Screening for colorectal cancer

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Abstract

Colorectal cancer (CRC) is the most common cancer in the Nordic countries after breast and prostate cancer. About 15 000 new cancers are diagnosed and more than 7 000 patients will die from CRC in 2005. CRC fulfils most of the criteria for applying screening; the natural history is well known compared with many other cancers. CRC may be cured by detection at an early stage and even prevented by removal of possible precursors like adenomas. Faecal occult blood test is the only CRC screening modality that has been subjected to adequately sized randomised controlled trials (RCT) with long-term follow-up results, using Hemoccult-II. Sensitivity for strictly asymptomatic CRC is less than 30% for a single screening round, but programme sensitivity has been estimated to be more. Biennial screening with un-rehydrated Hemoccult-II slides has shown a CRC mortality reduction of 15–18% after approximately 10 years of follow-up in those targeted for screening. For those attending, the mortality reduction has been estimated at 23%. Denmark has decided to do feasibility studies to try to evaluate whether a population-based screening run by the community will have the same effect as has been demonstrated in the randomised trials. In Norway the government has accepted no formal population-based screening. In Finland, the Ministry of Social Affairs and Health made a recommendation in 2003 to the municipalities to run a randomised feasibility study with FOBT screening for colorectal cancer as a public health policy that is repeated every second year. In 2004 the first municipalities started. It has been claimed that today Sweden cannot afford CRC screening despite the potential mortality benefit. There is sufficient evidence for the efficacy of screening for colorectal cancer with fecal occult blood test every second year. There is, however, only little evidence on the effectiveness of screening when run as a public health service and there is insufficient knowledge of harmful effects and costs, even in RCTs.

Burden of colorectal cancer

Colorectal cancer (CRC) is the most common cancer in the Nordic countries after breast and prostate cancer. About 15 000 new cancers are diagnosed [1] and more than 7 000 patients [2] will die from CRC in 2005. There is substantial geographical variation, the risk being highest in Denmark and Norway and lowest in Finland and Iceland. In age groups potentially subjected to screening these differences remain between countries. At ages 50–74 years the incidence per 100 000 varies from less than 100 (Finland) to more than 150 (Norway) in males, and from 70 to 130 in females.

The incidence has increased during the recent decades in Nordic countries. The risk is related to affluence, hence it is likely that the trends continue and the burden of colorectal cancer should be even larger in the future. The predictions up to 2022 [1] do not confirm this, however (Figure 1). It is possible that the changes in risk will be less.

The screening should be targeted at ages with high risk of CRC. At ages 50–54 the risk is about 50 or less per 100 000 person years. At ages 75–79 the incidence is up to 400 in males and 300 in females [3].

Biology and natural history related to screening

Colorectal cancer (CRC) fulfils most of the criteria for applying screening; the natural history is well known compared with many other cancers. CRC may be cured by detection at an early stage and even prevented by removal of possible precursors like adenomas. The development of CRC is through polypoid or non-polypoid (flat or depressed) adeno-

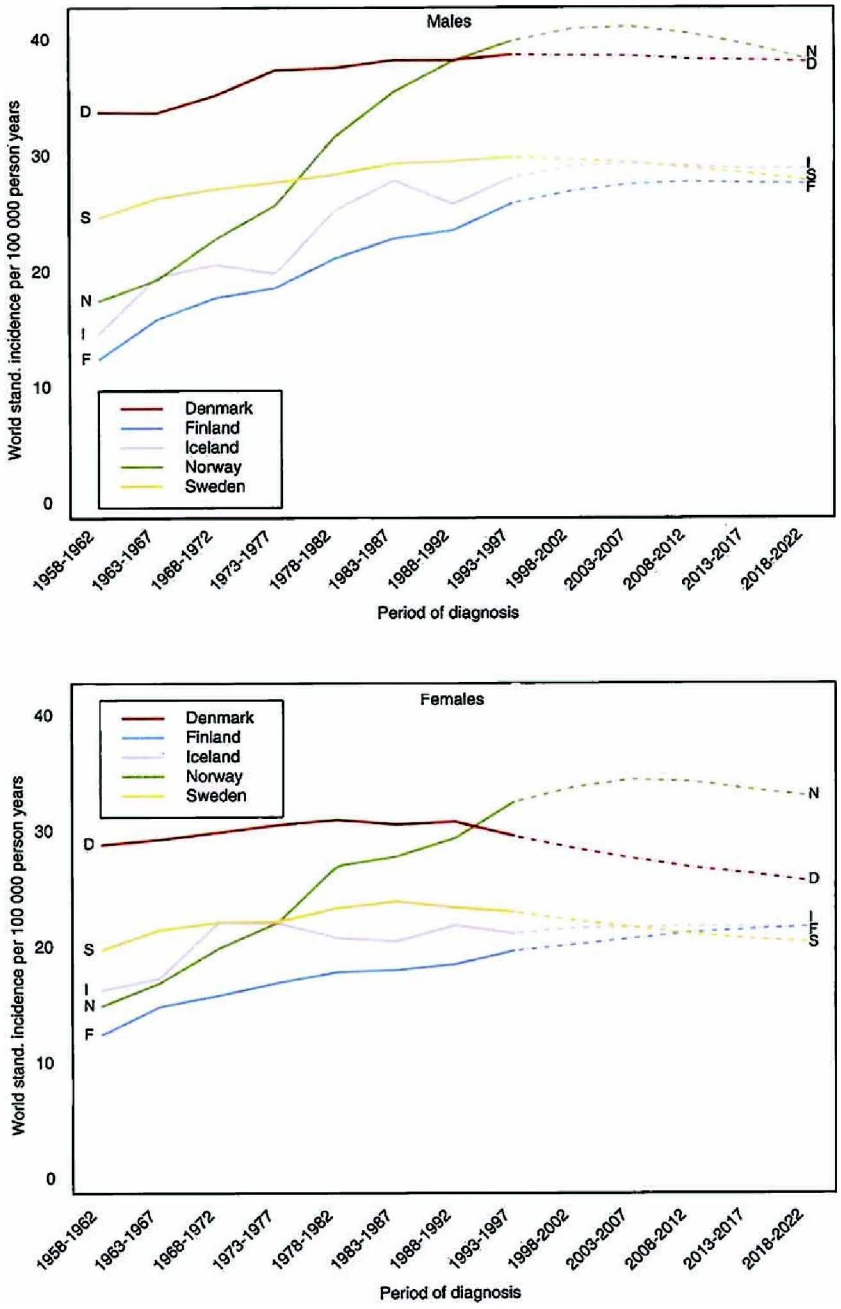

Figure 1. Observed and predicted age-adjusted incidence rates in the five Nordic countries: cancer of the colorectum. (Reproduced with permission from [1]).

mas and seldom from normal colonic epithelia; the process is usually slow, from 5–10 years [4], making screening attractive.

The evidence for the adenoma-carcinoma (A→C) sequence is manifold [5], but the ideal proof would require that adenomas were removed, sectionised for study, reassembled, returned to the original site and then allowed to continue to the ultimate outcome. Unfortunately, a biopsy of the presumed adenoma does not necessarily demonstrate all the significant features of the pathology.

Many specific molecular genetic alterations have been identified in CRC representing the continuum of the A→C sequence, but also many exceptions to the preferred sequence [6,7].

Evidence for the A→C sequence is presented in Table I. Severity of dysplasia in adenomas increases with size and degree of villousness, whereas multiplicity has not always been shown to be an independent risk factor.

Further evidence for the A→C sequence is found within cytogenetics, DNA ploidy and cell prolifera-

Table I. Evidence for the (A→C) sequence [5]

Similar distribution of adenomas and CRC
CRC is twice as common when adenomas are present
Adenomas are at least twice as common when CRC is present
The presence of contiguous adenomas and CRC
Patients with polyps ≥1 cm in diameter that are not removed have an increased risk of CRC
Removal of adenomas probably reduces risk of later CRC
Adenomas are diagnosed some years before CRC
High risk of metachronous neoplasia in patients with synchronous CRC and adenoma
Clustering among multiple adenomas, multiple CRC and between adenomas and CRC
Familial adenomatous polyposis (FAP) is followed by CRC in nearly 100% of the patients, when colon is left behind
Populations with high risk of CRC have the highest prevalence of adenomas

tion. K-ras mutations are frequent in adenomas and increase with size. The number of positive cases rises to 40–50% in CRC. Accumulation of mutated p53 is expressed in a minority of adenomas, but is correlated to degree of dysplasia. Other genes, adhesian molecules and other markers fully support the sequence and animal studies have demonstrated that adenoma cell lines may be transformed by exposure to a carcinogen and produce carcinoma.

The evidence against the A→C sequence is weaker and is presented in Table II. There is evidence from randomised controlled trials with fecal occult blood tests and flexible sigmoidoscopy that removal of more adenomas in the test groups reduces the incidence of CRC, but so far most of the reduction in mortality from CRC may be explained by the detection of a larger proportion of cancers at a favourable stage [8–10]. A trial randomising patients to polypectomy or no polypectomy, including large adenomas and long-term surveillance without polypectomy, will probably never be performed, but some knowledge will be obtained from randomisation of the intervals between colorectal examinations after polypectomy [11,12].

In summary, molecular biology strongly supports the (A→C) sequence, having shown that the defects in oncogenes and suppressor genes permit the formation of adenomas, but additional defects are necessary for the development of CRC. Extensive damage to the genes would have to occur within a short period of time to support the de novo theory, and so this seems less probable. The rational for screening is obvious and many clinical trials have been performed and are ongoing to detect adenomas and CRC in favourable stages, but the ideal instrument for that purpose has not yet been identified for the average risk population. High-risk groups with genetic syndromes like FAP and HNPCC only amount to a small proportion of the many cancers.

Table II. Evidence against the (A→C) sequence [5]

Small CRC without adenomatous remnants
Size of adenomas does not increase with age
Different sex distribution in patients with adenoma and carcinoma
Incidence of CRC in people with an initially adenoma-free colon is no less compared to the normal population
The risk of CRC is still increased after removal of adenomas

Conceptual considerations

The primary purpose of screening for cancer is to reduce mortality from the disease screened for. Screening has also other effects than that on the length of life span, notably on economic cost and on quality of life. Screening usually implies increase in the health expenditure. The effects on quality of life are both positive and negative compared to clinical practice without screening.

Effects other than mortality are in principle considered. However, in practice the public health policies to screen for cancer are invariably initiated, run and evaluated, on basis of effect on mortality. In fact, there is no good science-based agreement on how to apply the criteria other than mortality on the decision whether to start a public health policy or not. Such a decision assumes agreement on the magnitude of effect on these criteria, and how to weigh the benefits and harms in different dimensions of death, quality of life and cost. This Acta Oncologica expert report focuses on applicability of screening for colorectal cancer. Therefore, recommendations on routine screening at the end of this report are based mainly on mortality criteria while admitting the limitations, both scientific and practical, in such an approach.

Screening is a chain of activities from defining the target population to treatment and follow-up of screen-detected patients. A screening programme consists of these elements and links them together. They vary between screenings for specific cancer sites. For colorectal cancer screening with fecal occult blood test (FOBT) it is important that:

- the target population is defined and identified at the individual level,
- there is a system that can send out invitations with test kits, receive test kits, and inform on initial screening,
- there is an agreement on frequency of screening and ages at which screening should be performed,
- there is adequate capacity for work-up and treatment of screen positives,
- there are defined mechanisms for referral and treatment of the screen positive cases,

- there is an information system that can follow the coverage, participation, referrals, treatment and incident cases of and deaths from CRC in order to monitor and evaluate the programme,
- there is a quality control system that can affect any activity in the programme.

These criteria define organized screening versus opportunistic screening.

The success of the programme is predicted by performance indicators and described by outcome indicators. Probably the most essential element in the screening activity is the screening test, and the most essential indicator of the total programme is its effectiveness in terms of mortality. In the case of CRC, incidence should also be considered, assuming the importance of the A→C sequence of events.

The diagnostic test is evaluated by its sensitivity and specificity, the ability to detect those diseased and those healthy. When applied to screening, the future disease is of interest. The disease is unrecognized and in the detectable (by the test) preclinical phase (DPCP). There are no means to directly estimate the sensitivity of the screening test to detect cancer in the DPCP. Pragmatic measures have been agreed, and they are based on observation of failure instead of the success. Interval cancers after screen represent the failure of screening and provide indirect means to estimate success in terms of sensitivity, if compared to the expected overall risk (sensitivity by incidence method) or to screen-detected and interval cancers (detection method). The latter is biased if histopathological overdiagnosis exists, as are any methods to estimate sensitivity that are based only on screen-detected cancers without follow-up. It is useful to distinguish between the sensitivity of the test itself, screening episode (test and work-up) and the total programme. In periodic screening sensitivity is based on repeated tests that predict the effect on mortality of the screening. Much confusion is caused by the use of intermediate indicators or indirect evidence as the basis of routine screening. Good sensitivity is necessary but not sufficient for the total programme to be effective and the same applies to other indicators other than the mortality outcome.

The CRC mortality reduction in those screened in ideal conditions is called efficacy [13]. Estimate of efficacy is usually provided by randomised screening trials on volunteers. Design with intention to screen (in a normal population) yields also an efficacy estimate if the proportion of compliance or attendance and mortality among attenders and non-attenders are known [14]. This is accomplished by registration of target population, cancer and screening information and linkage of these three data sources. Miscomprehended ethical rules may prevent such a design and analysis.

Effectiveness is the term that describes the mortality reduction in real application as a public health policy. It describes the effect of routine screening in the target population, and is the ultimate public health measure of screening. A prediction of large enough effectiveness is a prerequisite for recommending screening as a public health policy. Estimating the effectiveness assumes intention to screen principle. It depends, e.g., on efficacy, participation, and quality of clinical service. It is to be done with scientific rigour. Any public health policy will be gradually implemented. As long as the screening is expanding, there are unscreened controls which provide means to evaluate the total programme by experimental principles including some randomization (individual or cluster randomization). Monitoring includes estimating the effectiveness of an established routine screening.

Screening tests

No ideal methods are available for screening the average risk population above 50 years of age, but most of them will probably decrease mortality from CRC and even reduce incidence.

Rigid sigmoidoscopy

Covers an area where no more than 25% of all the cancers are located, making it unattractive, but uncontrolled studies suggest that mortality from rectal cancer may be reduced by repeated sigmoidoscopy with removal of adenomas as well as early cancers.

A case-control study supported this suggestion, but found that sigmoidoscopy once every 10 years would be nearly as effective [15]. The rigid scope is no longer in use for screening.

Flexible sigmoidoscopy (FS)

Usually, a 60 cm long fiberscope or videoscope is used, covering the area where approximately 50% of CRC's are located. It carries a small risk of perforation, but sedation is not required and the procedure can be performed with a simple bowel preparation immediately before, at home or at the doctor's office. An overview of previous and ongoing studies with FS is presented in Table III. No results are available yet for incidence of and mortality from CRC, the one exception being the small study from Norway [16].

Screening with FS makes it possible to remove small precursors in the rectum and sigmoid colon during the examination. Most studies involve a once-

Table III. Flexible Sigmoidoscopy (FS) as a screening instrument.

Type of study Reference	Procedure and Target group	Incidence (Odds Ratio)	Mortality from CRC (Odds Ratio)	Status and Criticism
Case Control Newcomb et al.[68]	66 rectal and distal colonic cancers 196 controls		0.21 (95% C.I. 0.08–0.52) Sigmoidoscopy in 10% ~30%	FS was performed in 66% of endoscopies in cases and 59% of controls. The remaining being rigid sigmoidoscopy
Case Control Müller et al [69] and Müller et al. [70]	8,722 colonic cancers 7,629 rectal cancers 16,531 living controls 16,199 dead controls	Colonic cancer 0.56 (95% C.I. 0.46–0.67) Rectal cancer 0.61 (0.49–0.75)	0.41 (95% C.I. 0.33–0.50)	Complicated design evaluating FS, colonoscopy and polypectomy together
RCT, population based Thiis-Evensen et al. [16]	Once FS Performed FS 324/400 399 controls 50–59 years	0.2 (95% C.I. 0.03–0.95) (P = 0.02) Follow-up 13 year (2 cancers ~10 cancers)	At follow-up 3 controls had died from CRC and one in the screening group	Very small numbers
RCT, volunteer based UK FS-Screening Trial Investigators [32]	Once FS Performed FS 40.675/57.070 2 × 57,070 controls 55–64 years	No results yet	No results yet	Intake complete year 2000. Selection by letter to 368,597 among whom 194,650 were interested
RCT, volunteer based Segnan et al. [42]	Once FS Performed FS 9,791/16,769 16,679 controls 55–64 years	No results yet	No results yet	Intake completed year 1998. Same selection as in the UK study
RCT, population based Gondal et al. [28]	Once FS ±FOBT Performed FS 12,960 Controls 79,430 50–64 years	No results yet	No results yet	Intake completed year 2001.
RCT Gohagan et al. [17]	FS every 3 years FS 74,000 Controls 74,000 68–74 years	No results yet	No results yet	Planned to stop intake year 2000. Multiphasic screening program for more than one cancer.

FS at an average of 55–64 years, but the American study uses FS every 3 years [17].

Acceptability for FS has most often been below 50%, but higher numbers have been achieved in Norway.

FS is not always complete and the descending colon may be intubated in no more than 46% even after 60 cm has been inserted [17,18]. However, the presence of neoplasia within the reach of FS has some predictive value for neoplasia in the right site, whereas the opposite does not seem to be true.

Experienced nurse endoscopists may perform FS as safely and effectively as gastroenterologists.

Overall, no more than 25% of CRC's may be detected by a once-FS at age 60; 15% of CRC are diagnosed before year 60, acceptability may be 50% (optimistic view), 50% of CRC's is within the reach of FS (again an optimistic view), and no more than 25% of more proximal cancers may be found indirectly by colonoscopy as indicated by distal neoplasia.

Further details about screen-FS may be found in another recent review [19].

Colonoscopy

Has very high diagnostic accuracy and it is possible to remove most precursors of CRC during the examination. However, the drawbacks are several, and many would never consider colonoscopy as screening method in other than high-risk populations because of its complexity, risk of perforation, inconvenience to the screenees and demand of large economic as well as human resources.

No RCTs have been published, but there is some evidence suggesting a possible benefit (Table IV) and colonoscopy has recently become available in some countries for screening of average risk persons.

An American prospective multicentre study obtained a completeness of colonoscopy as high as 97% of cases in asymptomatic subjects aged 50–75 years [20].

Imaging

Double contrast barium enema may be a necessary supplement to colonoscopy, when the latter cannot

Table IV. Colonoscopy as a screening instrument.

Target group Reference	Accepted colonoscopy	Complete colonoscopy	Screen detected neoplasia	Serious complications	Criticism
Asymptomatic 50–75 years (62.9) 96.8% men; Lieberman et al. [71]	3,196/4,659 68.5%	97.7%	30 CRC (0.9%) 299 significant adenomas (9.3%)	0.3%	Selected population: 13 Veteran Affairs medical centers
Random population sample 63–72 years (67.4); Thiis-Evensen et al. [72]	241/356 67.6%	80.0%	2 CRC (0.8%) 38 high risk adenomas (15.7%)	None	47 had symptoms and 9 had increased risk of CRC
Asymptomatic 50–75 years negative H-II; Rex et al. [73]	210/5.000 4.2%	99.5%	2 CRC (0.9%) 11 subjects with adenomas ≥10 mm (5.2%)	0.5%	Selected population: physicians and dentists and their spouses

be completed. No RCTs have been performed, but FS and barium enema would be complementary. Virtual colonoscopy (colonography) may replace the barium enema, and the use of magnetic resonance avoids the risk of ionizing radiation. It is questionable whether virtual colonoscopy should be considered for screening average risk populations.

Fecal occult blood tests (FOBTs)

The Guaiac tests are based on peroxidase activity in all haemoglobin, heme and myoglobin, and non-heme peroxidases. Many case-control studies have been performed [19] as well as 4 major RCTs. One, the Swedish trial [21], has not reported end results. The other 3 RCTs (Table V), as well as the case control studies have demonstrated a relative reduction in mortality from CRC in biennial or annual screening. The most recent results demonstrated a relative reduction of mortality of 43% in persons having completed 9 biennial screening rounds with Hemoccult-II test (H-II) compared to the mortality in the control population [9]. Increasing the sensitivity of Hemoccult by rehydration, which was done in the American RCT [22], resulted in a reduction of incidence of CRC, which has not been demonstrated in the European studies. However, the number of colonoscopies increased substantially, because of many false positive tests. The American study was performed in volunteers, whereas the European studies were true population RCTs. In the European studies the intention to screen analysis showed a statistically significant effectiveness of 15–18% reduction in CRC mortality in the intervention group.

The rather low sensitivity of unhydrated H-II is not increased significantly by offering H-II on 6 days instead of 3, and acceptability decreases. Sensitivity is about 60% in a biennial program, and a once-screening with H-II should never be considered. Dietary restrictions may decrease the number of false positive tests, but in UK an unacceptable decrease in acceptability resulted.

It has been thought that interval cases (CRC detected between screening rounds) might fare worse than controls, but in the 2 European RCTs they had a longer survival than controls [9], due to better stage distribution. A systematic review of

Table V. The 3 large RCT's with Hemoccult-II.

Characteristic	Minnesota (50–80 years) [22] (volunteers)	Nottingham (45–74 years) [8] (normal population)	Funen (45–75 years) [10] (normal population)
Test group Controls	15,570 annual, 15.587 biennial 15,394	76,466 biennial 76,384	30,967 biennial 30,966
Period of screening	1975–82, 1986–1992	1981–1995	1985–2002
Positivity rate	9.8%	1.8–0.8%	3.8–0.8%
Pv_{pos} CRC	2% annual, 3% biennial	11–14%	5–21%
Dukes A (%)	30% annual, 27% biennial	20% 11%	22% 11%
Test group Controls	22%		
Mortality ratio for CRC	0.67(0.51–0.83) (a) 0.79 (0.62–0.97) (b)	0.85 (0.74–0.98)	0.82 (0.68–0.99)

5 trials has confirmed a reduction in mortality from CRC by FOBT-programs [23].

A more sensitive guaiac test, the HemeSensa, has not been evaluated in larger RCTs, but the specificity is lower than that of H-II and dietary restrictions probably are necessary.

Immunochemical human specific tests like HemeSelect also has a higher sensitivity and the specificity may be higher than that of HemeSensa, and the test may be automated, but it is much more expensive than the guaiac tests, and the number of false positives may be higher, depending on cut-off levels chosen.

Immunochemical tests have been used in routine screening in Japan [24]. Reducing testing to 1 instead of 3 days increases specificity and reduces sensitivity to a lesser degree, and acceptability probably increases [25]. Further increase of acceptability may be obtained by brush sampling instead of the commonly used spatula [26]. The 2-tier principle, e.g. using the less specific test first (HemeSensa), and the more specific (HemeSelect) in those with positive HemeSensa, makes the procedure more complicated.

Pilot studies with immunochemical tests are ongoing in Australia.

Flexible sigmoidoscopy+FOBT

No RCTs are available comparing a full FOBT program alone with a program including FS as a once-procedure or repeated with intervals of several years. The last has been recommended based on early studies with rigid proctoscopy and H-II [19]. A Danish study with FS as a once-procedure suggests that the same number of CRC's will be found during 3 screening rounds with H-II [27], but adding FS to the FOBT program may increase the sensitivity for CRC as well as large adenomas. Addition of a once only FOBT to a once-FS is probably of little benefit [27–29].

Molecular stool screening

DNA markers have been investigated in limited series. Multiple DNA changes must be looked for and each marker must be specific.

Screening for Kras and p53 alone has resulted in sensitivities that are no better than that of H-II. Including APC, BAT26, and long DNA increased sensitivity considerably in pilot studies [30].

The methods are presently labour-intensive and expensive, and it is not known whether they will improve efficacy of screening.

Implementation of CRC screening programmes

Based upon findings in literature the only evidence-based way of screening for colorectal cancer is to detect faecal occult blood (FOB) in the stool and offer those with a positive test a colonoscopy [8,10,22,23,31]. All other techniques like identifying risk groups with sigmoidoscopy [32], single colonoscopy [33] or looking for molecular markers in faeces [34] have not been established.

An important issue in screening for colorectal cancer is to establish the value of screening method in a population-based setting. All published randomised trials have been done within a research protocol and it is well known that results from research protocols are often better than offering the new technique into the community. Therefore, it is essential that feasibility studies will be done before routine population-based screening is started.

Taking into account different cultures it is important that each country wanting to embark on screening must do some type of evaluation before screening will be adopted. Most countries have screening program for risk-group families and patients. This is not a real screening- situation but merely a surveillance program. Population based screening for healthy subjects is a more important topic and has to be evaluated.

Surveillance of risk-group cohorts

Well-known risk-groups are those with inflammatory bowel diseases like Crohn's disease and ulcerative colitis. Others are those with hereditary cancers as FAP, HNPCC and family cancer syndromes. A third group is those with sporadic cancers or polyps who are followed within a surveillance program to detect metachronous tumours.

Ongoing population-based screening projects

United States of America. In the USA it has already been accepted that any CRC screening (FOBT, flexible sigmoidoscopy or colonoscopy) is to be recommended [35]. Accordingly, the reimbursement from different insurance systems do accept screening as a modality in the USA, although the government has not secured a screening programme for the relevant target population.

Australia, Austria, France, Germany, Italy and Switzerland. Based upon the same arguments as have been used in the USA, screening for colorectal cancer with FOB testing is also accepted in the reimbursement program. However, no population-

based studies have been done in these countries providing evidence that screening according to this model, has reduced CRC mortality.

Denmark and United Kingdom. In both countries two large randomised trials have been run showing the beneficial effect in terms of reduced mortality from CRC if screening with FOB is used [8,10]. Both countries have taken a more modest attitude to the outcome of these trials and have decided to do feasibility studies to try to evaluate whether a population-based screening run by the community will have the same effect as has been demonstrated in the randomised trials. The surrogate end-points found in the trials have been settled in UK where two large populations have been screened [36]. In Denmark this has not been done yet, but the government has decided to pay for a similar feasibility study in two counties to evaluate if population-based screening outside large trials is as effective as has been shown. Surrogate end-points like compliance, the proportion of tumours in stage I or stage II, complications to colonoscopy, completion rate at colonoscopy and logistics have been evaluated. Provided that all those surrogate end-points will be similar to those found in the three large randomised FOBT trials, it is likely that government based population screening will have an impact on CRC mortality.

Data from the feasibility study in UK have been published, indicating that population-based screening with FOB-testing might be worth-while [36].

The other Nordic countries. In Norway a single flexible sigmoidoscopy is tested in a research protocol, but the government has accepted no formal population-based screening.

In Finland, the Ministry of Social Affairs and Health made a recommendation in 2003 to the municipalities to run a randomised feasibility study with FOBT screening for colorectal cancer as a public health policy that is repeated every second year. In 2004 the first 23 municipalities started with more than 5 000 screenees in a target population of 35 000. The ultimate target population is approximately 500 000 individuals at 60–69 years of age. The programme is centralized public health policy with gradual or stepped initial phase covering 15% of the municipal specific population in the first year and 50% in the sixth year. The individuals are selected by random sampling. In 2004 one screening centre run by Cancer Organizations in Tampere covers the analyses of the tests and the organization of the programme is by the Mass Screening Registry of the Finnish Cancer Registry. [37]

In Sweden, it has been a task among physicians to start a feasibility study, as has been done in the UK, to evaluate the effect on the Swedish population. One randomised trial has been run in Sweden, the Gothenburg study, but only preliminary results have been reported in international literature [21]. However, the data have been reported on meetings to be similar to those found in the Funen and Nottingham trials. Still, the question is whether or not screening should be implemented in the Swedish health-care system. A similar implementation as in Finland has been proposed and scrutinized by the health authorities. It has been claimed that today Sweden cannot afford it despite the potential mortality benefit.

If the data from the Danish and English trials are extrapolated to the Nordic countries, then approximately 1500 patients per year will be prevented from dying of colorectal cancer. This figure is similar to that for cervical cancer screening, but larger than the benefit (1000 deaths prevented) expected with screening for breast cancer [2].

Opportunistic screening

The major problem of screening techniques in all countries, and especially in the Nordic countries, is that we do not really know if the findings from randomised trials could be transferred to population-based screening. Therefore, it is of outmost importance that feasibility studies are done in all countries, making this evaluation as good as possible. In a public health care system, as in the Nordic countries, it is even more important to evaluate this. Otherwise there is a clear risk that opportunistic screening will start. This can be very costly for the society and any evaluation is impossible. Health-conscious, low-risk individuals are likely to seek opportunistic screening, and it cannot be recommended [38]. It is most unfortunate that the World Organisation on Digestive Endoscopy (OMED) now recommends opportunistic screening ("case-finding"). [39]

A specific risk is the new testing tools available on the market. According to the rules within the common market in Europe, testing tools can be evaluated and accepted, i.e. receive a CE (Communauté Européenne) mark. After such recognition, it is free for a company to sell the test in not only pharmacies but also all other shops. This will probably increase the risk of opportunistic screening activities.

Performance and effect of CRC screening

There is strong indirect evidence that most cases of colorectal cancer (CRC) develop from adenomatous

precursor lesions and that polypectomy of adenomas may prevent CRC [40]. The high prevalence of adenomas, however, suggests that >90% of adenomas will never reach a stage of malignancy. Nevertheless, the efficacy of screening for CRC must take into account both the identification of asymptomatic, early CRC and benign, adenomatous precursor lesions. Efficacy should therefore be expressed in terms of mortality reduction as well as reduction in incidence as a consequence of polypectomy of screen-detected adenomas.

Faecal occult blood test. This is the only CRC screening modality that has been subjected to adequately sized randomised controlled trials (RCTs) with long-term follow-up results, using Hemoccult-II [8,10,22,23,31]. Sensitivity for strictly asymptomatic CRC is less than 30% for a single screening round [41], but programme sensitivity has been estimated to be more than 60% [19]. Biennial screening with un-rehydrated Hemoccult-II slides has shown a CRC mortality reduction of 15–18% after approximately 10 years in the British (Nottingham) and the Danish (Funen) studies (intention-to-screen analysis) [8,10]. Only these two studies recruited from the population registry, thus mimicking the effectiveness of a national screening programme. For those attending, the mortality reduction was 23% (efficacy). The third of these large-scale trials on Hemoccult-II (Minnesota), recruiting volunteers for randomisation, used rehydrated slides and obtained 33% mortality reduction (mimicking efficacy) after annual screening through a similar follow-up period [31]. In addition, after 18 years follow-up, the Minnesota trial could demonstrate a reduction in CRC incidence [22]. This was considered mostly due to >35% accumulated colonoscopy coverage of the screenees and polypectomies since FOBT itself has a poor performance for adenoma detection [40].

Flexible sigmoidoscopy (FS). There are three large-scale RCTs on FS underway with 5-year follow-up results expected in 2005–2007 (United Kingdom, Italy and Norway). So far, only baseline data have been published [28,32,42]. In addition, there is the large PLCO study in the USA where the first results are not expected until 2011 [43]. Using 'any adenoma' at FS screening as criterion for a positive test and threshold for work-up, FS has been estimated to have a 70% sensitivity both for cancer and advanced adenomas (adenoma ≥10 mm diameter, severe dysplasia or villous components) [29]. This threshold would imply that 15–20% of screenees would need colonoscopy [28]. The sensitivity of FS greatly exceeds that of a single round of FOBT, not only for large adenomas, but also for CRC [44]. The problem with FS compared with FOBT has been poor attendance in most studies, 40% in Denmark [44], 30–49% in Sweden [45,46], 10% estimated population coverage in Italy[42] and 39% in Great Britain [32]. Poor attendance will reduce the potential effectiveness (benefit to the population) and usually also efficiency (cost-effectiveness). Exceptions to poor attendance have been the small-scale Telemark Polyp Study (TPS-I) with 81% attendance rate [16] and the large-scale NORCCAP study with 65% attendance rate [28], both carried out in Norway. The latter also demonstrated that adding a very sensitive immunochemical FOBT (FlexSure OBT®) to FS resulted in 4% drop in attendance rate. This represented a loss in diagnostic yield, which could not be compensated for by the addition of FOBT among those attending.

Colonoscopy

As the reigning gold standard method for work-up of screen positives, whichever screening method is used, this is obviously the ultimate colorectal screening method in terms of efficacy. It has an estimated sensitivity of >90% for CRC [47,48]. No large-scale RCTs have been launched on screening colonoscopy with CRC mortality or incidence as end-points. Although the small-scale TPS-I study showed a 62% attendance for colonoscopy screening [16], the bowel preparation required seems to be a major barrier against attendance [49]. A poorer attendance rate than for FS may be anticipated, so that the gain in efficacy may be lost when it comes to effectiveness and efficiency.

Emerging methods

Virtual colonoscopy is emerging as an alternative to colonoscopy, recently reported to have similar sensitivity for protruding lesions ≥7 mm in diameter [50]. When, or if, the sensitivity can be improved for smaller and flat lesions, there will be a need for conventional endoscopy of about half of those submitted to virtual colonoscopy if it is accepted that 'any polyp' discovered requires a histological diagnosis.

Exfoliative markers in stools have the advantage that they are being shed continuously and not intermittently as blood from colorectal neoplasia. Some of these candidate markers expressing mutant DNA are K-ras, APC, p53, Bat-26 and L-DNA. In small studies using a full panel of these five candidate markers a positivity rate of 91% has been obtained

for CRC, 82% for adenomas and 7% for normals [41].

Whichever screening modality is applied, endoscopy will play a pivotal role in the foreseeable future, either as a primary screening tool or work-up method of screen positives. Efficacy is measured by the end result of the screening, work-up and treatment chain of events. Quality assurance programmes are therefore a must for the efficacy of screening. There is a great inter-endoscopist variation in pick-up rates for neoplasia [51,52] contributing to differences in efficacy.

Screening as a public health policy

Recent history

Colorectal screening, using any of the current screening modalities (FOBT, FS or colonoscopy) has been recommended for some years in the USA [53]. In 2003, the European commissioner on health recommended EU member states to consider screening with FOBT [38], but Germany, Italy and Poland [54] have already started national colonoscopy screening programmes. In Finland, a national CRC screening programme using FOBT started in 2004 as a public health initiative, invitees being randomised at individual level [37]. A pilot FOBT programme is now being launched in Denmark. In Norway, the largest regional health board (Helse Sør RHF) has recommended a large-scale RCT on colonoscopy screening. Norway has the highest CRC incidence among the Nordic countries, but no decision has been reached on a national strategy. Similar to other countries, health authorities are awaiting the results of on-going trials. In Sweden, it has been decided not to run FOBT screening programmes or feasibility studies despite the knowledge of efficacy and the risk of ineffective and expensive opportunistic screening.

Proven benefits and high attendance rates are prerequisites for a successful screening policy

In a public health perspective, high attendance rates are crucial for success. To achieve this, individual potential screenees must believe that there is something to be gained from participating. Thus, there may easily arise a conflict of interest between the screenee and the health care provider. Screenees attend to be reassured that they have no lesions and nothing to worry about, in which case only good quality colonoscopy will be adequate. The health care provider, on the other hand, wants to pick up as many prevalent cases of early CRC in the population as possible, in which case attendance is crucial and colonoscopy requiring extensive bowel cleansing may not be the best option.

In the USA there is concern about a poor and declining overall attendance for CRC screening [55], possibly with some increasing interest only for 'gold standard screening' (colonoscopy). This is happening in spite of much resources being spent on public awareness to convince the population of the benefits of screening. However, the very lack of convincing proof of these benefits have been reported to be an important barrier to participation [55]. It is also worth noting that an invitation for colonoscopy screening sent to 17 000 physicians, dentists and their spouses only gave 6% acceptance in USA in the early 1990's [56]. The attitude among health care professionals may have changed since then, but it should be pointed out that potential screenees do seek advice on screening with their MDs who, at least as late as the early1990's were not convinced on their personal benefits of colorectal screening in the USA.

The currently documented benefits of screening as demonstrated through RCTs are limited to FOBT. With a 5% lifetime risk of getting CRC, a 50% 5-year survival rate when diagnosed due to symptoms and a 16% relative CRC mortality reduction from FOBT screening, then screening can presently only reduce the CRC mortality risk from 2.5% to 2.1% of all deaths in invitees (intention-to-treat), possibly down to 1.9% of all deaths in those attending after 8–10 years follow-up [8,10]. Recently, the modest benefit demonstrated after 8–10 years was further reduced after 9 screening rounds (17 years) in the Danish Funen study [9]. This may be attributed mainly to the decreasing proportion of the screening group actually being screened and is not caused by increasing age or changes in sex ratio. In addition, the number of CRC deaths prevented through FOBT screening is small compared to all deaths and even less than the random fluctuation in total mortality [8,10,57,58]. These apparently modest absolute gains may be difficult to sell to the average risk population although they are better than or comparable to established screening programmes like mammography and cervical cancer screening [2]. Although somebody may be convinced of the benefits of screening, there is obviously a shortage of good data. A paternalistic attitude towards the public, based on poor level of evidence (apart from the RCT-based evidence on FOBT), possibly suppressing undesirable uncertainties for the good cause (high attendance rates), may bounce back after a few years of national screening. Some of these mechanisms may explain what we have seen through the recent years' debate on mammography screening. The epidemiological data on CRC has raised aware-

ness and a call for action in many countries, particularly within in the EU. However, one should not be trigger-happy enough to skip the RCT phase that should precede the introduction of any new treatment/intervention if at all possible. Very sensibly, the EU Commissioner on health is concerned about the quality of all steps of events from the screening phase itself, through work-up of screen positives to treatment [38]. If one can obtain a political, professional and public understanding that it takes time to build up high quality performance of all services required, then it should be possible to gain acceptance for a stepwise introduction of screening services through phases of RCT like presently started in Finland for FOBT [37]. A first-step RCT approach may also facilitate modifications of the initial screening modality through the succeeding stepping-up of a national programme and secure comparative data to supplement our limited knowledge on the wider consequences of screening. The next step may be an RCT phase using an immunochemical test for FOBT or a panel of molecular markers. A stepwise building up through e.g. '5-year steps' may combine the requirements for more robust data, which are particularly interesting and relevant to the target population, since they are the very source of the data. This again may further public awareness. There is probably nothing more persuasive to the public, professional critics and health care providers than good, robust data referable to the target population itself.

Quality of screening test and work-up

Sustaining high attendance over years in a screening programme requires that promises are kept. This includes the delivery of all services needed (screening, work-up and treatment), in addition to demonstration of quality in performance of these services. The analytical insight and memory of the general public should not be underestimated, nor the effect of advice sought from their GP (who may not be convinced) or the next-door neighbour (who may have had a "never-again" experience with a poor colonoscopist in his or her screen-positive work-up a year ago). Politicians and health-care workers should not be tempted to implement national screening without the political and financial will to provide adequate delivery of work-up, treatment and continuous quality control [59]. This can only be achieved through organised screening [38], and one does not know the quality of services in a country until looking for it. There has recently been demonstrated a considerable inter-endoscopist variation in the ability to identify colorectal polyps [51] and even high-risk adenomas [52], in spite of meticulous attention apparently being paid on quality issues. A recent survey of routine colonoscopy in Great Britain revealed $<60\%$ coecal intubation success using the only accepted criteria for complete colonoscopy (identification of the ileocoecal valve or intubation of the terminal ileum) [60], in spite of 94% being sedated. This compares to a small study from Finland showing that coecal intubation could be done successfully without sedation in 100% of cases and that sedation proved to have no major impact on the patients' experience of the examination [61] as painless colonoscopy is mostly a matter of applying the right technique. A recent survey on routine colonoscopy in a Norwegian hospital involving a number of endoscopists at all levels of experience showed 85% coecal intubation when only 6% were sedated [62]. In the Polish colonoscopy screening programme, centres not performing up to standards have been excluded from the programme. One effect of this has been that the coecal intubation rate has increased from 85% to 90% in the Polish programme (J Regula, pers. comm.).

Cost effectiveness

There are many uncertainties in cost-effectiveness estimates since knowledge on effectiveness is limited to FOBT and there is no experience even on FOBT when run as a national public health service. This is the most important limitation. In addition there are variations in which costs should be included in the analyses and there is great variation in expected compliance for the different screening modalities in different populations. In the absence of data on effectiveness, information on surrogate measures of effect has been used. One Dutch study, based on epidemiological data from Oslo, concluded that FS and colonoscopy screening could be more cost effective than already established mammography screening programmes [63]. Another estimate, based on data from the USA, has pointed out that all the three established screening modalities perform well in terms of cost-effectiveness, FOBT being the most cost-effective, but colonoscopy could easily be the most effective if cost per examination could be brought down [64]. It should be pointed out that most colonoscopies in the USA are carried out under sedation and, in France, even under general anaesthesia. One study, trying to demonstrate that on-demand sedation rather than routine sedation may be acceptable to the USA patients, showed that patients in the on-demand arm were billed on average $104 less than the routinely sedated group [65]. The cost per life year gained by FOBT screening has been estimated at £1584, based on

the experience of the Nottingham FOBT trial [66]. CRC screening can substantially reduce also the prediagnosis evaluation costs of CRC otherwise diagnosed due to symptoms [67].

CRC screening as health policy is not yet recommended by WHO, but EU encourages member states to consider establishing organised FOBT screening paying meticulous attention to quality issues. Attendance is crucial and public awareness with information based on the present level of knowledge appears to be insufficient in several countries. There is also a need for improved screening modalities. All these requirements and needs may be combined by national policies accepting that national screening programmes must be built up gradually through steps of RCTs. The potential gain in the Nordic countries is presented in Tables VI and VII, which are based on 20% effectiveness (as expected in FOBT screening) and on the assumption that organised screening programme was started in the mid-1990s [2].

Recommendations

There is sufficient evidence for the efficacy of screening for colorectal cancer with fecal occult blood test every second year. There is, however, only little evidence on the effectiveness of screening when run as a public health service and there is insufficient knowledge of harmful effects and costs, even in RCTs.

Recommendation 1. Run an organised screening programme. This should be started as feasibility studies, preferentially through stepwise randomisation.

Table VI. Predicted effect of screening for colorectal cancer on the numbers of deaths and age adjusted "world standard population" mortality rates, females. [2]

	Predicted number of deaths			Predicted mortality rates		
Period	Without screening	With screening	Difference	Without screening	With screening	Difference
Denmark						
1993–97	5661	5661	–	17.0	17.0	–
1998–02	5879	5434	445	17.1	15.5	1.7
2003–07	5962	5206	756	17.0	14.7	2.4
2008–12	5964	4928	1036	16.7	14.0	2.7
2013–17	6097	5038	1059	16.5	13.8	2.7
Total	29563	26267	3296	16.9	15.0	1.9
Finland						
1993–97	2880	2880	–	8.8	8.8	–
1998–02	3019	2793	226	8.7	7.9	0.8
2003–07	3123	2727	396	8.6	7.7	1.4
2008–12	3254	2686	568	8.4	7.0	1.4
2013–17	3335	2752	583	8.2	6.8	1.7
Total	15611	13838	1773	8.5	7.5	1.0
Iceland						
1993–97	115	115	–	9.6	9.6	–
1998–02	124	113	11	9.6	8.6	1.0
2003–07	136	117	19	9.6	7.7	1.9
2008–12	148	122	26	9.6	7.5	2.1
2013–17	160	132	28	9.6	7.5	2.1
Total	683	599	84	9.6	8.2	1.4
Norway						
1993–97	3877	3877	–	14.0	14.0	–
1998–02	4174	3855	319	14.3	12.8	1.5
2003–07	4397	3850	547	14.2	12.1	2.1
2008–12	4540	3673	867	13.9	11.5	2.4
Total	16988	15255	1733	14.1	12.6	1.5
Sweden						
1993–97	6472	6472	–	10.4	10.4	–
1998–02	6557	6071	486	10.0	9.0	1.0
2003–07	6531	5732	799	9.4	8.1	1.4
2008–12	6388	5270	1118	8.7	7.3	1.5
2013–17	6101	5029	1072	7.9	6.6	1.3
Total	32049	28573	3476	9.3	8.3	1.0

Table VII. Predicted effect of screening for colorectal cancer on the numbers of deaths and age adjusted "world standard population" mortality rates, males. [2]

	Predicted number of deaths			Predicted mortality rates		
Period	Without screening	With screening	Difference	Without screening	With screening	Difference
Denmark						
1993–97	5070	5070	–	22.1	22.1	–
1998–02	5099	4622	477	21.5	19.3	2.2
2003–07	5147	4406	741	20.9	17.9	3.0
2008–12	5194	4290	904	20.2	16.9	3.4
2013–17	5296	4373	923	19.8	16.5	3.3
Total	25806	22761	3045	20.9	18.5	2.4
Finland						
1993–97	2354	2354	–	12.9	12.9	–
1998–02	2634	2383	251	13.0	11.8	1.2
2003–07	2948	2516	432	13.1	11.3	1.8
2008–12	3267	2689	578	12.9	10.7	2.2
2013–17	3595	2956	639	12.8	10.6	2.2
Total	14798	12898	1900	12.9	11.4	1.5
Iceland						
1993–97	110	110	–	11.7	11.7	–
1998–02	121	110	11	11.7	10.4	1.2
2003–07	134	114	20	11.7	9.9	1.8
2008–12	149	122	27	11.7	9.6	2.1
2013–17	164	135	29	11.7	9.6	2.1
Total	678	591	87	11.7	10.2	1.4
Norway						
1993–97	4174	4174	–	21.8	21.8	–
1998–02	4602	4187	415	23.6	21.2	2.4
2003–07	5075	4367	708	25.4	21.7	3.6
2008–12	5686	4718	968	27.4	22.9	4.5
Total	19537	17446	2091	24.5	21.9	2.6
Sweden						
1993–97	6490	6490	–	14.4	14.4	–
1998–02	6647	6045	602	14.1	12.6	1.5
2003–07	6723	5758	965	13.6	11.5	2.0
2008–12	6744	5528	1216	12.8	10.6	2.2
2013–17	6709	5495	1214	11.8	9.8	2.0
Total	33313	29317	3996	13.4	11.8	1.6

Recommendation 2. Quality assurance. Avoid opportunistic screening and secure quality of all the elements of the programme.

Recommendation 3. Develop and evaluate new screening strategies by active research.

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