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Colorectal cancer: a spreading but preventable disease

Cancro colorettale: sempre più diffuso ma prevenibile

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Summary

A sharp increase in incidence and mortality for Colorectal Cancer (CRC) is characterizing the "non Western" nations of the Mediterranean area, but also the Far East, Australia and the Central/South America. Western style behaviours (diet, reduced physical exercise, etc) are considered as the underlying cause of such epidemiological patterns. *Primary prevention* may be achieved observing a low-fat diet, high in fruit and vegetables. In general, a low calories intake and regular physical exercise seem to be responsible for the protective effect. *Secondary prevention* of CRC may be achieved by screening which is today the most effective action to curb mortality and extend survival, but is implemented gradually only in more affluent nations. Some screening tests, well known to gastroenterologists worldwide, may save lives by detecting colorectal cancer in its earliest, most curable stage, and by detecting and removing polyps. The tests available are: 1) Faecal Occult Blood Tests (FOBT), widely employed and easily acceptable by healthy subjects; 2) Colonoscopy (TC), allowing also the removal of adenomas and the procedure of choice in high risk subjects; 3) Computed Tomographic Colonoscopy (CTC), emerging as a possible and

Riassunto

Un aumento significativo di incidenza e mortalità per cancro colo-rettale (CCR) caratterizza i paesi "non occidentali" del bacino del Mediterraneo, ma anche l'Estremo Oriente, l'Australia e i paesi del Centro/Sud America. L'assunzione progressiva di modelli di vita "occidentali" (dieta, scarso esercizio fisico, ecc) è considerata la causa di questi *trend* epidemiologici. Una *prevenzione primaria* può essere ottenuta con una dieta povera di grassi, ricca di frutta e verdura, e comunque un ridotto apporto calorico e un regolare esercizio fisico hanno dimostrato di avere un effetto protettivo. La *prevenzione secondaria* del CCR è possibile mediante lo *screening*, che è oggi riconosciuto come il mezzo più efficace per ottenere una diminuzione di mortalità ed un aumento della sopravvivenza. Purtroppo viene introdotto, e molto gradualmente, solo nei paesi a più elevato livello socio-economico. Alcuni test di *screening*, ben conosciuti da tutti i gastroenterologi, sono in grado di salvare vite permettendo la diagnosi di CCR in fase precoce, in un stadio quindi "curabile", ma anche di evidenziare e rimuovere i polipi adenomatosi. I test oggi disponibili sono: 1) test del sangue occulto fecale (FOBT), ampiamente impiegato e facilmente accettato da soggetti sani; 2) co-

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effective screening tool but with cost-effectiveness and sensitivity for minor or flat lesions to be further explored; 4) DNA in stools: being colorectal carcinogenesis the result of a series of acquired genetic alterations that occur in colonic epithelial cells, is now possible to recover analyzable DNA from the stools and test for the presence of these genetic alterations; costs and effectiveness are still under evaluation. In conclusion, screening is the most effective action for the control of CRC, but public health initiatives are scarce and suffer from the lack of awareness and more urgent priorities. Eur. J. Oncol., 13 (1), 21-32, 2008

Key words: **epidemiological trends of colorectal cancer, screening modalities**

lonscopia (TC), che permette anche la rimozione degli adenomi e che rappresenta comunque il test di scelta nei soggetti ad alto rischio; 3) colonscopia virtuale mediante TC (CTC), che sta consolidandosi anche come un possibile test di *screening*, ma ancora carente specie per lesioni piatte e di piccole dimensioni; 4) esame del DNA nelle feci: infatti la carcinogenesi colo-rettale è la conseguenza di una serie di alterazioni genetiche che avvengono nelle cellule epiteliali del colon ed è oggi possibile recuperare frammenti analizzabili di DNA dalle feci ed evidenziare la presenza di dette alterazione genetiche; costi ed efficacia sono però ancora oggetto di valutazione. In conclusione, lo *screening* è oggi la metodologia più efficace nel controllo del CCR, ma le iniziative in questo senso sono ancora limitate e risentono della scarsa conoscenza del problema e di ridotta disponibilità finanziaria conseguente ad altre misure prioritarie. Eur. J. Oncol., 13 (1), 21-32, 2008

Parole chiave: **andamenti epidemiologici del carcinoma colorettale, modalità di *screening***

Trends in epidemiology

Colorectal Cancer (CRC) is a deadly but preventable disease, becoming a relevant health problem even in developing nations as a consequence of extended life expectancy and adoption of "westernized" life style behaviours.

The global burden of CRC worldwide is reflected in more than one million new cases/year with a mortality of 520,000 cases in 2002[1]. In the world CRC ranks 3rd in incidence and 4th in mortality among all cancers. Incidence in developed nations contributes with 65% of cases, with CRC ranking 3rd among all cancers, whereas more than one third of incident cases is occurring in developing nations. While the rate of mortality out of incident cases is 47.1% in more developed countries, it is 60.2% in those less developed, as a consequence of late diagnoses (Table 1).

Data for cancer incidence and mortality in Europe show great variations with an Age-world-standardized incidence rate (ASR-W) ranging from 19.4 in Greece to 56.6 in Hungary in males (~ 3 times) with comparable figures in females; similar differences characterize mortality (Table 2).

Table 1 - Cancer incidence and mortality in "*less*" and "*more*" developed countries (Globocan 2002): in raw data[a]

	More developed countries		Less developed countries	
Incidence	M 353,390		M 196,037	
	F 312,341		F 159,664	
	T 665,731	65.2%	T 355,701	34.8%
Mortality	M 159,914		M 118,025	
	F 153,980		F 96,184	
	T 313,894	59.4%	T 214,209	40.6%

[a] From Ferlay *et al* [1]

Huge differences in CRC incidence and mortality are also observed in other world regions, such as, for example, in the Mediterranean area (fig. 1) and in the Asian countries (fig. 2).

The trends of CRC incidence in Europe show an increase in several nations (like Estonia, France,

Table 2 - Incidence and mortality of CRC in the European Union (EU) (Globocan 2002)[a]

Colon-rectum	Male (all ages)				Female (all ages)			
	Cases	ASR (W)	Deaths	ASR (W)	Cases	ASR (W)	Deaths	ASR (W)
Austria	2713	42.1	1325	20.1	2451	27.8	1325	13.9
Belgium	3304	37.0	1732	18.7	3130	26.8	1764	14.1
Bulgaria	1631	25.6	1114	17.1	1358	17.0	953	11.4
Cyprus	123	23.1	83	15.2	122	19.6	81	12.8
Czech Republic	4374	58.5	2559	34.0	3243	32.0	1938	18.0
Denmark	1828	41.0	1058	23.3	1800	33.0	1114	19.2
Estonia	282	31.7	160	17.9	350	23.2	199	12.6
Finland	1031	25.5	477	11.5	1146	21.1	573	9.8
France	19229	40.8	9078	18.2	15718	25.9	8019	11.8
Germany	31756	45.5	14396	19.9	32053	33.1	16467	15.7
Greece	1937	19.4	1025	9.7	1832	15.6	1006	8.0
Hungary	3977	56.6	2543	35.6	3509	33.7	2346	21.2
Ireland	1075	43.1	591	23.6	813	27.0	433	13.7
Italy	20457	39.2	9061	16.5	17276	26.6	7909	10.9
Latvia	372	24.2	279	18.0	488	17.9	368	12.3
Lithuania	615	26.5	424	18.0	616	16.8	434	11.3
Luxembourg	146	43.6	65	18.6	141	30.7	66	13.4
Malta	77	27.1	46	16.1	78	22.5	46	13.1
Poland	7671	31.9	4432	18.2	7909	23.5	4082	11.4
Portugal	2826	35.9	1643	20.0	2158	21.0	1307	11.9
Romania	3429	22.0	2172	13.6	2808	14.4	1843	9.0
Slovakia	1745	54.5	1071	33.2	1227	27.4	752	16.0
Slovenia	628	43.8	349	24.1	503	25.4	295	14.0
Spain	12418	36.8	6553	18.5	9546	22.5	5206	11.3
Sweden	2761	33.4	1273	14.9	2634	26.2	1209	11.1
The Netherlands	4940	40.9	2329	18.9	4582	30.8	2313	14.4
United Kingdom	19407	39.2	8912	17.5	16562	26.5	8278	12.4
EU	150752		74750		134053		70326	

[a] From Ferlay *et al* [1]

Italy, Netherlands, Poland, Slovakia, Slovenia and Spain), whereas a stable or downward trend is observed in the others. For some of the countries, where we observed an upward trend, a possible bias due to previous underreporting has to be considered[3].

If we compare these data with the ones generated by the Surveillance Epidemiology and End Results (SEER) in the US, we may observe the possible effect of screening actions implemented there in the mid eighties in the downward trend starting around the same period.

Mortality trends for CRC in the Asian countries are impressive inasmuch as the rates in Japan, Korea, Hong Kong, Singapore nearly doubled in the years 1970-1999[2]. In Japan, for instance, incidence of CRC increased from 10/100,000 in 1955 to 60/100,000 in 1990[4].

The 1 and 5 year survival rate in Europe is very variable, ranging from 50% to 70% at 1 year, but it is still as low as 30% at 5 years in some countries in comparison with the survival of up to 60% reported in several nations and the average of 50% for Europe as a whole (Table 3). The SEER data from the US show even better results: the 5 year survival is ranging from 57 to 65%. Poor survival, more evident in developing nations, characterizes also several European countries and is related to the absence of screening and to poor overall performance of the national health systems, partly due to limited resources allocated to health[5].

Impressive figures are those related to prevalence (i.e. the number of persons diagnosed with CRC still alive at 5 years and undergoing treatment), that is a good indicator of the overall efficiency but also of

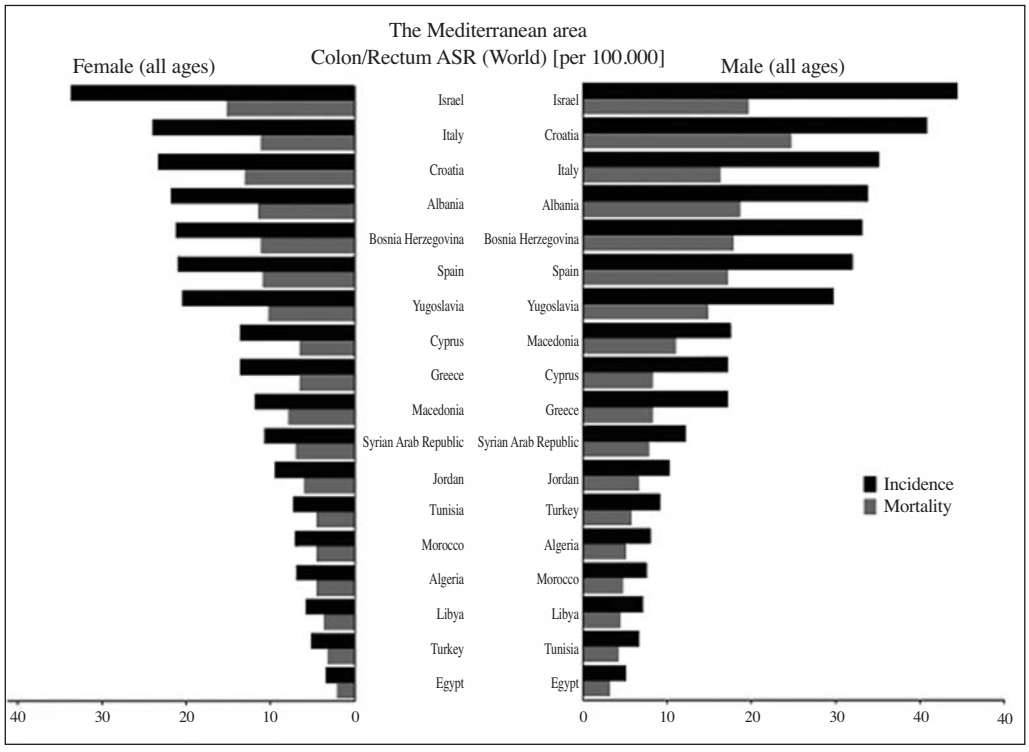

Fig. 1. CRC incidence and mortality in the Mediterranean area (Globocan 2002)[a]
[a] From Ferlay *et al*[1]

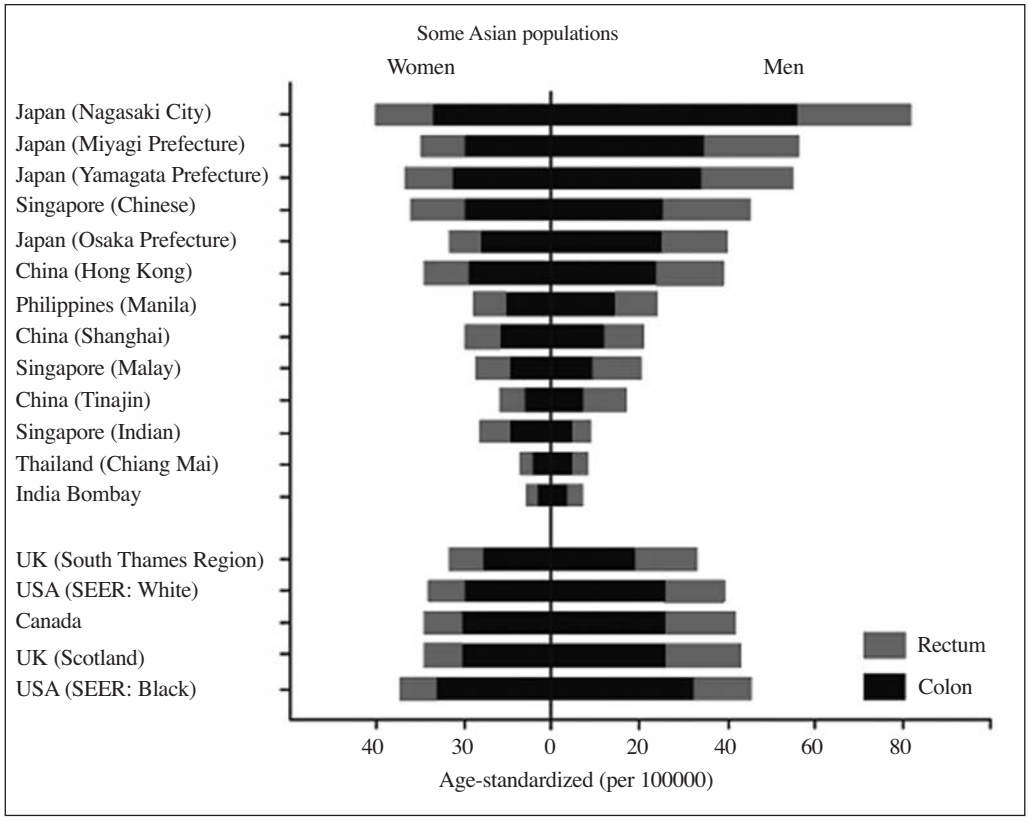

Fig. 2. CRC incidence in some Asian populations compared with US and UK (1993-1997)[a]
[a] From Sung *et al*[2]

the disease specific burden on the health system. Table 4 reports data from various areas of the world and is clearly showing again that more than one third of patients are in non Western nations, where screening facilities are not conceivable, the majority of cases is diagnosed at an advanced stage and palliative care is hampered by the lack of funds and facilities. Therapeutic management of CRC in its earlier stages, instead, is based mainly on surgery and would be widely available, allowing a good prognosis.

Table 3 - Survival at 1- and 5-years of CRC from Cancer Registries (EUROCARE 3)[a]

Country	Age-standardized relative survival (%), one year and five years after diagnosis (from cancer registries)			
	Men		Women	
	One year	Five years	One year	Five years
Austria	73.3	50.8	75.0	54.0
Czech Republic	59.2	32.3	61.5	37.1
Denmark	68.6	42.6	70.2	46.6
England	67.1	44.8	66.7	46.6
Estonia	57.9	35.5	55.7	33.5
Finland	73.5	51.7	73.2	52.0
France	76.5	54.1	77.8	60.0
Germany	72.6	49.0	74.8	53.5
Iceland	72.8	47.5	78.2	53.3
Italy	73.4	49.3	73.8	51.2
Malta	63.0	38.5	68.2	53.9
Netherlands	74.7	53.2	76.3	54.0
Norway	74.2	51.1	75.5	54.5
Poland	51.4	26.8	52.5	28.6
Portugal	71.5	46.3	70.8	43.6
Scotland	67.2	44.1	67.4	46.7
Slovakia	60.6	32.7	61.1	37.7
Slovenia	60.9	33.9	60.6	36.3
Spain	72.2	53.0	73.4	54.7
Sweden	76.3	52.3	77.9	55.4
Switzerland	77.8	55.2	78.3	56.9
Wales	58.2	40.1	56.4	38.2
Europe	70.6	47.6	71.7	50.5

[a] From Sant *et al*[5]

Table 4 - Prevalence at 5 years of CRC patients (Globocan 2002)[a]

	5 years prevalence
North America	618,403
Central America	28,350
South America	98,150
Europe	999,612
Africa	38,614
Asia	1,003,456
Australia and Pacific	43,630

[a] From Ferlay *et al*[1]

Primary prevention

As for several other cancers, primary prevention is the ideal target to curb the rising trends in incidence of CRC but, apart from few simple but seldom practiced lifestyle guidelines (Table 5), no specific etiological factors have been identified.

Unfortunately the prevailing trend, also in developing nations, is towards "western" habits, which, as a whole, are linked by many studies as a definite risk for CRC.

Several ongoing studies are also exploring the efficacy and feasibility of chemo-prevention, with non-steroid anti-inflammatory drugs in first place as effective agents, being aspirin the more cost-effective.

Screening

A viable and effective intervention, aimed at curbing mortality, is today mostly focussed on screening, i.e. secondary prevention.

The reduction in mortality and downstaging of CRC may be achieved as the result of:

1) diagnosis at an earlier stage;
2) removal of adenomatous polyps, the index precursor lesion for CRC.

In fact it has been demonstrated that the removal of adenomas reduces significantly the incidence, and therefore the mortality of CRC.

In populations with low incidence, it is important to concentrate the screening initiatives in subjects at high risk. High risk may be defined as individuals with:

– age over 50 years,
– one or more first degree relatives (parents, siblings) with CRC or adenomatous polyps,
– familiar aggregation of CRC beyond the first degree relatives,
– genetic syndromes, like Familiar Adenomatous Polyposis (FAP) and Hereditary Non Polyposis Colorectal Cancer (HNPCC).

Of interest for the subsequent surveillance schedules in subjects at risk is also the concept of "advanced adenoma", defined as adenomatous polyps with:

– a diameter larger than 1 cm,
– more than 25% of villous component at histology,
– high grade dysplasia (including what is sometimes defined as *in situ* or intramucosal carcinoma).

Table 5 - How individuals can reduce their risk of colorectal cancer

Increase intake of vegetables and fruit	Eat five servings of fruits and vegetables each day Replace snacks such as chocolate, biscuits and crisps with an apple, orange, or other fruit or vegetable
Reduce intake of calories	In particular animal fats; often replace beef, lamb and pork with fish and poultry
Increase physical activity	By activities of moderate intensity, such as brisk walking
Supplement vitamins	In particular folic acid
Long term hormonal replacement for women (?)	Still uncertain data

In addition:
– the number of adenomas (more than 3) is also a risk factor,
– invasive cancer within an adenoma (when cancer cells spread beyond the *muscularis mucosae*) has to be considered already a cancer stage Dukes A, but has a highly satisfactory clinical outcome and it is a good target for secondary prevention.

Table 6 - Sensitivity and specificity of screening tests for CRC[a]

	Sensitivity	Specificity
FOBT for polyps	10%	
FOBT for cancer	40%	90%
DCBE for polyps/cancer	70%	98%
Sigmoidoscopy for polyps/cancer (FS) *"in the limited segment examined"*	90%	98%
Colonoscopy for polyps/cancer	90-98%	100%

[a] modified from Winawer[6]

Available screening tests

There are several screening tests which may save lives by detecting colorectal cancer in its earliest, most curable stage, and by detecting polyps, which can be removed, preventing them developing into cancer.

For the tests available for screening the general population at intermediate risk, the choice is determined by the available resources and the epidemiological pattern of the area, as well as the perception of CRC screening as a priority by the health authorities, the doctors and the public. Guidelines are available in many countries that provide specific recommendations on when to start and how often these tests must be used.

Among the screening tests available we may list:
1. faecal occult blood test (FOBT),
2. double contrast barium enema (DCBE),
3. computed tomographic colonoscopy (CTC),
4. flexible sigmoidoscopy (FS),
5. colonoscopy (TC).

Up to now, only FOBT has extensively been employed in screening programmes on asymptomatic populations, whereas only limited initial experiences with FS and colonoscopy are available. The actual or possible sensitivity and specificity of the aforementioned screening tests is reported in Table 6.

Still debated are the data on sensitivity and specificity of Computed Tomography Colonoscopy (CTC) and will be discussed later.

Faecal occult blood tests (FOBTs)

The FOBTs are non invasive, acceptable by patients, of low cost and some of them may be easily performed also in the decentralized structures of a health network. It is the most accepted, low cost, simple technology test today available[7,8].

The rationale of the FOBTs is based on the fact that cancer and larger polyps bleed.

The most widely employed FOBT is the one based on the capability of guaiac to detect haemoglobin and its derivatives in faecal samples. Other tests, like

the ones based on ortho-toluidine or benzidine, have been discontinued because of their toxicity or excessive sensitivity.

The FOBT used in most of the population studies is the guaiac test known as Hemoccult II, based on two samples from each stool for three consecutive bowel movements. The samples are smeared directly by the subject and the completed test card is then delivered to the reference centre or doctor. A recent slightly modified test is the Hemoccult II SENSA, which allows a more clear-cut interpretation of positivity and is more sensitive in respect to Hemoccult II.

The FOBTs based on guaiac pose problems of false positive and false negative results related to diet. In fact, non-human haemoglobin from meat, as well as other dietary components with peroxidase activity (spinach, etc.), may give false positives and suggest the opportunity for dietary restrictions, whereas an excess of vitamin C may give false negatives.

The important problem of intermittent bleeding of early lesions is partially overcome by the sampling of three consecutive bowel movements, whereas the false negativity by peroxidase in stools is minimized by a delay in the development of the test of at least three days.

In the attempt to increase sensitivity without a significant loss in specificity, same new FOBTs, based on immunological methods, seem promising and are entering in clinical practice. The most commonly used is the one developed in Japan in 1984. The test is specific for human haemoglobin, has a high sensitivity and an acceptable specificity, but its cost is much higher than the guaiac test. This fact has lead to the suggestion of testing only one stool sample, or two, but this is in great conflict with the biological rationale of intermittent bleeding. In addition, the development of immunological tests is strictly a laboratory procedure and requires several different steps, with related increase in costs for laboratory equipment and manpower. In other words, the immunological tests entail a totally different approach and are not suitable for their development and interpretation even by appropriately trained doctors or nurses. In any case FOBTs use is spreading and automated machines for their development and interpretation are now of common use.

Allison *et al*[9] performed the three tests [Hemoccult II (HO), the immunological Hemeselect (HSel) and Hemoccult II SENSA (HOS)] on a cohort of over 8000 subjects and was able to confirm an increased sensitivity of HSel and HOS in respect to HO (HO 37.1 – HSel 68.8 - HOS 79.4 percent), with a specificity for CRC rather similar for the three tests (HO 97.7 – HSel 94.4 – HOS 86.7 percent). More recent iFOBTs have provided even better results.

The available data from large randomized controlled trials in the UK, US, Denmark, and in not randomized population studies in the US and France, are all based on guaiac Hemoccult II as screening test. A reduction in CRC mortality from 15-18% up to 33% was achieved[10-12]. In fact, the overall sensitivity and efficacy of FOBT is not based on a single testing but in its periodic repetition, as clearly demonstrated by the study in Sweden where a 55% reduction in CRC mortality was achieved in subjects who did comply with the periodic biennial testing[13, 14]. An important downstaging is also recorded in all the studies (40% in Duke's stage 1 or 2 in the screened group against 11% in controls)[10-12, 14].

Interesting results were obtained by a large prospective cohort study in Japan performed with FOBT on more than 42,000 subjects of both sexes[14]. A follow up of the cohort up to 2003, for a total of 551,459 person/years, showed a 72% reduced risk of death from CRC and a sharp decrease (59%) of advanced disease.

A crucial issue related to FOBTs is that they have to be repeated at yearly intervals, starting at the age of 45 or 50: only the yearly repetition is able to ensure early diagnoses in up to 90% of cases, considering the length of the adenoma/carcinoma sequence (8-10 years).

Double contrast barium enema (DCBE)

The DCBE is an invasive technique that uses a barium enema, which reveals filling defects, and a subsequent insufflation of air after most of the barium has been removed, allowing lesions in the mucosa to be outlined by the retained barium.

Results from the literature suggest that the sensitivity of DCBE is 50-80% for polyps < 1 cm, 70-90%

for polyps > 1 cm and 55-85% for Dukes' stage A and B cancers.

Several studies have concluded that the performance of DCBE is insufficient in detecting a substantial percentage of clinically relevant lesions considering the costs and complexity of this test, significantly "operator dependent".

Computed tomographic colonoscopy (CTC)

This new imaging modality is evolving as a possible alternative to TC and DCBE, and is based on high end CT scanners with multiple detectors (6 to 8). A dedicated software allows the reconstruction of the inner large bowel which simulates 3D endoluminal optical views. It delivers a low dose of X-rays but is not free of complications and discomfort due to the bowel preparation (similar to TC) and air insufflation. CTC has an acceptable sensitivity for cancer, similar to TC, but lower for minor polypoid lesions. Specificity for small lesions is lower than TC and 7 to 10% of cases have to undergo subsequent TC for characterization and removal of the lesions found. Cost-effectiveness is still debated and influenced by several variables. "Digital cleaning" of residual stools and fluids is at the moment a research priority because it could avoid bowel preparation, the most uncomfortable side of CTC and TC. As this latter one, CTC is an operator-dependent technique for the correct interpretation of the computer-generated images.

Flexible sigmoidoscopy (FS)

As a screening method, sigmoidoscopy has three important advantages in respect to FOBT or DCBE: 1) it allows a direct visualization of the mucosa; 2) lesions can be sampled or removed; 3) it has a high sensitivity and specificity also for polypoid lesions in the segment of bowel examined.

The distal bowel is usually prepared by giving a saline laxative enema 1-2 hours before the procedure. Patients are not sedated and approximately 10-15% of them experience at least moderate discomfort during the procedure. The major complication of sigmoidoscopy is bowel perforation; data from large series of FS show a perforation rate of 1 to 2/10,000 examinations. Slightly higher complication rates occur when biopsy or polypectomy are performed.

The rationale of using FS for screening is based on the assumption that any distal lesion in the lower bowel explored will lead to a subsequent TC. The fact is that up to 50% of patients with proximal adenomatous polyps or even advanced adenomas have no index distal polyps, as shown in several studies (Table 7). If these patients had undergone FS only, they would not have been identified as being at risk of CRC, harbouring significant lesions in the proximal colon.

Even the combination of FOBT and FS has been shown to miss 24% of proximal advanced lesions.

There are interesting preliminary results of a large randomized population study in the UK: the compliance to the invitation to undergo FS was very high in the randomized group (71%), but only 55% of the population initially invited accepted to undergo screening; only 5% of those screened had to be submitted to TC as a second level examination. Cancers in Duke's A stage were 62%, but no data are yet available from long-term follow-up and on the rate of missed lesions in the proximal colon, the most relevant problem.

In another study in Italy (SCORE) the compliance rate was much lower. Out of 236,568 people invited, only 56,539 (23.9%) accepted the proposal to

Table 7 - Miss rate of flexible sigmoidoscopy for proximal lesions in subjects with no-distal lesions

Author	Country and year of publication	Miss rate %
Betés M[15]	Spain 2003	39.3
Cash BD[16]	US 1999	76
Cheng TI[17]	Taiwan 2002	39.4
Imperiale TF[18]	US 2000	46
Lieberman D[19]	US 2000	52
Lin OS[20]	US 2005	58
Nakao FS[21]	Brazil 2001	22.8
Nicholson FB[22]	US 2000	25
Rex DK[23]	US 1999	65.5
Sciallero S[24]	Italy 1999	15.5
Segnan N[25]	Italy 2007	62.3
Schoenfeld P[26]	US 2003	69
Thiis-Evensen E[27]	Norway 1999	43

undergo screening FS, and 34,292 (60.6%) of those actually decided to participate, were enrolled and randomized. Of the 14,148 randomized to the screening group only 9,999 attended. The study is in progress to estimate the impact of this strategy on incidence and mortality of CRC.

Total colonoscopy (TC)

Colonoscopy is the only technique currently available that offers the potential both to find early cancer and remove premalignant lesions throughout the colon and rectum. FOBTs detect only those polyps and cancers that bleed; FS allows examination only of the distal third of the large bowel and DCBE, although it can image the entire large bowel, does not allow biopsy or polypectomy and has an important percentage of false negatives. TC is, in any case, the procedure of choice in high risk subjects[28, 29].

Recently the American College of Gastroenterology (ACG) issued guidelines for the management of high risk subjects which are today accepted worldwide for early diagnosis and proper follow-up of these conditions, where colonoscopy has been proven as the only efficient tool for screening and surveillance (Table 8).

TC is a highly invasive procedure that requires preparation of the bowel using laxatives, with or without enemas, or large volumes of oral cathartic solutions. Patients usually receive intravenous sedation or even deep sedation.

Sensitivity of TC is 90-95% both for polyps and cancer, with a specificity reaching 100%. The cecum is reached in 80-95% of good quality procedures. A retrospective study of 429 patients who had a preoperative colonoscopy found that the findings at TC correlated with the pathological surgical specimen in 97% of cases.

The disadvantages are linked to the capability and experience of the physician: the procedure takes 15-20 minutes for an experienced endoscopist, but much more for beginners. In a screening study on an asymptomatic population the cecum was reached in 98.6% of cases by experienced endoscopists, whereas that figure in community-based practice may be much lower.

Data from six prospective studies of colonoscopy indicate that it can be complicated by perforation (1/1,000), major haemorrhage (3/1,000), and respiratory depression due to sedation, arrhythmia, transient abdominal pain and nosocomial infection. The mortality rate is approximately 1-3/10,000.

A recent study on 3,196 subjects undergoing screening TCs reported 10 serious complications (total rate 3/1000; six bleeding, one had myocardial ischemia and one had a stroke), without perforation or death due to procedure.

In order to assess the rate of complications in an average community practice, a study in Sweden retrospectively measured the complication rate of diagnostic and therapeutic colonoscopies performed by community-based endoscopists. The overall morbidity was 0.4%, 0.2% for diagnostic and 1.2% for therapeutic procedures (polypectomy).

In a recent paper, it is shown how colonoscopy, in a screening setting, found an additional 24% of advanced neoplastic lesions in respect to FS and FOBT combined. Another recent study strengthens the value of TC in screening, since 36% of diagnosed adenomas were of the flat and depressed type, most probably "missed lesions" at DCBE and CTC colonography.

Colonoscopy has demonstrated its efficacy also in reducing the incidence of CRC in some studies, like the National Polyp Study (NPS), the Telemark study and the Italian multicentric study. In the latter one, a retrospective study performed in a usual care setting, the reduction in incidence was 66% in respect to the general population, a result comparable to the 76% reduction found in the NPS, a prospective study performed with a rigid protocol[30, 31]. The "protection" by TC lasts up to 8-10 years and, when performed at a significant "risk-age" (57 to 64 year) with negative results, it is hypothesized that it could become a

Table 8 - ACG recommendations for CRC screening in persons with positive family history (non HNPCC)[a]

- One first degree relative with CRC at > 60 yrs
  - Start screening at 40 yrs with TC every 10 yrs
- One first degree relative with CRC at <60 yrs or multiple relatives with CRC
  - Start screening at 40 yrs (or 10 yrs younger than age of younger relative with CRC) with TC every 3 to 5 yrs

[a] Acknowledged by the AssR Italian Guidelines for CRC

procedure "once in a lifetime"[32]. Limited initiatives based on primary screening colonoscopy are currently implemented in Europe[33].

Adherence to screening (compliance)

The major problems of CRC screenings are the rather low uptake of the tests and, in particular, the loss of interest in undergoing regular (annual/biennial) FOBT testing[34]. In fact, the overall sensitivity and efficacy of FOBT is not based on a single testing but in its periodic repetition, as clearly demonstrated by several studies.

A recent multicentre Italian study, where FOBT or TC were offered as a primary screening tool in a randomized way directly by the general practitioners (GPs), the attendance rate was overall 18.3%, being 28.6% (range 7.9-90.9%) for FOBT and 10.6% (range 0-54.9%) for TC. In addition, the compliance to TC showed a clear cut negative gradient north/south in relation to cultural predisposition by the subjects and even their GPs[35]. Lack of awareness on the benefits of CRC screening, embarrassment in discussing bowel matters with GPs and fear of cancer diagnosis, as well as variable persuasion by GPs in explaining the benefits of screening, are among the possible explanations for the low compliance and wide variability.

In another study (SCORE 3), performed on 18,447 subjects resident in towns located in northern Italy, the overall attendance rate was 32.3%, being 32.3% for FOBT, 32.3% for FS and 26.5% for TC. Also in this study FS would have detected only 27.3% of the proximal advanced neoplasms[36].

Despite this overwhelming evidence that screening is effective, in the 27 European Union nations only 14/27 (52%) have defined guidelines and some implemented CRC screenings, but several are still in a planning or discussion phase (M. Classen, personal communication, 2007). Scanty data are available on very limited pilot screening initiatives in Central/South America (Brazil, Uruguay). In Australia, where detailed guidelines were established many years ago and several pilot screening initiatives are ongoing, mostly based on immunological FOBT, a nationwide programme has been implemented starting in 2006.

In Japan, incidence of CRC is rapidly increasing, as reported, with incidence and mortality figures for CRC comparable to the highest reported in Western nations (USA, Central Europe). In 2005 more than 6 million subjects underwent screening by FOBT, with a detection rate of CRC of 0.16% (in line with the results of several other large studies). Of interest the fact that 70% of screen detected cancers are in the curable stages I or II[5]. Unfortunately, mostly for economic reasons, the screening uptake was very low, 18%[37].

Apart from FOBT, the other approaches to CRC screening, based on the limited experience with TC and FS, do not provide yet data on compliance in population studies. New methods, like CTC, show promising perspectives in wealthy nations but still need further testing. Of interest are the limited experiences with DNA stool testing but, again, population-based studies are lacking.

In countries with different health priorities and limited resources, screening aimed at high risk subjects (familiarity) is an option which is advocated but seldom yet implemented, but may be further promoted as a first step to raise awareness by the public, doctors and health authorities. In addition, CRC is developing at a younger age (< 40) in less developed countries: 16.4% *versus* 3.6% in more developed countries, an indirect stigma of familiar aggregation. In fact the selection of subjects at increased familiar risk is an easy and rather cheap method, entailing cultural awareness and proper education of health professionals in preventive medicine, unfortunately the neglected area of the medical curriculum.

Conclusions

It has to be recognised that CRC is not any more a Western disease, spreading rapidly also in less developed nations mainly as a consequence of "westernization" of lifestyles. Whereas in more developed nations the concept of implementing screening as the most valuable option is now acquired, with existing facilities, priority allocation of available resources and a general cultural gap by health professionals and the public hampers the diffusion of screening in many populations in need, where advanced disease, with intolerable suffering and premature death, characterize the majority of CRC cases.

References

1. Ferlay J, Bray F, Pisani P, *et al*. GLOBOCAN 2002 Cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. Lyon, IARC Press, 2004.
2. Sung JJY, Lau JYW, Leung WK. Increasing incidence of colorectal cancer in Asia: implications for screening. Lancet Oncol 2005; 6: 871-6.
3. Crespi M, Lisi D. Colon cancer in the EU: a major health priority – Epidemiology. Endoscopy 2008. In press.
4. Yiu HY, Whittemore AL, Shibata A. Increasing colorectal cancer incidence rates in Japan. Int J Cancer 2004; 109: 777-81.
5. Sant M, Aareleid T, Berrino F and the EUROCARE Working Group. EUROCARE-3 survival of cancer patients diagnosed 1990-94 – results and commentary. Ann Oncol 2003; 14: 61-118.
6. Winawer SJ, Fletcher RH, Miller L, *et al*. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112: 594-642.
7. Crespi M, Lisi D. Is colorectal cancer screening by fecal occult blood feasible? Ann Oncol 2002; 13: 47-50.
8. La Vecchia C. Reducing colorectal cancer though faecal occult blood screening: review of the evidence. Dig Liver Dis 2001;33:445-8
9. Allison JE, Tekawa IS, Ransom LJ, *et al*. A comparison of fecal occult-blood tests for colorectal cancer screening. N Engl J Med 1996; 334: 155-9.
10. Hardcastle JD, Chamberlain JO, Robinson MH, *et al*. Randomised controlled trial of faecal occult-blood screening for colorectal cancer. Lancet 1996; 348: 1472-7.
11. Kronborg O, Fenger C, Olsen J, *et al*. Randomised study of screening for colorectal cancer with faecal occult-blood test. Lancet 1996; 348: 1467-71.
12. Mandel JS, Church TR, Ederer F, *et al*. Colorectal cancer mortality: effectiveness of biennal screening for fecal occult blood. JNCI 1999; 91: 434-7.
13. Kewenter J, Brevinge H, Engaras B, *et al*. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. Scand J Gastroenterol 1994; 29: 468-73.
14. Lee KJ, Inoue M, Otani T, *et al*. Colorectal cancer screening using fecal occult blood test and subsequent risk of colorectal cancer: A prospective cohort study in Japan. Cancer Detect Prev 2007; 31: 3-11.
15. Betés M, Muñoz-Navas MA, Duque JM, *et al*. Use of colonoscopy as a primary screening test for colorectal cancer in average risk people. Am J Gastroenterol 2003; 98: 2648-54.
16. Cash BD, Schoenfeld PS, Ransohoff DF. Licensure, use, and training of paramedical personnel to perform screening flexible sigmoidoscopy. Gastrointest Endosc 1999; 49: 163-9.
17. Cheng TI, Wong JM, Hong CF, *et al*. Colorectal cancer screening in asymptomatic adults: comparison of colonoscopy, sigmoidoscopy and fecal occult blood tests. J Formos Med Assoc 2002; 101: 685-90.
18. Imperiale TF, Wagner DR, Lin CY, *et al*. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000; 343: 169-74.
19. Lieberman DA, Weiss DG, Bond JH, *et al*. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group. N Engl J Med 2000; 343: 162-8. Erratum in: N Engl J Med 2000; 343: 1204.
20. Lin OS, Gerson LB, Soon MS, *et al*. Risk of proximal colon neoplasia with distal hyperplastic polyps: a meta-analysis. Arch Intern Med 2005; 165: 382-90.
21. Nakao FS, Cury MS, Ferrari AP Jr. Colonoscopy or sigmoidoscopy: risk of isolated right colon lesions. Arq Gastroenterol 2001; 38: 168-71.
22. Nicholson FB, Korman MG, Stern AI, *et al*. Distribution of colorectal adenomas: implications for bowel cancer screening. Med J Aust 2000; 172: 428-30.
23. Rex DK, Chak A, Vasudeva R, *et al*. Prospective determination of distal colon findings in average-risk patients with proximal colon cancer. Gastrointest Endosc 1999; 49: 727-30.
24. Sciallero S, Bonelli L, Aste H, *et al*. Do patients with rectosigmoid adenomas 5 mm or less in diameter need total colonoscopy? Gastrointest Endosc 1999; 50: 314-21.
25. Segnan N, Senore C, Andreoni B, *et al*. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. Gastroenterology 2007; 132: 2304-12.
26. Schoenfeld P, Shad J, Ormseth E, *et al*. Predictive value of diminutive colonic adenoma trial: the PREDICT trial. Clin Gastroenterol Hepatol 2003; 1: 195-201.
27. Thiis-Evensen E, Hoff GS, Sauar J, *et al*. Flexible sigmoidoscopy or colonoscopy as a screening modality for colorectal adenomas in older age groups? Findings in a cohort of the normal population aged 63-72 years. Gut 1999; 45: 834-9.
28. Bond JH. The case for direct colonoscopy screening for colorectal cancer. Am J Gastroenterol 2006; 101: 263-5.
29. Regula J, Rupinsli M, Kraszewska E, *et al*. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Eng J Med 2006; 355: 1863-72.
30. Winawer SJ, Zauber AG. Colonoscopic polypectomy and the incidence of colorectal cancer. Gut 2001; 48: 753-6.
31. Citarda F, Tomaselli G, Capocaccia R, and the Italian Multicenter Study Group. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001; 48: 812-5.

32. Brenner H, Chang-Claude J, Seiler CM, *et al*. Does a negative screening colonoscopy ever need to be repeated? Gut 2006; 55: 1145-50.
33. Pox C, Schmiegel W, Classen M. Current status of screening colonoscopy in Europe and in the United States. Endoscopy 2007; 39: 168-73.
34. Lieberman D. Colorectal cancer screening in primary care (Editorial). Gastroenterology 2007; 132: 2391-4.
35. Crespi M, Lisi D. Compliance to different screening modalities for colorectal cancer in Italy. Dig Liver Dis 2007; 39: S215.
36. Segnan N, Senore C, Andreoni B, *et al*. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. Gastroenterology 2007; 132: 2304-12.
37. Saito H. Colorectal cancer screening using immunochemical faecal occult blood testing in Japan. J Med Screen 2006; 13 suppl 1: S6-7.