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Trends of colorectal cancer incidence and mortality rates from 2003 to 2014 in Italy

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Abstract

Objective: To evaluate the trends of colorectal cancer (CRC) incidence and mortality rates from 2003 to 2014 in Italy by age groups and regions.

Methods: We used the data of 48 cancer registries from 17 Italian regions to estimate standardized incidence and mortality rates overall and by sex, age groups (<50, 50–69, 70+ years), and geographic area (northwest, northeast, center, south, and islands). Time trends were expressed as annual percent change in rates (APC) with 95% confidence intervals (95% CI).

Results: Incidence rates decreased from 104.3 (2003) to 89.9 × 100,000 (2014) in men and from 64.3 to 58.4 × 100,000 in women. Among men, incidence decreased during 2007–2010 (APC −4.0, 95% CI −6.0 to −1.9) and 2010–2014 (APC −0.7, 95% CI −1.4 to 0.0), while in women it linearly decreased during the whole period (APC −1.1, 95% CI −1.4 to −0.8). Mortality rates showed a linear reduction both in men (APC −0.7, 95% CI −1.0 to −0.3) and women (APC −0.9, 95% CI −1.2 to −0.6) and decreased respectively from 41.1 to 39.2 × 100,000 and from 24.6 to 23.1 × 100,000.

In the 50- to 69-year-old range (screening target age), incidence showed a prescreening increase, followed by a peak after screening started, and a decline thereafter. Incidence and mortality rates significantly decreased in all areas but in the south and islands, where incidence increased and mortality remained stable.

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Conclusions: A renewed commitment by all regional health systems to invest in primary (i.e., lifestyle) and secondary (i.e., screening programs) prevention is of utmost importance.

Keywords
Colorectal cancer, incidence, mortality, screening

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of death among cancers worldwide.[1] In Italy, 51,300 new CRC cases were estimated in 2018[2] and 18,935 deaths due to CRC were recorded in 2015.[2] Italian incidence rates are among the highest in the world and similar to those reported in high-income countries.[1]

Behavioral risk factors, such as physical inactivity, alcohol consumption, and smoking, are responsive to modification. The International Agency for Research on Cancer (IARC) classified "sufficient evidence" linking the consumption of alcohol beverages,[3] physical inactivity, and overweight to CRC. The IARC also confirmed the conclusions previously made by the World Cancer Research Fund[4] asserting that red meat is a probable carcinogen (class 2A) and processed meat is a carcinogen (class 1).[5] Red and processed meats particularly increase the risk of CRC. The fraction of CRCs attributable to these modifiable lifestyle factors in Italy is approximately 50%.[6]

In Italy, CRC incidence rates increased from 1986 to 2005, while mortality rates decreased.[7–11] However, different factors are modifying CRC incidence and mortality rates. The prevalence of various risk factors is changing.[12,13] In the early 2000s, population-based screening programs started in different regions and progressively spread over the whole country. The proportion of the resident population invited to a screening increased from 4.8% in 2004 to 53.1% in 2012.[14,15]

The aim of this study was to provide reliable estimates of CRC incidence and mortality rate trends from 2003 to 2014 in Italy by age group and region. We further discussed the results taking into account geographic variations and changes over time of major known risk factors and screening programs.

Methods

Data

The study was based on the dataset collected by the Italian Association of Cancer Registries (AIRTUM). Incident cases are recorded by all cancer registries (CRs) according to a common protocol.[16] Routine indicators of data completeness and quality for Italian CRs are satisfactory.[17,18] In the present study, we used data from 48 CRs located in 17 out of the 20 Italian regions, including patients of all ages. Further details are described in the twin article published in the current issue.[19] Deaths were collected from local mortality registries (ReNCaM). The study period went from 2003 to 2014 for both AIRTUM and ReNCaM data. All ages were selected in the study.

As incidence and mortality data were not available for the whole study period for all CRs, the data matrix was completed by estimating the numbers of incident cases and deaths for calendar years with missing information. Lacking data were estimated by means of joinpoint log-linear model fitted on the last segment of the specific CR temporal trend. The method for estimates and projections to 2014 had been successfully used in the evaluation of the 1986–1997 and 1998–2005 incidence trends in Italy.[20,21]

Table 1 describes the number of new cases and deaths used in the analysis and the main features of population covered by cancer registration, according to region and macro-area.

Overall, in 2012, the study registries covered a resident population of almost 36 million subjects (35,799,991 as of December 31, 2012), corresponding to 60% of the whole Italian population (Table 1). Coverage of cancer registration was higher in the northeast (72%) and northwest (71%) and lowest in the center (25%). Between 2003 and 2014, overall 333,740 CRC incident cases and 134,160 deaths were analyzed.

Table 1 also reports data on CRC screening programs and main risk factors for each region included in the study: first year of screening activity with a widespread population coverage (>30% target population screened in the year) and screening coverage in 2010[15,22]; percentage of overweight and obese (body mass index ⩾25) in 2011–2014[12]; and percentage of individuals with low physical activity (subjects reporting neither heavy occupational nor recreational physical activity).[23]

In most regions, CRC screening programs consist of a biennial invitation to all 50- to 69-year-old residents to undergo a single fecal immunochemical test (FIT), followed by colonoscopy when positive at fecal test. The Piedmont region, however, offers as screening program a once-in-life flexible sigmoidoscopy to 58-year-old residents or a biennial FIT to those who refuse flexible sigmoidoscopy. During the study period, CRC screening programs reached a widespread coverage of the target population in

Table 1. Number of analyzed (observed and estimated) incident cases and deaths and main characteristics of the study population, by region/macro-area.

Macro-area/region	Resident population ×1000 (as of December 31, 2012)	Coverage with cancer registration, %	Study period	Analyzed incident cases, n	Analyzed deaths, n	First year of screening coverage >30%	Screening coverage in 2010[a]	Overweight and obese in 2011–2014, %[b]	Low physical activity in 2011–2014, %[c]
Northwest	15,862	71		117,196	45,472	2007	29		
Piemonte	4374	30	2003–2012	14,642	6067	2010	39	37	30
Val d'Aosta	128	100	2007–2014	1165	406	2006	45	36	24
Liguria	1565	55	2003–2010	11,711	4999	2013	11	34	30
Lombardia	9795	92	2003–2012	89,678	34,000	2007	40	37	33
Northeast	11,516	72		86,744	34,359	2006	46		
Trentino Alto Adige	1035	100	2003–2010	8515	3827	2012	42	34	17
Veneto	4882	53	2003–2010	26,324	10,120	2007	46	40	23
Friuli Venezia Giulia	1222	100	2003–2010	14,673	6032	2009	41	42	21
Emilia-Romagna	4377	80	2003–2014	37,232	14,380	2006	47	42	21
Center	11,681	25		31,561	12,795	2016	19		
Toscana	3693	33	2003–2010	13,079	5015	2006	41	36	26
Umbria	886	100	2003–2013	10,498	4195	2007	46	43	22
Marche	1545	0	–	–	–	2014	9	42	23
Lazio	5557	15	2003–2012	7984	3585	–	3	41	33
South and islands	20,621	65		98,239	41,534	–	2		
Abruzzo	1313	0	–	–	–	–	1	46	35
Molise	313	0	–	–	–	2015	11	49	22
Campania	5770	71	2003–2014	26,709	10,761	–	3	42	43
Puglia	4051	54	2003–2012	16,504	6562	–	0	45	38
Basilicata	576	100	2006–2010	5182	1992	2005	27	46	62
Calabria	1958	64	2003–2010	9376	3840	–	2	47	46
Sicilia	5000	91	2003–2013	34,810	15,887	–	1	47	43
Sardegna	1640	42	2003–2012	5658	2492	–	7	38	26
Italy	59,680	60		333,740	134,160	2017	21	42	31

[a]Proportion of 50- to 69-year-old residents who were screened.[19]
[b]Available at: http://www.epicentro.iss.it/passi/dati/sovrappeso.asp9
[c]Available at: http://www.epicentro.iss.it/passi/dati/attivita.asp20

all the northern regions, in 2 out of 3 regions in the Center, and only in one region (Basilicata) in the south and islands.

Statistics

Incidence and mortality rates were stratified by sex, age group (<50, 50–69, 70+ years), anatomic site (colon: ICD-10 code C18, rectum: ICD-10 codes C19–C20), and geographic area (northwest, northeast, center, and south and islands). Age-adjusted rates were calculated using the European 2013 standard population.

Time trends were assessed by log-linear models and expressed as annual percent change in rates (APC) with 95% confidence intervals (95% CI); significant changes in time trends were investigated by the permutation test carried out using the Joinpoint Regression Program 4.6 version.[24]

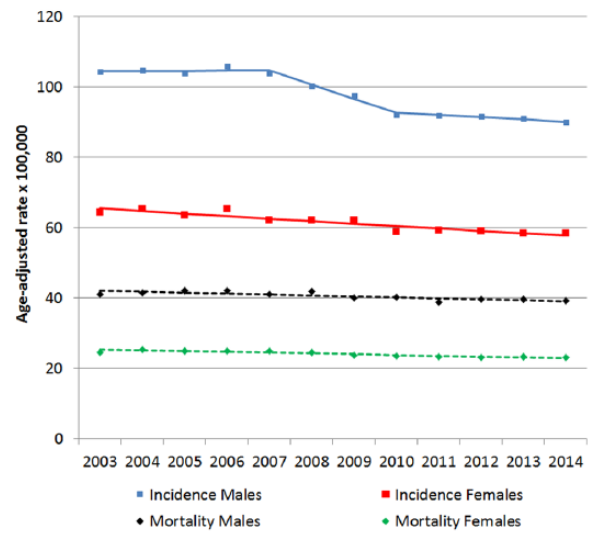
Results

At the beginning of the study period, incidence rates in the pool of all Italian registries included in the study were 104.3 ×100,000 in men and 64.3 ×100,000 in women.

Among men, CRC incidence rates remained stable from 2003 through 2007, with an approximately 4% yearly decrease since then, from 2007–2010 (95% CI −6.0 to −1.9), and 0.7% from 2010–2014 (95% CI −1.4 to 0.0) (Figure 1). Such a 3-phase trend of overall incidence rates was determined by the trends in colon cancer (APC 2003–2006: +1.1, 95% CI −0.2 to 2.4; 2006–2010: −3.3, 95% CI −4.6 to −2.0; 2010–2014: −1.0, 95% CI −1.8 to −0.2) (see online Appendix 1), while incidence rates for rectum cancer decreased by 1.6% (95% CI −2.2 to −1.1) per year over the whole study period (see online Appendix 2).

In women, the incidence of CRC decreased during the whole period by an annual 1.1% (95% CI −1.4 to −0.8). Therefore, in 2014, incidence rates were 89.9 ×100,000 men and 58.4 ×100,000 women. The decrease for rectum cancers was larger (APC −1.2, 95% CI −1.5 to −1.0) than that for colon cancers (−1.1, 95% CI −1.4 to −0.7).

CRC mortality rates showed a statistically significant linear annual decrease of 0.7% in men (95% CI −1.0 to −0.3) and went from 41.1 ×100,000 in 2003 to 39.2 ×100,000 in 2014. The mortality reduction for rectum cancers was greater (APC −1.2, 95% CI −1.7 to −0.7) than that for colon cancers (APC −0.5, 95% CI −0.9 to −0.1). CRC mortality rates significantly decreased by an annual 0.9% also in women (95% CI −1.2 to −0.6) and went from 24.6 ×100,000 in 2003 to 23.1 ×100,000 in 2014. Also in women, the decrease for rectum cancers was higher (APC −1.5, 95% CI −2.3 to −0.7) than that for colon cancers (2003–2006: APC +0.8, 95% CI −0.9 to 2.6; 2006–2014: APC −1.1, 95% CI −1.5 to −0.7).



		Period		APC	95% CI	
Male	Incidence	2003	2007	0.1	-0.7	0.8
		2007	2010	-4.0	-6.0	-1.9
		2010	2014	-0.7	-1.4	0.0
	Mortality	2003	2014	-0.7	-1.0	-0.3
Female	Incidence	2003	2014	-1.1	-1.4	-0.8
	Mortality	2003	2014	-0.9	-1.2	-0.6

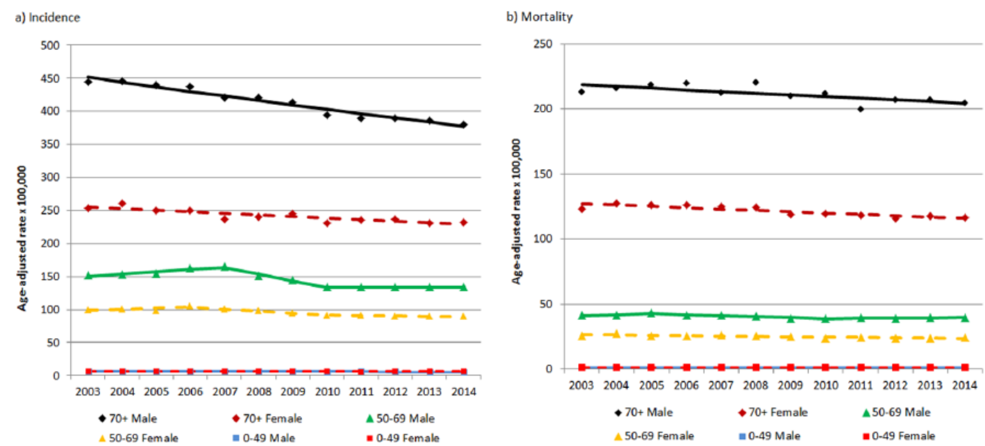
Figure 1. Colorectal cancer incidence and mortality trends with annual percent change (APC) and 95% confidence intervals (95% CI), according to sex. Italy, 2003–2014. All ages. Age-standardized (European population 2013).

Trend by age

During the study period, in individuals younger than 50 years, CRC incidence rates significantly decreased by an annual 1.6% in men and by 1.1% in women, while mortality rates significantly decreased annually by 1.5% and 1.6%, respectively (Figure 2). Focusing on 40- to 49-year-old patients, the APC were as follows: 40- to 44-year-old men −1.2 (95% CI −2.2 to −0.2), women −0.9 (95% CI −1.6 to −0.2); 45- to 49-year-old men −1.6 (95% CI −2.3 to −0.9), women −1.5 (95% CI −2.2 to −0.8) (data not shown).

Incidence rates in the intermediate 50- to 69-year age range, i.e., the target age of screening programs, showed a 3-phase pattern for both sexes. The first period was characterized by a significant 2.1% annual increase until 2007 in men and by a nonsignificant 1.8% annual increase until 2006 in women. The second phase showed a significant 6.5% annual decrease in men and 3.1% in women until 2010, statistically significant for both sexes, while the rates stabilized during 2010–2014. Mortality decreased over the whole period, with a significant variation of 1.9% between 2005 and 2010. In women, mortality decreased by 1.0% per year during the whole study period.

In the older age class (70+ years), CRC incidence rates homogeneously decreased by 1.6% per year in men and by



a) Incidence

		Period	APC	95% CI	
Male	0-49	2003-2014	-1.6	-2.1	-1.1
	50-69	2003-2007	2.1	0.3	4.0
		2007-2010	-6.5	-11.8	-0.9
		2010-2014	0.0	-1.9	1.9
	70+	2003-2014	-1.6	-1.9	-1.4
Female	0-49	2003-2014	-1.1	-1.7	-0.4
	50-69	2003-2006	1.8	0.0	3.7
		2006-2010	-3.1	-4.9	-1.3
		2010-2014	-0.6	-1.7	0.6
	70+	2003-2014	-1.0	-1.3	-0.6

b) Mortality

		Period	APC	95% CI	
Male	0-49	2003-2014	-1.5	-2.8	-0.2
	50-69	2003-2005	1.7	-2.6	6.2
		2005-2009	-1.9	-3.2	-0.5
		2009-2014	0.4	-0.9	1.8
	70+	2003-2014	-0.6	-1.0	-0.2
Female	0-49	2003-2014	-1.7	-2.7	-0.6
	50-69	2003-2014	-1.0	-1.4	-0.6
	70+	2003-2014	-0.8	-1.2	-0.5
		2010-2014	-0.6	-1.7	0.6
	70+	2003-2014	-1.0	-1.3	-0.6

Figure 2. Colorectal cancer incidence (a) and mortality (b) trends with annual percent change (APC) and 95% confidence intervals (95% CI), according to age class and sex. Italy, 2003–2014. Age-standardized (European population 2013).

1.0% per year in women, while mortality rates decreased by 0.9% and 1.0%, respectively, in men and women.

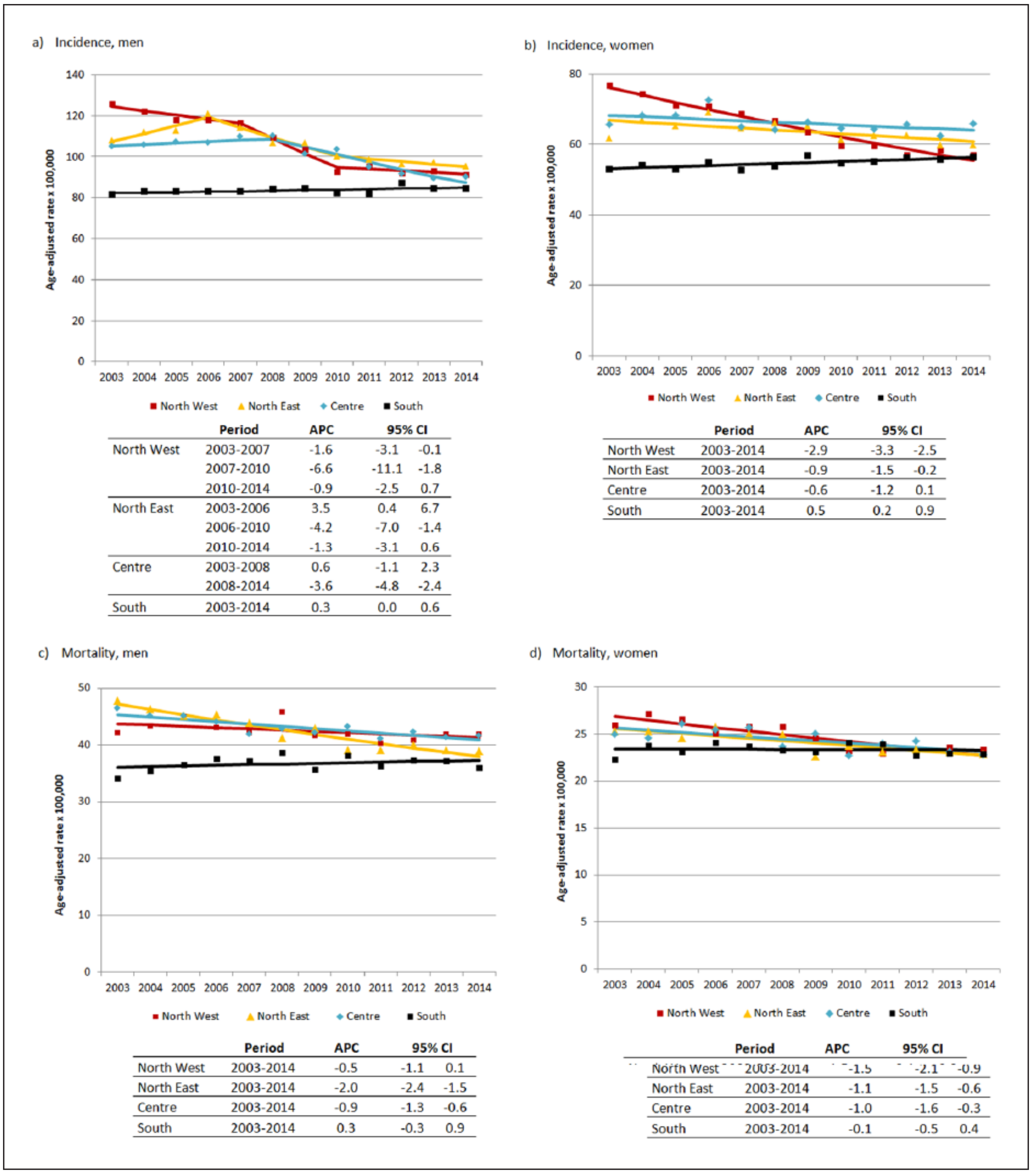
Trend by macro-area

At the beginning of the study period, relevant differences in incidence rates were observed between geographic macro-areas for both sexes, rates being highest in the northwest (125.9 ×100,000 in men; 76.8 ×100,000 in women), intermediate in the northeast and center, and lowest in the south and islands (81.4 ×100,000 in men; 53.0 ×100,000 in women) (Figure 3). During 2003–2014, incidence rates significantly decreased in the northwest, northeast, and center both in men and women, although with different patterns among areas and at different times. For example, in the northeast, an incidence peak took place in 2005, followed by a sharp reduction, this pattern being more evident in male patients. However, in the south and islands, a significantly increasing trend was recorded in both sexes. Thus, by the end of the study period the differences in incidence rates among macro-areas had almost disappeared in both sexes.

The findings were more striking in the target population of screening (Figure 4). In the south and islands, incidence rates significantly increased yearly by +0.5% both in male (95% CI 0.0 to 1.0) and female patients (95% CI 0.1 to 0.9), while in the rest of Italy they significantly increased during the first study years, when screening programs began (APC male patients 2003–2007: +2.2, 95% CI −0.4 to 4.9; female patients 2003–2006: +1.9, 95% CI 0.1 to 3.7) (data not shown). They subsequently dropped by 8.4% (95% CI −16.1 to −0.0) per year in male patients (2007–2010) and by 3.7% (95% CI −4.5 to −2.9) in female patients (2006–2012), and finally stabilized in both sexes (APC male patients −0.7, 95% CI −3.6 to 2.2; female patients +0.5, 95% CI −3.2 to 4.4). Consequently, the excess in incidence rates observed at the beginning of the study in the northern and central regions as compared with the south and islands almost disappeared by the end of the study both in male patients (2003: 171.2 vs 116.1 ×100,000; 2014: 137.7 vs 126.4 ×100,000) and in female patients (2003: 107.7 vs 83.6 4 ×100,000; 2014: 90.7 vs 88.3 ×100,000) (data of the rest of Italy not shown).

In 2003, mortality rates were lower in the south and islands (34.1 ×100,000 in men; 22.3 ×100,000 in women) as compared with the rest of Italy, the highest figures being in the northeast in men (47.8 ×100,000) and in the northwest in women (26.0 ×100,000). During the study period, mortality rates linearly decreased both in male and female patients in all areas but the south and islands, where they were stable. By the end of the study, the values showed limited differences in men, ranging from 39.0 ×100,000 in the northeast to 36.0 ×100,000 in the south and islands, and in women (range 23.4 ×100,000 in the northwest; 22.9 ×100,000 in the south and islands).

Concerning the screening target population in the south and islands, mortality rates were stable during the study period in both men (APC 0.3, 95% CI −0.3 to 1.0) and



a) Incidence, men

	Period	APC	95% CI	
North West	2003-2007	-1.6	-3.1	-0.1
	2007-2010	-6.6	-11.1	-1.8
	2010-2014	-0.9	-2.5	0.7
North East	2003-2006	3.5	0.4	6.7
	2006-2010	-4.2	-7.0	-1.4
	2010-2014	-1.3	-3.1	0.6
Centre	2003-2008	0.6	-1.1	2.3
	2008-2014	-3.6	-4.8	-2.4
South	2003-2014	0.3	0.0	0.6

b) Incidence, women

	Period	APC	95% CI	
North West	2003-2014	-2.9	-3.3	-2.5
North East	2003-2014	-0.9	-1.5	-0.2
Centre	2003-2014	-0.6	-1.2	0.1
South	2003-2014	0.5	0.2	0.9

c) Mortality, men

	Period	APC	95% CI	
North West	2003-2014	-0.5	-1.1	0.1
North East	2003-2014	-2.0	-2.4	-1.5
Centre	2003-2014	-0.9	-1.3	-0.6
South	2003-2014	0.3	-0.3	0.9

d) Mortality, women

	Period	APC	95% CI	
North West	2003-2014	-1.5	-2.1	-0.9
North East	2003-2014	-1.1	-1.5	-0.6
Centre	2003-2014	-1.0	-1.6	-0.3
South	2003-2014	-0.1	-0.5	0.4

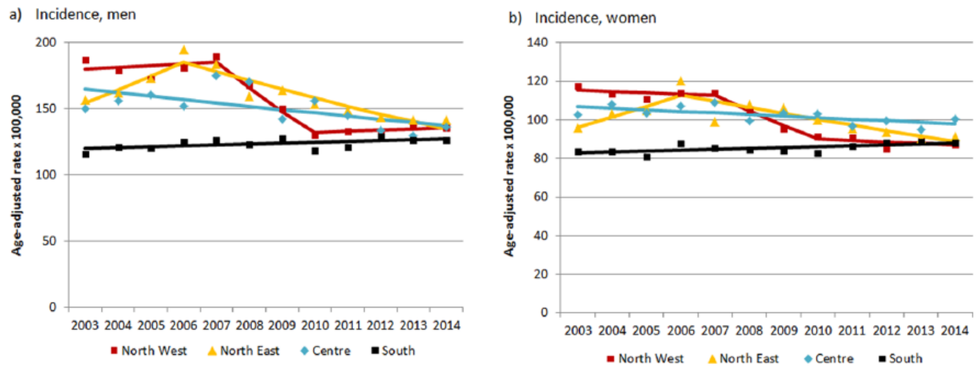
Figure 3. Colorectal cancer incidence (men: a; women: b) and mortality (men: c; women: d) trends with annual percent change (APC) and 95% confidence intervals (95% CI), according to geographic macro-area. Italy, 2003–2014. All ages. Age-standardized (European population 2013).

women (APC −0.2, 95% CI −0.9 to 0.5), while in the northern regions, they linearly decreased in both sexes. In the center, they were stable in women, while they dropped in men by 4.0% yearly from 2003 to 2008 to stabilize thereafter. When comparing the rest of Italy with the south and islands, the differences in mortality rates, at the end of the study, were markedly reduced in male patients (2003: 44.8 vs 35.1 ×100,000; 2014: 41.1 vs 36.6 ×100,000) and even more in female patients (2003: 26.8 vs 23.6 ×100,000; 2014: 24.4 vs 24.2 ×100,000) (data not shown).

Discussion

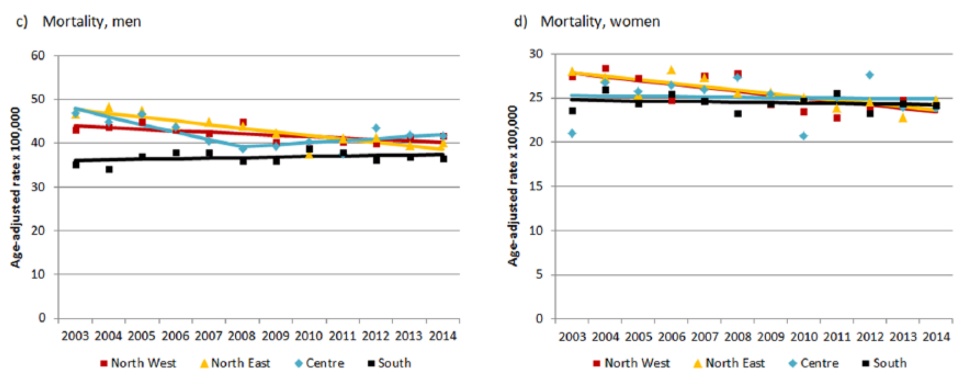
In Italy, from 2003 to 2014, CRC incidence and mortality rates showed a significant decrease in both sexes. The analysis by geographic macro-area highlighted a wide variability in incidence and mortality levels at the beginning of the observed period (2003). However, geographic variability in incidence and mortality decreased during the study period due to differences in time trends across areas.

The Italian figures observed in this study were much different from the increasing CRC incidence rates reported in the United States[25] and in various European countries (e.g., England, the Netherlands, Norway, Slovakia, Slovenia, and Spain).[26] However, in Europe, different patterns of incidence trends have been described according to country and to anatomic site. For example, incidence rates for colon cancer are increasing in Croatia and Denmark, stable in Bulgaria, Ireland, Scotland, and Switzerland, and



	Period	APC	95% CI	
North West	2003-2007	0.72	-2.6	4.2
	2007-2010	-10.6	-20.3	0.1
	2010-2014	0.7	-3.2	4.7
North East	2003-2006	6.23	0.1	12.7
	2006-2014	-3.9	-5.1	-2.6
Centre	2003-2014	-1.7	-3.1	-0.2
South	2003-2008	0.5	0.0	1.0
	2008-2014	-3.6	-4.8	-2.4
South	2003-2014	0.3	0.0	0.6

	Period	APC	95% CI	
North West	2003-2007	-0.60	-3.8	2.7
	2007-2010	-7.14	-17	3.8
	2010-2014	-0.87	-4.4	2.8
North East	2003-2006	5.50	-1.2	12.7
	2006-2014	-2.94	-4.3	-1.5
Centre	2003-2008	-0.80	-1.4	-0.2
South	2003-2014	0.53	0.1	0.9



	Period	APC	95% CI	
North West	2003-2014	-0.8	-1.5	-0.1
North East	2003-2014	-1.9	-2.6	-1.2
Centre	2003-2008	-4.0	-6.9	-0.9
	2008-2014	1.1	-1.2	3.6
South	2003-2014	0.3	-0.3	1.0

	Period	APC	95% CI	
North West	2003-2014	-1.55	-2.5	-0.6
North East	2003-2014	-1.48	-2.2	-0.8
Centre	2003-2014	-0.14	-1.9	1.6
South	2003-2014	-0.20	-0.9	0.5

Figure 4. Colorectal cancer incidence (men: a; women: b) and mortality (men: c; women: d) trends with annual percent change (APC) and 95% confidence intervals (95% CI), according to geographic macro-area. Italy, 2003–2014. Age 50–69 years. Age-standardized (European population 2013).

decreasing in France and Germany, while rectum cancer is stable in all those countries.[26]

Notably, we did not observe the same increase in CRC incidence rates among subjects younger than 50 years that was recently described in Australia[27] and in the United States,[28] which induced the American Cancer Society to update its recommendations for CRC screening by lowering the age for starting screening from 50 to 45.[29]

The observed pattern of incidence trends across geographic regions mirrors the impact of screening programs, which reached a very different coverage of the target population among regions. In fact, only the areas with well-established screening programs showed a significant decrease in both incidence and mortality rates, while in the south and islands, where screening activity was still very limited by the end of the study period, incidence rates increased and mortality rates were stable.

The analysis according to age confirmed the impact of screening on epidemiologic indicators already reported in the literature.[30] In the screening age group, incidence showed the expected pattern: an early peak associated with the diagnostic anticipation of cancers when a screening program starts, followed by a reduction due to the removal of CRC precursors (advanced adenomas) during colonoscopy. Some factors may have diluted the expected 2-phase impact of screening on incidence rates, which was evident only in some subgroup analyses (e.g., males in the pool, males in the northeast, colonic location). Indeed, screening programs started at different times among Italian regions; furthermore, the coverage of the programs' target populations was highly variable, and rarely exceeded 50%,[15,22] while the study analyzed the entire resident population.

Changes in lifestyle and dietary factors in previous decades contributed to the trends that we observed. In particular, the nutritional characteristics of the reference Italian–Mediterranean diet have been progressively abandoned over the last 4 decades.[31] This is particularly worrisome for the typical Mediterranean areas of Italy (i.e., southern regions) where an increased consumption of meat and refined sugars has been reported in recent decades.[32] Southern regions also showed a consistently higher prevalence of overweight and obesity and higher proportion of physically inactive population (Table 1). More alarming for future trends of CRC is the higher prevalence of overweight in children and adolescents of southern Italian regions in comparison with northern and central Italy.[33]

Compared with the proportion of obese people reported in the United States,[34] the Italian picture appears much better, even if a negative trend has taken place in the last few years (obesity: from 10.3% in 2008 to 10.9% in 2017; overweight: from 41.7% in 2008 to 42.8% in 2017). Both these trends are statistically significant.[12] Recently, sufficient evidence of the carcinogenicity of tobacco smoking also for CRC in humans has been reported.[35] In Italy, the prevalence of smokers is decreasing (from 29.7% in 2008 to 25.3% in 2017), as well as the median number of cigarettes smoked,[36] following a decreasing trend that started in the 1970s.[37] These trends in smoking habits may, at least partially, contribute to CRC incidence and mortality decrease.

As this study was based on data from all the Italian CRs, covering about 60% of the whole Italian population, the results of this analysis are likely highly representative of the actual national situation. Another strength of this study was the homogeneously high quality of data; in all CRs, we had more than 82% microscopic verification, less than 2% death certificate only, and less than 52% of mortality–incidence ratio.[19]

Mortality rates estimated here only partially describe the real impact of screening as some of the patients, who died of CRC within the study period, were diagnosed before the beginning of the screening program. In order to evaluate the effect of screening on mortality, we should have calculated the incidence-based mortality, including only deaths that occurred from cancers diagnosed after the first invitation to screening.[38]

The assumption of linearity of the method for estimates and projections to 2014 may not always be justified. However, each trend may be considered linear in a sufficiently short period of time and fitting the model on the last segment resulting by joinpoint analysis should allow valid estimates even for those cancer sites with significant variations in trends. On the other hand, projecting on a large number of years, a trend observed in a short period may not be safe.

The comparison of incidence and mortality trends in areas where widespread screening programs are available with those where they are not suggests a large potential impact of screening. Furthermore, screening programs are expected to specifically deplete their target populations of advanced stage CRCs,[39,40] whose treatment is becoming increasingly expensive due to new high-cost drugs. Therefore, the expected advantage in terms of cost-efficacy of screening programs should be much higher than reported in the literature.[41–43]

From this point of view, the case of the incidence and mortality trends in the south and islands (respectively increasing and stable rates over the study period versus a statistically significant decrease in the rest of Italy) illustrates how the regions of this area are missing an opportunity to reduce CRC morbidity and mortality in their population, and to keep the costs of treatment down.

Conclusions

In Italy overall, both CRC incidence and mortality rates are decreasing in all age groups in both sexes. However, relevant differences emerged among areas, reflecting different levels of screening programs activation and the underlying risk factors for CRC in the south and islands. These results suggest a renewed commitment of the regional health systems to invest more in primary and secondary prevention.

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References

1. Ferlay J, Ervik M, Lam F, et al. *Global Cancer Observatory: Cancer Today*. Lyon, France: International Agency for Research on Cancer; 2018. https://gco.iarc.fr/today (accessed 18 October 2018).
2. AIOM, AIRTUM Fondazione AIOM, Istituto Superiore di Sanità. *I Numeri del Cancro 2018*. Brescia: Intermedia; 2018.

3. Cai S, Li Y, Ding Y, et al. Alcohol drinking and the risk of colorectal cancer death: a meta-analysis. *Eur J Cancer Prev* 2014; 23: 532–539.
4. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. *Diet, nutrition, physical activity and colorectal cancer*. https://www.wcrf.org/sites/default/files/Colorectal-cancer-report.pdf (accessed 18 October 2018).
5. International Agency for Research on Cancer. *IARC Monograph: Red Meat and Processed Meat*. Lyon, France: WHO; 2015.
6. La Vecchia C, Braga C, Franceschi S, et al. Population-attributable risk for colon cancer in Italy. *Nutr Cancer* 1999; 33: 196–200.
7. AIRTUM. *Gli andamenti temporali della patologia oncologica in Italia: i dati dei Registri tumori (1986–1997): Rapporto 2004*. https://www.registri-tumori.it/cms/pubblicazioni/gli-andamenti-temporali-della-patologia-oncologica-italia-i-dati-dei-registri-tumori (accessed 18 October 2018).
8. AIRTUM. *I Tumori in Italia: Rapporto 2009: I trend dei tumori negli anni duemila (1998–2005)*. https://www.registri-tumori.it/cms/pubblicazioni/i-tumori-italia-rapporto-2009-i-trend-dei-tumori-negli-anni-duemila-1998-2005 (accessed 18 October 2018).
9. AIRTUM Working Group. Cancer trend (1998–2005). *Epidemiol Prev* 2009; 33(1 suppl): 1–169.
10. Crocetti E, Buzzoni C, Quaglia A., et al. Ageing and other factors behind recent cancer incidence and mortality trends in Italy. *J Geriatr Oncol* 2012; 3: 111–119.
11. Rossi S, Crocetti E, Capocaccia R, et al. Estimates of cancer burden in Italy. *Tumori* 2013; 99: 416–424.
12. Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute. *La sorveglianza PASSI: Sovrappeso e obesità*. http://www.epicentro.iss.it/passi/dati/sovrappeso.asp (accessed 18 October 2018).
13. Costa G, Crialesi R, Migliardi A, et al, eds. *Salute in Italia e Livelli di Tutela: Approfondimenti dalle Indagini ISTAT Sulla Salute*. Rome: Istituto Superiore di Sanità; 2016. (Rapporti ISTISAN 16/26.) http://old.iss.it/binary/publ/cont/16_26_web.pdf (accessed 30 October 2018).
14. Zorzi M, Grazzini G, Senore C and Vettorazzi M. Screening for colorectal cancer in Italy: 2004 survey. *Epidemiol Prev* 2006; 30 suppl 3: 41–50.
15. Zorzi M, Da Re F, Mantellini P, et al. Screening for colorectal cancer in Italy: 2011–2012 survey. *Epidemiol Prev* 2015; 39 (3 suppl 1): 93–107.
16. Ferretti S and Giacomin A. *2010 Cancer Registration Handbook*. https://www.registri-tumori.it/cms/pubblicazioni/cancer-registration-handbook-2010 (accessed 18 October 2018).
17. AIRT Working Group 2006. Italian cancer figures: report 2006: incidence, mortality and estimates. *Epidemiol Prev* 2006; 30 (suppl 2). http://www.registri-tumori.it (accessed 18 October 2018).
18. Bray F, Colombet M, Mery L, et al, eds. *Cancer Incidence in Five Continents, Vol. XI* (electronic version). Lyon, France: International Agency for Research on Cancer; 2017. http://ci5.iarc.fr (accessed 25 October 2018).
19. Buzzoni C, Crocetti E, Guzzinati S, et al. Cancer incidence and mortality trends in Italy. *Tumori J* (in press 2019).
20. Crocetti E, Capocaccia R, Casella C, et al. Population-based incidence and mortality cancer trends (1986–1997) from the Network of Italian Cancer Registries. *Eur J Cancer Prev* 2004; 13: 287–295.
21. Crocetti E, Capocaccia R, Casella C, et al. Cancer trends in Italy: figures from the cancer registries (1986–1997). *Epidemiol Prev* 2004; 28 (2 suppl): 1–6.
22. Zorzi M, Fedato C, Grazzini G, Sassoli De' Bianchi P, et al. Screening for colorectal cancer in Italy, 2010 survey. *Epidemiol Prev* 2012; 36 (6 suppl 1): 55–77.
23. Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute. *La sorveglianza PASSI: Attività fisica*. http://www.epicentro.iss.it/passi/dati/attivita.asp (accessed 18 October 2018).
24. Joinpoint Regression Program software, Version 4.6. https://surveillance.cancer.gov/joinpoint/download (accessed 12 March 2019).
25. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974–2013. *J Natl Cancer Inst* 2017; 109 (8).
26. Ferlay J, Colombet M and Bray F. *Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9* [Internet]. Lyon, France: International Agency for Research on Cancer; 2018. http://ci5.iarc.fr (accessed 18 October 2018).
27. Feletto E, Yu XQ, Lew JB, et al. Trends in colon and rectal cancer incidence in Australia from 1982 to 2014: analysis of data on over 375,000 cases. *Cancer Epidemiol Biomarkers Prev* 2019; 28: 83–90.
28. Siegel RL, Miller KD and Jemal A. colorectal cancer mortality rates in adults aged 20 to 54 years in the United States, 1970–2014. *JAMA* 2017; 318: 572–574.
29. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin* 2018; 68: 250–281.
30. Zorzi M, Fedeli U, Schievano E, et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. *Gut* 2015; 64: 784–790.
31. Alberti-Fidanza A and Fidanza F. Mediterranean Adequacy Index of Italian diets. *Public Health Nutr* 2004; 7: 937–941.
32. Cialfa E and Saba A. Aspetti territoriali dei consumi alimentari. In: *Atti Preliminari del 5° Convegno Nazionale Sugli Studi di Mortalità*; Firenze; 24–26 October, 1990; 149–157.
33. Gargiulo L, Bologna E and Iannucci L. Epidemiologia dell'obesità in Italia e alcuni aspetti della qualità della vita. In: *AAVV 8° Rapporto sull'Obesità in Italia. Il Pensiero Scientifico Editore*; 2017.
34. Hales CM, Carroll MD, Fryar CD, et al. *Prevalence of obesity among adults and youth: United States, 2015–2016:* NCHS data brief, no. 288. Hyattsville, MD: National Center for Health Statistics; 2017.
35. Secretan B, Straif K, Baan R, et al. WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens: part E: tobacco,

areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009; 10: 1033–1034.
36. Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute. *La sorveglianza PASSI: l'abitudine al fumo*. http://www.epicentro.iss.it/passi/dati/fumo.asp (accessed 18 October 2018).
37. Sardu C, Mereu A, Pitzalis G, et al. Smoking trends in Italy from 1950 to 2000. *J Epidemiol Community Health* 2006; 60: 799–803.
38. Njor S, Nyström L, Moss S, et al. Breast cancer mortality in mammographic screening in Europe: a review of incidence-based mortality studies. *J Med Screen* 2012; 19 (suppl 1): 33–41.
39. Zorzi M, Mangone L, Sassatelli R, et al. Incidence trends of colorectal cancer in the early 2000s in Italy: figures from the IMPACT study on colorectal cancer screening. *Epidemiol Prev* 2015; 39 (suppl 1): 115–125.
40. Zorzi M, Mangone L, Anghinoni E, et al. Characteristics of the colorectal cancers diagnosed in the early 2000s in Italy: figures from the IMPACT study on colorectal cancer screening. *Epidemiol Prev* 2015; 39 (suppl 1): 108–114.
41. Senore C, Hassan C, Regge D, et al. Cost-effectiveness of colorectal cancer screening programmes using sigmoidoscopy and immunochemical faecal occult blood test. *J Med Screen* 2018; Sep 4.
42. Sharp L, Tilson L, Whyte S, et al. Cost-effectiveness of population-based screening for colorectal cancer: a comparison of guaiac-based faecal occult blood testing, faecal immunochemical testing and flexible sigmoidoscopy. *Br J Cancer* 2012; 106: 805–816.
43. Heitman SJ, Hilsden RJ, Au F and et L. Colorectal cancer screening for average-risk North Americans: an economic evaluation. *PLoS Med* 2010; 7: e1000370.