# Epidemiologia e prevenzione del carcinoma del colon-retto

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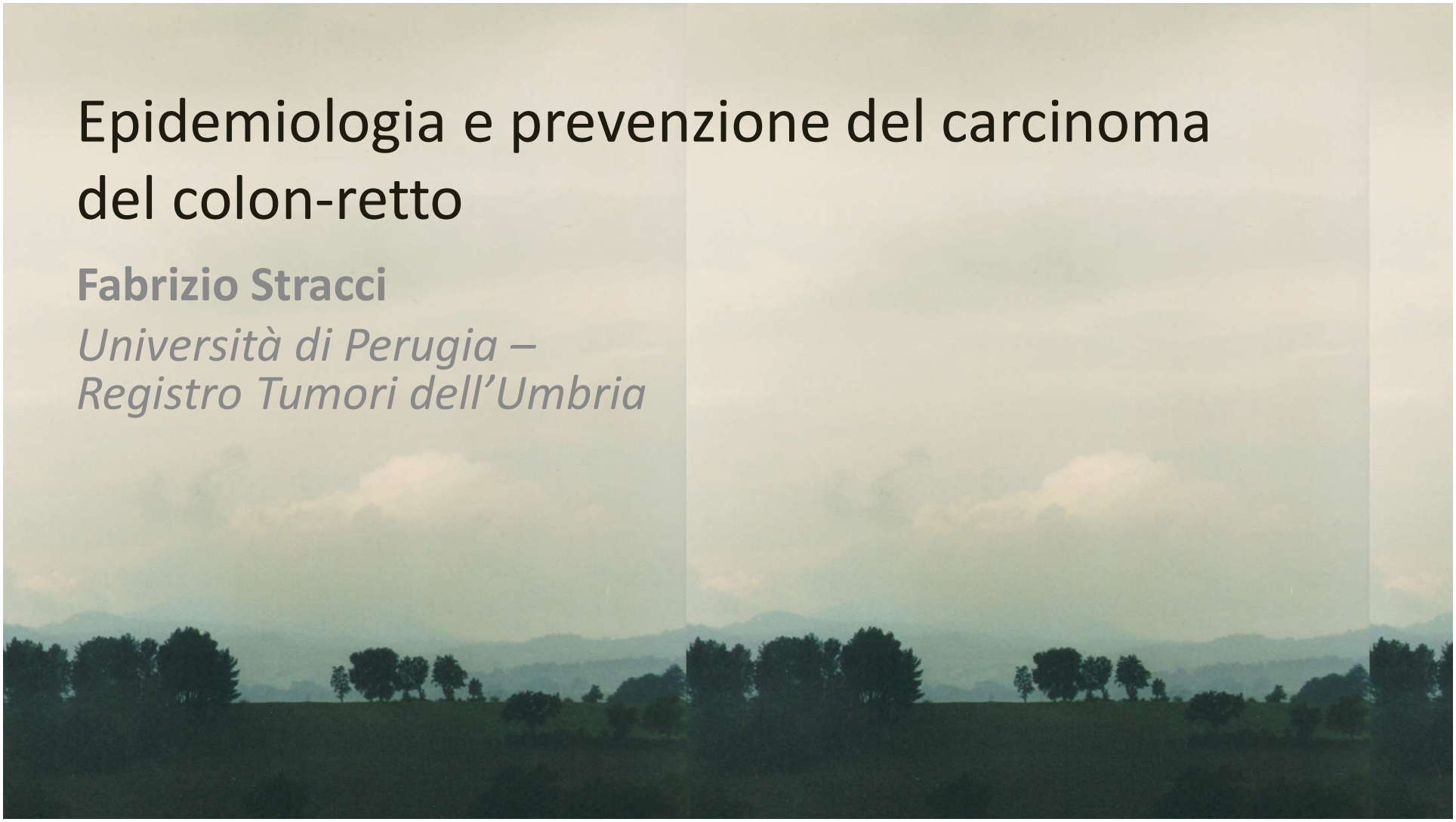
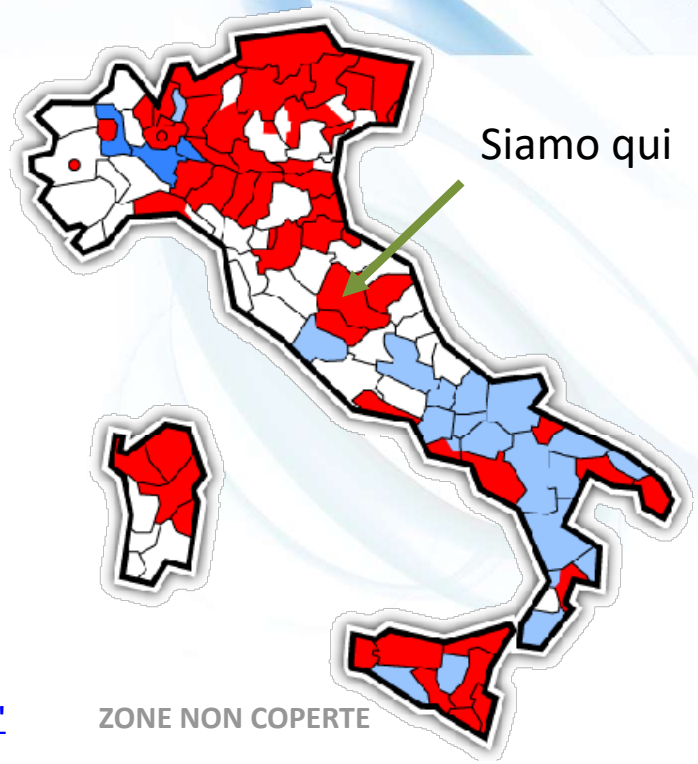


# Elementi chiave

- Rilevanza: il cancro del grosso intestino è una delle maggiori cause oncologiche di malattia e di morte in Italia
- Controllo: lo screening ha un ruolo centrale nel controllo del cancro del colon-retto

- Utilizziamo delle stime per descrivere l'incidenza del cancro del colon-retto (CCR) in Italia
- …MIAMOD method …based on a back-calculation approach to estimate and project the morbidity … from mortality and patient survival…

*Rossi S et al. Estimates of cancer burden in Italy. Tumori 2013; 99:416-24*




| | RT ACCREDITATI | IN ACCREDITAMENTO | IN ATTIVITA' | ZONE NON COPERTE |
|---|---|---|---|---|
| **COPERTURA** | 51% | 2% | 18% | 29% |
| **POPOLAZIONE 2011** | 30.406.126 | 1.100.000 | 10.656.328 | 17.457.401 |

# Il CRC è, per frequenza, il 2° tumore nei maschi

**Table 2A - Estimated incidence, mortality and prevalence by cancer site for the year 2012 in Italy. Number of cases and deaths, crude and European age-standardized (age-std) rates per 100,000 person-years and crude prevalence proportion per 100,000 persons. Age 0-99 years, men.**

| | Incidence | | | Mortality | | | Prevalence | |
|---|---|---|---|---|---|---|---|---|
| Cancer site | Number of cases | Crude rate | Age-std rate | Number of deaths | Crude rate | Age-std rate | Number of cases | Crude proportion |
| Prostate | 42,604 | 145.6 | 89.7 | 8,030 | 27.4 | 14.7 | 322,614 | 1,102.7 |
| Stomach | 7,879 | 28.8 | 18.2 | 5,272 | 19.3 | 11.8 | 37,981 | 138.9 |
| Colon-rectum | 31,102 | 113.8 | 70.1 | 11,035 | 40.4 | 23.9 | 191,704 | 701.2 |
| Lung | 26,334 | 96.2 | 60.7 | 21,984 | 80.3 | 49.5 | 63,499 | 232.0 |
| Melanoma | 6,595 | 24.1 | 18.7 | 807 | 3.0 | 2.1 | 59,324 | 217.0 |

Colon-rectum 31,102 113.8 70.1

# Il CRC è, per frequenza, il 2° tumore nelle femmine

**Table 2B - Estimated incidence, mortality and prevalence by cancer site for the year 2012 in Italy. Number of cases and deaths, crude and European age-standardized (age-std) rates per 100,000 person-years and crude prevalence proportion per 100,000 persons. Age 0-99 years, women.**

| | Incidence | | | Mortality | | | Prevalence | |
|---|---|---|---|---|---|---|---|---|
| Cancer site | Number of cases | Crude rate | Age-std rate | Number of deaths | Crude rate | Age-std rate | Number of cases | Crude proportion |
| Breast | 50,396 | 174.0 | 115.1 | 10,238 | 35.3 | 18.5 | 609,001 | 2,102.3 |
| Stomach | 5,681 | 19.6 | 9.3 | 3,884 | 13.4 | 6.1 | 28,158 | 97.2 |
| Colon-rectum | 23,633 | 81.6 | 38.4 | 8,582 | 29.6 | 12.9 | 168,362 | 581.2 |
| Lung | 10,221 | 35.3 | 19.0 | 7,780 | 26.9 | 13.8 | 25,504 | 88.1 |
| Melanoma | 5,746 | 19.8 | 16.0 | 581 | 2.0 | 1.2 | 72,784 | 251.4 |
| Cervix | 1,515 | 5.3 | 4.0 | 697 | 2.4 | 1.5 | 16,819* | 58.9* |

*Limited-duration prevalence at 15 years.

Colon-rectum 23,633 81.6 38.4

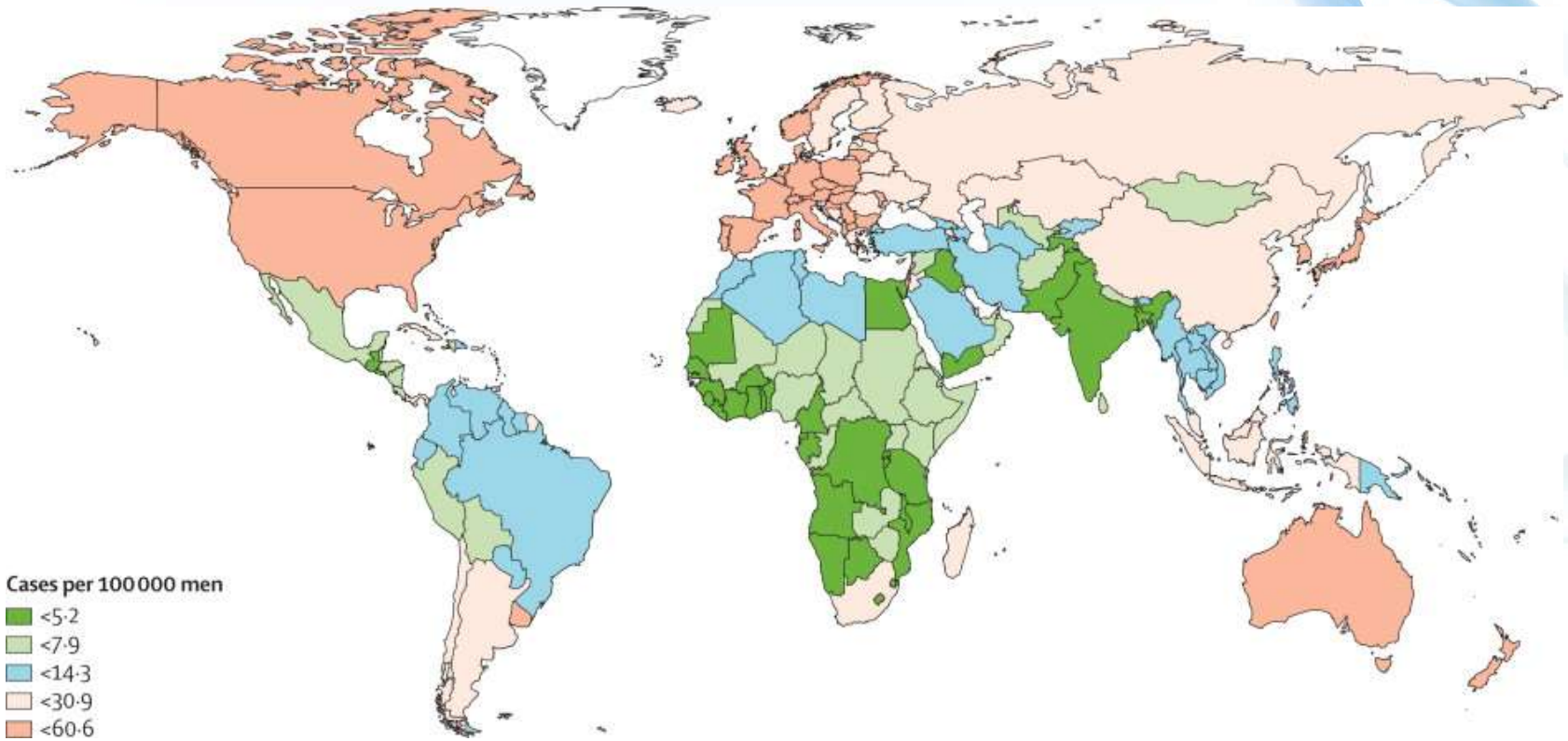
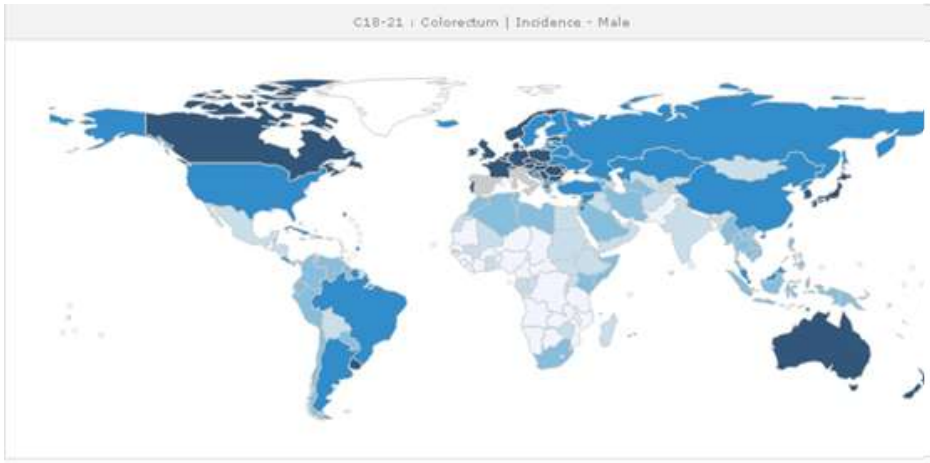
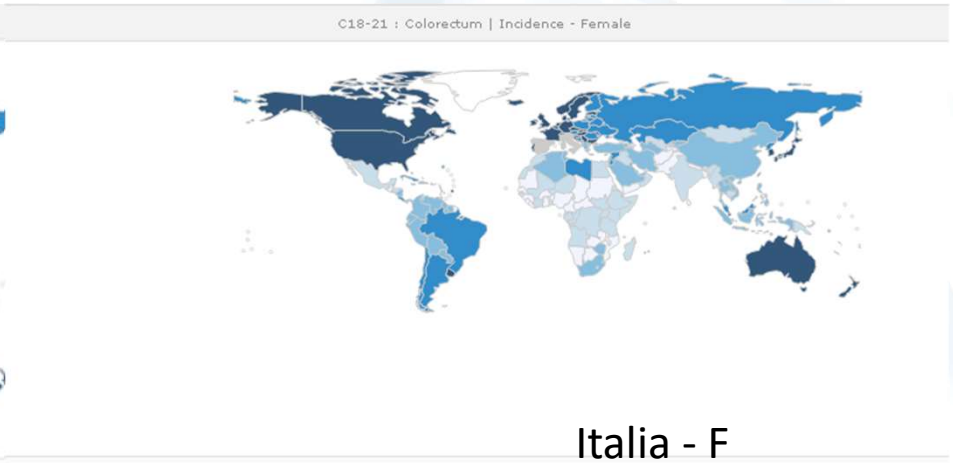



Figure 1. Estimated age-standardised colorectal cancer incidence for men in 2008
Data from Globocan 2008. *in Brenner H. Colorectal cancer. Lancet. 2014; 383:1490-502.*

http://globocan.iarc.fr/ia/World/atlas.html

# Cancro del grosso intestino – Incidenza GLOBOCAN 2012



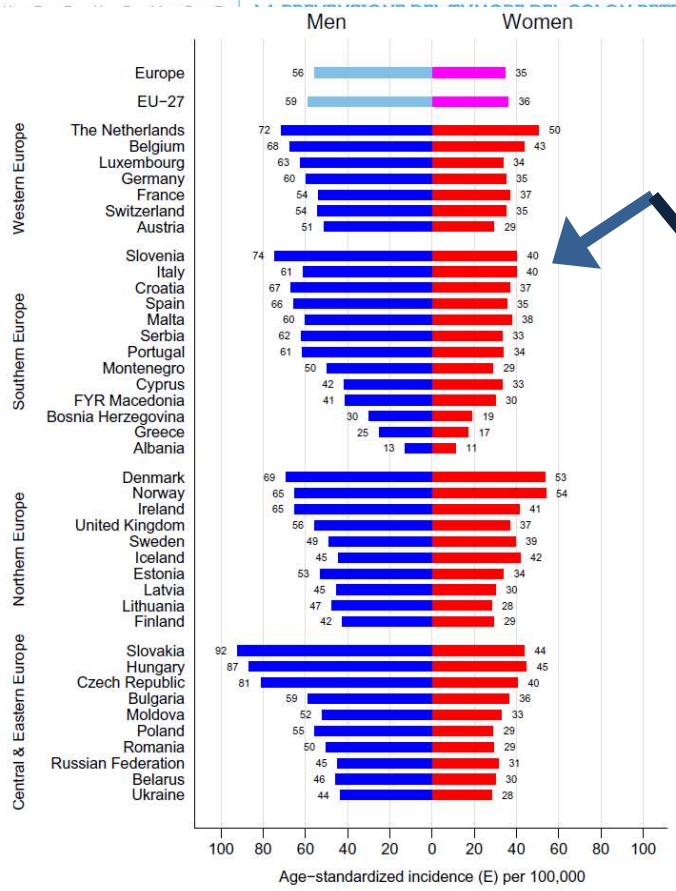




Italia - F

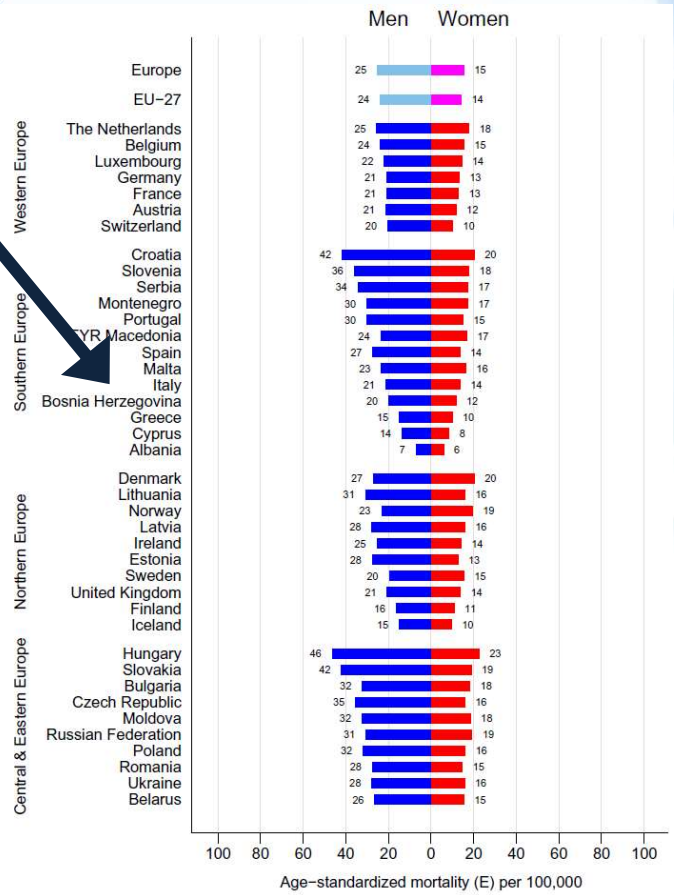
Italia - M

Spagna - M

Spagna - F

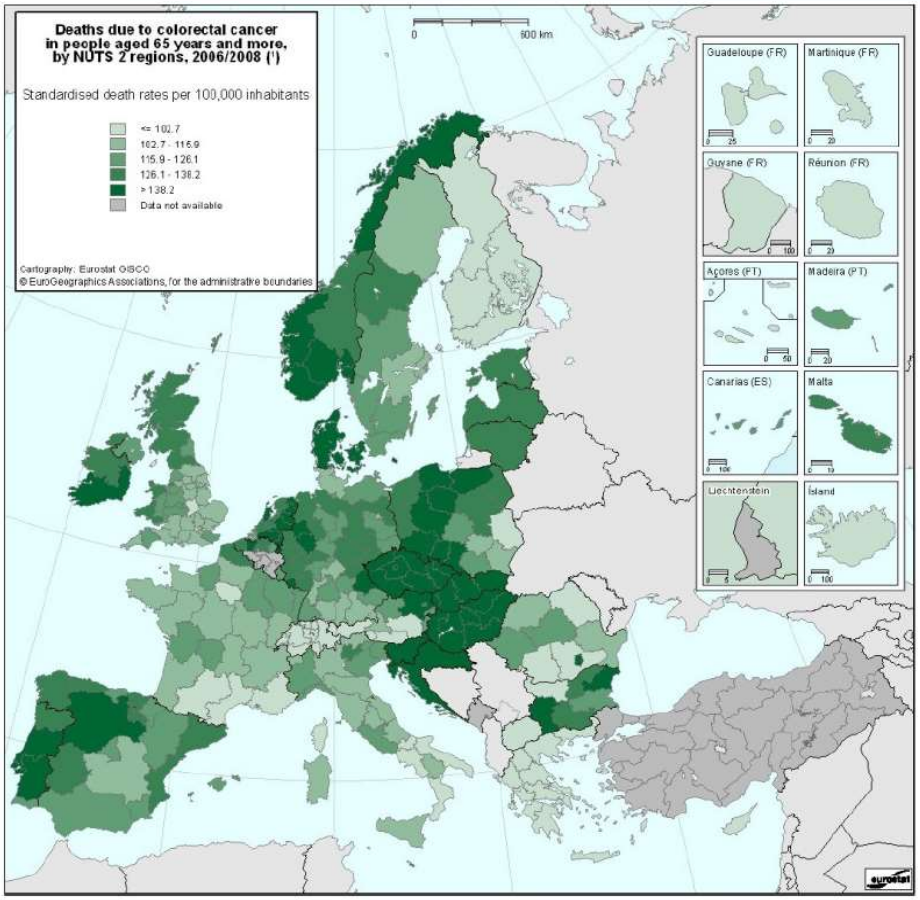



CRC **incidence** in European countries




CRC **mortality** in European countries

*Ferlay J et al.* Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. *Eur J Cancer. 2013; 49:1374-403*




(1) MT, UK, CH 2005/2007; BE 2000/2002; Scotland, NUTS1 level; DK, SI, HR national level.

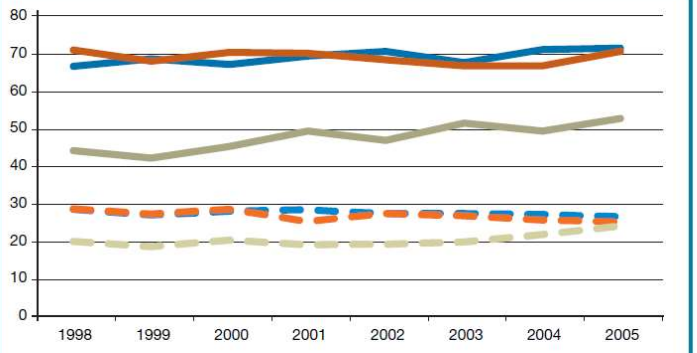
- Elevati tassi di mortalità in Europa orientale
- In Italia attenuato gradiente nord-sud

2011 Eurostat

# Incidenza e mortalità per area geografica

**Standardized incidence and mortality rates by area x 100,000**

**MALE COLORECTAL CANCER**

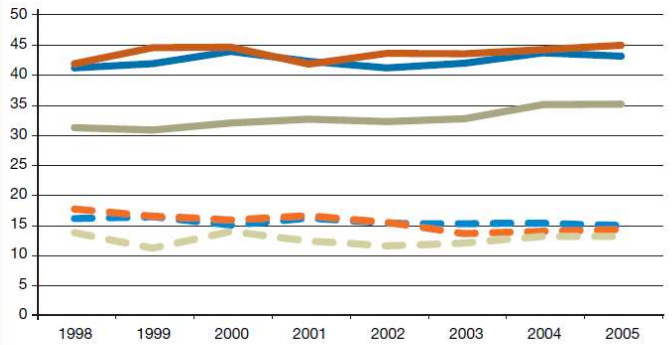



| AREA | INCIDENCE | | |
|---|---|---|---|
| North | 1998-2005 APC (95% CI) | +0.8* | (+0.1 ; +1.6) |
| Centre | 1998-2005 APC (95% CI) | -0.4 | (-1.3 ; +0.6) |
| South | 1998-2005 APC (95% CI) | +2.9* | (+1.4 ; +4.5) |

| AREA | MORTALITY | | |
|---|---|---|---|
| North | 1998-2005 APC (95% CI) | -0.7 | (-1.5 ; +0.1) |
| Centre | 1998-2005 APC (95% CI) | -1.6* | (-3.0 ; -0.2) |
| South | 1998-2003 APC (95% CI) | +0.1 | (-4.1 ; +4.5) |
| | 2003-2005 APC (95% CI) | +11.5 | (-6.0 ; +32.3) |

**Standardized incidence and mortality rates by area x 100,000**

**FEMALE COLORECTAL CANCER**




| AREA | INCIDENCE | | |
|---|---|---|---|
| North | 1998-2005 APC (95% CI) | +0.5 | (-0.5 ; +1.4) |
| Centre | 1998-2005 APC (95% CI) | +0.5 | (-0.5 ; +1.5) |
| South | 1998-2005 APC (95% CI) | +1.9* | (+1.1 ; +2.7) |

| AREA | MORTALITY | | |
|---|---|---|---|
| North | 1998-2005 APC (95% CI) | -1.1* | (-2.2 ; -0.0) |
| Centre | 1998-2005 APC (95% CI) | -3.3* | (-5.0 ; -1.7) |
| South | 1998-2005 APC (95% CI) | -0.1 | (-3.4 ; +3.3) |

AIRTUM Working Group: Italian cancer figures, report 2009: Cancer trend (1998-2005). Epidemiol Prev, 33 (4-5 Suppl 1): 1-168, 2009

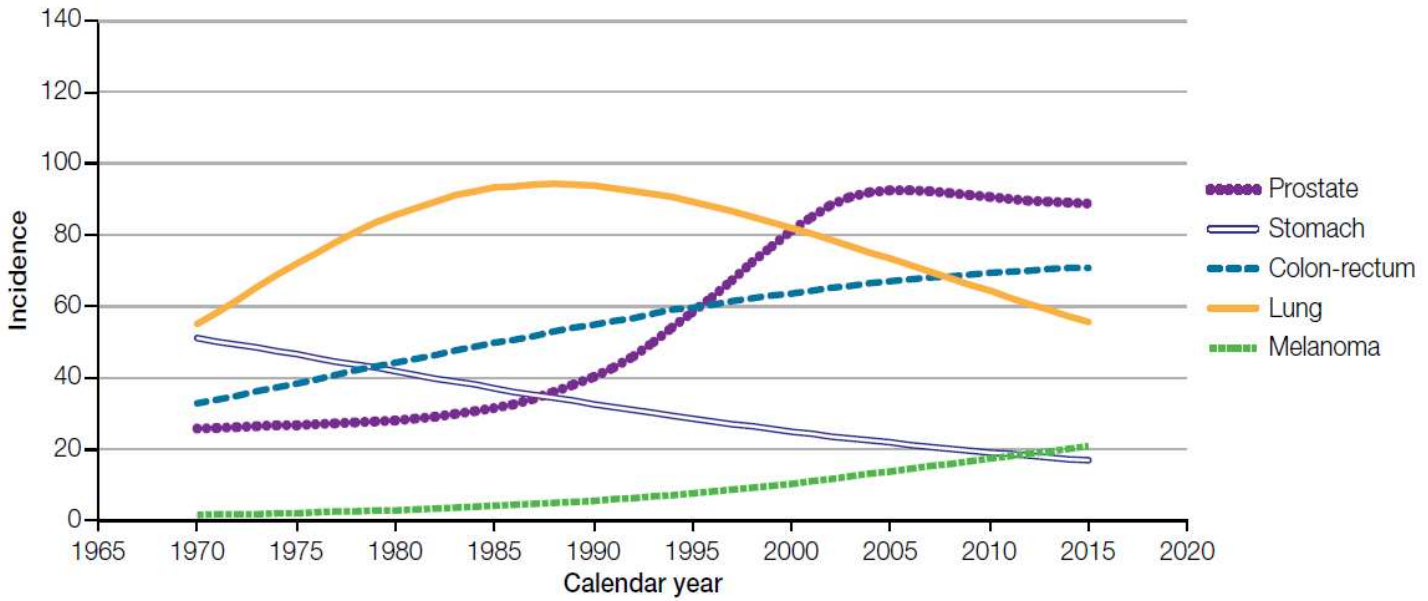



Figura 1 - Incidence estimates by cancer site in Italy in the period 1970-2015. Age-standardized rates (European population) per 100,000 person-years. Age 0-99 years, men.

The age-standardized incidence rates of colorectal cancer were estimated to **increase in males** during the whole period up to a projected value of **71 per 100,000 person-years in 2015**, even if the slope tended to flatten in the most recent years.

Rossi S et al. Estimates of cancer burden in Italy. Tumori 2013; 99:416-24

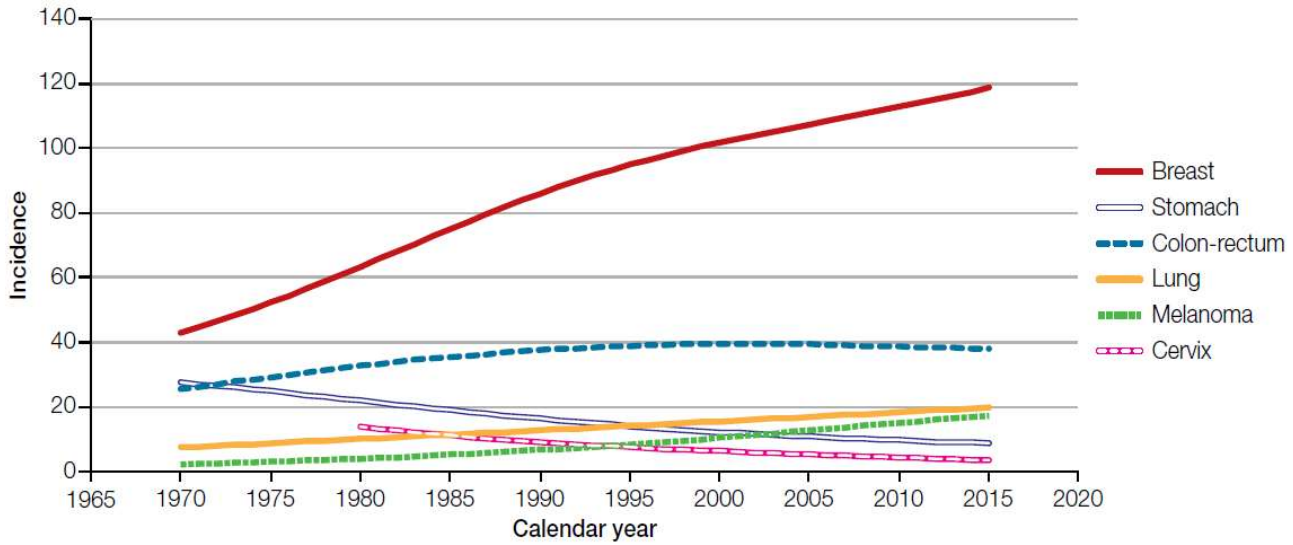



Figura 2 - Incidence estimates by cancer site in Italy in the period 1970-2015. Age-standardized rates (European population) per 100,000 person-years. Age 0-99 years, women.

In women the trend was similar but it preceded the male trend by several years. The rates in women were always lower than in men, and **were first increasing and then slightly decreasing from 40 to 38 per 100,000/year** during the period 2004-2015.

| | Risk |
|---|---|
| **Sociodemographic factors** | |
| Older age | ↑↑↑ |
| Male sex | ↑↑ |
| **Medical factors** | |
| Family history | ↑↑ |
| Inflammatory bowel disease | ↑↑ |
| Diabetes | ↑ |
| *Helicobacter pylori* infection | (↑) |
| Other infections | (↑) |
| Large bowel endoscopy | ↓↓ |
| Hormone replacement therapy | ↓ |
| Aspirin | ↓ |
| Statins | (↓) |
| **Lifestyle factors** | |
| Smoking | ↑ |
| Excessive alcohol consumption | ↑ |
| Obesity | ↑ |
| Physical activity | ↓ |
| **Diet factors** | |
| High consumption of red and processed meat | ↑ |
| Fruit and vegetables | (↓) |
| Cereal fibre and whole grain | (↓) |
| Fish | (↓) |
| Dairy products | (↓) |

# Difficile controllo mediante la prevenzione primaria

- …the other risk factors, which are more common and are **in principle modifiable**, account for a larger proportion of the disease burden at the population-level, despite lower relative risks (**mostly between 1·2 and 2·0**)
- …rapid **increases in previously low-risk countries**, such as Spain and several countries in eastern Europe and east Asia, have been noted, which have been ascribed to **changes in dietary patterns and risk factors towards a so-called western lifestyle**

*Brenner H. Colorectal cancer. Lancet. 2014; 383:1490-502.*

# Trend sfavorevoli in assenza di screening

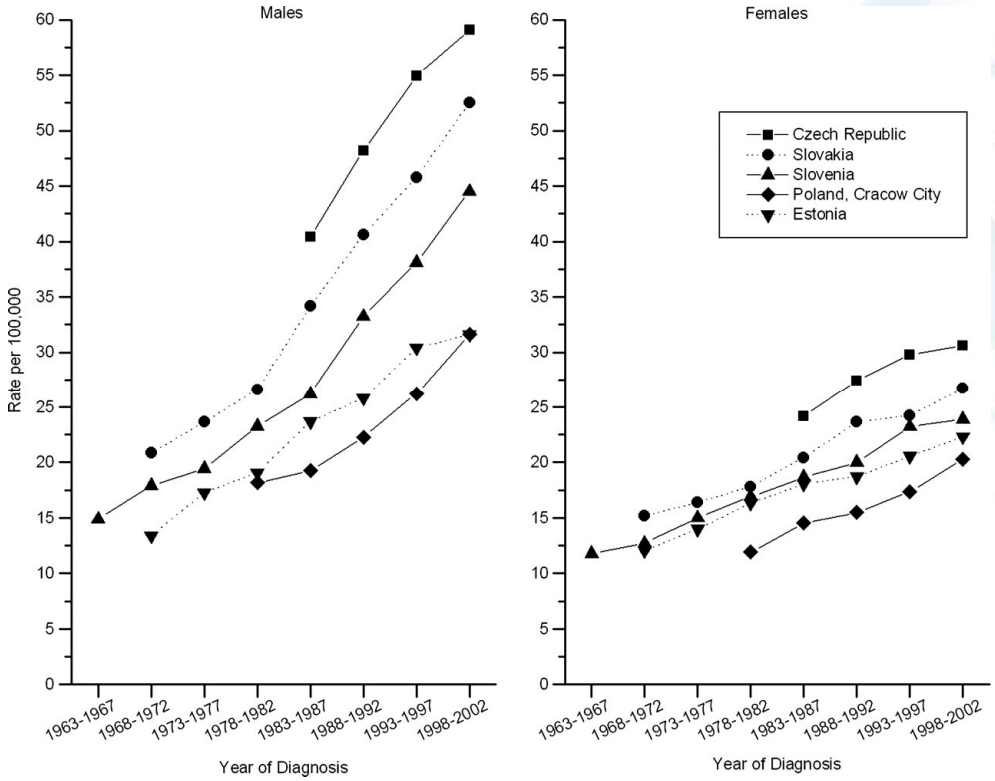
- **Colorectal cancer incidence rates continue to increase in economically transitioning countries**, with incidence rates among men in the Czech Republic and Slovakia exceeding the peak incidence observed in the United States…

**Center M M et al. Cancer Epidemiol Biomarkers Prev 2009;18:1688-1694**

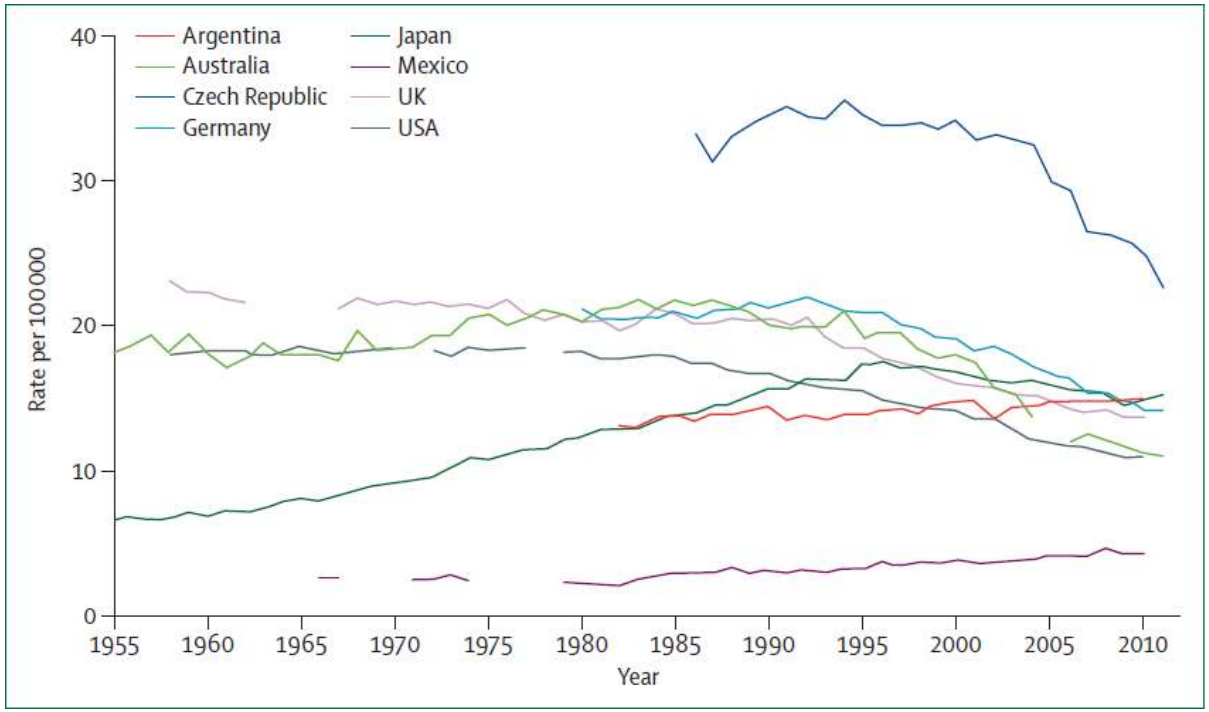
- **Cancer mortality** from some common cancers (including colorectum and lung) is still comparatively low in Latin America, and decreasing trends continue for other cancer sites …However, there were **upward trends for colorectal cancer mortality for both sexes**

**Chatenoud L et al. Trends in mortality from major cancers in the Americas. Ann Oncol. 2014**

# Trends in colorectal cancer incidence rates in select countries of Eastern Europe by sex (Cancer Incidence in Five Continents, 1963-2002).




Center M M et al. Cancer Epidemiol Biomarkers Prev 2009;18:1688-1694

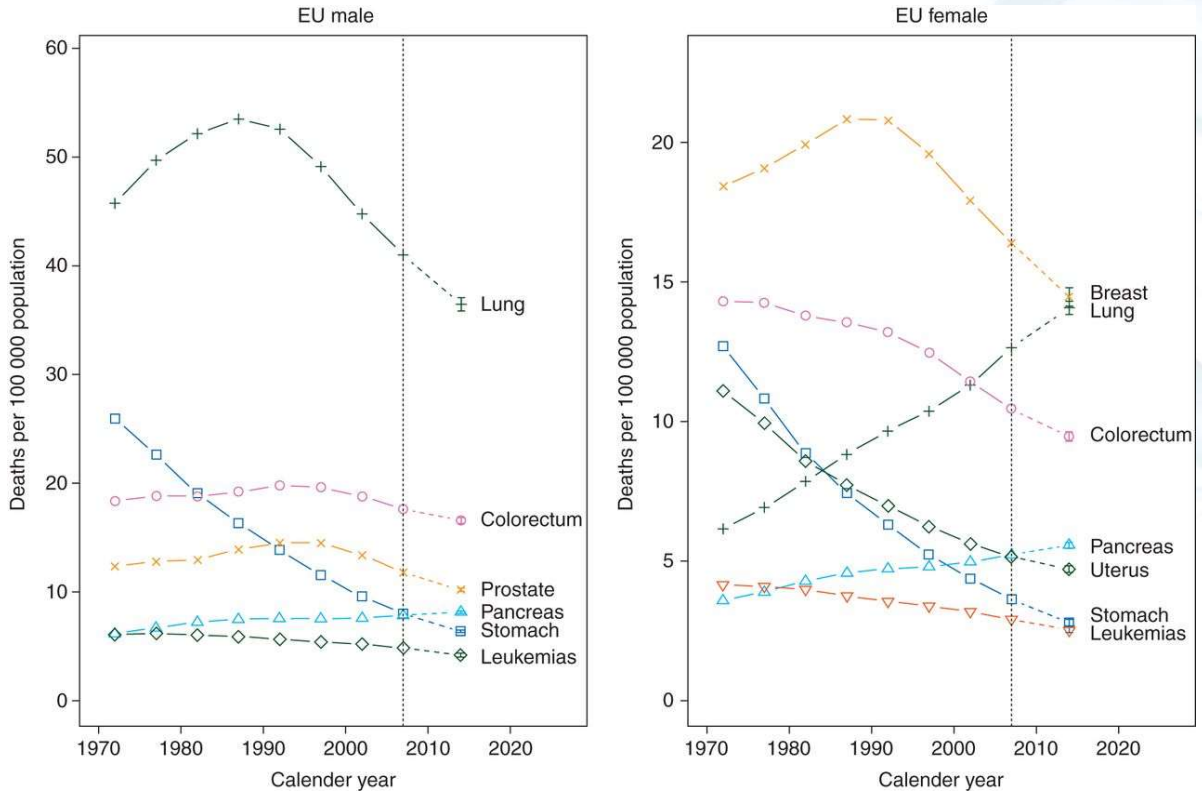



In several high-income countries and countries of east Asia and eastern Europe, **mortality has been decreasing** since the 1980s, probably because of **improved early detection and treatment**

*Brenner H. Colorectal cancer. Lancet. 2014; 383:1490-502.*

***Figure 2: Trends in age-standardised colorectal cancer mortality for men in selected countries, 1955–2010*** Data from WHO mortality database

## Age-standardized (world population) EU male and female cancer mortality in quinquennia from 1970–1974 to 2005–2009 and predicted rates for 2014.




**Malvezzi M et al. Ann Oncol 2014;25:1650-1656**

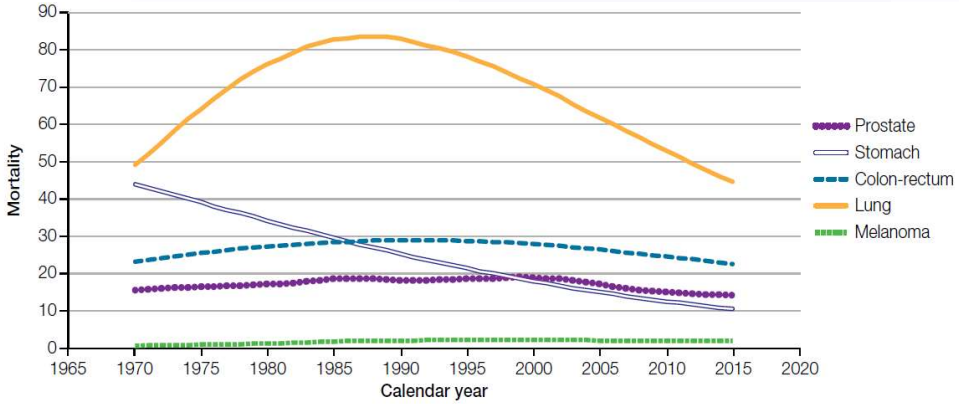



Figura 3 - Mortality estimates by cancer site in Italy in the period 1970-2015. Age-standardized rates (European population) per 100,000 person-years. Age 0-99 years, men.

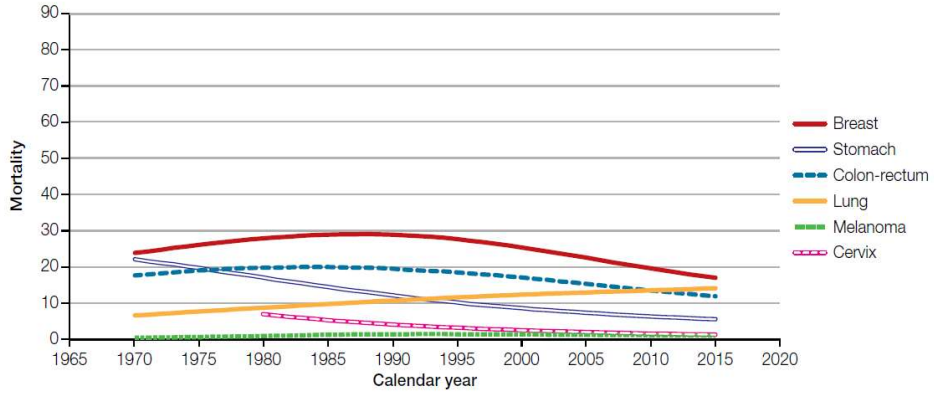
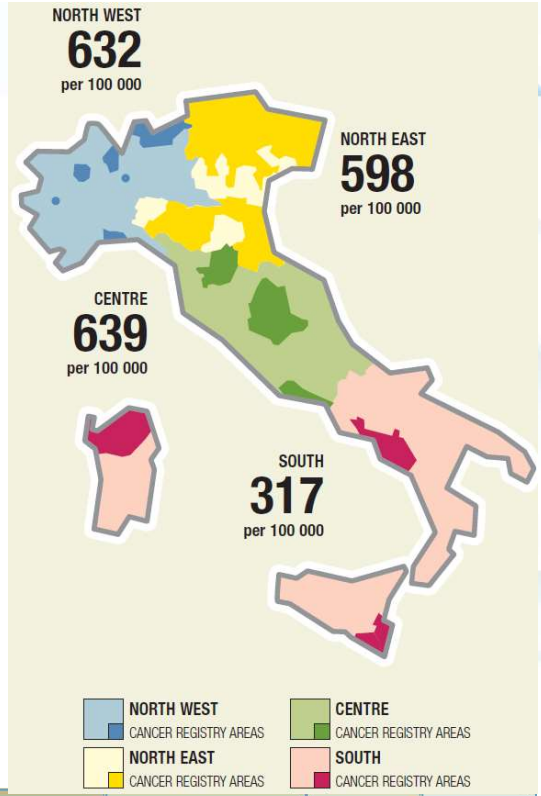



Figura 4 - Mortality estimates by cancer site in Italy in the period 1970-2015. Age-standardized rates (European population) per 100,000 person-years. Age 0-99 years, women.

Rossi S et al. Estimates of cancer burden in Italy. Tumori 2013; 99:416-24 [Mortality]

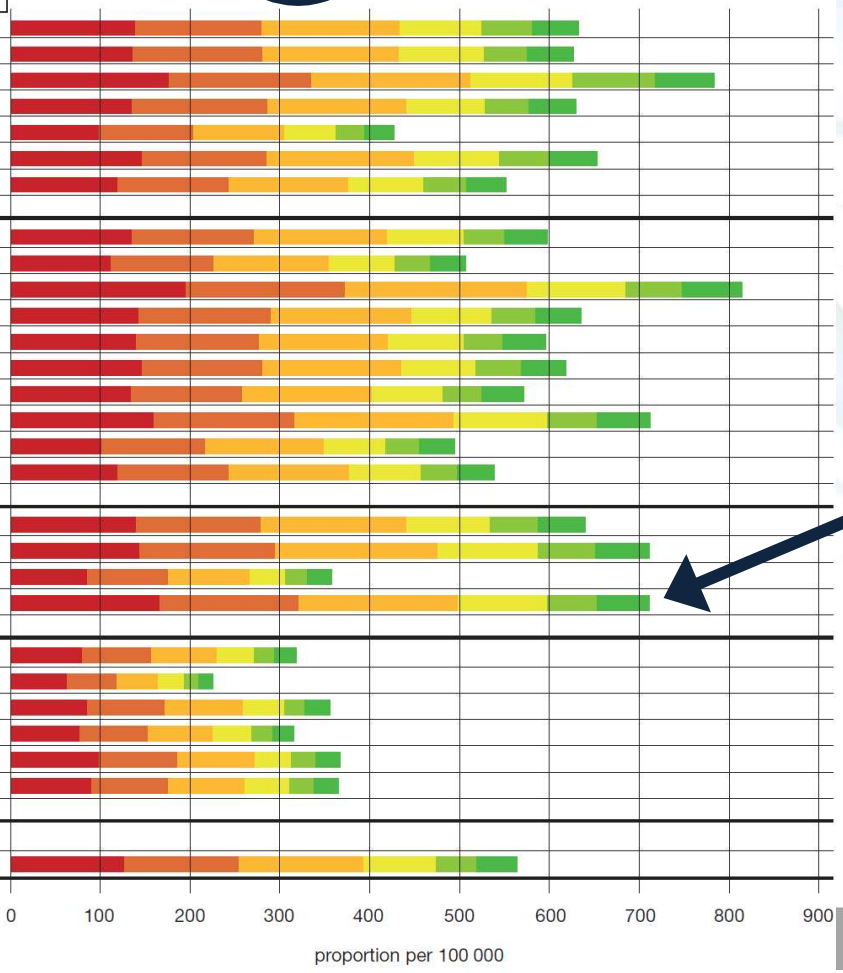
# Prevalenza di malattia in Italia


| 23% | 23% | 24% | 14% | 8% | 8% |
|---|---|---|---|---|---|
| **68 041** | **67 620** | **71 971** | **42 251** | **23 228** | **23 577** |
| ≤ 2 years | 2-5 years | 5-10 years | 10-15 years | 15-20 years | > 20 years |

| Number of total prevalent subjects | | | Macro-area Cancer Registry (CR) |
|---|---|---|---|
| M | F | M&F | |
| | | | **North West** |
| 583 | 590 | 1 173 | Biella |
| 2 349 | 2 453 | 4 802 | Genova |
| 3 964 | 4 241 | 8 205 | Milano |
| 359 | 406 | 765 | Sondrio |
| 2 892 | 2 981 | 5 873 | Torino |
| 2 362 | 2 286 | 4 648 | Varese |
| | | | **North East** |
| 1 233 | 1 197 | 2 430 | Alto Adige |
| 1 455 | 1 413 | 2 868 | Ferrara |
| 4 003 | 3 699 | 7 702 | Friuli V.G. |
| 2 064 | 1 898 | 3 962 | Modena |
| 1 349 | 1 235 | 2 584 | Parma |
| 1 473 | 1 370 | 2 843 | Reggio Emilia |
| 2 649 | 2 641 | 5 290 | Romagna |
| 1 250 | 1 174 | 2 424 | Trento |
| 5 040 | 4 602 | 9 642 | Veneto |
| | | | **Centre** |
| 4 382 | 4 080 | 8 462 | Firenze Prato |
| 1 006 | 866 | 1 872 | Latina |
| 3 189 | 2 981 | 6 170 | Umbria |
| | | | **South** |
| 624 | 630 | 1 254 | Napoli |
| 559 | 534 | 1 093 | Ragusa |
| 1 766 | 1 671 | 3 437 | Salerno |
| 939 | 775 | 1 714 | Sassari |
| 752 | 701 | 1 453 | Siracusa |
| 46 242 | 44 424 | 90 666 | **Pool** |
| **Italy** (estimates) | | | |
| 151 660 | 145 027 | 296 687 | |

**Complete prevalence by years since diagnosis, CRs and macro-area, M&F 01.01.2006 (proportion per 100 000)**



# Cosa è screening

- Una modalità di diagnosi precoce caratterizzata dalla applicazione di test diagnostici da parte di personale sanitario a soggetti asintomatici
- Gli screening oncologici possono essere classificati in:
- **Programmato**
- Opportunistico
- Misto
- Effetto collaterale

# Lo screening di popolazione

**Table 6.1 . Defining criteria for organized screenings according to Hakama and colleagues**

a. The target population has been identified; +

b. individual people are identifiable; +

c. mechanisms are implemented to guarantee high coverage and attendance (e.g., a personal letter of invitation);+

d. there are adequate field facilities for performing the screening tests; +

e. there is a defined quality control program concerning how the tests are performed and interpreted; +

f. adequate facilities exist for diagnosis and for the appropriate treatment of confirmed abnormalities; +

g. there is a carefully designed and agreed upon referral system, an agreed link between the participant, the screening center, and the clinical facility for diagnosis of an abnormal screening test, for management of any abnormalities found, and for providing information about normal screening tests; and

h. **evaluation and monitoring of the total program is organized in terms of incidence and mortality rates among those attending, among those not attending, at the level of the total target population. Quality control of the epidemiologic data should be established**.

*Hakama M, Chamberlain J, Day NE, Miller AB, Prorok PC (1985). Evaluation of screening programmes for gynaecological cancer. Br J Cancer* ***52,669 – 673.***

# Lesioni identificate e conseguenze

- Carcinomi infiltranti in fase precoce (mammella, colon retto, melanoma)
- Carcinomi in situ – lesioni premaligne (cervice uterina, colon retto, melanoma, mammella)

- Effetto della individuazione di carcinomi in fase precoce è l'aumento della sopravvivenza
- Effetto della individuazione di lesioni premaligne evolutive è la riduzione della incidenza

# Test ed evoluzione

Variazione minore

- FOBT
- FIT

Variazione maggiore

- FIT
- Colonscopia

# Variazioni minori ed evidenze

- as new versions of the tests emerge, performance should be evaluated to determine test positivity, sensitivity and specificity, and adherence

# Screening per il cancro del colon retto

- Average-risk individuals account for 70%–75% of patients with CRC.
- Screening of average-risk populations provides opportunities for early cancer detection and prevention by detection and removal of cancer precursors

# Due gruppi di test

ACS-MSTF-ACR guideline distinguished 2 categories of screening tests:

- **stool-based tests**, which primarily detect early cancer, and
- **structural colon tests**, which detect early cancer and cancer precursor lesions.

# Due strategie

- Europa: gFOBT – iFOBT molto più diffusi
- US: Colonscopia test maggiormente utilizzato

- Europa: screening programmato in età 50-69(74) anni di solito basato su un solo test
- US screening opportunistico basato sulla preferenza tra i test disponibili

# Screening sesso ed età

- Women have a lower age-adjusted risk of CRC and large polyps (9 mm) compared with men. There is a lag time of about 7–8 years, such that a 50-year-old man has roughly the same risk of CRC as a 58-year-old woman. There is evidence that women have a relatively low risk of CRC until menopause

- Decision-modeling studies have concluded that after age 75, the benefit (extended life as a result of prevention of CRC or early detection) is reduced and that screening should not be offered routinely

**Table 1.** The CRC Screening Guidelines for the United States in 2008

| Screening test | ACS-MSTF-ACR[5] | USPSTF[6,7] | ACG[8] | Recommended interval |
|---|---|---|---|---|
| gFOBT | Yes, requires >50% sensitivity for CRC | Yes | Yes, high-sensitivity test only | Annually |
| FIT | Yes, requires >50% sensitivity for CRC | Yes | Yes, preferred as cancer detection test | Annually |
| Stool DNA | Yes, requires >50% sensitivity for CRC | No, insufficient evidence | Yes, every 3 y | Uncertain |
| Flexible sigmoidoscopy | Yes, requires insertion to 40 cm or splenic flexure | Yes, with FOBT every 3 y | Yes, every 5–10 y | 5 y |
| Barium enema | Yes, but only if other tests are not available | Not recommended | Not recommended | 5 y |
| CTC | Yes, with referral to colonoscopy if polyps ≥6 mm are seen | No, insufficient evidence | Yes | 5 y |
| Colonoscopy | Yes | Yes | Yes, preferred | 10 y |

ACG, American College of Gastroenterology.

**Table 2.** Types of CRC Screening Tests and Efficacy in Clinical Trials

| Screening test | Evidence | Mortality reduction | Incidence reduction | One-time sensitivity for CRC | One-time sensitivity for advanced adenoma |
|---|---|---|---|---|---|
| Stool-based tests | | | | | |
| gFOBT-standard[9,13–16] | RCTs | 15%–33% | 18% | 13%–50% | 11%–24% |
| gFOBT-SENSA[7,13] | Cross-sectional | — | — | 50%–75% | 20%–25% |
| FIT[7] | Cross-sectional | — | — | 60%–85% | 20%–50% |
| Stool DNA-old[14] | Cross-sectional | — | — | 51% | 18% |
| Stool DNA-new[15] | Cohort | — | — | 80%+ | 40% |
| Structural examinations of colon | | | | | |
| CTC[27–30] | Cross-sectional | — | — | >90% | 90% |
| Sigmoidoscopy[41–43] | Case-control RCT | 60% distal colon | — | >95% distal colon | 30%–70% |
| Colonoscopy[27–30,42–44,47–51] | Case-control cohort | 31% | 53%–72% | 95% | 88%–98% |

# gFOBT Hamza S et al. (2014) Long-term effect of faecal occult blood screening on incidence and mortality from colorectal cancer. Dig Liver Dis

- Two randomized studies in well-defined European populations [1] and [2] aged 45, or 50, to 74 years demonstrated a decrease in CRC mortality varying between 14% and 18% with biennial guaiac FOBT, followed by a colonoscopy if the test was positive, and a median follow-up of 8 to 10 years [1] and [2].
- A 16% reduction in CRC mortality was also reported in France in a population invited to screening matched with a non-screened population [3].
- A US randomized trial in Minnesota, conducted among volunteers, also indicated the efficacy of FOBT screening [4].

# Screening e incidenza

colonoscopy

- Observational cohort and case-control studies have estimated that colonoscopy results in a 53%–72% reduction in CRC incidence

g/iFOBT

- With the exception of the quantitative FIT, sensitivity for advanced neoplasia is less than 50% and in most studies ranges from 25% to 30%
- Current versions of the test do not detect precursor lesions with high levels of sensitivity and are likely to achieve only modest reductions in cancer incidence among screened individuals

# Sangue occulto e riduzione incidenza

- So far, only the MinnesotaTrial, which used a faecal occult blood test based on guaiac (gFOBT)[2], has shown a decrease in cancer incidence; however, the results were questioned due to the large proportion of people (around 40%)who underwent at least one colonoscopic examination as a consequence of a gFOBT-positive result

Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, Church TR. **Long-term mortality after screening for colorectal cancer**. N Engl J Med. 2013;369:1106-14.

- Minnesota gFOBT 30 year follow-up
- Screening reduced colorectal-cancer mortality (relative risk with annual screening, 0.68; 95% confidence interval [CI], 0.56 to 0.82; relative risk with biennial screening, 0.78; 95% CI, 0.65 to 0.93) through 30 years of follow-up.
- The reduction in colorectal-cancer mortality was larger for men than for women in the biennial-screening group (P=0.04 for interaction).
- **Conclusions. …**The sustained reduction in colorectal-cancer mortality supports the effect of polypectomy.

# FIT >gFOBT

- Fecal immunochemical test is increasingly considered a better test than gFOBT because of better accuracy, compliance, and cost- effectiveness.
- Moreover, FIT showed better sensitivity than gFOBT for advanced neoplasia and this feature should also result in a larger decrease of CRC incidence
- By 2010, the evidence of FIT superiority over the standard gFOBT was clear and sufficiently convincing for the European guidelines for quality assurance in CRC screening and diagnosis to recommend adoption of FIT in preference to gFOBT

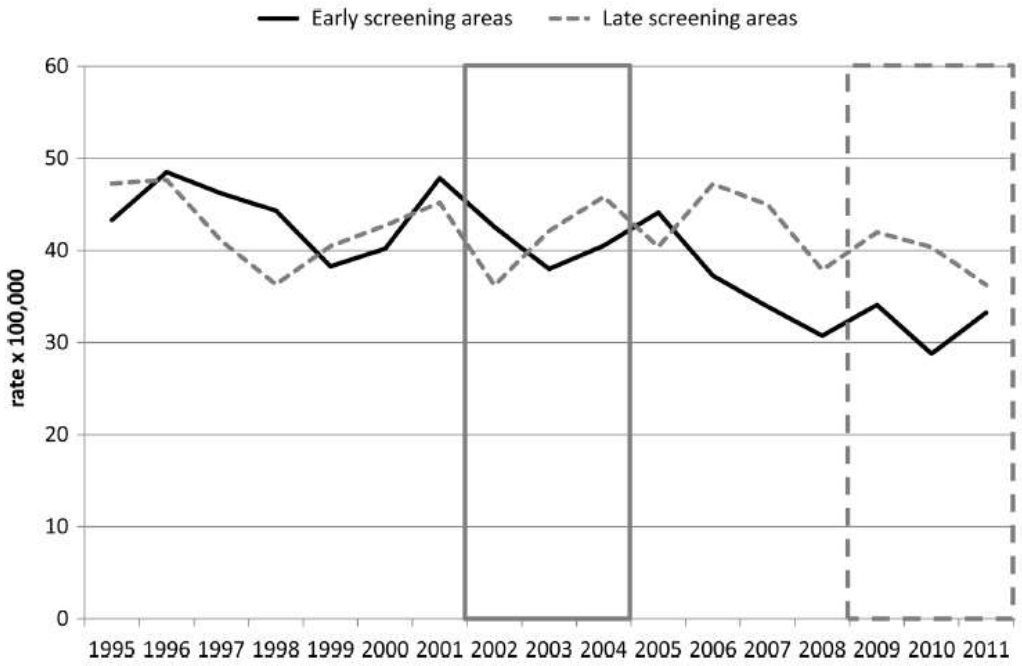



**Figure 3** Age-standardised (European standard population) colorectal cancer mortality rates, by year and period of activation of the screening programme; 50–74-year-old subjects, 1995–2011. Grey and dotted boxes: period of activation of colorectal screening programme in early and late screening areas, respectively.

# Mortalità in riduzione in seguito alla introduzione dello screening (FIT) Zorzi M, et al. Gut 2014;0:1–7

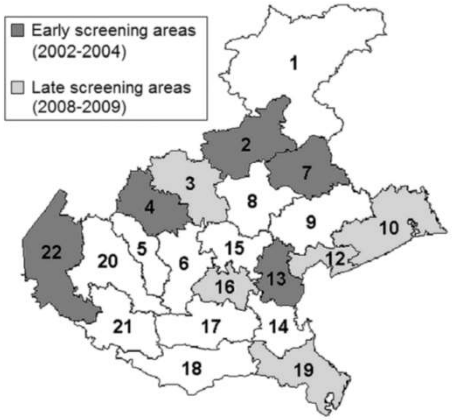
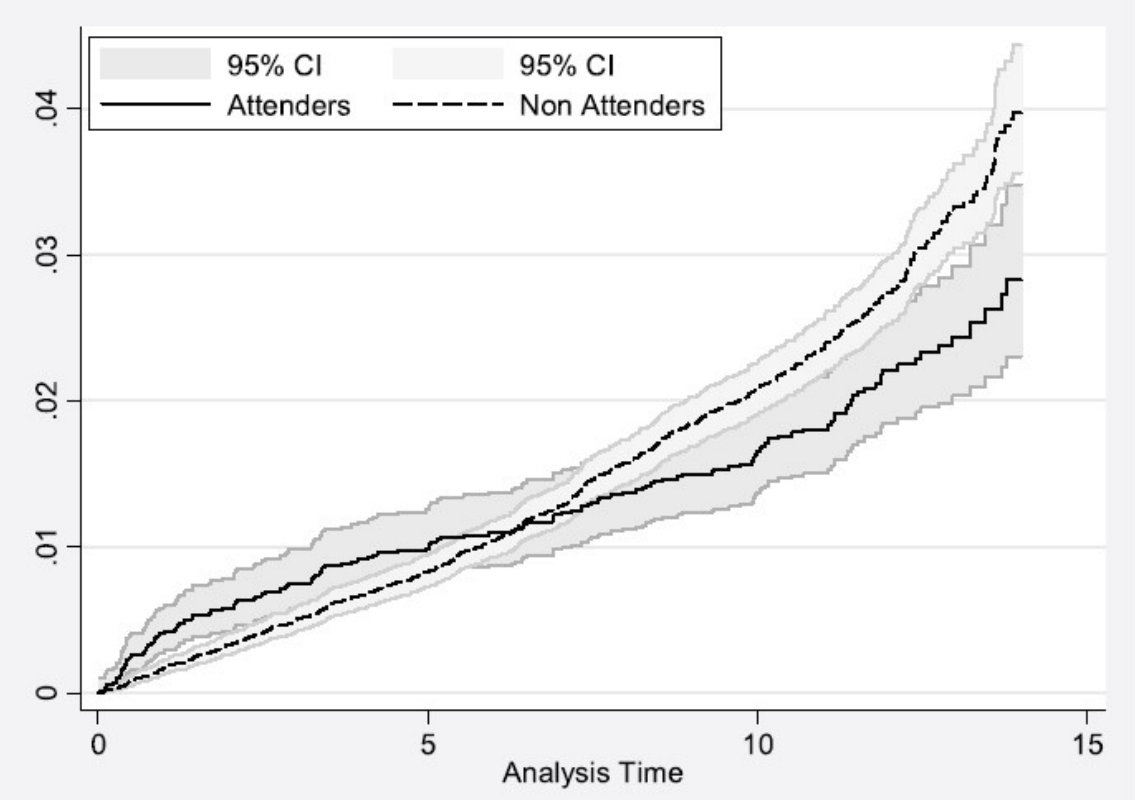



**Figure 1** Map of local health units of the Veneto Region by period of activation of a colorectal screening programme.




Le evidenze disponibili indicano che il FIT determina una riduzione dell'incidenza di CRC grazie alla diagnosi delle lesioni pre-maligne

"The Cox model…, adjusted for sex and age, showed an overall statistically significant reduction in CRC incidence of 22% (HR = 0.78, 95%CI: 0.65–0.93) in the attenders' versus the nonattenders' cohort."

Ventura L, et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. Dig Liver Dis. 2014; 46:82-6

# DNA nelle feci

- Combinations of markers generally perform better than single markers. In stool, predominantly combinations of different DNA mutations in *APC, KRAS and p53, MSI, and DNA integrity are* tested
- **DNA methylation of phosphatase and actin regulator 3 detects colorectal cancer in stool and complements FIT**: promettenti anche come test addizionali con FIT
- Although some markers show better performance compared with the current FOBT test in initial studies, at this moment, no marker is yet suitable for population wide screening purposes
- Bosch LJ, et al. **Molecular tests for colorectal cancer screening**. *Clin Colorectal Cancer*. ***2011*** Mar;10:8-23. Review.

# Nuovi risultati per il DNA fecale

Imperiale TF, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;370:1287-97

The DNA test includes quantitative molecular assays for *KRAS* mutations, aberrant *NDRG4* and *BMP3* methylation, and β-actin

**Table 1. Sensitivity and Specificity of the Multitarget Stool DNA Test and the Fecal Immunochemical Test (FIT) for the Most Advanced Findings on Colonoscopy.**

| Most Advanced Finding | Colonoscopy (N=9989) | Multitarget DNA Test (N=9989) | | FIT (N=9989) | |
|---|---|---|---|---|---|
| | | Positive Results | Sensitivity (95% CI) | Positive Results | Sensitivity (95% CI) |
| | *no.* | *no.* | % | *no.* | % |
| Colorectal cancer | | | | | |
| Any | 65 | 60 | 92.3 (83.0–97.5) | 48 | 73.8 (61.5–84.0) |
| Stage I to III* | 60 | 56 | 93.3 (83.8–98.2) | 44 | 73.3 (60.3–83.9) |
| Colorectal cancer and high-grade dysplasia | 104 | 87 | 83.7 (75.1–90.2) | 66 | 63.5 (53.5–72.7) |
| Advanced precancerous lesions† | 757 | 321 | 42.4 (38.9–46.0) | 180 | 23.8 (20.8–27.0) |
| Nonadvanced adenoma | 2893 | 498 | 17.2 (15.9–18.6) | 220 | 7.6 (6.7–8.6) |
| | | | Specificity (95% CI) | | Specificity (95% CI) |
| All nonadvanced adenomas, non-neoplastic findings, and negative results on colonoscopy | 9167 | 1231 | 86.6 (85.9–87.2) | 472 | 94.9 (94.4–95.3) |
| Negative results on colonoscopy | 4457 | 455 | 89.8 (88.9–90.7) | 162 | 96.4 (95.8–96.9) |

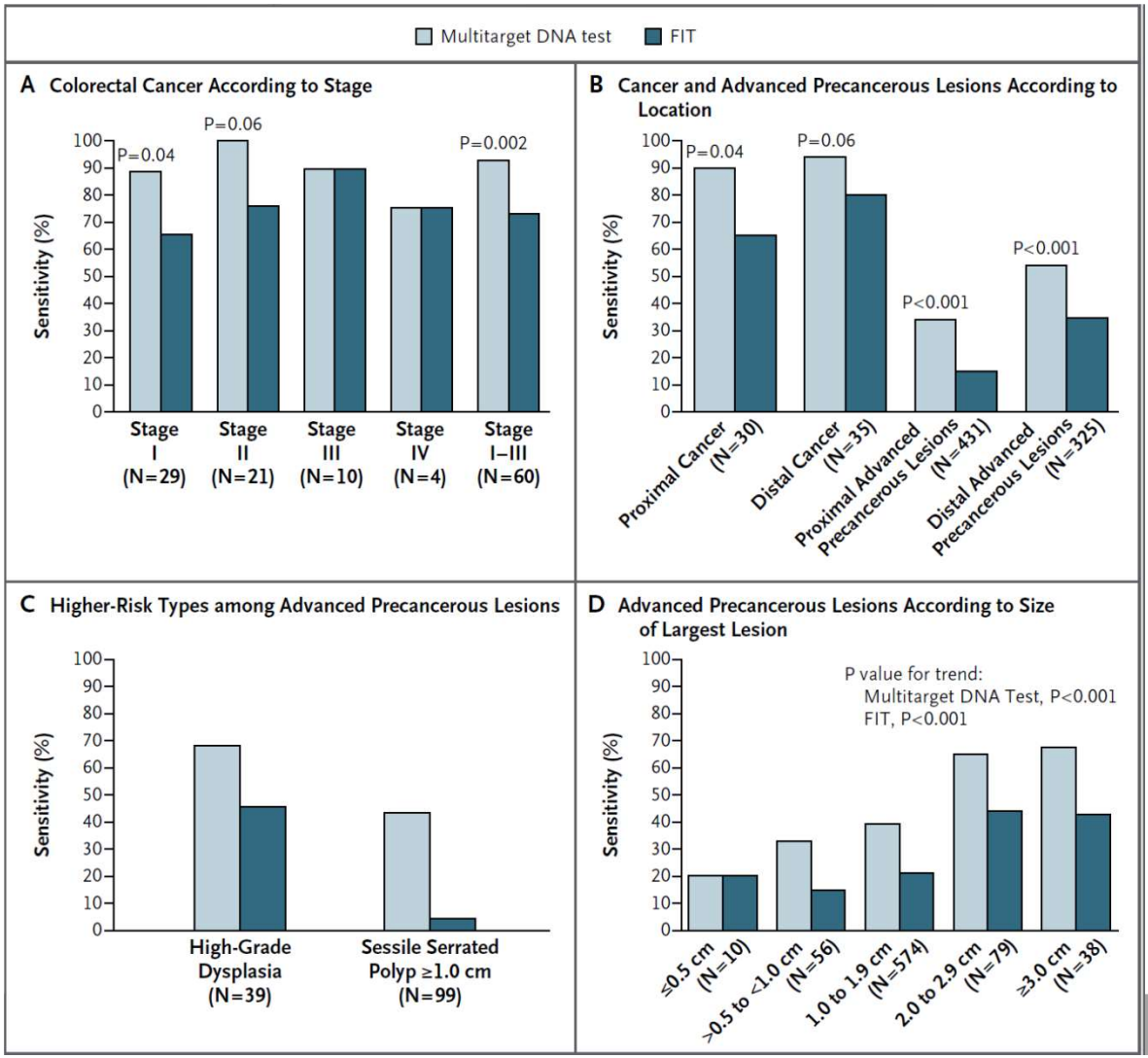



**Figure 2. Sensitivity of the Multitarget Stool DNA Test and the Commercial Fecal Immunochemical Test (FIT), According to Subgroup.**

Regione Umbria

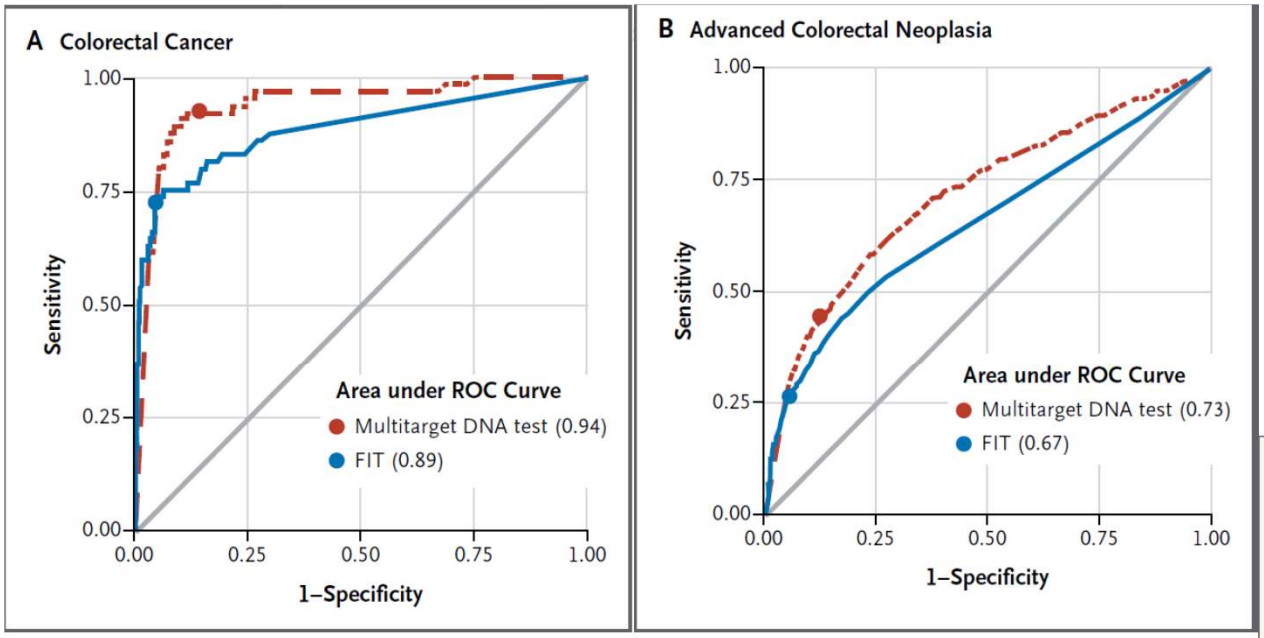



**Figure 3. Receiver Operating Characteristic (ROC) Curves Comparing DNA Testing and FIT for the Detection of Colorectal Cancer and Advanced Colorectal Neoplasia.**

Shown are ROC curves for the multitarget stool DNA test and FIT for the detection of colorectal cancer (Panel A) and advanced colorectal neoplasia (colorectal cancer plus advanced precancerous lesions) (Panel B). For colorectal cancer, the area under the ROC curve was 0.94 for the DNA test and 0.89 for FIT (95% confidence interval [CI] for the difference in area, 0.003 to 0.10; P=0.04). For advanced colorectal neoplasia, the area under the ROC curve was 0.73 for the DNA test and 0.67 for FIT (95% CI for the difference in area, 0.04 to 0.09; P<0.001). The respective performance thresholds were a value of 183 or more for the DNA test and more than 100 ng of hemoglobin per milliliter of buffer for FIT.

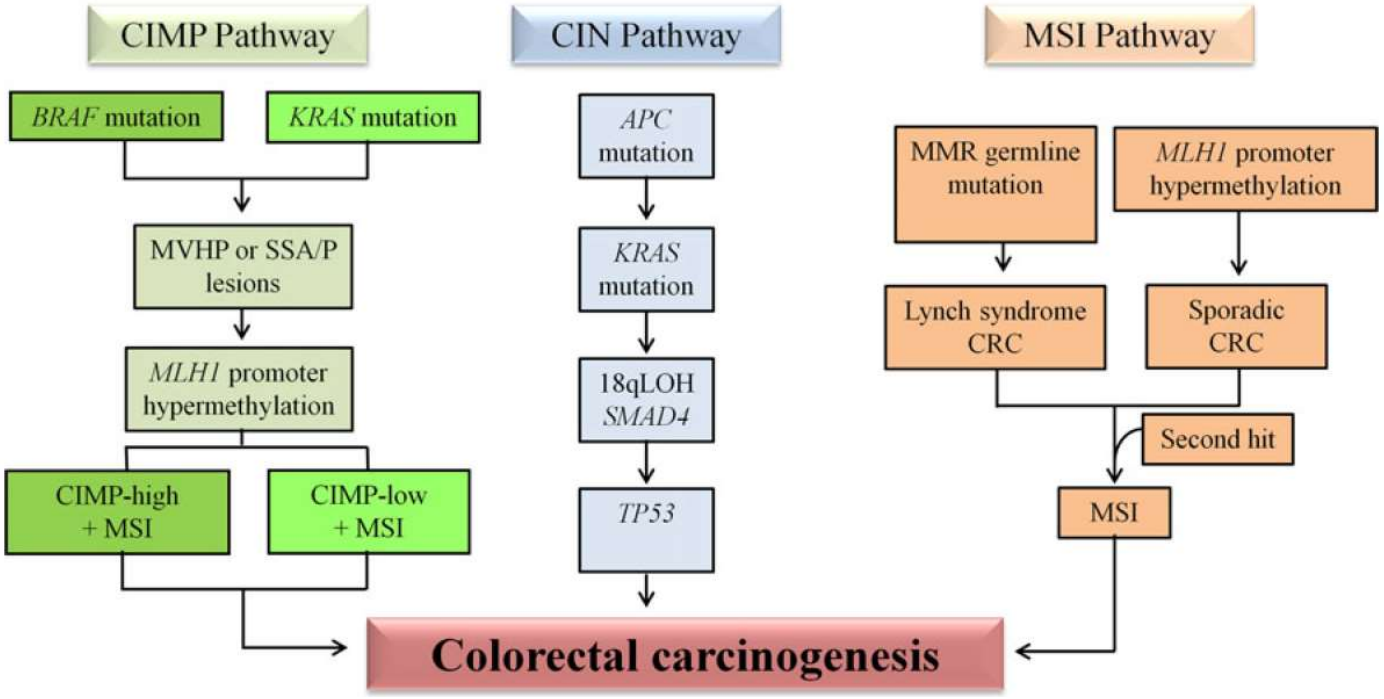
**Colorectal-Cancer Screening — Coming of Age**

Theodore R. Levin, M.D., and Douglas A. Corley, M.D., Ph.D.

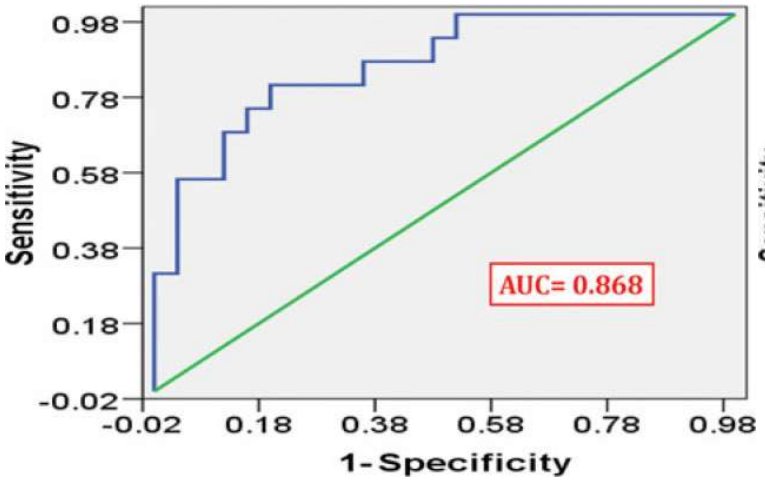
N Engl J Med 2013; 369:1164-1166 September 19, 2013

- Confirming previous reports, the authors (i.e. *Nishihara and colleagues*) found that cancers diagnosed within 5 years after colonoscopy were more likely than those diagnosed more than 5 years after colonoscopy to have the CpG island methylator phenotype and microsatellite instability,…
- The cancers that become evident earlier after screening may either grow more quickly or be more difficult to detect by means of colonoscopy than later cancers, in part owing to their altered biologic characteristics.

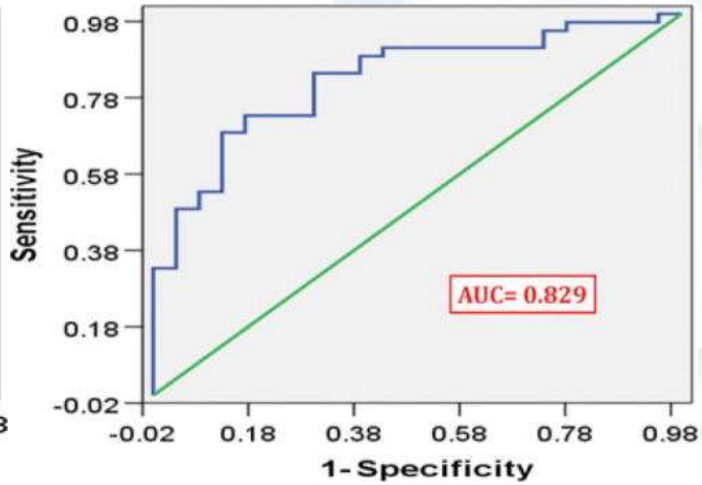
Gyparaki MT, Basdra EK, Papavassiliou AG.DNA methylation biomarkers as diagnostic and prognostic tools in colorectal cancer.
J Mol Med (Berl). 2013;91:1249-56.



Kanaan Z, Roberts H, Eichenberger MR, Billeter A, Ocheretner G, Pan J, Rai SN, Jorden J, Williford A, Galandiuk S. A plasma microRNA panel for detection of colorectal adenomas: a step toward more precise screening for colorectal cancer. Ann Surg. 2013;258:400-8.




After testing these 15 miRNAs in the validation group, a combined panel of miR-532-3p, miR-331, miR-195, miR-17, miR-142-3p, miR-15b, miR-532, and miR-652 identified CR adenomas accurately. The 8-miRNA panel demonstrated an AUC of 0.868 [95% CI: 0.76–0.98]




ROC curves for the panel of miR-431 and miR-139-3p for “all stages CRC validation” group (n = 45) vs individuals without CR neoplasia (n = 26). AUC = 0.829.

# Trial relativi ad efficacia della sigmoidoscopia

- Evidenze da trial e meta-analisi relative a riduzione di incidenza e mortalità
- An advantage of FS with polypectomy is that it appears to be an effective, low-cost, one-time intervention in the large majority of patients, and is therefore particularly suitable for
- delivery in middle- and low-resource nations and
- to those with health care access barriers in the United States


- Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012; 9: e1001352.

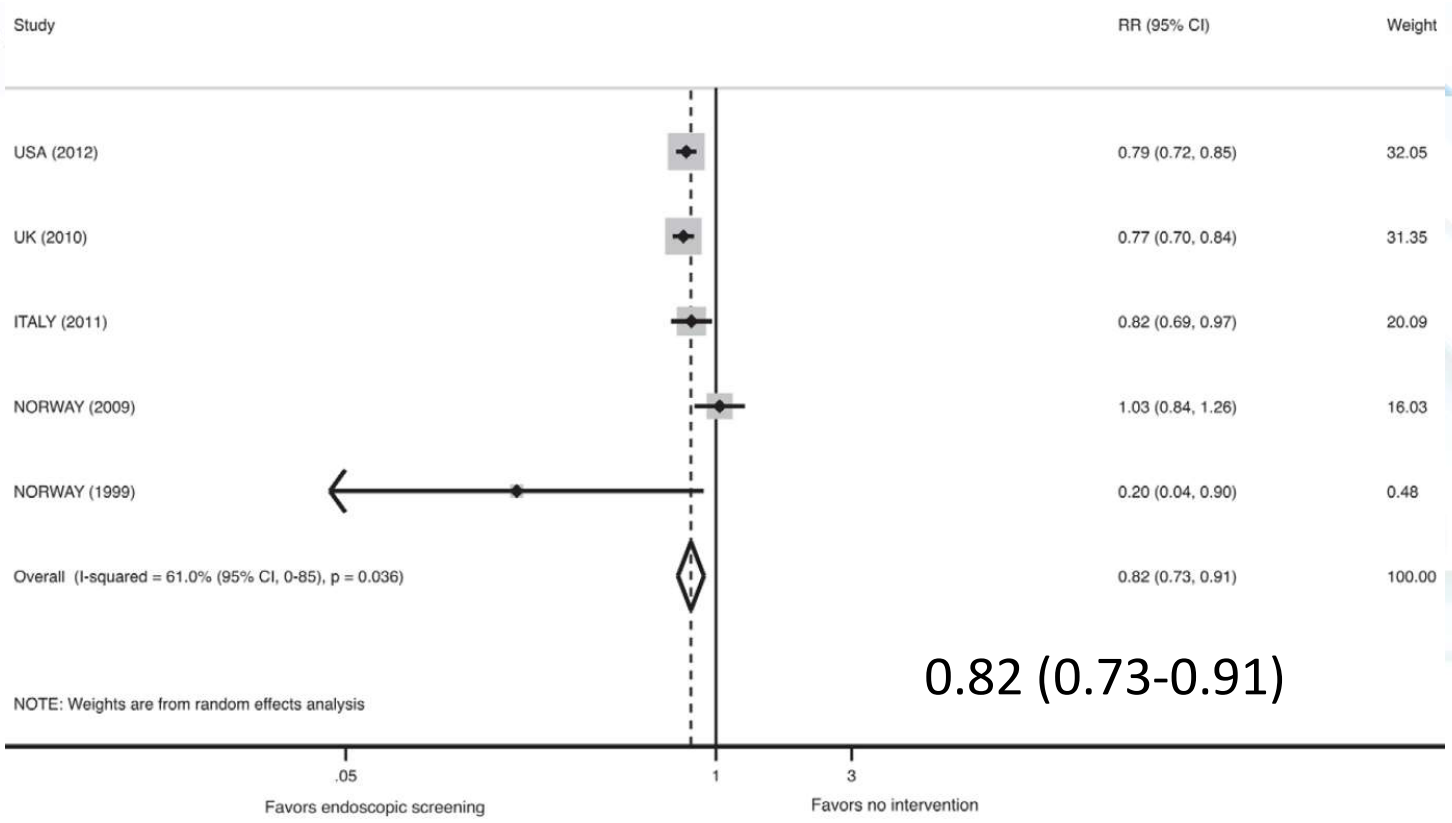



Figure 2. Meta-analysis of the effect of endoscopic screening on the **incidence** of colorectal cancer. (A) Pooled relative risk of ITT analyses.

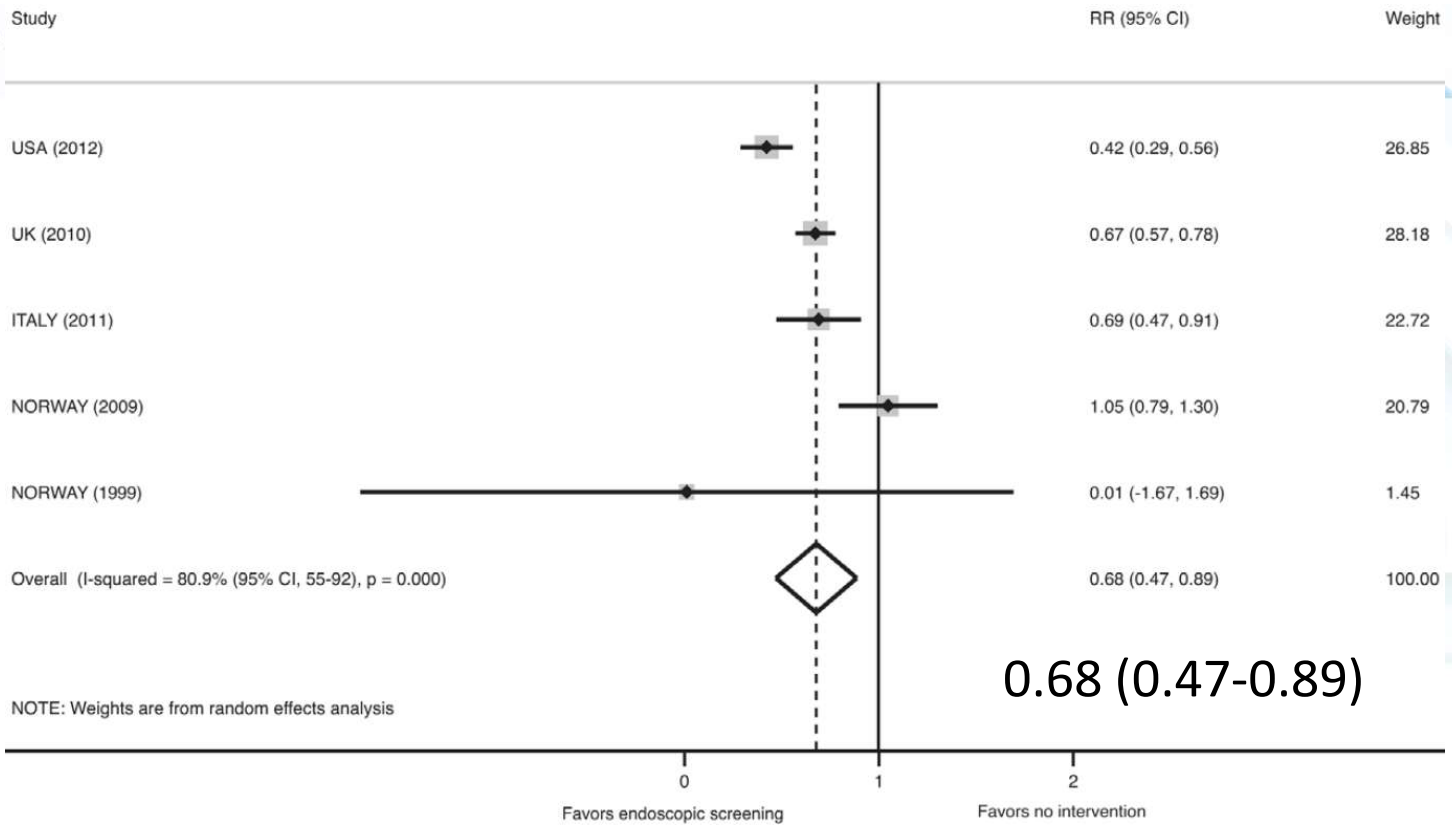



Figure 2. Meta-analysis of the effect of endoscopic screening on the **incidence** of colorectal cancer. (B) Pooled relative risk of efficacy estimates

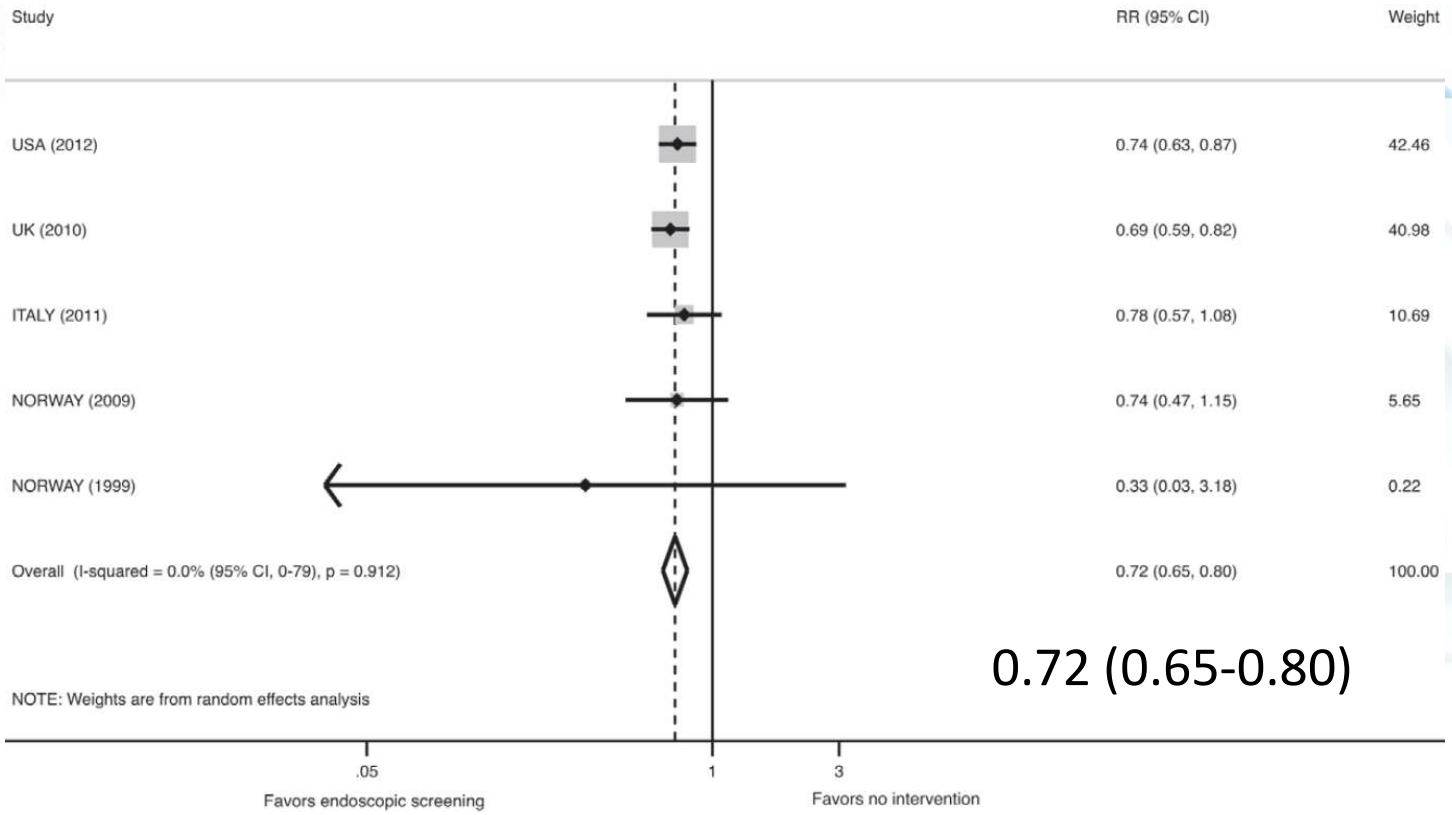



Figure 3. Meta-analysis of the effect of endoscopic screening on colorectal cancer **mortality**. (A) Pooled relative risk of ITT analyses.

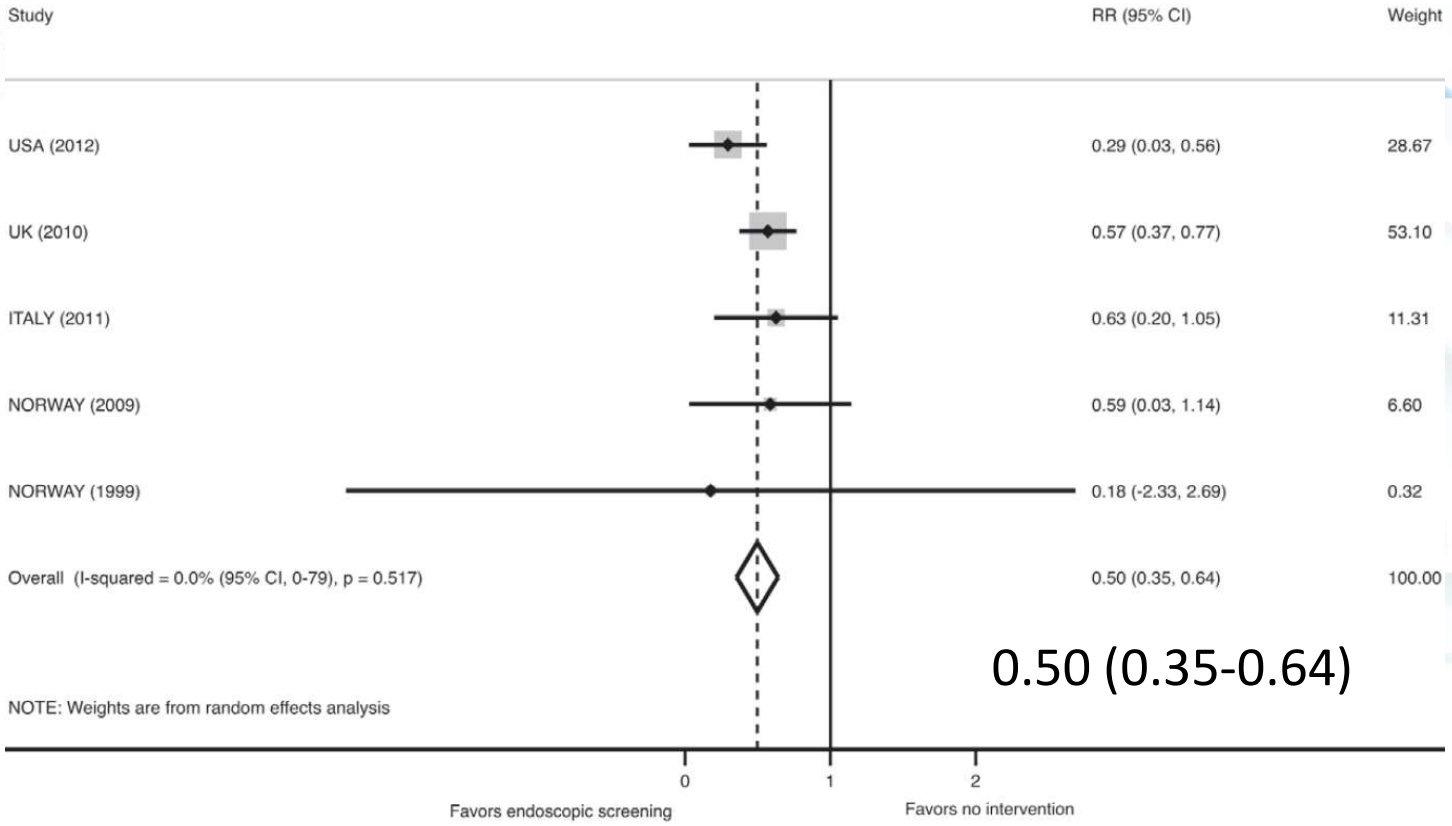



Figure 3. Meta-analysis of the effect of endoscopic screening on colorectal cancer **mortality**. (B) Pooled relative risk of efficacy estimates.

# Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. Brenner H et al 2014 BMJ

Table 2| **Overview and meta-analysis of randomised controlled trials on impact of flexible sigmoidoscopy: results on colorectal cancer incidence and mortality. Values are relative risks (95% confidence intervals) unless stated otherwise**

| | Incidence | | | Mortality | | |
|---|---|---|---|---|---|---|
| **Type of analysis and studies** | **Any site** | **Proximal** | **Distal** | **Any site** | **Proximal** | **Distal** |
| Intention to screen: | | | | | | |
| Hoff et al 2009[12] | 1.02 (0.83 to 1.25)* | NR | NR | 0.73 (0.47 to 1.13) | NR | 0.63 (0.34 to 1.18) |
| Atkin et al 2010[13] | 0.77 (0.70 to 0.84) | 0.98 (0.85 to 1.12) | 0.64 (0.57 to 0.72) | 0.69 (0.59 to 0.82) | NR | NR |
| Segnan et al 2011[14] | 0.82 (0.69 to 0.96) | 0.91 (0.69 to 1.20) | 0.76 (0.62 to 0.94) | 0.78 (0.56 to 1.08) | 0.85 (0.52 to 1.39) | 0.73 (0.47 to 1.12) |
| Schoen et al 2012[15] | 0.79 (0.72 to 0.85) | 0.86 (0.76 to 0.97) | 0.71 (0.64 to 0.80) | 0.74 (0.63 to 0.87) | 0.97 (0.77 to 1.22) | 0.50 (0.38 to 0.64) |
| Meta-analysis: | | | | | | |
| No of studies | 4 | 3 | 3 | 4 | 2 | 3 |
| Pooled estimate | 0.82 (0.75 to 0.89) | 0.91 (0.83 to 0.99) | 0.69 (0.63 to 0.74) | 0.72 (0.65 to 0.80) | 0.95 (0.77 to 1.17) | 0.54 (0.43 to 0.67) |
| Heterogeneity: $I^2$ (%)/$\tau^2$/P value | 52/0.004/0.10 | 0/0.0/0.38 | 24/0.002/0.27 | 0/0.0/0.90 | 0/0.0/0.63 | 0/0.0/0.52 |

# Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality…

- Compelling and consistent evidence from randomised controlled trials and observational studies shows that screening sigmoidoscopy and screening colonoscopy prevent the majority of deaths from distal colorectal cancer.
- Data suggest added value of colonoscopy versus sigmoidoscopy, especially for prevention of deaths from cancer of the proximal colon,
- which should be elaborated in further research and weighed against the higher costs, complexity, discomfort, complication rates, and high quality capacities and quality assurance needed,64-67 as well as possible differences in compliance

# Evidenze per colonscopia

- While a small RCT of screening colonoscopy revealed a non-statistically significant 23% reduction in overall CRC incidence,
- Large scale randomized trials are eagerly awaited to allow accurate estimation of the effect of full colonoscopy on right-sided cancer.
- Three such studies are underway, however results may not be available for another 9–14 y

# Efficacia della colonscopia

TC is considered an effective screening test for CRC based on the following arguments:

(i) evidence available for FS applies to TC as well since both tests are based on direct visualization of intestinal lumen;

(ii) mortality reduction achieved with FOBT tests depends on colonoscopy as the confirmatory test; and

(iii) available observational studies confirm that TC is highly effective in reducing CRC mortality and incidence

# In ogni caso colonscopia

- There is indirect clinical evidence to support the efficacy, feasibility, and accuracy of colonoscopy in screening for CRC.
- Observational cohort and case-control studies have estimated that colonoscopy results in a 53%–72% reduction in CRC incidence and a 31% reduction in CRC mortality among participants who received screening colonoscopy examinations
- The effectiveness of all screening programs depends on the quality of colonoscopy because colonoscopy is used to evaluate positive screening tests in all programs

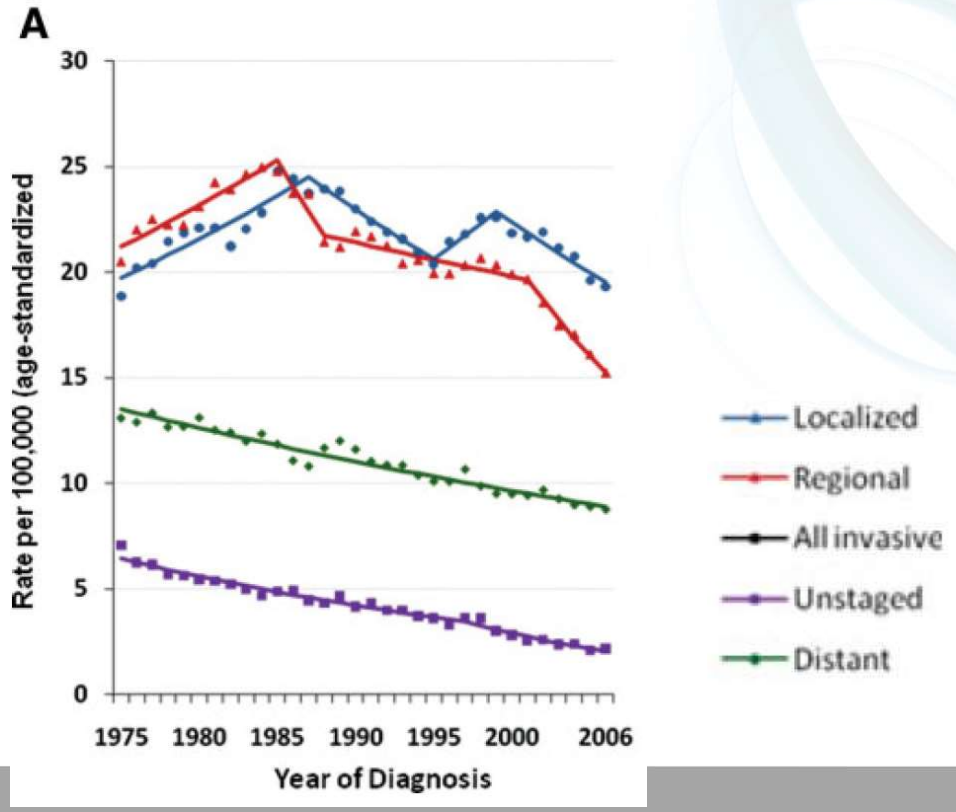
Lieberman D.Progress and challenges in colorectal cancer screening and surveillance. Gastroenterology. 2010;138:2115-26.

Nishihara R, Wu K, Lochhead P, et al.

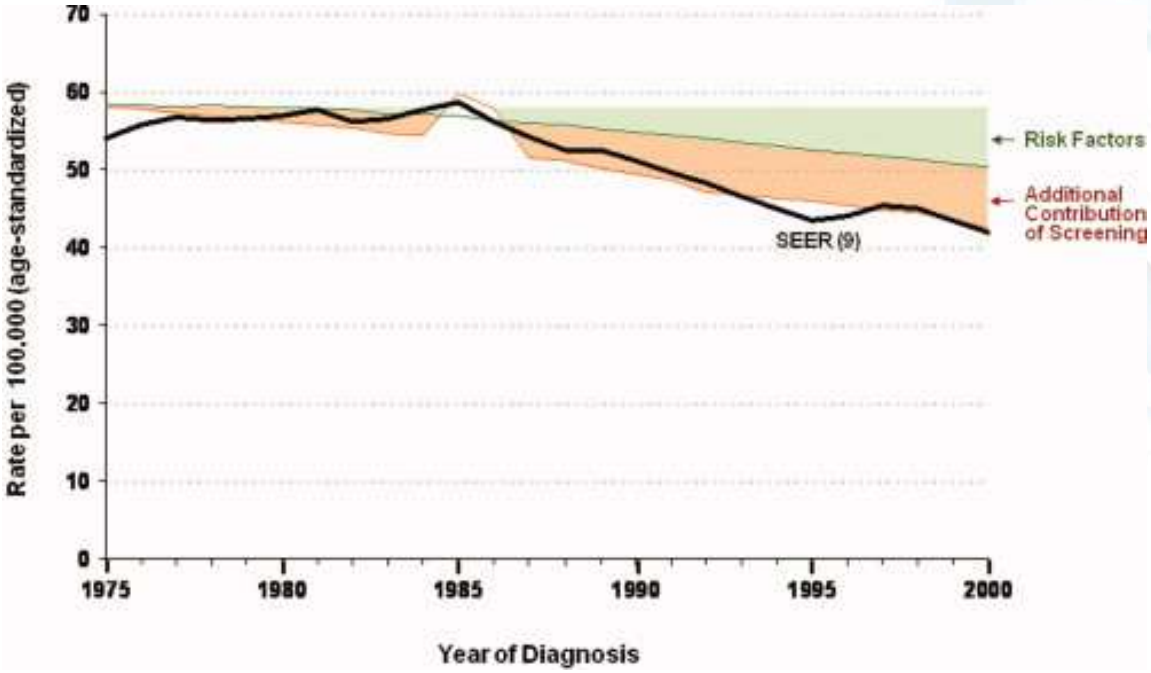
## Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013; 369:1095-105

- We estimated that 40% of colorectal cancers (including 61% of distal colorectal cancers and 22% of proximal colon cancers) that developed during follow-up would have been prevented if all the participants in our study had undergone colonoscopy.
- Moreover, screening sigmoidoscopy and screening colonoscopy were associated with lower mortality from colorectal cancer, as compared with no endoscopy, although only screening colonoscopy was associated with lower mortality from proximal colon cancer
- [analisi di 2 studi di coorte: We used data from two prospective cohort studies: the **Nurses' Health Study**, which included 121,700 U.S. female nurses, 30 to 55 years of age at enrollment in 1976; and the **Health Professionals Follow-up Study**, which included 51,529 U.S. male health professionals, 40 to 75 years of age at enrollment in 1986]

# Trend per stadio (US area SEER)

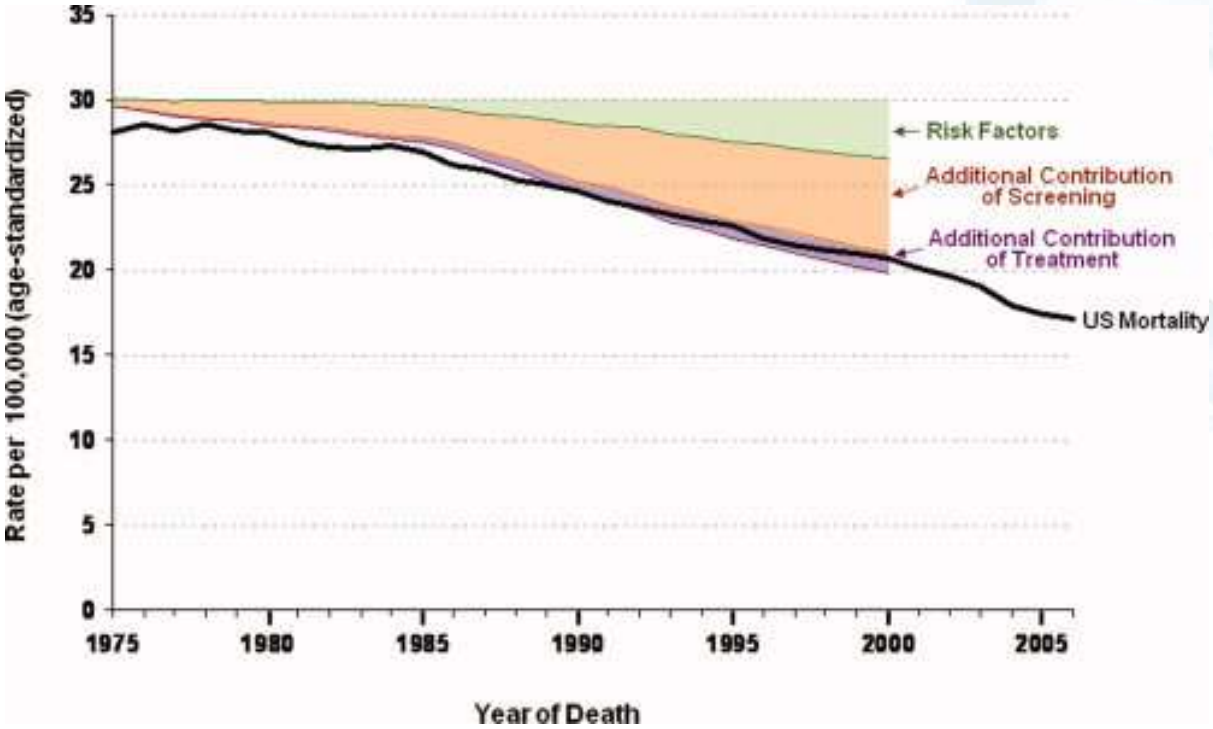


**Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates**

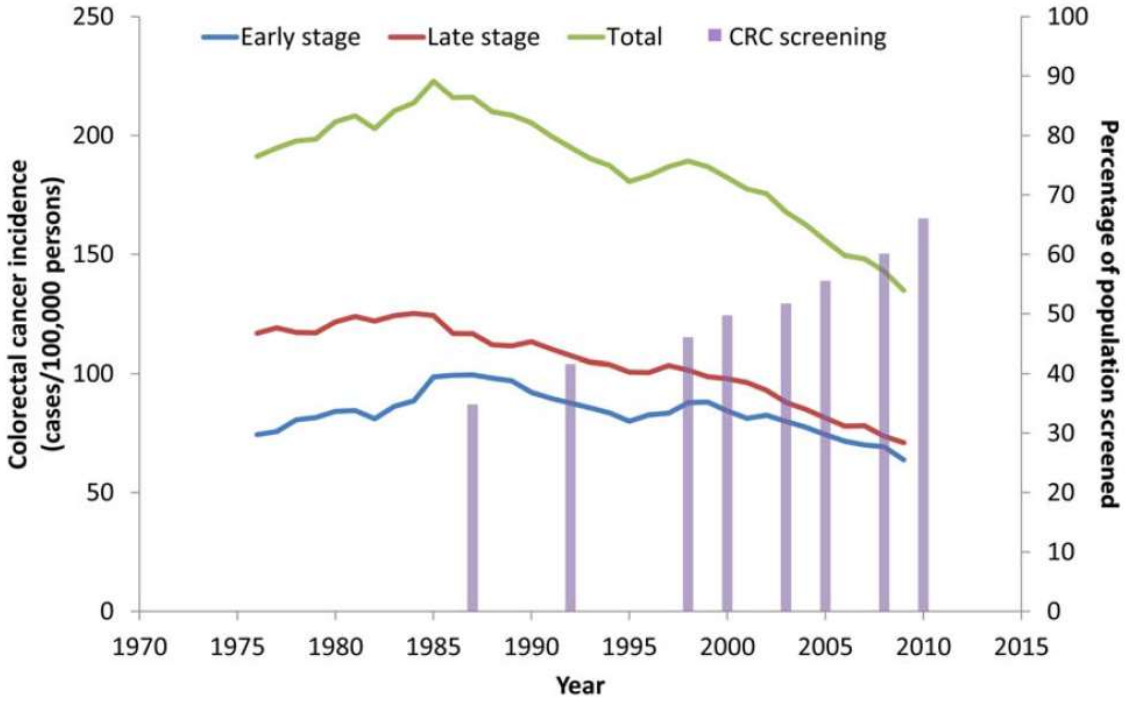



**Cancer**
Volume 116, Issue 3, pages 544-573, 7 DEC 2009 DOI: 10.1002/cncr.24760
http://onlinelibrary.wiley.com/doi/10.1002/cncr.24760/full#fig3

**Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates**




**Cancer**
Volume 116, Issue 3, pages 544-573, 7 DEC 2009 DOI: 10.1002/cncr.24760
http://onlinelibrary.wiley.com/doi/10.1002/cncr.24760/full#fig4




Riduzione dell'incidenza in funzione dell'attività di screening negli US

Yang DX et al. Estimating the Magnitude of Colorectal Cancers Prevented During the Era of Screening 1976 to 2009. Cancer. 2014;120:2893-901

# US: Screening storico e trend di incidenza favorevole

- Although several factors may account for the observed changes in overall cancer incidence,
- the most likely reason for the reduction in colorectal cancer rates is the *primary prevention* of cancers by **removal of adenomatous polyps during flexible sigmoidoscopy or colonoscopy**…

Yang DX et al. Estimating the Magnitude of Colorectal Cancers Prevented During the Era of Screening 1976 to 2009. Cancer. 2014;120:2893-901

# Adesione allo screening

- Despite its central role in CRC control and the availability of a range of effective tests, CRC screening is typically under-used.
- In the US participation in CRC screening has been increasing since its introduction in the 80s but was still below 70% in 2010

# Miglioramento

- Passaggio da opportunistico a organizzato
- Invito ad aderire (mezzi di comunicazione, medici di famiglia)
- Combinazione di test
- Offerta in sequenza
- Nuovi test più accettabili

# Italia: screening più recente e prevalenza FIT

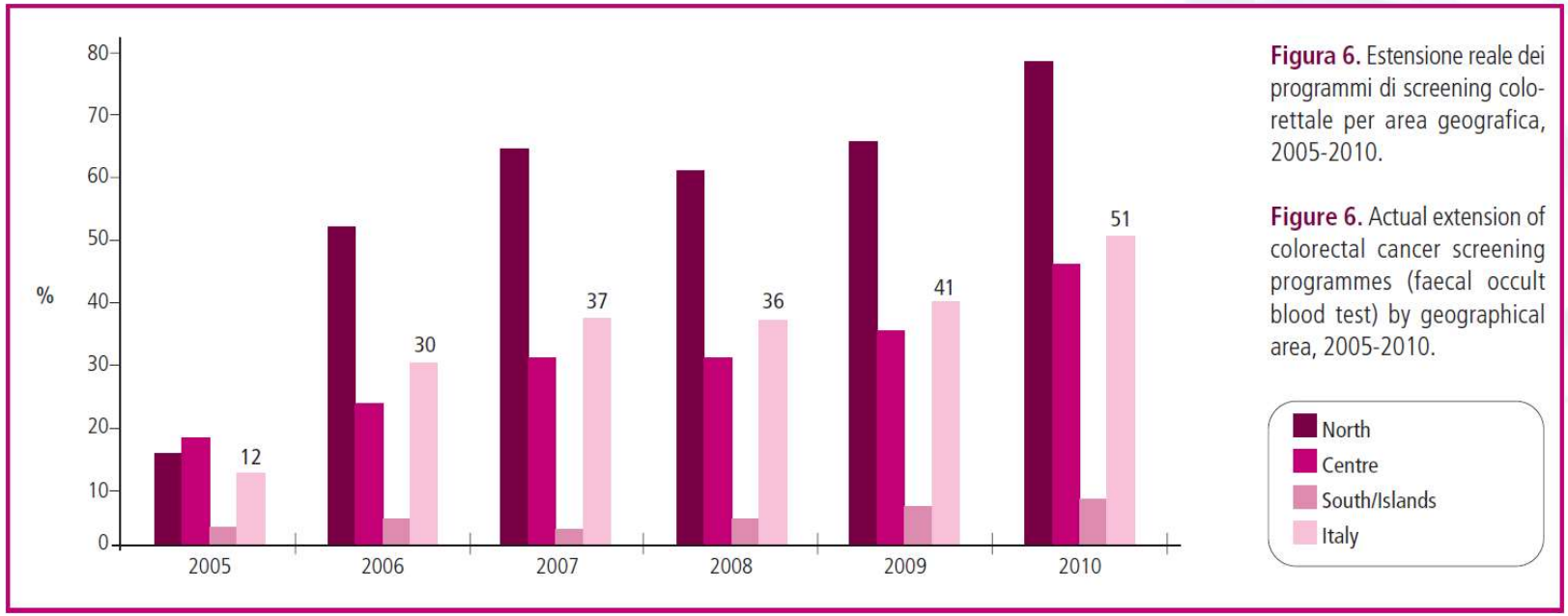



**Figura 6.** Estensione reale dei programmi di screening colorettale per area geografica, 2005-2010.

**Figure 6.** Actual extension of colorectal cancer screening programmes (faecal occult blood test) by geographical area, 2005-2010.

Zappa M et al. The diffusion of screening programmes in Italy, year 2010. Epidemiol Prev. 2012;36(6 Suppl 1):3-7.

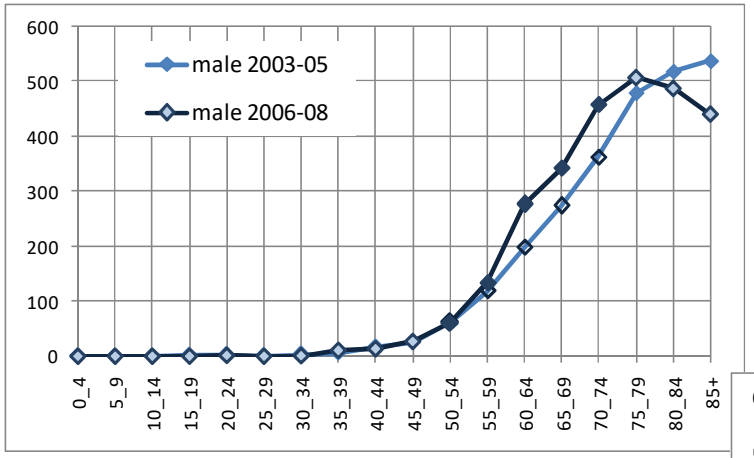
Regional colorectal cancer screening: red actived, white not yet actived, red and white partial actived

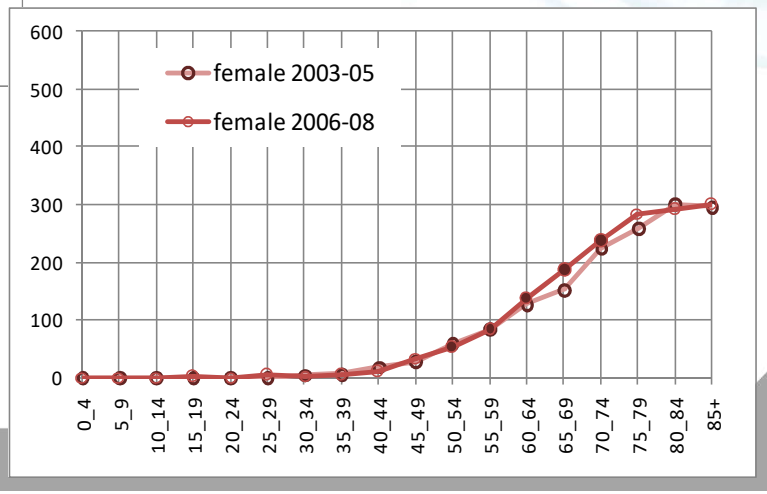

Ricerca del sangue occulto nelle feci, eseguita negli ultimi due anni – Persone 50-69enni .Prevalenze Passi 2010-12 Pool: 31,7% (31,2-32,2%)

# RT e screening in Umbria

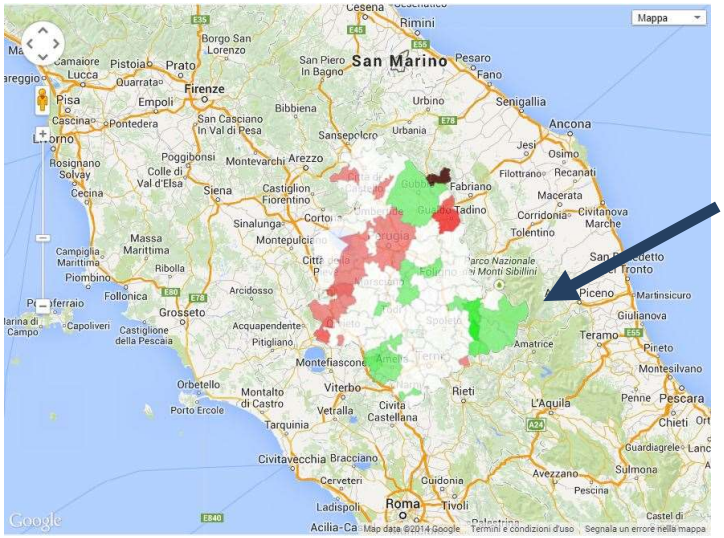
| Periodo | n. casi | | Tasso grezzo | | Tasso st Europa | |
|---|---|---|---|---|---|---|
| *Incidenza* | Maschi | Femmine | M | F | M | F |
| 2009-10 | 507 | 386 | 116.8 | 82.7 | **72.0** | **42.9** |
| 2007-08 | 576 | 404 | 134.8 | 88.4 | **85.1** | **46.3** |
| 1994-96 | 369 | 304 | 93.6 | 72.5 | **62.1** | **41.7** |
| *Mortalità* | | | | | | |
| 2011-12 | 195 | 159 | 45.6 | 34.2 | **23.6** | **13.9** |
| 2009-10 | 199 | 153 | 45.7 | 32.7 | **25.0** | **12.7** |
| 1994-96 | 165 | 133 | 41.8 | 31.8 | **27.4** | **16.3** |

# Tassi di incidenza età specifici prima e dopo l'introduzione dello screening per sesso



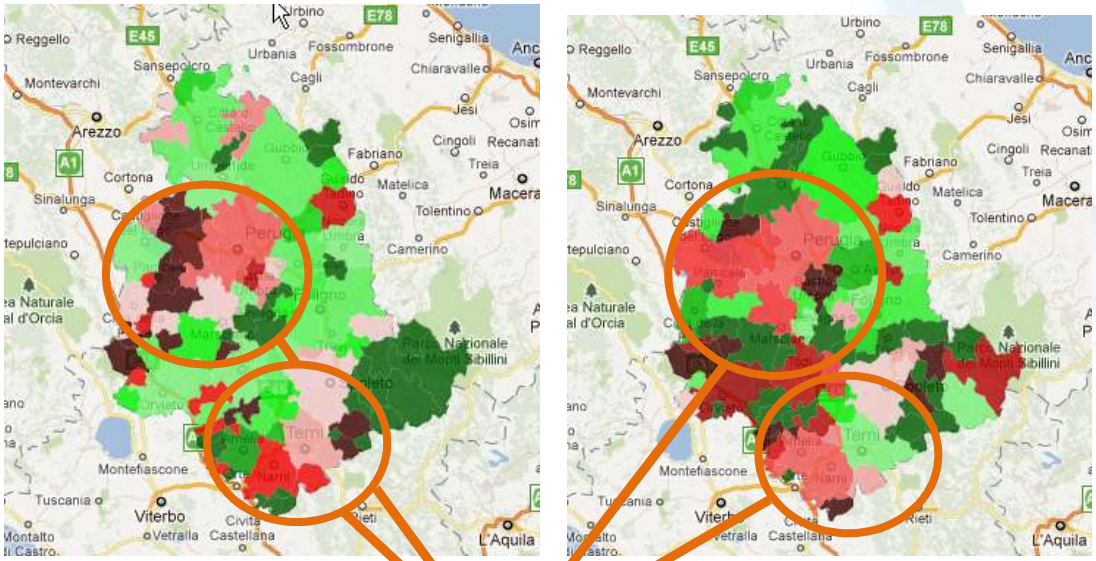
## Maschi




## Femmine


Distribuzione dell'incidenza del cancro del colon retto in Umbria (2006-2010, fascia di età 50-74)

# SIR displasia severa per comune, periodo 2006-2008

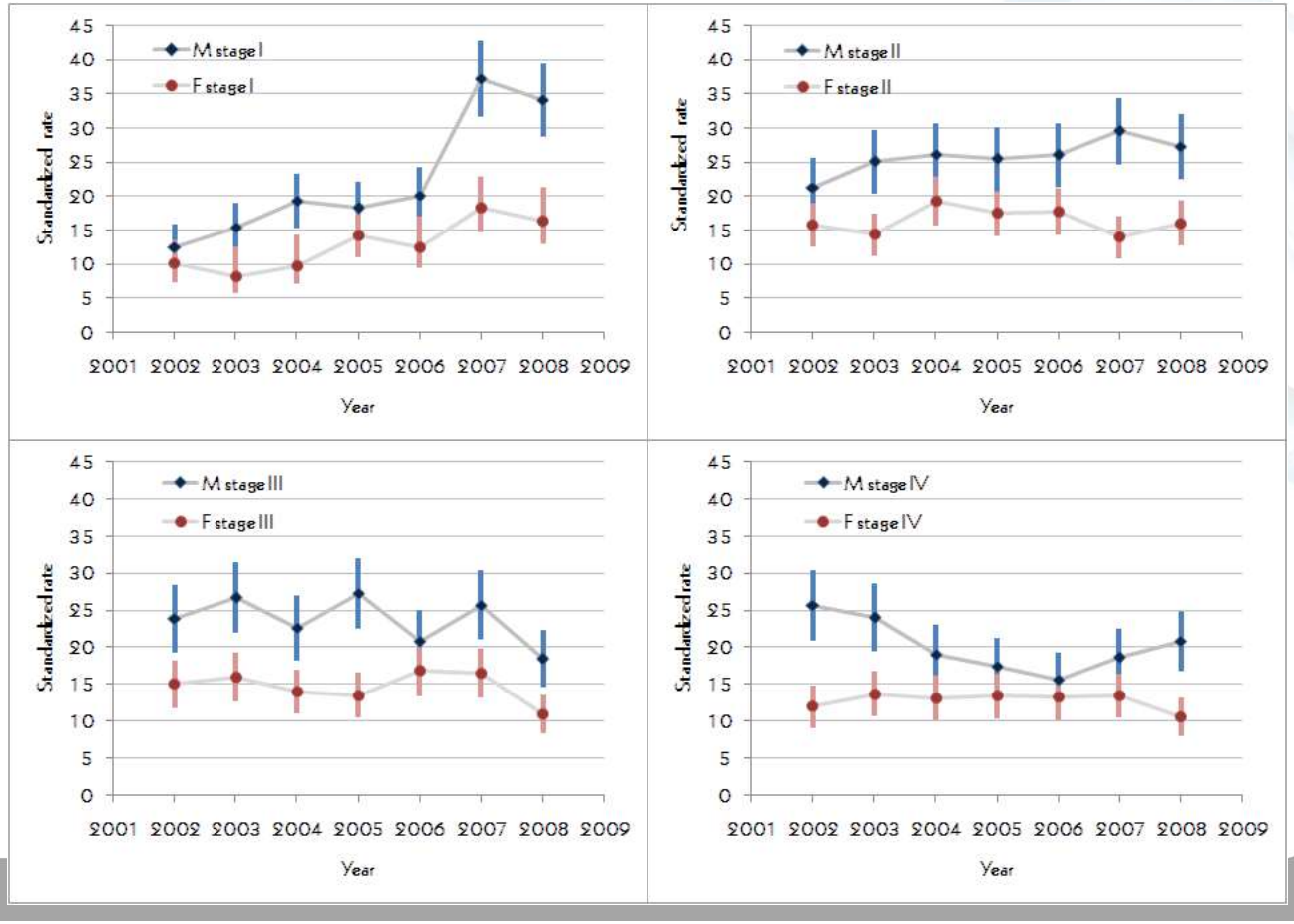



maschi

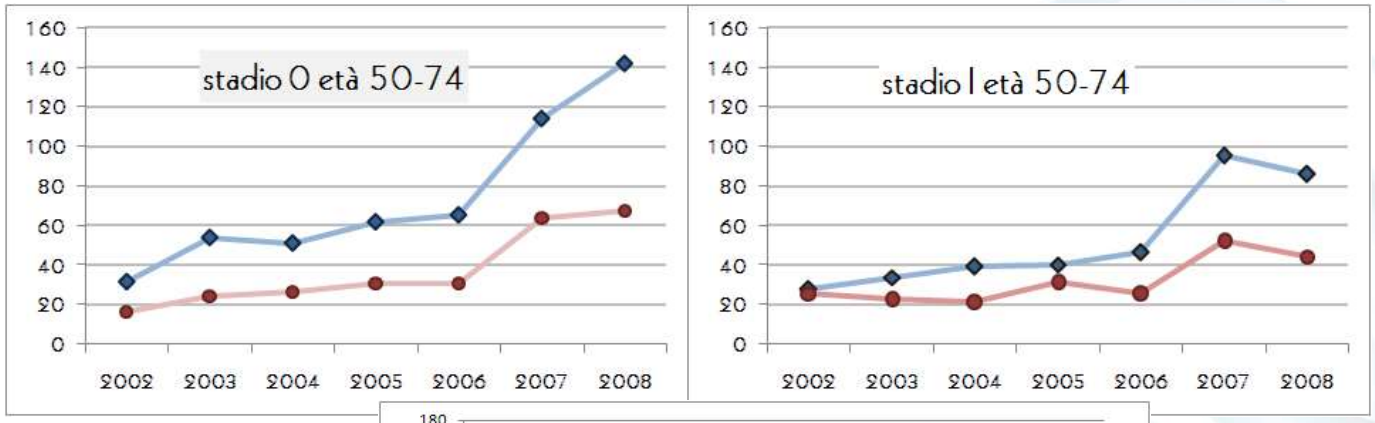
femmine

## Aree urbane o USL 2 e 4

# Trend di incidenza per stadio e sesso (2002-08)- GISCoRe 2011

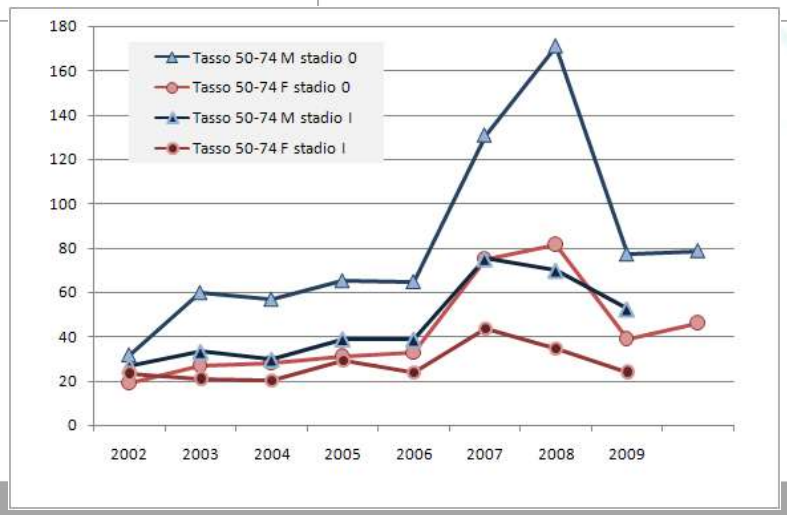


# Nella classe d'età screening



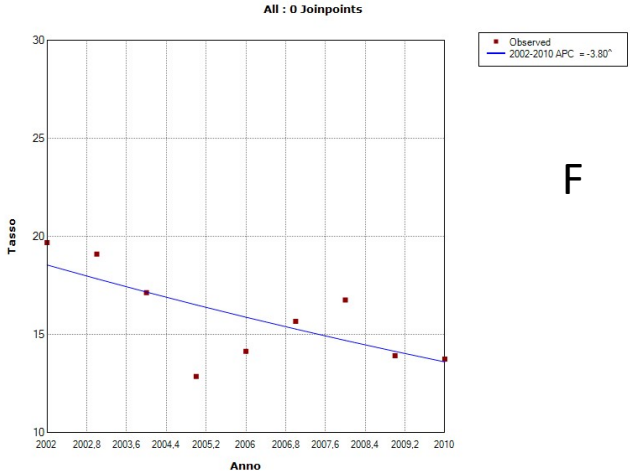






Tutte le età

M

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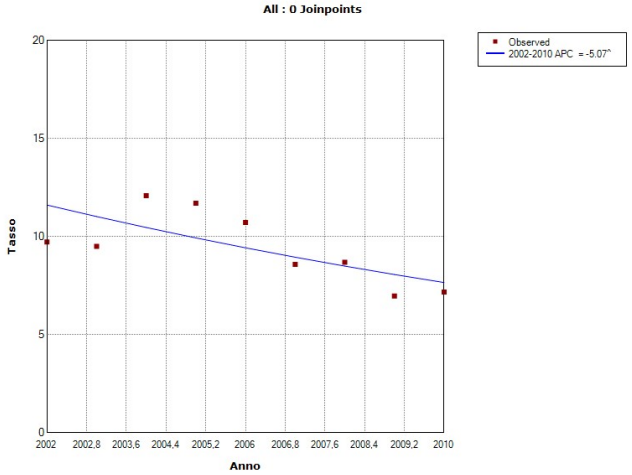
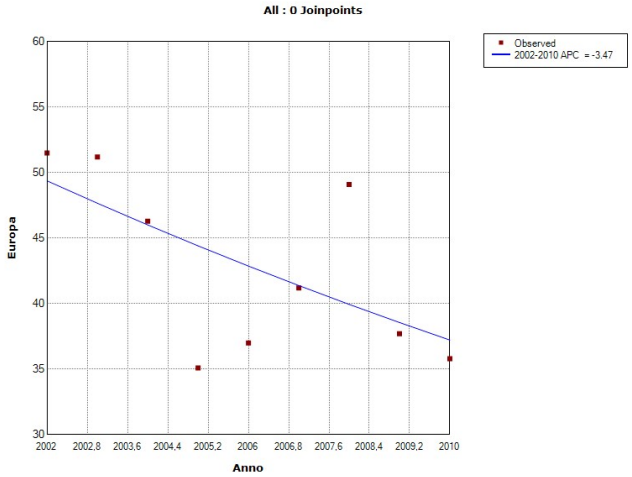
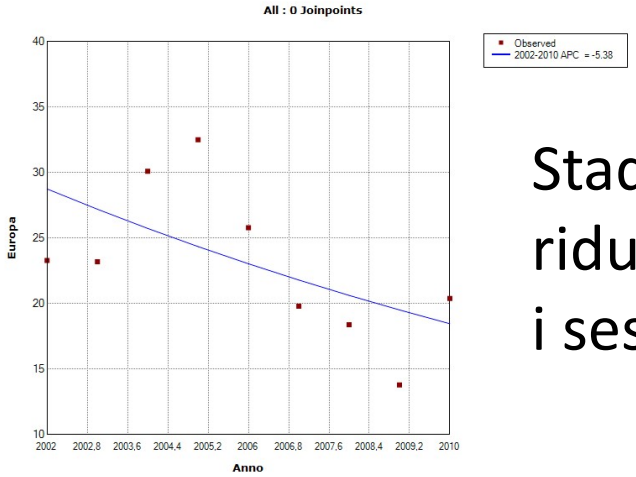


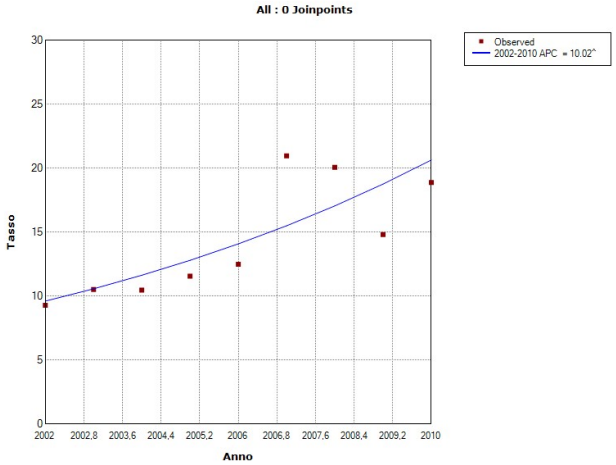

50-74 anni

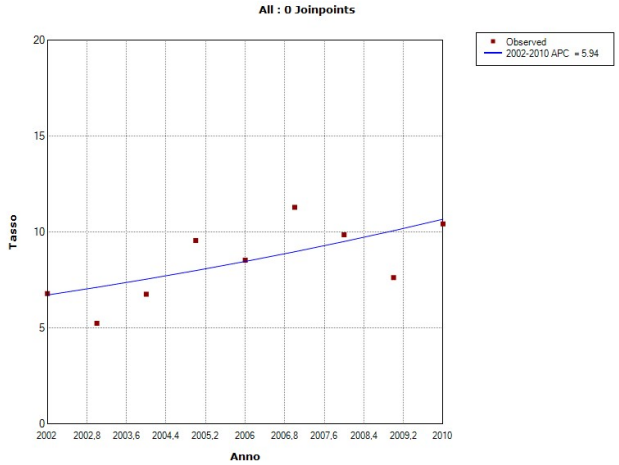


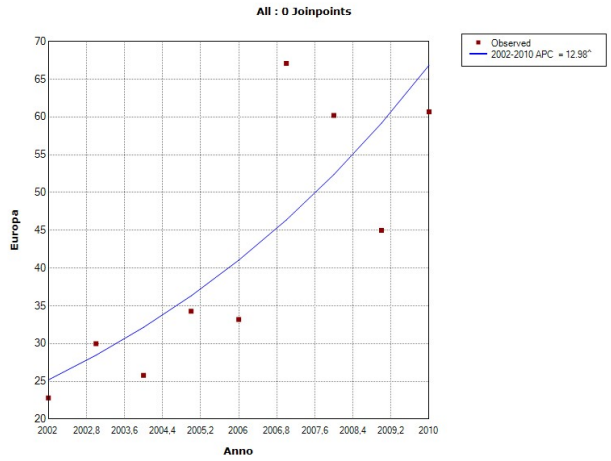

Stadio IV 2002-2010: riduzione in entrambi i sessi

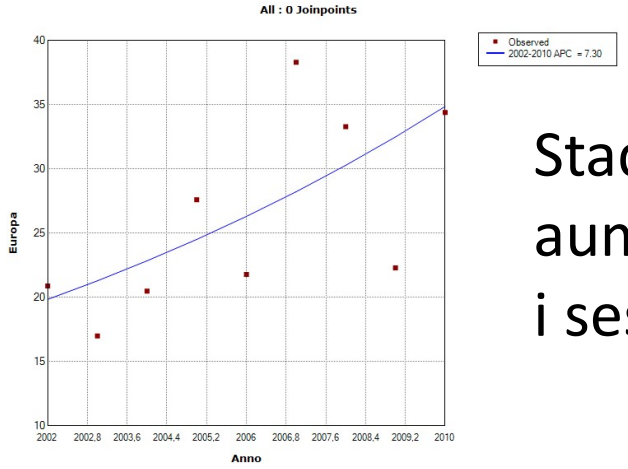
M




Tutte le età



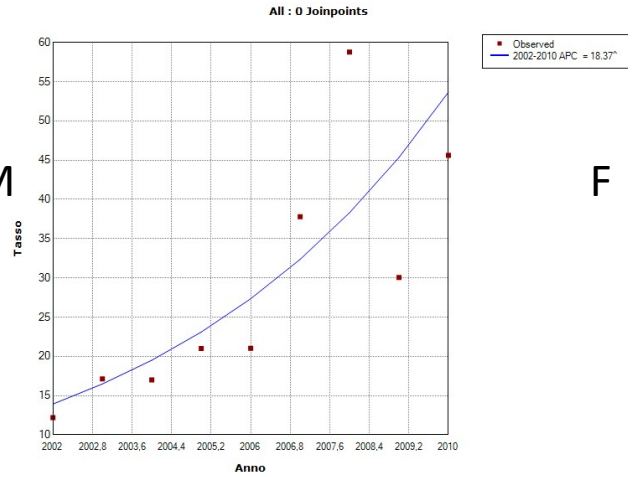




50-74 anni

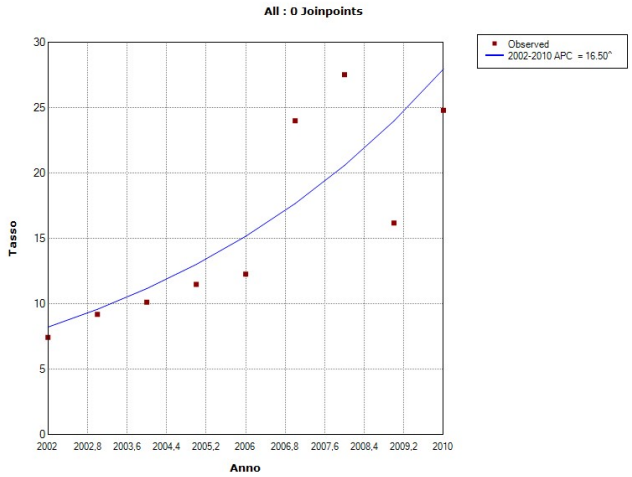
Stadio I 2002-2010: aumento in entrambi i sessi

Tutte le età

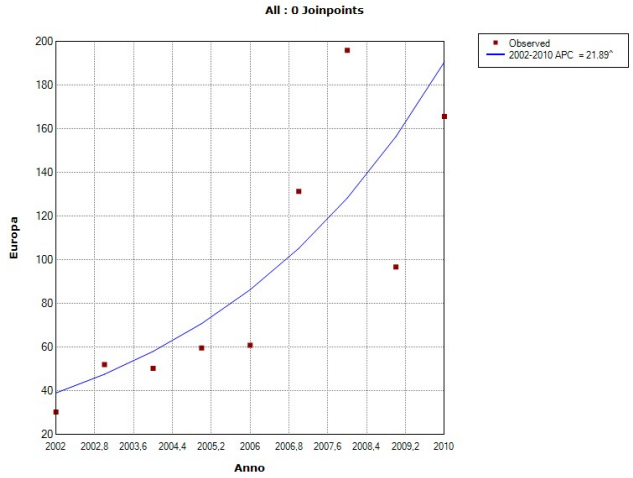
M

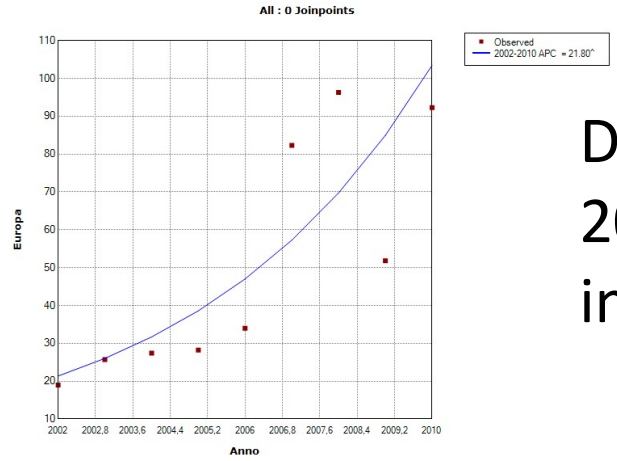



F




50-74 anni



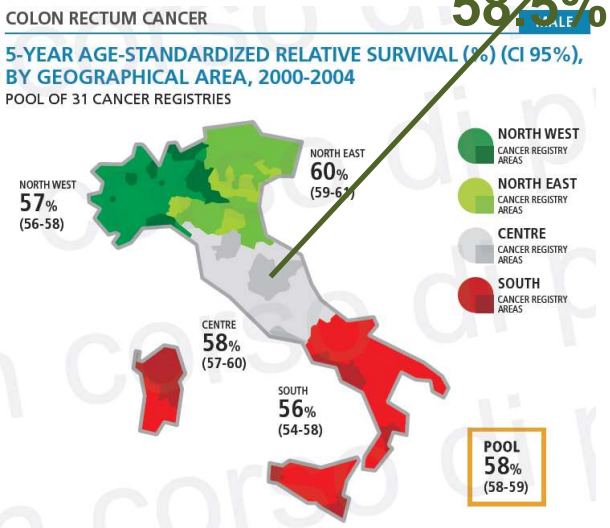

Displasia severa 2002-2010: aumento in entrambi i sessi

Regione Umbria

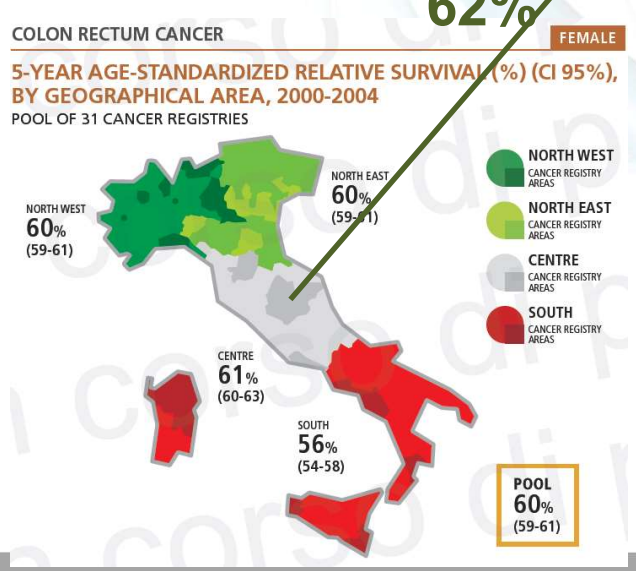

# Sopravvivenza relativa pre-screening

fonte: Monografia AIRTum

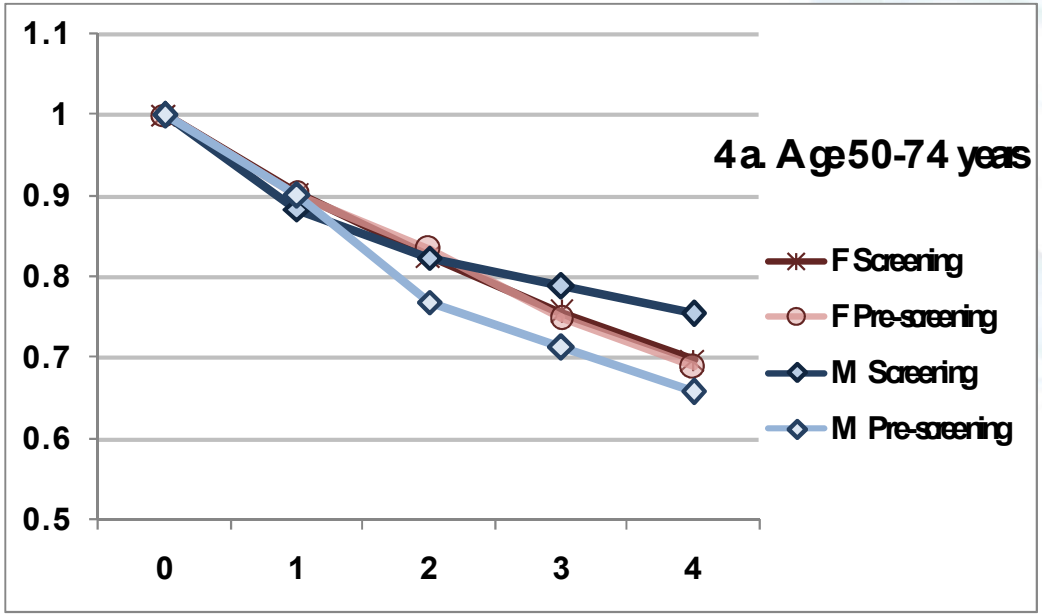
**Umbria M 58,5%**




**Umbria F 62%**

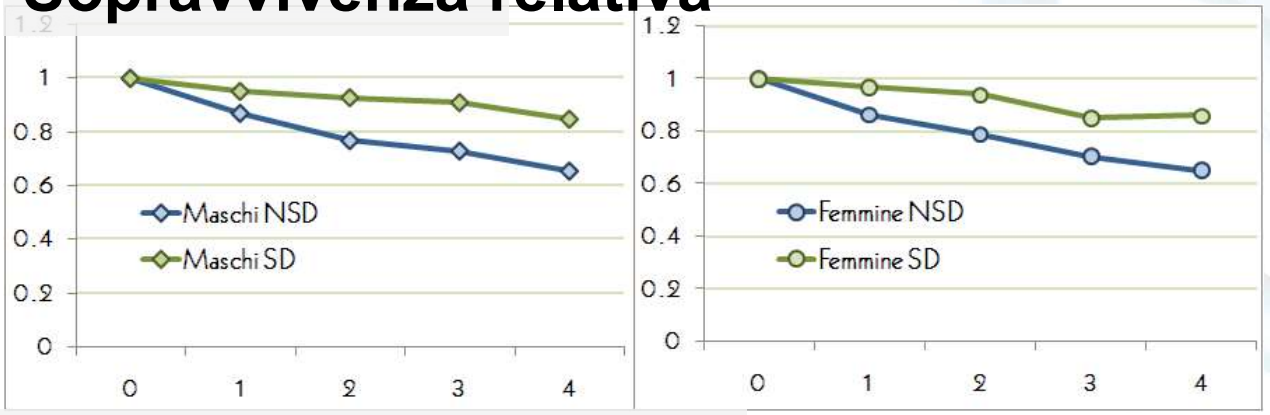


# Sopravvivenza relativa prima e durante il periodo di screening per sesso – età 50-74

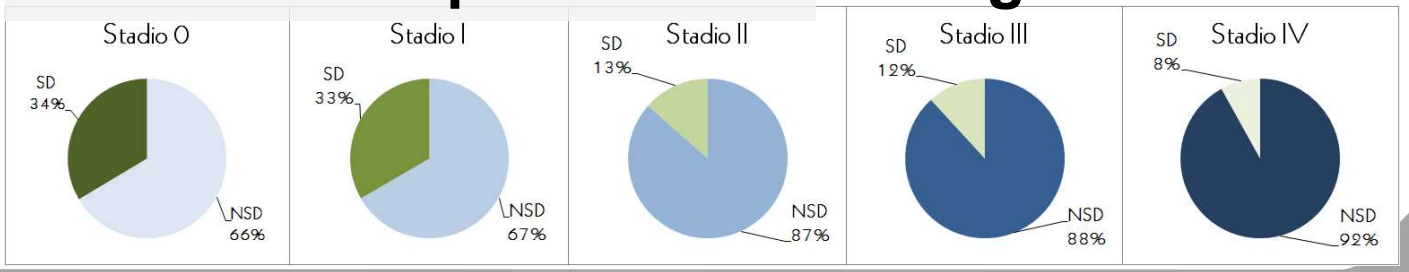


# Confronto tra lesioni diagnosticate allo screening e sintomatiche (2006-08)

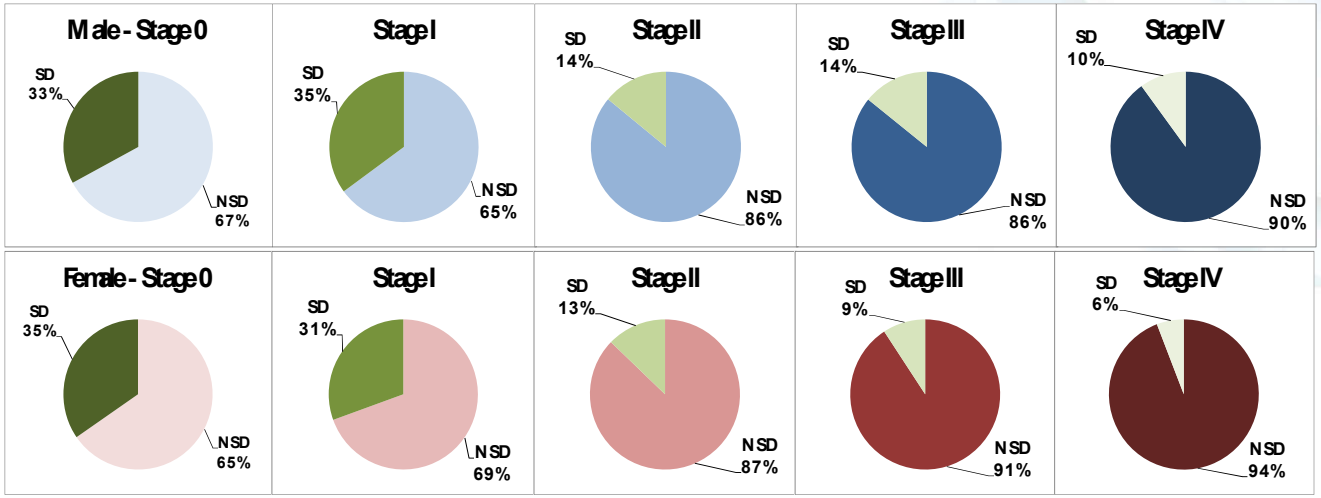
## Sopravvivenza relativa



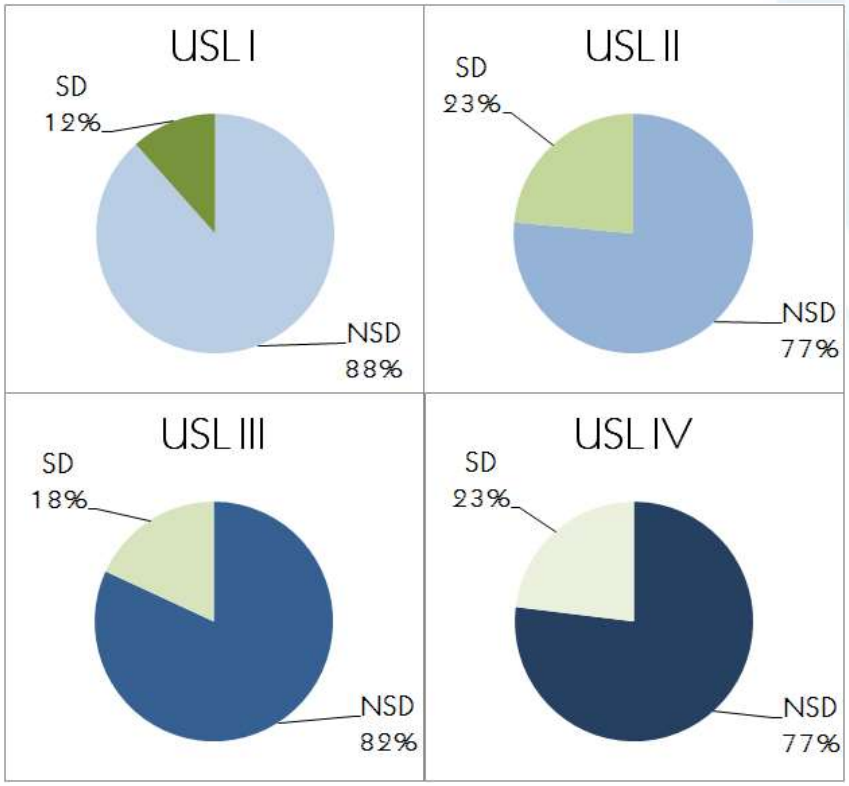

## Distribuzione per stadio alla diagnosi



# Distribuzione per sesso, stadio e modalità di diagnosi 2006-2008

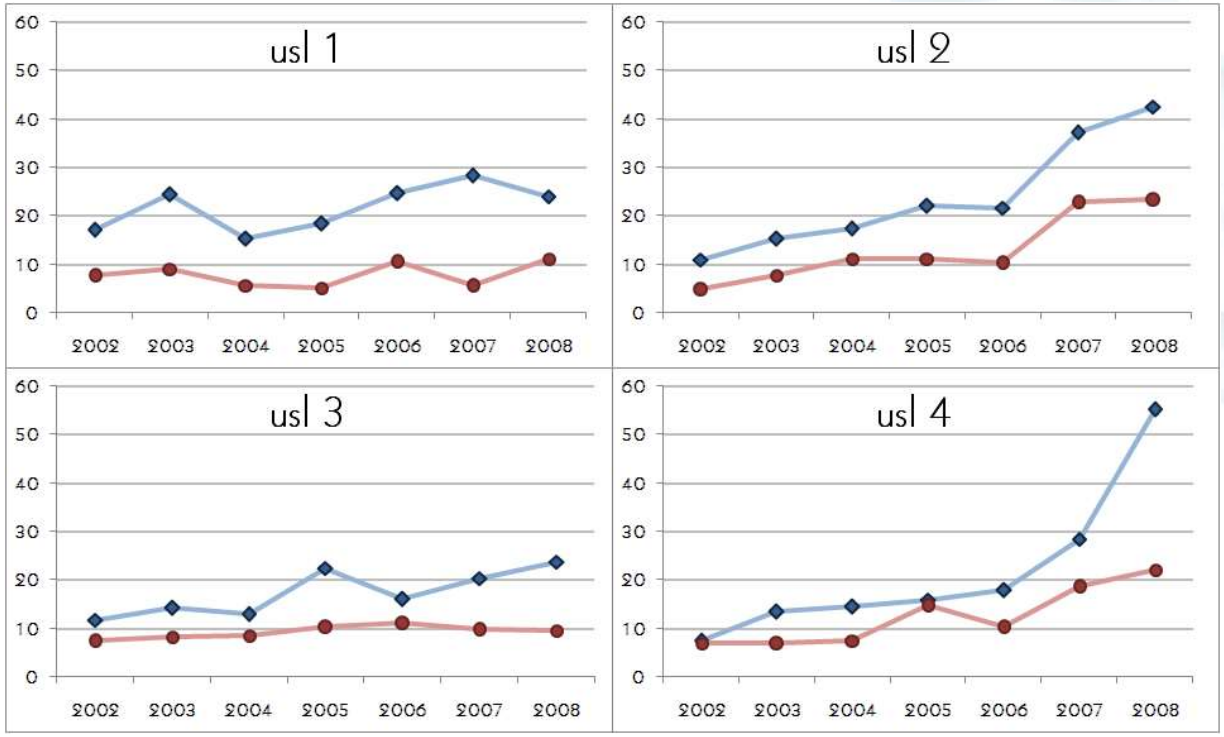


# Per servizio di screening: % casi individuati allo screening

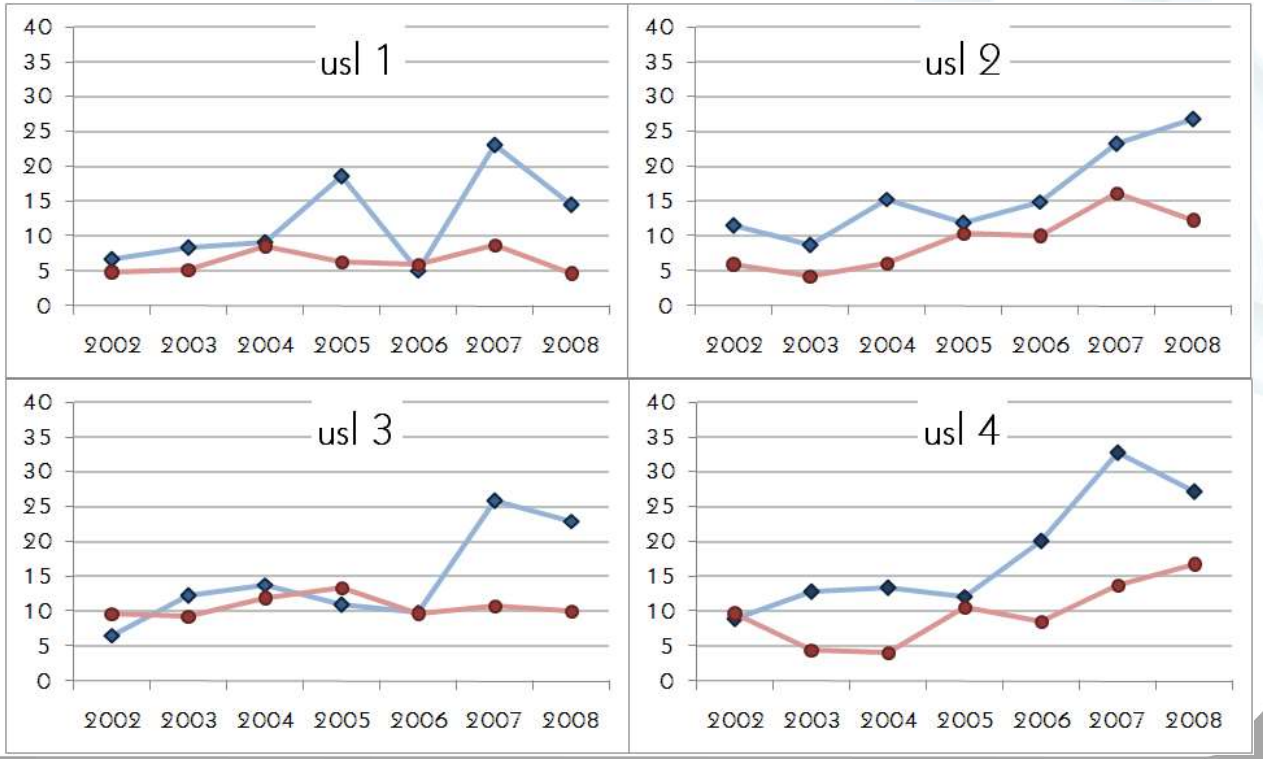


# Stadio 0 per USL

*(le USL hanno servizi di screening indipendenti)*



# Stadio I per USL

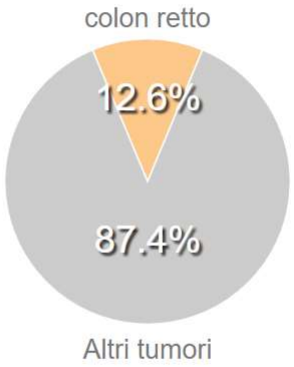


# Incidenza dei carcinomi colorettali: 809 casi per anno

## 1° TUMORE IN TUTTA POPOLAZIONE

16171 casi nel periodo 1994-2013

In media 809 casi per anno

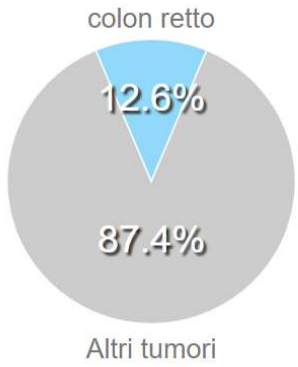



Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
**89.98**

## 2° TUMORE NEI MASCHI

8987 casi nel periodo 1994-2013

In media 449 casi per anno

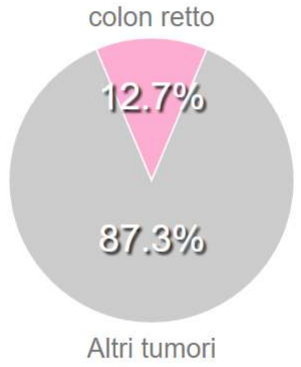



Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
**115.47**

## 2° TUMORE NELLE FEMMINE

7184 casi nel periodo 1994-2013

In media 359 casi per anno



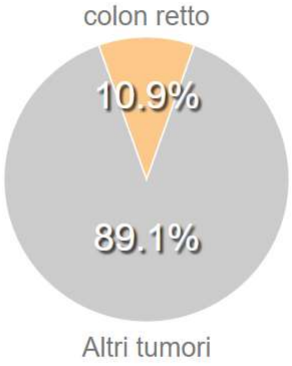

Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
**70.79**

# Mortalità per cancro del colon-retto

## 2° TUMORE DI TUTTA LA POPOLAZIONE

6941 casi nel periodo 1994-2014

In media 331 casi per anno

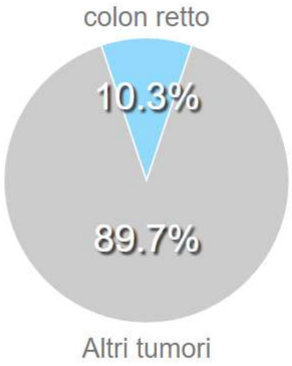



Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
**36.59**

## 2° TUMORE NEI MASCHI

3809 casi nel periodo 1994-2014

In media 181 casi per anno

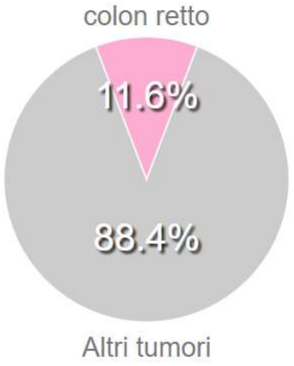



Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
**48.75**

## 2° TUMORE NELLE FEMMINE

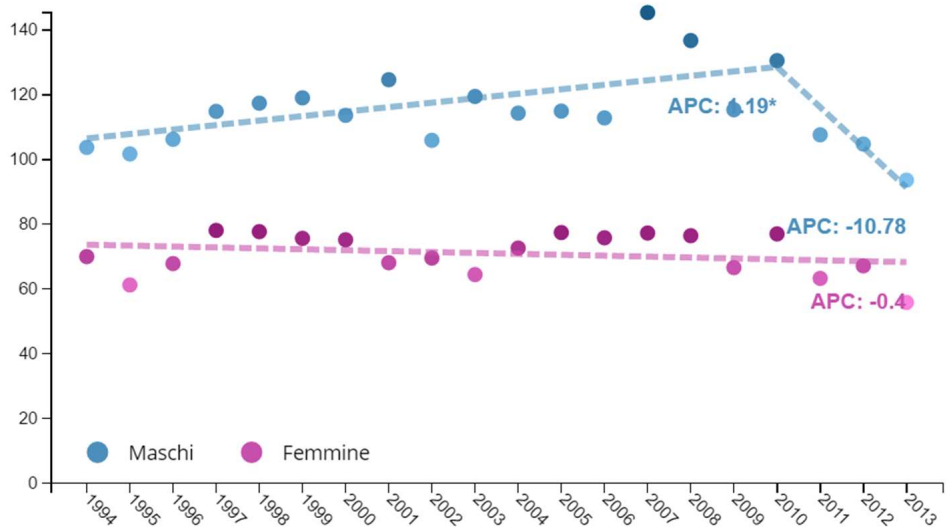
3132 casi nel periodo 1994-2014

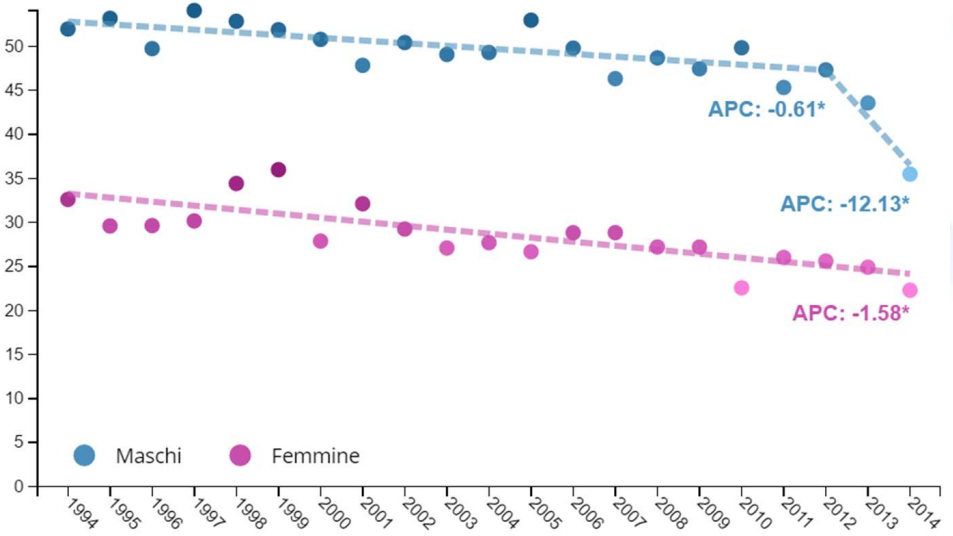
In media 149 casi per anno




Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
**28.11**

# Trend di incidenza e mortalità per sesso




1994-2010 **APC 1.19*** ; IC 95% 0.5 ; 2.8

2010-2013 APC -10.8 IC 95% -5.6 ;-10.4

APC -0.4; IC 95% -1.1 ; 0.5

**APC -0.61*** IC 95% -1.0 ; -0.2

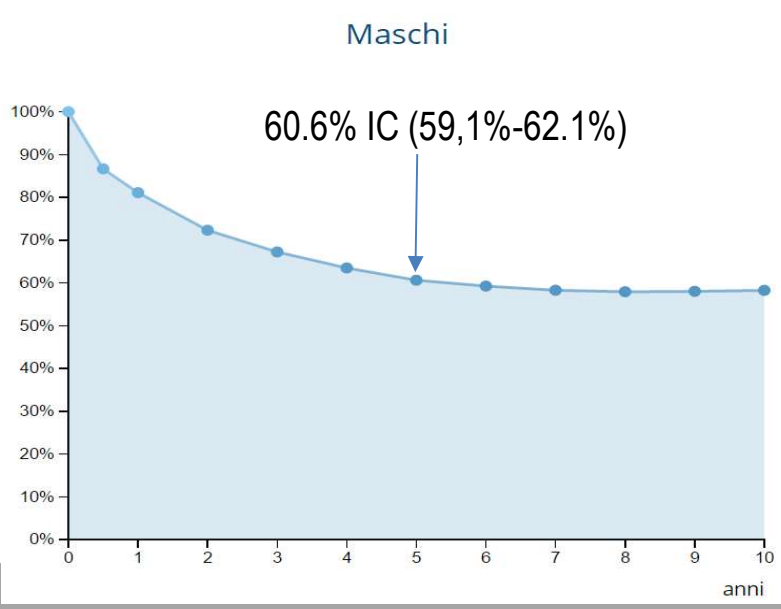
**APC -12.13*** IC 95% -12.2 ;-21.3

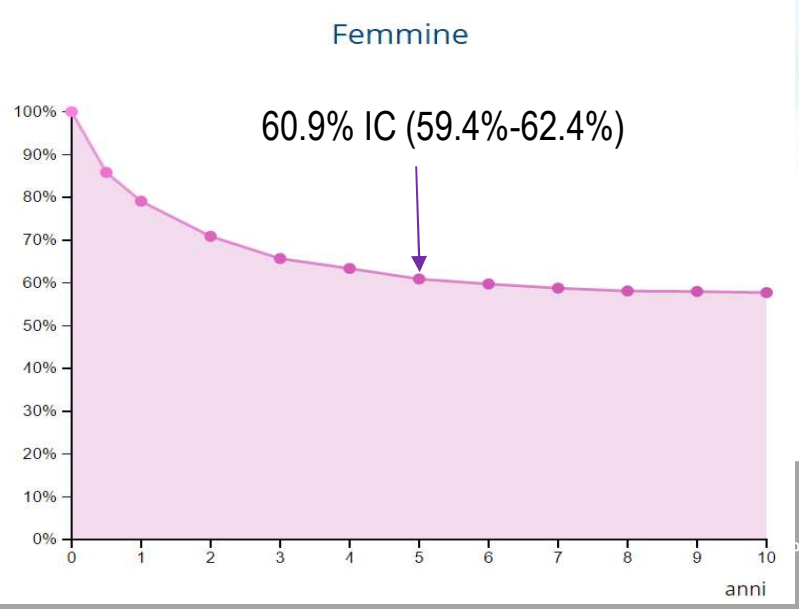
**APC -1.58*** IC 95% ( 2.1 ; -1.0)

# SOPRAVVIVENZA RELATIVA PER SESSO – COLON-RETTO. UMBRIA

## PERIODO DI STUDIO: 1994-2013, FOLLOW-UP AL 31-12-2015.

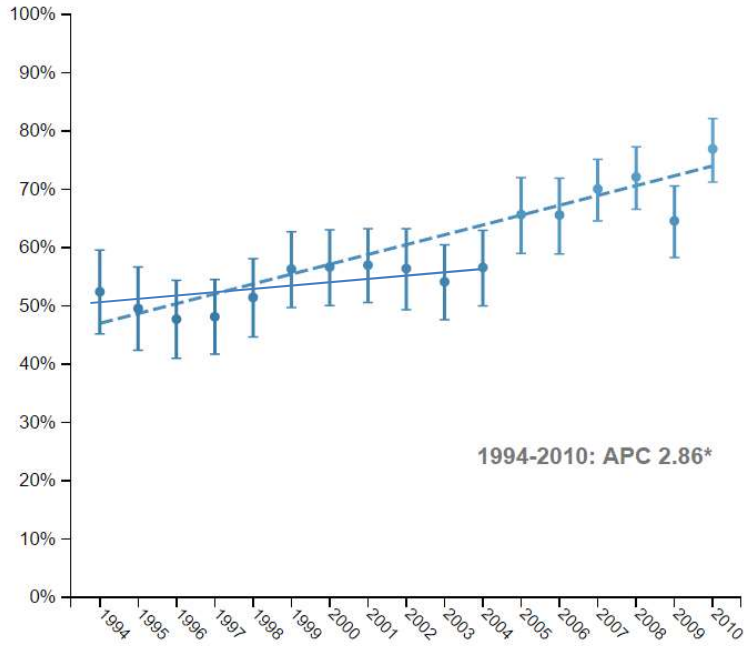
| | | | |
|---|---|---|---|
| 12921 casi in studio | 7061 54.6% maschi | 5860 45.4% femmine | 3.9 anni tempo mediano di follow up |
| 72 anni età mediana alla diagnosi | 71 anni età media alla diagnosi | 62% 7970 decessi nell'intervallo in studio | 39% 4990 decessi causa specifica |



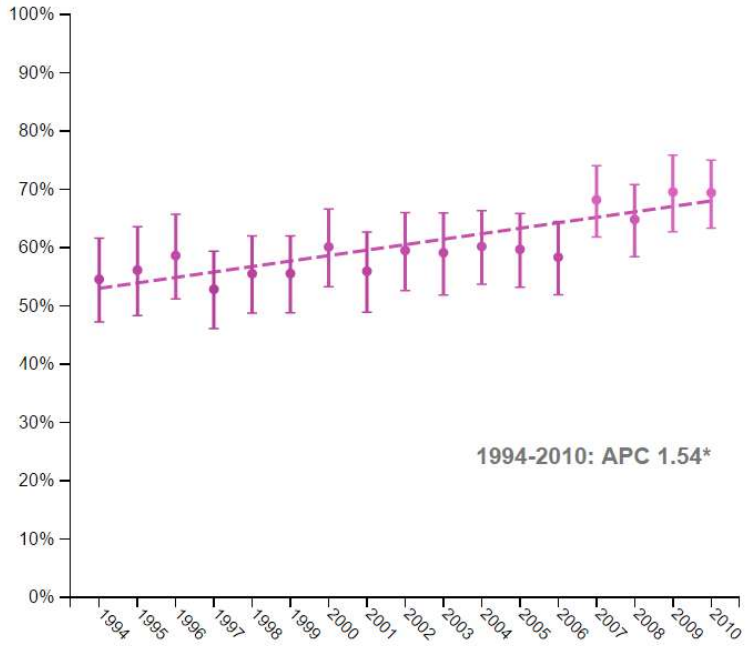



# TREND DI SOPRAVVIVENZA A 5 ANNI– COLON-RETTO

## Maschi



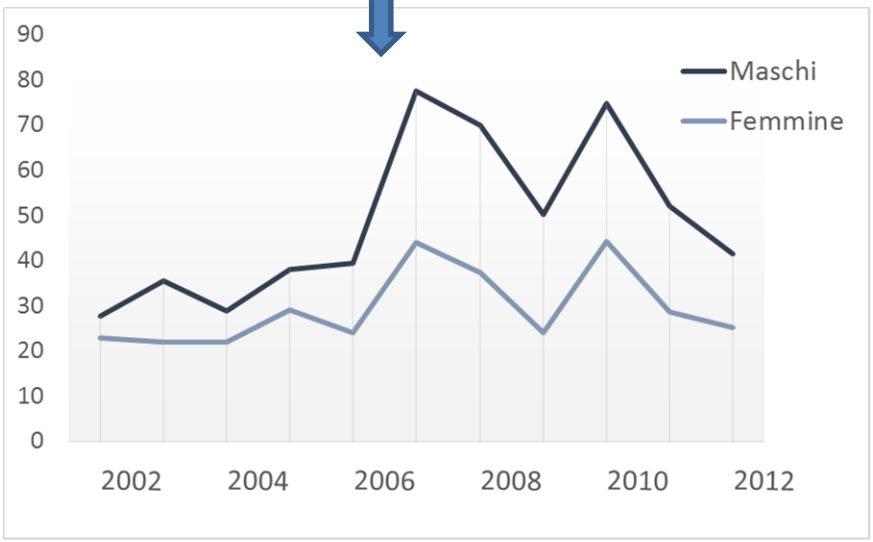

## Femmine



# Cancro del colon-retto – tassi di incidenza per stadio e sesso

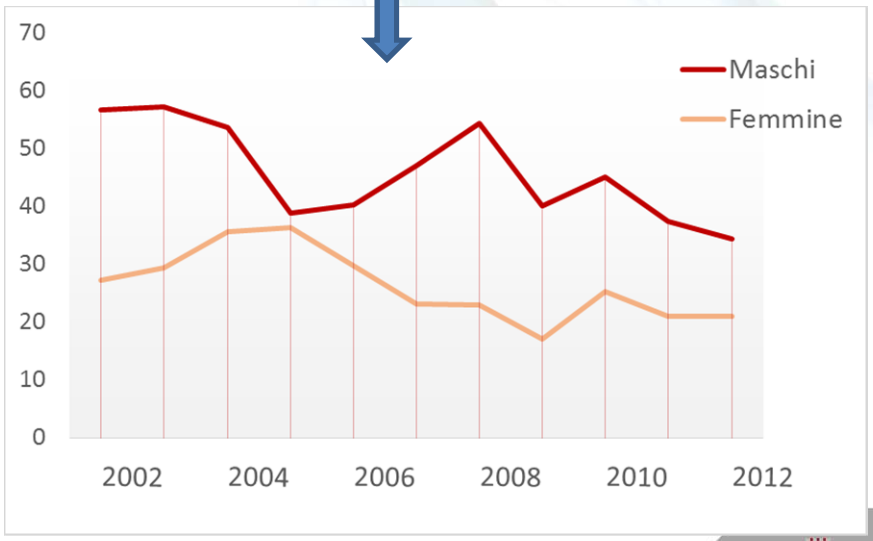
**Stadio I**

screening



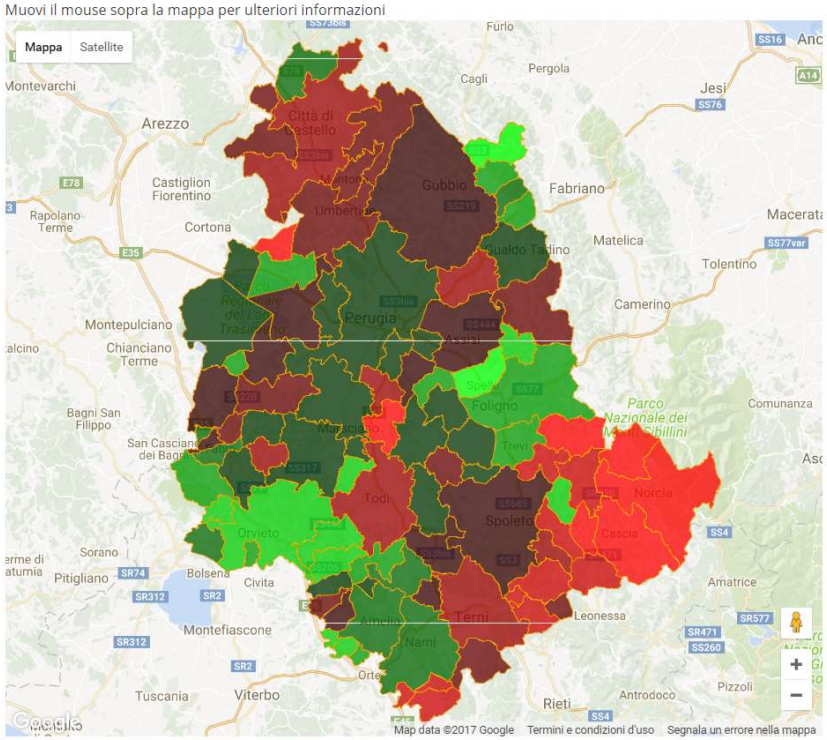

**Stadio IV**

screening

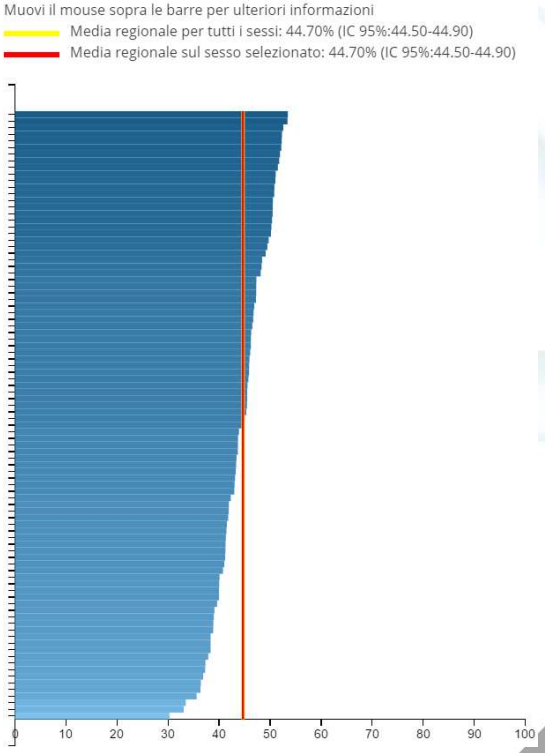


# Adesione

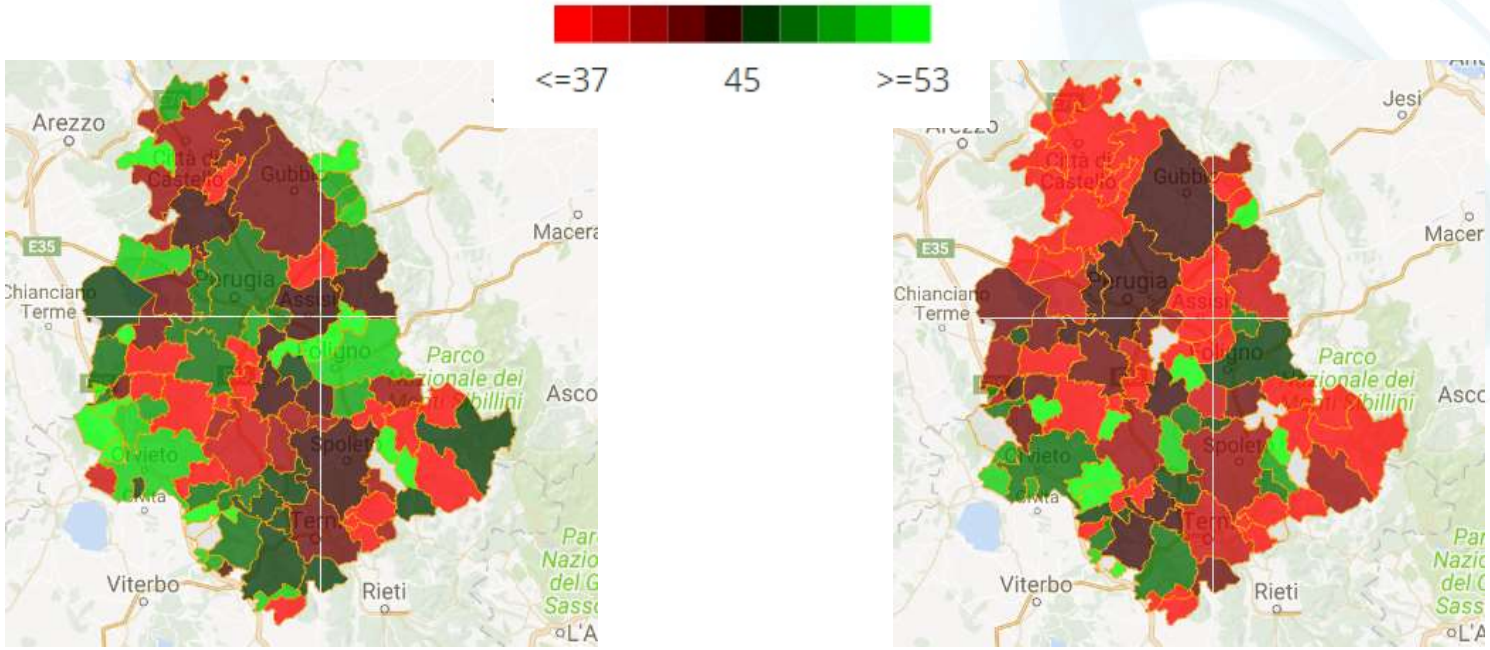
Muovi il mouse sopra la mappa per ulteriori informazioni




Muovi il mouse sopra le barre per ulteriori informazioni



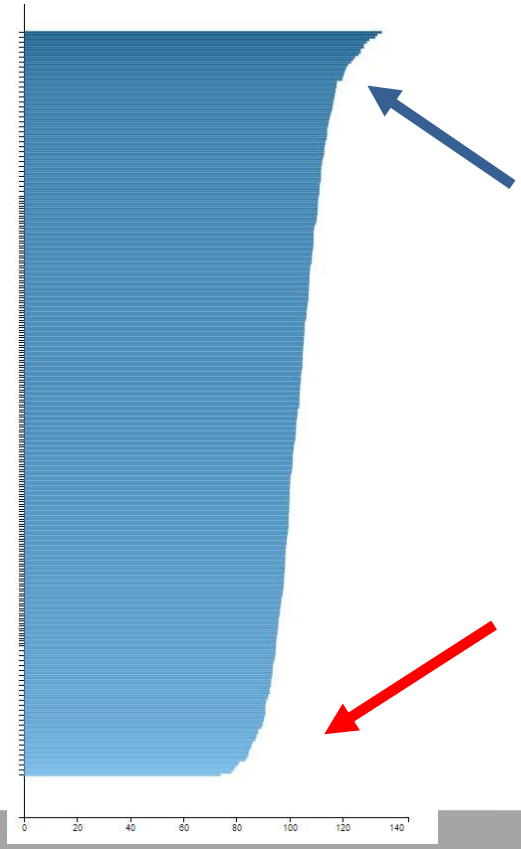
# Adesione per livello deprivazione

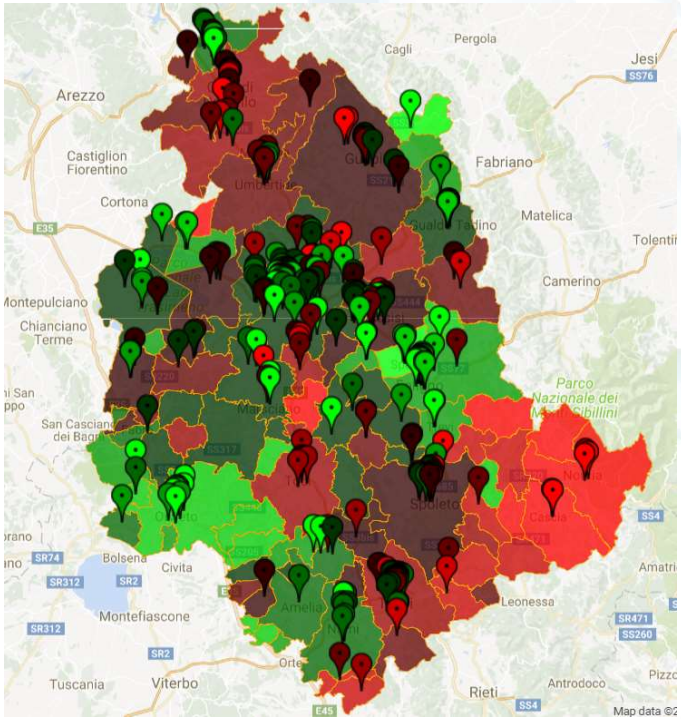



I quintile

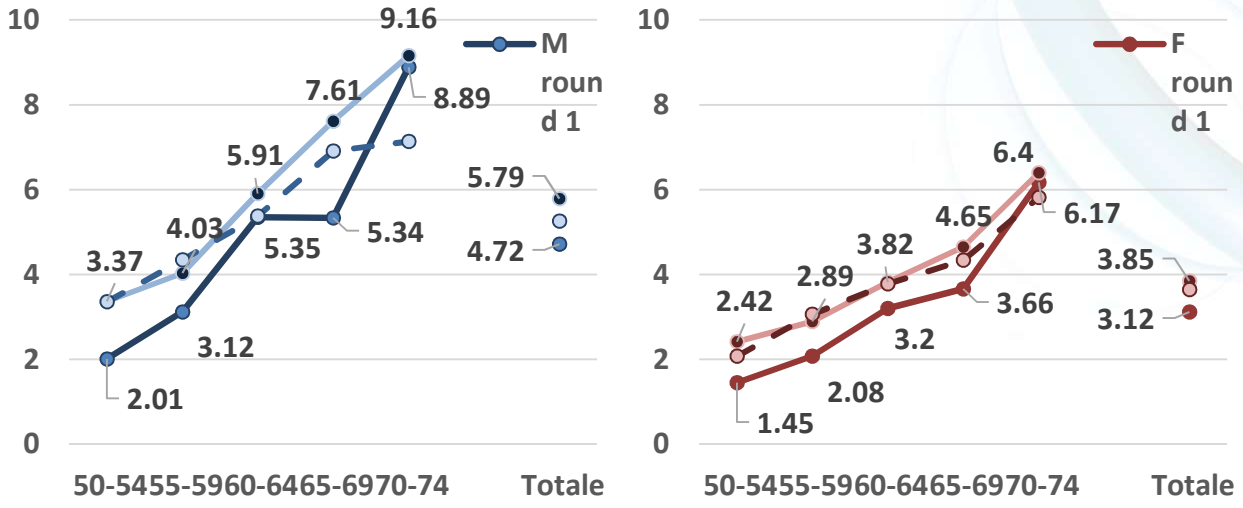
V quintile

# Adesione per MMG



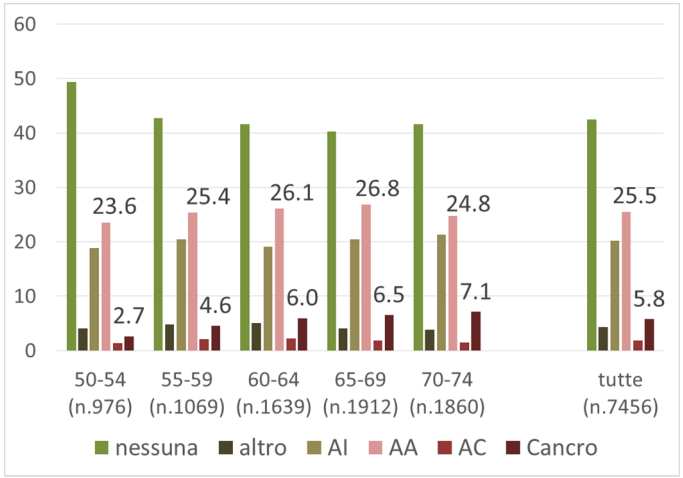



# % positivi con colonscopia per sesso, round e classe d'età

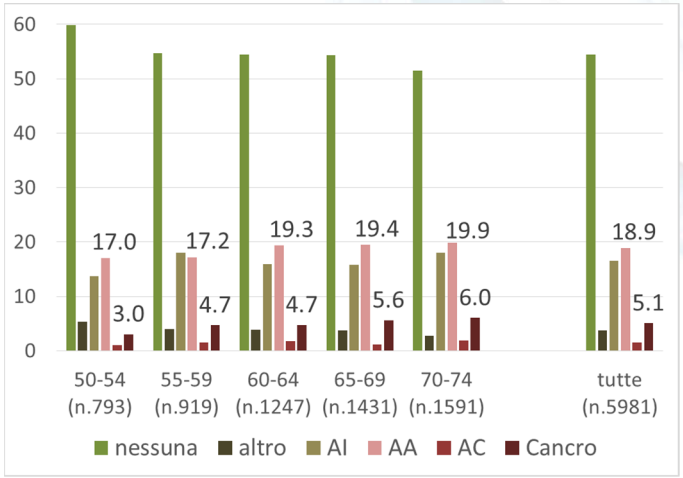


# Distribuzione per sesso e classe d'età delle lesioni

## Maschi

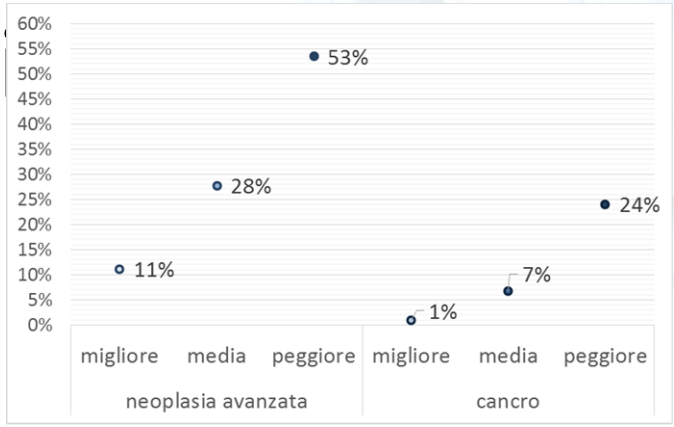



## Femmine



# neoplasia avanzata o di cancro per persone con diverse combinazioni di

| *Lesione* | *Caratteristiche* | *p* | *IC 95%* | |
|---|---|---|---|---|
| Neoplasia avanzata | f-Hb qt1 età 50-54 sesso F | **11%** | 9.5% | 12.8% |
| | media | **28%** | 27.0% | 28.5% |
| | f-Hb qt1 età 70-74 sesso M | **53%** | 50.4% | 56.6% |
| | | | | |
| Cancro | f-Hb qt1 età 50-54 *sesso F* | **1%** | 0.5% | 1.2% |
| | media | **7%** | 6.3% | 7.1% |
| | f-Hb qt1 età 70-74 sesso M | **24%** | 20.6% | 27.6% |



- Increasing the **starting age from 50 to 55 years** resulted in a total decrease in colonoscopy demand of 14%; however, this was at the expense of missing 9% of ANs …
- If solely the **cutoff was increased from 10 to 20 mg Hb/g feces**, this resulted in a decreased colonoscopy demand of 37% at the expense of missing 20% ANs and 7% cancers. *(modificato)*

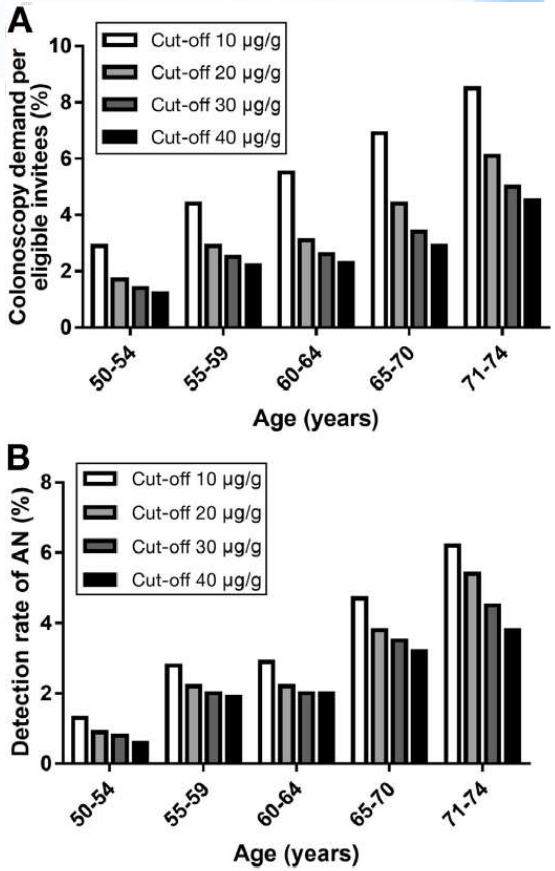



**Figure 3.** (*A*) Colonoscopy demand and (*B*) detection rate of AN per age category and cutoff concentration in µg Hb/g feces.

*Wieten E et al. Effects of Increasing Screening Age and Fecal Hemoglobin Cutoff Concentrations in a Colorectal Cancer Screening Program. Clin Gastroenterol Hepatol. 2016. pii: S1542-3565(16)30559-6.*

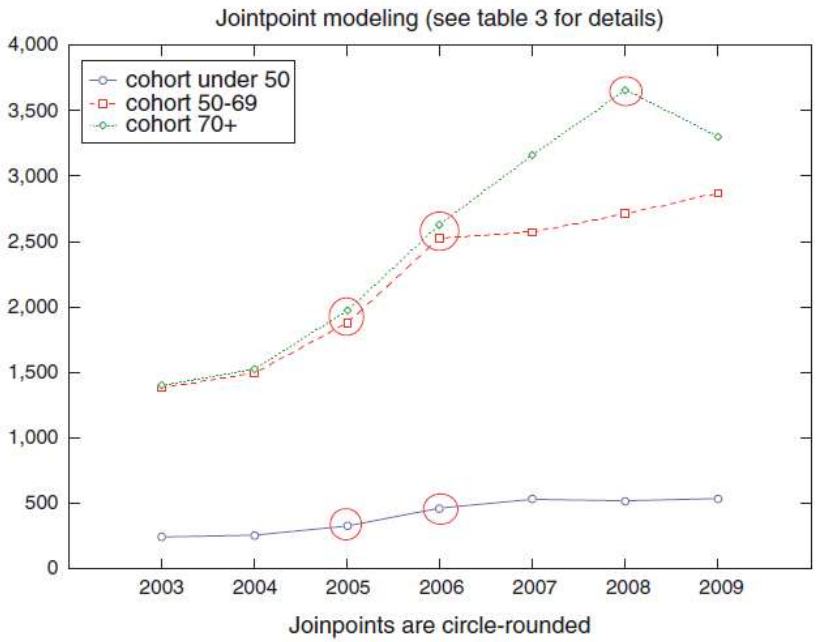



**Figure 2.** Colonoscopy rates by age cohort during the study period (2003–2009).

…but mainly attributable to a marked increase in demand for both FOBT and colonoscopy for " extra-screening patients. "

*Parente F et al. Impact of a population-based colorectal cancer screening program on local health services demand in Italy: a 7-year survey in a northern province. Am J Gastroenterol. 2011;106:1986-93.*

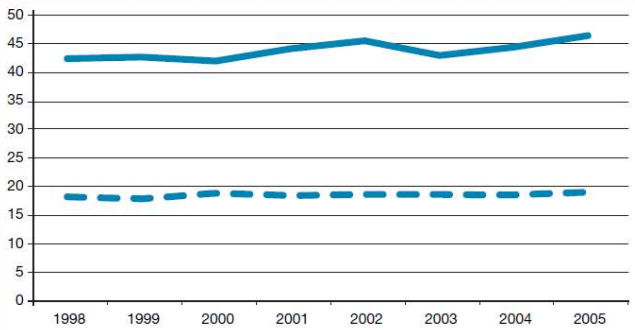
# Conclusioni

- Il CRC è uno dei tumori maligni con maggiore impatto sulla salute
- La mortalità è in diminuzione e ci aspettiamo che la progressiva diffusione dello screening accentui questo trend
- L'incidenza è condizionata dai fattori di rischio e dall'effetto di prevalenza degli screening e non mostra ancora un andamento favorevole
- La strategia basata prevalentemente sull'uso del FIT dovrebbe nei prossimi anni determinare una riduzione di incidenza
- L'effetto del FIT sull'incidenza sarà molto importante nel confronto con i test di screening endoscopici


Grazie

# Per colon e retto

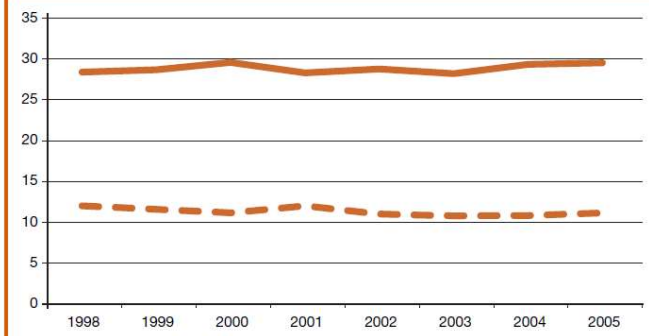
**MALE COLON CANCER**




INCIDENCE 1998-2005 APC (95% CI) **+1.2*** (+0.2 ; +2.1)

MORTALITY 1998-2005 APC (95% CI) **+0.6*** (+0.1 ; +1.1)

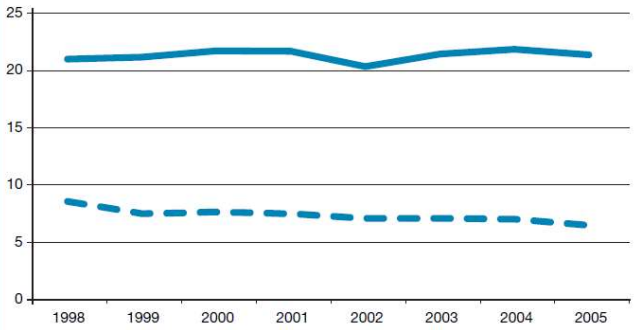
**FEMALE COLON CANCER**




INCIDENCE 1998-2005 APC (95% CI) **+0.3*** (-0.4 ; +1.1)

MORTALITY 1998-2005 APC (95% CI) **-1.3*** (-2.5 ; -0.0)

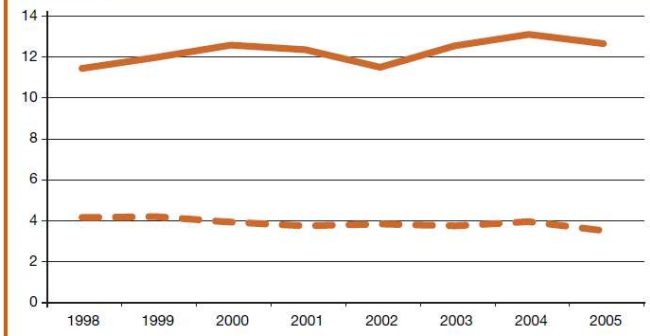
**MALE RECTUM CANCER**




INCIDENCE 1998-2005 APC (95% CI) **+0.2** (-0.7 ; 1.1)

MORTALITY 1998-2005 APC (95% CI) **-3.1*** (-4.4 ; -1.8)

**FEMALE RECTUM CANCER**



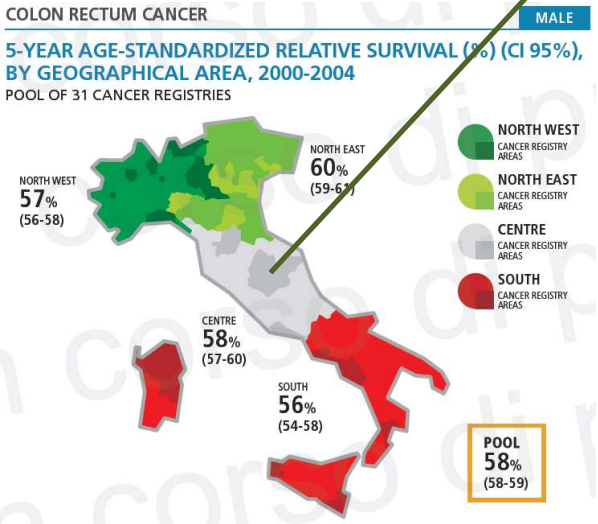

INCIDENCE 1998-2005 APC (95% CI) **+1.3** (-0.2 ; 2.8)

MORTALITY 1998-2005 APC (95% CI) **-1.9*** (-3.4 ; -0.5)

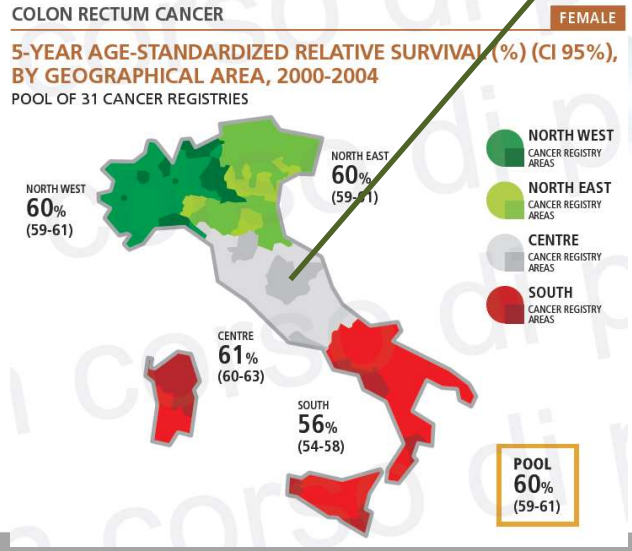
# Sopravvivenza relativa pre-screening

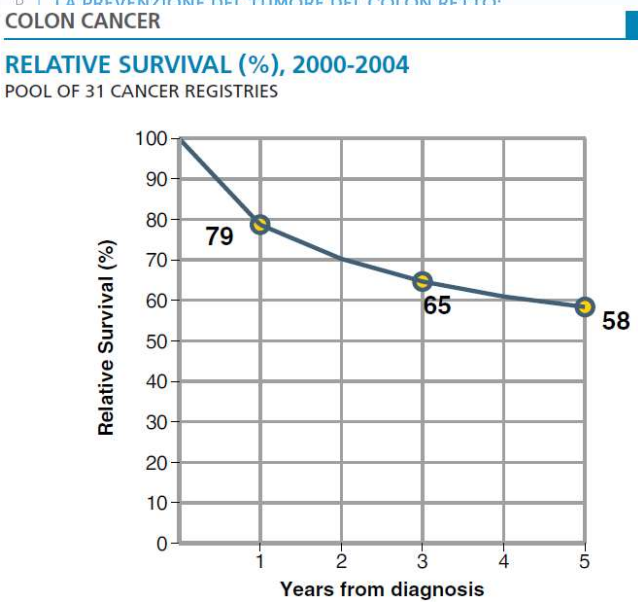
fonte: Monografia AIRTum

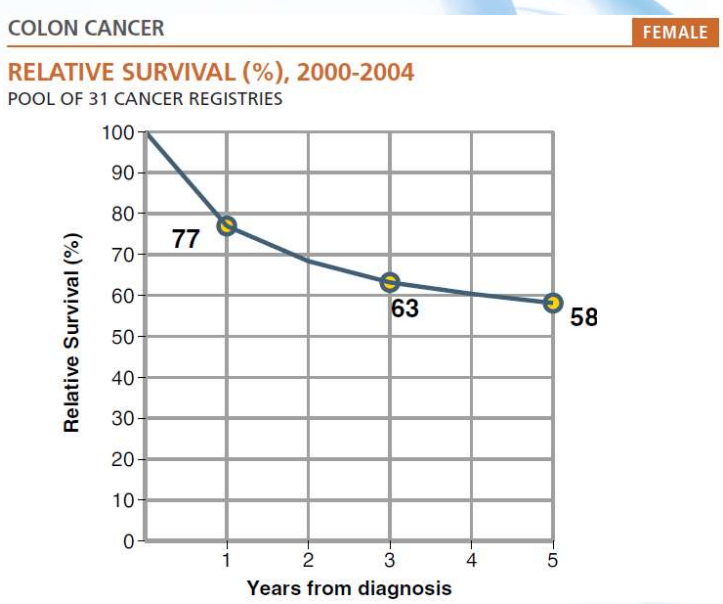
**Umbria M**
**58.5%**




**Umbria F**
**62%**





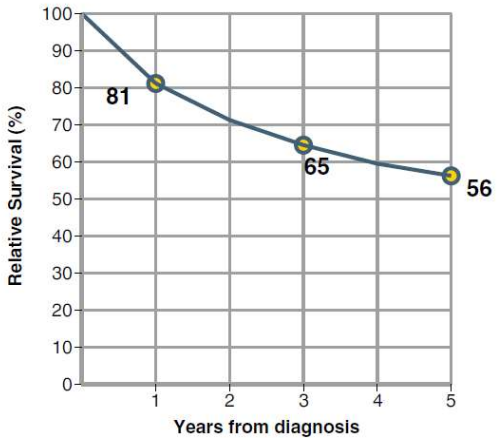




# Curve di sopravvivenza relativa a 5 anni per sesso

RECTUM CANCER — MALE

**RELATIVE SURVIVAL (%), 2000-2004**

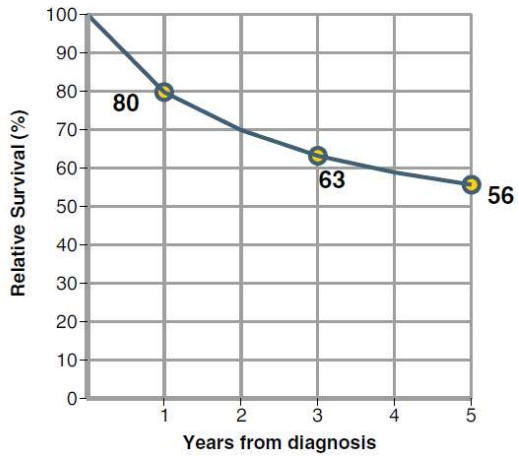
POOL OF 31 CANCER REGISTRIES




RECTUM CANCER — FEMALE

**RELATIVE SURVIVAL (%), 2000-2004**

POOL OF 31 CANCER REGISTRIES

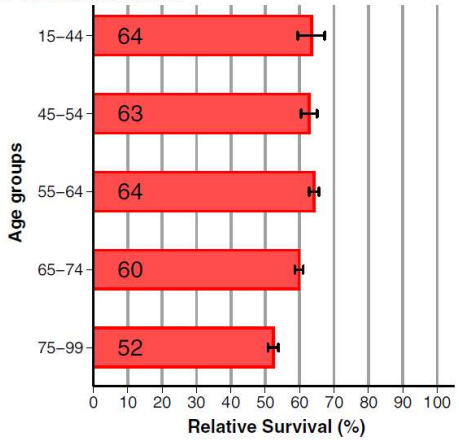



# Curve di sopravvivenza relativa a 5 anni per sesso

## COLON CANCER — MALE

### 5-YEAR RELATIVE SURVIVAL (%) BY AGE, 2000-2004

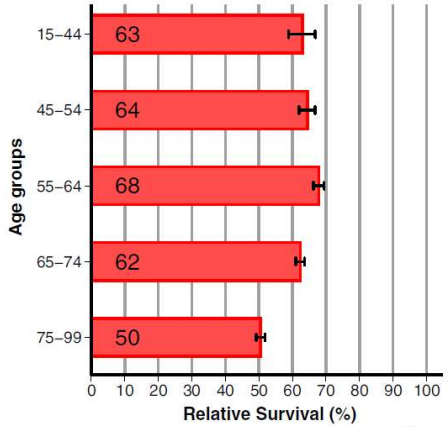
POOL OF 31 CANCER REGISTRIES




## COLON CANCER — FEMALE

### 5-YEAR RELATIVE SURVIVAL (%) BY AGE, 2000-2004

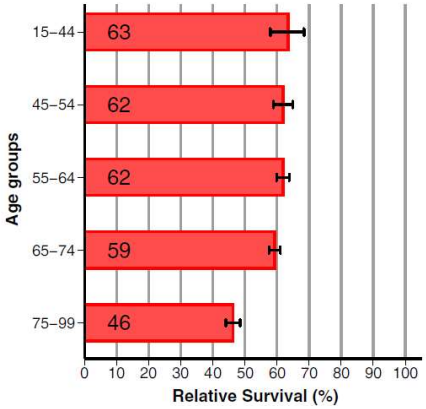
POOL OF 31 CANCER REGISTRIES




## RECTUM CANCER — MALE

### 5-YEAR RELATIVE SURVIVAL (%) BY AGE, 2000-2004

POOL OF 31 CANCER REGISTRIES




## RECTUM CANCER — FEMALE

### 5-YEAR RELATIVE SURVIVAL (%) BY AGE, 2000-2004

POOL OF 31 CANCER REGISTRIES