Age–period–cohort effects in utilization of diagnostic procedures leading to incidental colorectal cancer detection

Andrea Salvatori[a,b], Anita Andreano[a], Adriano Decarli[a] and Antonio Giampiero Russo[a]

Background and aim **Despite the overall decrease in colorectal cancer (CRC) incidence, a small but constant rise has been recently observed in people younger than 50 years across several countries. This phenomenon can be explained by environmental or lifestyle factors, but it may also be partially justified by an increasing tendency in younger cohorts to undertake diagnostic procedures that may lead to CRC incidental diagnosis.**

Methods **We performed an age–period–cohort analysis on 1 815 694 diagnostic procedures undertook by the population of the City of Milan, served by the Agency for Health Protection of Milan, between 1999 and 2018. We considered all instances of colonoscopy, rectoscopy, fecal occult blood test (FOBT) and ultrasonography. We stratified by gender, nationality and quintile of socioeconomic deprivation.**

Results **Incidence of utilization rose with age for all procedures but rectoscopy; there was a marked increase from 2005 to 2010 for FOBT and colonoscopy. A strong all-procedures cohort effect was observed, greater for FOBT and colonoscopy. A steady increase of diagnostic procedures utilization started in cohorts born in the late 1950s, with a relative effect rising from 0.91 [95% confidence interval (CI) 0.90–0.92] for the 1950 cohort to 5.03 (95% CI, 4.58–5.48) for the 1990 one.**

Conclusion **We found a growing tendency in younger cohorts to undertake diagnostic procedures, explainable by inappropriate access to endoscopic procedures, that can lead to an incidental diagnosis of CRC. This finding may at least partially explain the observed rising incidence of early-onset CRC.** ***European Journal of Cancer Prevention*** **31: 26–34 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Keywords: colorectal cancer, colorectal cancer screening, early-onset colorectal cancer, epidemiology, screening

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Introduction

Being the third most common type of cancer worldwide (10.2% of all new cases in 2018) and the second leading cause of death among malignancies (9.2% of all cancer deaths in the same period) (Ferlay *et al.*, 2020), colorectal cancer (CRC) represents an important threat to global public health and well-being. Along with most cancers, CRC incidence rises with age, with 90% of cases and deaths occurring after the age of 50 years (Keum and Giovannucci, 2019).

In the last decade, CRC incidence and mortality have been influenced by secondary prevention procedures, that is, screening programs, including the noninvasive detection of not visible tumor bleeding [fecal occult blood test (FOBT)], and the endoscopic exploration of the large intestine (colonoscopy or rectoscopy) with the removal of precancerous lesions. A more or less pronounced reduction in CRC mortality rates has been observed after the introduction of a CRC screening program in different states. Conversely, incidence rates, after a ubiquitous initial rise due to the detection of asymptomatic malignant lesions in the first screening round (Keum and Giovannucci, 2019), behaved differently depending on the Country. In Latvia, Poland and Spain, they continued to increase, while in Austria, Czech Republic, Israel, Japan and the USA, they stabilized or decreased after a variable time-lag from the introduction (Arnold *et al.*, 2017). In Italy, recent national data show an overall incidence decrease after 2007, following the introduction of screening in 2005. However, both the first year of screening and the incidence rates are not uniform across regions (Masseria, 2010).

In this context of overall lowering incidence, a recently emerged and alarming trend is the rising of CRC rates in people younger than 50 in several countries. A rise in early-onset CRC (EO-CRC) was observed in Asia (Sung *et al.*, 2019), North America (Siegel *et al.*, 2009; Ahnen *et al.*, 2014; Amri *et al.*, 2015; Bailey *et al.*, 2015; Brenner *et al.*, 2017; Siegel *et al.*, 2017; Kasi *et al.*, 2019), Oceania (Gandhi

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et al., 2017; Troeung *et al.*, 2017), the Middle-East (Abou-Zeid *et al.*, 2017; Hessami Arani and Kerachian, 2017) and Europe (Ullah *et al.*, 2018; Vuik *et al.*, 2019).

The majority of EO-CRC does not affect individuals with a family history of CRC, hereditary cancer syndrome, or inflammatory bowel disease: the etiology of such malignancies is still not fully known, with the available evidence suggesting a role for environmental exposure (Mousavi *et al.*, 2012) and for changed diet and behaviors, including high consumption of red/processed meats, physical inactivity and the growing proportion of overweight young people, obesity being a well-known important risk factor for CRC (World Cancer Research Fund, American Institute for Cancer Research, 2020).

However, the increase in EO-CRC incidence may be also partially due to a phenomenon similar to the aforementioned observed rising CRC incidence rates right after the introduction of a screening program. It may be hypothesized, and needs to be investigated that there has been, in recent years, an increasing number of young people undertaking diagnostic procedures capable of detecting asymptomatic lesions, anticipating diagnosis, outside organized screening programs which are usually directed to people of age 50 years and older (Schreuders *et al.*, 2015). Among those procedures, there are endoscopies and FOBTs performed for any reason outside screening programs, but there may be also transrectal ultrasounds for prostatic or gynecological issues.

To verify the presence of increased utilization, by the youngest cohorts, of procedures that can detect an asymptomatic CRC through incidental diagnosis (cohort-effect) we used records of diagnostic procedures from the outpatient database of the City of Milan and applied an age–period–cohort (APC) approach. Such approach has been typically used to modelize age, period and cohort effects in incidence rates of diseases (La Vecchia *et al.*, 2015) or in mortality rates (Malvezzi *et al.*, 2010), and apparently, it has not yet been used to analyze trends in the utilization of diagnostic procedures.

Population and methods

We performed a retrospective cohort study based on the health databases of the Agency for Health Protection (AHP) of Milan. All data linkage procedures were performed within the AHP protected environment.

Consent and approval

Ethics approval and consent to participate were not required, as this is an observational study based on data routinely collected by the Agency for Health Protection (ATS) of Milan, a public body of the Regional Health Service, Lombardy Region. The ATS has among its institutional functions, established by the Lombardy Region legislation (R.L. 23/2015), the government of the care pathway at the individual level in the regional social and healthcare system, the evaluation of the services provided to, and the outcomes of, patients residing in the covered area. This study is also ethically compliant with the National Law (D.Lgs. 101/2018) and the 'General Authorization to Process Personal Data for Scientific Research Purposes' (n.8 and 9/2016, referred to in the Data Protection Authority action of 13 December 2018). Data were anonymized with a unique identifier before being used for the analyses.

Cohort construction

We identified from the outpatient database the following diagnostic procedures, performed for residents in the City of Milan between years 1999 and 2018 [in brackets the Lombardy Region codes for outpatient services (Ministero della Salute, 2020), mainly based on ICD-9-CM classification]: flexible optical colonoscopy (45.23), flexible optical ileocolonoscopy (45.23.1), flexible sigmoidoscopy (45.24), endoscopic biopsy of the large intestine (45.25), endoscopic polypectomy of the large intestine (45.42), endoscopic destruction of other lesion or tissue of large intestine (45.43.1–45.43.2), dilation of the intestine (46.85.1), rigid proctosigmoidoscopy (48.23), endoscopic biopsy of rectum (48.24), colorectal endoscopy with transmural biopsy (48.24.1), proctosigmoidoscopy (48.29.2), transrectal ultrasonography (code 88.79.8) and FOBT (90.21.4).

We collected place of residence in the municipality territory and census block, together with the nationality of the patient (categorized as Italian or not), and his or her gender through record linkage with the AHP view of the civil registry of Milan, using the tax code of the patient. The socioeconomic deprivation index was derived from Italian 2011 census data, available from the National Institute of Statistics (ISTAT) at the census block of residence level (Caranci *et al.*, 2010), and normalized on the population of the City of Milan. Being the purpose of this work to detect a rise in the utilization of diagnostic procedures that may anticipate CRC diagnosis, we excluded all procedures performed on patients with any cancer from diagnosis date (derived from the AHP population cancer registry) onwards, and procedures in patients affected by IBD. Patients with IBD were identified through the medical exemption database, using the disease-specific codes. Postpolypectomy procedures were removed upon consideration that those patients would have been regularly tested through follow-up from that moment onwards, interrupting the well-known adenoma–carcinoma sequence and making it improbable for subsequent procedures to detect cancer. We also chose to remove from the database all instances of endoscopy (either colonoscopy or rectoscopy) performed in the 180 days following an instance of FOBT, assuming the latter procedure being motivated by a positive FOBT. We also excluded all procedures recorded within one day from a previous one, being either two elements or a repeated registration of the same procedure.

After the described performed linkages, the database was anonymized, attributing to each patient a randomly generated numerical code for the analyses.

Statistical analysis

The diagnostic procedures were grouped into four categories: colonoscopy (codes 45.23, 45.231, 45.25, 45.42, 45.431, 45.432, 46.851, 48.241 and 48.292), rectoscopy (codes 45.24, 48.23 and 48.24), transrectal ultrasonography (code 88.79.8) and FOBT (code 90.21.4).

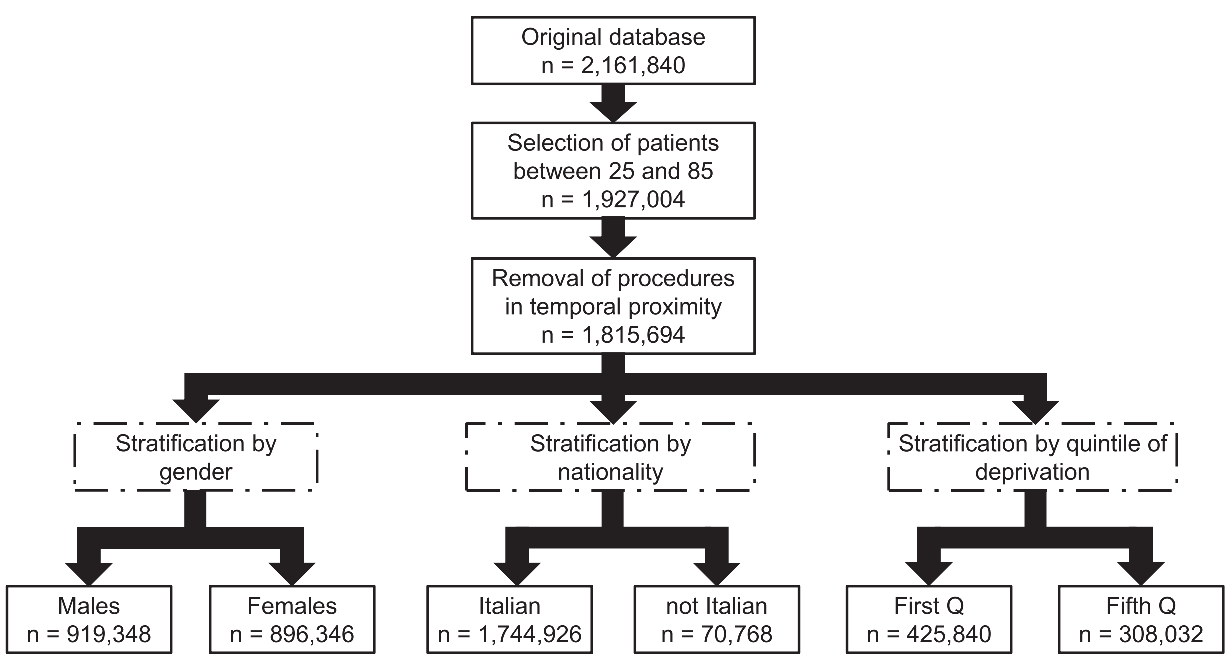
We described the cohort overall, and stratified by gender, by nationality and contrasting the first and fifth deprivation index quintiles (Caranci *et al.*, 2010). We computed age-specific incidence rates (each year of age from 25 to 85) for all the diagnostic procedures together, and for the four subgroups, overall and in each stratum of gender, nationality and deprivation index, for each year from 1999 to 2018. We used data from ISTAT (ISTAT population data, 2020) for the construction of rates' denominators in the gender and nationality stratifications. A reconstruction of the total resident population by age (25–85 years) using data from the Milan civil registry was performed to calculate rates in the first and fifth deprivation index quintiles.

Finally, we used an APC approach to disentangle the different contributions of age, period and cohort effects to variations in procedures rates across the 20 years under scrutiny. The contribution of the cohort effect was of particular interest since it may demonstrate the presence of different behavior, in different cohorts, toward the utilization of the investigated diagnostic procedures. APC modeling was performed using time periods of one year, both for age and cohort of the patient and for the year of procedure. In the nationality stratification alone, we resorted to 5-year time periods (ages from 25 to 84), since the numerousness of procedures in the older age groups for not Italians was too low to obtain reliable estimates from the Poisson model. For the same reason, we could not perform stratified analysis by nationality for each of the four procedures alone and in females for transrectal ultrasonography—the frequency distribution of procedures across ages in all other stratifications allowed to maintain a year-by-year approach. The APC models were fitted using R [package 'apc' version 1.0 (Decarli *et al.*, 2014)], following Osmond and Gardner method (Osmond and Gardner, 1982); while age models are expressed as incidence rates (per person-years) for individuals of different age, period and cohort models convey effects as rate ratio of observed over expected cases. This ratio represents a 'risk of utilization ratio' for a certain procedure in that year (or for that cohort of birth) considering as equal to 1 the mean of all year (or cohort of birth) effects, weighted by numerosity. Confidence intervals were estimated by performing a parametric bootstrap simulation using 1000 replicates.

Results

The construction and stratification of the cohort are summarized in Fig. 1, with the indication of the number of

Fig. 1



Flowchart of construction and stratification of cohorts, with n = number of observations at each step. Q: quintile.

Table 1 Number of procedures by type, gender, nationality and quintile of deprivation of the patient

	Males (%)	Females (%)	Total
All procedures			
Whole population	919 348 (51)	896 346 (49)	1 815 694
Nationality			
Italian	891 420 (51)	853 506 (49)	1 744 926
Not Italian	27 928 (39)	42 840 (61)	70 768
Deprivation			
First Q	211 575 (50)	214 265 (50)	425 840
Fifth Q	156 084 (51)	151 948 (49)	308 032
FOBT			
Whole population	565 819 (43)	745 696 (57)	1 311 515
Nationality			
Italian	547 269 (44)	709 905 (56)	1 257 174
Not Italian	18 550 (34)	35 791 (66)	54 341
Deprivation			
First Q	130 356 (42)	179 506 (58)	309 862
Fifth Q	95 974 (43)	125 507 (57)	221 481
Colonoscopy			
Whole population	126 431 (50)	128 954 (50)	255 385
Nationality			
Italian	122 231 (50)	123 095 (50)	245 326
Not Italian	4 200 (42)	5859 (58)	10 059
Deprivation			
First Q	29 330 (49)	30 077 (51)	59 407
Fifth Q	21 923 (50)	22 354 (50)	44 277
Ultrasonography			
Whole population	207 449 (98)	4753 (2)	212 202
Nationality			
Italian	203 333 (98)	4463 (2)	207 796
Not Italian	4 116 (93)	290 (7)	4406
Deprivation			
First Q	47 916 (98)	1063 (2)	48 979
Fifth Q	34 494 (98)	871 (2)	35 365
Rectoscopy			
Whole population	19 649 (54)	16 943 (46)	36 592
Nationality			
Italian	18 587 (54)	16 043 (46)	34 630
Not Italian	1062 (54)	900 (46)	1962
Deprivation			
First Q	3973 (52)	3619 (48)	7592
Fifth Q	3693 (53)	3216 (47)	6909

FOBT, fecal occult blood test; Q, quintile.

procedures remaining after each step. The initial database, once we excluded procedures following a cancer diagnosis, patients with the diagnosis of IBD, and follow-ups of polypectomies, comprised 2 161 840 cases, which lowered to 1 927 004 once we excluded patients under 25 or over 85. Once procedures were filtered by the proximity in time criteria (colonoscopy after FOBT and one day apart procedures), the database was reduced to the finally analyzed 1 815 694 cases, 919 348 (51%) in males and 896 346 (49%) in females. Stratifying for nationality 1 744 926 (96%) procedures were on Italians and 70 768 (4%) on not Italians, while for socioeconomic deprivation index 425 840 (23%) procedures were performed on individuals in the first and 308 032 (17%) on individuals in the fifth deprivation index quintile.

Globally, there were 1 311 515 (72%) instances of FOBT, 255 385 (14%) of colonoscopy, 212 202 (12%) of ultrasonography, and 36 592 (2%) of rectoscopy. Table 1 shows the distribution of the different diagnostic procedures, by gender, across nationality and deprivation index strata.

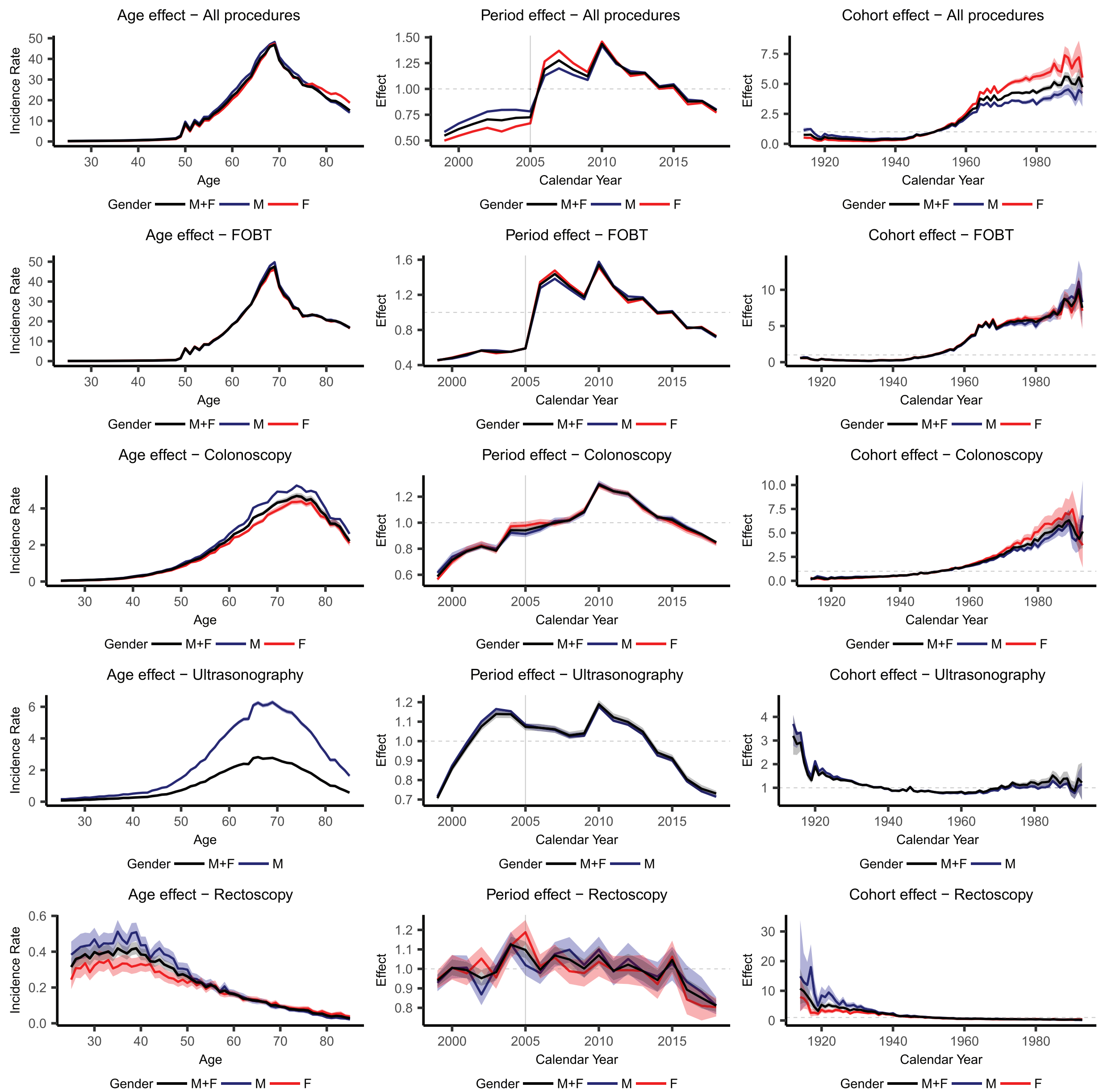
Graphical representation of the APC models' results, for the entire population and by gender, for each procedure is depicted in Fig. 2. The incidence rate of performing a diagnostic procedure increased with age (age effect, first column) for colonoscopies, peaking around 75 years, and for FOBT and ultrasonography, both reaching maximum just before age seventy. Only rectoscopy had a greater occurrence in younger people, peaking between 30 and 40 years. Period effect for FOBT clearly showed the consequences of the introduction of population screening by the AHP in 2005, rising from 0.55 (95% CI, 0.54–0.56) in 2004 to 1.32 (95% CI, 1.31–1.33) in 2006, and followed by a gradual decrease after 2010. The period effect for colonoscopies rose from the beginning of the study period until 2010 (1.29; 95% CI, 1.27–1.31), gradually declining afterward. We did not detect relevant period effects for rectoscopies and ultrasonographies. However, the utilization rate of all procedures declined after 2010. The increase in the birth cohort effect for younger cohorts was very pronounced for colonoscopy and FOBT, the two most common procedures, accounting for the marked all-procedure cohort effect. Overall, there was a continuous increase of utilization of diagnostic procedures starting in cohorts born in the late 1950s with an effect that rose from 0.91 (95% CI, 0.90–0.92) for the 1950 cohort to 3.73 (95% CI, 3.65–3.81) for the 1970 one, and to 5.03 (95% CI, 4.58–5.48) for those born in 1990. This increase is slightly more evident for women due to rising colonoscopy rates. Cohort effects were reversed (lower effect for younger cohorts) for rectoscopies, and no effect of the birth cohort was evident for ultrasonography.

Period and cohort effects for each of the four examined diagnostic procedures are compared in Fig. 3. While period effects converged for all procedures, increasing until 2010, afterward, they similarly had a slightly decreasing trend. FOBT and colonoscopy both showed a strong positive increase of utilization in younger cohorts, rectoscopy in the older ones, and no effect was detected for ultrasonography.

Figure 4 depicts the APC models for Italian and not-Italian patients, by 5-year age classes (from 25–29 to 80–84) and time periods (from 1999–2003 to 2014–2018) for all procedures combined. Increasing utilization rates with age were more evident for foreign older patients, with 66 examinations/100 vs. 34/100 subjects at age 70–74. No differences between Italians and foreigners were evident for the period effect, while the increasing usage of the diagnostic procedure by younger cohorts, existing in both nationality groups, appeared to be stronger for Italians.

Figure 5 shows the graphical representation of the APC models for the first and fifth quintiles of deprivation index. Age, period and cohort effects for all diagnostic procedures were very similar in the two deprivation index groups, with the exception of the age effect for FOBT, which was higher in older patients in the fifth deprivation index quintile (most deprived), with a utilization rate of 53/100 vs. 44/100 at peak age of 68 years.

Fig. 2



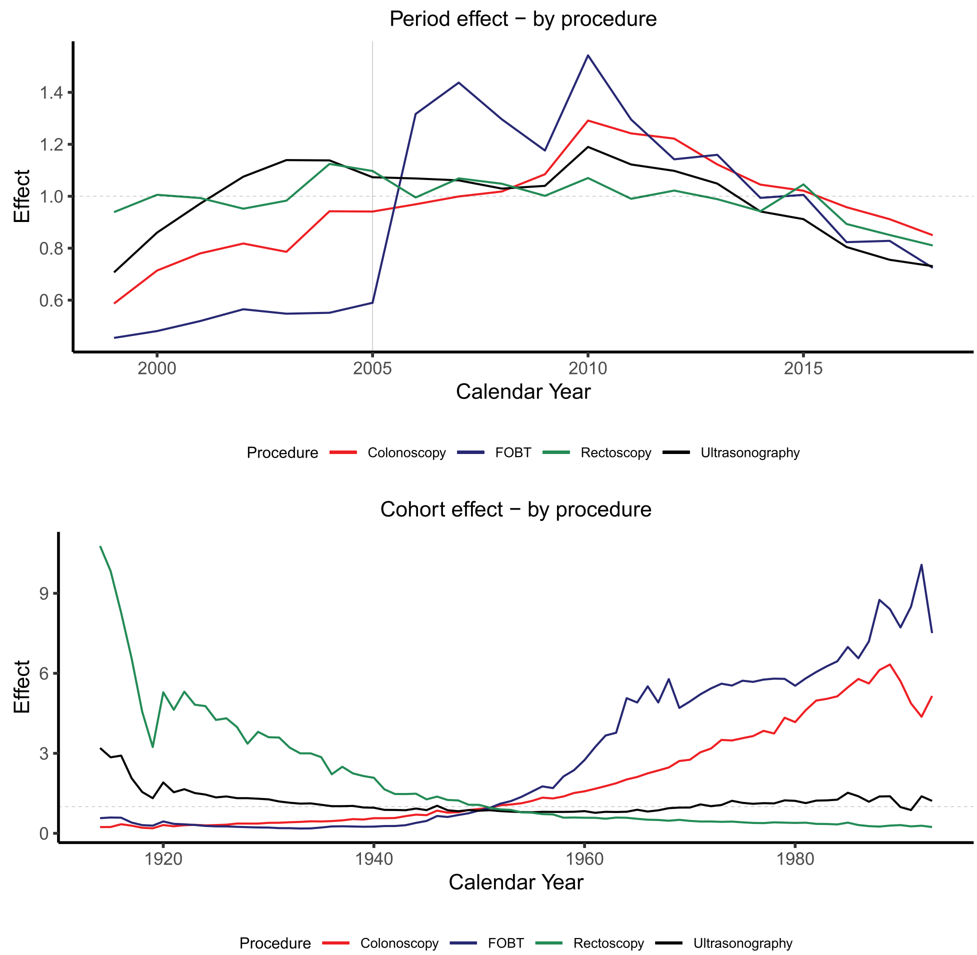
Estimated age, cohort and period effects from the APC model in the entire population. Shaded areas are confidence intervals. Incidence rates are per 100 person-years. Horizontal line in period and cohort graphs at effect = 1, vertical line in period graphs marks the year of introduction of colorectal cancer screening by fecal occult blood test (2005). APC, age–period–cohort; FOBT, fecal occult blood test.

Discussion

A strong increasing utilization rate for all procedures combined was found in younger cohorts compared to older ones, largely imputable to colonoscopies and FOBTs. This cohort effect was estimated from a APC model, accounting for the period effect, so it is not due to a calendar time-related increase of utilization of those diagnostic procedures as one may expect from greater availability of those exams in the latest years. On the contrary, the analysis of the period effect showed a decrease for all procedures after 2010. The underlying causes of the cohort effect should be further investigated. We can hypothesize that they may be related to a higher education level, increased socioeconomic status or decreased household size, for which an association with utilization of colonoscopy (Hermann *et al.*, 2015) and FOBT (de Klerk *et al.*, 2018) has been observed.

The described cohort effect may contribute to the observed rising incidence of EO-CRC (Siegel *et al.*, 2009; Ahnen *et*

Fig. 3



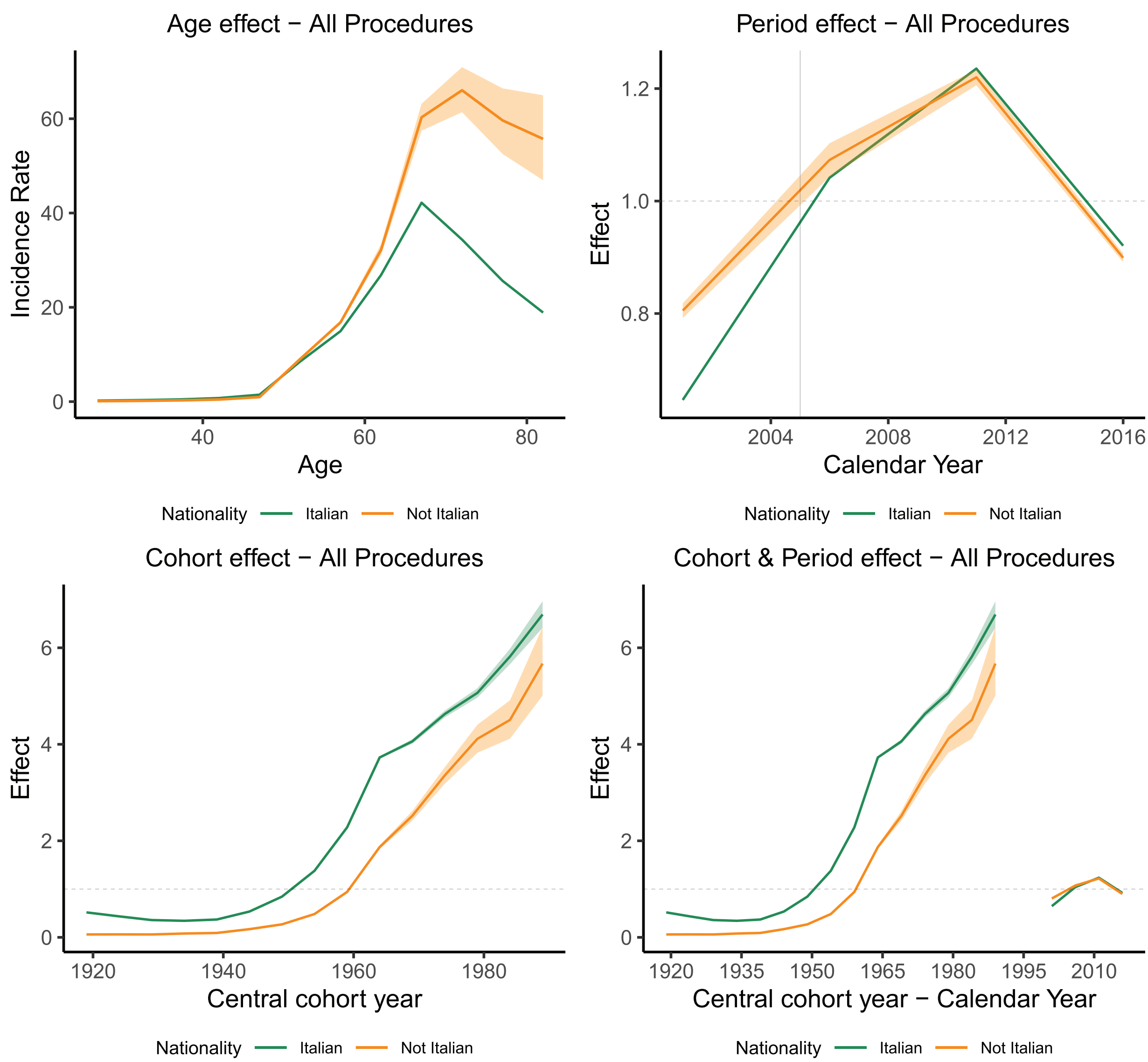
Estimated cohort and period effects from the APC model in the entire population, comparing the effects for every single procedure. Horizontal line at effect = 1, vertical line in period graphs marks the year of introduction of colorectal cancer screening by a fecal occult blood test (2005). APC, age–period–cohort; FOBT, fecal occult blood test.

al., 2014; Amri *et al.*, 2015; Bailey *et al.*, 2015; Abou-Zeid *et al.*, 2017; Brenner *et al.*, 2017; Gandhi *et al.*, 2017; Hessami Arani and Kerachian, 2017; Siegel *et al.*, 2017; Troeung *et al.*, 2017; Ullah *et al.*, 2018; Kasi *et al.*, 2019; Sung *et al.*, 2019; Vuik *et al.*, 2019). In fact, this increase may be at least partially due to an anticipation of diagnosis related to the incremented access to diagnostic procedures in younger cohorts, rather than being caused exclusively by actual anticipation of the age of onset of CRC.

It is important, however, to point out that 20–50% of colonoscopies are performed for inappropriate indications, and several studies found that that inappropriate colonoscopy is also associated with younger patients, women, and symptoms of abdominal pain or diarrhea (Telford, 2012; Andújar *et al.*, 2015). The access to endoscopic procedures, not prescribed by specialists but by general practitioners, combined with an increase of neoplastic lesions (risk factors) or a change in diagnostic criteria (severe dysplasia – early adenocarcinoma) could partly also explain the increases in CRC incidence observed.

On this topic, a recent retrospective study (Russo *et al.*, 2019) based on the Milan municipality population (1.3 million inhabitants) was performed on incident CRC cases between 1999 and 2015. Adopting an APC approach, it demonstrated a reduction in CRC risk for cohorts born up to 1979, followed by a sharp rise for the younger ones. Compared to the 1925 cohort, CRC risk doubled for 1987 one, and compared to the 1979 cohort, the risk for those born in 1993 was seven-fold. Regarding EO-CRC rates, they rose by 0.7% per year, 2.6% if considering only colon cancer. The described study has been conducted on the same population and roughly in the same period of time of the present investigation. It is thus possible to observe that the increasing utilization rate of

Fig. 4



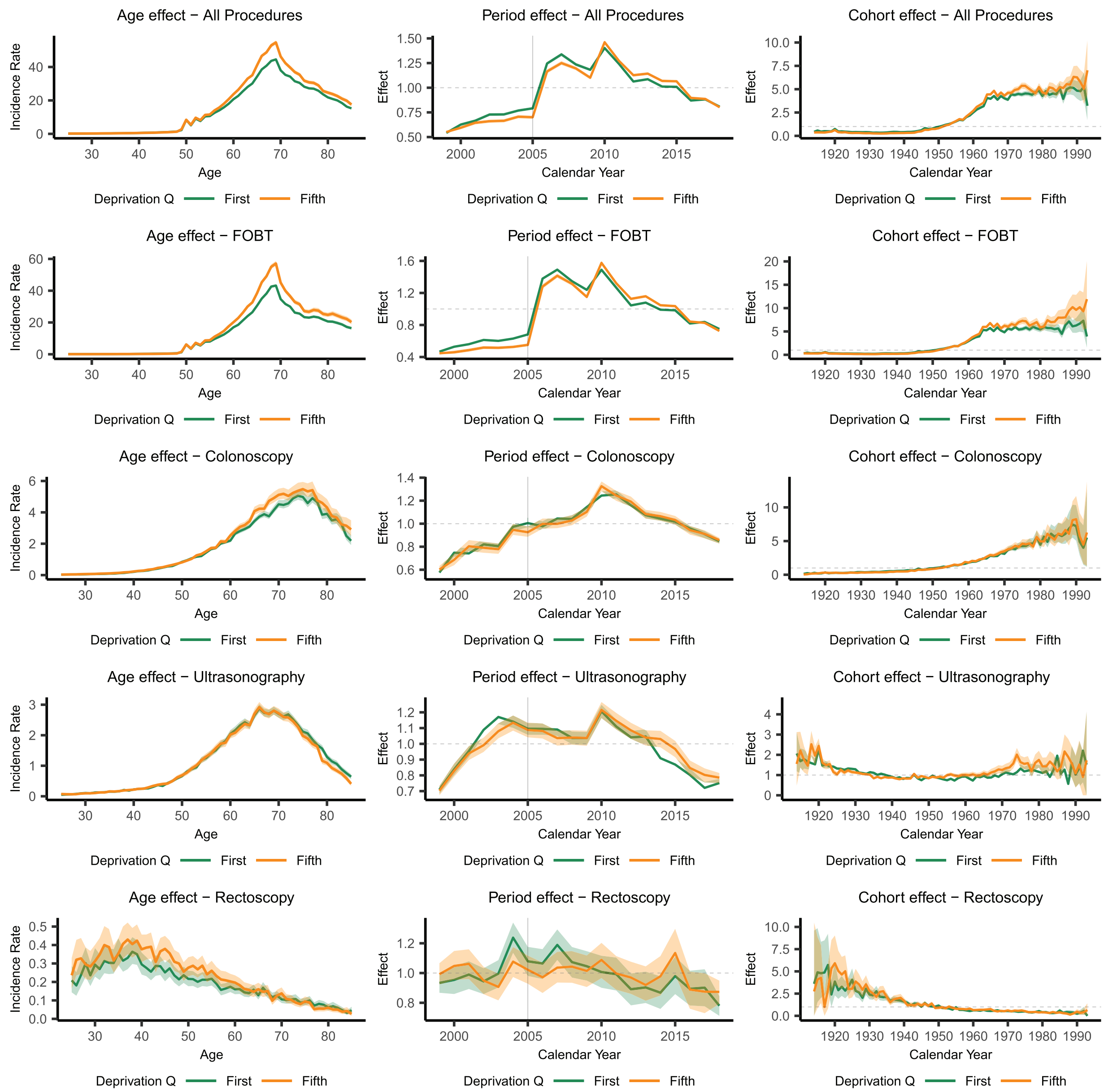
Estimated age, cohort and period effects from the APC model, Italian and not-Italian patients. Shaded areas are confidence intervals. Incidence rates are per 100 person-years. Horizontal line in period and cohort graphs at effect = 1, vertical line in period graphs marks the year of introduction of colorectal cancer screening by fecal occult blood test (2005). APC, age–period–cohort; FOBT, fecal occult blood test.

diagnostic procedures for younger cohorts mimics the rise in the incidence of CRC for the same cohorts, allowing to hypothesize that the observed higher propensity of younger people to undertake colonoscopies and FOBTs might explain, at least in part, the rise in EO-CRC over the recent years in the municipality of Milan.

Limitations

We extracted our data from the health databases of the AHP of Milan, which contains records from public and private health providers having agreements for being reimbursed from the Regional Health Service. Despite representing the vast majority of performed procedures in the study area, there is still a quota of private providers whose services are not recorded in AHP databases. Those missing data may still be of relevance when interpreting our findings regarding the quintiles of deprivation and not-Italian patients, being private health services in Italy typically affordable by the more affluent segments of the population: only 2.55B € of the total 39.9B € spent in 2018 for private health services were disbursed by households earning less than 15k € per year (Censis, 2018). Globally, 8.8% (3.5B €) of the total out-of-pocket expenditure in 2018 concerned diagnostic services (Del Vecchio *et al.*,

Fig. 5



Estimated age, cohort and period effects from the APC model, patients from first and fifth quintile of deprivation. Shaded areas are confidence intervals. Incidence rates are per 100 person-years. Horizontal line in period and cohort graphs at effect = 1, vertical line in period graphs marks the year of introduction of colorectal cancer screening by fecal occult blood test (2005). APC, age–period–cohort; FOBT, fecal occult blood test; Q, quintile.

2019); for those reasons, our models may underestimate the effects for the first deprivation index quintile compared to the fifth quintile, and for Italian compared to not-Italian patients.

Further research needed

Since the use of APC to model 'incidence rates' of diagnostic procedures is a novel approach, while being APC models commonly used for incidence rates of diseases or death, it would be of interest to investigate if similar utilization trends exist in other geographical areas where a rising trend in EO-CRC has been observed.

Conclusion

We found a growing tendency in younger birth cohorts to undertake diagnostic procedures that can lead to an incidental diagnosis of CRC. This finding may at least partially explain the observed rising incidence of EO-CRC.

Acknowledgements

A.S. conceptualized, curate the data, formally analyzed, wrote the original draft and wrote, reviewed and edited the article. A.A. conceptualized, wrote the original draft, and wrote, reviewed and edited the article. A.D. conceptualized and wrote, reviewed and edited the article.

A.G.R. designed the study, conceptualized, curate the data and wrote, reviewed and edited the article.

Conflicts of interest

There are no conflicts of interest.

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