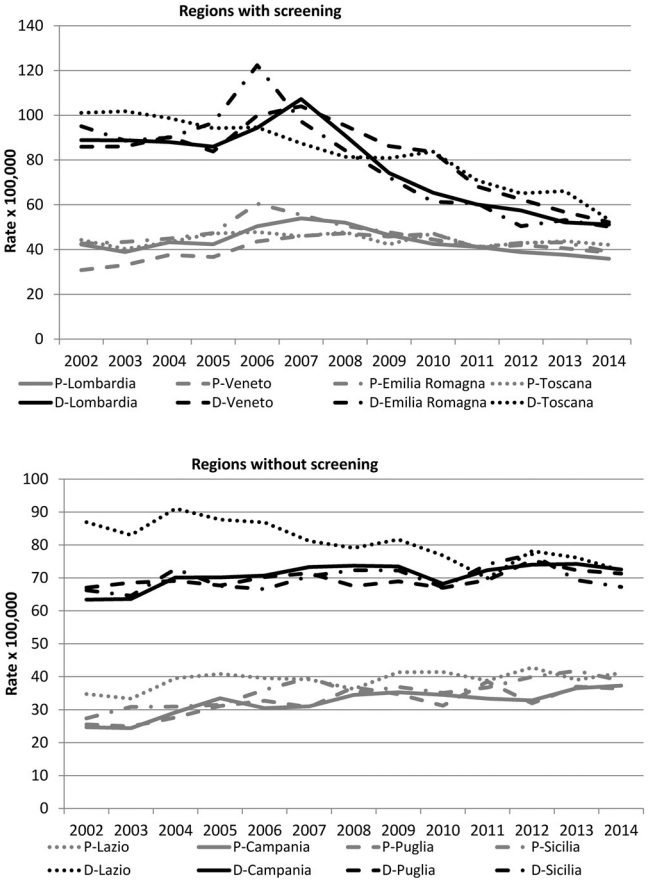

Fig. 1. Age-standardized (European standard population) rates of distal (D) and proximal (P) colorectal cancer resection in eight major Italian regions with and without established screening.

Table 3
Age-Standardized of proximal and distal colorectal cancer resection rates in 8 Italian Regions, 2002–2014.

	Age-Std rate × 100,000		Trend 1		Trend 2		Trend 3	
	2002	2014	Period	APC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)
Distal								
With screening	91.6	51.62	2002–2007	1.7 (−1.0 to 4.4)	2007–2014	−9.1* (−10.6 to −7.7)		
Lombardy	88.86	51.17	2002–2007	3.6* (0.9–6.3)	2007–2010	−13.6* (−23.0 to −3.0)	2010–2014	−6.3* (−9.6 to −2.8)
Veneto	85.93	52.24	2002–2007	4.7* (1.1–8.4)	2007–2014	−9.3* (−11.1 to −7.4)		
Emilia-Romagna	95.08	50.20	2002–2006	4.2 (−3.3 to 12.3)	2006–2014	−10.0* (−12.2 to −7.6)		
Tuscany	101.06	53.32	2002–2010	−3.2* (−4.6 to −1.7)	2010–2014	−8.7* (−12.6 to −4.6)		
Without screening	70.11	68.60	2002–2014	−0.2 (−0.7 to 0.4)				
Lazio	86.95	72.29	2002–2014	−1.7* (−2.4 to −1.0)				
Campania	63.40	72.56	2002–2005	−4.4 (−0.6 to 9.6)	2005–2014	0.3 (−0.6 to 1.2)		
Puglia	67.05	71.32	2002–2014	0.5* (0.0–1.0)				
Sicily	66.24	67.22	2002–2014	0.6 (−0.3 to 1.4)				
Proximal								
With screening	40.34	38.12	2002–2007	5.8* (2.5–9.0)	2007–2014	−4.1* (−5.8 to −2.4)		
Lombardy	42.27	35.89	2002–2007	6.0* (2.1–10.1)	2007–2014	−5.4* (−7.5 to −3.3)		
Veneto	30.82	38.59	2002–2008	7.7* (5.3–10.1)	2008–2014	−3.7* (−5.8 to −1.6)		
Emilia-Romagna	42.61	38.87	2002–2006	8.1* (3.6–12.8)	2006–2014	−4.3* (−5.7 to −2.9)		
Tuscany	44.27	42.13	2002–2014	−0.2 (−1.2 to 0.8)				
Without screening	28.11	37.20	2002–2005	7.4* (3.6–11.2)	2005–2014	1.0* (0.4–1.7)		
Lazio	34.77	41.09	2002–2014	1.2* (0.2–2.2)				
Campania	24.70	37.31	2002–2005	10.0* (1.0–19.8)	2005–2014	1.5* (0.0–3.1)		
Puglia	25.53	36.38	2002–2014	3.0* (1.6–4.4)				
Sicily	27.39	38.78	2002–2014	2.8* (1.7–3.9)				

Abbreviations: 95% CI, 95% confidence interval; APC, annual percent change; Std, standardized.
* P < 0.05.

Table 4
Rate Ratios (RR) with 95% Confidence Intervals (CI) for proximal and distal colorectal cancer (CRC) surgical resection rates estimated by Poisson regression.

	Regions with CRC screening		Regions without CRC screening	
	Distal RR (95% CI)	Proximal RR (95% CI)	Distal RR (95% CI)	Proximal RR (95% CI)
Age, y				
55–59 vs 50–54	1.60 (1.30–1.96)	1.70 (1.55–1.87)	1.76 (1.49–2.07)	1.70 (1.50–1.92)
60–64 vs 50–54	2.33 (1.94–2.80)	2.80 (2.59–3.03)	2.57 (2.21–2.99)	2.84 (2.56–3.16)
65–69 vs 50–54	3.18 (2.64–3.84)	4.18 (3.87–4.52)	3.62 (3.10–4.22)	4.42 (3.96–4.94)
70–74 vs 50–54	3.64 (3.01–4.41)	5.42 (4.99–5.88)	4.53 (3.82–5.37)	6.40 (5.76–7.12)
Sex				
Female vs male	0.58 (0.54–0.62)	0.71 (0.67–0.74)	0.63 (0.58–0.68)	0.71 (0.67–0.76)
Screening effects				
Trend before screening	1.00 (0.99–1.02)	1.03 (1.01–1.04)	0.99 (0.99–1.01)	1.02 (1.01–1.02)
Immediate change after screening	1.12 (1.05–1.19)	1.12 (1.06–1.19)	–	–
Change in trend after screening	0.90 (0.89–0.92)	0.94 (0.92–0.95)	–	–

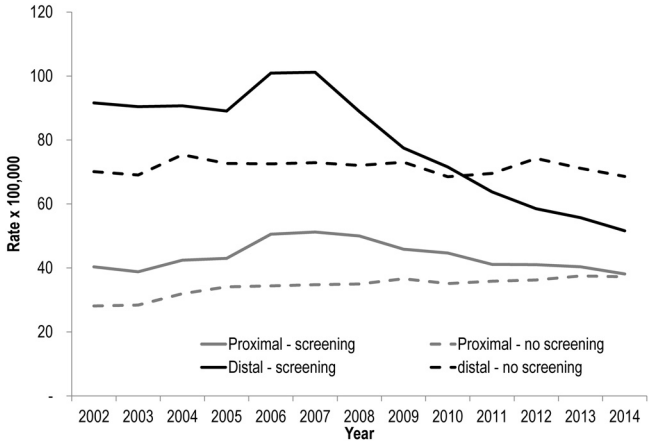

Fig. 2. Pooled data from regions with and without established colorectal cancer screening: age-standardized (European standard population) rates of distal and proximal cancer resection.

Fig. 2 shows that at baseline regions with screening displayed higher surgery rates both for distal (91.6 × 100,000 vs. 70.1 in non-screening regions in 2002) and for proximal CRC (40.3 vs. 28.1 × 100,000). After the implementation of screening programs, with respect to regions without screening, rates were much lower for distal CRC (51.6 vs 68.6 × 100,000 in 2014), and similar for proximal CRC (38.1 vs. 37.2 × 100,000).

Results of regression models show that the trends observed in the pre-intervention period in regions with CRC screening were similar to those registered across all study years in regions without screening: resection rates significantly increased for proximal and remained stable for distal CRC (Table 4). In regions with established programs, an immediate increase in rates (by about 12%) could be observed at screening implementation for both sub-sites, followed by a decline that was steeper for distal (yearly decline by 10%) compared to proximal CRC (6%).

4. Discussion

The implementation of screening programs based on the FIT deeply affects surgery rates for CRC. Our analysis, based on the Italian National Discharge Database, showed divergent trends according to anatomic site in areas with and without screening. The largest impact of screening was on surgery rates for distal CRC, with a peak at screening onset followed by a greater reduction than for proximal CRC. The effect was less pronounced for the latter, possibly due both to the counter-effect of the increase in surgery rates in the prescreening period, and to the lower performance of the FIT on proximal lesions [10,11]. We could not identify any reliable alternative explanation of the observed results other than screening. In particular, the three-phased shape of surgery rates – especially for distal CRC – i.e., a stable pre-screening trend, a peak contemporary with screening onset, and a subsequent decrease, could hardly be produced by any other factor. Thus, we are confident that the observed trends of surgery rates were actually the effect of screening.

A first consequence of the divergent trends by cancer subsite is evident in regions with screening: while in the first study period, surgery rates for distal CRC were more than double than for proximal CRC in both regions with and without implementation screening programs, by the end of the study period – i.e., 7–8 years after screening implementation – resection rates for the two sub-sites were almost overlapping in regions where screening was implemented, but remained unchanged in regions without screening.

As a further consequence of the introduction of CRC screening, the geographical variability in surgery rates is rapidly changing. Regions with established screening programs are located in the North and Centre of Italy, which in the first part of the study period were characterized by higher CRC incidence rates than Southern regions [6]. Thus, the pre-screening differences in surgery rates between the two areas are not surprising and reflect actual differences of incidence rates. By the end of the study, the screening areas showed lower rates for distal and similar rates for proximal CRC with respect to the non-screening areas. The inversion of the historical rate ratio between geographical areas, particularly for distal colon, further highlights the potential impact of screening not only on CRC mortality but also on its incidence. The few studies analyzing the impact of FIT screening on CRC incidence showed a significant reduction of incidence rates [2,12], but did not carry out site-specific estimates, with a dilution of the specific effect of screening on the distal site.

The analysis of areas that differ in so many relevant aspects (e.g., coverage with screening, CRC incidence rates at baseline) allowed to investigate the impact of screening introduction, but might also represent an intricacy in the interpretation of study findings. However, the four regions that implemented CRC screening showed very similar temporal patterns of surgery rates, apart from Tuscany. With this respect it should be noted that, differently from the other regions where screening programs were activated during the study period, in Tuscany the first CRC screening programs started in 1982 limited to small areas [13], and coverage at the regional level progressively increased through the following years. This explains why we did not observe any peak of surgery rates in that region.

We did not quantify the economic and resource savings associated with the reduction of surgery rates deriving from screening, nor with the overall costs for the therapy of CRC patients, of which surgery represents only a part. However, when comparing

the two extreme study years, the decrease by more than 40% of resection rates for distal CRC in the screening areas represents a huge saving of hospital admissions and related resources. Similarly, our study does not allow direct comparisons with the impact of screening programs based on different schedules or screening tests. Even if most countries recommend FIT every two years starting at 50–55 years, there is wide variability regarding both the starting age, ranging between 40 and 60 years, and the test adopted, including guaiac fecal occult blood test, flexible sigmoidoscopy, and colonoscopy [14]. However, different studies showed a larger sensitivity of FIT for advanced adenoma as compared to guaiac-FOBT [15]. Therefore it is likely that screening programs based on the latter test will hardly obtain comparable effects as with the FIT. As regards comparing our results with a screening based on primary colonoscopy, in a very recent analysis on a cohort of subjects repeatedly screened with FIT, the 5-FIT cumulative detection rates of CRC and of advanced adenoma were much similar to those reported by once-only colonoscopy-based screening programs [16]. This could explain the similarity between the findings of the present study and those from Myer's analysis on the impact of colonoscopy-based screening on surgery rates in the United States [5].

Diverging incidence trends by CRC sub-site have been reported in several countries. In the US, the decrease in incidence from the early 1980s to the early 2010s was limited to screening ages, and was larger for distal CRC [17]. In Japan CRC incidence rates increased significantly through the 1978–2004 period for proximal colon, leveled off for distal colon, and started to decrease for rectal cancer [18]. The only available study from Italy reported in Tuscany for the 1985–2005 period a stable incidence for distal and an increasing trend for proximal CRC [19]. A less favorable trend for proximal CRC could be the result both of different trends in etiologic factors, and of the introduction of screening programs. In fact, type 2 diabetes has been associated specifically with proximal colon cancer risk, especially in females [20,21], and the current diabetes epidemic might represent a force driving towards an increase in proximal CRC.

A more pronounced reduction in incidence for distal CRC determined by screening programs could be due to different reasons [22]. First, the accuracy of FIT in detecting neoplasia is lower for the proximal colon [9,10,23]. Second, the ability of colonoscopy to prevent CRC after the removal of high risk adenomas is suboptimal, right-sided location and piecemeal removal being some of the stronger risk factors related to CRC in the same site after polyp removal [24,25]. Piecemeal resection of sessile polyps is more frequently performed in the caecum and right colon, in order to minimize the rate of severe complications that are more frequent in those sub-sites after endoscopic mucosal resection [26–28]. Third, sessile serrated adenomas (SSA) are more frequent in the proximal colon and the cancer risk for SSA is greater in case of proximal location of these lesions [29]. The sensitivity of FIT for SSA has been reported to be suboptimal [30]. Furthermore, as SSA are sessile or flat, they can be overlooked during colonoscopy, as confirmed by the large variability in their detection rates, which has been reported especially in the proximal colon [31,32]. The worst performance of screening on proximal colon is confirmed by the higher rates of interval cancers that affect the right colon [33–35]. Referring to third-level centers patients with large or defiant polyps for proper eradication might reduce such unbalance [36].

This study was based on data obtained from the National Italian Hospital Discharge Database. The accuracy of this database has been demonstrated to be satisfactory for surveillance of geographical and temporal variation of colorectal cancer by validation studies involving regions of Northern, Central, and Southern Italy [37,38]. However, there was no information on cancer stage. Advance in endoscopic resection technology in recent years has impacted the treatment of CRC, especially for superficial T1 cancers, and has reduced the likelihood of surgical resection. Nonetheless, the proportion of screen detected cases that were T1 and were exclusively treated through endoscopy is low (in the Veneto Region, in 2013 they were 35 out of 377 screen detected cases, corresponding to 3.0% of the 1173 CRC diagnosed in 50–69 olds overall) [39,40]. Regarding CRCs diagnosed outside screening, in a large multicenter Italian study involving CRCs diagnosed during 2000–2008, no changes in stage distribution took place between pre-screening vs. no-screening cases [41]. Furthermore, according to the Italian Behavioural Risk Factor Surveillance System PASSI [8], the recourse to spontaneous (i.e., outside an organized screening program) colonoscopy for prevention and/or early diagnosis was permanently lower than 8% between 2010 and 2016 among 50–69 year olds, and the vast majority of early CRC that may be treated exclusively through endoscopic resection is still represented by screen detected cases. This mechanism, through which screening programs further reduce CRC surgery rates, could not be disentangled from the reduction of CRC incidence by our study.

The association between coverage with screening and surgery rates was carried out with an ecological approach, i.e., comparing different populations with different characteristics without individual data on exposure and outcome. However, in our study we aimed at analyzing the "real world" impact of screening programs on CRC surgery rates, without estimating the benefit for participants to CRC screening at the individual level.

CRC risk factors (diet, life style, etc.) and awareness toward CRC (or CRC early symptom) by the public may also change over time and affect CRC incidence and hence surgical rates of CRC. However, it is unlikely that these factors have changed with such a differential pattern between our study areas, with/without screening, to explain the observed trends in surgery rates.

In conclusion, major changes in CRC resection rates could be observed in Italy. Following the implementation of screening programs in Northern regions, surgery rates steeply decreased, and an already existing trend toward the increasing share represented by proximal cancer was accelerated. Furthermore, in Southern regions delays in the activation of screening determined an inversion of the baseline geographical pattern, with higher surgery rates observed at the end of the study period with respect to Northern Italy. The present findings underline the deep impact of FIT-based screening programs both on the overall burden of CRC, and on its characteristics at presentation, including the distribution by sub-site.

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