Epidemiologia dei Tumori colonrettali
Evidenze scientifiche
Situazione Italiana

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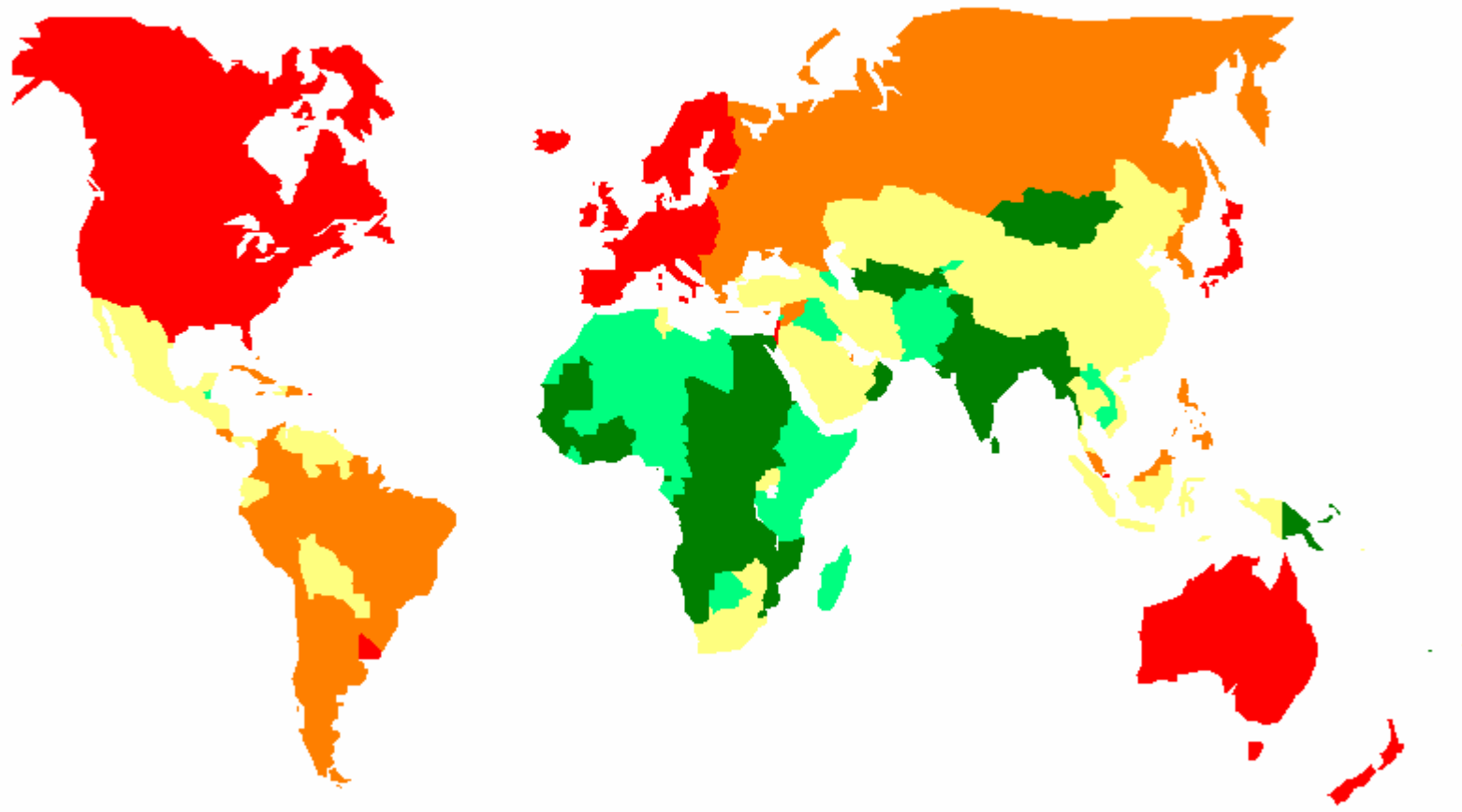
CENTRO
PER LO STUDIO
E LA PREVENZIONE
ONCOLOGICA

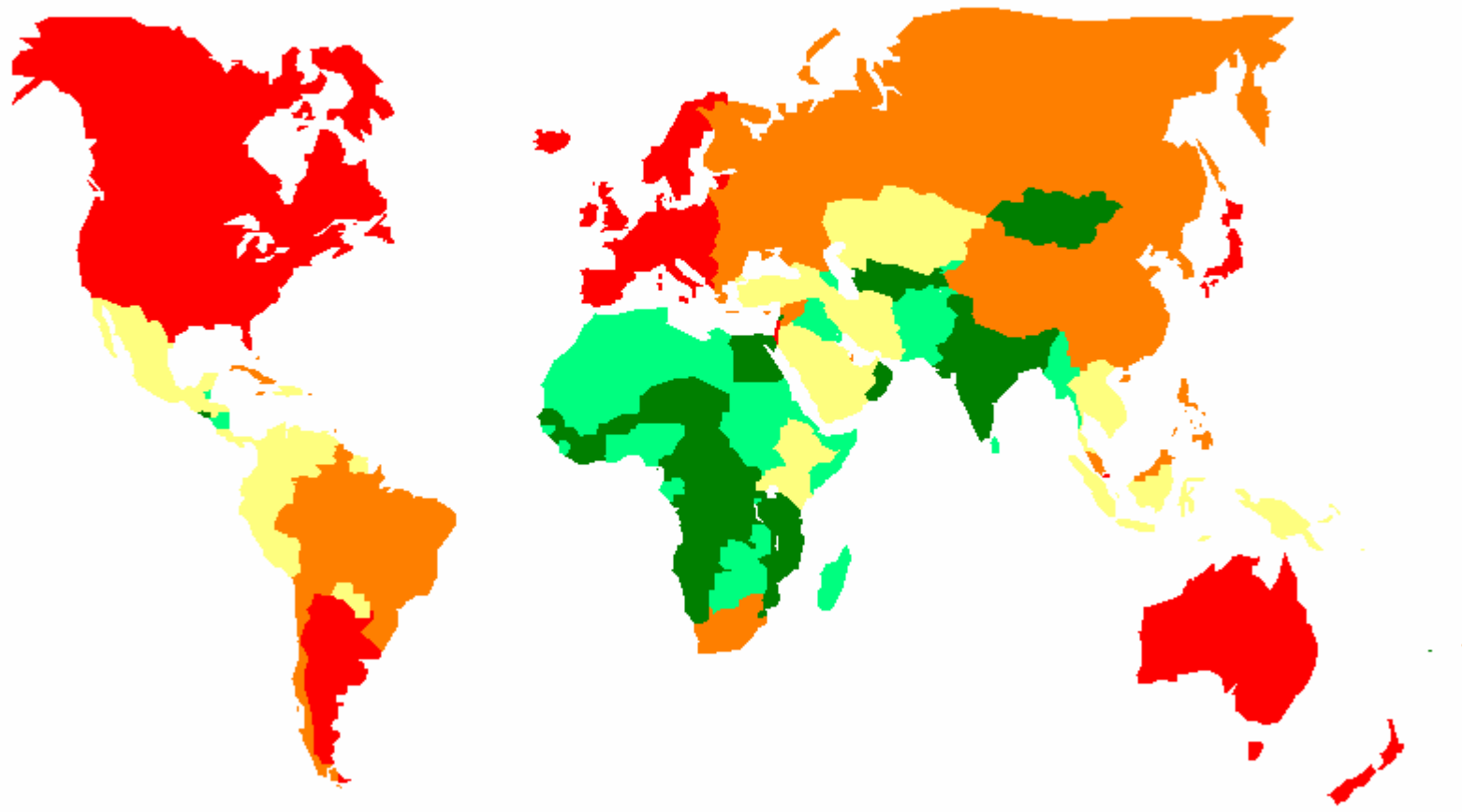
Istituto Scientifico
della Regione Toscana

Colon and rectum, Females
Age-Standardized incidence rate per 100,000



GLOBOCAN 2002, IARC

Colon and rectum, Males
Age-Standardized incidence rate per 100,000



< 4.8 < 7.2 < 12.3 < 27.6 < 58.5

GLOBOCAN 2002, IARC

Italy 2002

SITE: Colon and rectum

	Incidence			Mortality		
Sex	**Cases**	**Crude Rate**	**ASR(W)**	**Deaths**	**Crude Rate**	**ASR(W)**
Males	**20457**	73.6	39.3	**9061**	32.6	16.5
Females	**17276**	58.5	26.6	**7909**	26.8	10.9

Methods:
Incidence: National mortality data and modeling
Mortality: National data

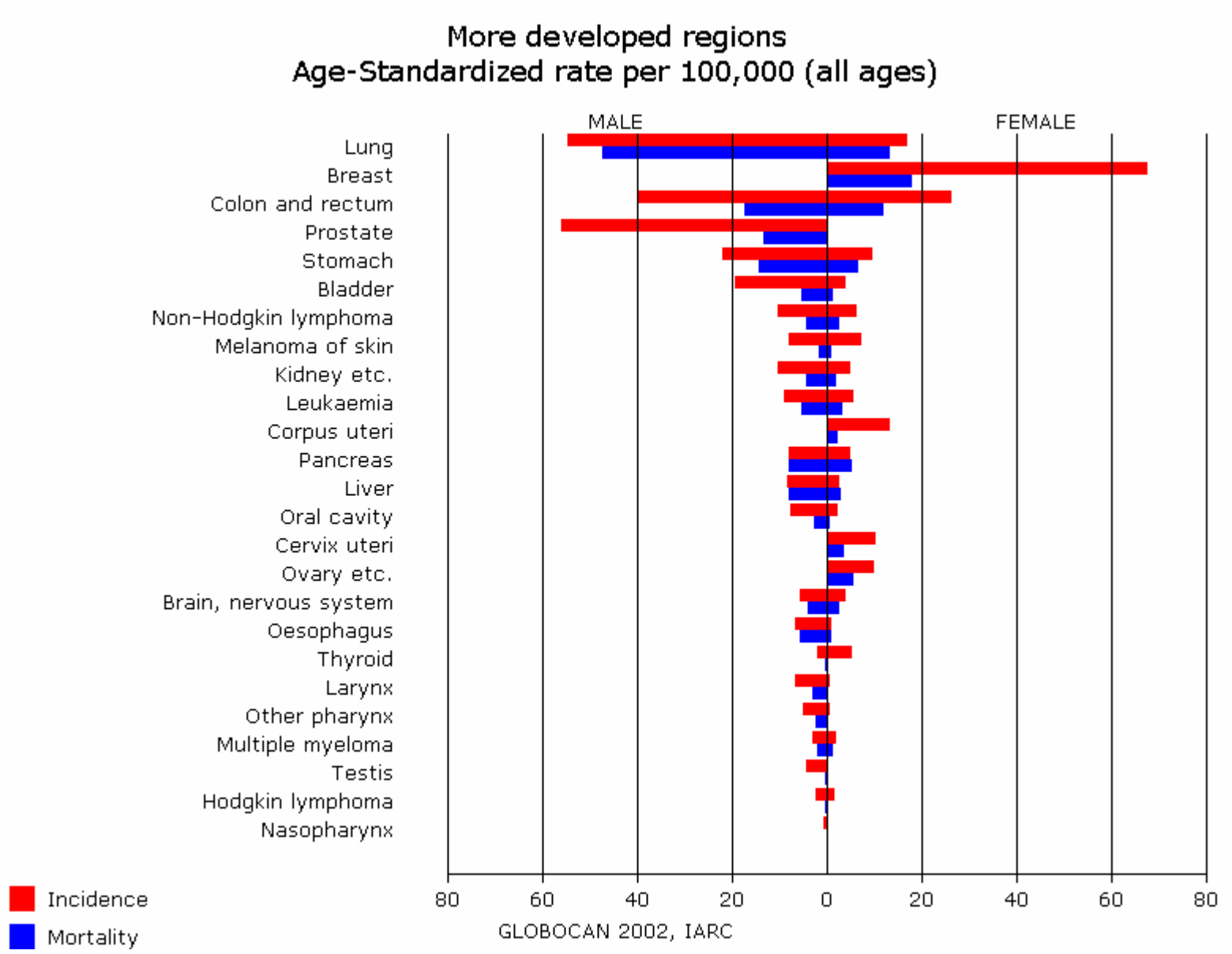
Crude and Age-Standardised (World) rates, per 100,000

GLOBOCAN 2002, IARC

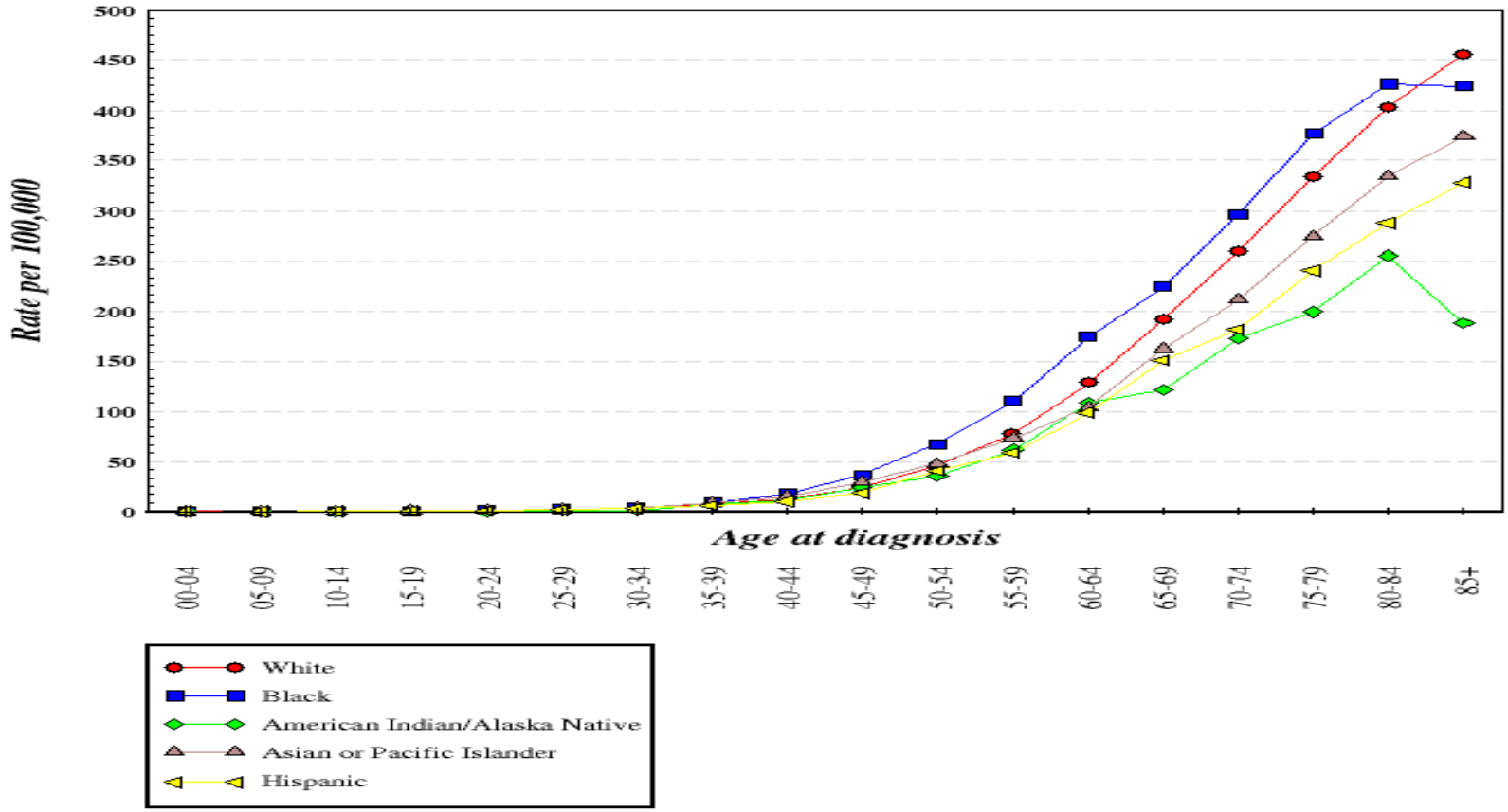
Incidenza e Mortalità per tumori Colorettali
ITALIA

- Rischio Cumulativo di sviluppare un CCR (0-74 anni)
  Maschi= 4.5% Femmine=2.7%

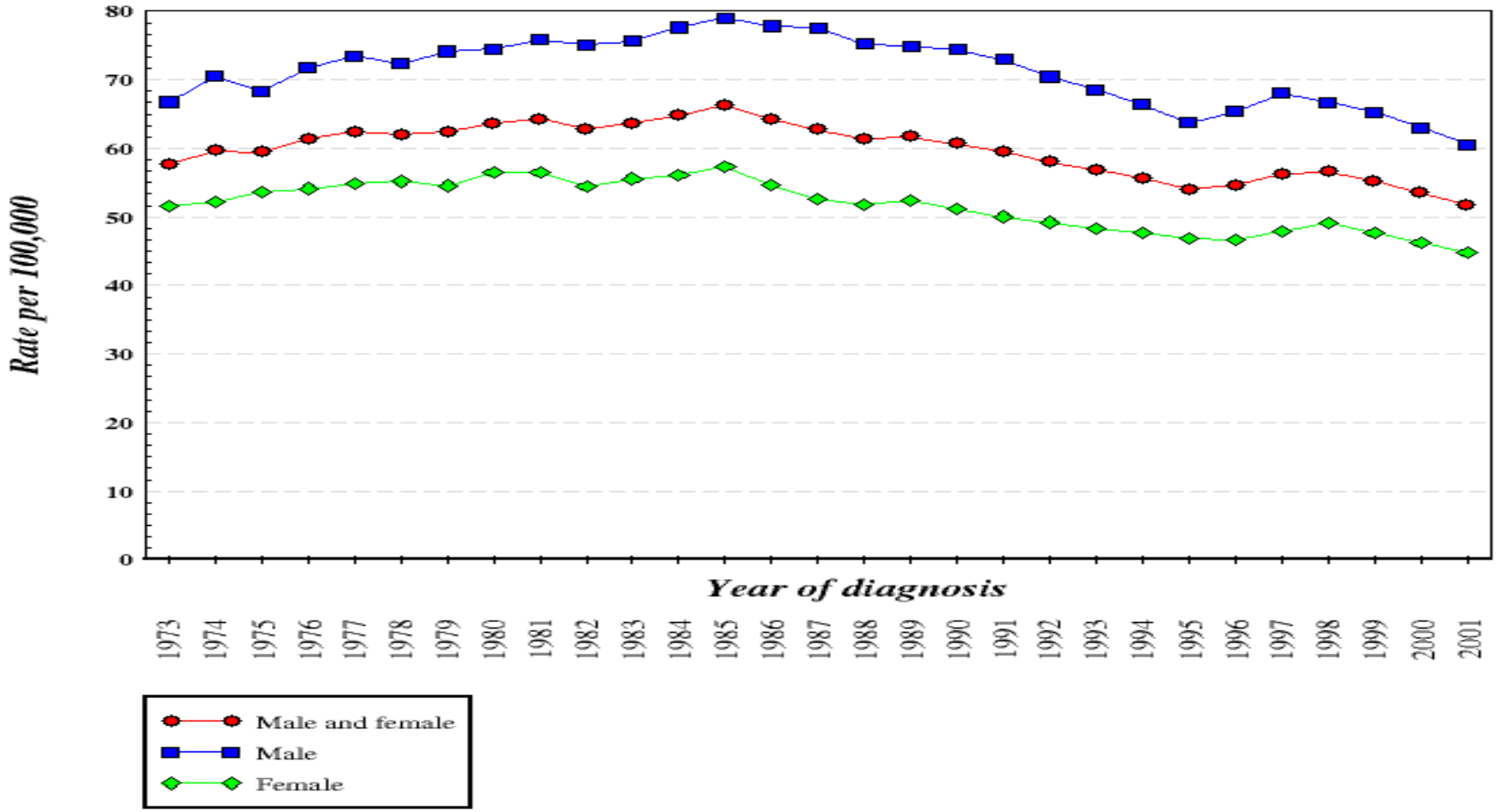
- Rischio Cumulativo di morte per CCR (0-74 anni)
  Maschi=1.9% Femmine=1.1%


More developed regions
Age-Standardized rate per 100,000 (all ages)
MALE
FEMALE
Lung
Breast
Colon and rectum
Prostate
Stomach
Bladder
Non-Hodgkin lymphoma
Melanoma of skin
Kidney etc.
Leukaemia
Corpus uteri
Pancreas
Liver
Oral cavity
Cervix uteri
Ovary etc.
Brain, nervous system
Oesophagus
Thyroid
Larynx
Other pharynx
Multiple myeloma
Testis
Hodgkin lymphoma
Nasopharynx
80
60
40
20
0
20
40
60
80
Incidence
Mortality
GLOBOCAN 2002, IARC

Distribuzione dei CCR per età e sesso fonte*: SEER*

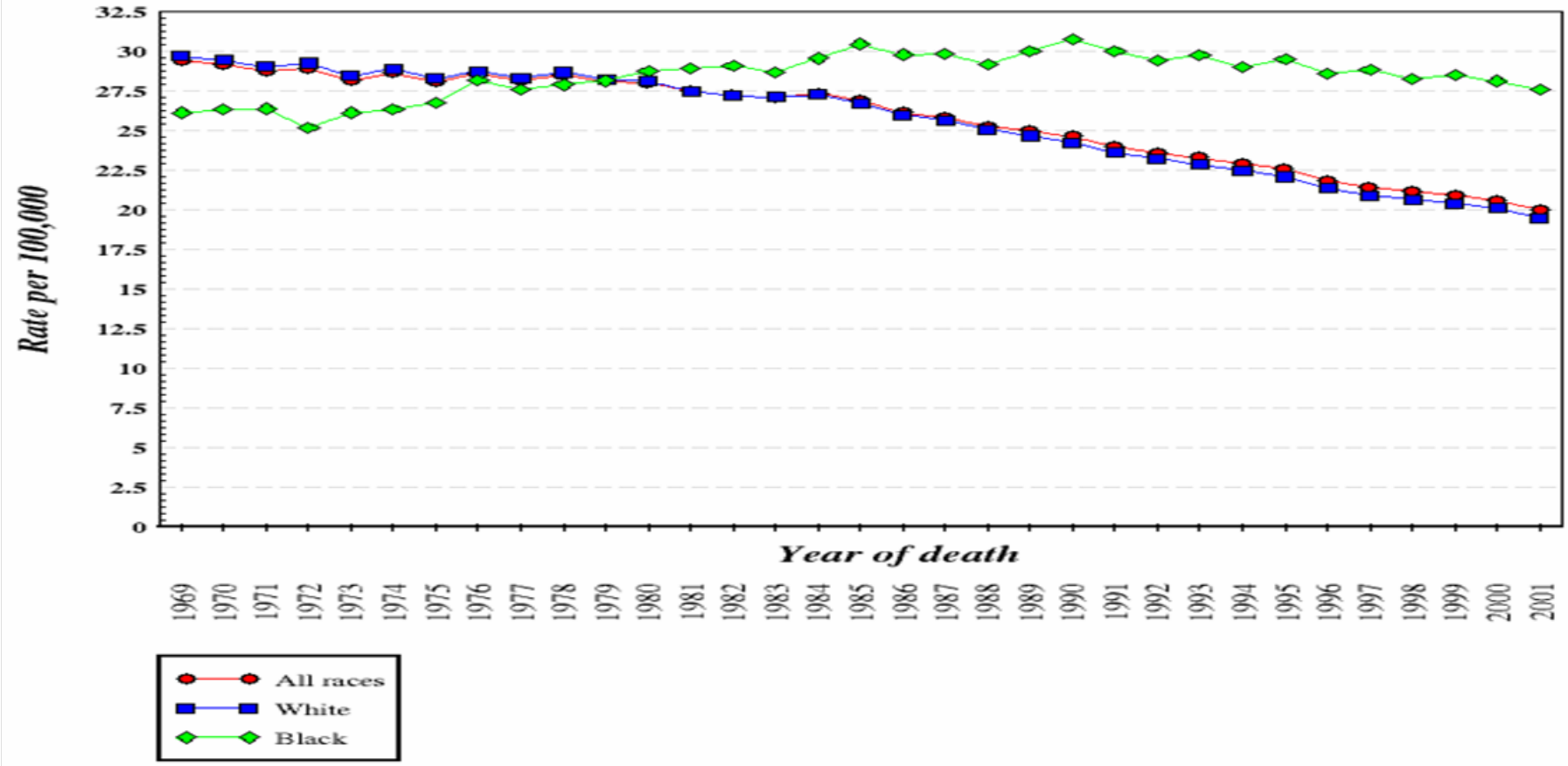


Trends temporali del CCR negli USA
fonte: *SEER*



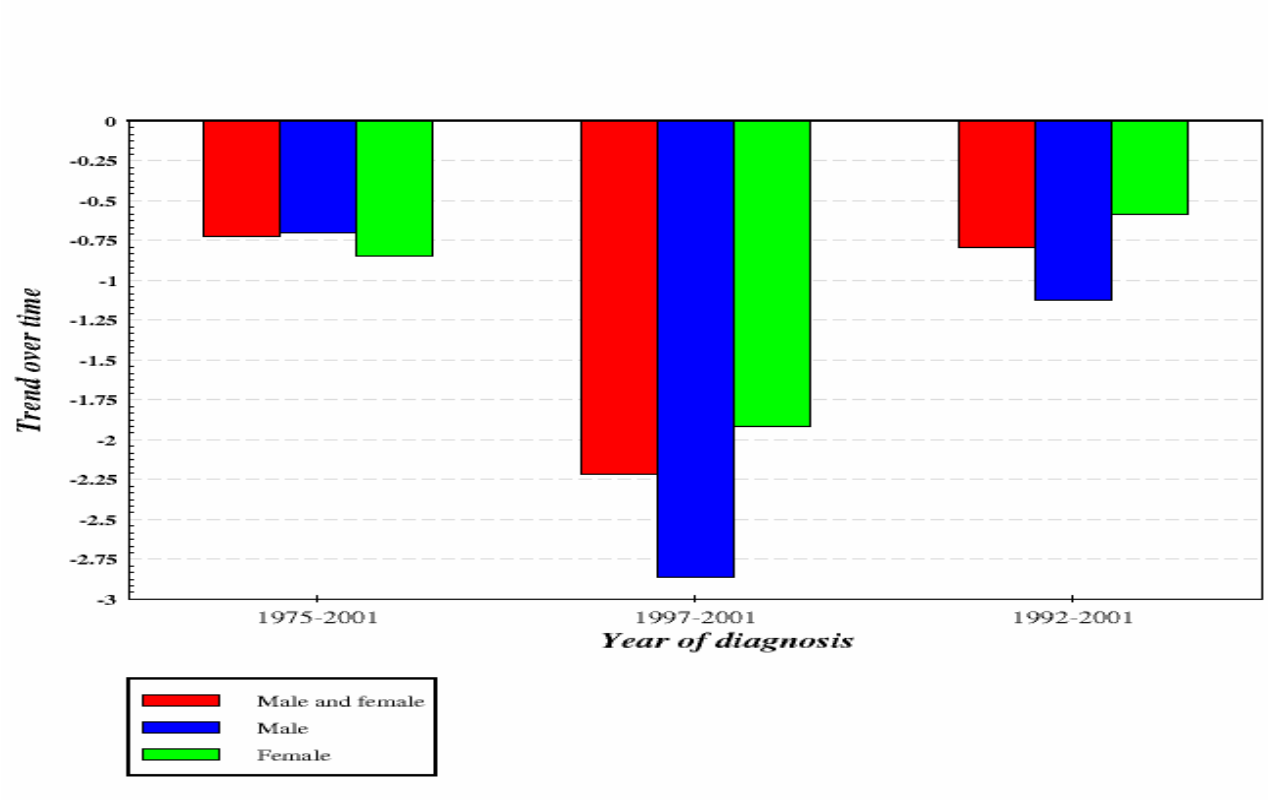
Trend della Mortalità per CCR in US .

Source SEER

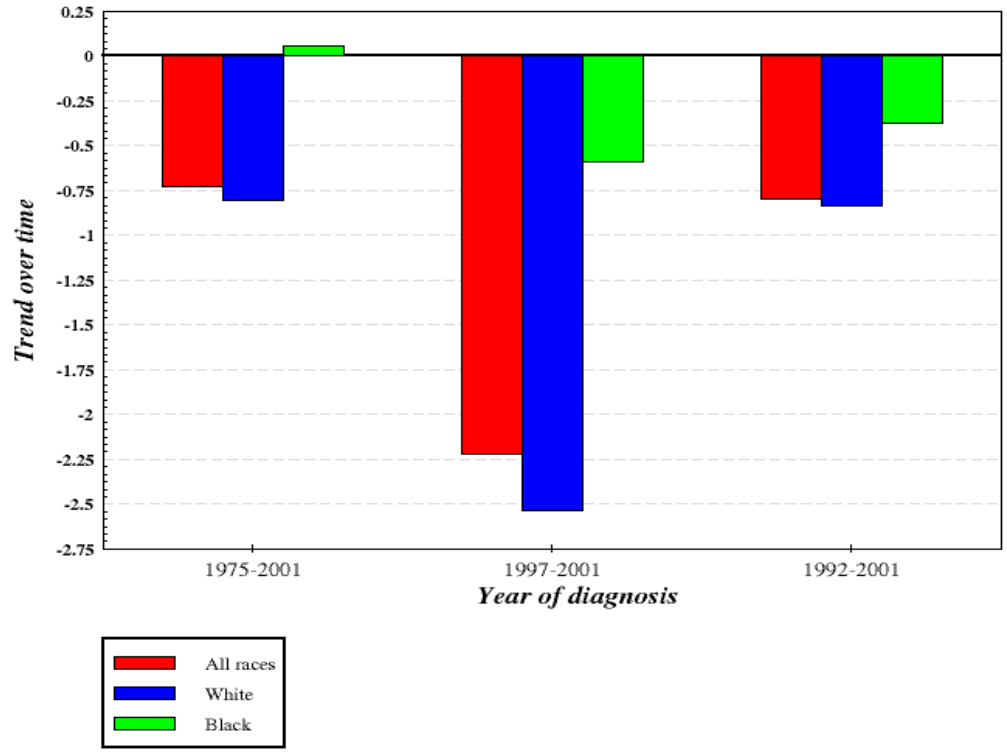


TREND INCIDENZA (EAPC) DEL CARCINOMA COLON-RETTO negli USA

fonte SEER

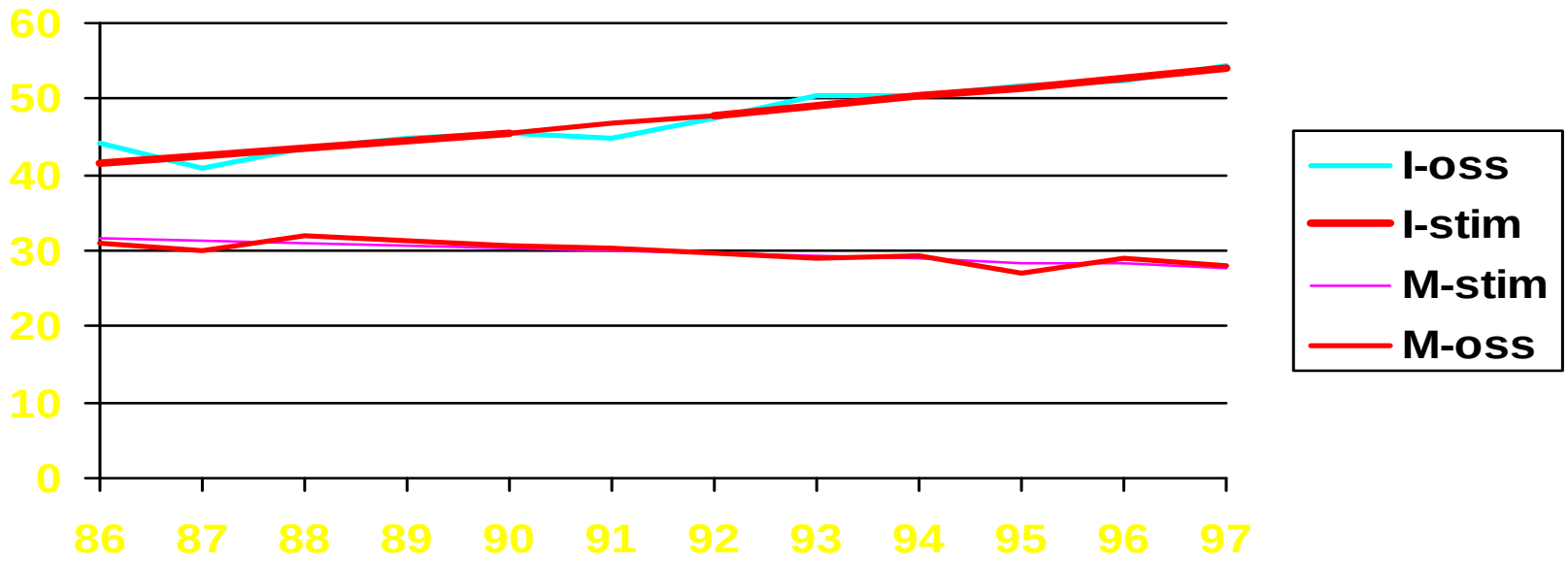


Trends of CCR **incidence** By race (EAPC)

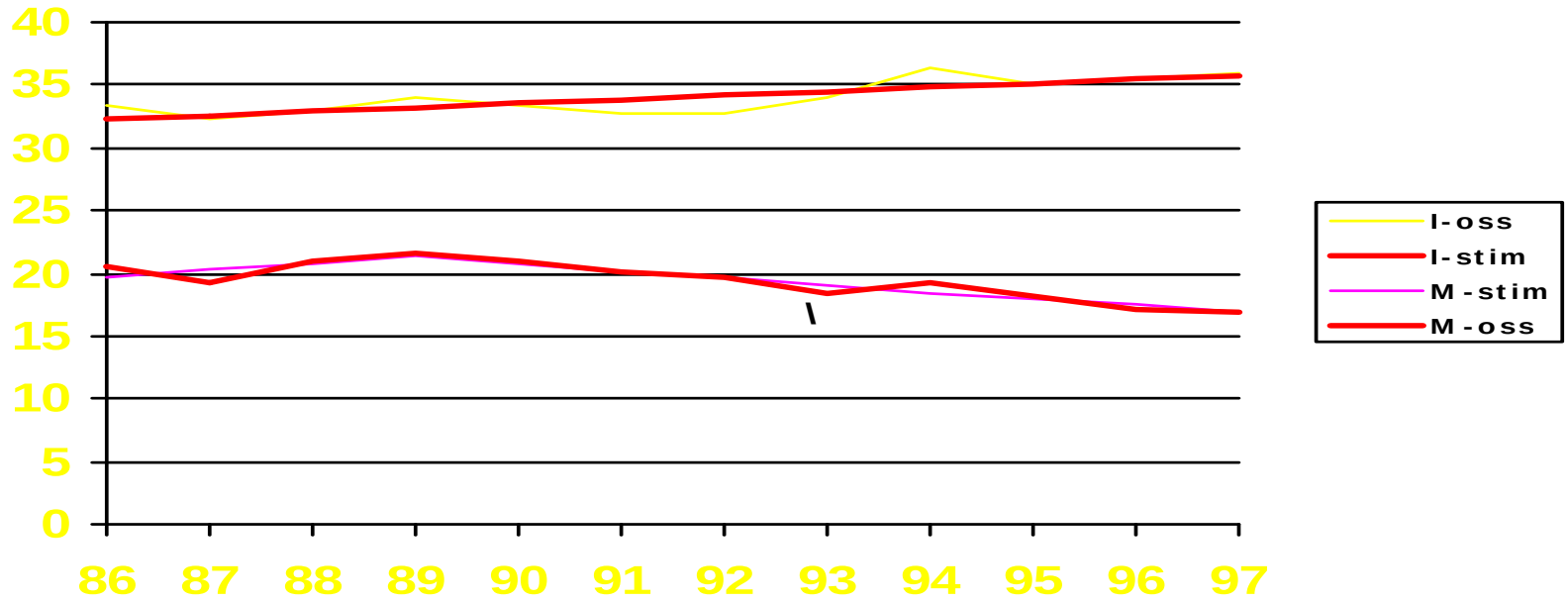


US CCR **MORTALITY** (EAPC) source:seer

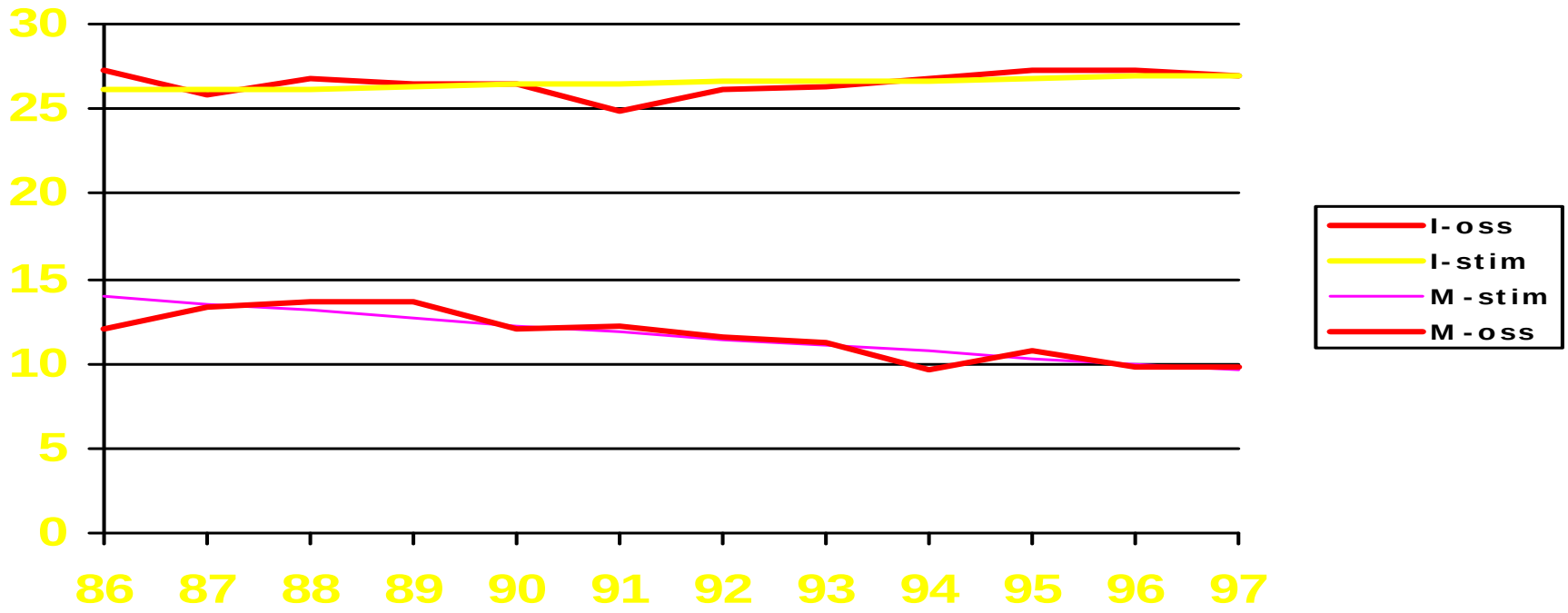
Trend Incidenza - Colon maschi
Tassi Standardizzati 1986-1997 –
Registri Tumori Italiani



Trend Incidenza - Colon Femmine
Tassi Standardizzati 1986-1997
Registri Tumori Italiani

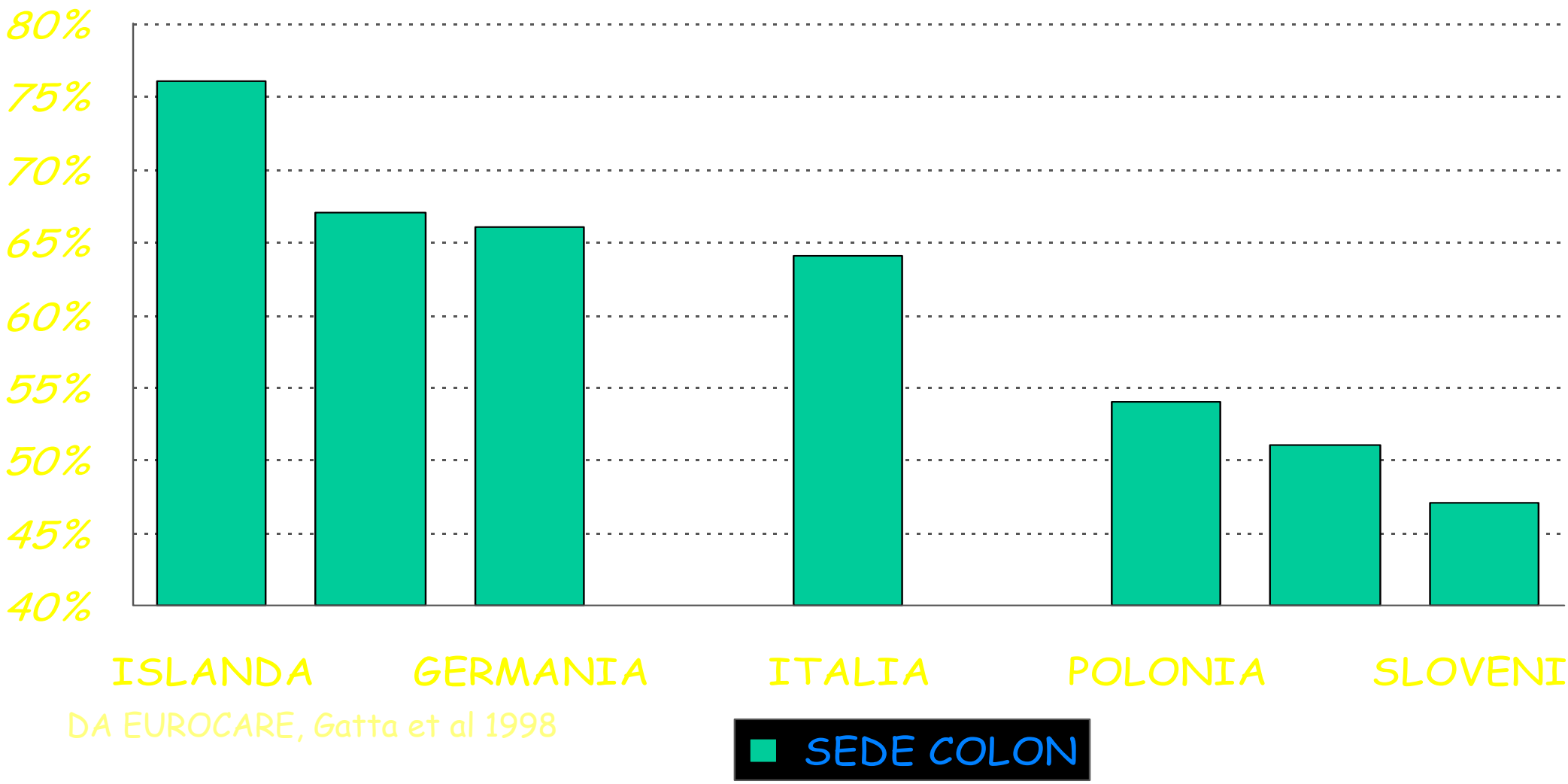


Trend Incidenza - Retto maschi
Tassi Standardizzati 1986-1997
Registri Tumori Italiani



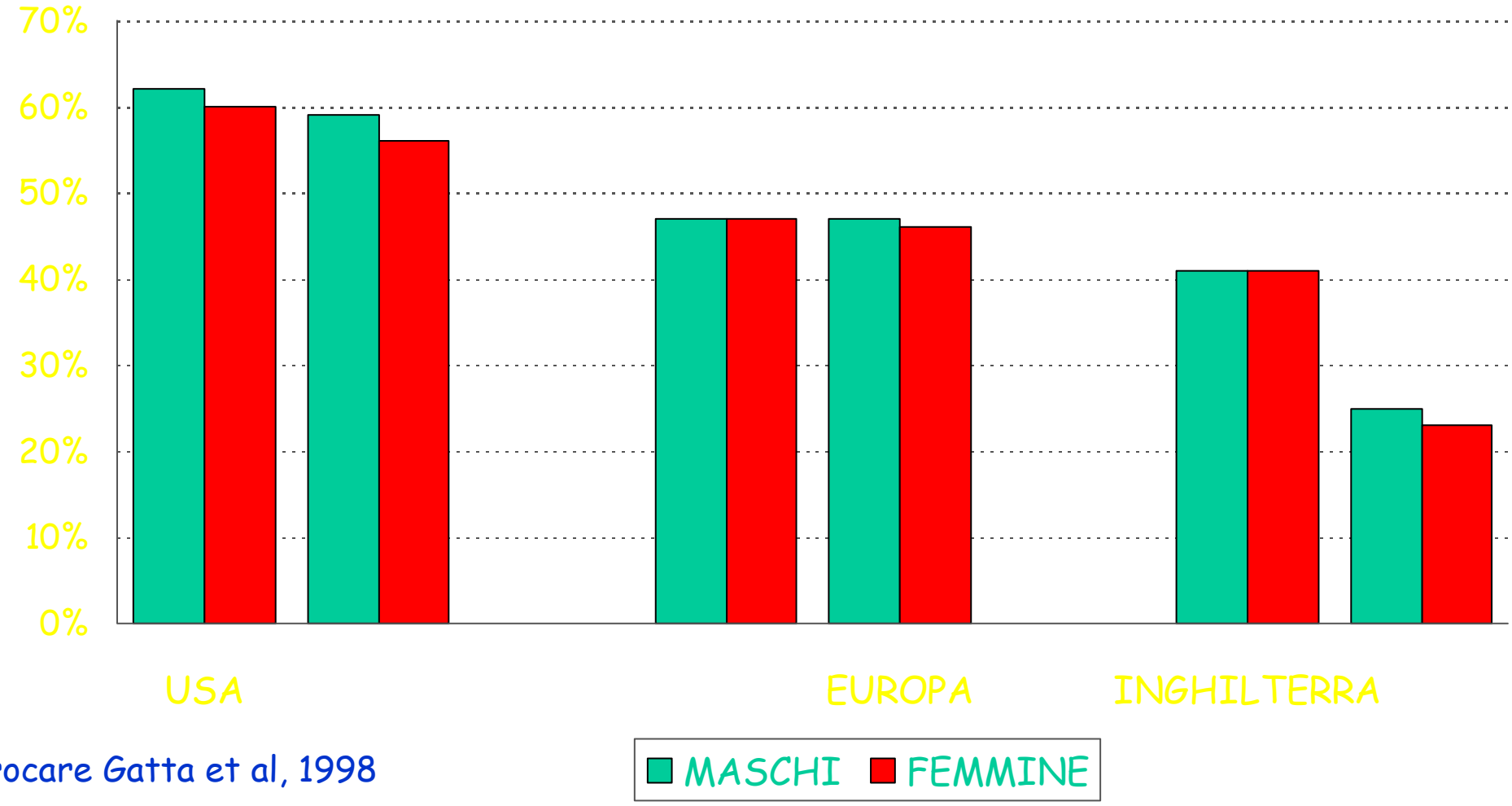
LOCALIZZAZIONE CRC

% a sede Colon sul totale dei CRC



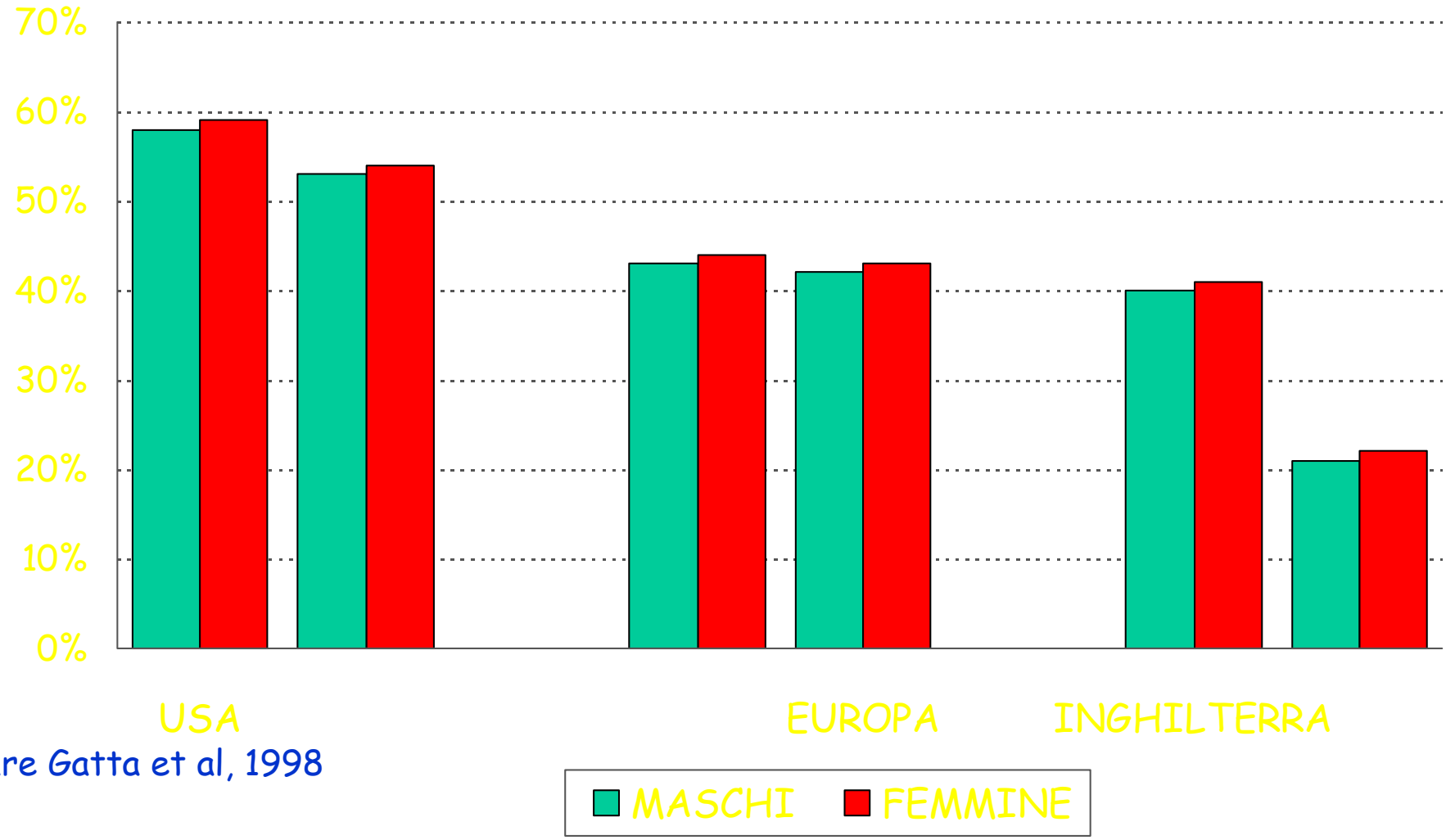
DA EUROCARE, Gatta et al 1998

SOPRAVVIVENZE RELATIVE *(A 5 ANNI)* IN DIFFERENTI PAESI
CARCINOMA DEL COLON



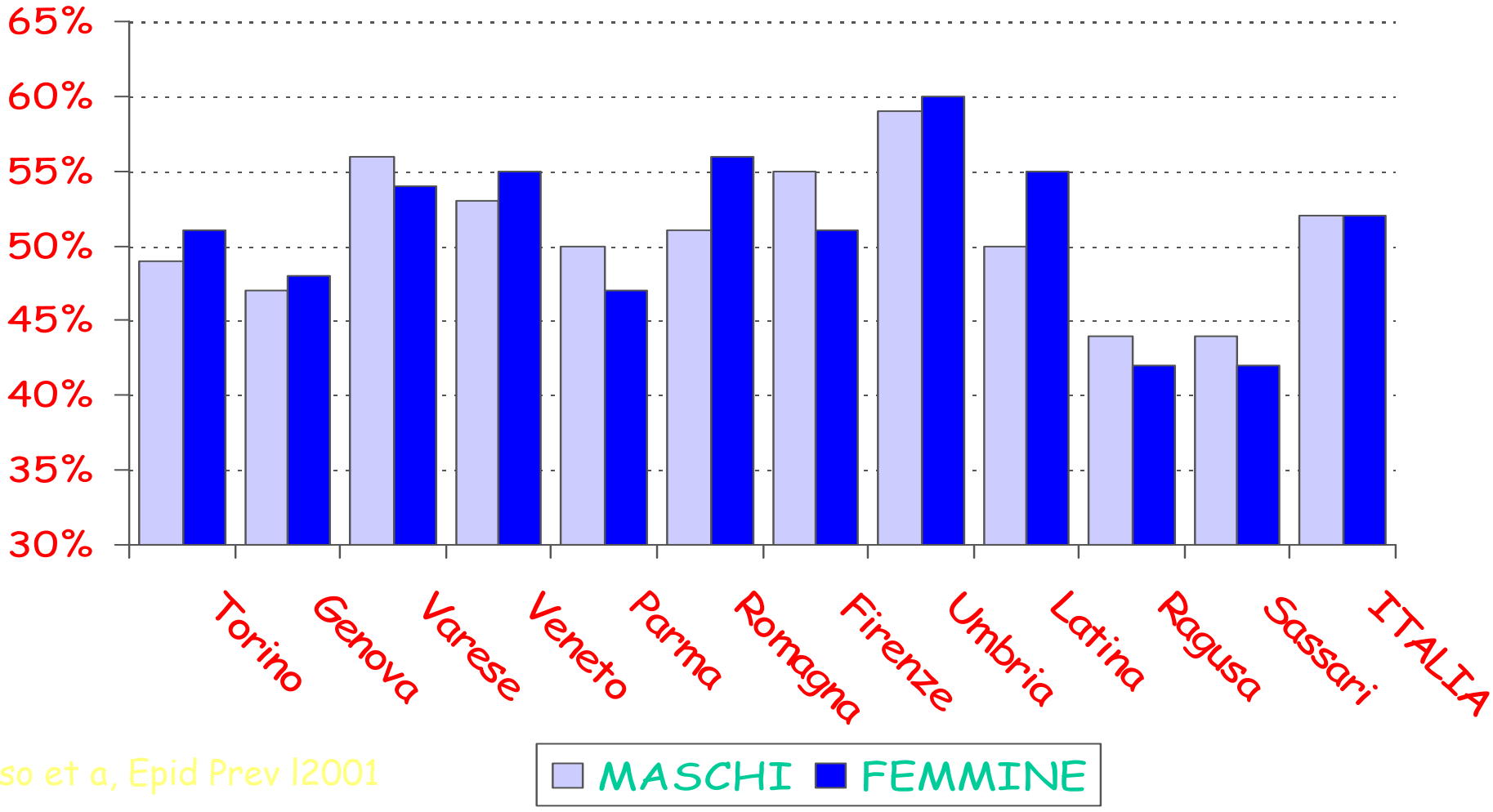
da Eurocare Gatta et al, 1998

SOPRAVVIVENZE RELATIVE (a 5 anni) IN DIFFERENTI PAESI
CARCINOMA DEL RETTO



da Eurocare Gatta et al, 1998

SOPRAVVIVENZE RELATIVE *(A 5 ANNI)* - Registri Tumori Italiani - CARCINOMA DEL COLON-RETTO



: Rosso et a, Epid Prev l2001

Vi è overdiagnosi nello screening colorettale ?

L’attività di screening comporta l’individuazione e il trattamento di lesioni che non sarebbero mai comparse altrimenti ?

Adenoma ➔ Carcinoma sequence

Normal colon➔ small adenoma➔

➔large Adenoma with villous component ➔ large adenoma with severe diplasia➔ large ademomas with invasive cancer➔ Invasive cancer

- Some ColoRectal Cancers (CRC) do not follow this pathway

- ➔ Overdiagnosi di Carcinomas
- ➔ Overdiagnosi of Adenoma

Trial Randomizzati per il FOBT

	Period	Sample and age	FOBT	Interval	At least one FOBT
US Minnesota Mandel	76-92	46,551 *Age 50-80*	Rehydrated	Annual Biennial	90.2% 89.9%
UK Nottingham Hardcastle	85-95	150,251 *Age 45-74*	Not Rehydrated	Biennial	59,6%
Denmark Funen Kromborg	85-95	61,933 *Age 45-74*	Not Rehydrated	Biennial	67%

Trial Randomizzati per il FOBT

		All deaths (%)	Cardiovascular Deaths (%)	% colonoscopy	
Minnesota	Annual	*3,361 (21.6)*	1,079 (6.9)	38%	
	Biennial	*3,396 (21.8)*	1,073 (6.9)	28%	
	Control	*3,340 (21.7)*	1,025 (6.7)	Not stated	
Denmark	Biennial	*6,228 (20.1)*	2,497 (8.1)	4.3%	
	Control	*6,303 (20.4)*	2,443 (7.9)	Not stated	
Nottingham	Biennial	*12,624 (16.8)*	Not stated	4%	
	Control	*12,515 (16.7)*	Not stated	Not stated	

Minnesota Trial: Mortality of colorectal cancer *1000. According to study group , during the 13 years after randomization. *Mandel et al NEJM 1993*

	Annual screening	Biennial screening	Control
Person Years	184,160	183,934	181,966
Deaths from CRC cases	82	117	121
Cumulative mortality *1000	5,88	8.33	8.83
95% CI	4,6-7,2	6,8-9,8	7,3-10,4

Mortality of colorectal cancer *1000. According to study group , during the 18 years after randomization. *Mandel et al JNCI 1999*

	Annual screening	Biennial screening	Control
Person Years	240,325	240,163	237,420
Deaths from CRC cases	121	148	177
Cumulative CRC mortality *1000 95%CI	9,46 4,6-7,2	11,19 6,8-9,8	14,09 7,3-10,4
Cumulative CRC mortality ratio	0.67 0.51-0.83	0.79 0.62-0.97	1

Incidence of colorectal cancer *1000. According to study group , during the 13 years after randomization. *Mandel et al NEJM 1993*

	Annual screening	Biennial screening	Control
Person Years	184,160	183,934	181,966
CRC cases	323	323	356
Cumulative incidence *1000	23	23	26
95% CI	21-26	20-25	23-28

Incidence of colorectal cancer *1000. According to study group , during the 18 years after randomization. *Mandel et al NEJM 2000*

	Annual screening	Biennial screening	Control
CRC cases	417	435	507
Rate Ratio	0.80	0.83	1
95% CI	0.70-0.90	0.73-0.94	-

FUNEN STUDY Mortality of colorectal cancer *1000. According to study group , 13 years after randomization. *Kromborg et al, Gut 2001*

	Study Group	Control Group	
Deaths from CRC	255	310	
Mortality rate * 1000	0.72	0.88	
Mortality ratio	0.82	-	
95% CI	0.69-0.97	-	

FUNEN STUDY Incidence of colorectal cancer *1000. According to study group , 13 years after randomization. *Jorgensen al, Gut 2001*

	Study Group	Control Group	
No patients with CRCs	649	637	
Incidence rate * 1000	1.84	1.81	
Incidence ratio	1.02	-	
95% CI	0.91-1.14	-	

NOTTINGHAM STUDY Mortality of colorectal cancer *1000. According to study group , 11 years after randomization. Hardcastle *et al, Lancet 1996*

	Study Group	Control Group	
Deaths from CRC	360	420	
Mortality rate * 1000	0.60	0.70	
Mortality ratio	0.85	-	
95% CI	0.74-0.98	-	

NOTTINGHAM STUDY Incidence of colorectal cancer *1000. According to study group , 11 years after randomization. Hardcastle *et al, Lancet 1996*

	Study Group	Control Group	
Deaths from CRC	893	856	
Incidence rate * 1000	1.49	1.44	
Incidence Ratio	1.01	-	
95% CI	0.95-1.14	-	

Conclusioni

- Overdiagnosi di CRC , se esiste è piccola e mascherata dalla diminuzione di mortalità conseguente alla rimozioni di adenomi.

- ➔ Overdiagnosis Adenomas

Overdiagnosis Adenomas problems:

➔Gli adenomi sono generalmente asintomatici

➔I Registri tumori non registrano queste lesioni

➔Esiste un problema di definizioni …..

TRASFORMAZIONE ADENOMA → CARCINOMA

Quale è il tempo di passaggio (dwelling time) ?

- Wagner (1995) 5 - 10 anni
- Eddy (1990) 7 anni da 1cm a CRC
- Atkin (1993) 10 - 35 anni
- Knigth (1989) minimo 5 anni in media 10-15 anni
- Winawer (1997) 10 anni da < 1cm a CRC

National Polip study :evidence for regression of adenomas *Loeve F, Boer R et al Int J cancer 111 633-699 2004*

- Data fron National Polipi study iwas used for testing assumptions on the adenoma-carcinoma sequence
- Comparison with MISCAN-COLON model
- Several models variants (sensitivity for adenoma and cancer, adenoma incidence, spontaneous regression, no fast-growing adenomas,) were tested
- The goodnes of fit of each set of model assumptions is evaluated by the deviance which compare 5 outcomes of the model with the Observed National Polyp study results

Summary of main assumptions used in MISCAN COLON

- Dwelling time ditributions in preclinical stages: exponential.
- Mean Total duration of preclinical stage of lesions that grow into cancer :16.4 yrs.
- Mean duration of preclinical cancer 3.6 yrs
- Sensitivity of colonoscopy for adenomas: from 80% to 85%
- Sensitivity of colonoscopy for cancer 100%

Models	Deviance
A: expert MISCAN-COLON assumption	84
B: low adenoma sensitivity	32
C: high adenoma incidence	28
D:high adenoma incidence+spontaneous regression	24
E: no fast growing adenomas	104
F High cancer sensitivity +	83
G:no fast growing adenoma ,high adenoma incidence+spontaneous regression	27
H High cancer sensitivity , high adenoma incidence + spontaneous regression	23

Prevalence of adenomas in selected autopsy studies

	years	Sample	
Baltimore–Offerhaus et al, 1991	1980-89	4,230	1.2%
HAWAII Stemmermannn et al 1988	1969-1984	163	48%
Liverpool Williams et al 1982	1976-79	365	33.2%
Barcelona bombi 1988	1985	212	21.7%
Mexico city	1988	450	2.7%

Prevalence of distal adenomas in sigmoidoscopy randomized trials

Trials	Invited group	Screened Age 55-64	% of any Polips	% of Any adenoma	% any High Risk Adenomas
UK Flexible Sigmoidoscopy Screening Trial ***Lancet 2002***	57,254	40,674	20%	12.3%	5.0%
Italy **Segnan et al *JNCI 2002***	17,148	9,911	18.3%	10.8%	3.4%

Prevalence of adenomas in colonoscopies series

Trials66	Invited group	No of Screened (mean Age)			% any High Risk Adenomas	
Veterans Cooperative Group Libermann et al NEJM *2001*	17,732	3,121 (63 yrs) 98% males			9.5%	
Italy Population based *(SCORe 3)*	6,028	1,512 (57 yrs) 50% males			6.2%	

Nottingham Study Incidence of colorectal adenoma *1000. According to study group , during the 11 years after randomization. *Hardcastle et al Lancet 1996*

Adenomas	Study Group	Control Group	Ratio
< 10 mm	253	129	1.96
10-19 mm	481	140	3.43
>= 20 mm	267	100	2.67
Total	1001	370	2.70

Funen study; Incidence of colorectal adenoma *1000. According to study group , 11 years after randomization. *Kromborg et al Lancet 1996*

Adenomas	Study Group	Control Group	Ratio
> = 10 mm	413	174	2.4

Costis dell’ overdiagnosi

- ➔ Side effects dell’endoscopia della polipectomia
- ➔ Follow up dei pazienti con adenoma

Maior complications rates for screening tests from Colorectal Cancer Screening : Clinical guidelines and rationale *Gastroenterology 1997 modified*

Screening test	Complication Rate (perforazioni ed emorragie maggiori)	Morti	
Sigmoidoscopy	1-2/10,000	<1/10000	
Diagnostic Colonoscopy	1-3/1,000	1-3/10000	
Operative Colonoscopy	2-5/1,000	?	

Adverse sequalae of colonoscopy and polipectomy:

- Hemorrhage
- 0.03% for diagnostic colonscopies
- 1.9% for polipectomy

(Kavic and Basson 2001)

- Perforation:
- 0.2% for diagnostic colonscopies
- 0.4% for polipectomy

(Araghized et al 2001 Dis Col Rectum 2001 44:713:6)

Adverse sequalae in UK Pilot Study based on FOBT:

- Overall 3600 colonoscopies in FOBT+ subjects
- 22 patients post colonoscopy bleeding admitted for one day and discharged the following day
- 2 perforations post polipectomy
- 1 death post colonoscopy not attributed to to the colonoscopy itself
- 3 deaths after surgery (all attributed to known cardiac conditions)

Endoscopic surveillance after polipectomy

ACS guidelines

- 1 adenoma < 1cm — 3-6 yrs
- >1 adenoma or adenoma > 1cm or villous component or severe displasia — 3 yrs x 2

ACG e AGA

- 1-2 tubular adenoma < 1cm — 5 yrs
- >2 adenoma or adenoma > 1cm or villous component or severe displasia or familiarity for CRC — 3 yrs

Rex DK. Rev. Gastroenterol. Disord., 2003

Follow up

- ‘In patients with only a small tuubular adenoma… surveillance may be not of value because the risk of cancer is so low….’ Atkin W et al NEJM 1992

- In Italia gli intervalli effettivi sono più corti

Conclusioni

- Overdiagnosi of adenoma è rilevante
- The risks for the single soggetto è relativamente piccoloo
- Sovraccarico per la struttura sanitariaa è grande

Programma di screening per il Cancro Colon Rettale

- Programma di prevenzione mediante FOBt inserito come LEA (Livelli Essenziali di Assistenza)

- L-138/2004 stanzia fondi per l'attivazione di un programma di screening a livello nazionale

- ➔ Programma nazionale di screening

Opportunita’

- La situazione attuale è una situazione avanzata rispetto alla situazione Europea

- Gran Bretagna , dopo lo studio pilota su 2 aree, ha deciso di partire con un programma nazionale esteso a tutto il territorio nazionale.

- Alle spalle l’esperienza dello screening mammografico e cervicale

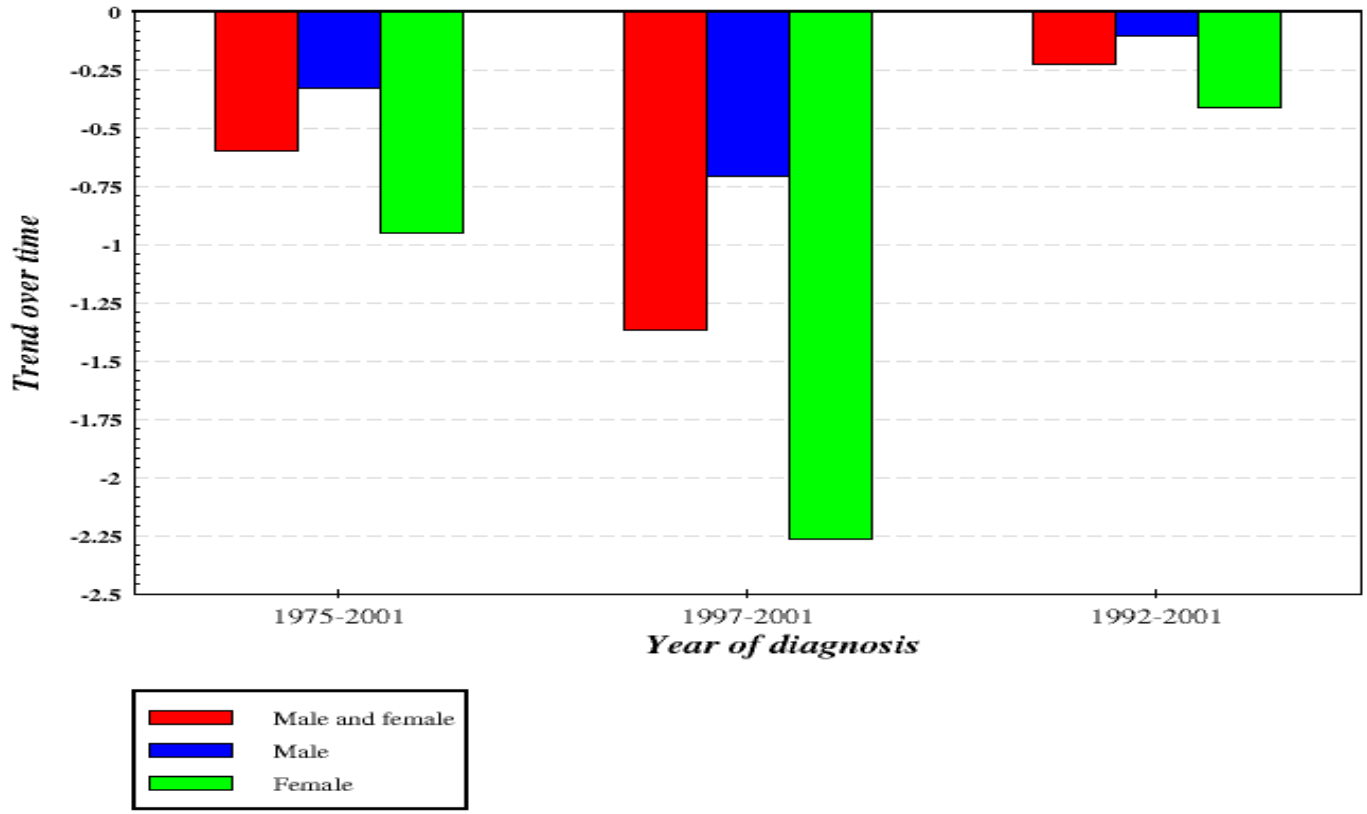
OSSERVATORIO NAZIONALE SCREENING

- Collaborazione con le società scientifiche degli screening (GISCor)
- Tavolo congiunto con la conferenza nazionale Degli Assessorati Regionale alla Salute
- Mandato dal Ministero della Salute a monitorare l’andamento dei programmi di screening

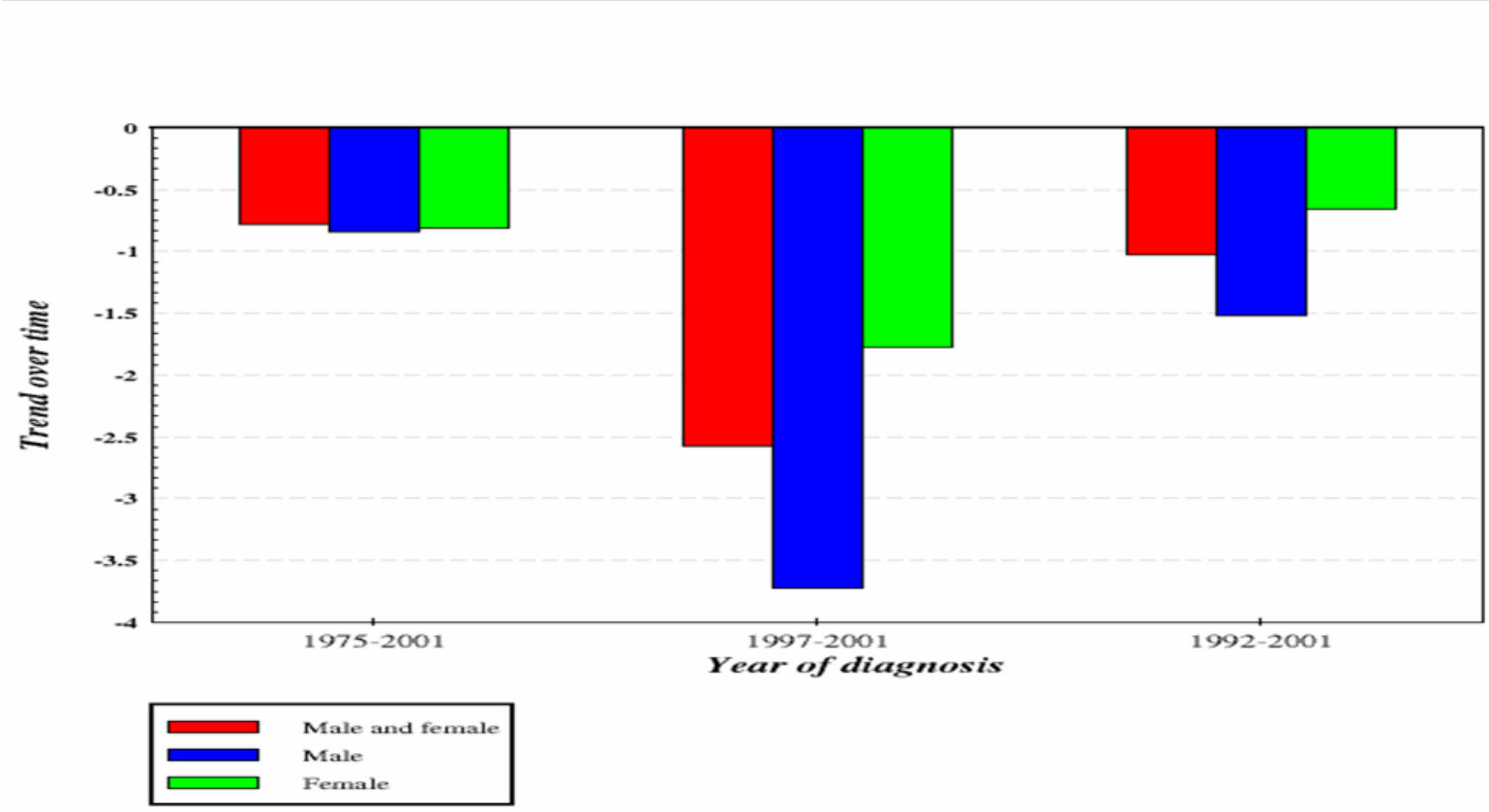
OSSERVATORIO NAZIONALE SCREENING

- Formazione
- Verifica e promozione della qualità
- Comunicazione/Informazione

US CCR Incidence over time <65 aa



CCR **Incidence:**Trends over time **> 65 yrs**



The Telemark polip 1 study

Hoff et al Scand J Gastroenterol 1996,
Thiis-Evensen et al, Scand J Gastroenterol 1999

- 1983 799 people aged aged 50-59, were randomized
- 400 ➔ Flexible sigmoidoscopy (attendance rate 81%)
- Follow up polyps ’85 and ‘89
- In 1996 both groups (aged 63-72) colonoscopy

Telemark polip study 1

	Screening group	Control group	
CRC cancer	2	10	P=0.02
No of polyps removed *CRC prevented	37		
No of adenomas removed * CRC prevented	15		
Deaths from CVD	27	14	P<0.01

Side effects of endoscopy: Cardiovascular disease.

Increase of cardiovascular disease related to :

- Pure random effect ?

- Spasmolythic –induced tachicardia?
- Manipulation of colon itself could cause cardivascular compromise.

- Change in lyfestyle after negative results?