Cancer Epidemiology 60 (2019) 134–140

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Increased incidence of colon cancer among individuals younger than 50 years: A 17 years analysis from the cancer registry of the municipality of Milan, Italy

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ARTICLE INFO

Keywords:
Colorectal cancer
Incidence
Young age
Age-period-cohort

ABSTRACT

Background: Colorectal cancer (CRC) overall incidence has been decreasing in the last decade. However, there is evidence of an increasing frequency of early-onset CRC in young individuals in several countries. The aim of this study is to evaluate the trends of CRC occurrence over 17 years in the municipality of Milan, Italy, focusing on early-onset CRC.

Population and methods: This retrospective study was performed using the Cancer Registry of the municipality of Milan, including all cases of CRC diagnosed 1999-2015. Incidence rates were stratified by age and anatomic subsite, and trends over time were measured using the estimated annual percentage change. Age-period-cohort modelling was used to disentangle the different effects.

Results: 18,783 cases of CRC were included. CRC incidence rates among individuals aged 50–60 years declined annually by 3% both in colon and in rectal cancer. Conversely, in adults younger than 50 years, overall CRC occurrence increased annually by 0.7%, with a diverging trend for colon (+2.6%) and rectal (−5.3%) cancer. Among individuals aged 60 years and older, CRC incidence rates increased by 1.0% annually up to 2007, and decrease thereafter by 4% per year, both for colon and rectal cancer. Age-period-cohort models showed a reduction of CRC risk for the cohorts born up to 1979, followed by an increase in younger cohorts. In contrast, rectal cancer among women showed a systematic risk decrease for all birth cohorts.

Conclusions: The study highlights increasing incidence of colon cancer in younger subjects and a decrease in incidence rates for rectal cancer in females.

1. Introduction

Colorectal cancer (CRC) represents the third most common malignancy in high-income countries where it also ranks as the third leading cause of cancer deaths, being prominent among non-smokers [1]. Overall, CRC occurrence and mortality have declined drastically after 1990 due to a multiplicity of factors, including increased screening in the middle-age population [2–4]. The diffusion of colonoscopy as a screening procedure in adults aged 50–75 years reduced the annual incidence rate of about 4% per year in the United States between 2008 and 2012, in both genders. This effect is mediated by the resection of pre-malignant lesion i.e. adenomas [5,6]. However, 11% of colon and 18% of rectal cancers are nowadays diagnosed among adults below 50 years (early-onset CRC; EO-CRC). In the United States, CRC incidence under 50 years of age raised by 1.5% per year in men and 1.6% in women from 1992 to 2005. More in detail, the average annual increase was of 2.7% for colon and 3.9% for rectal cancer from 2001 to 2007 [7–9]. Based on current trends, in the United States colon and rectal cancer incidence rates are expected to increase by 124% for patients aged 20–34 years, and by 46% for patients ages 35–49 years by 2030 compared with 2010 [10]. Similar trends were also described in Canada [11], Australia [12] and New Zealand [13]. No recent large population study reporting on CRC incidence among young individuals is available in Europe [14,15]. Despite the described increasing incidence trend in young adults, screening is not routinely recommended in this age group for individuals without a known hereditary cancer syndrome or family history [1,16].

The aim of this study is to describe CRC incidence trends and to examine the age, period and cohort effects in the municipality of Milan from 1999 to 2015, using data from the population-based Cancer

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https://doi.org/10.1016/j.canep.2019.03.015
Received 6 December 2018; Received in revised form 9 March 2019; Accepted 26 March 2019

Registry, focusing on early-onset CRC.

2. Population and methods

A retrospective cohort study was performed including all new diagnosis of colon and rectal cancer occurring, from 1999 to 2015, in the population of the Milan Municipality (1,300,000 inhabitants). This area is covered cancer register accredited by IARC that has continuously collected all new invasive cancers from January 1999. Starting from 2016, the Milan Municipality is part of cancer register of the Metropolitan area of Milan, included in Cancer Incidence in Five Continents – XI, covering the entire provinces of Milan for 3,176,180 inhabitants.

For the purpose of this study, CRC was defined using the International Classification of Diseases for Oncology (3rd edition, ICD-O-3) topography codes C18-C20. Each tumour was also classified in an anatomic sub-site, according to the ICD-O-3: proximal colon (C18.0, C18.2-C18.5), distal colon (C18.6-C18.7), and rectum (C19.9, C20.9). Extra-nodal lymphomas (ICD-O-3 morphologic codes: 9673/3, 9687/3), and sarcomas (9120/3, 8936/3, 9140/3, 8890/3) were excluded from the analysis.

Patient characteristics included gender and age at diagnosis. Considering 50 years as the lower cut-off for screening being recommended and 65 years as the expected age of retirement, the cohort was also divided into three age groups: < 50, 50–65, and > 65 years. Available tumour characteristics included ICD-O-3 coded morphology, histologic grade, and Dukes' pathological stage at diagnosis [17].

Age specific CRC incidence rates by gender were computed for the following age groups: < 45, 45–54, 55–64, 65+ years. To disentangle the age-period-cohort effects, three separate analyses were carried out. First, a graphical approach was used: age specific (< 45, 45–54, 55–64, 65+ years) incidence rates were computed by birth cohort (10-years intervals from 1915 to 1975) for colon and rectum, and plotted against the central year of the birth cohort. The points corresponding to the same age group were joined, to allow an easier reading of the cohort effect on the ordinate. Secondly, age-specific incidence trends and Annual Percentage Change (APC) were estimated using the joinpoint regression approach [18]. A joinpoint is a time point conjoining two segments with significantly different slopes, i.e. incidence trends. This method allows to estimate and select the simplest model with the best fitting linear segments, minimizing the sum of the weighted least squares distances from data points to segments. A maximum of 3 joinpoints was allowed and the fitted models were linear on the natural logarithm of the rates. APCs indicates the average annual change in cancer incidence rate for each period segment. This model was used to investigate CRC incidence trends by age group and separately for colon and rectum. Thirdly, an age-period-cohort approach was used to enhance the understanding of disease trends by attempting to disentangle factors that influence all ages (period effects), such as changes in medical practice, from those that vary by generation (cohort effects), typically because of behavioural changes. A R macro [19] was used to fit the age-period-cohort models following Osmond and Gardner method [20], combining in a single general multiplicative risk model the evaluation of the three dependent effects.

Using data from the Italian National institute of Statistics (ISTAT), we also examined changes in the age-structure of the municipality of Milan between 2002 (first available year with data) and 2015 (http://demo.istat.it/). We constructed population pyramids for the two years.

3. Results

A total of 18,783 cases of CRC were reported to the Cancer Registry of the municipality of Milan from 1999 to 2015, including 14,658 (78%) colon cancers. Of those 6628 (45%) were located in the right (including transverse) colon (Table 1). The remaining 4125 individuals (22%) presented with rectosigmoid or rectal cancers. Distributions of demographic and tumour characteristics of the cohort, overall and by tumor sub-site are reported in Table 1. Among people with colon cancer, males were 50.8% while they were 54.4% amid those with rectal cancer. Tumors of the rectum were more frequent compared to colon cancer in adults younger than 50 years (3.6% vs. 4.6%). Excluding individuals with missing information, G3 tumors were 22.4% of colon and 18.7% of rectal cancers, and Dukes-A stage neoplasia amounted to 11.2% and 14.4%, respectively. Mucinous and signet ring cell tumor (SRC) morphologies represented 9.0% of colon and 5.6% of rectal cancers. Advanced stages (Dukes D) were more represented among young CRC patients (25.0%) compared to those aged more than 65 years (18.8%). Mucinous and SRC morphologies were more frequent in the youngest age group (12.0%) compared to oldest (8.3%).

Age-specific CRC incidence rates for each age group calculated by year of birth (Fig. 1) showed a decreasing trend across birth cohorts after age 44 years and stable rates up to 44 years, for both males and females.

The analysis of age-specific annual incidence trends for all colorectal cancers (Fig. 2, first row), showed a significant decrease in the 50–60 age group for the entire period (APC, −3.0%; 95%CI, −4.1 to −1.9). In the same age group, similar trends were documented for colon (Fig. 2, central row; APC, −2.8%; 95%CI, −3.9 to −1.7) and rectal cancers (Fig. 2, bottom row; APC −3.6: 95% CI −5.3; −1.8). In people older than 60 years, a non-significant uptrend up to 2006 (APC 1.0; 95%CI, −0.1–2.1) was followed by a consistent and significant decrease in annual incidence during the period 2007–2015 (APC, −4.2; 95%CI, −5.3 to −3.1). Separate analysis for colon and rectal sites showed a similar uptrend, significant for colon only (APC, 1.4; 95%CI, 0.4–2.3), followed by a downtrend starting in 2007. The decrease in incidence was more pronounced for rectal (APC, −6.9; 95%CI, −9.1 to −4.7) compared with colon cancer (APC, −3.4; 95%CI −4.3 to −2.5).

In patients aged less than 50 years (Fig. 2, first column), the overall CRC incidence rates increased from 1.9 to 2.1 per 100,000 (APC, 0.7%; 95%CI, −1.9 to 3.3) and for colon cancer from 1.2 to 1.8 per 100,000 (APC, 2.6%; 95% CI −0.9 to 6.2), albeit the annual change was not statistically significant. In contrast, rectal cancer showed a decreasing trend from 0.9 to 0.4 per 100,000, not statistically significant, also among patients younger than 50 years (APC, -5.3%; 95%CI, -10.6 to 0.3).

Fig. 3 shows graphically the results of the age-period-cohort models for colon cancer by gender. For the age effect (***panel A***), the expected increase of age specific rates with increasing age was documented. The cohort effect analysis (***panel B***) shows the incidence trend between 1925 and 1998, using the mean of the entire period as the reference value. A reduction of cancer risk was detected for the cohorts born up to 1979, followed by an increase for the more recent cohorts. The risk doubled for those born after 1987 compared to 1925, and continued to rise up to the 1993 birth-cohort, having a sevenfold risk compared to 1979. Concerning period effects (***panel C***), a moderate increase of cancer risk from 1999 to 2015 was found. The trends for colon cancer were similar in males and females. In contrast, the age-period-cohort analysis of rectal cancer showed a modifier effect of gender (Fig. 4). In men, trends are consistent with those seen in colon cancer, while women showed an opposite pattern with a considerable risk reduction in the most recent cohorts.

The changes in the age structure of the population of the municipality of Milan over the study period were modest (Supplementary Fig. 1). In 2002, the population aged 50 years or younger was 62.1% for males and 53.3% for females, while in 2015 it was 63.2% and 55.5%, respectively.

4. Discussion

The results of the study document, from 1999 to 2015, an increase in the incidence of colorectal cancer in patients younger than 50 years from 1.9 to 2.1 per 100,000, although the overall rates of CRC in the

Table 1
Distribution of main characteristics of colorectal cancers cases. (Cancer Registry of Milan 1999–2015, Italy).

	Site of the Primary Tumor		Age Groups (years)			Total CRC cases
	Colon	*Rectum*	*< 50*	*50-64*	*65+*	
Years Incidence						
1999–2003	4349 (29.67%)	1397 (33.87%)	216 (30.04%)	1250 (35.03%)	4280 (29.53%)	**5746**
2004–2007	3707 (25.29%)	1115 (27.03%)	161 (22.39%)	926 (25.95%)	3735 (25.77%)	**4822**
2008–2011	3524 (24.04%)	888 (21.53%)	182 (25.31%)	764 (21.41%)	3466 (23.91%)	**4412**
2012–2015	3078 (21.00%)	725 (17.58%)	160 (22.25%)	628 (17.60%)	3015 (20.80%)	**3803**
Age groups (years)						
< 50	530 (3.62%)	189 (4.58%)	–	–	–	**719**
50–64	2584 (17.63%)	984 (23.85%)	–	–	–	**3568**
65+	11,544 (78.76%)	2952 (71.56%)	–	–	–	14,496
Gender						
Males	7440 (50.76%)	2243 (54.38%)	363 (50.49%)	1971 (55.24%)	7349 (50.70%)	**9683**
Females	7218 (49.24%)	1882 (45.62%)	356 (49.51%)	1597 (44.76%)	7147 (49.30%)	**9100**
Grading						
G1	897 (6.12%)	273 (6.62%)	52 (7.23%)	245 (6.87%)	873 (6.02%)	**1170**
G2	7742 (52.82%)	2138 (51.83%)	338 (47.01%)	2004 (56.17%)	7538 (52.00%)	**9880**
G3	2496 (17.03%)	554 (13.43%)	124 (17.25%)	569 (15.95%)	2357 (16.26%)	**3050**
missing	3523 (24.03%)	1160 (28.12%)	205 (28.51%)	750 (21.02%)	3728 (25.72%)	**4683**
DUKES staging						
A	1331 (9.08%)	440 (10.67%)	56 (7.79%)	424 (11.88%)	1291 (8.91%)	**1771**
B	2632 (17.96%)	633 (15.35%)	102 (14.19%)	565 (15.84%)	2598 (17.92%)	**3265**
C	5690 (38.82%)	1411 (34.21%)	278 (38.66%)	1476 (41.37%)	5347 (36.89%)	**7101**
D	2232 (15.23%)	571 (13.84%)	145 (20.17%)	512 (14.35%)	2146 (14.80%)	**2803**
missing	2773 (18.92%)	1070 (25.94%)	138 (19.19%)	591 (16.56%)	3114 (21.48%)	**3843**
Mucinous[a]						
No	13,339 (91.00%)	3894 (94.40%)	633 (88.04%)	3311 (92.80%)	13,289 (91.67%)	**17,233**
Yes	1319 (9.00%)	231 (5.60%)	86 (11.96%)	257 (7.20%)	1207 (8.33%)	**1550**
Total	**14,658**	**4125**	**719**	**3568**	**14,496**	**18,783**

[a] Mucinous and signet ring cell tumors.

same period were declining. Previous reports in high-income non-European countries documented a similar phenomenon [10–13].Particularly in the US, Bhandari et al., using SEER data, found that CRC is a leading cause of cancer incidence and mortality among young adults in the United States [21]. Additional analyses of US data showed an increase of colorectal cancer incidence among young adults, due to an increase in left-sided tumors, particularly in the rectum [8]. Cress et al., using all races combined SEER data from 1992 to 2001, documented an increase of rectal cancer incidence in the population under 50 years, but not for colon cancer [22]. Other authors reported an increase in incidence rates among young adults aged 20–39 years, for both colon and rectal cancers (SEER 1973–1999) [23]. This latter study however excluded cases 40–49 year olds, who represent 73% of CRC patients under the age of fifty.

The present study is population-based and used high-quality cancer registry data collected over a 17-year period. In addition, multiple statistical approaches were applied to understand the possible mechanisms involved in this trend changes: a more traditional graphical approach, the joinpoint model estimating the APC- robust and largely used – and, finally, the age-period-cohort models that disentangle the age, cohort, and period effects allowing to analyse them separately. A birth cohort effect can be induced by exposure to a risk or protective factor acting on the early-stages of the carcinogenesis process (initiators), with long latency periods. In contrast, a period effect can be attributed either to a risk or protective factor involved in the last stages of the carcinogenesis process (promoters) and acting on all age groups, or to changes in medical practice, including screening. SEER data [4] suggest an impact of screening on decreased incidence and mortality for CRC. Introduced in 2005, the organized screening of the Lombardy region for CRC consisted, up to 2016, of a free fecal occult blood test every two years, offered through mail invitation to the population between 50 and 69 years. In the metropolitan area of Milan, adhesion to screening has always been lower than 40% from 2005 to 2015. At the regional level, women adhere more than men (51 vs. 44%) and 65–69 year-olds more than 50–54 year-olds (53% vs. 42%). The inflection point evident at APC analysis in 2007 for the oldest age-group is coherent with screening introduction, as 2006–2007 can be considered the first round of the screening, with the recruitment of the prevalent cases accumulated in the population, followed by the expected incidence reduction from 2008. However, the trends documented in this study cannot be attributed entirely to the introduction of screening, also because no decreasing period effect was found in the age-period-cohort model. The evidence of a decreasing birth cohort effect for those born up to 1979 suggests that the overall decrease can be largely attributed to risk factors modification or/and to the healthier lifestyles. This trend reversed for those born in the eighties or after. The observed increasing incidence of CRC among patients younger than 50 years of age in different high-income countries has been attributed to behavioural factors: obesity, physical inactivity and diet are all risk factors associated with an increased risk for CRC [24,25]. These are potentially modifiable factors with a favourable cost-benefit balance for the health care system and may influence reducing the health effects for many cancer sites and cardiovascular diseases. In Italy, data from surveys representative of the general adult population indicated - from 1983 to 2008 - an increase of overweight of 10.5% in males and of 4.2% in females and of obesity of 3.6% in males and of 1.4% in females (0.056% per year). Obesity, that represents a surrogate of multiple risk factor exposure (high-risk diet profile, hyperglycemia and low physical activity), is more evident in males than in females and more evident in the population younger than 50 years [26].

Comparing the findings of this study with the previous reports in the non-European countries [10–13], the main difference is that an opposite trend between colon and rectal cancer was found in Milan in people younger than 50 years and in the female population, with rectal cancer declining in a similar way as in older patients. Particularly, in females rectal cancer had decreasing trends in both birth cohort and period

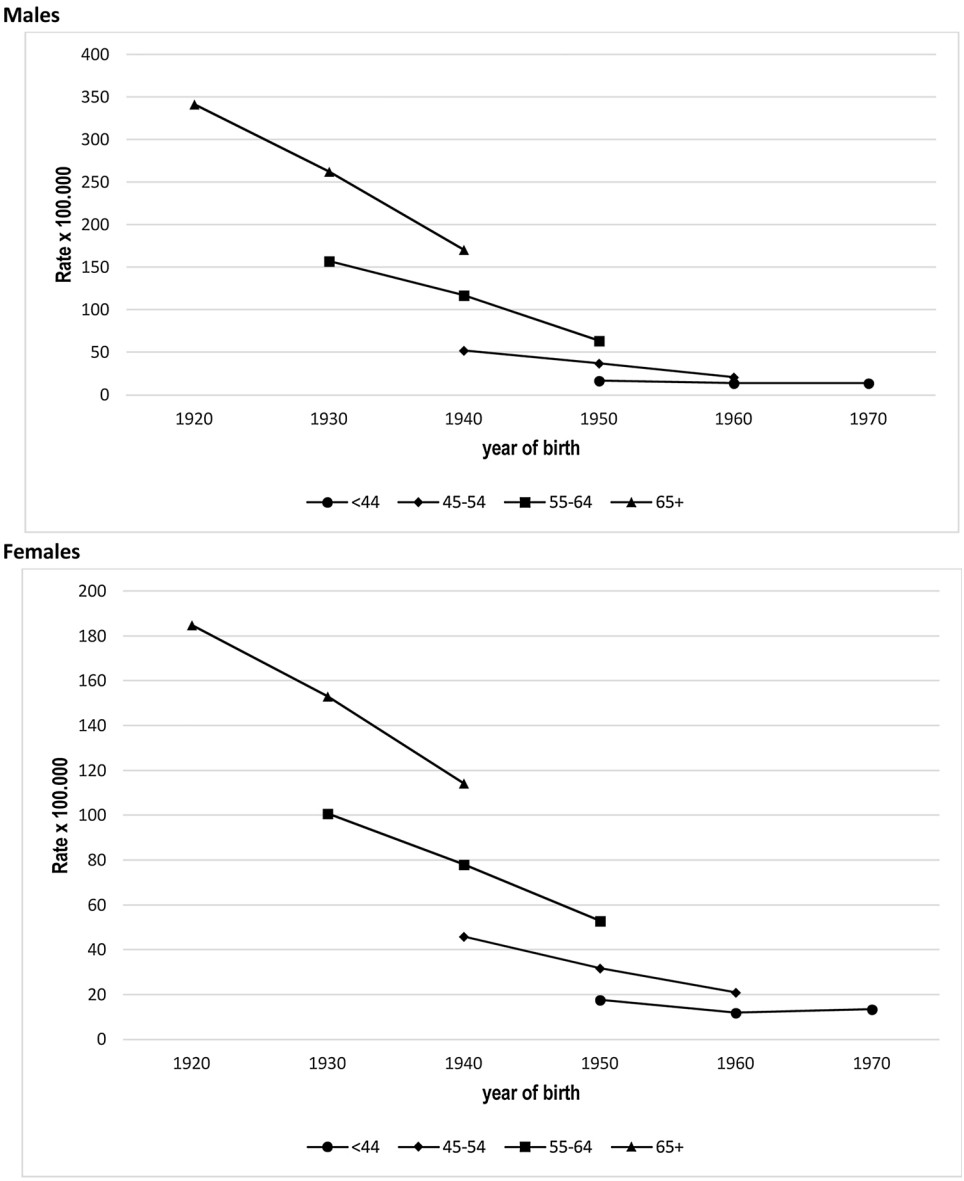

Fig. 1. Age-specific colorectal cancer incidence rates per 100,000 from 1999 to 2015 by cohort (year of birth) and gender. (Cancer Registry of the Municipality of Milan, Italy).

analyses, while in males there was a growing trend by period and for cohorts born from the end of '70 onwards. Although based on a limited number of cases, this finding would require additional investigations to define which risk and/or protective factors are involved, including the life-style changes mentioned above [26] that have a different prevalence between sexes. One of the additional aspects to study is represented by the access of the female population to at least one gynaecological examination each year between 30 and 50 years, which could induce a rectosigmoidoscopy with removal of the preneoplastic lesions in case of bleeding adenomas. Also, the finding of different trends in colon and rectal cancer incidence between Milan, located in southern Europe, and US suggest that the underlying causes inducing CRC in young individuals might be several and differently represented in different regions, even within high income countries.

Early-onset CRC is a hallmark of inherited cancer predisposition and approximately 15–30% of cases are expected to have a significant familial history and/or genetic predisposition [27]. In this study, early-onset CRC were more likely to be diagnosed at advanced stages (III and IV) and more frequently mucinous or signet-ring cancers, if compared to the overall population, in agreement with previous publications [28–31].

For subjects without a familial history and/or known genetic predisposition, CRC screening in Italy has been extended to the 50–74 year old population from 2016. In this age group, the incidence and mortality reduction for screening attenders have been documented [3–5]. The opposite trend observed among adults younger than 50 years may be partly due to the lack of indication to screening with FOBT in this age group [3–5]. Recently, a study reporting results of the first attempt to extend screening to lower ages has been published, but definitive data supporting this topic are still far from being presented [32].

5. Conclusion

The available evidences about the increase in the incidence of colorectal cancer among young adults compared to the decrease for the population over the age of 50 pose the problem to identify and reduce modifiable risk factors and improving healthy lifestyles in this age group. Also, the effectiveness of extending screening to younger ages should be evaluated.

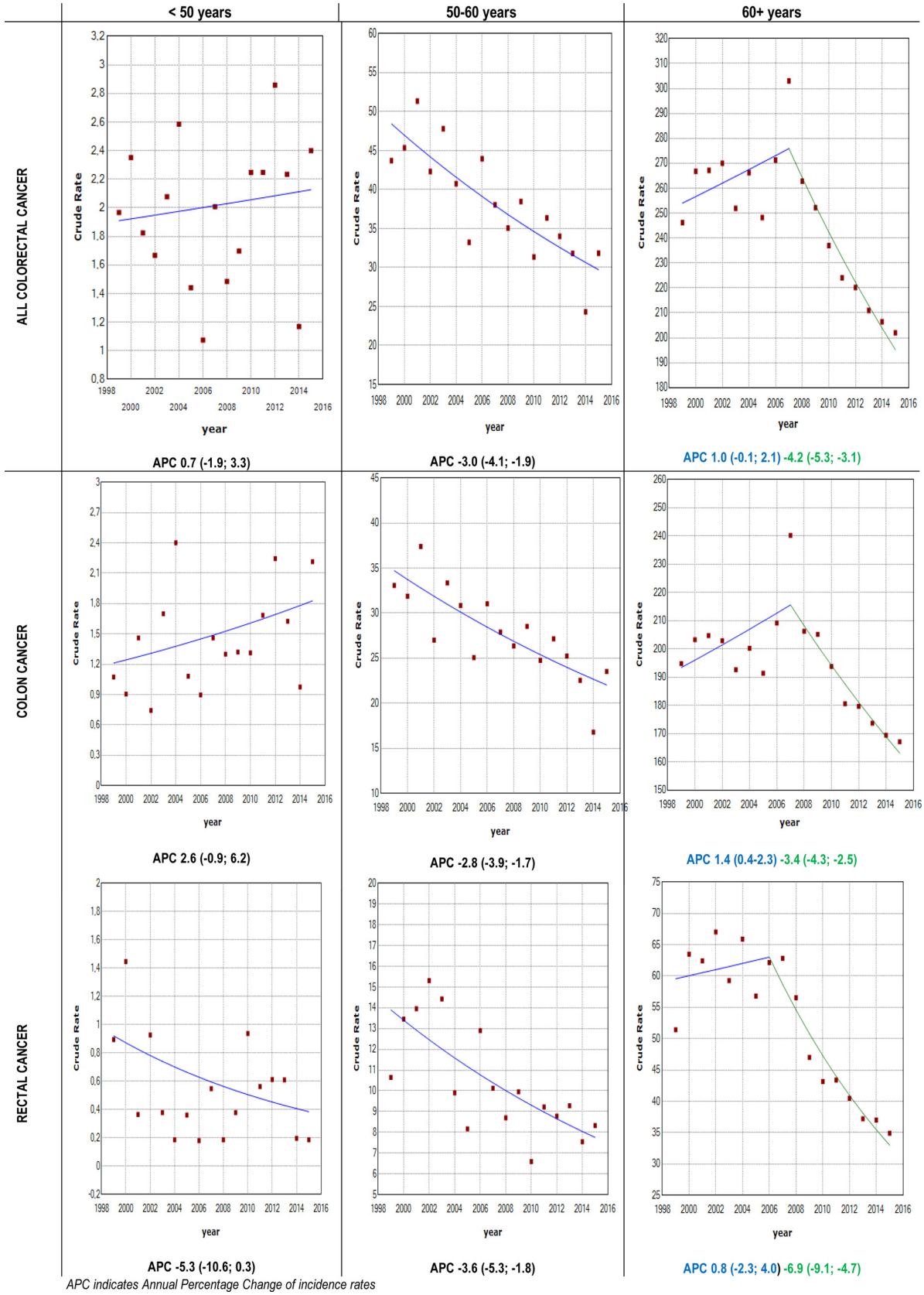

Fig. 2. Trends in age-specific (age groups, < 50, 50–60 and 60+ years) annual incidence rates per 100,000 for colorectal (upper panels), colon (middle panels), and rectal (lower panels) cancers (Cancer Registry of the Municipality of Milan, Italy, 1999–2015).

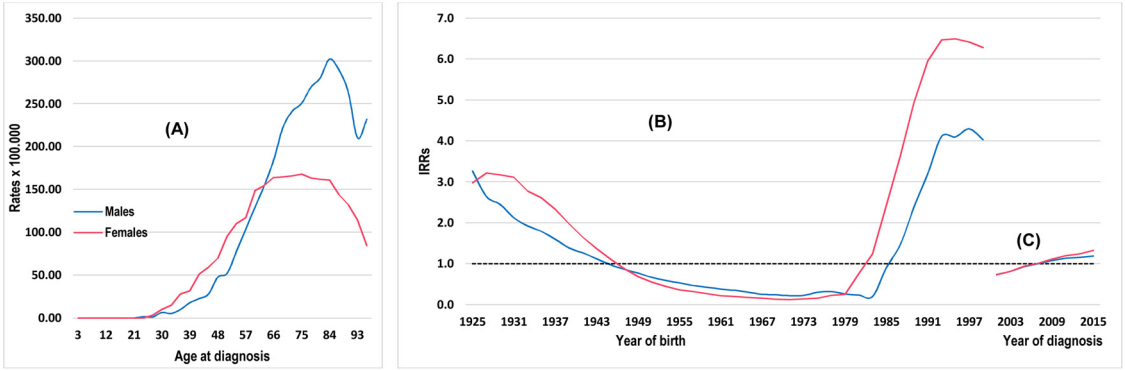

Fig. 3. Estimated (A) age, (B) cohort and (C) period effect from the APC model for colon cancer incidence - Cancer Registry of Milan 1999–2015, Italy.

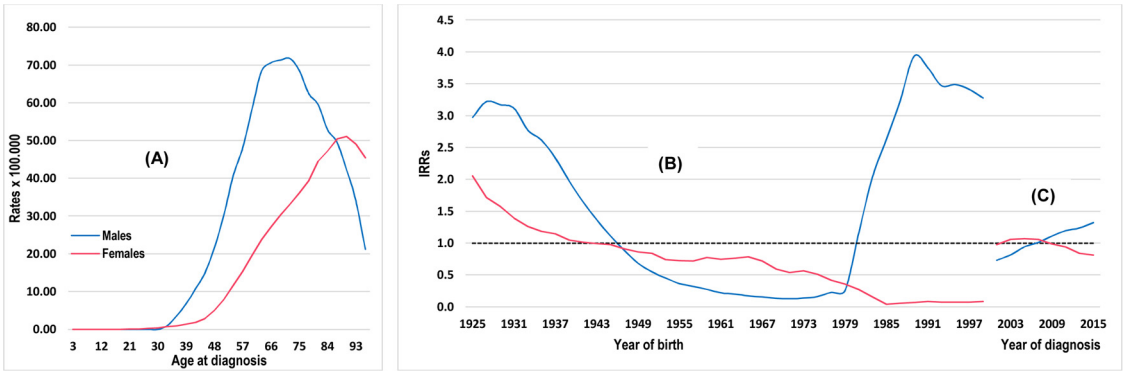

Fig. 4. Estimated (A) age, (B) cohort and (C) period effect from the APC model for rectal cancer incidence - Cancer Registry of Milan 1999–2015, Italy.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

Authors are supported by grants from the Associazione italiana per la ricerca sul cancro (AIRC) grant AIRC 5 xMille Special Program Molecular Clinical Oncology Project ID 51000, AIRC Investigator Grant Program NO-CUT Project ID 20685, and AIRC Special Program 5 x Mille Metastases Project ID 21091; from CORDIS Community Research and Development Information Service, Horizon 2020 Project ID 635342 grant Molecularly Guided Trials with Specific Treatment Strategies in Patients with Advanced Newly Molecular Defined Subtypes of Colorectal Cancer (MoTriColor); from Fondazione Oncologia Niguarda Onlus, grant Terapia Molecolare dei Tumori and grant Studies to Develop Therapies Against Colorectal Cancer in Young Adults.

Ethics approval and consent to participate

The study was carried out according to the principles laid down in the Declaration of Helsinki. This study did not require institutional review board because it was based on government-issued data. It was determined to be a retrospective analysis of de-identified data and was determined to be exempt from requiring written informed consent.

Authors' CONTRIBUTIONS

Antonio Giampiero Russo is the Director of Cancer Registry of Milan, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Antonio Giampiero Russo, Salvatore Siena

Statistical analysis: Antonio Giampiero Russo

Interpretation of data: Antonio Giampiero Russo, Anita Andreano, Adriano Decarli and Salvatore Siena

Drafting of the manuscript: Antonio Giampiero Russo, Anita Andreano, Andrea Sartore Bianchi, Gianluca Mauri, Adriano Decarli, Salvatore Siena

All authors gave final approval of the version to be submitted.

Acknowledgements

The authors are indebted to the Cancer Registry personnel of the Epidemiology Unit of the Agency for Health Protection of Milan.

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