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

Manuel Zorzi,[1] Lucia Calciano ,[1] Nicola Gennaro,[1] Laura Memo,[1] Silvia Rizzato,[1] Carmen Stocco,[1] Emanuele D L Urso,[2] Silvia Negro,[2] Gaya Spolverato,[2] Salvatore Pucciarelli ,[2] Marta Sbaraglia,[3] Stefano Guzzinati[1]

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[1]Epidemiological Department, Azienda Zero, Padova, Italy
[2]Department of Surgical, Oncological and Gastroenterological Sciences (DiSCOG), University of Padua, Padova, Italy
[3]Department of Medicine (DIMED), Pathology and Cytopathology Unit, University of Padua, Padova, Italy

**Correspondence to**
Dr Lucia Calciano;
lucia.calciano@azero.veneto.it

## 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.

### 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.

## 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 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 'distrate' 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 model[49] 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 'distrate' 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).

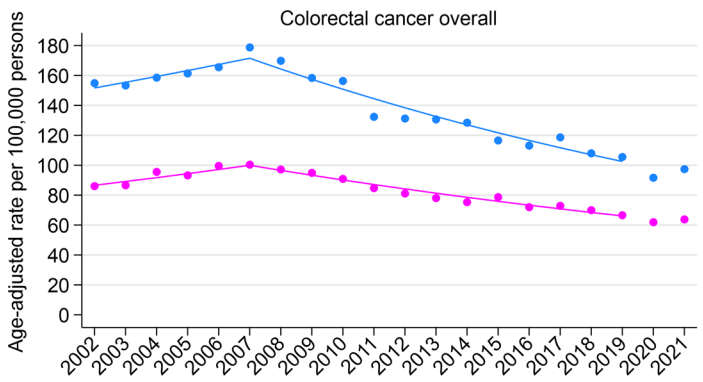
The analysis for the 40–49 age group (figure 2) showed no statistically significant change in the age-adjusted surgical resection rate for proximal colon cancer but statistically significant downward trends for both distal colon (since 2008) and rectal (between 2006 and 2016) cancers. For individuals 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).

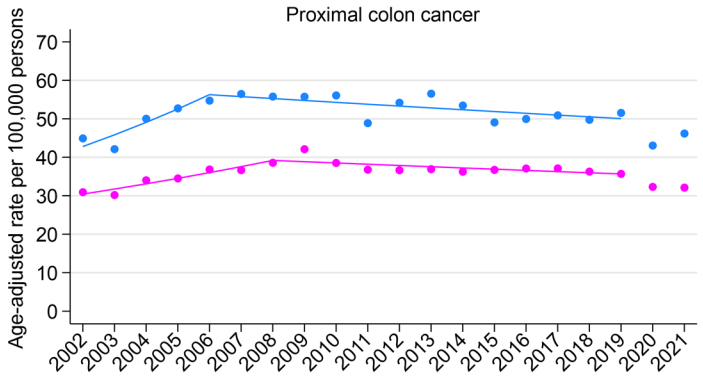
| | Female | | | Male | | | Female-to-male RR | |
|---|---|---|---|---|---|---|---|---|
| | **2002–2006 n (SR)** | **2017–2021 n (SR)** | **PC (95% CI)** | **2002–2006 n (SR)** | **2017–2021 n (SR)** | **PC (95% CI)** | **2002 to 2006 RR (95% CI)** | **2017 to 2021 RR (95% CI)** |
| Overall CRC | 5997 (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.

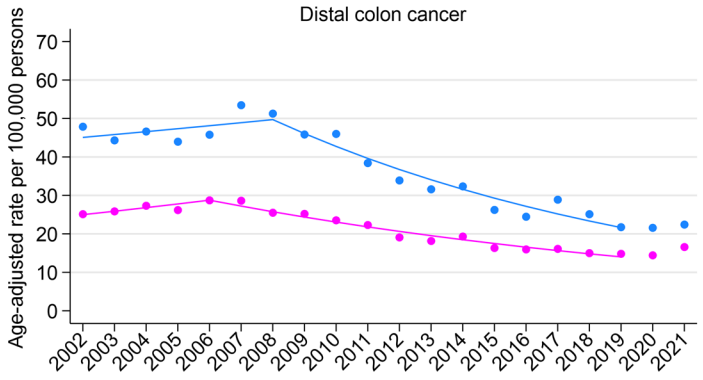
*Truncated (40–89 years) age-standardised rates (2013 European Standard Population).
†Change from 2002–2006 to 2017–2021.
CRC, colorectal cancer; PC, percent change; RR, rate ratio; SR, surgical resection rates.



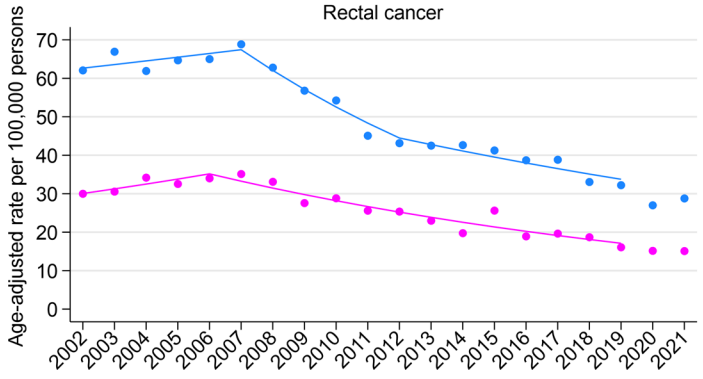

| | Time period | APC | 95%CI |
|---|---|---|---|
| Male | 2002-2007 | 2.5* | 0.3 to 6.2 |
| | 2007-2019 | -4.2* | -5.0 to -3.6 |
| Female | 2002-2007 | 2.9* | 1.0 to 6.1 |
| | 2007-2019 | -3.4* | -4.1 to -2.9 |




| | 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 |

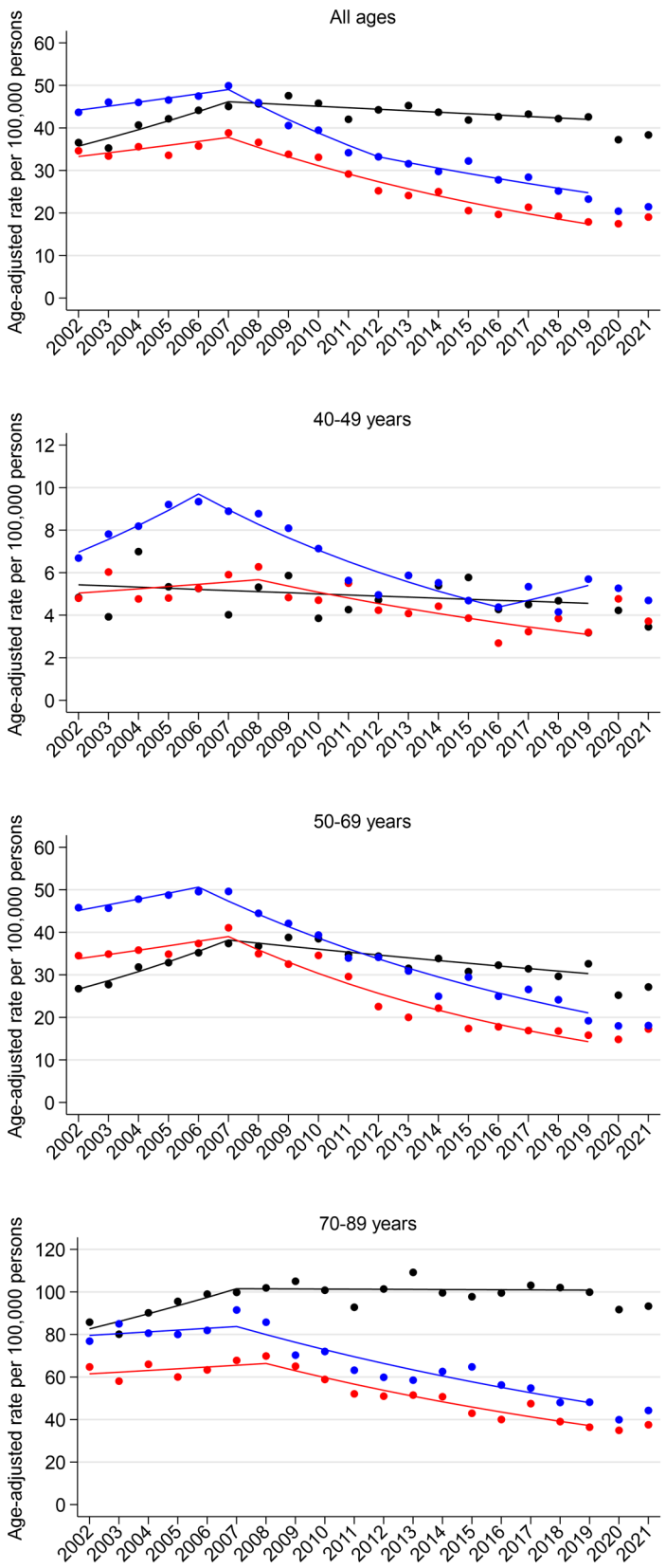



| | Time period | APC | 95%CI |
|---|---|---|---|
| Male | 2002-2008 | 1.6 | -2.4 to 12.0 |
| | 2008-2019 | -7.3* | -11.1 to -5.8 |
| Female | 2002-2006 | 3.6* | 0.3 to 8.5 |
| | 2006-2019 | -5.4* | -6.1 to -4.8 |




| | 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). [a]Truncated (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.




| | 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 |

**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). [a]Truncated 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.

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

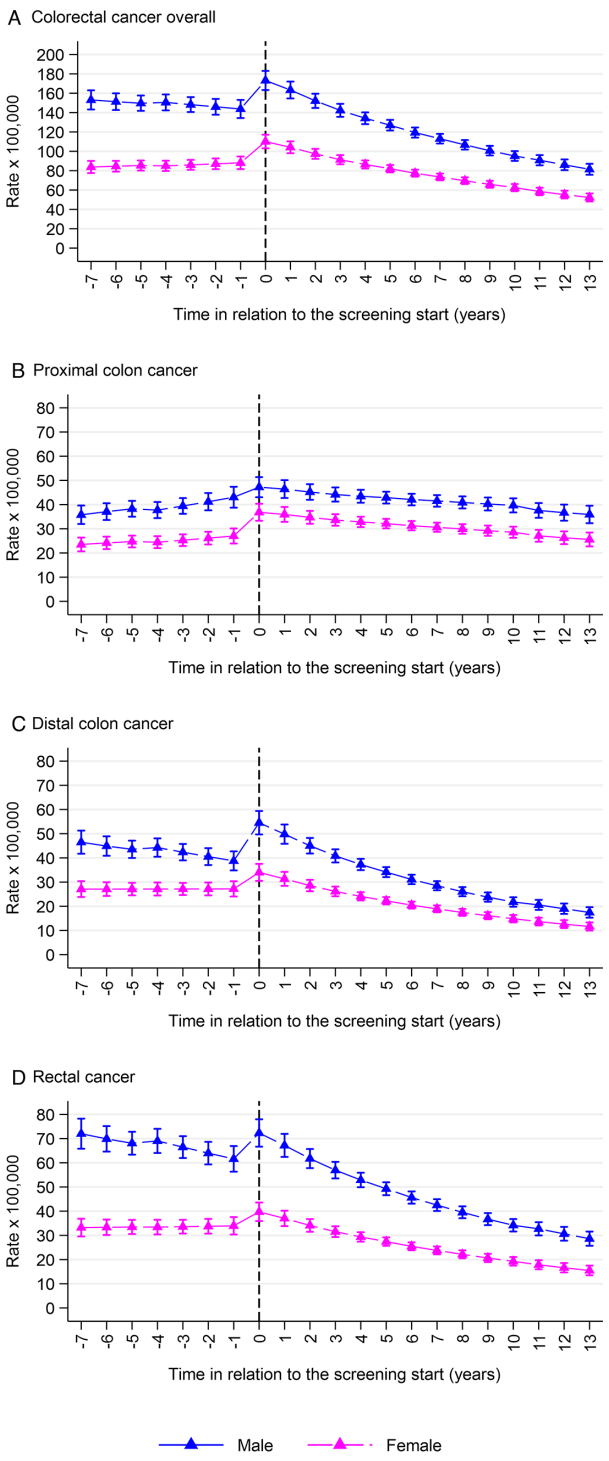



**Figure 3** Trends in surgical resection rates of colorectal cancer pre-FIT and post-FIT implementation in the target population (50–69 years) by anatomic site and sex (2002–2019). The dashed line indicates the time when the screening was implemented. FIT, faecal immunochemical test.

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.

**Contributors** MZ and LC conceived and designed the study, developed the statistical analysis plan, interpreted the results and drafted the manuscript. MZ is the guarantor. LC and NG performed the statistical analysis.LM, SR and CS collected and assembled the data. EDLU, SN, GS, SP, MS and SG contributed to the interpretation of the results. All authors critically reviewed the article for important intellectual content, gave final approval of the version to be published and accepted responsibility for submitting the manuscript for publication.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** Neither approval from an ethical committee nor formal consent by the patients is required for governmental surveillance activities in Italy, which are performed under the Legislative Decree no.101 of 10 August 2018 adopting the EU Regulation 2016/679 on the protection of individuals with regard to the processing of personal data.

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**Data availability statement** Data are available on reasonable request. The data that support the findings of this study are available from the corresponding author, LC, on reasonable request.



**ORCID iDs**

Lucia Calciano http://orcid.org/0000-0001-9801-5080
Salvatore Pucciarelli http://orcid.org/0000-0001-5289-9925

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## SUPPLEMENTARY MATERIALS

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

Manuel Zorzi[1], Lucia Calciano[1], Nicola Gennaro[1], Laura Memo[1], Silvia Rizzato[1], Carmen Stocco[1], Emanuele Damiano Urso[2], Silvia Negro[2], Gaya Spolverato[2], Salvatore Pucciarelli[2], Marta Sbaraglia[3], Stefano Guzzinati[1]

[1]Epidemiological Department, Azienda Zero, Padova, Italy
[2]Department of Surgical, Oncological and Gastroenterological Sciences (DiSCOG), Università degli Studi di Padova, Padova, Italy
[3]Department of Medicine (DIMED), Pathology and Cytopathology Unit, Università degli Studi di Padova, Padova, Italy

**Corresponding author:**

Lucia Calciano

lucia.calciano@azero.veneto.it

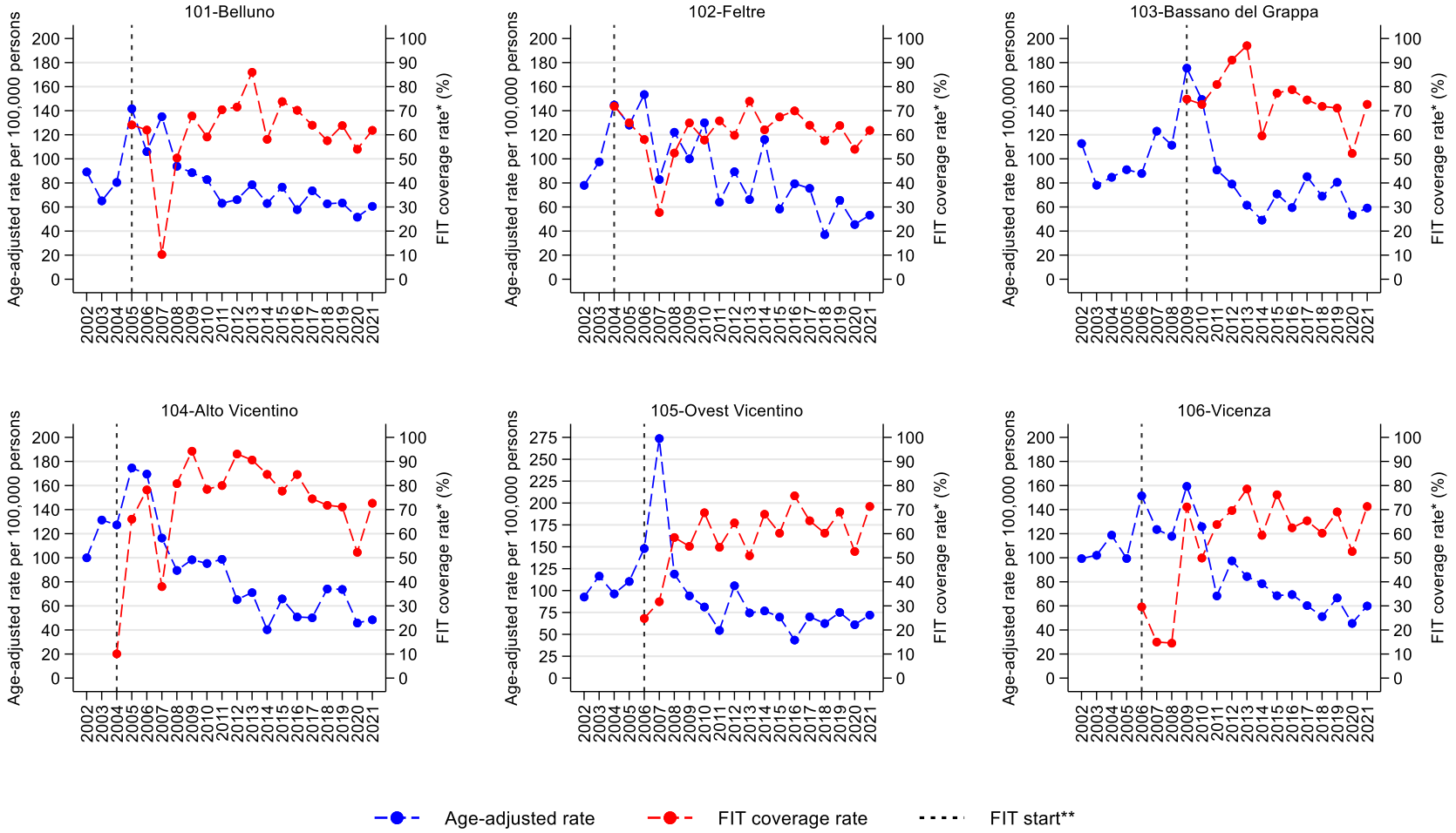
**Table S1. Annual coverage rate* (%) of the FIT-based screening programme (2002-2021) by local health units (LHUs). LHUs included in ITS analysis are in bold.**

| LHU | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | FIT start ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *101-Belluno* | - | - | - | 64.1 | 62.0 | 10.3 | 50.4 | 67.9 | 59.1 | 70.5 | 71.6 | 86.0 | 58.1 | 73.8 | 70.2 | 64.0 | 57.6 | 63.9 | 54.0 | 61.9 | 2005 |
| *102-Feltre* | - | - | 71.8 | 65.0 | 58.1 | 27.8 | 52.4 | 65.0 | 57.9 | 65.8 | 59.8 | 74.0 | 62.1 | 67.5 | 70.0 | 64.0 | 57.6 | 63.9 | 54.0 | 61.9 | 2004 |
| ***103-Bassano del Grappa*** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **74.8** | **72.7** | **80.9** | **91.1** | **97.0** | **59.6** | **77.3** | **78.8** | **74.5** | **71.8** | **71.1** | **52.3** | **72.7** | **2009** |
| *104-Alto Vicentino* | - | - | 10.1 | 66.1 | 78.2 | 38.0 | 80.8 | 94.3 | 78.4 | 80.0 | 93.1 | 90.6 | 84.7 | 77.7 | 84.6 | 74.5 | 71.8 | 71.1 | 52.3 | 72.7 | 2004 |
| ***105-Ovest Vicentino*** | **-** | **-** | **-** | **-** | **24.8** | **31.8** | **58.5** | **54.8** | **68.7** | **54.4** | **64.5** | **50.9** | **68.1** | **60.2** | **75.8** | **65.4** | **60.2** | **69.1** | **52.6** | **71.3** | **2006** |
| ***106-Vicenza*** | **-** | **-** | **-** | **-** | **29.6** | **15.0** | **14.5** | **71.1** | **49.9** | **63.8** | **69.7** | **78.6** | **59.4** | **76.2** | **62.5** | **65.4** | **60.2** | **69.1** | **52.6** | **71.3** | **2006** |
| *107-Pieve di Soligo* | 3.9 | 69.1 | 78.6 | 69.4 | 74.2 | 34.4 | 67.7 | 75.8 | 71.1 | 78.0 | 87.7 | 98.7 | 73.2 | 98.7 | 82.0 | 65.0 | 74.8 | 70.3 | 63.9 | 78.1 | 2003 |
| ***108-Asolo*** | **-** | **-** | **-** | **4.1** | **0.0** | **20.2** | **65.9** | **71.9** | **76.5** | **75.4** | **62.7** | **81.0** | **72.3** | **73.3** | **75.7** | **65.0** | **74.8** | **70.3** | **63.9** | **78.1** | **2007** |
| ***109-Treviso*** | **-** | **-** | **-** | **-** | **16.7** | **29.0** | **49.5** | **28.9** | **55.9** | **55.3** | **70.5** | **74.2** | **67.4** | **57.0** | **74.0** | **65.0** | **74.8** | **70.3** | **63.9** | **78.1** | **2006** |
| ***110-Veneto Orientale*** | **-** | **-** | **-** | **-** | **-** | **0.9** | **4.2** | **15.4** | **24.8** | **43.2** | **49.2** | **56.6** | **57.1** | **54.4** | **47.8** | **41.7** | **42.7** | **46.4** | **15.0** | **52.7** | **2009** |
| ***112-Veneziana*** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **8.9** | **22.5** | **33.6** | **42.5** | **50.4** | **41.2** | **53.9** | **44.7** | **56.9** | **45.3** | **56.3** | **37.6** | **56.3** | **2009** |
| *113-Mirano* | 22.2 | 34.1 | 24.8 | 33.8 | 90.0 | 22.0 | 41.0 | 59.1 | 66.1 | 69.0 | 70.3 | 65.6 | 57.7 | 68.7 | 53.0 | 56.9 | 45.3 | 56.3 | 37.6 | 56.3 | 2002 |
| ***114-Chioggia*** | **-** | **-** | **-** | **3.2** | **9.1** | **5.2** | **31.9** | **23.1** | **23.2** | **35.4** | **21.3** | **31.5** | **44.9** | **67.4** | **29.1** | **56.9** | **45.3** | **56.3** | **37.6** | **56.3** | **2006** |
| ***115-Alta Padovana*** | **-** | **-** | **-** | **0.3** | **13.3** | **0.0** | **3.6** | **20.0** | **38.1** | **67.5** | **66.8** | **67.2** | **58.4** | **66.6** | **68.5** | **52.8** | **55.3** | **51.0** | **47.3** | **51.7** | **2006** |
| ***116-Padova*** | **-** | **-** | **-** | **-** | **-** | **-** | **40.0** | **17.1** | **53.3** | **58.2** | **62.2** | **49.5** | **52.9** | **43.9** | **55.0** | **52.8** | **55.3** | **51.0** | **47.3** | **51.7** | **2008** |
| ***117-Este*** | **-** | **-** | **-** | **-** | **36.1** | **6.6** | **17.7** | **32.7** | **44.1** | **34.4** | **52.3** | **55.6** | **44.0** | **71.7** | **58.8** | **52.8** | **55.3** | **51.0** | **47.3** | **51.7** | **2006** |
| *118-Rovigo* | - | - | - | 5.9 | 2.6 | 14.2 | 42.6 | 56.1 | 58.4 | 82.2 | 70.5 | 57.7 | 68.8 | 56.1 | 59.7 | 55.8 | 65.0 | 55.6 | 60.0 | 56.1 | 2005 |
| ***119-Adria*** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **54.9** | **66.7** | **54.4** | **79.8** | **65.6** | **67.0** | **61.3** | **70.7** | **55.8** | **65.0** | **55.6** | **60.0** | **56.1** | **2009** |
| ***120-Verona*** | **-** | **0.5** | **1.5** | **1.1** | **10.8** | **19.3** | **57.2** | **78.4** | **45.5** | **56.5** | **42.8** | **24.4** | **48.5** | **13.4** | **37.6** | **56.3** | **60.6** | **56.2** | **19.7** | **87.1** | **2006** |
| *121-Legnago* | - | - | - | 26.3 | 58.6 | 25.1 | 50.9 | 52.4 | 29.3 | 11.9 | 58.6 | 55.2 | 90.2 | 51.9 | 89.9 | 56.3 | 60.6 | 56.2 | 19.7 | 87.1 | 2005 |
| *122-Bussolengo* | - | - | 10.3 | 39.9 | 58.8 | 20.0 | 67.3 | 63.3 | 66.8 | 51.9 | 57.4 | 71.6 | 50.1 | 73.8 | 66.5 | 56.3 | 60.6 | 56.2 | 19.7 | 87.1 | 2004 |

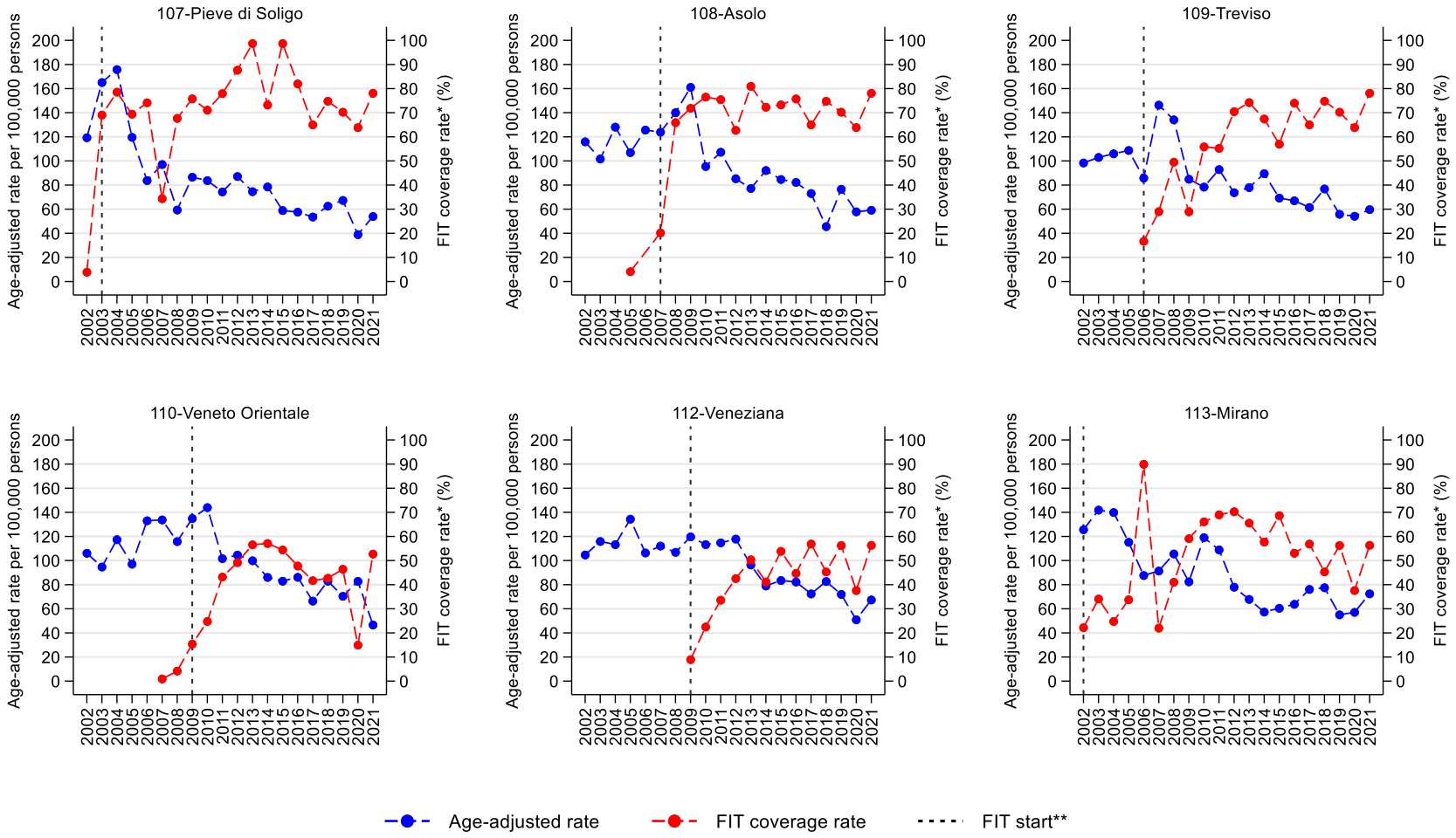
*The coverage rate was calculated as the ratio of the number of subjects who received FIT to the total number in the target population.

**FIT start indicates the year when FIT was implemented in each LHU, which was defined as the first year in which the annual coverage rate of FIT is greater than or equal to 5%.

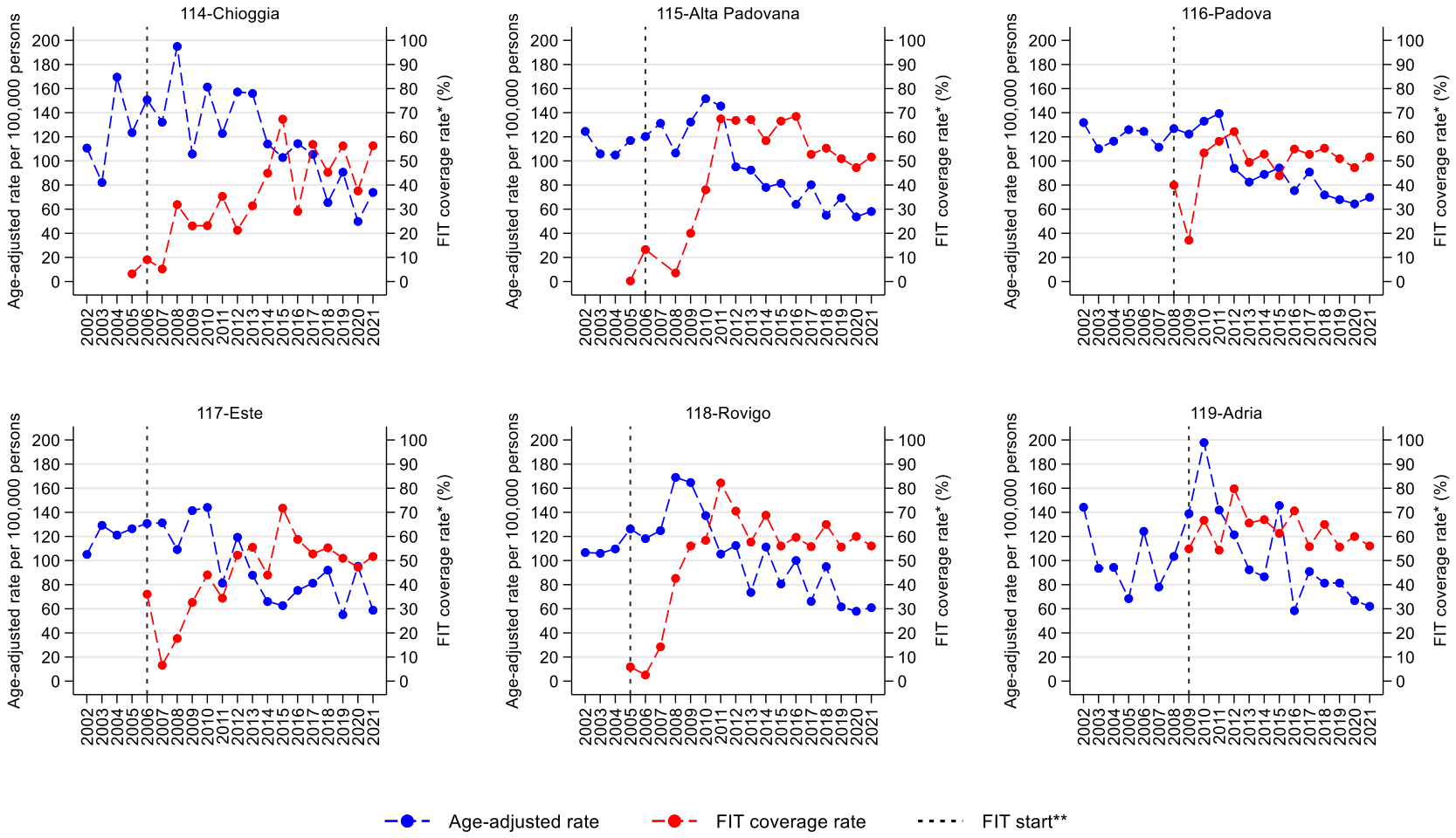
**Figure S1. Target population (50-69 yrs): Colorectal cancer surgical resection age-adjusted rate and annual coverage rate* (%) of the FIT-based screening programme (2002-2021) by local health units (LHUs).**



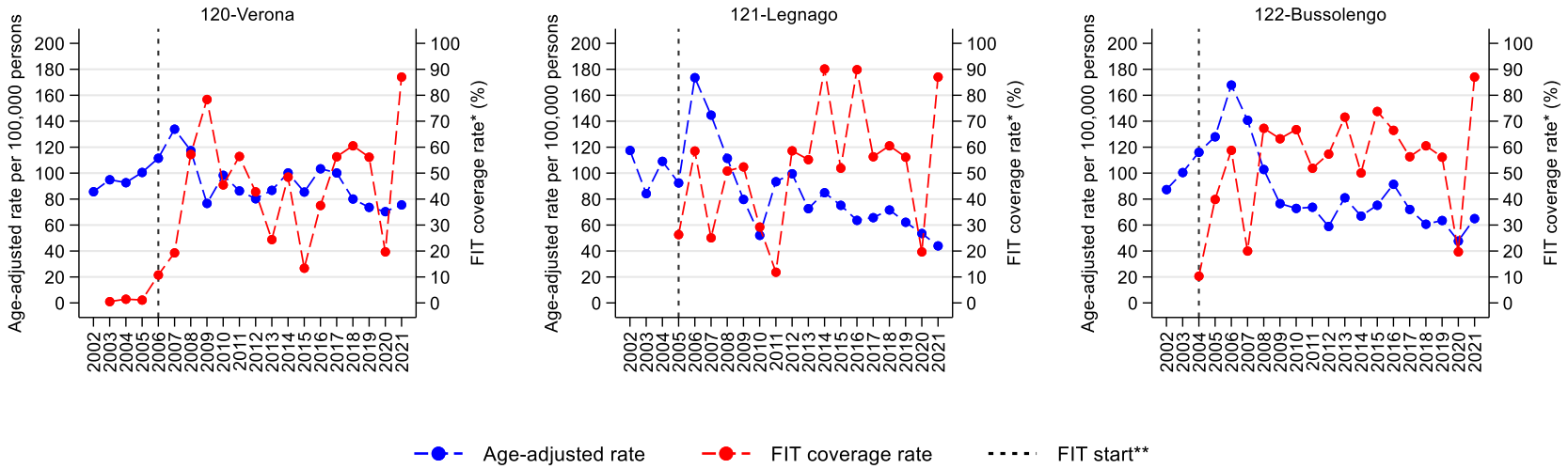
*(Continued)*


107-Pieve di Soligo
108-Asolo
109-Treviso
110-Veneto Orientale
112-Veneziana
113-Mirano
Age-adjusted rate per 100,000 persons
FIT coverage rate* (%)
Age-adjusted rate
FIT coverage rate
FIT start**

*(Continued)*


114-Chioggia
115-Alta Padovana
116-Padova
117-Este
118-Rovigo
119-Adria
Age-adjusted rate per 100,000 persons
FIT coverage rate* (%)
Age-adjusted rate
FIT coverage rate
FIT start**

*(Continued)*




*The coverage rate was calculated as the ratio of the number of subjects who received FIT to the total number in the target population.

**FIT start indicates the year when FIT was implemented in each LHU, which was defined as the first year in which the annual coverage rate of FIT is greater than or equal to 5%.