



Trends in colorectal cancer surgical resection rates during the screening era: a retrospective study in Italy

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ABSTRACT

Background Faecal immunochemical test (FIT)-based screening is effective in reducing colorectal cancer (CRC) incidence, but its sensitivity for proximal lesions remains low.

Objectives We compared age-adjusted CRC surgical resection rates across anatomic sites (proximal colon, distal colon, rectum), age groups and sex over 20 years in a large Italian population. We particularly focused on changes in trends following FIT-screening implementation in the target population (50–69 years).

Design This retrospective study analysed data from the Veneto Region's administrative Hospital Discharge Dataset, involving over 54 000 patients aged 40–89 (43.4% female) who underwent CRC surgery between 2002 and 2021.

Results Overall, surgery rates increased until 2007 (annual percentage changes: 2.5% in males, 2.9% in females) and then declined (–4.2% in males, –3.4% in females). This decline was steeper for distal and rectal cancers compared with proximal cancer, suggesting a shift towards more right-sided CRC surgery.

In males, the prescreening increase in proximal surgery was reversed after screening implementation (slope change: –6%) while the prescreening decline accelerated for distal (–4%) and rectal (–3%) surgeries. In females, stable prescreening trends shifted downward for all sites (–5% for proximal, –8% for distal and –7% for rectal surgery). However, the change in trends between prescreening and postscreening periods was not different across anatomic sites for either sex (all slope change differences in pairwise comparisons were not statistically significant).

Conclusion The shift towards proximal surgery may not be entirely due to the FIT's low sensitivity but may reflect an underlying upward trend in proximal cancers independent of screening.

INTRODUCTION

Colorectal cancer (CRC) stands as one of the most prevalent global cancers, ranking third in terms of incidence (with 1.9 million new cases, excluding anal cancer) and second in terms of mortality (with 0.9 million deaths) in 2020.¹ Within the European Union (EU), CRC poses a substantial burden, as evidenced by age-standardised incidence and mortality

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research suggests a higher faecal immunochemical test (FIT) sensitivity for distal colorectal lesions compared to proximal ones.

WHAT THIS STUDY ADDS

⇒ We observed a shift towards proximal colon surgeries during the 20-year study period. However, similar reductions in surgery resection rates across all anatomic sites (distal, proximal and rectum) took place following FIT programme implementation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings shed new light on the effectiveness of FIT-based screening, suggesting that the shift towards higher proximal surgical resection rates may not only be explained by the lower sensitivity of the FIT test but also by an underlying higher cancer risk in this anatomic site. However, further studies directly investigating the incidence of colorectal cancer are needed to validate this hypothesis.

rates of 69.4 and 32.9 per 100 000 population, respectively.²

The trend of CRC incidence and mortality rates varies considerably among countries worldwide.^{1 3 4} The decrease in CRC incidence observed in some high-income countries over the last decade is partly attributed to the implementation of population-based screening programmes.^{3 5} However, recent data reveal an increase in incidence rates among younger generations.^{5 6}

Disparities in epidemiological outcomes have been highlighted when considering tumour location, with notable differences between left-sided and right-sided CRC.^{7 8} CRC predominantly occurs on the right side in females and older individuals, whereas left-sided tumours are more common in males and younger individuals.^{9–11} Interestingly, a shift from left-sided to right-sided CRC has been observed in several developed

high-income countries, including the USA (1973–2015),¹² Japan (1978–2004),¹³ Norway (1962–2006)¹⁴ and England (1971–2014).¹⁵ However, a recent reversal towards left-sided tumours, linked to an increase in rectal cancer incidence, has been observed over the past decade in the USA.⁵ This shift is noteworthy, considering the generally higher efficacy of screening in preventing left-sided tumours.^{16–18}

Recognising the effectiveness of screening, the EU Council in 2003 called on its Member States to implement organised CRC screening programmes using faecal tests.¹⁹ The quantitative faecal immunochemical test for haemoglobin (FIT) became the test of choice for population screening. Studies have reported its effectiveness in reducing both CRC mortality^{20–23} and incidence,^{22–25} thereby affecting surgical interventions rates.^{26,27} However, the sensitivity of FIT screening for cancer and its precursors is different for proximal versus distal lesions.^{28,29} In particular, a suboptimal sensitivity has been described for sessile serrated polyps, which play a key role in the pathway of proximal CRC.^{30–32} Furthermore, previous studies reported a lower protective effect of colonoscopy (ie, the exam suggested for the diagnostic workup after a positive FIT) against serrated polyps, which are more likely to be missed or incompletely removed during endoscopy due to their flat and pale appearance.^{33–35} The serrated pathway is more frequent in females, which may in part explain the lower impact of FIT-based screening on CRC incidence rates in this population compared with males.^{29,36–40}

Colorectal surgery consists of major procedures, related to high rate of postoperative complications and not negligible mortality, which ranges between 1% and 3%.^{41,42} In particular, rectal resections are associated with an increased risk of severe impairment of bowel function and quality of life.⁴³ Oncological resections of the colon and rectum are expensive procedures and the cost increases in case of complications and reoperations.⁴⁴

Limited research has addressed how CRC surgery rates have changed in the era of screening programmes. This study aimed to fill this gap by evaluating trends in surgical resection rates for proximal colon, distal colon and rectal cancer in both males and females over a 20-year period in Italy's Veneto region. This time frame coincides with the widespread adoption of an FIT-based screening programme, enabling us to assess potential changes in surgical resection rate trends before and after the implementation of this public health intervention in the target population.

METHODS

Setting

In the Veneto region (Italy; approximately 4.9 million residents), a FIT-based screening programme began in 2002 and was progressively implemented in all 21 local health units (LHUs), which are public agencies that organise and administer health services including screening

programmes, achieving full regional territorial coverage by 2009 (online supplemental table 1). The target population consists of residents aged 50–69 years, invited every 2 years to undergo a single FIT; individuals with a positive test (defined by a cut-off value of 20 µg Hb/g faeces) are referred for a total colonoscopy at an endoscopic referral centre.

Study design and study population

In this observational retrospective study, we used data from the Veneto Region's administrative Hospital Discharge Dataset. This dataset contains information on patient demographics, hospital admission and discharge dates, discharge diagnoses (primary and up to five secondary diagnoses) and procedures or interventions (up to six) coded according to the International Classification of Diseases, ninth Revision, Clinical Modification (ICD-9-CM).

The study included all patients residing in the Veneto region aged 40 years or older who underwent surgical resection for CRC in any Italian hospital between 1 January 2002 and 31 December 2021. A case of CRC resection was defined based on a hospital admission that included both an ICD-9-CM primary diagnosis code for malignant neoplasm of the colon (153.x) or rectum (154.0, 154.1, 154.8) and a procedure code for colorectal resection (45.7x, 45.8, 48.35, 48.49, 48.5, 48.6x and 45.95). Only the first hospitalisation with these codes was considered for individuals with multiple admissions. Patients who had been admitted for CRC surgery before 1 January 2002 were excluded.

Based on the anatomic site where the primary tumour originated, CRC was categorised as proximal or right-sided colon cancer (caecum to transverse colon: codes 45.72–45.74), distal colon cancer (splenic flexure to sigmoid colon: codes 45.75, 45.76) and rectal cancer (rectum: codes 48.35–48.36, 48.49, 48.5–48.6). Distal colon cancer and rectal cancer were collectively referred to left-sided CRC. Note that surgeries performed after neoadjuvant therapy for rectal lesions were included in the study because the first admission with both CRC diagnosis codes and CRC resection intervention codes was considered. In case where the procedure lacked anatomic site specification, the primary discharge diagnosis (proximal colon 153.0–153.1, 153.4–153.6; distal colon 153.2–153.3, 153.7; rectum 154) was used for categorisation.^{26,45}

Statistical analyses

To investigate trends in CRC surgical resection rates from 2002 to 2021, direct age-adjusted rates (based on the 2013 European Standard Population) were calculated for each year, stratified by anatomic site (proximal colon, distal colon and rectum) and demographics (sex or age groups: 40–49, target population 50–69 and 70–89 years). Standardisation was performed using the 'distrat' command in Stata software (V.18.0),⁴⁶ with 95% CIs estimated based on a gamma distribution.⁴⁷

Changes in trends over time were analysed using the Joinpoint Regression Programme (V.5.0.2).⁴⁸ Statistically significant trend-changing points (joinpoints) were identified by selecting the best-fitting log-linear regression model⁴⁹ based on the least-weighted Bayesian information criterion.⁵⁰ The joinpoint regression model was implemented under the assumption of heteroscedastic (based on the variance structure provided by the 'distrat' command) and the following predefined set of specifications: maximum of three joinpoints, minimum of three observations from a joinpoint to either end of the data and minimum of four observations between joinpoints. Temporal trends were expressed as annual percentage changes (APCs) with 95% CIs calculated using the empirical quantile method. Note that age-adjusted rates for 2020 and 2021 were excluded from the Joinpoint analysis due to potential COVID-19 impact.⁵¹

Changes in trends of CRC surgical resection rates following the implementation of the FIT-based screening programme within the target population (2002–2019) were assessed using an interrupted time series (ITS) analysis in a multiple baseline design.⁵² This design accounts for the gradual introduction of the screening programme across different LHUs at different times. Our ITS analysis followed a segmented approach,⁵³ where the impact of the screening programme implementation (referred to as 'intervention') was assessed by dividing the data into preintervention and postintervention periods and by comparing the postintervention trend to the counterfactual scenario (ie, the expected trend in the absence of the intervention given the pre-existing trend). The main strength of this approach is that both known and unknown/unmeasured time-invariant confounders are controlled by design. However, caution is necessary when interpreting ITS results as evidence of a causal relationship due to the potential presence of unknown time-varying confounders and lead-time effects that could bias the results.⁵³

The ITS analysis was performed using a segmented generalised mixed effect regression model for negative binomial-distributed data,⁵³ which accounted for the nested structure of the data, with subjects (level 1) nested into LHU area (level 2) and addressed data overdispersion. The regression model included a random intercept term at level 2 and the following covariates as fixed effects: age (continuous), time in years from the study start (T), the indicator variable (X) dividing observations prescreening and postscreening implementation in each LHU, and their interaction term ($T \times X$) to account for the change in slope postscreening implementation. Sex-specific expected rates for each anatomical site were simultaneously estimated by adding sex, site and their interaction term, along with interaction terms between each covariate (T , X and $T \times X$) and the combined sex-site interaction, to the fixed-effects part of the model. The FIT coverage rate (ie, the ratio of the number of subjects who received FIT to the total number in the target population) was included as a level 2 variable to account for

variation across LHUs. The logarithm of the population size was used as the offset term. Rate ratios (RRs) were calculated by exponentiating the relevant model coefficients and reported in the results section. Additionally, the same regression model without the anatomic site and their interaction terms was used to obtain estimates for CRC overall. Note that LHUs where screening was introduced before 2006 were excluded from the ITS analysis in order to ensure an adequate number of observations both preintervention and postintervention periods (details in online supplemental table 1). ITS analysis was performed by using Stata software (V.18.0).

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 54 784 patients aged 40–89 underwent surgical resection for CRC between 2002 and 2021, with 31 012 males (56.6%) and 23 772 females (43.4%). Among these, 22 087 surgeries involved the proximal colon (40.3%), 14 292 in the distal colon (26.1%) and 18 405 in the rectum (33.6%).

Age-adjusted surgical resection rates decreased considerably between the initial and final 5-year periods under study, with a 27.3% reduction in females and 34.3% in males. This decline was more pronounced for distal colon (–42.2% in females vs –47.6% in males) and rectal (–47.5% vs –50.1%) cancers compared with proximal colon cancer, which showed a slight increase of 4.2% in females and a decrease of 1.2% in males. Consequently, the right-to-left-sided CRC surgeries RR approximately doubled from 2002–2006 to 2017–2021 for both females and males (table 1).

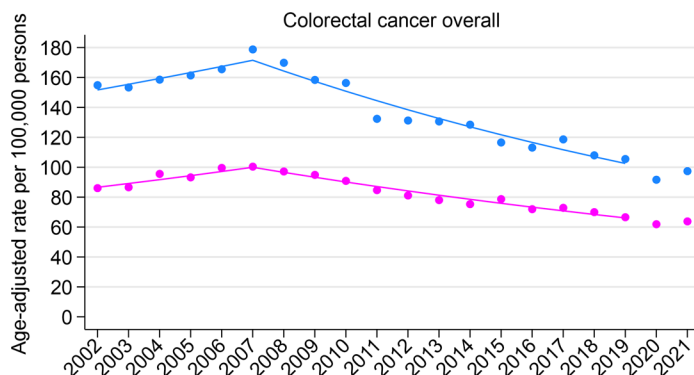
Joinpoint regression model

Analysing the entire study period, both males and females displayed similar trends in age-adjusted resection rates, with males consistently having higher rates across all anatomic sites (figure 1). Specifically, an initial increase trend in rates observed until 2007 (APC=2.5 in males and 2.9 in females) was followed by a significant decrease until 2019 (APC=–4.2 in males and –3.4 in females), with a steeper decline for distal colon and rectal cancers compared with proximal colon cancer in both sexes (figure 1).

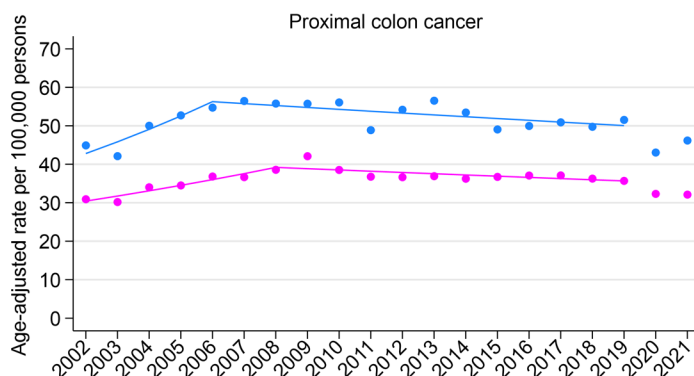
The analysis for the 40–49 age group (figure 2) showed no statistically significant change in the age-adjusted surgical resection rate for proximal colon cancer but statistically significant downward trends for both distal colon (since 2008) and rectal (between 2006 and 2016) cancers. For individuals aged 50 years and older, the surgical resection rate for distal colon and rectal cancer remained stable until 2008 before declining while the surgical resection rate for the proximal colon increased significantly until 2007 before decreasing (in the 50–69)

Table 1 Surgical resection for colorectal cancer in patients aged 40–89 years (2002–2006 vs 2017–2021).

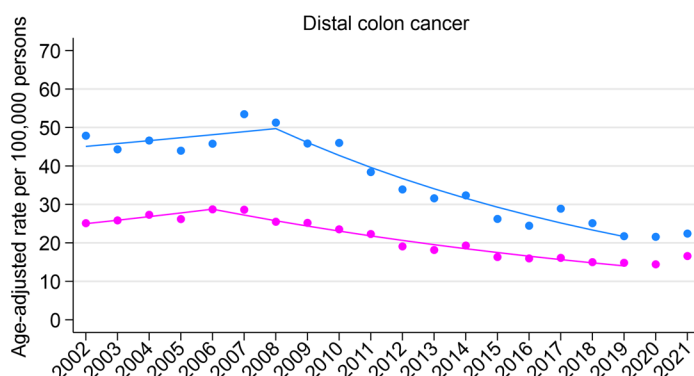
	Female			Male			Female-to-male RR		
	2002–2006 n (SR)	2017–2021 n (SR)	PC (95% CI)	2002–2006 n (SR)	2017–2021 n (SR)	PC (95% CI)	2002 to 2006 RR (95% CI)	2017 to 2021 RR (95% CI)	
Overall CRC	5997 (92.3)	5361 (67.1)	–27.3% (–32.7% to –21.8%)	7955 (158.8)	6839 (104.3)	–34.3% (–41.1% to –27.6%)	0.58 (0.55 to 0.62)	0.64 (0.58 to 0.71)	
Proximal colon	2175 (33.3)	2792 (34.7)	4.2% (–3.6% to 12.0%)	2355 (48.9)	3137 (48.3)	–1.2% (–10.7% to 8.2%)	0.68 (0.60 to 0.76)	0.72 (0.66 to 0.78)	
Distal colon	1720 (26.7)	1224 (15.4)	–42.2% (–47.6% to –36.8%)	2317 (45.7)	1558 (24.0)	–47.6% (–55.0% to –40.1%)	0.58 (0.55 to 0.62)	0.64 (0.56 to 0.72)	
Rectum	2102 (32.3)	1345 (17.0)	–47.5% (–55.1% to –39.8%)	3283 (64.1)	2144 (32.0)	–50.1% (–56.8% to –43.4%)	0.50 (0.47 to 0.53)	0.53 (0.44 to 0.62)	
Right-to-left-sided CRC RR (95% CI)	0.57 (0.53 to 0.61)	1.07 (0.97 to 1.17)	–	0.45 (0.41–0.48)	0.86 (0.75–0.97)	–	–	–	
Patient count (n), sex-specific SR [†] and PC in rates [†] , and female-to-male RR by anatomic site									
95% CI: Statistically significant estimates at the alpha=0.05 level are shown in bold.									
*Truncated (40–89 years) age-standardised rates (2013 European Standard Population).									
†Change from 2002–2006 to 2017–2021.									
CRC, colorectal cancer; PC, percent change; RR, rate ratio; SR, surgical resection rates.									



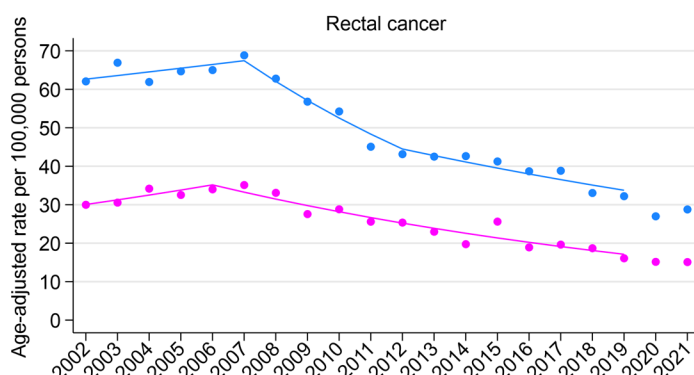
	Time period	APC	95%CI
Male	2002-2007	2.5*	0.3 to 6.2
	2007-2019	-4.2*	-5.0 to -3.6
Female	2002-2007	2.9*	1.0 to 6.1
	2007-2019	-3.4*	-4.1 to -2.9



	Time period	APC	95%CI
Male	2002-2006	7.1*	3.5 to 12.9
	2006-2019	-0.9*	-1.6 to -0.3
Female	2002-2008	4.3*	2.6 to 7.7
	2008-2019	-0.8*	-1.7 to -0.2



	Time period	APC	95%CI
Male	2002-2008	1.6	-2.4 to 12.0
	2008-2019	-7.3*	-11.1 to -5.8
Female	2002-2006	3.6*	0.3 to 8.5
	2006-2019	-5.4*	-6.1 to -4.8



	Time period	APC	95%CI
Male	2002-2007	1.5	-0.8 to 6.5
	2007-2012	-8.0*	-9.9 to -5.7
	2012-2019	-3.9	-5.9 to 1.0
Female	2002-2006	4.0	-1.7 to 11.9
	2006-2019	-5.4*	-7.6 to -4.5

Figure 1 Colorectal cancer surgical resection rates^a in patients aged 40–89 by anatomic site and sex (2002–2021). Dots represent the observed rates (males in blue, females in pink). Curves are from Joinpoint regression model (results in the table). ^aTruncated (40–89 years) age-standardised rates (2013 European Standard Population). *The APC is significantly different from zero at the $\alpha=0.05$ level. Last two data points (COVID-19 Outliers) were excluded in the joinpoint trends. APC, annual percentage changes.

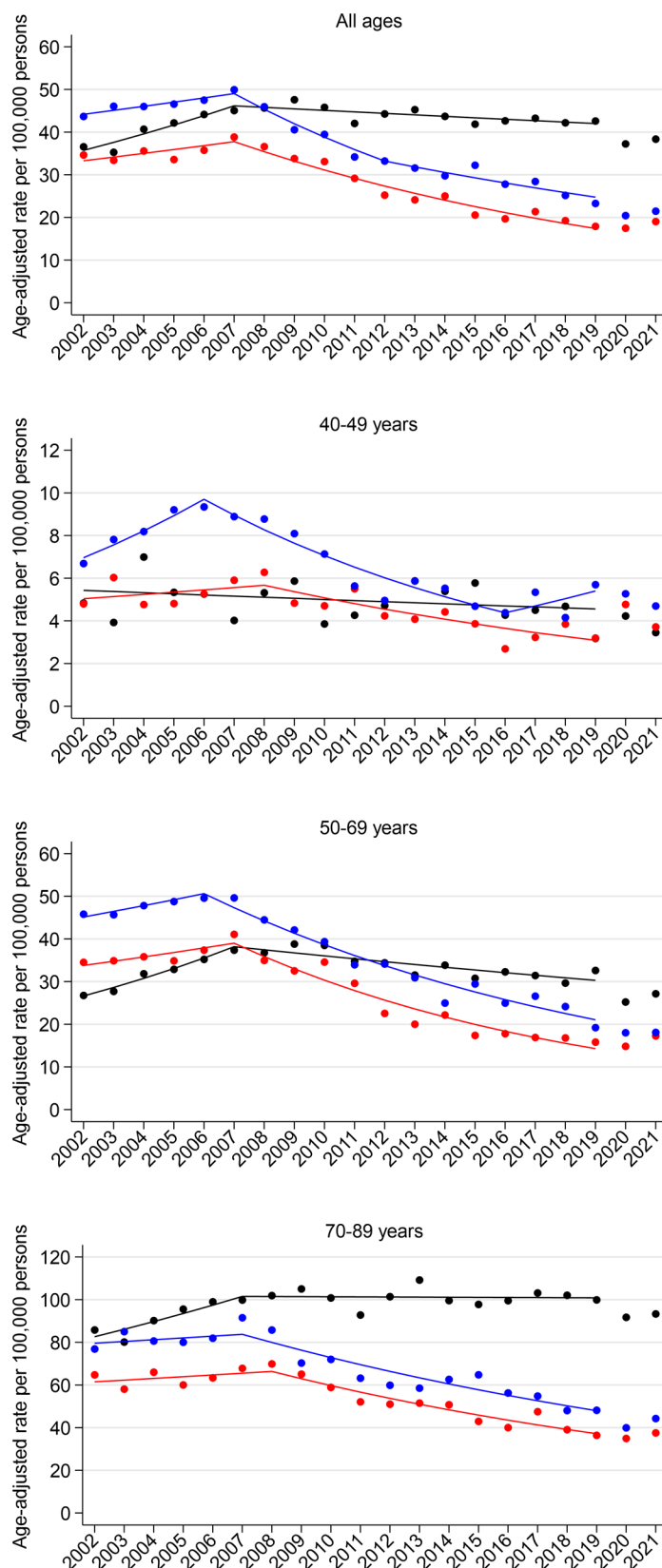


Figure 2 Colorectal cancer surgical resection rates^a by age group and anatomic site (2002–2021). Dots represent the observed rates (proximal colon cancer in black, distal colon cancer in red and rectal cancer in blue). Curves are from joinpoint regression model (results in the table). ^aTruncated age-standardised rates (2013 European Standard Population) *The APC is significantly different from zero at the $\alpha=0.05$ level. Last two data points (COVID-19 Outliers) were excluded in the joinpoint trends. APC, annual percentage changes.

	Time period	APC	95%CI
Proximal	2002-2007	5.3*	3.4 to 8.0
	2007-2019	-0.8*	-1.3 to -0.3
Distal	2002-2007	2.6	-0.3 to 7.1
	2007-2019	-6.3*	-7.4 to -5.5
Rectal	2002-2007	2.1*	0.1 to 5.7
	2007-2012	-7.5*	-8.9 to -5.7
	2012-2019	-4.1*	-5.3 to -0.4

	Time period	APC	95%CI
Proximal	2002-2019	-1.0	-3.3 to 1.4
Distal	2002-2008	2.0	-2.4 to 15.4
	2008-2019	-5.4*	-14.5 to -3.5
Rectal	2002-2006	8.6*	2.0 to 19.4
	2006-2016	-7.6*	-11.7 to -6.2
	2016-2019	7.3	-3.3 to 14.2

	Time period	APC	95%CI
Proximal	2002-2007	7.5*	4.8 to 11.7
	2007-2019	-1.9*	-2.7 to -1.2
Distal	2002-2007	2.9	-1.0 to 10.1
	2007-2019	-8.0*	-9.8 to -6.9
Rectal	2002-2006	2.9	-0.9 to 9.3
	2006-2019	-6.5*	-7.6 to -5.8

	Time period	APC	95%CI
Proximal	2002-2007	4.2*	1.8 to 8.8
	2007-2019	-0.05	-1.1 to 0.5
Distal	2002-2008	1.3	-2.0 to 11.1
	2008-2019	-5.1*	-9.8 to -3.9
Rectal	2002-2007	1.0	-2.7 to 9.8
	2007-2016	-4.5*	-10.6 to -3.5

Table 2 Interrupted time series by anatomic site and sex in the target population of FIT-based screening (50–69 years)

	Parameter	Overall RR (95% CI)	Proximal RR (95% CI)	Distal RR (95% CI)	Rectal RR (95% CI)
Male	Pre-FIT slope	0.99 (0.97 to 1.00)	1.05 (1.01 to 1.08)	0.96 (0.93 to 0.99)	0.96 (0.94 to 0.99)
	Level change	1.25 (1.14 to 1.38)	1.07 (0.93 to 1.24)	1.50 (1.29 to 1.74)	1.24 (1.09 to 1.41)
	Slope change	0.96 (0.94 to 0.98)	0.94 (0.91 to 0.97)	0.96 (0.92 to 0.99)	0.97 (0.94 to 0.99)
	Post-FIT slope	0.94 (0.94 to 0.95)	0.99 (0.97 to 1.00)	0.91 (0.90 to 0.93)	0.93 (0.92 to 0.94)
Female	Pre-FIT slope	1.01 (0.99 to 1.03)	1.03 (1.00 to 1.07)	1.00 (0.97 to 1.04)	1.00 (0.97 to 1.04)
	Level change	1.27 (1.14 to 1.41)	1.35 (1.14 to 1.59)	1.28 (1.07 to 1.52)	1.19 (1.01 to 1.39)
	Slope change	0.94 (0.92 to 0.96)	0.95 (0.91 to 0.98)	0.92 (0.89 to 0.96)	0.93 (0.90 to 0.96)
	Post-FIT slope	0.95 (0.94 to 0.96)	0.97 (0.96 to 0.99)	0.93 (0.92 to 0.95)	0.93 (0.92 to 0.94)

Statistically significant estimates at the alpha=0.05 level are shown in bold.

'Pre-FIT slope' represents the trend before the screening implementation. 'Level change' indicates the level change in the mean outcome that occurs in the period immediately following the screening implementation. 'Slope change' indicates the difference between prescreening and postscreening implementation slopes of the mean outcome. 'Post-FIT slope' represents the postscreening implementation trend. FIT, faecal immunochemical test; RR, rate ratio.

or stabilising (in 70–79 age group). Consequently, proximal colon cancer became the most frequent surgery site for individuals aged 50–69 in the later study period and the most frequent overall for those aged 70–89.

ITS analysis on the target population (aged 50–69 years)

Before the implementation of the screening programme, overall CRC resection rates remained stable in both males (pre-FIT slope, RR (95% CI): 0.99 (0.97 to 1.00)) and females (1.01 (95% CI 0.99 to 1.03)) within the target population (table 2 and figure 3). However, prescreening trends varied by anatomic site within sexes. Males showed an increasing trend in resection rates for proximal colon (1.05 (95% CI 1.01 to 1.08)) and a decreasing trend for both distal colon (0.96 (95% CI 0.93 to 0.99)) and rectum (0.96 (95% CI 0.94 to 0.99)) while females maintained stable trends across all anatomic sites.

Immediately after the screening implementation, both sexes experienced a significant increase in overall resection rates (level change: +25% for males, +27% for females) (table 2 and figure 3). Notably, the most pronounced increases occurred in the distal colon for males (+67%) and in the proximal colon for females (+35%).

Subsequently, postscreening trends diverged from the prescreening period within each anatomic site and sex (all 'slope change' parameters were found statistically significant) (table 2 and figure 3). Specifically, in males, the previously observed upward trend in proximal cancer rates reversed after screening implementation (post-FIT slope, RR (95% CI): 0.99 (0.97 to 1.00)), and the existing downward trend for both distal colon (0.91 (95% CI 0.90 to 0.93)) and rectal (0.93 (95% CI 0.92 to 0.94)) cancers accelerated. Conversely, in females, a decline from previously stable trends across all anatomic sites was found after the screening implementation. However, despite these divergent trends, neither males nor females showed any significant differences between the change in trends from prescreening to postscreening across the different

anatomic sites (slope changes differences in pairwise comparisons: all p values >0.20).

DISCUSSION

This study investigated trends in surgical resection rates for CRC in over 54 000 patients aged 40–89 years who underwent surgery between 2002 and 2021 in Italy's Veneto Region. Our analysis revealed differences in trends based on tumour location, patient age and sex over the 20-year period. Additionally, it highlighted the potential impact of implementing the FIT-based screening programme on CRC surgical resection rates.

Changes in trends over time

Over the last 20 years, we observed an approximately one-third reduction in surgery rates, driven by a halving of the rates of surgical interventions in the distal colon and in the rectum while surgery rates in the proximal colon remained stable. Consequently, during the most recent study period, over half of all CRC surgeries involved the proximal colon.

When comparing the last 5-year study period with the first, the drop in surgery rates was more pronounced in males (–36.2%) than in females (–28.4%). In females aged 70 years and older, interventions in the proximal colon were already more frequent at the beginning of the study, and the gap between the distal colon and rectum notably increased during the observation period. In contrast, in males, the initial pattern was characterised by a lower proportion of proximal surgeries compared with females, and this was reversed during the study period due to the drop in distal surgery rates.

Changes in trends following implementation of fit-based screening programme in the target population (aged 50–69 years)

The results of ITS analysis appear to be consistent with previous research,⁵⁴ which reported a dual effect of the

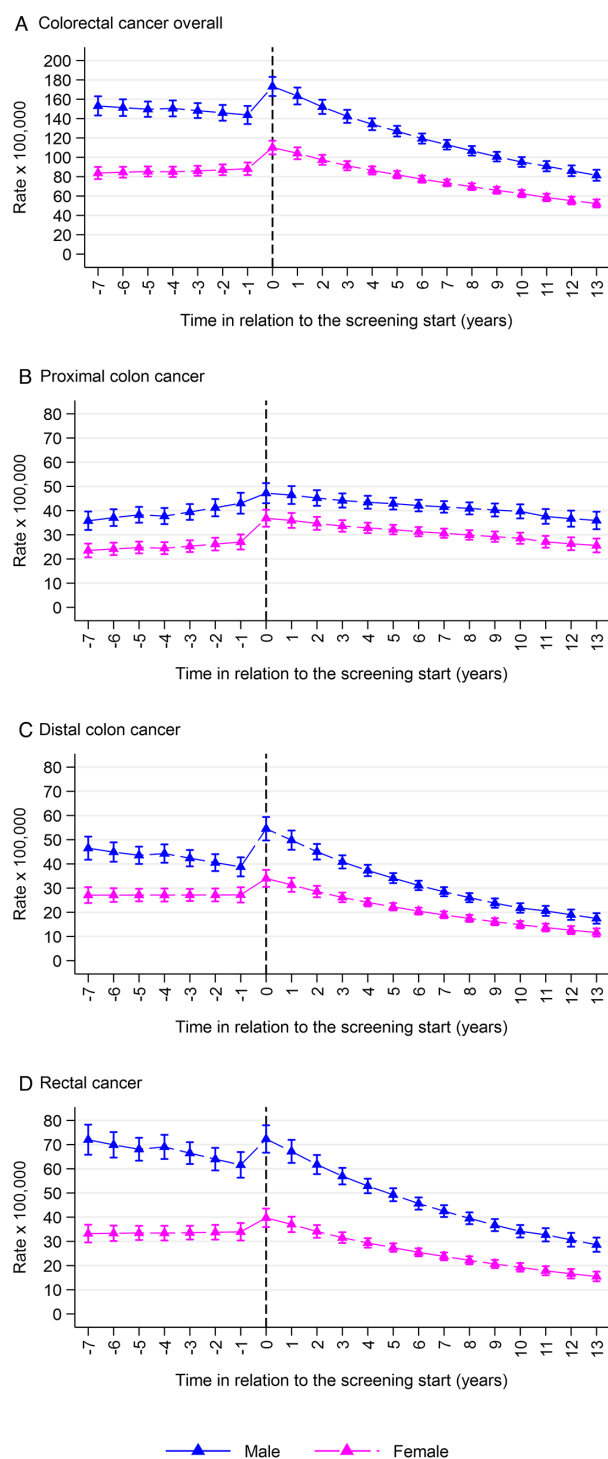


Figure 3 Trends in surgical resection rates of colorectal cancer pre-FIT and post-FIT implementation in the target population (50–69 years) by anatomic site and sex (2002–2019). The dashed line indicates the time when the screening was implemented. FIT, faecal immunochemical test.

screening programme: an initial rise in resection rates due to earlier detection of cancers that would have otherwise been diagnosed later, followed by a long-term reduction likely due to the removal of precancerous lesions.

While our joinpoint analysis aligns with existing evidence suggesting the FIT-based screening's effectiveness in reducing CRC incidence and surgeries, particularly

for males and distal colonic and rectal lesions,^{28 29 34 36–40} the ITS analysis reveals a different perspective. Specifically, surgical resection rates for the distal colon and rectum were already decreasing in males before the screening programme's launch while remaining stable in females. Following screening implementation, these pre-existing downward trends became more pronounced in males, with a similar decrease observed in females. Furthermore, the previously observed increasing trend in surgical resection rates for the proximal colon in both sexes was reversed after widespread screening began. Consequently, despite initial variations in prescreening trends, the change in trends observed after the screening programme's start was similar for both sexes and across all anatomic sites. This suggests that FIT screening might have had a similar impact on reducing precancerous lesions regardless of tumour location.

These findings might offer a new perspective in the comprehension of the performance of FIT-based screening according to anatomic site. Previous research, evaluating the incidence of 'interval cancers' (ie, CRC detected shortly after a negative FIT result), suggests lower sensitivity for detecting proximal lesions compared with distal ones.^{28 29 55–57} The results of ITS analysis lead us to speculate that the observed excess of proximal interval cancers could be partially explained by an inherently higher underlying risk of cancer, rather than solely attributed to a low sensitivity of the FIT test. However, further investigations are needed to confirm this hypothesis. Future studies evaluating CRC incidence, rather than solely relying on surgery rates, are necessary for a clearer understanding.

Strengths and limitations of the study

Incomplete incidence data represent a limitation in our study because the regional cancer registry only covered approximately 50% of the population until 2012. A discrepancy between CRC incidence and surgery rates might be explained by a very small percentage of early screen-detected CRCs, which were exclusively managed via polypectomy during second-level colonoscopy without the need for surgery. Specifically, this subset comprised only 47 out of 392 screen-detected CRCs out of an estimated total of approximately 3600 incident cases in the Veneto region in 2021.⁵⁸ Moreover, an increasing proportion of patients with rectal cancer who exhibited complete response following preoperative radiochemotherapy have been enrolled in rectum sparing clinical trials over the past 15 years. This group of patients who did not undergo resection represents up to 20% of rectal cancers underwent neoadjuvant treatment in certain Hospitals of Veneto Region.⁵⁹

On the other side, the main strength of this study is represented by the long period of observation over a large population, based on high-quality data from consolidated databases that are used for administrative purposes.

Conclusions

Our 20-year study revealed a shift towards proximal colon surgery due to a rise in proximal surgery rates, which seems to be only partially contrasted by the suboptimal performance of both FIT (in detecting advanced proximal lesions) and colonoscopy (in detecting and removing precancerous lesions in the same anatomic site). More sensitive screening tests and improved endoscopic technologies are needed to overcome the current limitations of FIT-based screening in order to reduce proximal colectomies.

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REFERENCES

- Sung H, Ferlay J, Siegel RL, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
- Dyba T, Randi G, Bray F, *et al.* The European cancer burden in 2020: incidence and mortality estimates for 40 countries and 25 major cancers. *Eur J Cancer* 2021;157:308–47.
- Arnold M, Abnet CC, Neale RE, *et al.* Global burden of 5 major types of gastrointestinal cancer. *Gastroenterology* 2020;159:335–49.
- Wong MCS, Huang J, Lok V, *et al.* Differences in incidence and mortality trends of colorectal cancer worldwide based on sex, age, and anatomic location. *Clin Gastroenterol Hepatol* 2021;19:955–66.
- Siegel RL, Wagle NS, Cercek A, *et al.* Colorectal cancer statistics, 2023. *CA A Cancer J Clinicians* 2023;73:233–54.
- Cavestro GM, Mannucci A, Balaguer F. Associazione italiana familiarità ereditarietà tumori; collaborative group of the americas on inherited gastrointestinal cancer; european hereditary tumour group, and the international society for gastrointestinal hereditary tumours delphi initiative for early-onset colorectal cancer (direct) international management guidelines. *Clin Gastroenterol Hepatol* 2023;21:581–603.
- Iacopetta B. Are there two sides to colorectal cancer? *Int J Cancer* 2002;101:403–8.
- Baran B, Mert Ozupek N, Yerli Tetik N, *et al.* Difference between left-sided and right-sided colorectal cancer: a focused review of literature. *Gastroenterology Res* 2018;11:264–73.
- Nawa T, Kato J, Kawamoto H, *et al.* Differences between right- and left-sided colon cancer in patient characteristics, cancer morphology and histology. *J Gastroenterol Hepatol* 2008;23:418–23.
- Benedix F, Kube R, Meyer F, *et al.* Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum* 2010;53:57–64.
- Weiss JM, Pfau PR, O'Connor ES, *et al.* Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results--medicare data. *J Clin Oncol* 2011;29:4401–9.
- Yang L, Liu S, Xiong Z, *et al.* Changes in colorectal cancer incidence by site and age from 1973 to 2015: a SEER database analysis. *Aging Clin Exp Res* 2021;33:1937–46.
- Nakagawa H, Ito H, Hosono S, *et al.* Changes in trends in colorectal cancer incidence rate by anatomic site between 1978 and 2004 in japan. *Eur J Cancer Prev* 2017;26:269–76.
- Larsen IK, Bray F. Trends in colorectal cancer incidence in norway 1962–2006: an interpretation of the temporal patterns by anatomic subsite. *Int J Cancer* 2010;126:721–32.
- Exarchakou A, Donaldson LJ, Girardi F, *et al.* Colorectal cancer incidence among young adults in england: trends by anatomical sub-site and deprivation. *PLoS One* 2019;14:e0225547.
- Zhang J, Cheng Z, Ma Y, *et al.* Effectiveness of screening modalities in colorectal cancer: a network meta-analysis. *Clin Colorectal Cancer* 2017;16:252–63.
- Cardoso R, Guo F, Heisser T, *et al.* Proportion and stage distribution of screen-detected and non-screen-detected colorectal cancer in nine european countries: an international, population-based study. *Lancet Gastroenterol Hepatol* 2022;7:711–23.
- Zorzi M, Urso EDL. Impact of colorectal cancer screening on incidence, mortality and surgery rates: evidences from programs based on the fecal immunochemical test in italy. *Dig Liver Dis* 2023;55:336–41.
- The Council Of The European Union. Council recommendations of 2 december 2003 on cancer screening (2003/878/EC). *O J Eur Union* 2003;327:34–8.
- Zorzi M, Fedeli U, Schievano E, *et al.* Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. *Gut* 2015;64:784–90.
- Chiu H-M, Chen SL-S, Yen AM-F, *et al.* Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the one million taiwanese screening program. *Cancer* 2015;121:3221–9.
- Levin TR, Corley DA, Jensen CD, *et al.* Effects of organized colorectal cancer screening on cancer incidence and mortality in a large community-based population. *Gastroenterology* 2018;155:1383–91.
- Buskermolen M, Cenin DR, Helsing LM, *et al.* Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study. *BMJ* 2019;367:15383.
- Ventura L, Mantellini P, Grazzini G, *et al.* The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. *Dig Liver Dis* 2014;46:82–6.
- Bucchi L, Mancini S, Baldacchini F, *et al.* Emilia-romagna region workgroup for colorectal screening evaluation. how a faecal immunochemical test screening programme changes annual colorectal cancer incidence rates: an italian intention-to-screen study. *Br J Cancer* 2022;127:541–8.
- Fedeli U, Zorzi M, Urso EDL, *et al.* Impact of fecal immunochemical test-based screening programs on proximal and distal colorectal cancer surgery rates: a natural multiple-baseline experiment. *Cancer* 2015;121:3982–9.
- Zorzi M, Gennaro N, Capodaglio G, *et al.* Colorectal cancer screening: the surgery rates they are A-changing. A nationwide study on surgical resections in Italy. *Dig Liver Dis* 2019;51:304–9.

- 28 Zorzi M, Fedato C, Grazzini G, *et al*. High sensitivity of five colorectal screening programmes with faecal immunochemical test in the veneto region, Italy. *Gut* 2011;60:944–9.
- 29 van der Vlugt M, Grobbee EJ, Bossuyt PMM, *et al*. Interval colorectal cancer incidence among subjects undergoing multiple rounds of fecal immunochemical testing. *Gastroenterology* 2017;153:439–47.
- 30 Imperiale TF, Ransohoff DF, Itzkowitz SH, *et al*. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 2014;370:1287–97.
- 31 Chang L-C, Shun C-T, Hsu W-F, *et al*. Fecal immunochemical test detects sessile serrated adenomas and polyps with a low level of sensitivity. *Clin Gastroenterol Hepatol* 2017;15:872–9.
- 32 Mowat C, Digby J, Strachan JA, *et al*. Low sensitivity of fecal immunochemical tests (FIT) for detection of sessile serrated adenomas/polyps confirmed over clinical setting, geography, and FIT system. *Dig Dis Sci* 2019;64:3024–6.
- 33 Kaku E, Oda Y, Murakami Y, *et al*. Proportion of flat- and depressed-type and laterally spreading tumor among advanced colorectal neoplasia. *Clin Gastroenterol Hepatol* 2011;9:503–8.
- 34 Kim NH, Jung YS, Jeong WS, *et al*. Miss rate of colorectal neoplastic polyps and risk factors for missed polyps in consecutive colonoscopies. *Intest Res* 2017;15:411–8.
- 35 Rösch T, Altenhofen L, Kretschmann J, *et al*. Risk of malignancy in adenomas detected during screening colonoscopy. *Clin Gastroenterol Hepatol* 2018;16:1754–61.
- 36 Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. *Am J Gastroenterol* 2010;105:2457–64.
- 37 Chacko L, Macaron C, Burke CA. Colorectal cancer screening and prevention in women. *Dig Dis Sci* 2015;60:698–710.
- 38 Digby J, Fraser CG, Carey FA, *et al*. Can the performance of a quantitative FIT-based colorectal cancer screening programme be enhanced by lowering the threshold and increasing the interval? *Gut* 2018;67:993–4.
- 39 Wieten E, Schreuders EH, Grobbee EJ, *et al*. Incidence of faecal occult blood test interval cancers in population-based colorectal cancer screening: a systematic review and meta-analysis. *Gut* 2019;68:873–81.
- 40 Toes-Zoutendijk E, Kooyker AI, Dekker E, *et al*. Incidence of interval colorectal cancer after negative results from first-round fecal immunochemical screening tests, by cutoff value and participant sex and age. *Clin Gastroenterol Hepatol* 2020;18:1493–500.
- 41 Buunen M, Veldkamp R, Colon Cancer Laparoscopic or Open Resection Study Group. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol* 2009;10:44–52.
- 42 van der Pas MH, Haglind E, Cuesta MA, *et al*. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 2013;14:210–8.
- 43 Hernandez MC, Wong P, Melstrom K. Low anterior resection syndrome. *J Surg Oncol* 2023;127:1271–6.
- 44 Franks PJ, Bosanquet N, Thorpe H, *et al*. Short-term costs of conventional vs laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial). *Br J Cancer* 2006;95:6–12.
- 45 Myer PA, Mannalithara A, Singh G, *et al*. Proximal and distal colorectal cancer resection rates in the united states since widespread screening by colonoscopy. *Gastroenterology* 2012;143:1227–36.
- 46 StataCorp. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC, 2023.
- 47 Consonni D, Coviello E, Buzzoni C, *et al*. A command to calculate age-standardized rates with efficient interval estimation. *Stata J* 2012;12:688–701.
- 48 Joinpoint Regression Program, Version 5.0; Statistical Methodology and Applications Branch. Surveillance Research Program, National Cancer Institute.
- 49 Irimata KE, Bastian BA, Clarke TC, *et al*. Guidance for selecting model options in the national cancer institute joinpoint regression software. *Vital Health Stat* 2022;1:1–22.
- 50 Kim H-J, Chen H-S, Midthune D, *et al*. Data-driven choice of a model selection method in joinpoint regression. *J Appl Stat* 2023;50:1992–2013.
- 51 Mariotto AB, Feuer EJ, Howlader N, *et al*. Interpreting cancer incidence trends: challenges due to the COVID-19 pandemic. *J Natl Cancer Inst* 2023;115:1109–11.
- 52 Hawkins NG, Sanson-Fisher RW, Shakeshaft A, *et al*. The multiple baseline design for evaluating population-based research. *Am J Prev Med* 2007;33:162–8.
- 53 Saeed S, Moodie EEM, Strumpf EC, *et al*. Segmented generalized mixed effect models to evaluate health outcomes. *Int J Public Health* 2018;63:547–51.
- 54 Morrison AS. Screening in Chronic Disease 2nd ed. New York: Oxford University Press, 1992.
- 55 Giorgi Rossi P, Carretta E, Mangone L, *et al*. Incidence of interval cancers in faecal immunochemical test colorectal screening programmes in Italy. *J Med Screen* 2018;25:32–9.
- 56 Mlakar DN, Bric TK, Škrjanec AL, *et al*. Interval cancers after negative immunochemical test compared to screen and non-responders' detected cancers in slovenian colorectal cancer screening programme. *Radiol Oncol* 2018;52:413–21.
- 57 Portillo I, Idigoras I, Bilbao I, *et al*. Colorectal cancer screening program using FIT: quality of colonoscopy varies according to hospital type. *Endosc Int Open* 2018;6:E1149–56.
- 58 Registro Tumori Veneto, Available: <https://www.registrotumori veneto.it/en/about-us/introduction> [Accessed 26 Mar 2024].
- 59 Bushati M, Pucciarelli S, Gennaro N, *et al*. Local excision in rectal cancer patients with major or complete clinical response after neoadjuvant therapy: a case-matched study. *Int J Colorectal Dis* 2019;34:2129–36.